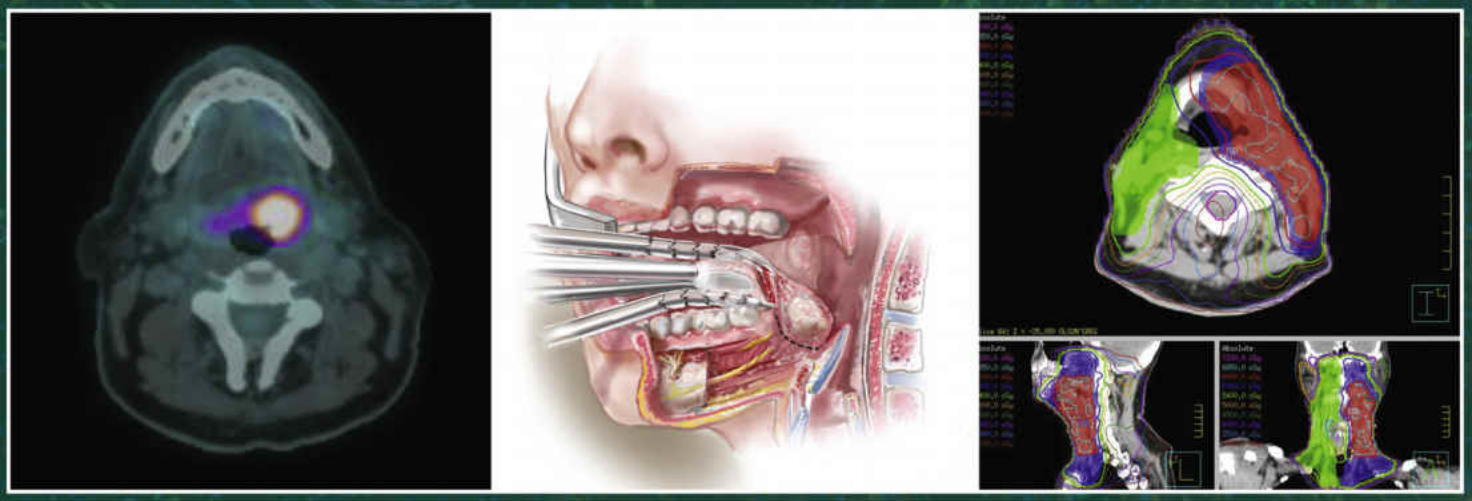
ORAL, HEAD AND NECK ONCOLOGY AND RECONSTRUCTIVE SURGERY

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Oral, Head and Neck Oncology and Reconstructive Surgery

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To all whose lives are inexorably touched by
the capriciousness of head and neck cancer:
your grace and tenacity inspire us to do better.

RBB

RPF

PEA

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Foreword

In the past several decades, we have witnessed major advances in our understanding of cancer pathogenesis with corresponding improvements in treatments. This ranges from an understanding of intrinsic molecular drivers of cancer, micro-environmental changes that facilitate the development of cancer, a more complete recognition of how cancers evade immunological control, and, in the case of head and neck tumors, the critical contribution of human papillomavirus to disease pathogenesis. This knowledge has translated into numerous therapies targeting specific molecular features of cancer along with highly effective immune-targeted therapies. At the same time, there have been remarkable improvements in surgical and radiation technologies that allow for improved patient outcomes. All of these new advances are rapidly being incorporated into new standards of care that require multi-disciplinary teams to most effectively manage patients with cancer. Against this backdrop, R. Bryan Bell and his colleagues provide a comprehensive textbook for managing the most common adult head and neck cancers, with an emphasis on technological innovations in oncologic and reconstructive surgery, rehabilitation, as well as the emerging therapeutics, such as immunotherapy and molecularly targeted therapy. This textbook will serve as an important point of reference for continued improvements in treatment paradigms that will lead to even better outcomes for patients with head and neck cancers, and we all look forward to these future advancements.

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1 Epidemiology

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PART 1: GLOBAL PERSPECTIVE

Newell W. Johnson, Hemantha K. Amarasinghe

Introduction and Scope

The term *head and neck cancer* is generally used to describe the range of malignant neoplasms of soft tissue origin that develop in the oral cavity including the lips, nasal cavity, paranasal sinuses, pharynx, larynx, and salivary glands. The skin is included in many descriptions, but not usually ocular and intracranial neoplasms, nor those of endocrine or lymphatic origin—thus excluding thyroid and parathyroid cancers, lymphomas, and sarcomas.

Approximately 90% of head and neck cancers are squamous cell carcinomas (SCCs), which originate from the epithelium of the mucosal lining of the upper aerodigestive tract (UADT), and adenocarcinomas from associated secretory glands. Head and neck squamous cell carcinoma (HNSCC) is strongly associated with environmental and lifestyle risk factors, particularly tobacco use, both smoked and "smokeless"; the chewing of areca nut (i.e., betel nut); regular alcohol consumption, diets poor in antioxidant vitamins and minerals; ultraviolet (UV) light from the sun; indoor and outdoor air pollution; occupational exposures to radiation or chemical carcinogens; and, increasingly, certain viruses, perhaps sexually transmitted—notably "high-risk" genotypes of the human papillomavirus (HPV) family (particularly HPV16 and HPV18, especially when originating in the tonsil, base of tongue, and elsewhere in the oropharynx), and some human herpesviruses (HHVs; Epstein-Barr virus [EBV] with nasopharyngeal carcinoma). There is a modest inherited susceptibility. Chronic trauma and chronic inflammation are reemerging as significant cofactors. Around the world, with the exception of HPV-related cancers, HNSCC is predominantly a disease of the poor; inequalities and contributing factors have been analyzed by Johnson and colleagues.[1]

HNSCC is known for its capricious biologic behavior and is characterized by local tissue destruction, early and frequent metastasis to the cervical lymph nodes, and a relatively high rate of distant metastases. A large proportion of patients have recurrence of the primary lesion and/or develop a second primary neoplasm, even after effective local therapy. Respiratory and cardiovascular comorbidities are common, usually resulting from tobacco and alcohol abuse and/or poor nutrition.

HPV-associated HNSCC is a distinct clinical and biologic entity that responds much better than HPV-negative carcinomas to conventional therapies. However, HPV-related disease is much less frequent in oral cavity and larynx cancers (<5%) than it is in cancers of the oropharynx (40–80%).[2] The prevalence of HPV in oropharyngeal cancers significantly increased in recent years, and the annual number of HPV-positive oropharyngeal cancers will be likely higher than the number of cervical cancers by the year 2020.[3,4] Whereas the incidence and survival rates of oropharyngeal cancer are greatly increased because of HPV infection, the majority of patients with oral cavity and laryngeal cancer develop locoregional relapse (56%), and as many as a third (34%) will also develop distant metastases despite technologic improvements in local therapies.[5] Indeed, only two biotherapies have been approved by the U.S. Food and Drug Administration (FDA) for HNSCC in the past 10 years: monoclonal antibodies directed at blocking the family of epidermal growth factor receptors (cetuximab) on the surface of malignant keratinocytes, in neoplasms with overexpression of these molecules; and, more recently, an immunotherapy targeting programmed cell death receptor 1 (PD-1), pembrolizumab. New therapeutic strategies for recurrent/metastatic (R/M) oral squamous cell carcinoma (OSCC) are thus urgently needed, particularly in the HPV-negative patient.

The first part of this chapter focuses primarily on the epidemiology of non–HPV-related head and neck cancer, which comprises the greatest burden to society worldwide. Data come from a variety of sources, and certainly cancer registries play a vital role in monitoring the incidence of and mortality from cancers. However, the quality of data available across the globe is highly variable. Many parts of the world produce no data at all, and in others (often among the most populous), the data may come from localized, atypical regions. Hospital-based cancer registries naturally gather biased information—only from patients who are seen in the hospital; in many developing countries, patients may not come to attention at all, either because of fear or because of the inability of poor people to access hospital services. Data may be even more unreliable

because, in many resource-poor countries, follow-up, even of treated patients, is impossible. Death certification is not always compulsory, and there is limited international standardization in the categories for cause of death, let alone calibration of those signing death certificates.

Fortunately, many nations have high-quality population-based cancer registries, with compulsory reporting of all malignancies. These are guided by, and quality assured by, both national authorities and the positive influence of the World Health Organization (WHO), mostly through its constituent body, the International Agency for Research on Cancer (IARC), headquartered in Lyon, France. Increasingly, hospital records contain information on lifestyle and other known or suspected risk factors. The growth of biologic "tumor banks" or "tissue banks" from which molecular markers and mechanisms can be researched is encouraging, and there are several large, international consortia using such banks to unravel the genome of all cancers—notably the International Cancer Genome Project, which has several collaborating centers dealing with head and neck cancers (https://icgc.org); the Cancer Genome Atlas in the United States (www.genome.gov/17516564), and the Wellcome Trust Sanger Institute Cancer Genome Project in the United Kingdom (www.sanger.ac.uk/research/projects/cancergenome).

Data from all over the world are collated and are available from the websites of all of these bodies; this includes free access to programs that allow online interrogation of the databases. Many of the tables and graphs in this chapter have been generated in this way. Within the United States, the website of the Surveillance, Epidemiology and End Results (SEER) Program of the National Cancer Institute provides similar sophisticated opportunities to registered users. It is based on data from, currently, 20 population-based registries, and although these by no means cover the whole nation, they provide insight into evolving epidemiologic trends (http://seer.cancer.gov/registries/list.html).

History

Evidence of head and neck malignancies has been found in ancient skulls. The oldest known tumor is contained in a fossil found in East Africa by Leakey that dates back more than 500,000 years. Some historians speculate that a high incidence of nasal cancer may have been present in some ancient populations because of the inhalation of wood smoke in poorly ventilated huts. In approximately 400 BC, Hippocrates described a common chronic ulcer at the edge of the tongue that he attributed to the presence of sharp teeth rubbing against the tongue: a challenge to differential diagnosis that is still real today! Even earlier, in the sixth century BC, the classical Sanskrit text on surgery, the *Sushruta Samhita,* described the removal of tumors from the head and neck. Modern Western medicine received its foundation from early Roman medical writings. Nevertheless, real advances in the management of head and neck cancers had to wait until the advent of comparatively safe and effective anesthesia and surgical excision in the 18th century.

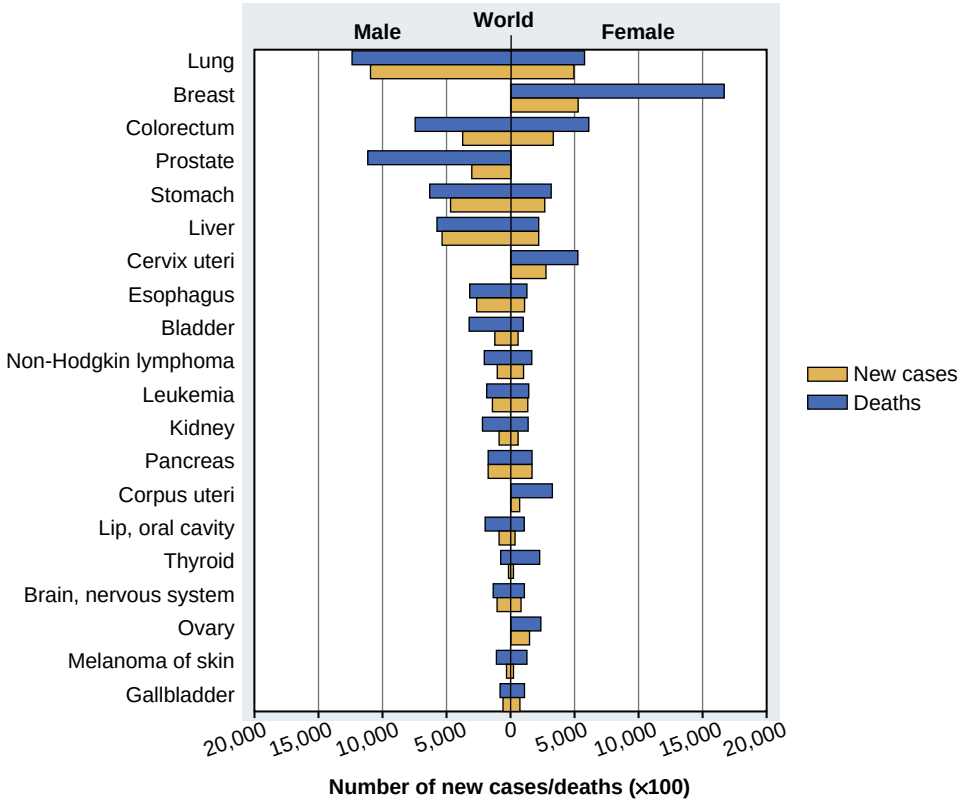
Global Prevalence of Head and Neck Cancer

Depending on the number of anatomic sites and subsites included, head and neck cancer (*International Statistical Classification of Diseases and Related Health Problems,* 10th revision [ICD-10]: C00–C14) is the seventh most common type of cancer, representing about 4.3% of all cases and accounting for an estimated 599,637 new cases and 224,834 cancer deaths worldwide every year. Fig. 1.1 compares several head and neck cancers with cancers affecting other body sites. Numbers of new cases and of deaths attributed to cancer at these anatomic sites are given for males and females; males predominate in all head and neck sites.

Data extracted from the Cancer Incidence in Five Continents database for the period 2003–2007 also facilitate a global overview.[6] When oral and pharyngeal cancers are considered, the annual estimated incidence is around 300,373 cases for cancers of the lip and oral cavity (ICD-10: C00–C08) and 142,378 for other pharyngeal cancers (C09–C10, C12–C14) excluding the nasopharynx; two thirds of these cases occurred in developing countries.[2] There is wide geographic variation in the incidence rates of oral cancer, nasopharyngeal cancer, "other pharynx" cancer, cancer of the larynx, and cancer of the esophagus (Table 1.1). Furthermore, there are marked differences among countries in the same geographic region. For example, oral cancer has the highest crude rates in the world in Melanesia, the Maldives, Sri Lanka, Bangladesh, France, and Hungary.[2] The extremely high rates in the relatively small populations of the Melanesian Islands have not been comprehensively researched, but data from Papua New Guinea (see later) define the importance of areca nut (betel) chewing (called *buai* in Papua New Guinea) and smoking habits as the major risk factors.

The majority of HNSCCs continue to be related to tobacco in various forms, betel quid chewing, heavy alcohol drinking, and dietary micronutrient deficiency.[7] There is a clear dose-response relationship (Fig. 1.2). Worldwide, four times more men than women smoke. In 2002 there were 941 million male smokers, which was 43% of all men older than 15 years. The largest population of male smokers lives in China, where men are more likely to smoke than not to smoke. Even Puerto Rico and Sweden, with the lowest percentages of men who smoke, still have 17% who are smokers.

The Global Adult Tobacco Survey (GATS) is the global standard for systematic monitoring of adult tobacco use (smoking and smokeless) in the world. In India alone, the GATS survey, conducted in 2009–10 by the International Institute for Population Sciences (IIPS) Mumbai, covered about 99.9% of the total population of India. The survey revealed that more than one third (35%) of adults in India used tobacco in some form or another—48% of males and 20% of females; 21% of adults used only smokeless tobacco, 9% only smoked, and 5% smoked and used smokeless tobacco. Thus, in India there were approximately 275 million tobacco users, 164 million users of only smokeless tobacco, 70 million smokers only, and more than 42 million users of both smoking and smokeless tobacco. The distribution of tobacco use in India has been well mapped by Gupta.[8,9]



• **Fig. 1.1** Global scenario of the burden of cancer: new cases and deaths per annum, in 2012, for the top 20 cancers. (Data from Ferlay J, Soerjomataram I, Ervik M, et al, editors: *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012.* Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

TABLE 1.1 World Standardized Incidence Rates for Upper Aerodigestive Tract Cancers per 100,000 per Year

	Mouth (ICD-10: C00–08)		Nasopharynx (ICD-10: C11)		Remainder of Pharynx (ICD-10: C09–10 Plus C12–14)		Larynx (ICD-10: C32)		Esophagus (ICD-10: C15)	
	Lip, all of tongue, all of mouth, and major salivary glands		Data for C30, Malignant neoplasm of nasal cavity and middle ear; and for C31, Malignant neoplasm of accessory sinuses; and for C32, Malignant neoplasm of larynx, are not included here		Tonsil, remainder of oropharynx, pyriform fossa, hypopharynx, and sites not otherwise specified among C00–C13				This code excludes cancers arising at the gastroesophageal junction which are included in stomach cancers, the majority of which are adenocarcinomas; included here, therefore, are mostly SCCs sharing common risk factors with the mouth	
Country	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**	**Male**	**Female**
World	5.5	2.5	1.7	0.7	3.2	0.7	3.9	0.5	9.0	3.1
More developed	7.0	2.6	0.6	0.2	4.7	0.8	5.1	0.6	6.4	1.2
Less developed	5.0	2.5	2.0	0.8	2.8	0.7	3.5	0.4	10.1	4.1
Africa	3.3	2.0	1.5	0.8	1.1	0.6	2.7	0.3	5.6	3.5
Eastern Africa	4.5	2.8	1.9	1.1	1.0	0.6	2.3	0.3	11.9	7.8
Middle Africa	3.5	1.8	1.3	0.6	1.7	0.6	1.4	0.2	4.2	2.0
Northern Africa	2.8	1.8	2.3	1.0	0.8	0.7	4.2	0.4	2.4	1.5

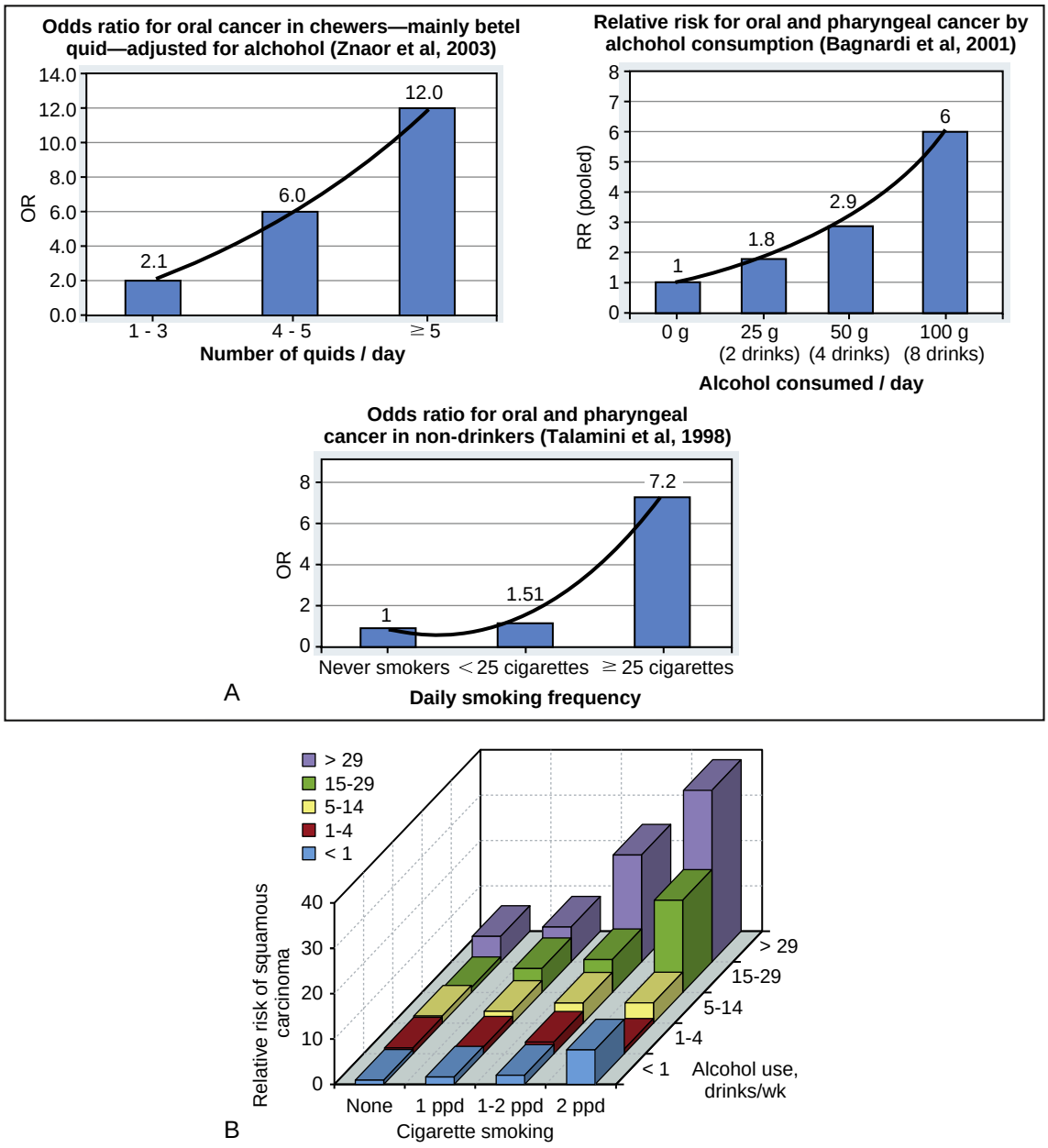
TABLE 1.1 World Standardized Incidence Rates for Upper Aerodigestive Tract Cancers per 100,000 per Year—cont'd

	Mouth (ICD-10: C00–08)		Nasopharynx (ICD-10: C11)		Remainder of Pharynx (ICD-10: C09–10 Plus C12–14)		Larynx (ICD-10: C32)		Esophagus (ICD-10: C15)	
Country	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
Southern Africa	6.3	2.3	0.4	0.2	3.9	1.5	5.0	0.9	13.7	6.7
Western Africa	1.7	1.4	0.7	0.4	0.6	0.1	1.4	0.1	0.8	0.4
Caribbean	4.8	1.8	0.4	0.2	3.6	0.9	7.9	0.9	4.6	1.2
Central America	2.6	1.7	0.2	0.1	1.0	0.3	4.0	0.6	1.7	0.6
South America	5.3	2.4	0.5	0.2	3.0	0.5	5.2	0.7	7.0	2.0
Northern America	7.2	3.2	0.7	0.3	4.2	1.0	4.0	0.9	5.4	1.1
Asia	5.2	2.5	2.3	0.9	3.1	0.7	3.3	0.4	11.4	4.3
Eastern Asia	2.4	1.1	2.5	1.0	1.3	0.2	2.2	0.2	16.9	5.4
Southeastern Asia	4.0	2.5	6.4	2.4	2.6	0.7	2.7	0.5	3.6	1.0
South Central Asia	9.9	4.7	0.6	0.2	6.2	1.4	4.6	0.6	6.5	3.9
Western Asia	2.7	1.6	1.3	0.5	0.8	0.4	6.5	0.9	2.9	2.1
Europe	7.5	2.5	0.6	0.2	5.2	0.9	6.2	0.6	5.8	1.2
Central and Eastern Europe	9.1	2.0	0.6	0.2	5.3	0.5	7.9	0.4	5.6	0.8
Northern Europe	5.9	3.1	0.4	0.2	3.4	1.0	3.4	0.6	8.1	2.7
Southern Europe	5.8	2.1	0.7	0.3	3.4	0.5	7.2	0.6	3.2	0.6
Western Europe	7.9	3.2	0.5	0.2	7.5	1.6	4.9	0.7	6.8	1.6
Australia	8.8	3.9	0.6	0.3	3.3	0.7	3.1	0.3	5.4	1.7
New Zealand	5.5	2.7	0.9	0.3	2.4	0.4	2.3	0.4	5.6	1.8
Melanesia	22.9	16.0	0.4	0.1	3.4	0.4	2.7	0.6	3.6	1.4
Micronesia	4.9	0.0	3.3	2.0	0.0	0.0	0.0	0.0	3.3	0.0
Polynesia	4.1	1.8	2.0	0.8	3.8	0.0	3.2	0.4	3.0	0.3

Adapted from Ferlay J, Soerjomataram I, Ervik M, et al, editors: *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012*. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.
SCC, squamous cell carcinoma.

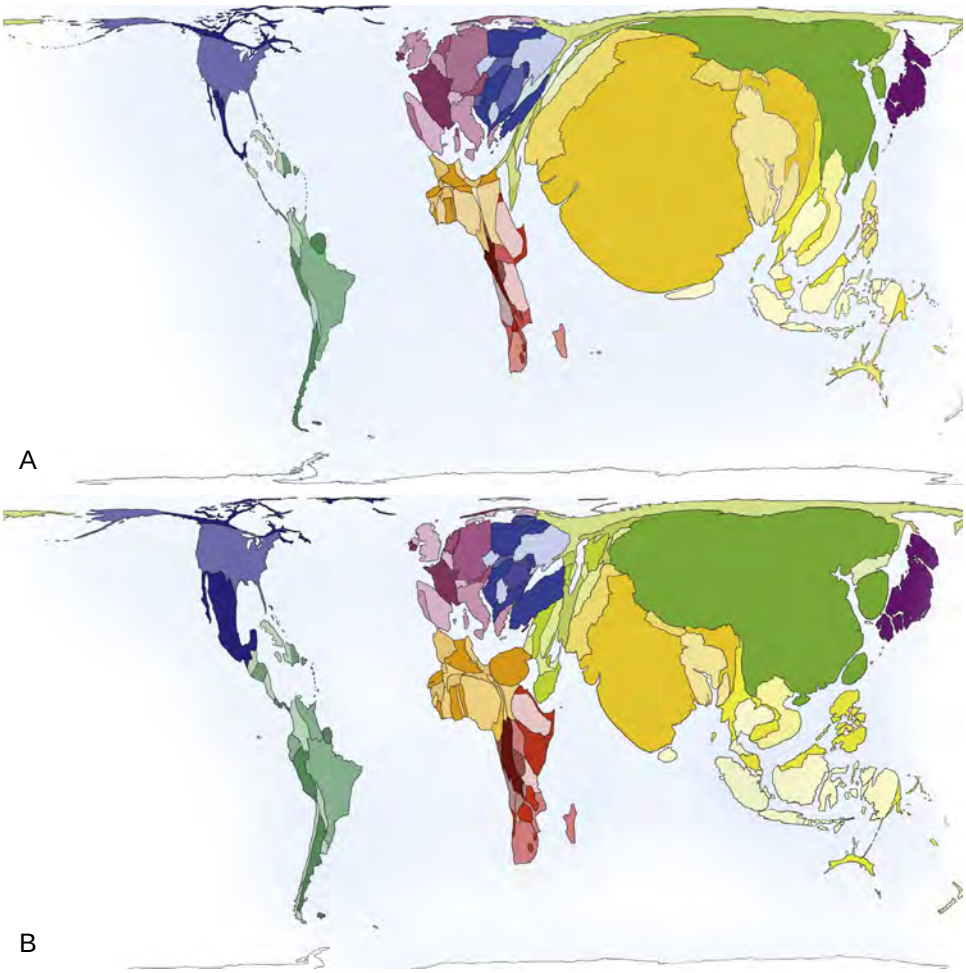
With the data taken as a whole, it is apparent that the public health burden of HNSCC is predominantly a result of smoking and is borne by Eastern Europe, Central and Eastern Asia, and South Asia (Fig. 1.3). China is the major storehouse of tobacco-related morbidity and mortality in the world, a nation where more than half the population continues to smoke. Yemen, Indonesia, Mongolia, Armenia, and Kenya are the five top-ranked countries for smoking prevalence, at 77%, 69%, 69%, 68%, and 67%, respectively.

In the developing world, tobacco and areca nut, used either alone or in combination, account for the vast majority of HNSCCs and oral potentially malignant disorders (OPMDs).[10] WHO has classified areca nut, a common component of many different chewing habits, as carcinogenic to humans.[10–13] UV radiation is relevant to lip cancer. Despite the significance of tobacco and alcohol as risk factors, in the West there are distinct subgroups of patients without these traditional risk factors: younger males who never smoked yet



• **Fig. 1.2** **A** and **B,** The dose-response relation for the major risk factors for oral and pharyngeal cancers. *OR,* odds ratio; *ppd,* packs per day; *RR,* relative risk. (**A** from Johnson NW, Warnakulasuriya S, Gupta PC et al: Global oral health inequalities in incidence and outcomes for oral cancer: causes and solutions. *Adv Dent Res* 23:237–246, 2011. Sources: Znaor A, Brennan P, Gajalakshmi V, Mathew A, et al. Independent and combined effects of tobacco smoking, chewing and alcohol drinking on the risk of oral, pharyngeal and esophageal cancers in Indian men. *Int J Cancer*. 2003;105[5]:681–686. Bagnardi V, Blangiardo M, La Vecchia C, Corrao G. A meta-analysis of alcohol drinking and cancer risk. *Br J Cancer*. 2001;85[11]:1700–1705. Talamini R, La Vecchia C, Levi F, et al. Cancer of the oral cavity and pharynx in nonsmokers who drink alcohol and in nondrinkers who smoke tobacco. *J Natl Cancer Inst*. 1998;90[24]:1901–1903. **B** from Schottenfeld D, Fraumeni JF, editors: *Cancer epidemiology and prevention,* ed 2, New York, 1996, Oxford University Press.)

develop oropharyngeal cancer; elderly women in whom etiologic factors are not clear[14]; and younger females in whom it has been suggested that estrogen deficiency may influence susceptibility to oral cancer. In the case of young nonsmoker males, it has become apparent that oncoviruses are an important cause of HNSCC, especially in Western Europe and North America, where "high-risk" genotypes of the HPV family cause cancer in the tonsil, base of tongue, and other oropharyngeal sites. In Asia, EBV is a major cause of nasopharyngeal carcinoma. Significantly, younger mean age at menopause and higher rates of hysterectomy may influence the higher rates of oral cancer seen among younger women.[15] Data presented in this chapter are, whenever possible, separated by sex. In addition, one of the major limitations of the existing databases is the "lumping"



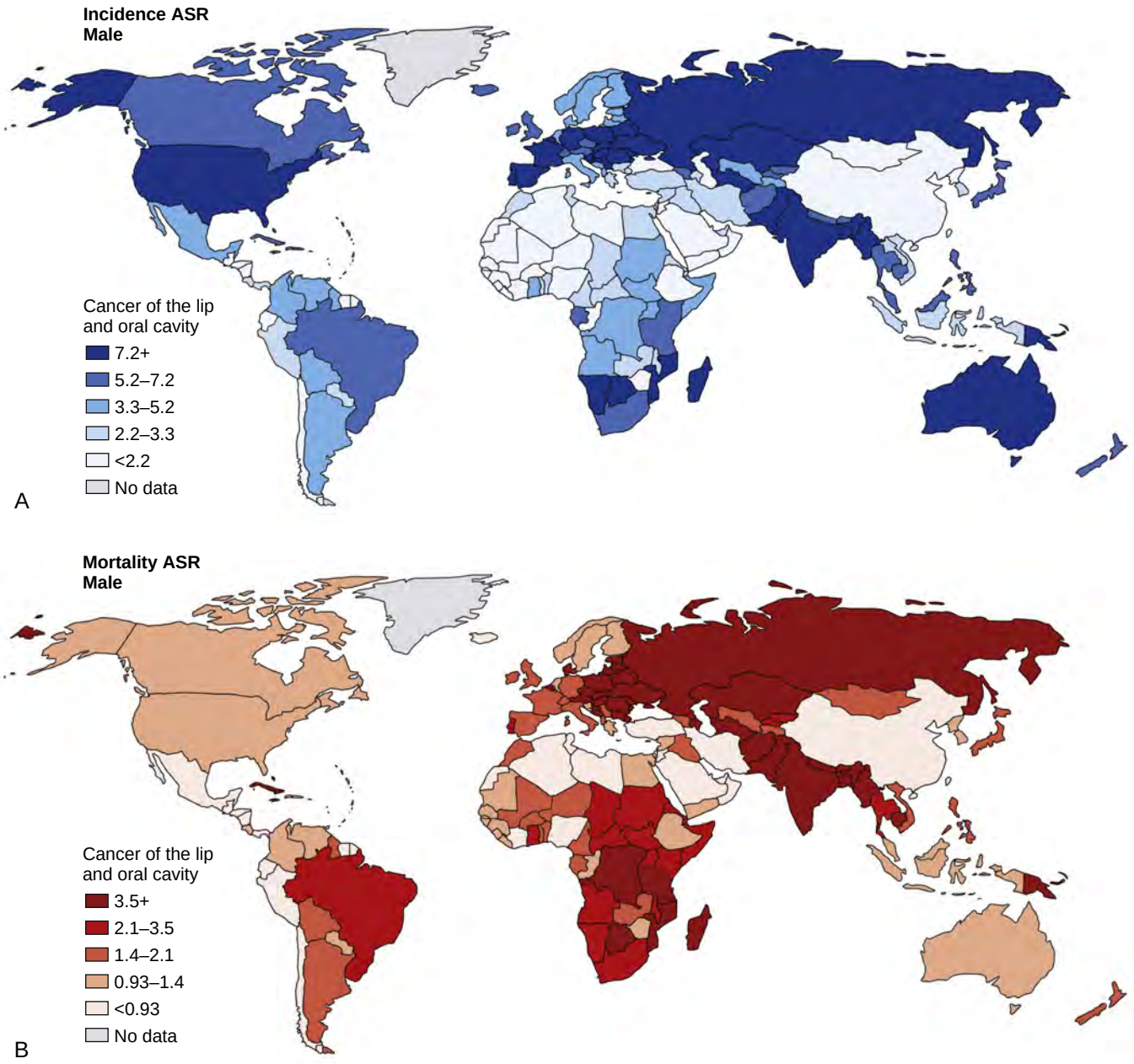
• **Fig. 1.3** These two maps (shown only for males here) distort countries on the basis of the number of deaths by mouth and pharynx cancer **(A),** and the number of male smokers **(B).** They show that the public health burden is borne by Eastern Europe, Central and Eastern Asia, and South Asia. China is the major storehouse of tobacco-related morbidity and mortality in the world, a nation where more than half the population continues to smoke. Yemen, Indonesia, Mongolia, Armenia, and Kenya are the five top-ranked countries for smoking prevalence, at 77%, 69%, 69% 68%, and 67%, respectively. Territory size shows the proportion of men who smoke who live there. (From www.worldmapper.org/display_extra.php?selected=419. Used with permission.)

of oral cavity cancers with cancers of the pharynx. With the evolving role of HPV in the Western world, it is clear that these are biologically distinct and should, in fact, be separated epidemiologically. We have attempted to do this whenever possible, and HPV-related oropharyngeal cancer, a disease that is clinically and biologically distinct from its non-HPV counterpart, will be covered in the second part of this chapter.

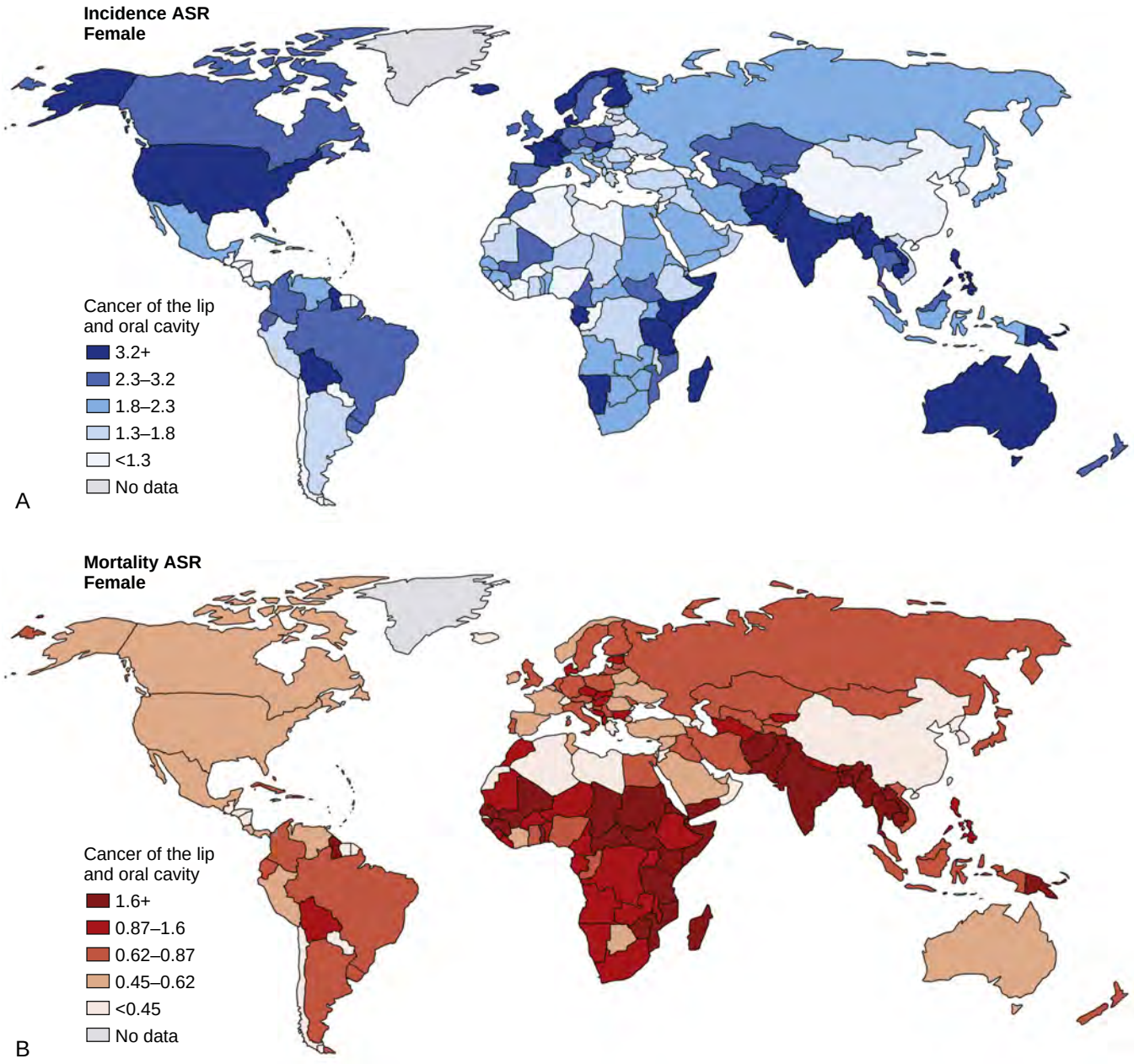
Geographic Differences

The world maps reproduced in this chapter (Figs. 1.4 to 1.9), although simplifying data by aggregation to national averages, contain important information. As with the tables, maps are shown for each of the important head and neck sites. It has been apparent for decades that the global picture for head and neck cancer is dominated by the incidence of oral cancer in southern Asia and of oral cavity plus nasopharyngeal cancer in East Asia. In the 1980s, in India, Bangladesh, Pakistan, and Sri Lanka, oral cancer was the most common site and accounted for about one third of all cancers: it is still the most common cancer among men in Sri Lanka.[16–18] The proportion is falling, partly owing to increased detection of other cancers by more extensive screening programs and improved techniques.[9] Even within the subcontinent there are striking differences in incidence rates. The highest rate for tongue and mouth cancer is reported for men living in South Karachi, Pakistan; the second highest is for those in Trivandrum city in Kerala, India. Extremely high rates for women are seen in the Tamil community in Malaysia—higher even than in Tamil Nadu itself; upper aerodigestive tract sites in Indian females in Peninsular Malaysia are the second most common cancers, behind cancers of the breast and before cancers of the uterine cervix.[19]

According to GLOBOCAN 2012, the highest incidence of oral cancers (ICD-10: C00–C08) is found in Melanesia (astounding rates of 22.9 per 100,000 men and 16.0 per 100,000 women, although there are caveats regarding the



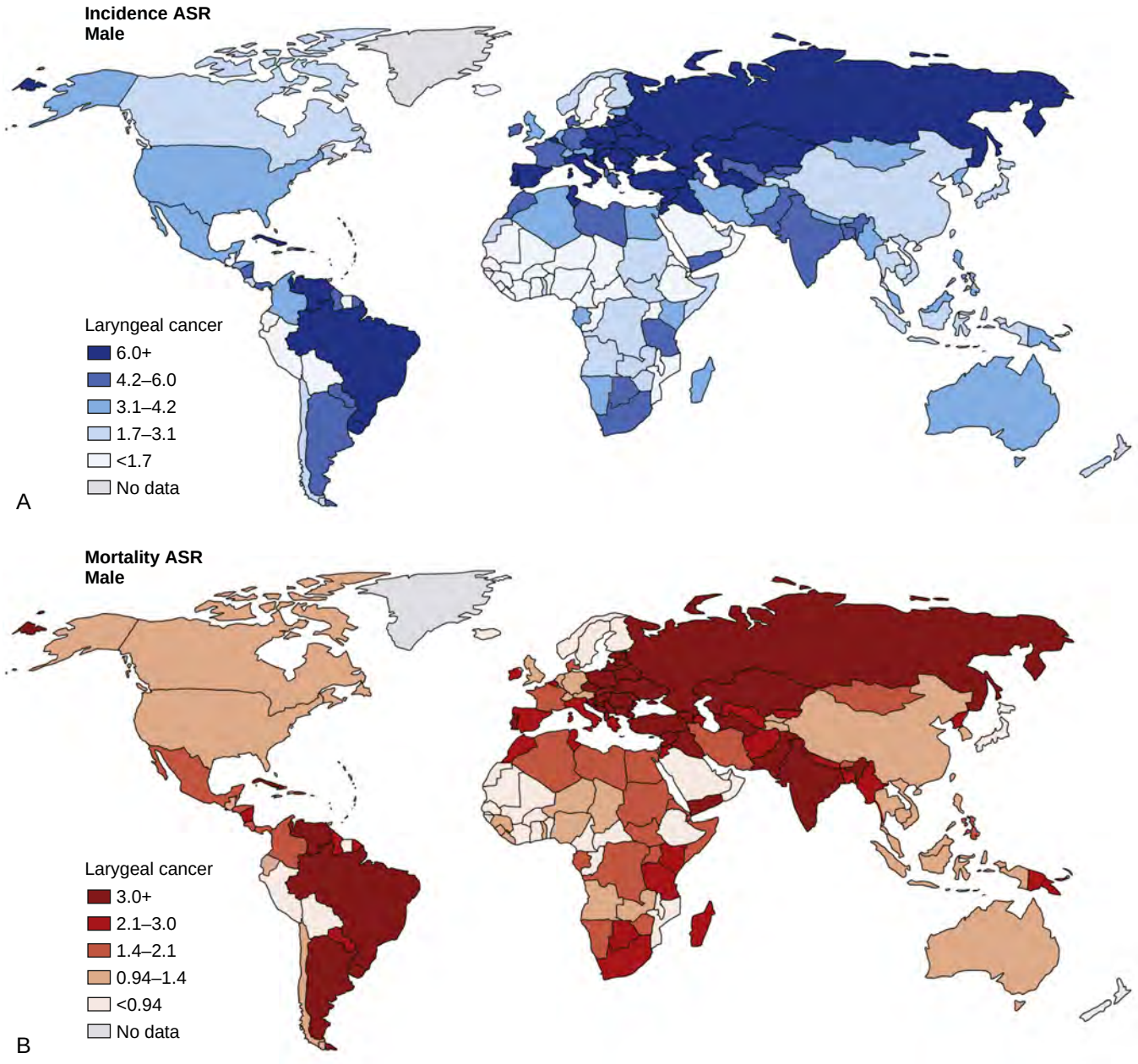
• **Fig. 1.4** **A,** Incidence and **B,** mortality age-standardized rates (ASR) for lip and oral cavity cancer in males, in quintiles, by country. A quick comparison of these maps makes a number of points. The "traditional" high-incidence areas of central Asia and the Indian subcontinent stand out; much of this is a result of betel quid use, with or without smokeless tobacco, plus smoking, sometimes alcohol abuse, and poor diet. Note that parts of both Western and Eastern Europe remain in the top quintile (see text). The African data are not particularly robust. Australia shows a high incidence owing to ultraviolet light–induced lip cancer in a fair-skinned population; mortality rates are not comparably high because lip cancer is comparatively easily treated. Eastern Europe and the former Soviet Republics have high mortality, partly related to low socioeconomic status, limited treatment facilities, and the fact that many patients have substantial comorbidities. As already mentioned, Papua New Guinea and surrounding Melanesian islands of the Western Pacific are in the top quintile both in incidence and mortality; indeed, Melanesia had the highest recorded rates in the world at the beginning of this millennium—associated with chewing of areca nut and tobacco use. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)



• **Fig. 1.5** **A,** Incidence, age-standardized rates (ASR), in females—lip and oral cancers. **B,** Mortality rate, ASR, in females—lip and oral cancers. Note the serious situation in the Indian Subcontinent, much of northern Asia, South America, and parts of the Middle East including the southern provinces of Saudi Arabia and Yemen. In parts of India, oral cancer is the leading cancer among women, because of heavy use of betel quids. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

quality of these data).[2] In India alone, over 100,000 cases of oral cancer are registered every year, and the numbers are rising. Although men predominate overall, among women a very high incidence is found throughout South Central Asia (4.7 per 100,000). In terms of countries, the Maldives and Sri Lanka have the highest incidence of oral cancer in the South Asian region. Poor access to health services contributes to high mortality.

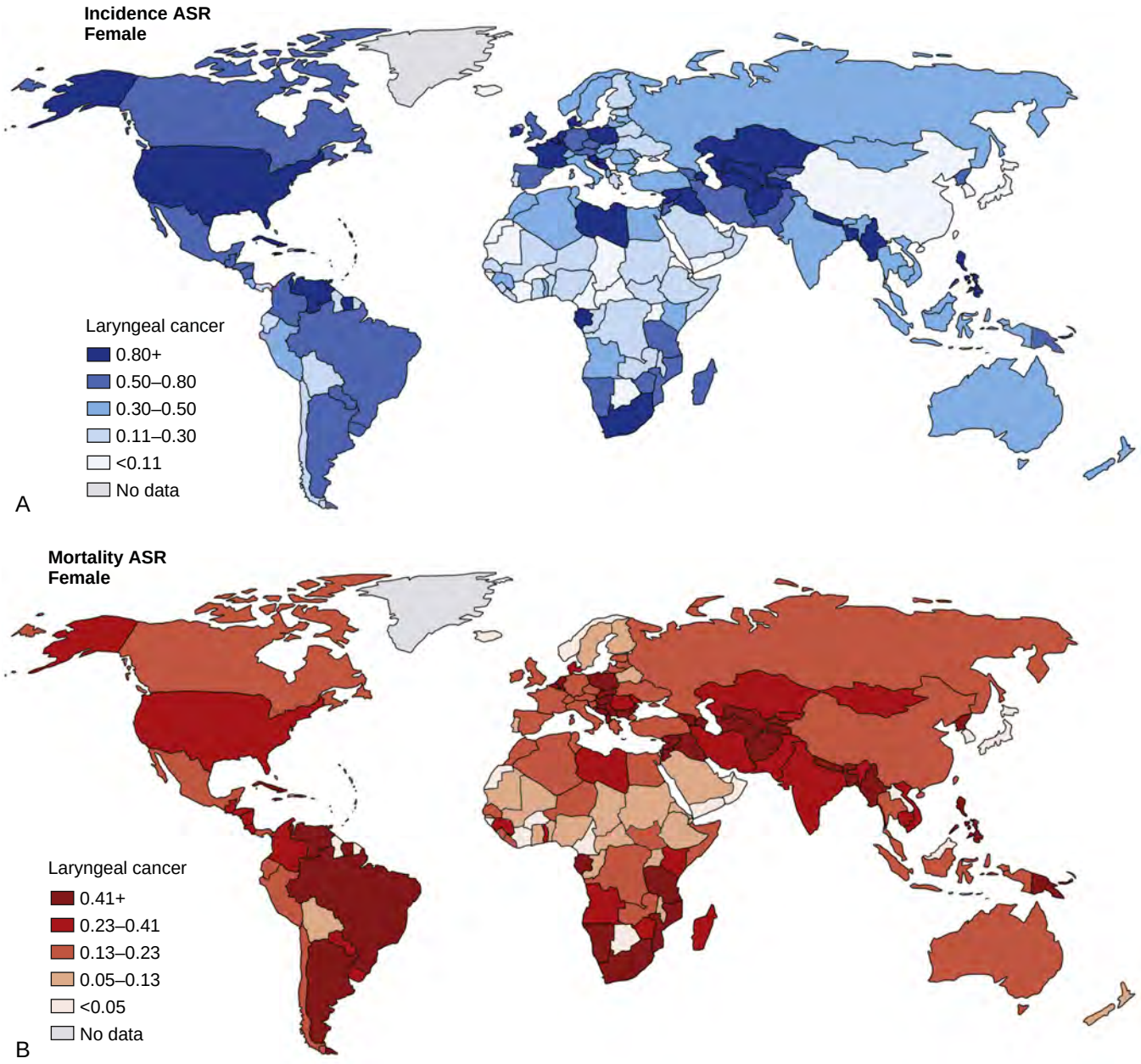
More than 126,000 cases of oral cancer (ICD-10: C00-C08) occur every year in South and Southeast Asia alone, with poor prospects for survival. About 90% of these cases are attributable to smoking and chewing habits. It is encouraging that overall rates in India are showing a decreasing trend in successive birth cohorts; declining trends were observed for mouth (ICD-10: C03–C06) and tongue (C01–C02) cancers among females and tongue cancers among males between 1982 and 2000,[11] and this has continued. However, population growth in the subcontinent means that the disease burden continues to rise. Better primary prevention is essential[12] (Fig. 1.10). There is growing concern that commercial areca nut and tobacco



• **Fig. 1.6** **A,** Incidence, age-standardized rates (ASR), in males—laryngeal cancer. **B,** Mortality, ASR, in males—laryngeal cancer. Rates of laryngeal cancer largely reflect smoking rates in men around the globe, with the surprising exceptions of China and Japan, where incidence **(A)** and mortality **(B)** among men are comparatively low, despite prevalence rates of smoking in males of 50% or higher; however, as noted earlier, Japanese rates are on the rise. The proportionately higher death rate in Eastern Europe, Russia, and the former Soviet Republics is again related to late stage at diagnosis and high rates of comorbidities associated with low socioeconomic status and difficulties with access to care. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

products will contribute to future rises in the incidence of oral submucous fibrosis (OSF) and of subsequent oral cancer.[13]

The overall incidence of smoking-related cancers appears to be decreasing in many parts of the world (Figs. 1.11 to 1.16). For cancers of the oropharynx and tonsils, as well as the hypopharynx, the highest combined incidence rate is currently seen in France, and this is increasing. For women, the highest age-standardized rate (ASR) for mouth and tongue cancer specifically was in India.[6] Data from Japan show a dramatic increase in oral and pharyngeal cancer incidence (ICD-10: C01–C14) for both sexes; there was a 4.4-fold increase for males and 3.8-fold increase for females in the total numbers between 1965 and 1999—noted from data retrieved from the Osaka Cancer Registry.[20] There is also an upward trend for

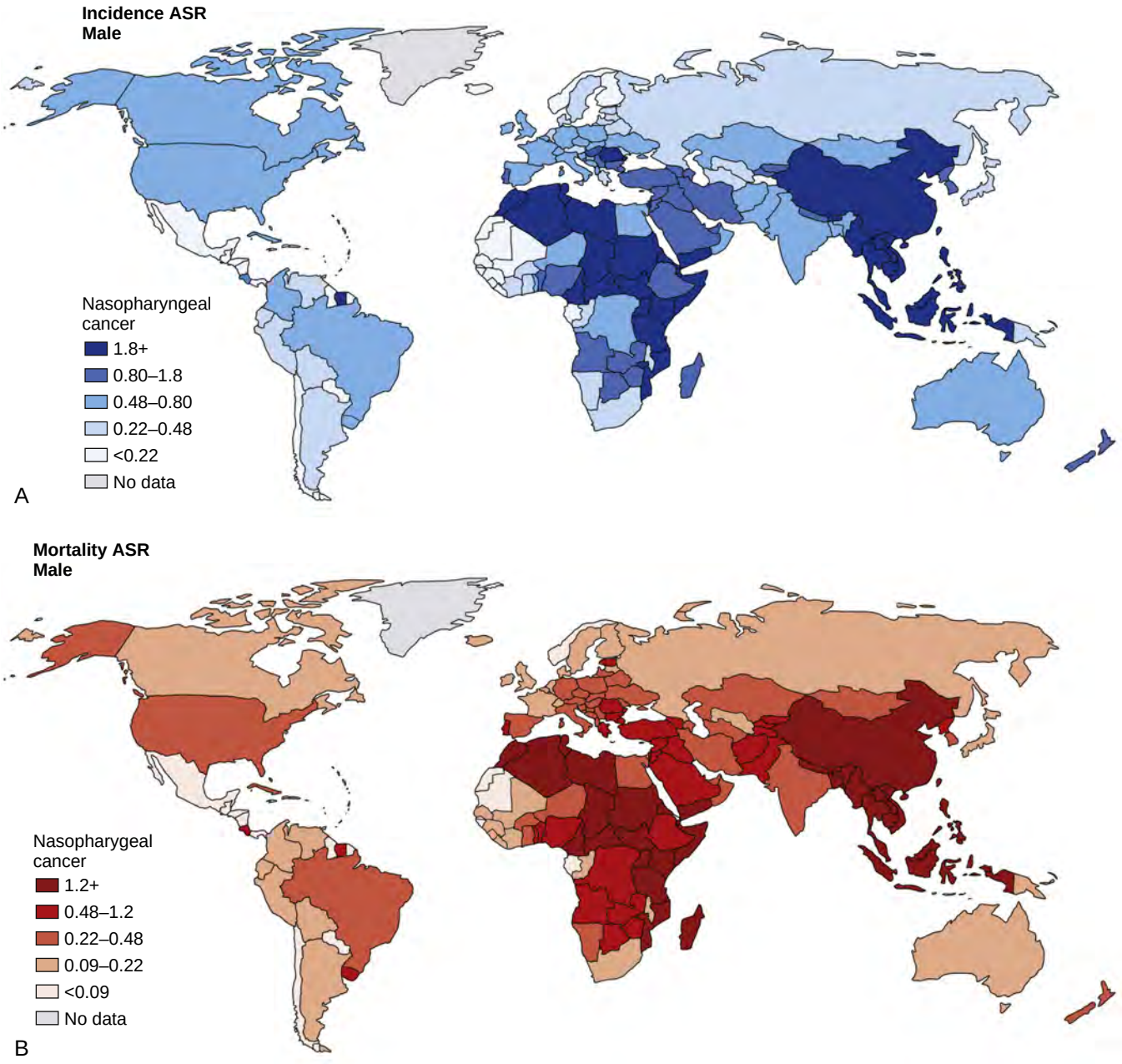


• **Fig. 1.7** **A,** Incidence, age-standardized rates (ASR), in females—laryngeal cancer. **B,** Mortality, ASR, in females—laryngeal cancer. Because smoking is far less prevalent in women than in men in most societies, the laryngeal cancer rates are low worldwide, and less can be read into this aspect of "geographic pathology." Nevertheless, there are clear challenges to be met in much of the continent of South America, in Central Europe, and in the United States. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

both males and females in Australia and among the non-Maori population in New Zealand. Lip cancer in fair-skinned populations, particularly due to UV light, is a growing problem.[21]

A study in Mumbai, India, indicated a decreasing trend in oral cancer incidence among Indian men, which, it was suggested could have been due to a decrease in the use of betel quid or pan and associated oral smokeless tobaccos over this period.[22] However, there continues to be a high prevalence of smokeless tobacco use among young adult men and women, especially in the form of Pan Parag/Gutka-type products, and cigarette smoking is increasing.

In the United States, the estimated numbers of incident cases for tongue, mouth, and other oral cavity cancers in 2008 were 15,250 cases for men and 7650 for women; for the pharynx, the number of incident cases for men was 10,060, and 2350 for women (3% of all cancer cases in men). For cancer of the larynx, 12,250 incident cases were estimated, of which 9680 were in men. The incidence rates for cancers of the oral cavity and pharynx or throat were stable or declining for men and women in most age groups during the period 1973–2003 in the United States, probably related to changes in tobacco

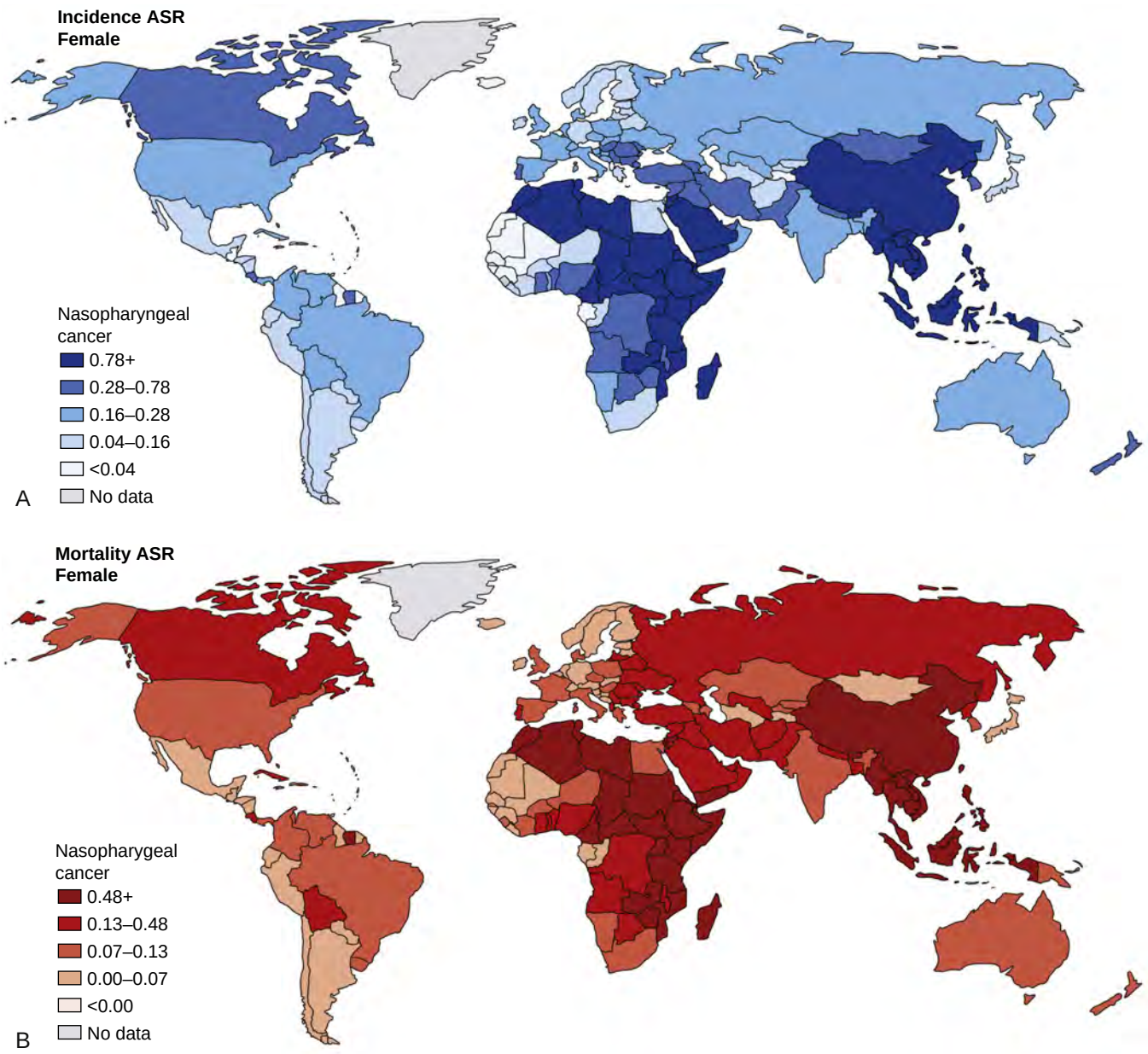


• **Fig. 1.8 A,** Incidence, age-standardized rates (ASR), in males—nasopharyngeal cancer. **B,** Mortality, ASR, in males—nasopharyngeal cancer. Risk factors for nasopharyngeal cancer are comparatively well understood. It is a biologically distinct disease, driven by Epstein-Barr virus, in subjects with genetic susceptibility, compounded by toxins in particular cultural dietary practices. Both incidence **(A)** and mortality rates **(B)** are historically high in North, Central, and East Africa, in Indonesia, and in China—particularly Guangdong Province, Hong Kong, and emigrant communities from these areas. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

and alcohol consumption. This is a highly pleasing situation, common to many countries with advanced care facilities but not reflected in most of the high incidence countries elsewhere in the world. Cancer of the larynx has always been a serious public health problem in nations with high smoking prevalence, and this remains problematic in China and Eastern Europe and the former Soviet Union. Trends for laryngeal cancer reflect continuing high rates of tobacco consumption in many societies (see Fig. 1.13).

Sex Differences

Worldwide, the incidence of head and neck cancers overall is higher for males than females. According to the IARC,[2] the age-specific incidences of "oral cavity," "nasopharynx," and "other pharynx" cancers were 5.5, 1.7, and 3.2 per 100,000 population for males in 2012 and 2.5, 0.7, and 0.7 for females, respectively (see Table 1.1). The higher rates in males may result from their greater exposure to the most important risk factors, such as heavy



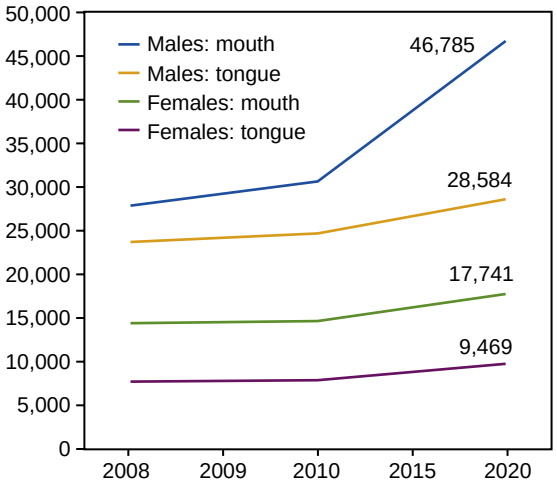
• **Fig. 1.9** **A,** Incidence, age-standardized rates (ASR), in females—nasopharyngeal cancer. **B,** Mortality, ASR, in females—nasopharyngeal cancer. (From Ferlay J, Soerjomataram I, Ervik M, et al, editors. GLOBOCAN 2012 v1.0, cancer incidence and mortality worldwide: IARC CancerBase No. 11 [Internet]. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.)

alcohol and tobacco consumption for intraoral cancer and sunlight for lip cancer in those who work outdoors. However, oral cancer in females is increasing in some parts of the world. For instance, a study from Argentina showed the male/female ratio to be 1.24:1 for the period 1992–2000 compared with 7.1:1 for the 1950–1970 period.[23] The incidence of tongue and other intraoral cancers for women can be greater than or equal to that for men in high-incidence areas such as India, where betel quid/areca nut chewing (and sometimes smoking) are common among women—although this varies considerably from region to region.

Early this century in Europe, the incidence of oral cavity and pharyngeal cancers (ICD-10: C00–C14) among males varied substantially between 5.9 (Finland) and 32 (France) per 100,000 per annum.[24] Incidence rates among females were highest in Northern and Western Europe but were consistently lower than those for males. The male-to-female ratio decreased during the past 10 years and recently varied from 1.5 to 2.5 in Northern Europe to 7.7 in Lithuania. Between 1990 and 1999, the incidence rates for oral cancers in the United Kingdom rose in males of all ages from 6.5 to 8.3 per 100,000 (an increase of 18%) and in females from 2.6 to 3.6 per 100,000 (an increase of 30%) and continues to be a concern.[25]

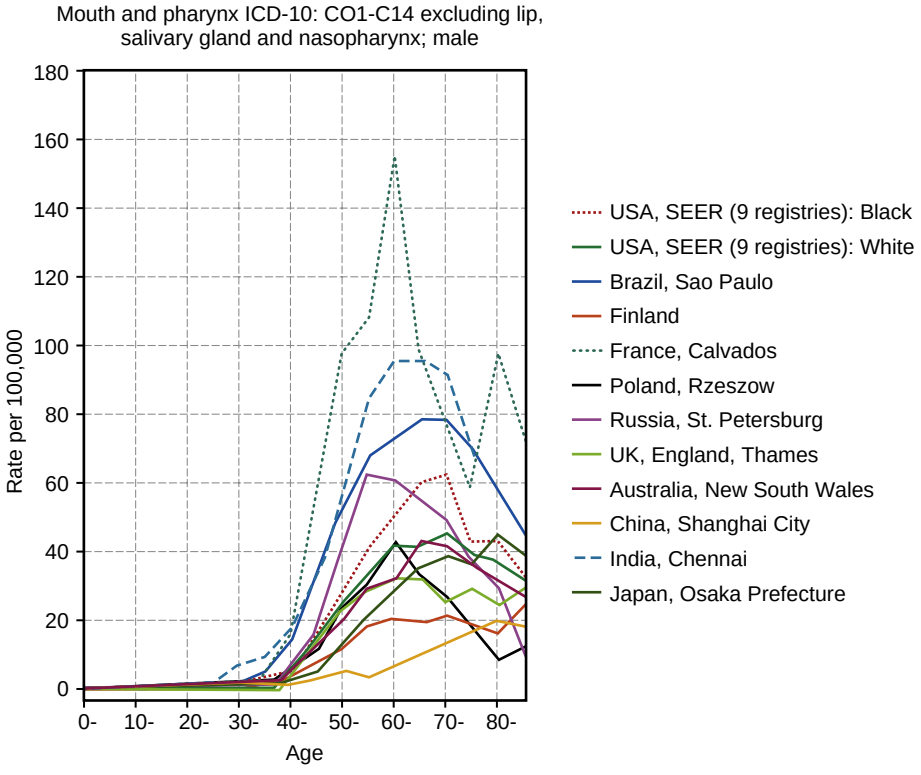
Ethnic Differences

Variations by ethnicity are largely due to social and cultural practices and the influence of dietary and genetic factors, although the latter are less well quantified. Variations in

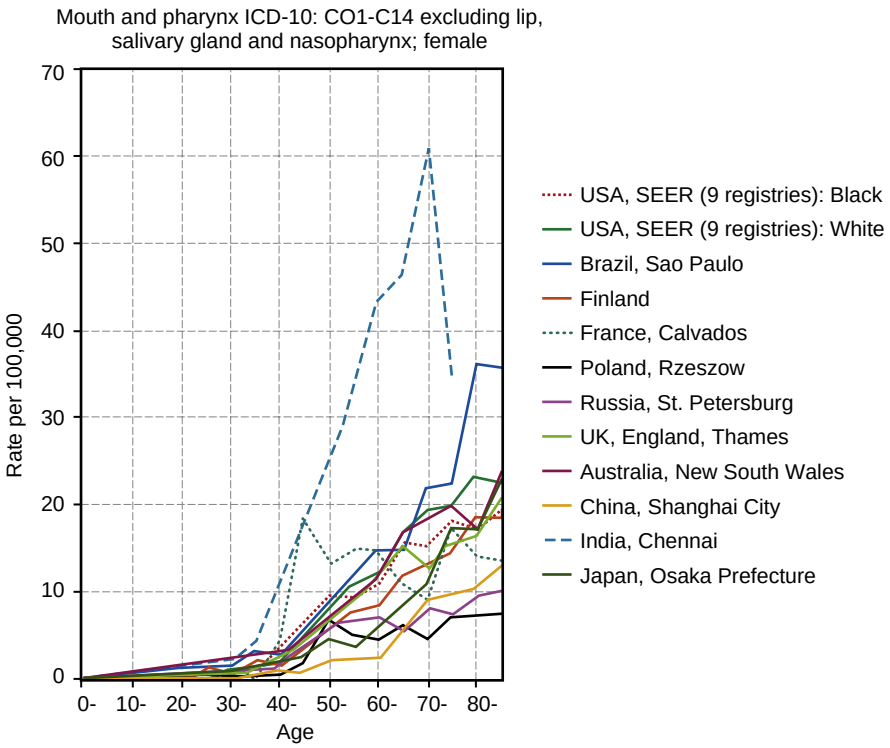


• **Fig. 1.10** Projected increases in the burden of mouth and tongue cancer in India in the next decade. (From Gupta B, Ariyawardana A, Johnson NW: Oral cancer in India continues in epidemic proportions: evidence base and policy initiatives. *Int Dent J* 53:12–25, 2013.)

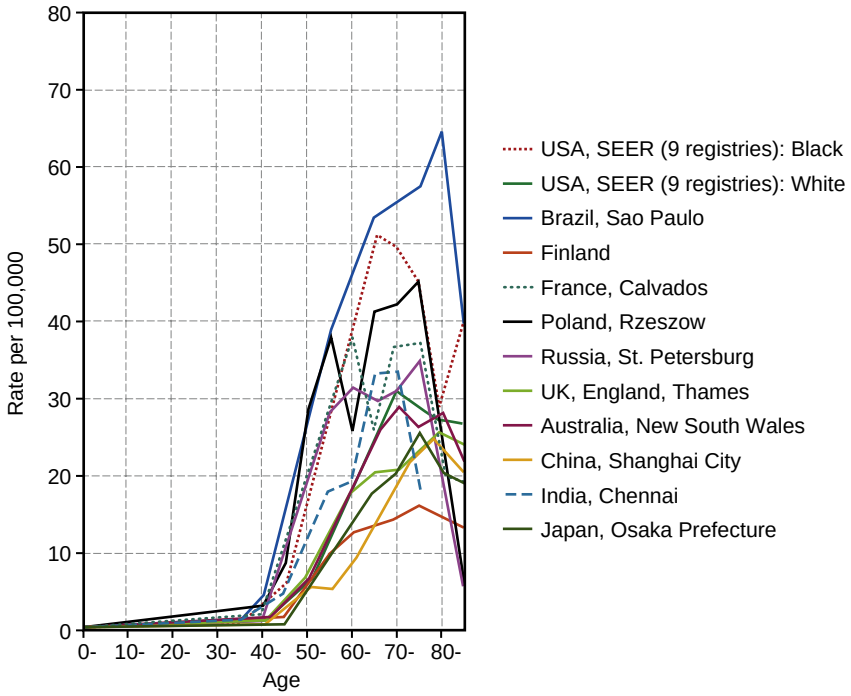
outcome are also affected by differences in access to health care. Where cultural practices represent risk factors, their continuation by emigrants from high-incidence regions to other parts of the world results in comparatively high cancer incidence in immigrant communities. This can also affect the subsites of oral cancer most commonly affected, as shown in a study from California.[26] The highest age-adjusted oral cancer rates in the United States are found among non-Hispanic men (17.5/100,000) followed by non-Hispanic women (6.6/100,000), with Asian and Hispanic populations showing lower incidence rates compared with white (Caucasian) ethnic groups. Tongue cancer was the most common type of oral cancer among every ethnicity. Asians were more likely to develop their malignancy in the buccal mucosa, a reflection of continuing areca and tobacco chewing habits. Another study showed that Native Americans and Alaskan Natives overall had significantly lower incidence rates than non-Hispanic whites.[27] Several studies from the United States have demonstrated that black patients with oral cancer have poorer overall and disease-specific survival than whites, mainly because of their comparatively poor access to health care.[28,29] This is especially concerning because the incidence of oral plus



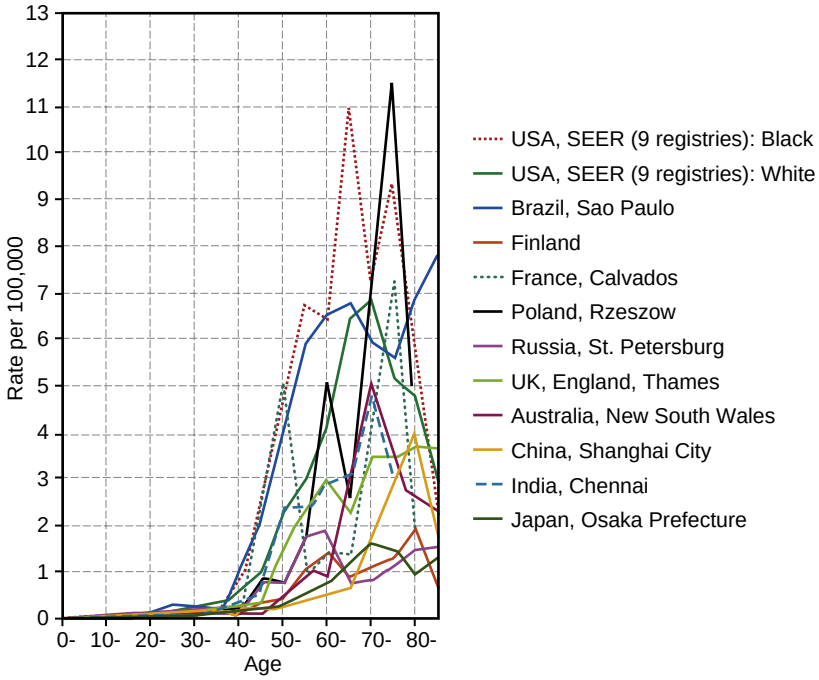
• **Fig. 1.11** Male age-specific incidence curves for oral and pharynx for selected countries. All upper aerodigestive tract cancers show a similar distribution. Most cases occur in the fifth to seventh decades of life, presumably because decades of exposure to tobacco, alcohol, and poor nutrition take time to synergize with other agents in triggering malignant transformation—or in allowing this to survive the host response. Nevertheless, a significant minority of cases appear in the third and fourth decades of life. These attract much interest; although associations with early commencement of smoking and with unsafe alcohol use can be demonstrated, a substantial minority of cases arise without exposure to traditional risk factors. Here, dietary inadequacies and human papillomavirus infection are likely to be important, and inherited predisposition may play a role. *SEER,* Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



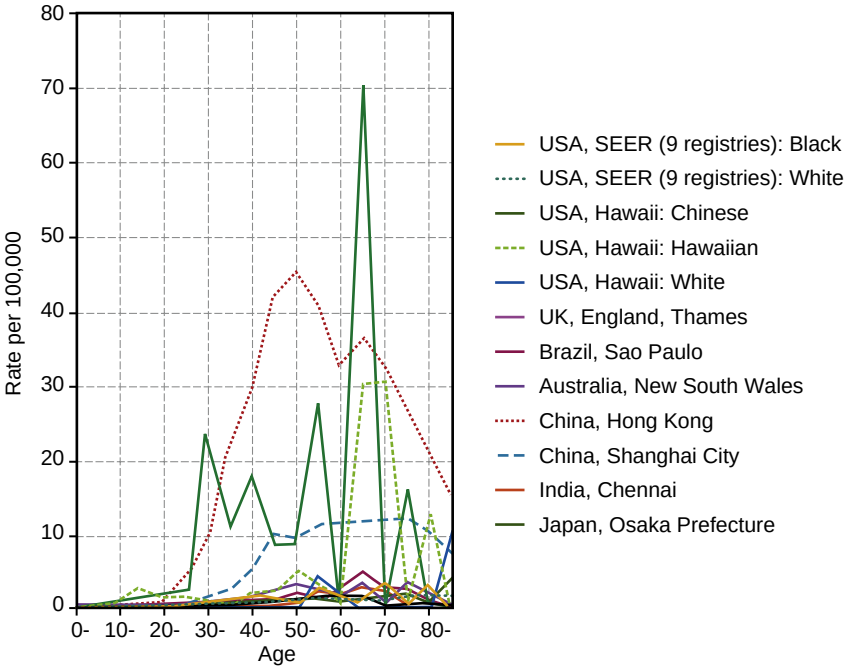
• **Fig. 1.12** Female age-specific incidence curves for oral and pharynx for selected countries. Rates for females are lower, and international differences are less marked. Rates in women in South India stand out; this is related to use of betel quid and tobacco, together with low socioeconomic status. *SEER*, Surveillance, Epidemiology, and End Results. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



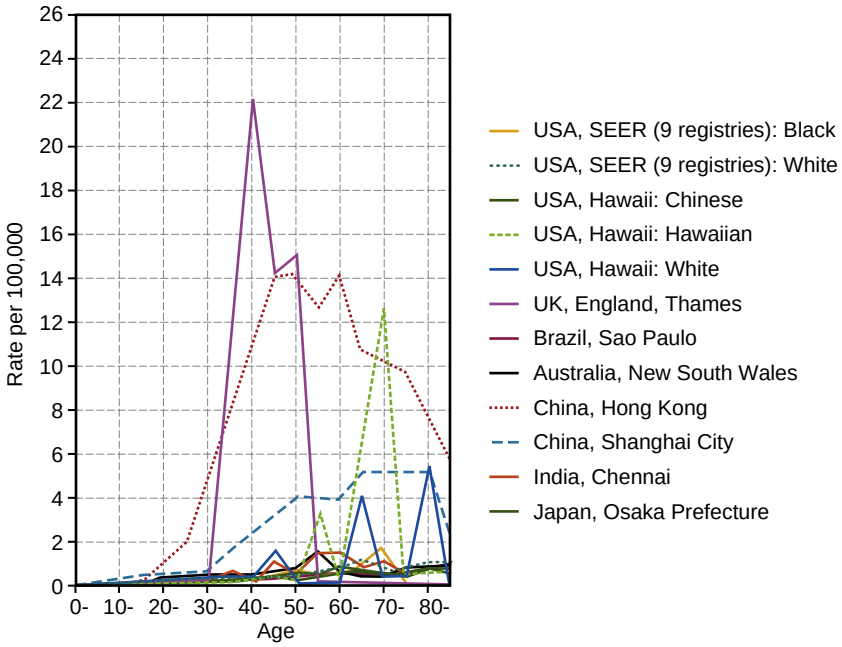
• **Fig. 1.13** Larynx—male. Many of the differences among populations are likely to be explained by smoking and other traditional risk factors. Serious public health challenges exist in the Brazilian example. Poland and the Russian example are consistent with the major concerns we have for Eastern Europe, Russia, and the former Soviet Republics as a whole. Blacks do poorly in the United States. Finland provides encouragement; indeed, this was the first country in the world to reach the World Health Organization target for the year 2000 of having less than 20% of the adult population smoking. Japan and China remain enigmas. *SEER*, Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.14** Larynx—female. Although at first glance the spread for women looks larger, the rates are much lower than for men. Poland, as with much of Eastern Europe; American blacks; and Brazil again stand out. *SEER*, Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.15** Nasopharynx—male. Nasopharyngeal cancer is a distinct disease. These countries have been chosen to reflect differences by population. Southern Chinese men are particularly susceptible—hence the alarming data from Hong Kong and to a lesser extent from Shanghai. Although the data are fragmentary, the markedly higher rates in Chinese Hawaiians compared with other racial groups are consistent with the ethnic bias. *SEER*, Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.16** Nasopharynx—female. The highest rates of nasopharyngeal cancer in women are in Chinese women. *SEER,* Surveillance, Epidemiology, and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

pharyngeal cancer for black men in the United States is so high, and the oropharynx is the sixth most common site for malignant disease in this group.[30]

In the Republic of South Africa, among Asian/Indian South Africans, oral and oropharyngeal cancer age-specific incidence rates (ASIR) were higher among females (ASIR, 4.60) than among males (ASIR, 3.80). Excluding those involving the lip, these cancers were highest among Coloureds (ASIR, 5.72) and lowest among blacks (ASIR, 3.16). Incidence rates increased significantly among Coloured South Africans over the period from 1992 to 2001 ($p < .05$), particularly for the oropharynx (available at http://repository.up.ac.za/bitstream/handle/2263/32412/AyoYusuf_Trends(2013).pdf?sequence=1).[30a] The age-adjusted incidence rate for oral and pharyngeal cancers is higher for South Asians than for other residents in England, particularly among females.[31] It is interesting to note that this study showed that British South Asian males have significantly better survival than their non–South Asian peers in the southeast of England, possibly a reflection of the more indolent progress of tobacco- and areca nut–induced lesions.[31]

Overall, there is an approximately 4- to 10-fold difference in HNSCC incidence among ethnicities, with disturbingly high rates in northwest France, Brazil, and South India. Note the much worse situation in American blacks compared with whites, explained by a mixture of risk-factor and socioeconomic reasons. Finland does comparatively well—not surprising in view of that nation's success in reducing the prevalence of smoking, though alcohol abuse remains a social problem. What is surprising are the low rates recorded for Shanghai, in spite of high smoking prevalence in this large city. China is currently developing a more comprehensive, nationwide cancer registry system, so more cogent data will soon be available.

Age Distributions

HNSCC is usually a disease that occurs in men after the fifth decade of life. The mean age at presentation is in the fifth and early sixth decades in Asian populations compared with the seventh and eighth decades in the North American population.[32–39] Statistics in the United States for 1975–2011 show that the median age at diagnosis for cancer of the oral cavity and pharynx was 62 years.[38]

Several studies have suggested that 4–6% of oral cancers now occur at ages younger than 40 years.[39] An alarming increase in incidence of oral cancers among younger people has been reported from many parts of the world,[40–43] a trend that appears to be continuing and is likely related to the increase in prevalence of HPV infection, which will be further explored in the second part of this chapter. There was a significant increase in the incidence of cancers in the tongue and tonsil among 20- to 40-year-olds in the United States between 1973 and 2001.[44] In Germany, Czechoslovakia, and Hungary, within one generation there has been an almost 10-fold rise in mortality from oral cancer in men aged 35–44.[45] Robinson and Macfarlane showed a dramatic increase in incidence rates for younger males in Scotland from the 1980s to the 1990s.[46] In the high prevalence areas of the world, in many cases patients are less than 40 years old, probably owing to heavy use of various forms of tobacco from an early age, although some recent data from India have not shown this.[47]

It is also clear that a number of cases of SCC occur in both young and old patients in the absence of traditional risk factors; in these patients the disease may pursue a particular aggressive course, more so in the elderly. A study conducted in southern England concluded that in a substantial proportion of cases of

younger people diagnosed with oral cancer, the disease occurs in the absence of known risk factors.[48] This, together with the relatively short duration of exposure in users, suggests that factors other than tobacco and alcohol are implicated in the development of oral cancer in a significant minority of cases. Diets poor in fresh fruits and vegetables were identified as conferring significant risk. There is now substantial evidence that HPV infections are driving this rise in younger adults; fortunately, HPV-related oropharyngeal cancers respond well to radiotherapy, permitting treatment deescalation and improved quality of life. It is also suggested that greater attention should be paid to familial antecedents of malignant neoplasms in younger patients with oral cancer.[49]

Mortality Trends

Current WHO mortality and trends of age-standardized (world population) mortality rates for the head and neck cancer sites of interest, within selected countries over the past three to six decades,[50] are presented in Table 1.2 and Figs. 1.17 to 1.22. Death rates for oral and pharyngeal cancer in males around the world are shown vividly in Fig. 1.17. There was a steady rise in oral cancer mortality in men from the 1950s to the late 1980s in most Western European countries[51]; rising rates have declined since that time in France, China, and Hong Kong, which had exceedingly high rates in the past. Unfortunately, in most countries in Central and Eastern Europe, oral cancer mortality in men continued to rise, reaching exceedingly high rates in Hungary, Slovakia, Slovenia, and the Russian Federation at the end of the past century. Hungary, Ukraine, Estonia, and Bulgaria showed more than a 100% increase in mortality rates for men during the 20-year period up to the turn of the millennium. Even though the rates of oral cancer are comparatively low among women (see Fig. 1.18), there was an increase in several countries in Europe (notably Hungary, Belgium, Denmark, and Slovakia) over this period. These disturbing rises are thought to have been related to high drinking and smoking patterns in these societies, together with poor diet in lower socioeconomic groups. Fortunately, improvements are now evident. Trends for laryngeal cancer reflect continuing high rates of tobacco consumption in many societies (see Figs. 1.19 and 1.20). Trends for nasopharyngeal cancer, both good and bad, are shown for high-incidence countries (see Figs. 1.21 and 1.22).

In Europe, Hungary has the highest incidence and mortality of oral and pharyngeal cancer for both sexes.[52] Between 1984 and 1994, the Hungarian mortality rates for oral cancers rose by 83.5% and 72.3% in males and females, respectively, but this has now stabilized. Trends in the mortality rate among Italian and French males peaked in the 1980s, and rates decreased after 1990.[53] However, some persisting upward trends were registered for Belgium, Denmark, Greece, Portugal, and Scotland.[54] In the United States, the mortality rates per 100,000 population per annum for cancer of the oral cavity and pharynx for men were 5.61 in 1990 and 3.98 in 2004, the absolute decrease being 1.63 per 100,000, contributing to a 3% reduction in mortality for all sites. For women, the decrease across the same period was 0.56, contributing to a 2.5% reduction for all sites.[11]

In the United States, mortality from HNSCC appears to be declining. The death rates for cancer of the oral cavity and pharynx per 100,000 population in 2007–2011 were 3.8 for males and 1.4 for females,[12] down from 6.9 and 2.3, respectively, in 1975. This substantial improvement is not reflected in most of the rest of the world. The SEER Program in the United States reported an overall fall in the mortality from oral and pharyngeal cancer, between 1975 and 2004, of 1.87% per annum (Fig. 1.23). Table 1.3 shows a fall in all mortality rates for oral and pharyngeal cancer in the United States between 2002 and 2011. There was considerable fall in mortality among both black men and black women (annual percent change of −3.7 and −2.7, respectively). Furthermore, the SEER data show higher 5-year relative survival rates for whites (64.3%) and blacks (43.7%), who were diagnosed during the period 2004–2011 than for those who were diagnosed during the period 1974–1976 (when rates for whites and blacks were 55% and 36.3%, respectively).[13] The 5-year survival rates in the SEER registries range from a high of 72.1% for white women in Utah to a low of 24.8% for black men in metropolitan Atlanta. These striking differences are likely to be explained by a number of factors including socioeconomic condition, age, stage at diagnosis, continued presence or absence of environmental risk factors, and access to hospital services. African American patients have consistently poorer survival outcomes.[55]

What the SEER data do make clear is that there has been very little improvement in overall survival (OS) for patients with cancer of the oral cavity and larynx, whereas substantial improvement has been witnessed in cancer of the oropharynx (Fig. 1.24). Although this improvement was initially thought to be related to improved therapeutic modalities, it is now clear that it was the disease that changed and not the therapy. Non–HPV-related cancers continue to be associated with a poor prognosis, and better treatments are needed. The favorable response rates to conventional therapy associated with HPV-related oropharyngeal cancer have made de-escalation of treatment a high priority for clinicians.

Indeed, population-based survival rates around the world show little evidence of improvement over recent decades, despite vast improvements in treatment modalities. Cure rates and survival rates have improved with advances in surgical and other techniques in highly specialized, high-volume treatment institutions. Regrettably, such highly expert management is not yet uniformly available, and it may be decades before these results are reflected in population trends.

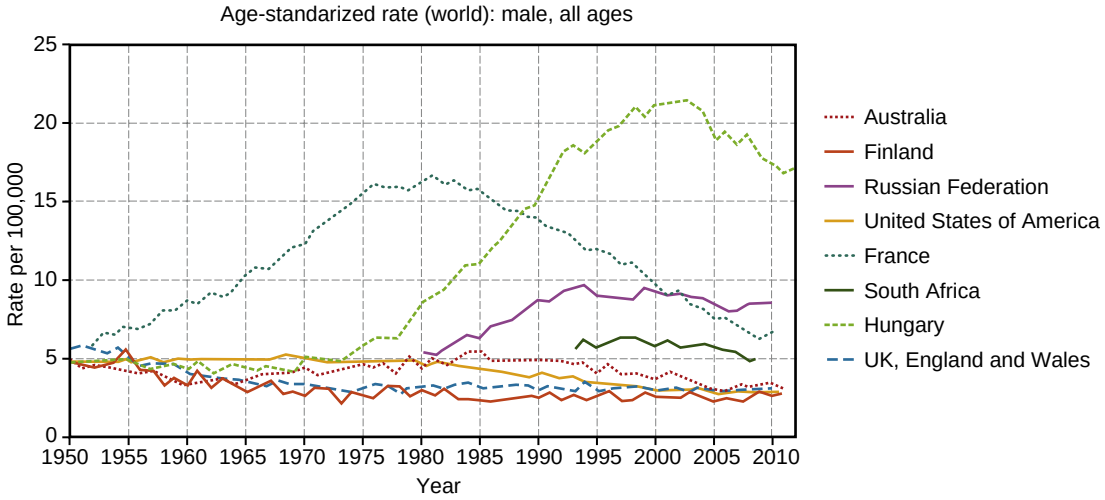
Mortality Trends by Birth Cohort and Forward Projections

Birth cohort statistics are a valuable way for interpreting time trends. Cases of particular cancers are transformed back, in 5-year age groups, to the date of birth of the affected individuals. Curves derived from the WHO mortality database for particularly instructive countries are given in Figs. 1.23 to 1.26.[51] In general, these show that for most UADT cancers in most

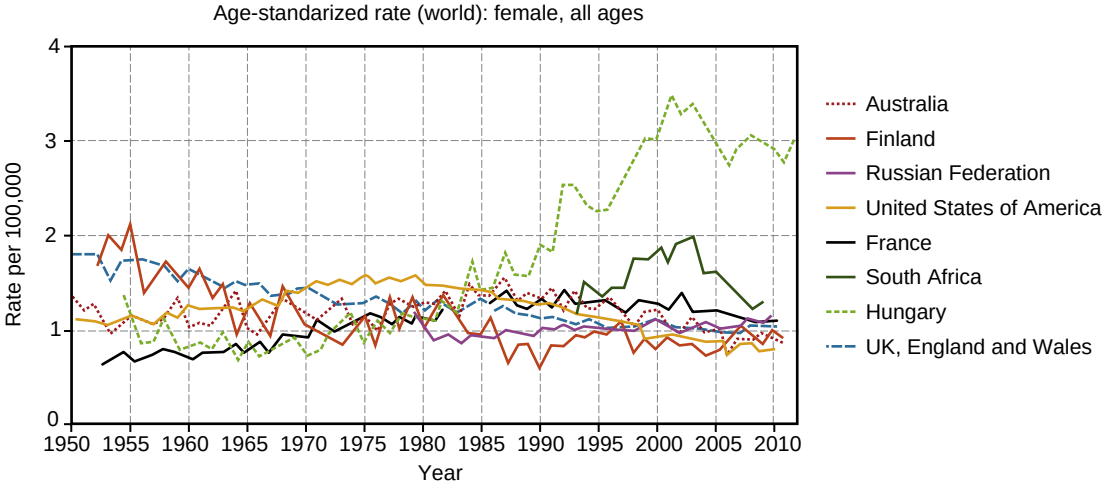
TABLE 1.2 Mortality Data Extracted from the GLOBOCAN 2012 Database, for Comparison with the Incidence Data in Table 1.1

Country	Mouth (ICD-10 : C00–C08)		Nasopharynx (ICD-10: C11)		Other Pharynx (ICD-10: C09–C10, C12–C14)		Larynx (ICD-10: C32)		Esophagus (ICD-10: C15)	
	Lip, all of tongue, all of mouth, and major salivary glands		Data for C30, Malignant neoplasm of nasal cavity and middle ear; and for C31, Malignant neoplasm of accessory sinuses; and for C32, Malignant neoplasm of larynx, are not included here		Tonsil, remainder of oropharynx, pyriform fossa, hypopharynx, and sites not otherwise specified among C00–C13		Cancer of the supraglottic, glottic, and subglottic larynx		This code excludes cancers arising at the gastroesophageal junction which are included in stomach cancers, the majority of which are adeno-carcinomas; included here, therefore, are mostly SCCs sharing common risk factors with the mouth	
	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
World	2.7	1.2	1.0	0.4	2.2	0.5	2.0	0.2	7.7	2.7
More developed	2.3	0.6	0.2	0.1	2.2	0.3	2.2	0.2	5.2	0.9
Less developed	2.8	1.4	1.3	0.5	2.2	0.5	2.0	0.3	9.0	3.6
Africa	2.1	1.3	1.1	0.6	0.9	0.4	1.5	0.2	5.3	3.3
Eastern Africa	3.2	1.9	1.4	0.9	0.9	0.5	1.5	0.2	11.2	7.3
Middle Africa	2.9	1.4	1.1	0.6	1.6	0.6	1.1	0.2	4.0	1.8
Northern Africa	1.3	0.8	1.4	0.6	0.6	0.6	2.0	0.2	2.3	1.4
Southern Africa	2.8	1.0	0.2	0.1	2.2	0.6	2.5	0.4	12.8	6.2
Western Africa	1.2	1.0	0.6	0.3	0.5	0.1	0.9	0.1	0.8	0.4
Caribbean	2.0	0.6	0.3	0.1	2.4	0.6	4.0	0.5	4.1	1.0
Central America	0.8	0.5	0.1	0.0	0.7	0.2	1.5	0.2	1.6	0.5
South America	2.2	0.7	0.2	0.1	2.2	0.4	3.3	0.4	5.6	1.5
Northern America	1.2	0.5	0.2	0.1	1.2	0.3	1.2	0.2	5.0	1.0
Asia	3.0	1.4	1.4	0.5	2.4	0.5	1.9	0.2	9.9	3.8
Eastern Asia	1.1	0.5	1.5	0.6	0.7	0.1	1.1	0.1	14.1	4.5
Southeastern Asia	1.9	1.2	3.8	1.4	2.1	0.5	1.3	0.2	3.3	0.9
South Central Asia	6.3	3.0	0.4	0.1	5.3	1.2	3.0	0.4	6.0	3.6
Western Asia	1.0	0.6	0.7	0.3	0.6	0.3	2.9	0.4	2.7	1.9
Europe	3.0	0.7	0.3	0.1	2.7	0.4	3.0	0.2	4.9	0.9
Central and Eastern Europe	5.1	0.7	0.3	0.2	3.8	0.3	4.9	0.2	5.0	0.6
Northern Europe	1.7	0.7	0.2	0.1	1.4	0.3	1.3	0.2	7.2	2.3
Southern Europe	1.9	0.6	0.3	0.1	1.8	0.3	2.9	0.2	2.8	0.5
Western Europe	2.0	0.6	0.2	0.1	2.7	0.5	1.5	0.2	5.0	1.2
Australia	1.3	0.6	0.2	0.1	1.2	0.3	1.0	0.1	4.7	1.3
New Zealand	1.4	0.7	0.3	0.1	1.0	0.2	0.8	0.1	4.4	1.6
Melanesia	14.4	10.2	0.3	0.1	2.8	0.4	1.9	0.4	3.4	1.4
Micronesia	2.0	0.0	1.3	1.0	0.0	0.0	1.1	0.0	3.3	0.0
Polynesia	1.4	0.0	0.6	0.0	2.0	0.3	2.0	0.7	3.0	0.3

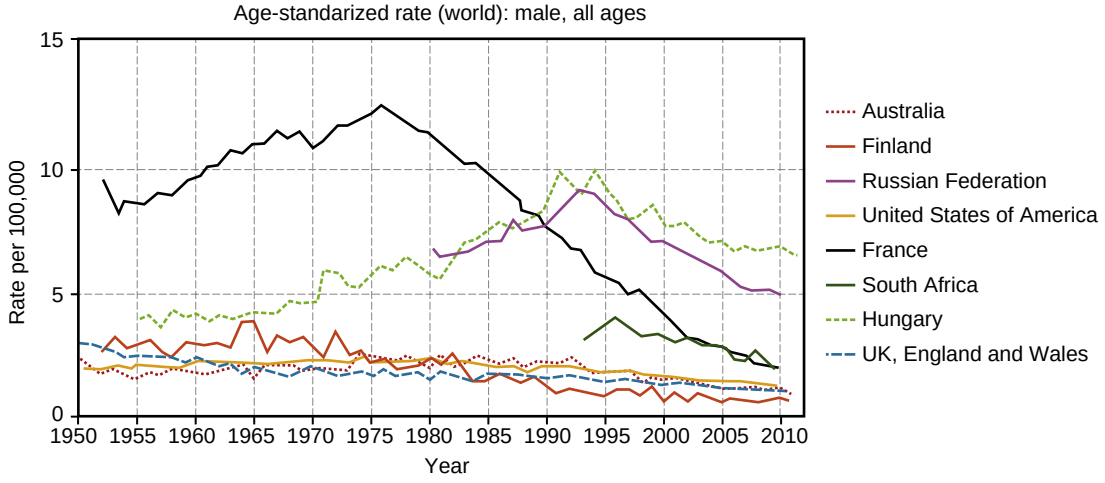
Adapted from Ferlay J, Soerjomataram I, Ervik M, et al, editors: *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012*. Lyon, France, 2013, International Agency for Research on Cancer. Retrieved from http://globocan.iarc.fr.
SCC, Squamous cell carcinoma.



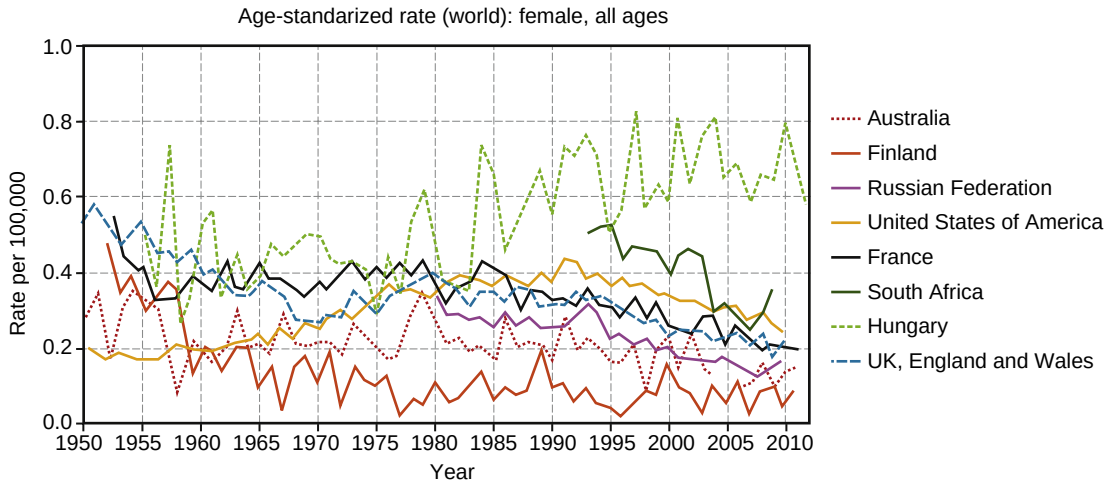
• **Fig. 1.17** Mortality from lip, oral cavity, and pharynx cancer—male. Trends in mortality over time are important to track and to understand. Mortality rates in Hungary are high, although a declining trend is evident from the year 2003. Russia remains a concern. France demonstrates what can be achieved. The overall modest downward trend in the other countries illustrated is encouraging. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



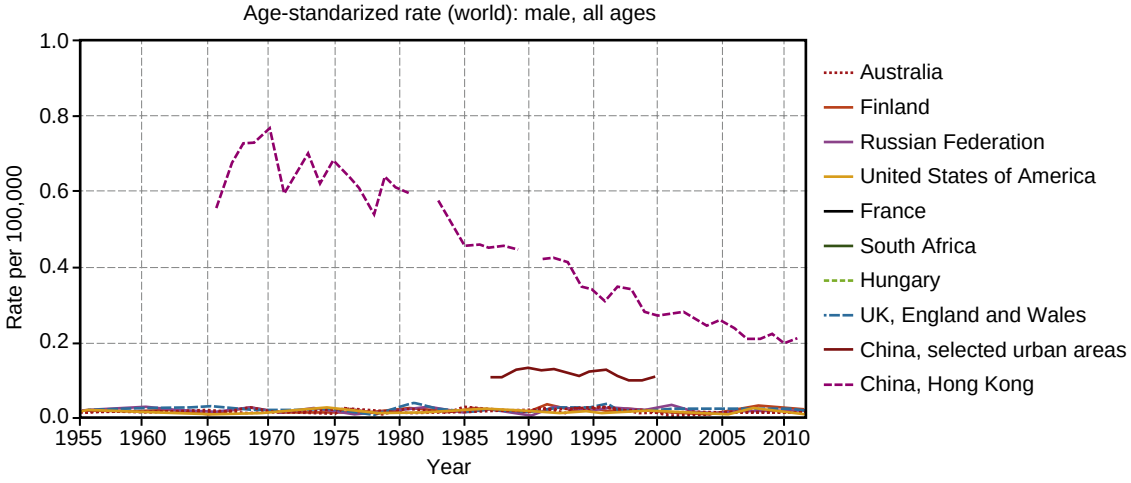
• **Fig. 1.18** Mortality from lip, oral cavity, and pharynx cancer—female. Although only approximately a tenth of the mortality rate in males, mortality rates in Hungarian females remain a challenge. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.19** Mortality from laryngeal cancer—male. Another success demonstrated for France, followed by healthy trends for the Russian Federation and Hungary. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)



• **Fig. 1.20** Mortality from laryngeal cancer—female. This is a "noisy" curve because of the comparatively low mortality rates in women. Worryingly, but not surprisingly, it suggests an upward trend in Hungary. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

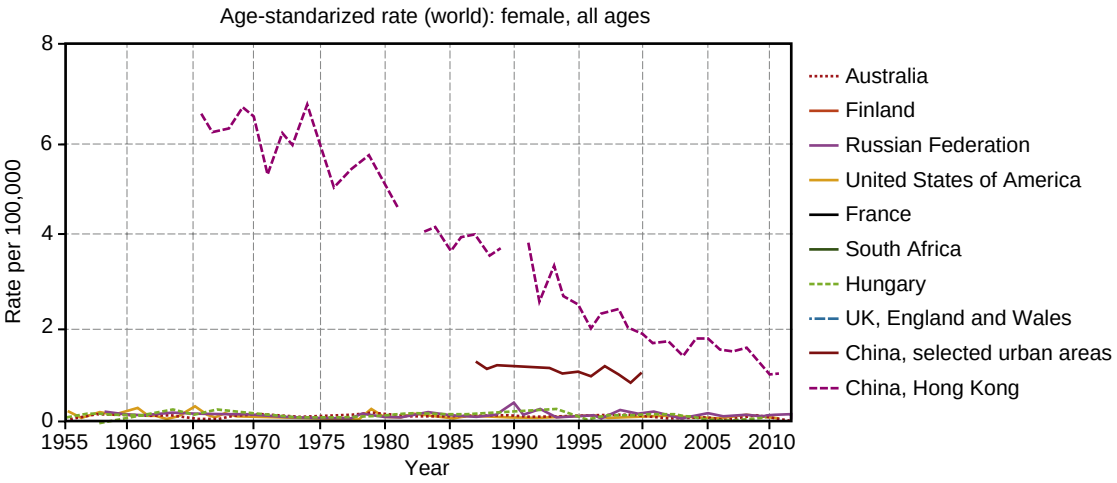


• **Fig. 1.21** Mortality from nasopharyngeal cancer—male. It is hoped that the successes in Hong Kong can be replicated in other high-risk groups. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

developed countries, rates fell in the later part of the 19th and early part of the 20th centuries. This trend has continued in, for example, the United States (see Fig. 1.23) and the United Kingdom (Fig. 1.25). However, in Hungary (Fig. 1.26) (and the same is true for most of Eastern Europe, Russia, and the former Soviet Republic), those born in the first half of the 20th century showed alarming rises in death rates. All members of these birth cohorts have now died, or they are in the highest-risk age groups; in these countries, we have thus seen a growing epidemic of UADT cancer. Indeed, the increasingly aging populations in many countries mean that crude rates, and thus disease burden, will continue to rise, as seen in the data from the United States and United Kingdom (see Fig. 1.23 to Fig. 1.25). It is encouraging to note that the curves now indicate that Hungary, for example, is showing control in younger people (see Fig. 1.26).

Etiology of Head and Neck Cancer

The majority of OSCCs are related to tobacco in various forms, betel quid chewing, heavy alcohol drinking, and dietary micronutrient deficiency. There is a clear dose-response relationship. Nevertheless, in the West, a distinct subgroup of patients without these traditional risk factors exists—predominantly elderly women in whom etiologic factors are not clear. In the developing world, use of tobacco and areca nut, either alone or in combination, accounts for the vast majority of oral cancers and OPMDs. WHO has classified areca nut, a common



• **Fig. 1.22** Mortality from nasopharyngeal cancer—female. From a lower initial base, Hong Kong women share this success story. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

component of many different chewing habits, as carcinogenic to humans. UV radiation is relevant to lip cancer, and there is increasing evidence regarding the role for "high-risk" genotypes of the HPV family, especially for cancer of the tonsil, base of tongue, and other oropharyngeal sites.

Betel Quid

A betel quid generally contains betel leaf, areca nut, and slaked lime, and may contain tobacco. Other substances, particularly spices, including cardamom, saffron, cloves, aniseed, turmeric, mustard or sweeteners, are added according to local preference.[11]

Betel Leaf

The leaves of the *Piper betel* vine (a member of the pepper family) contain betel oil, a volatile liquid, which contains several phenols including hydroxychavicol, eugenol, betel phenol, and chavicol. These compounds may to some extent be protective, sharing some of the antioxidant properties of many plant polyphenols. Vitamin C, a large amount of carotene, and 36 trace elements have also been reported in the betel leaf—clearly beneficial micronutrients.[56]

Betel Inflorescence

Apart from the leaf, other parts of the vine such as the stem and inflorescence (the flowers or pods; catkins) are also consumed with areca nut. Consumption of the inflorescence is common in Melanesia and parts of Taiwan and in China, and it is mostly added to the quid for its aromatic flavor.[11] Betel inflorescence contains a high concentration of phenolic compounds including hydroxychavicol, eugenol, isoeugenol, eugenol methyl ester, and safrole. Safrole itself, a major phenolic compound, is classified as a weak carcinogen in rats and is banned as a food and cosmetic additive by the FDA in the United States, inter alia; however, there is no direct evidence for its carcinogenicity in humans.

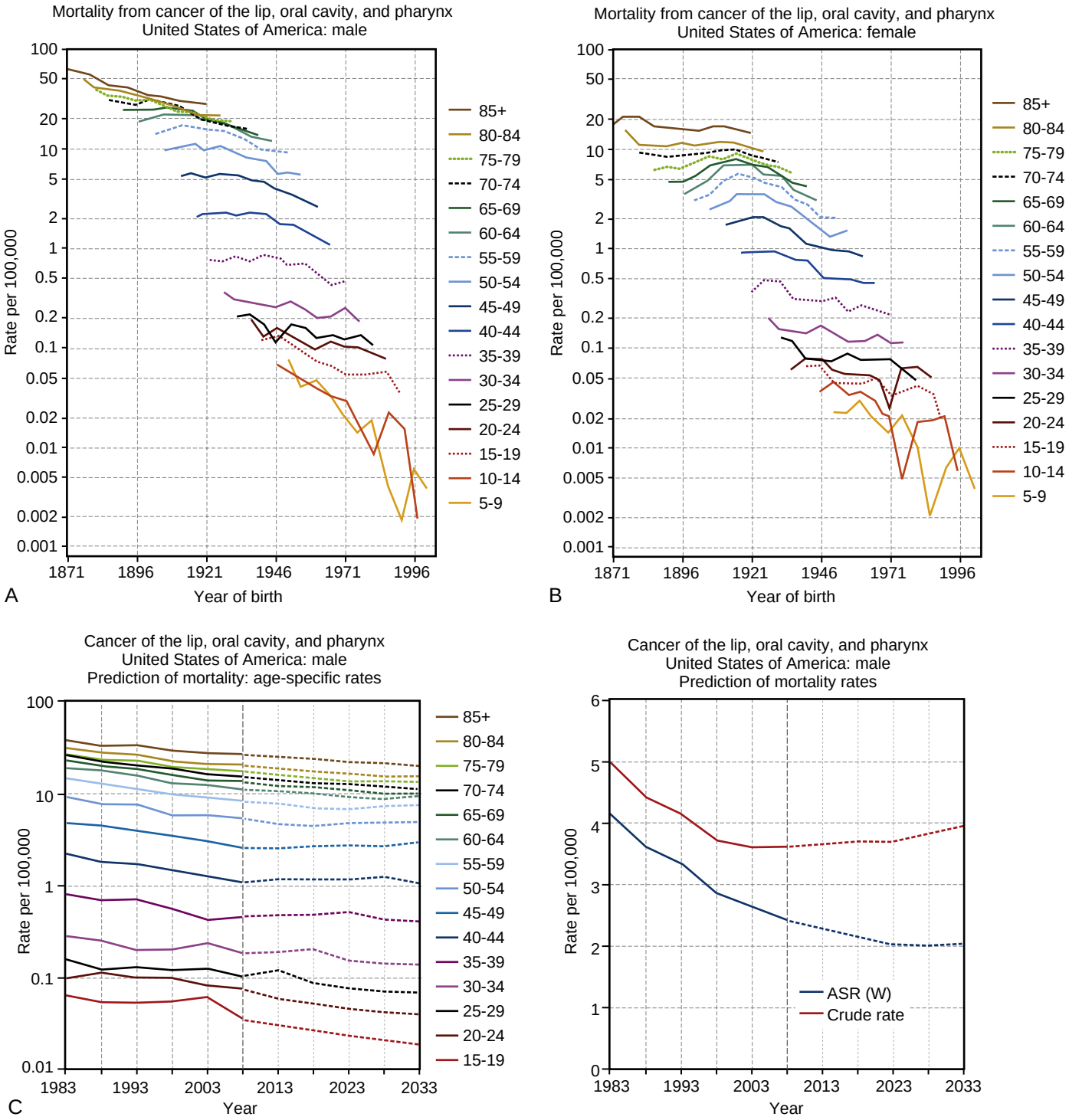
Areca Nut

Areca nut is the seed of the fruit of the oriental palm *Areca catechu.* It is the basic ingredient of a variety of widely used chewed products. The consumption of areca nut is indigenous to India, Sri Lanka, Bangladesh, Myanmar, Taiwan, and numerous islands in the South Pacific. It is also popular in parts of Thailand, Indonesia, Malaysia, Cambodia, Vietnam, Philippines, Laos, and China and in emigrant communities from these countries. It is believed that *A. catechu* may be native to Sri Lanka, West Malaysia, and Melanesia. Areca nut is used as a masticatory substance by approximately 600 million people worldwide. It is estimated that 10–20% of the world's people chew areca nut in some form, often mixed in betel quid (pan).[57] Patterns of use across South and Southeast Asia[58] and the growing public health problem across the Pacific Islands have been extensively documented.[59]

Screening in Saipan and Guam has shown a prevalence of OPMDs of almost 20% among users of betel when other ingredients were added.[60]

The major constituents of the nut are carbohydrates, fat, proteins, fiber, polyphenols (flavonols and tannins), alkaloids, and mineral matter. Among the chemical constituents, alkaloids are the most important chemical. The nut has been shown to contain at least six related alkaloids, of which four (arecoline, arecaidine, guvacine, and guvacoline) have been conclusively identified.[61]

Nitrosamine derivatives from each of the four major areca alkaloids are produced by nitrosation of the alkaloids in dried stored nuts, in the mouth, and especially in the acid conditions found in the stomach, in the presence of nitric oxide generated by bacterial action. Two of these derivatives are accepted as carcinogenic in animal studies, especially MNPN

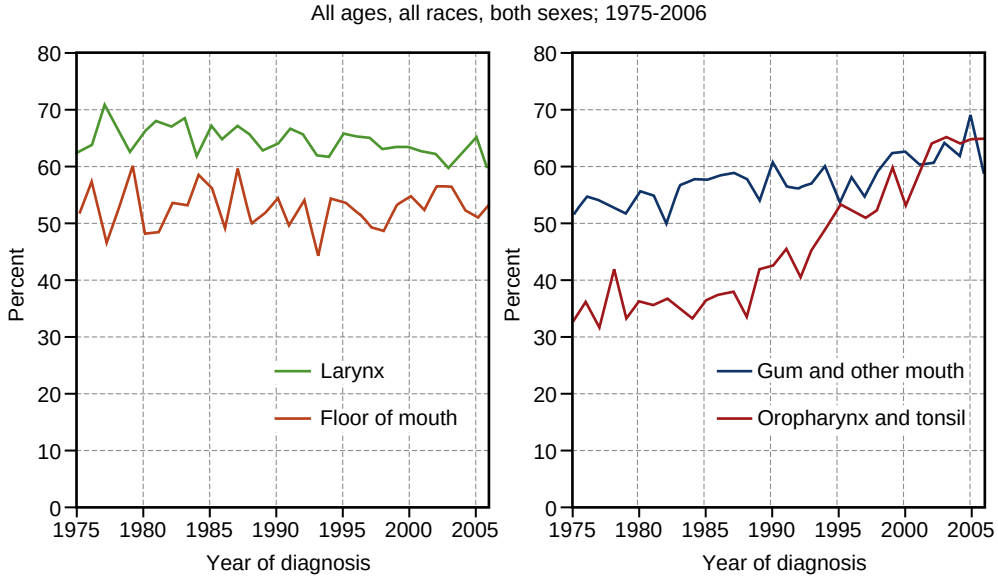


• **Fig. 1.23 A,** Mortality from oral cancer, United States—male. **B,** Mortality from oral cancer, United States—female. Trends in mortality rates for cancers of the lip, oral cavity, and pharynx combined in American women born between approximately 1870 and the turn of the 21st century. There has been a steady decline at all ages, most marked in the youngest cohorts. **C,** Age-specific mortality from oral cancer, United States—male. There has been a steady decline at all ages, most marked in the younger cohorts. This presentation of the age-specific mortality rates for lip, oral cavity, and pharyngeal cancers combined for U.S. males confirms the data above. Although there have been declines in all age groups, projections show rising disease burden in the decades ahead because of the aging of the population. *ASR(W),* Age-standardized incidence rate (world). (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

TABLE 1.3 Mortality Trends (Annual Percentage Change) for Oral and Pharyngeal Cancer in the United States Between 2002 and 2011, by Race and Sex

	All Races			Whites			Blacks		
	Total	Males	Females	Total	Males	Females	Total	Males	Females
All ages	−1.0*	−0.9*	−1.5*	−0.6*	−0.4*	−1.3*	−3.4*	−3.7*	−2.7*

Data from Surveillance, Epidemiology, End Results (SEER) program. Cancer Statistics review, 1975–2011, published in 2014.
*Indicates that the annual percentage change in rate is statistically significantly different from zero ($p < .05$).



• **Fig. 1.24** Five-year relative survival comparison of primarily human papillomavirus (HPV)–unrelated cancers, floor of mouth, gum and other mouth, larynx vs. primarily HPV-related cancers (oropharynx). (From Surveillance, Epidemiology, and End Results (SEER) data, 1975–2010.)

(methylnitrosaminoproprionitrile). Endogenous nitrosation is significantly higher in subjects with poor oral hygiene as determined by volumes of dental plaque.[62] This implies that, on the basis of the availability of substrates from both areca nut and tobacco, there is a more extensive formation of nitrosamine in subjects with poor oral hygiene if they also chew tobacco.[63] Moreover, direct evidence that reactive oxygen species (ROS), such as the hydroxyl radical (HO), are generated in the oral cavity owing to auto-oxidation of polyphenols contained in areca nut and enhancement by the alkaline pH from slaked lime has been reported.[11,64]

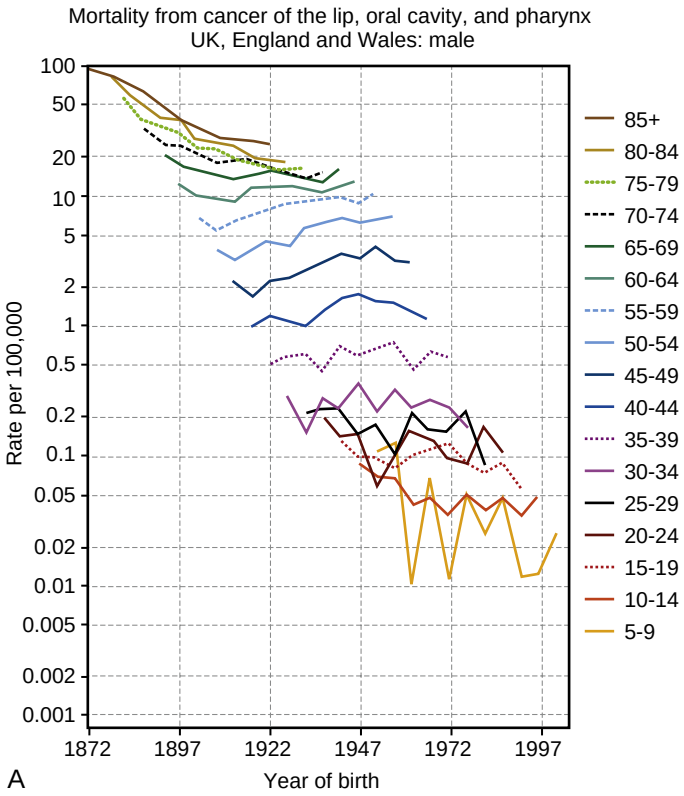
Areca Nut–based Industrially Packaged Products. A variety of packaged areca products are now available. These are mostly manufactured in India and Pakistan, and exported worldwide where they are used by old and new habitués. The most common are *gutka* and *pan masala.* Gutka is a dry, relatively nonperishable commercial preparation containing areca nut, slaked lime, catechu, condiments, and powdered tobacco. The same mixture without tobacco is called *pan masala.*[65]

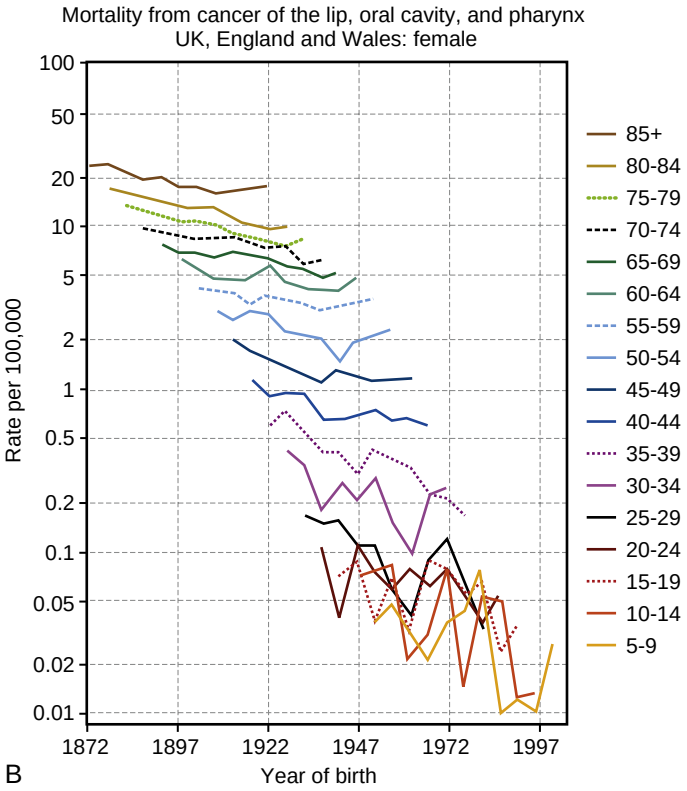
Systemic Effects of Areca Nut. Although largely beyond the scope of this chapter, it is important to realize that areca nut has widespread systemic ill effects.[66] These include psychological and behavioral disturbances due to inhibition of uptake of gamma-aminobutyric acid; neurotoxicity and addiction; cardiac arrhythmias and increased risk of myocardial infarction; hyperlipidemia and metabolic syndrome; hypothyroidism; and premature birth and infertility. Furthermore, the IARC monograph makes it clear that areca nut contributes not only to cancers of the mouth and oropharynx, but also to cancers of the esophagus, liver and biliary tract, lung, and uterus.

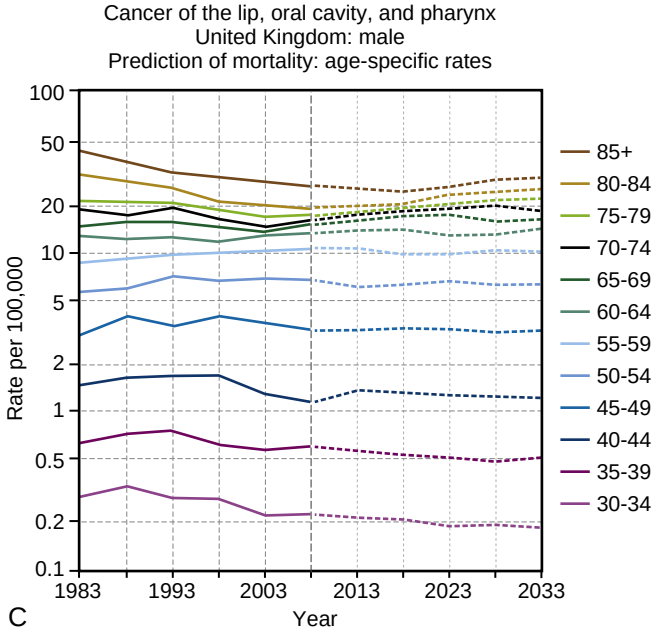
Damage to Oral Soft Tissues From the Chewing of Areca Nut and Related Products

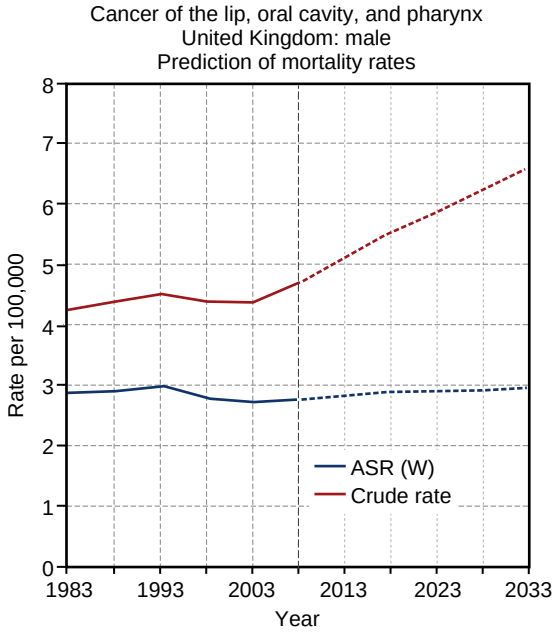
Lichenoid Lesions. Areca-induced lichenoid lesions, mainly on buccal mucosa and tongue, are recognized. They are considered to be type IV contact hypersensitivity-type lesions that resemble oral lichen planus (OLP) clinically.[67]

Betel Chewer's Mucosa. Betel chewer's mucosa was first described by Mehta and colleagues (1971) and is characterized by a brownish-red discoloration of the oral mucosa. It is often

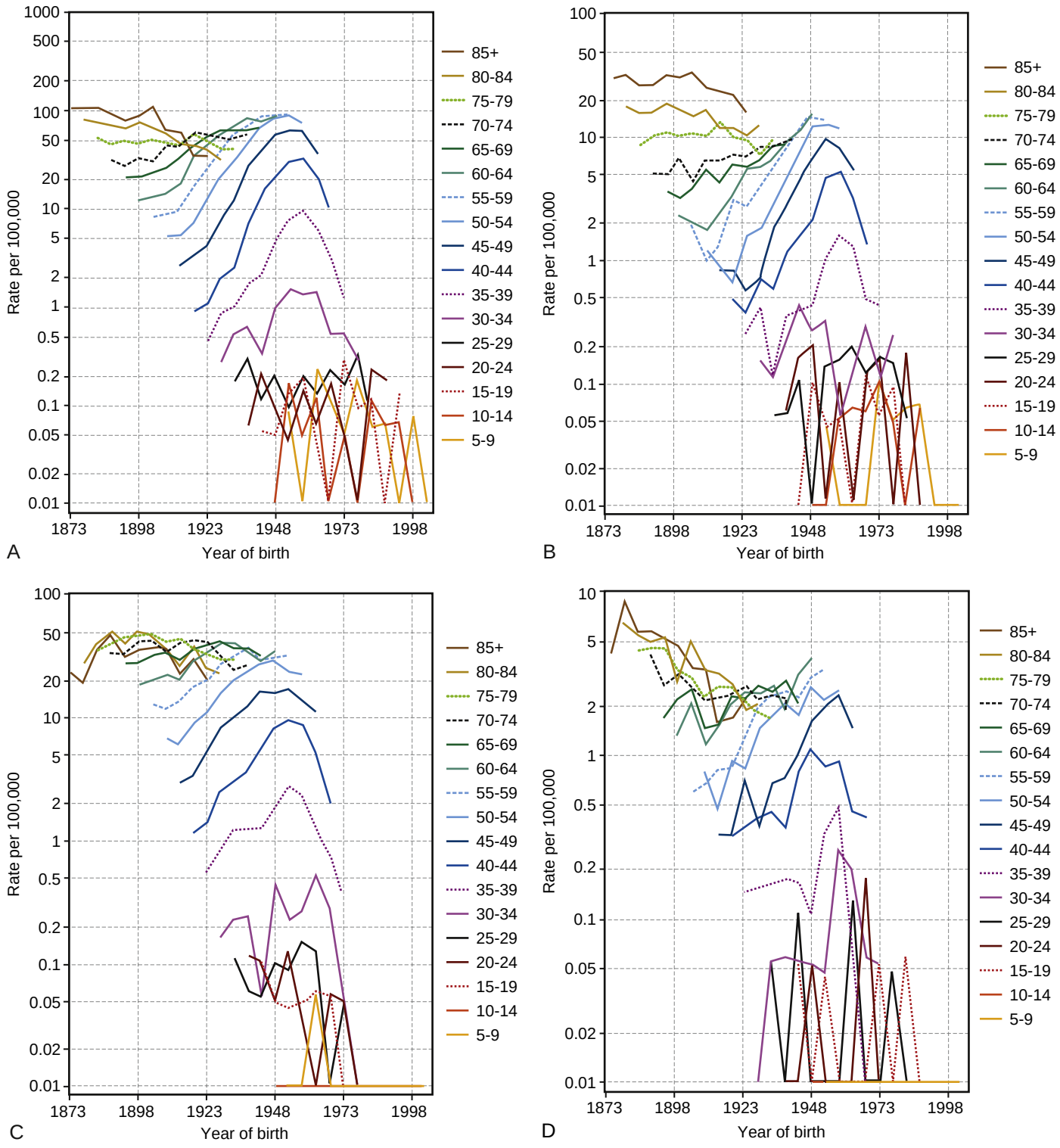








• **Fig. 1.25** **A,** Mortality from oral cancer, United Kingdom—male. **B,** Mortality from oral cancer, United Kingdom—female. **C,** Age-specific mortality from oral cancer, United Kingdom—male. Birth-cohort curves of the mortality rates for lip, oral cavity, and pharyngeal cancers for males **(A)** and females **(B)** in England and Wales. The projected rises in numbers in the years ahead, due to aging of the population, are alarming **(C).** (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.) *ASR (W),* Age-specific rate in women.



• **Fig. 1.26** **A,** Mortality rates for lip, oral cavity, and pharyngeal cancers for males in Hungary. **B,** Mortality rates for lip, oral cavity, and pharyngeal cancers for females in Hungary. **C,** Mortality rates for laryngeal cancers for males in Hungary. **D,** Mortality rates for laryngeal cancers for females in Hungary. Birth-cohort curves of the mortality rates for lip, oral cavity, and pharyngeal cancers for males **(A)** and females **(B),** and for laryngeal cancer (**C** and **D**) in Hungary. The challenge for Hungary, apparent in other curves, is confirmed here. Males born in the first half of the 20th century had rising rates of death from oral and pharyngeal cancer. Those born after 1950 had lower rates. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

accompanied by encrustation of the affected mucosa with quid particles, which are not easily removed, and with a tendency for desquamation and peeling. Both chemical and traumatic effects of the betel quid on the oral mucosa are likely. The presence of tobacco in the quid is not essential for the development of chewer's mucosa.[68]

Oral Leukoplakia. A case-control study conducted in Taiwan, where areca is chewed without tobacco, found the odds ratio (OR) for developing leukoplakia to be 7.43 (95% confidence interval [CI], 1.94–156.27) for areca nut chewers. These authors demonstrated that the cessation of areca chewing resulted in regression of 62% of leukoplakias.[68]

Oral Submucous Fibrosis. It is now accepted that chewing areca is the single most important etiologic factor for the development of OSF,[69–71] although the pathogenesis is not fully understood. In vitro studies have shown that areca nut alkaloids such as arecoline and its hydrolyzed product arecaidine can stimulate cultured fibroblasts to proliferate and synthesize collagen. In addition, flavonoids from the nut have been shown to enhance the cross-linking of collagen, thereby increasing its resistance to degradation by collagenases, as part of normal tissue homeostasis. The copper content of areca nut is high,[72] and the possible role of copper as a mediator of fibrosis is supported by the demonstration of upregulation of lysyl oxidase in OSF biopsies.[73] The current state of knowledge on the molecular changes in oral tissues associated with areca nut and tobacco use is clearly laid out by Dionne and colleagues,[74] and the pathogenesis, including familial patterns and genetic predisposition, has been explored in Bengali populations by J. Gopal Ray in a series of excellent, so-far largely unpublished studies.

Oral Squamous Cell Carcinoma. Historical evidence dating back nearly a century indicates that areca nut is involved in the development of OSCC. Subsequently, many case-control studies[75,76] have confirmed that betel quid chewing increases the risk of development of OSSC, especially when the quid contains tobacco.[77,78] A South African study found that 68% of cheek cancers and 84% of tongue cancers developed in individuals who consumed areca *without* tobacco.[79] A large number of animal studies have confirmed that areca products and derivatives such as arecoline and areca-derived nitrosamines have the ability to induce neoplastic changes in experimental models, and the IARC has now formally designated areca and betel quids without tobacco as carcinogenic to humans.[11,13] The role of commercial forms of areca nut and tobacco in the continuing rise in oral cancers in Ahmedabad has been confirmed.[80]

Slaked Lime

Slaked lime (calcium hydroxide) is added to betel quids in most of South Asia. In coastal areas of Sri Lanka and the Pacific it is obtained by heating seashells or harvested from corals. In inland areas it is quarried from limestone. When added to betel quids it causes erosion of oral mucous membranes, which facilitates penetration of betel-quid carcinogens through the mucosa.

Smokeless or Chewing Tobacco

Tobacco is often added to the quid mixture. Edible tobacco in the India subcontinent is prepared from sun-dried and partly fermented, coarsely cut leaves of *Nicotiana rustica* and/or *Nicotiana tabacum* without further processing. Chewing tobacco results in local exposure of oral mucosa to at least 16 carcinogens, including tobacco-specific nitrosamines (TSNAs) and polycyclic aromatic hydrocarbons (PAHs).[81] Unusually high levels of carcinogenic TSNAs (e.g., *N*-nitrosonornicotine [NNN] and nicotine-derived nitrosamine ketone [NNK]) were reported in saliva of oral snuff users in the Sudan[82] and in tobacco chewers in India.[83] NNK is a potent carcinogen, and human buccal epithelial cells (in culture) have been shown to metabolize NNK. The formation of macromolecular DNA adducts after NNK metabolism is correlated with carcinogenesis in animal models.[84] Adducts of NNN and NNK lead to mutations of oncogenes and of tumor suppressor genes.[85] The serious situation that continues in India has been comprehensively reviewed,[86] and an exhaustive treatise was published in late 2014 by the U.S. Department of Health and Human Services.[87] Three meta-analyses have confirmed the importance of smokeless tobacco use across South Asia as a whole.[77,78,88] The form of oral smokeless tobacco used in northeastern Africa and parts of the Middle East (known as *Toombak* in the Sudan and *Shammah* in Yemen and Saudi Arabia)[82,89] is a mixture of powdered tobacco, lime, ash, black pepper, oils, and flavorings. This is responsible for the epidemic of oral cancer in this region.[82,90,91]

Betel chewing also releases large amounts of ROS, especially while the betel quid is actually present. Both TSNA and ROS are major genotoxic agents involved in chewing tobacco–associated oral cancer.[78] Clear dose-response relationships between quid use and the risk of oral cancer and of potentially malignant oral disorders have been demonstrated in many OPMDs. Most forms of oral smokeless tobacco—oral snuff—consumed in Scandinavia and in North America are not flue-cured and contain relatively low amounts of TSNs. Although the topic is controversial, many of these products are not highly carcinogenic, and it has even been suggested that they have a role as nicotine replacement products in achieving smoking cessation.[92] It is, however, important to remember that there is no such thing as safe tobacco. Most smokeless tobaccos have high levels of nicotine and are addictive; indeed, there is evidence that they can be initiators of smoking.[93] Furthermore, they have significant cardiovascular effects[94] and certainly produce oral mucosal lesions and local damage to the periodontium.[95]

Contaminants

Areca nut can be contaminated with fungi such as *Aspergillus flavus, Aspergillus niger,* and *Rhizopus* species. Almost 40% of samples of areca nut from India analyzed by use of thin layer chromatography contained aflatoxins.[96] These are established carcinogens.

Tobacco Use

Tobacco is identified as the leading preventable cause of premature death worldwide. It is estimated that 4.9 million people died

of tobacco-related illness in 2000, and by 2020, it is expected that this figure will rise to 10 million deaths per year, of which 70% will be in developing countries.[86] Tobacco is a major independent risk factor for the development of oral and pharyngeal cancer and other malignancies of the UADT. Tobacco is consumed in different ways: smoked as cigarettes, cigars, or beedi/bidi; reverse smoking; and use of smokeless tobacco products such as oral snuff or tobacco in moist pouches. Tobacco smoke contains more than 60 carcinogenic combustion products. In particular, NNK, NNN, and PAHs have been causally linked to UADT cancer. The activity of carcinogens is generally exerted through DNA adducts.[96,97] Tobacco smoking and quid chewing both cause oxidative stress to tissues—that is, the sustained presence of ROS, which initiates free radical reactions. ROS can damage proteins, lipids, carbohydrates, and DNA. Minor DNA damage can result in mutations that can be part of the causal chain for malignant transformation, and sustained DNA damage can result in further perturbations of cell cycle control.[98] As a form of smoking, bidis, a traditional form of raw tobacco handwrapped in a temburni leaf and common throughout South Asia, are particularly toxic. A strong interaction was found between alcohol consumption and bidi smoking (OR, 19.6; 95% CI, 4.6–83.5) in an Indian study.[99]

In addition to extensive literature on the carcinogenicity of tobacco smoke in cell and animal models, numerous case-control and cohort studies have affirmed the key role of tobacco smoke in the development of cancer in humans, and the supermultiplicative synergism with alcohol drinking[100] (see Fig. 1.2). Both smoked and smokeless tobaccos have considerable adverse effects on the UADT, apart from cancer and OPMDs. The severity and extent of periodontal disease are increased by as much as a relative risk of 7 in smokers, depending on the definition of disease, and smoking contributes to poor wound healing, implant failure, and increased dental caries, although the evidence for the latter is weak.[101]

The International Head and Neck Cancer Epidemiology Consortium conducted a comprehensive meta-analysis and concluded that cessation of smoking for 1–4 years reduces the risk of a head and neck cancer (OR 0.70 compared with current smoking) but that it takes 20 years to reach the risk of a person who never smoked.[102] The same is true when oral cancer alone is considered.[101] It is essential to stop smoking after treatment for head and neck cancer, because continued smoking increases the risk of a second tobacco-related cancer by a factor of at least four.[103] The WHO Framework Convention on Tobacco Control has supported many countries in reducing smoking, although there remain nonsignatories and progress is uneven[104–106] (Table 1.4).

Alcohol

Unsafe consumption of alcohol, including so-called binge drinking, is a major public health problem worldwide—for

TABLE 1.4 Interventions and Their Effectiveness in Reducing Tobacco Consumption

Intervention	Effectiveness
Large, regular increases in excise taxes that reduce affordability	Fifty percent higher prices reduce consumption by approximately 20% (10% quit, 10% reduce the amount smoked). This is always controversial because smoking prevalence is higher in lower socioeconomic groups in most countries.
Mass media counter-advertising, warning labels, plain packaging, and epidemiologic studies (such as deaths from smoking on death records)	Difficult to quantify but does increase cessation rates. Australia was the first country to introduce plain packaging and successfully defended a legal challenge from big tobacco companies. Other countries are planning legislation. Cost-effectiveness studies are awaited. Anti-tobacco advertisements in mass media, placed by governments and health promotion agencies, have long been common in many countries; it is encouraging to see the growth of newspaper, radio, and television warnings about areca products becoming common in India and Sri Lanka.
Complete bans on tobacco advertising, promotion, and sponsorship	Reduces consumption by approximately 15% in low- and middle-income countries.
Complete ban on smoking in public places, including all workplaces	Reduces consumption by 3–14%. Enforcement is critical; the experience of Hong Kong in sending a cadre of anti-smoking officials into public places has proven effective.
Cessation support for smokers, brief medical advice, pharmacotherapy	At 6 months, brief medical advice doubles the quit rates (from 2–5% unaided to 4–8%); medications triple the quit rates (to 8–12%). Dentists and dental practices can achieve comparable results.
Anti-smuggling technologies: local language labels, improved tax administration, increased customs and international efforts to target smuggling	Ten percent higher spending on anti-smuggling efforts reduces smuggling by 5% and consumption by 2%.

Adapted from Jha P, MacLennan M, Yurekli A, et al: Global hazards of tobacco and the benefits of smoking cessation and tobacco tax. In *Cancer,* vol. 3, Chapter 10, 2015. Retrieved from http://dcp-3.org/chapter/1152/global-tobacco-control)

example, contributing to 5000 and 40,000 deaths in the United Kingdom annually.[107] The possible beneficial effects of moderate alcohol consumption have been widely canvassed, because of the so-called J-shaped relationship between alcohol intake and all-cause mortality, as shown in a number of meta-analyses.[108] The initial upstroke of this J-curve is thought to be due to the cardioprotective effect of moderate alcohol consumption: In particular, alcohol increases high-density lipoprotein levels, inhibits platelet aggregation, and promotes fibrinolysis.[109] On the other hand, it has always been recognized that above an intake of around 10 g of alcohol per day, the detrimental effects of alcohol predominate.[108] WHO in Europe is very concerned about the impact of alcohol on population health and has published a comprehensive report on use and abuse of alcohol in member countries, proposing measures to minimize risk.[110]

Alcohol is argued to account for about 4% of cancer deaths overall: predominantly breast cancer in women, and cancer of the UADT and esophagus in men.[111] Increases in oral cancer reported in younger subjects in the United Kingdom were related, at least in part, to growing alcohol use and abuse in that society.[48] The difficulty of accurately quantifying the influence of alcohol in the etiology of head and neck cancer stems from the fact that most people who drink heavily also smoke. It is also difficult to obtain reliable information from individuals regarding their intake of alcohol. Nevertheless, many studies have shown a dose-response relationship between alcohol use and particularly oral and pharyngeal cancer,[112] and the survival of HNSCC patients who continue to abuse alcohol is reduced, although not necessarily because of recurrence or second primary neoplasm.[113]

The health education council in the United Kingdom recommends a weekly intake of no more than 14 units for women and 21 units for men. One in 4 men and 1 in 10 women in that country are believed to be drinking over this limit, with the number of habitual heavy drinkers estimated at 4 million.[114] Although the legal age for drinking is 18 years, the average age at which drinking starts has fallen since the early 1970s from around 17 to around 11 years, in boys and girls. The emergence of "alcopops" (alcoholic drinks that mimic the taste of nonalcoholic drinks) has resulted in wide uptake among those younger than 18 years.

Internationally, there is a developing view that *any* consumption of alcohol is detrimental, and even the French government now publicly recommends severe constraint or abstinence: The French National Cancer Institute has declared "there is no amount of alcohol, however small, which is good for you."[115] WHO policy is to minimize alcohol use in all societies,[116] and the Australian Guidelines to Reduce Health Risks from Drinking Alcohol summarize the science cogently.[117] These state that for healthy men and women, drinking no more than two standard drinks (i.e., 10 g of ethanol) on any day reduces the risk of harm from alcohol-related disease or injury over a lifetime. Drinking no more than four standard drinks on a single occasion reduces the risk of alcohol-related injury arising from that occasion.

Ethanol and water are the main components of most alcoholic beverages, which also contain volatile and nonvolatile flavor compounds. The major alcohol-metabolizing enzymes are alcohol dehydrogenase, which oxidizes ethanol to acetaldehyde, and aldehyde dehydrogenase, which detoxifies acetaldehyde to acetate. Acetaldehyde is responsible for the oral carcinogenic effect of ethanol, owing to its multiple mutagenic effects on DNA. Acetaldehyde can be produced by oral microorganisms through the metabolism of ethanol. To account for the different sources of acetaldehyde production, some studies have examined the interplay between alcohol consumption, oral hygiene (as a proxy measure for the growth of microorganisms), and alcohol metabolizing genes *(ADH1B* and *ALDH2).*[118] Specific alcoholic beverages have been shown to contain specific impurities or contaminants that can be carcinogenic. *N*-nitrosodiethylamine is present in some beer and whiskey and has been associated with an increased risk of oral cancer. PAHs, some of which are considered to be carcinogenic, are found in many brands of whiskey.[119]

Alcohol also acts in the following ways to promote oncogenesis:[119]

- Ethanol damages the phospholipids of cell membranes and increases permeability. It has been shown to enhance the penetration of tobacco-specific carcinogens across the oral mucosa.[120]
- Ethanol impairs DNA repair mechanisms.
- Ethanol possibly catalyzes the activation of tobacco carcinogens.
- Alcohol is highly calorific. It lessens the protective effect of beneficial foods such as fruits and vegetables by depressing hunger.
- Ethanol is hepatotoxic, thus reducing the effectiveness of those enzyme systems central to detoxification of carcinogens, especially the glutathione-*S*-transferases and cytochrome P450 systems.

A case-control study in Uruguay conducted between 1992 and 1996 is worthy of note.[121] Histologically confirmed cases (471) of SCC of the oral cavity and pharynx in males admitted to four major hospitals in Montevideo were matched with the same number of other patients admitted for a variety of non–smoking- and non–drinking-related conditions as controls. Alcohol consumption was assessed by interview, and the number of grams of ethanol consumed per day calculated. Ever-drinking was associated with a 4.5-fold increased risk of oral-pharyngeal cancer compared with nondrinkers, although no clear dose-response relationship was observed. Consumption of hard liquor was associated with a 3.6-fold increased risk, whereas pure wine drinking showed only a 2.1-fold increased risk. When risks were analyzed by subsites, the highest ORs were observed for oral cavity cancer.

Another case-control study conducted in Italy and Switzerland between 1992 and 1997 included 749 cases of oral or pharyngeal cancer and 1772 hospital controls. Alcohol consumption was measured by the number of drinks consumed per day, with one drink corresponding to approximately 125 mL of wine, 330 mL of beer, or 30 mL of spirits (i.e., about 12 g of ethanol). Compared with light drinkers (one or two

drinks per day), the adjusted OR for three or four drinks was 2.1 (95% CI, 1.5–2.9), and 21.1 (95% CI, 14–31.8) for more than 12 drinks per day. Wine drinkers who consumed more than 12 drinks per day were at a 16.1-fold higher risk compared with the abstainers. Consumption of more than three beers per day resulted in a 2.3-fold risk compared with the non–beer drinkers. In contrast to the Uruguayan study, there was only a 1.9-fold increased risk for consumption of spirits as compared with non–spirit drinkers.[122]

A substantial longitudinal cohort study conducted in the Netherlands,[123] commencing with over 120,000 participants in 1986, followed subjects for more than 17 years, at which time 395 individuals with head and neck cancer and 4288 without head and neck cancer were available. For any head and neck cancer, the multivariable adjusted incidence relative risk (RR) ratio was 2.74 (95% CI, 1.85–4.06) for those drinking 30 g of ethanol or more per day compared with abstainers. It is important to note that this study demonstrated risk by anatomic subsites: RRs were 6.39 for the oral cavity, 3.52 for oropharynx plus hypopharynx, and 1.54 for laryngeal cancer. Compared with those who had never smoked cigarettes, current smokers had an RR of 4.49 (95% CI, 3.11–6.48) for head and neck cancer overall: 2.11 for the oral cavity, 8.53 for the oropharynx plus hypopharynx, and 8.07 for the larynx. A significant, positive, multiplicative interaction between alcohol consumption and cigarette smoking was found for head and neck cancer overall.

A recent meta-analysis computes increased risk of UADT second primary cancers (RR, 2.97; 95% CI, 1.96–4.50) associated with the drinking of alcohol, with a dose-response effect: An increase in alcohol intake of 10 g/day resulted in a modest but significantly increased RR of 1.09 (95% CI, 1.04–1.14) for UADT second primary cancers.[124] Somewhat controversially, in a meta-analysis of published studies in which it was possible to isolate users of alcohol who had never smoked tobacco or used betel quid, alcohol appeared to be protective.[125]

There are many confounders in population studies. Most people drink a variety of beverages, and accurate controlling for tobacco, diet, socioeconomic status, and other variables is challenging. Nevertheless, it seems reasonable to conclude that, unfortunately, the benefits of cessation of alcohol on reduction of risk of HNSCC are not evident for at least 20 years.[102]

Mouthwashes

There has been considerable interest in the possible risks of head and neck cancer associated with use of alcohol-containing mouthwashes, leading some manufacturers to use "alcohol-free" as a marketing tool. Epidemiologic findings have not been consistent, and control for other major risk factors, including smoking, is not always easy to ascertain from the published work.[126] Some reviews have argued that daily mouthwash use may be an independent cause of cancers of the head, neck, and esophagus.[127,128] It is well established that ethanol increases the permeability of lining mucosa, allowing carcinogens to penetrate more freely. Acetaldehyde, the proximal metabolite of ethanol, can accumulate in the mouth from bacterial action, and as explained earlier, this is an established carcinogen. However, four case-control studies have shown nonsignificant, lower or similar oral cancer risks among self-reported mouthwash users compared with nonusers.[129,130] The most recent meta-analysis has not demonstrated excess risk for oral cancer from alcohol-containing mouthwashes.[131–133] There is, however, a plausible biologic basis for risk associated with alcohol-containing mouthwashes, especially in smokers, and it is always prudent to remember that absence of evidence is not evidence of absence.

Combined Effects of Habits

Although the supermultiplicative effects of smoking and drinking have been understood since the classical studies of Blot and colleagues in the 1980s,[134] the true extent of such synergisms of habits, which are bound to vary by ethnicity, have been difficult to assess. A meta-analysis by Petti and colleagues of studies from Southeast Asia puts pooled ORs for smoking, drinking, chewing, and smoking-drinking-chewing, respectively, at 3.6, 2.2, 7.9, and 40.1, all of which are statistically significant. Among habitués of all three habits, the individual effects accounted for 6.7% (smoking), 3.1% (drinking), and 17.7% (chewing) of the risk, with the interaction effect accounting for the remaining 72.6%. Some 44,200 oral cancer cases in Southeast Asia annually occur among smoking-drinking-chewing–exposed individuals and 40,400 of these are exclusively associated with the interaction effect.[135] This has clear implications for public health policies of the type put into effect by Amarasinghe and colleagues in Sri Lanka in 2010. We used a simple algorithm by which a cumulative score involving these three habits is used to identify high-risk individuals in population screening studies.[136]

In the West, reduced smoking rates and a rise in the proportion of HPV-associated HNSCC have resulted in a much lower rate of second primary neoplasms in treated patients—for example, in France[137,138] and Canada. This is also reflected in less frequent synchronous primary cancers.[139]

Diet and Nutrition in the Etiology of Head and Neck Cancer

Dietary factors are estimated to account for approximately 30% of all cancers in Western countries.[140] This proportion is currently thought to be about 20% in developing countries and is projected to increase in the future.[141] Poor diet is a significant risk factor for all head and neck cancers[142–148] and appears to be second only to tobacco as a cause of oral cancers worldwide.[3] A case-control study of laryngeal cancer in Italy and Switzerland revealed that a diet not only rich in, but also varied in, fruits and vegetables confers decreased risk of laryngeal cancer.[145] Low consumption of fruits and vegetables, and high consumption of meat with high tobacco and alcohol use led to 10- to over 20-fold excess risk of cancer of the oral cavity and pharynx,[149] and the classic Mediterranean diet is strongly protective.[150] In the extensive National Institutes of Health (NIH) database in the United States, abdominal adiposity is directly associated with increased risk.[151]

Evidence comes from case-control and cohort studies and animal and in vitro experiments. The roles of protective and unhealthy foods are well understood and form the basis of health education messages in most countries. The micronutrients that confer benefits are also well understood. Vitamin A and related carotenoids (in particular beta carotene), vitamins C and E, and selenium appear to be particularly protective against most epithelial cancers,[152–154] and much of the effect is attributable to their antioxidant activities. Antioxidants act by reducing free radical reactions that can cause DNA mutations and changes in lipid peroxidation of cellular membranes.[155] Other protective roles of micronutrients are modulation of carcinogen metabolism, maintenance of appropriate cell differentiation, inhibition of cell proliferation and oncogene expression, maintenance of immune function, and inhibition of formation of endogenous carcinogens.[99]

A meta-analysis on oral cancer, based on 15 case-control studies and one cohort study, was able to use dietary data from nearly 5000 subjects. The resulting estimate was that each portion of fruits or vegetables consumed per day reduced the risk of oral cancer by around 50%.[156] These effects are also demonstrable with OPMDs. In a population-based case-control study in Japan, where there were 48 cases of oral leukoplakia and 192 control subjects, serum levels of lycopene and beta carotene were significantly lower in those with leukoplakia. Logistic regression showed that high levels of beta carotene were related to low risk of oral leukoplakia (OR = 0.16).[157] Our study of OPMDs in Sri Lanka initially showed a protective effect of diets rich in beta carotene–containing fruits and vegetables, but this is negated by the adverse effects of betel quid, smoking, and alcohol.[158]

Intervention studies are also encouraging in this respect. In a major double-blind placebo-controlled trial in Kerala,[159] up to one third of subjects showed regression of their oral leukoplakias after 12 months of supplementation with oral beta carotene. Extensive studies from the M.D. Anderson Cancer Center in the United States are progressively identifying the most effective combinations of antioxidants in the regression of OPMDs and the prevention of recurrences and second primary neoplasms in head and neck cancer, although it has to be recognized that these agents do not always prevent the progression of an OPMD to overt cancer.[160] Folate emerges as a strong protective dietary factor in the extensive meta-analyses from the International Head and Neck Cancer Epidemiology Consortium (INHANCE).[161] There is current interest in the protective effects of tea, especially green tea, which contains high levels of polyphenols.[162] These are powerful antioxidants able to counteract both initiation and promotion of carcinogenesis.[155] Nutrition care is very important in the management of patients with HNSCC.[4]

Genetic Predisposition

There is considerable evidence for a minor component of inherited, genetic predisposition in UADT cancers, related to polymorphisms in carcinogen-metabolizing enzyme systems.[163] A recent extensive meta-analysis[89] pooled individual-level data from across 12 case-control studies including 8967 patients with head and neck cancer cases and 13,627 control subjects. After adjustment for potential confounding factors, a family history of head and neck cancer in first-degree relatives increased the risk (OR = 1.7; 95% CI, 1.2–2.3). The risk was higher when the affected relative was a sibling (OR = 2.2; 95% CI, 1.6–3.1) rather than a parent (OR = 1.5; 95% CI, 1.1–1.8) and for more distal head and neck sites (hypopharynx and larynx). The OR rose to 7.2 (95% CI, 5.5–9.5) among subjects with family history, who were alcohol and tobacco users. No association was observed for family history of non–tobacco-related neoplasms and the risk of head and neck cancer (OR = 1.0; 95% CI, 0.9–1.1). This was confirmed in a recent study from northern India, in which GSTM1 and GSTT1 null genotype frequencies were significantly higher in patients (adjusted OR = 2.18, $p < .001$; and OR = 1.61, $p = .031$, respectively) and in first-degree relatives of patients with HNSCC compared with controls ($p = .004$ and $p = .041$, respectively). Tobacco chewing and GSTM1 null genotype interaction was identified as the strongest gene-environment model to predict HNSCC.[5]

Rare cancer syndromes can involve the head and neck: Cowden syndrome, caused by mutations in the tumor suppressor gene *PTEN,* and dyskeratosis congenita, in which oral white lesions in young people have a risk of malignant transformation.[164]

Microorganisms

Microorganisms have been implicated in the etiology of oral leukoplakia for more than a century, beginning with the classic dorsal leukoplakia of syphilitic glossitis. Today tertiary syphilis is rare, but the fungus *Candida albicans,* a common oral commensal, is frequently found invading the upper epithelium in histologic sections of leukoplakia, more so in the mouth than in the pharynx or larynx,[165] and this involvement is associated with a higher risk of malignant transformation.[166] The terms *candidal leukoplakia* and *hyperplastic candidiasis* have been used to describe such lesions. Oral cancer patients harbored higher numbers of *Candida* species of different genotypic strain than matched controls, but it cannot be concluded whether this is cause or effect.[167]

Studies of the role of bacteria in the etiology of UADT cancers are relatively recent. Endogenous production of acetaldehyde and reduction of nitrate to nitrites by oral flora is higher in drinkers with poor oral hygiene.[122] Understanding the role of the oral flora is certainly important in the management of the distressing mucositis associated with much cancer therapy.[168] Since the Nobel Prize in Physiology or Medicine was awarded to Barry J. Marshall and J. Robin Warren in 2005 for discovery of the causal association of *Helicobacter pylori* and gastritis, peptic ulcer, and gastric cancer, and the now widespread availability of next-generation sequencing, studies of the whole microbiome—mycome, bacteriome, and virome—associated with head and neck cancer are emerging.[169] To repeat, association does not prove cause and effect. Nevertheless, such studies can be hypothesis generating. As with the conversion of ethanol to acetaldehyde by bacterial enzymes, mentioned earlier, microorganisms may promote carcinogenesis, or progression

of the neoplasm by, inter alia, induction of pro-inflammatory cytokines and other inflammatory mediators. In studying the cancer-associated microbiome, care is necessary in choice of control individuals and sites and in avoidance of contamination between subjects and samples.

It is now clear that high-risk HPV genotypes, particularly HPV16 and HPV18, are important cofactors, especially in cancers of the tonsil and elsewhere in the oropharynx.[170–172] However, a significant association with oral cancer, albeit less frequently,[173] along with traditional risk factors, has been shown in a growing number of studies from many parts of the world—for example, in China.[174]

The rise in oropharyngeal cancer, particularly in younger males, is mostly attributable to HPV, which is sexually transmitted.[175] Although cases in which sexual partners appear to share a cancer of the uterine cervix and an oropharyngeal cancer in the male have been described, it appears that virus passed from an oropharyngeal cancer patient to the oropharynx of a partner is rapidly cleared; carriage rates in oral rinses in such partners are no different from the population carriage rate as a whole—at least, in the United States.[176,177] However, self-inoculation in women from genitals to mouth is demonstrable.[178]

The risk of a second primary neoplasm in patients treated for HPV-related HNSCC is substantially less than for tobacco- and alcohol-related cancers, according to an analysis of data from the United States.[179] Vaccination of young women—and increasingly young men—against the main oncogenic types of HPV is now widespread in many countries. This is already having an impact on the incidence of cervical dysplasia and cervical intraepithelial carcinoma. The probable effect on oropharyngeal cancer incidence will take some time to become fully apparent.

Interest in HHVs and HNSCC has waxed and waned over the years. EBV is clearly causally related to nasopharyngeal carcinoma, and an association with oral cancer, particularly in betel quid chewers, has been described in northern Thailand.[180] The current state of knowledge regarding HPVs, EBV, and HNSCC is dealt with later in this book.

Dental Factors

Apart from poor oral hygiene, trauma from sharp teeth or ill-fitting appliances may play a role in developing oral cancer. Such trauma may focus the site at which malignant transformation occurs in the context of a field of molecular change and continuing presence of local carcinogens. The number of missing teeth and the wearing of metal dentures (OR = 5.5) were associated with oral cancer independent of other risk factors in a much quoted study from Beijing published in 1990.[181] Several more recent studies have reported associations of this sort.[182,183] There is an association between poor periodontal status and oral cancer, with a significant OR of 3.53, according to a recent meta-analysis,[184] and of 2.63 in another,[185] but it must be remembered that association does not equate to cause and effect.[186]

Air Pollution

Part of the urban-rural difference in the incidence of head and neck cancer has been related to atmospheric pollution. For example, mean sulfur dioxide and smoke concentrations in the atmosphere were positively correlated with squamous cancer of the larynx and, to a lesser extent, the pharynx in data collected some time ago from the West Midland region of England in 1950–1990.[187] Indoor air pollution resulting from the use of solid fuel such as wood, crop residue, animal dung, and coal for cooking and heating is a significant health problem in many developing countries where a greater proportion of people use such fuels, frequently in poorly ventilated areas. Many studies have identified indoor air pollution as a risk factor for head and neck cancer.[13,188,189] A monograph from the IARC has identified indoor air pollution from coal use as a known human carcinogen, and from other biomass (primarily wood) as a probable human carcinogen.[190] Studies carried out in China and Brazil have reported exposure to wood smoke as a risk factor for oral cancer,[191] nasopharyngeal cancer,[192] and cancer of the UADT.[193]

Solar Radiation

Prolonged exposure to sunlight represents an important risk factor for the development of SCC of the lip in people with fair complexions and those with outdoor occupations. Usually the lower lip is involved because it receives considerably more direct sunlight than the upper lip.[194] Evidence comes from many countries, including those at latitudes with clean air through which UV light penetrates easily, such as Finland[195] and Sweden,[196] and from countries closer to the equator with regular long hours of sunshine such as rural Greece, where lip cancer can account for 60% of oral cancers,[197] and in India—for example, in fishermen[7]—although some protection may exist in darker-skinned races or individuals. In Finland, the increased risk for lip cancer is confounded by smoking and social class, whereas that for cancer of the oral cavity and pharynx is not; at these latter sites, alcohol was a much stronger confounder than tobacco.[198] A study from California shows that risk for women is strongly related to lifetime solar radiation exposure, but lipstick and other sunscreens are protective.[199] Although the observation goes back over a decade, there has been concern that modern cosmetic lip glosses may enhance UV damage to the lips, including increased risk of cancer.[199] Decreases in the incidence of lip cancer have been interpreted as due to reduced occupational exposure to sunlight and to reduced pipe and cigar smoking.[200,201]

Global Scenario of Oral Potentially Malignant Disorders and Laryngeal Leukoplakia

The term *oral potentially malignant disorders* was recommended by an international Working Group convened by the WHO Collaborating Centre for Oral Cancer and Precancer in London in 2005.[202] It conveys that not all disorders described under this umbrella will transform to invasive cancer—or not within the time frame of the lifespan of an affected individual. Leukoplakia, erythroplakia, OSF, lichen planus, palatal lesions in reverse smokers, actinic keratosis, discoid lupus erythematosus, dyskeratosis congenita, and epidermolysis bullosa are included under the broad definition of OPMDs.[202,203]

Global Prevalence of Oral Potentially Malignant Disorders

Estimates of the global prevalence of OPMDs range from 1% to 5%,[204] although much higher prevalence rates have been reported from Southeast Asia, usually with a male preponderance—for example, in Sri Lanka (11.3%),[10] Taiwan (12.7%),[205] and Pacific countries such as Papua New Guinea (11.7%).[206] Wide geographic variations across countries and regions are mainly due to differences in sociodemographic characteristics, the type and pattern of tobacco use, and clinical definitions of disease (Table 1.5). In Western countries the overall prevalence is low and a decreasing trend over time is observed.

TABLE 1.5 Summary of the Prevalence of Oral Potentially Malignant Disorders (OPDMs) Reported in the Literature

Ref No.	Country (Year)	Sampling Method	Male/Female	Age Group	Disease Entity	Definition Used	Prevalence (%)
63	Sri Lanka (2008)	MSSC	0.6/1.0	≥30	OPMD	WHO, 1994	11.3 Weighted for sex and geographic location
67	Taiwan (2005)	Random	0.9/1.0	≥15	OPMD	Not given	12.7
					Leukoplakia		7.4
					Erythroplakia		1.9
					Lichen planus		2.9
					OSF		1.6
68	United States (2003)	MSSC	0.9/1.0	≥20	Leukoplakia	Kramer, 1978 Kramer, 1980	0.5–0.3
69	Sri Lanka (2003)	MSSC		35–44 yr and 65–74 yr	OPMD	WHO, 1994	4.1
					Leukoplakia/ erythoplakia		2.6
					OSF		0.4
70	Spain (2002)	Stratified, random	0.8/1.0	≥ 30	Leukoplakia	WHO, 1978 Axell et al, 1984	1.6
71	Germany (2000)	Stratified, random	1.0/1.0 0.7/1.0	35–44 yr 65–74 yr	Leukoplakia Leukoplakia	Axell, 1976 Zain, 1995 WHO-ICD-DA	1.6 1.0
72	Japan (2000)	All invited	0.4/1.0	Male >40, female >20	Leukoplakia		0.19
					Lichen planus		0.21
73	Malaysia (1997)	Stratified, random	0.7/1.0	≥25	Leukoplakia	WHO, 1978 Axell et al, 1984	0.96
					Erythroplakia		0.01
					OSF		0.06
					Lichen planus		0.38
74	Netherland (1996)	Waiting room	0.9/1.0	13–93 yr	Leukoplakia	Axell, 1984 Axell, 1996 Schepman, 1995	0.6
75	Hungary (1991)	Random	0.7/1.0	All age groups	Leukoplakia	Axell, 1984	1.3
					Lichen planus		0.1
76	Japan (1991)	Factory workers	0.5/1.0	18–63 yr	Leukoplakia	Axell, 1984	2.5
77	Sweden (1987)	Stratified random	Not found	≥15	Lichen planus	Axell, 1976	1.9
78	Sweden (1987)	All-invited residents	0.9/1.0	≥15	Leukoplakia	Axell, 1976	3.6

ICD-DA, International Classification of Diseases to Dentistry and Stomatology; *MSSC,* multistage stratified cluster; *WHO,* World Health Organization.

Petti (2003)[207] conducted a meta-analysis of 23 primary studies on oral leukoplakia, from international data published between 1986 and 2002. The point-prevalence estimates were 1.49% (95% CI, 1.42–1.56%) and 2.6% (random effect; 95% CI, 1.72–2.74%). Leukoplakia was significantly more prevalent among males (prevalence ratio [PR], 3.22), but no difference was found among geographic areas and between younger and older adults. Using these data, these researchers calculated that the crude annual oral cancer incidence rate attributable to leukoplakia would be between 6.2 and 29.1 per 100,000, thus suggesting that the global number of oral cancer cases is probably underreported. Table 1.5 provides a summary of the prevalence of OPMDs reported in the literature.

Age and Sex Distribution of Oral Potentially Malignant Disorders

Age and sex distributions vary considerably, mainly depending on lifestyle and thus on ethnicity and geographic location. In the developed world, leukoplakia is usually found between the fourth and seventh decades of life; in the developing world, it is found some 5–10 years earlier.[208] Females are less commonly affected, largely reflecting greater presence of relevant habits in men.

Malignant Transformation of Oral Potentially Malignant Disorders

Risk of malignant transformation varies from site to site within the mouth, from population to population, and from study to study.[209–211] A classic study conducted in the 1970s of over 30,000 Indian villagers with follow-up over 7 years showed transformation rates of 10–24 per 100,000 per year.[210] Another classic study from the early 1980s, a hospital-based study in Californian patients with oral leukoplakia, with a mean follow-up period of 7.2 years, revealed a malignant transformation rate of 17.5%.[211] Rates for hospital-based studies are, unsurprisingly, consistently higher than community-based studies because of sampling bias.

Petti[207] has estimated a mean global prevalence of 2.6% for leukoplakia, and a mean global transformation rate of 1.36% per year (95% CI, 0.69–2.03). Extrapolating from these figures suggests that considerably more OSCC should have been reported in recent times, a possible reason being underreporting of cases of oral cancer in the developing world. More recently, a careful study of 1357 patients with an OPMD from the South of England revealed that 2.6% of cases transformed to invasive cancer, for a total person follow-up time of 12,273 years (mean 9.04 years). The severity of epithelial dysplasia was a significant predictor for malignant transformation,[212] especially if aneuploid.[213] Similar findings came from a study of leukoplakia in Shanghai.[214] A study from a dysplasia clinic in the north of England confirmed the lateral tongue as a high-risk site and that nonsmokers were 7.1 times more likely to undergo malignant transformation compared with heavy smokers.[215]

Controversy continues as to whether or not OLP should be considered an OPMD. Published studies have given rates of transformation from 0% to 3.5%, over varying time periods. A comprehensive systematic review evaluated 7806 patients with OLP, among whom a mere 85 (1.09%) developed SCC in an average follow-up time of 51.4 months. Average age at onset of SCC was 60.8 years, with a slight female preponderance. The most common subsite of malignant transformation was the tongue.[216] Size is also a critical determinant.[217]

Epidemiology of Laryngeal Leukoplakia

Epithelial precursor lesions of the larynx, clinically defined as leukoplakia and chronic laryngitis, are mostly seen in adults and affect men more often than women. This sex disparity is more pronounced after the sixth decade of life.[218] Epidemiologic studies of laryngeal precursor lesions are scarce, and the incidence differs worldwide and depends on the amount, manner, and types of exposure to relevant carcinogens. A comprehensive literature review and analysis of the situation in Slovenia,[219] covering a region with approximately 800,000 inhabitants or 40% of the population, has reported that 1268 patients were clinically diagnosed with laryngeal leukoplakia and chronic laryngitis during the period from 1979 to 2004. Among these, 12 of 1089 (1.1%) patients with hyperplasia or mild dysplasia progressed to cancer compared with 17 of 179 (9.5%) of those with severe dysplasia.

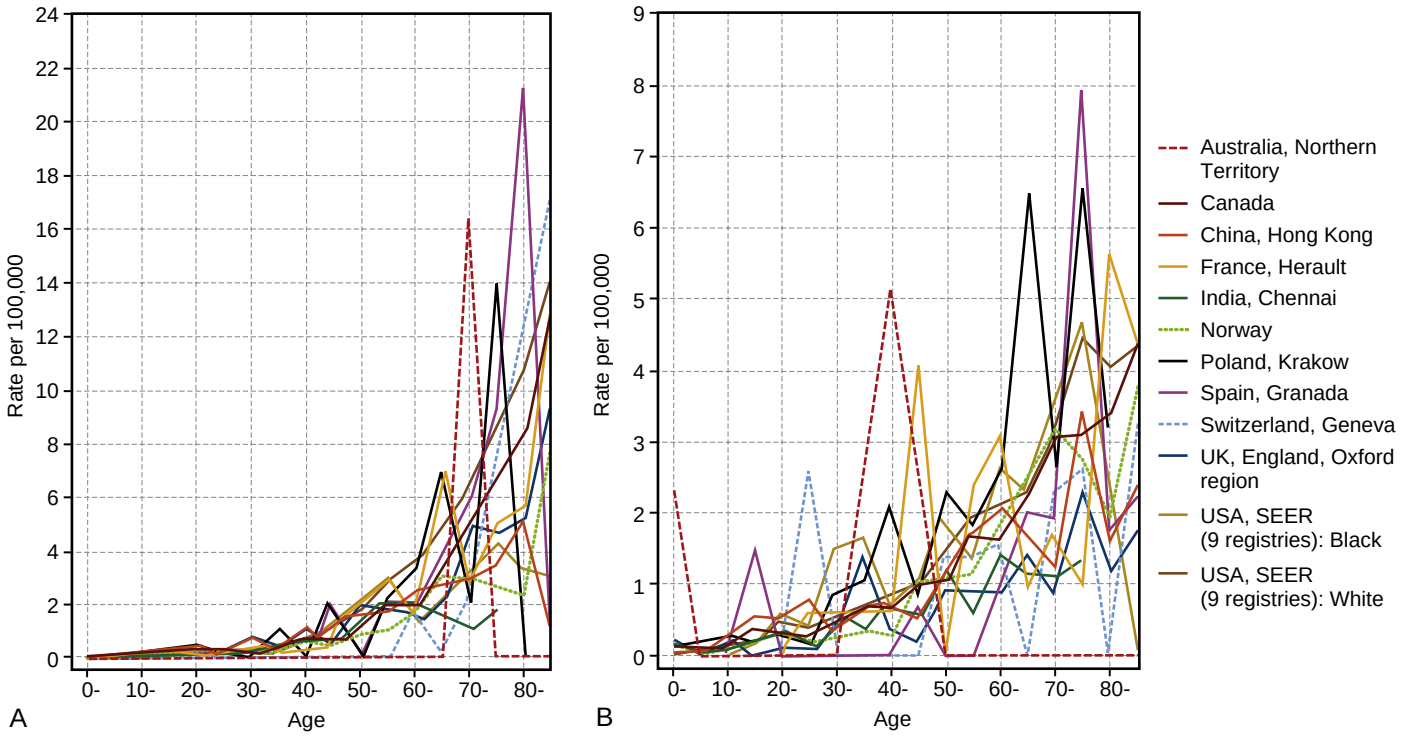
Etiology of Laryngeal Leukoplakia

Laryngeal leukoplakic lesions are strongly associated with tobacco smoking and alcohol use, especially in combination.[220–222] Other risk factors are: industrial pollution, specific occupational exposures, nutritional deficiency, and hormonal disturbance.[223–225] A meta-analysis has shown a weak association between HPV16 and laryngeal cancer.[226] Several authors have devoted much attention to the potential role of gastroesophageal reflux disease, but the results have not been conclusive.[220,227]

Salivary Gland Neoplasms

Epidemiology

Neoplasms arising in the salivary glands are relatively uncommon, yet they represent a wide variety of both benign and malignant histologic subtypes (Fig. 1.27). The reported annual incidence, when all salivary gland tumors are considered, varies widely among countries and regions.[228] According to GLOBOCAN 2012, the world's highest incidence of salivary neoplasms was reported in the Northern Territory indigenous community of Australia (although the number



• **Fig. 1.27** **A,** Salivary gland neoplasms—male. **B,** Salivary gland neoplasms—female. The incidence of salivary gland neoplasms rises steadily with age, but cases are found in all age groups. Data from selected countries are given in Fig. 1.26 (**A,** males; **B,** females). Note that the scales are, as usual with such data presentations, logarithmic. There is a clear male preponderance. *SEER,* Surveillance, Epidemiology and End Results program. (From Ferlay J, Bray F, Steliarova-Foucher E, Forman D. Cancer incidence in five continents, CI5plus. IARC CancerBase No. 9 Lyon, France, 2014, International Agency for Research on Cancer. Retrieved from http://ci5.iarc.fr.)

of cases in this thinly populated area was too small—only three—to place credence on this value); the second highest was seen in the United States, in Hawaii Filipino individuals. Within Japan, the highest rates are reported in the region of Nagasaki, regarded as long-term effects of the atomic bomb explosion in 1945. The estimated annual incidence in the United States is 1.5 cases per 100,000 population per annum, constituting only about 6% of all head and neck neoplasms[229] (Table 1.6).

Site, Age, and Sex Distribution

Nearly 80% of these neoplasms arise in parotid glands, 15% in submandibular glands, with the remainder distributed across the sublingual and minor salivary glands of the oral and oropharyngeal mucosae.[230] In most series, benign neoplasms are the majority, representing 54–79% of cases described. Pleomorphic adenoma is by far the most common, accounting for about 50% of all salivary gland neoplasms. Warthin tumor is second in frequency among benign neoplasms, and in most large studies mucoepidermoid carcinoma is the most common malignancy.[228] The average ages of patients with benign or malignant tumors are 46 and 47 years, respectively, with peak incidence of most of the specific types in the sixth and seventh decades (see Fig. 1.27). However, the highest incidence of pleomorphic adenomas, mucoepidermoid carcinomas, and acinic cell carcinomas occurs in patients who are significantly younger—in the third and fourth decades. Salivary neoplasms are rare in young people, and in patients younger than 17 years a neoplasm of a major gland is as likely to be mesenchymal as epithelial in origin.[231–234]

Etiology of Salivary Gland Neoplasms

The etiology of salivary gland neoplasms is still poorly understood. Furthermore, especially with neoplasms that have mixed cellularity, notably pleomorphic adenomas and carcinomas arising therein, which show epithelial, myoepithelial, and mesenchymal characteristics, controversy remains as to whether there is a single or more than one type of cancer stem cell.[228]

Viruses

Studies have shown a strong association between EBV and lymphoepithelial carcinomas[235,236] with geographic variations, including a preponderance for Asian patients[237] and Greenlandic Inuits.[238] Salivary tissue is an established reservoir for EBV, but a clear oncogenic role for EBV or cytomegalovirus (CMV) has not being demonstrated in other

TABLE 1.6 Incidence of Salivary Neoplasms: Cases per 100,000 per annum[6]

Population	ASRW Male	ASRW Female
Australia—Northern Territory	0.5	0.9
Canada	0.9	0.7
China, Hong Kong	0.8	0.6
Croatia	0.9	0.6
France, Herault	0.9	0.7
India, Chennai	0.5	0.4
Japan, Nagasaki	0.9	0.3
Norway	0.5	0.6
Poland, Kraków	0.8	0.9
Spain, Granada	0.8	0.4
Switzerland, Geneva	0.4	0.5
United Kingdom, Oxford region	0.7	0.4
United States, black SEER (nine registries)	0.7	0.9
United States, District of Colombia, white	0.9	0.6
United States, white SEER (nine registries)	1.1	0.7

ASRW, Age-standardized rate (world); *SEER,* Surveillance, Epidemiology and End Results program.

salivary gland carcinomas or in benign parotid neoplasms.[236] SV40 sequences have been postulated in human pleomorphic adenomas,[239] but there is no convincing association between human salivary gland neoplasms of epithelial origin and other viruses, including polyomavirus and papillomavirus. EBV is important in lymphoid neoplasms of salivary glands, as at other sites of lymphomata.

Radiation

There is convincing evidence implicating exposure to ionizing radiation and the development of salivary gland neoplasms. Long-term follow-up studies of the survivors of the atomic bomb explosions in Hiroshima and Nagasaki show an increased relative risk of 3.5 for benign and 11 for malignant salivary neoplasms.[240,241] The risk was directly related to the level of exposure to ionizing radiation. There was a high frequency of both mucoepidermoid carcinoma and Warthin tumors in these patients.[242] Therapeutic radiation, especially in the head and neck region, has been linked to significantly increased risk.[243,244] Iodine 131, used in the treatment of thyroid disease, is thought to produce neoplasms, as the isotope is also concentrated in salivary glands.[245]

Several studies have suggested that exposure to routine dental radiographs may be associated with an increased risk of salivary neoplasms, although the evidence is inconclusive.[246,247] Exposure to UV radiation has also been implicated,[248–250] although this seems biologically improbable. There appears to be no excess risk in those exposed to radon[251] or to the microwaves of cellular telephones.[252,253]

Occupation

There is literature relating salivary gland neoplasms to occupation. Suggested risks include rubber manufacturing,[254] exposure to metal in the plumbing industry[255] and nickel compounds,[254] woodworking in the automobile industry,[256] and employment in hairdressing and beauty shops.[257,258] An increased risk of salivary gland cancers was reported in people living in certain Quebec counties where asbestos was mined, and this risk was inversely proportional to distance from the mines.[259]

Lifestyle and Nutrition

Tobacco and alcohol, which are highly associated with head and neck SCC, have not been shown to play a major role in the development of salivary malignancies.[260] However, tobacco smoking has been associated with the development of Warthin tumor. Exposure to silica dust and kerosene as a cooking fluid increased the risk of salivary neoplasms in a Chinese population,[261] and an increased risk of parotid neoplasms was associated with exposure to nickel, chromium, asbestos, and cement dust.[262] An elevated level of risk has been described in those with a high cholesterol intake.[263]

Hormonal Influences

Estrogen activity or upregulation of estrogen receptors has been described in pleomorphic adenomas in some studies[264] but was absent in another.[265] Progesterone and androgen receptors are present in some salivary neoplasms,[264,266] and binding of hormones to these may influence tumor progression.

Malignant Melanoma

Malignant melanoma is recorded by cancer registries separately from mucosal and other cancers. These data represent all skin sites, but the management of melanoma often falls into the hands of head and neck clinicians, so the data are of interest here (Table 1.7). DNA damage from UV light, especially acute sunburn and especially early in life, is the major risk factor. This explains the high incidence rates in Australia, New Zealand, and Northern Europe (especially Scandinavia) and among white South Africans; for head and neck melanoma, the risks associated with UV light are most marked at low latitudes and high altitudes.[267] Melanoma of UADT mucosa is a serious, usually fatal, disease. Global epidemiologic data are "buried" in the graphs and tables mentioned earlier. Such data as are available have been reviewed by van der Waal and colleagues.[268]

The death-to-registration ratio (D/R) for melanoma can be readily calculated. For Australia and New Zealand, it ranges from 0.09 to 0.18; in Northern Europe, the average approaches double this—that is, 0.16 for women and 0.26 for men (Table 1.8). Women have better survival rates all over the world, possibly

TABLE 1.7 World Standardized Incidence Rate per 100,000 per Year for Melanoma

Country	Melanoma Skin Cancer (ICD-10: C43)	
	Male	Female
World	3.3	2.8
More developed	10.2	9.3
Less developed	0.8	0.7
Africa	1.0	1.1
Eastern Africa	0.8	1.3
Middle Africa	1.4	2.0
Northern Africa	0.3	0.4
Southern Africa	5.0	3.7
Western Africa	0.6	0.6
Caribbean	0.8	0.7
Central America	1.9	1.3
South America	2.9	2.2
Northern America	16.1	12.2
Asia	0.5	0.4
Eastern Asia	0.6	0.5
Southeastern Asia	0.5	0.3
South Central Asia	0.3	0.2
Western Asia	1.8	1.6
Europe	8.6	8.9
Eastern Europe	4.5	4.6
Northern Europe	14.0	15.4
Southern Europe	8.1	8.3
Western Europe	11.5	12.8
Australia	40.5	30.0
New Zealand	39.2	33.1
Melanesia	3.4	3.8
Micronesia	4.0	2.1
Polynesia	4.0	2.7

Data from Ferlay J, Soerjomataram I, Ervik M, et al, editors: *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012*. Lyon, France, 2013, International Agency for Research on Cancer (IARC). http://globocan.iarc.fr.

TABLE 1.8 World Standardized Mortality Rate per 100,000 per year for Malignant Melanoma

Country	Melanoma Skin Cancer (ICD-10:C43)	
	Male	Female
World	0.9	0.6
More developed	2.0	1.2
Less developed	0.4	0.3
Africa	0.5	0.4
Eastern Africa	0.6	0.4
Middle Africa	1.0	1.5
Northern Africa	0.2	0.2
Southern Africa	1.6	0.8
Western Africa	0.5	0.5
Caribbean	0.3	0.2
Central America	0.6	0.4
South America	1.0	0.6
Northern America	2.6	1.2
Asia	0.3	0.2
Eastern Asia	0.4	0.3
Southeastern Asia	0.3	0.2
South Central Asia	0.2	0.1
Western Asia	0.6	0.5
Europe	2.0	1.3
Eastern Europe	2.0	1.4
Northern Europe	2.5	1.6
Southern Europe	1.6	1.0
Western Europe	2.0	1.3
Australia	5.8	2.3
New Zealand	6.9	2.8
Melanesia	2.1	2.3
Micronesia	1.0	0.0
Polynesia	1.0	0.7

Data from Ferlay J, Soerjomataram I, Ervik M, et al, editors: *GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012*. Lyon, France, 2013, International Agency for Research on Cancer (IARC). Retrieved from http://globocan.iarc.fr.

because they seek treatment earlier. Note that these outcomes are substantially better than for oral cancer. In Australia and New Zealand there are highly effective public education campaigns regarding protection against sun damage, and many screening and treatment facilities. In spite of this, the comparatively poor outcomes perhaps reflect a degree of complacency toward very common sun-induced lesions, many of which are benign.

The Future of Head and Cancer Epidemiology

As with many aspects of life, global inequalities are increasing in the incidence rates of head and neck cancers, in the provision and quality of prevention and screening programs, and in access to and quality of patient care.[1] The drivers of these inequalities are sociopolitical: war, poverty,

pestilence, climate change, and lack of food and water security.[269] The problems do not derive primarily from ignorance of causes and mechanisms of disease, but from ineffective or absent implementation of the right policies, and from lack of resources to implement them. As scientists and clinicians devoted to head and neck oncology, we all have a moral responsibility to contribute to these wider social and political challenges. The knowledge necessary to apply best practices is within the pages of this book. The leadership of many local and national bodies is acknowledged; these activities need to be conducted in dialogue and synergy with global leadership through agencies such as WHO, the IARC, the Union for International Cancer Control (UICC), the International Federation of Head and Neck Oncologic Societies, the International Academy of Oral Oncology, and others. The International Association for Dental Research launched an initiative in 2010 seeking to reduce global inequalities in oral cancer (and in other orofacial diseases and disorders), and this led to the formation of the Global Oral Health Inequalities Research Network.[270]

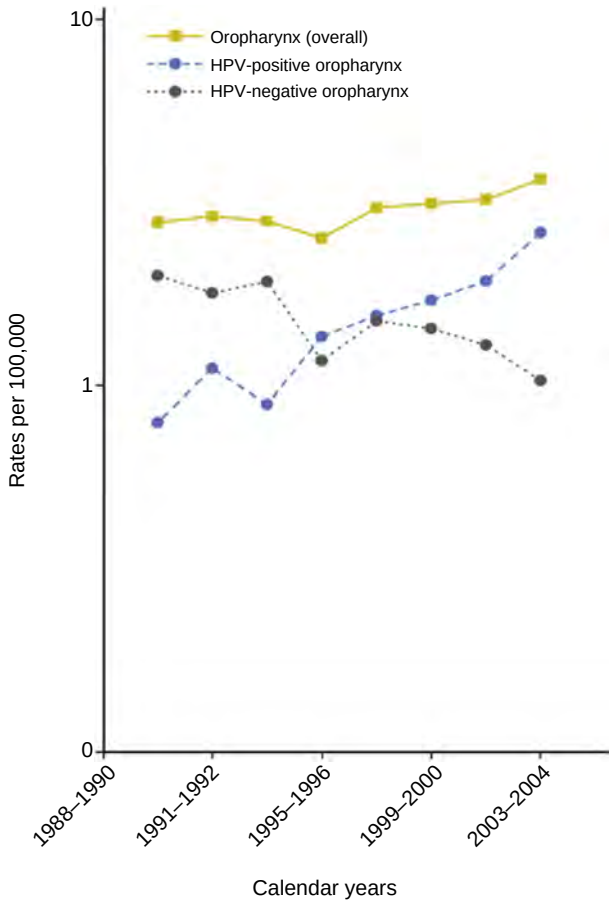
It is a truism that however sophisticated and effective our diagnostic and treatment armamentarium becomes, head and neck cancer rates around the world will never be reduced by such interventions—although, of course, hundreds of thousands of lives may be saved or improved. The emphasis must be on primary and secondary prevention, on the implementation of policies that work to these ends, and on their continued evaluation and improvement.[1]

Sections from Part 1 from Johnson NW, Amarasinghe HK. Epidemiology and aetiology of head and neck cancers. In Bernier J (Ed.): *Head and Neck Cancer.* New York: Springer, 2016. With permission of Springer Nature.

PART 2: HUMAN PAPILLOMAVIRUS–RELATED HEAD AND NECK CANCER

Jesse R. Qualliotine, Carole Fakhry

The epidemiology of HNSCC has evolved in recent decades and is an area of active research. Perhaps better known for its association with cervical cancer, HPV has also been linked to malignancies in the head and neck, particularly in the oropharynx. Oropharyngeal squamous cell carcinomas (OPSCCs) comprise an etiologically heterogeneous group, with one subgroup strongly linked to the classic risk factors of tobacco and alcohol use, and the other to oral HPV infection. HPV, a sexually transmitted infection, has been implicated in a growing number of oropharyngeal HNSCCs, the majority of which arise in the lingual and palatine lymphoid tissue of the oropharynx (Fig. 1.28). HPV-positive oropharyngeal squamous cell carcinoma (HPV-OPSCC) has unique risk factors, demographic profile, and prognosis, which may confer unique therapeutic considerations in the future. This section reviews the evolving epidemiology and etiology of oral HPV infection and HPV-OPSCC, including the clinical implications of tumor HPV status.



• **Fig. 1.28** Cancers of the oral cavity and pharynx. (From Sturgis EM, Cinciripini PM: Trends in head and neck cancer incidence in relation to smoking prevalence. *Cancer*, 2007.Oct 1;110[7]:1429-35.)

Epidemiology of Oral Human Papillomavirus Infection

Oral HPV infection is confirmed by detection of viral DNA with polymerase chain reaction (PCR) using PGMY primers and linear array genotyping[271] in oral rinse samples, which samples both the oral cavity and the oropharynx. National Health and Nutrition Examination Survey (NHANES) data were drawn from a random sampling of the U.S. noninstitutionalized, civilian, adult population and are the most robust cross-sectional data available to date on oral HPV infection, with gold standard detection methods. The study estimated the prevalence of any oral HPV infection to be 6.9% (95% CI, 5.7–8.3%).[177] This estimation included detection of both types that are recognized to be carcinogenic (high-risk types), as well as those without oncogenic potential (low-risk types). This figure extrapolated to the entire population suggests that in 2009–2010 there were approximately 15 million adults in the United States with an oral HPV

infection. The vast majority of HPV-OPSCC is caused by oral HPV16 infection.[272] NHANES reported HPV16 to be the most commonly detected type of oral HPV infection, with a prevalence estimate of 1% of the U.S. population.[177]

Nonmodifiable factors associated with oral HPV infection include sex, age, and race. Oral HPV infection is not equally distributed by sex; the prevalence of infection in males is at least twice that in females.[273–276] Notably, for oral HPV16 infection the proportion of male to females infected was even higher; oral HPV16 infection was five times more likely in males than in females in the United States (PR, 5.4; 95% CI, 2.1–13.8).[177] Offering an explanation for this observed sex imbalance, a recent analysis of NHANES data from 2009–2012 found that men had more sexual partners than women (mean 18 vs. 7, $p < .001$) and that the per–sexual partner increase in prevalence was significantly stronger among men than women (adjusted synergy index 3.3; 95% CI, 1.1–9.7).[277]

Prevalence estimates of oral HPV infection vary by age as well. A bimodal distribution in oral HPV infection has been observed. In NHANES data, an early prevalence peak at ages 30–34 and a later, higher peak at ages 60–64 were modeled. This bimodal age distribution is present among men and women, but is more pronounced among men.[177] Race also modifies pre-test probability for oral HPV infection of all types. One study demonstrated its prevalence among non-Hispanic blacks to be 61% higher than among whites (PR 1.61; 95% CI, 1.01–2.57).[177] These findings are consistent with previous studies that demonstrated a significant association between black race and presence of an oral HPV infection.[275] However, when analyzed separately for high- and low-risk HPV infections, the higher prevalence among blacks than whites is observed only for low-risk infections.[177,275] By contrast, oral HPV16 infection was significantly more common in whites than blacks.[278]

In addition to nonmodifiable risk factors, oral HPV infection risk appears to be modulated by several behavioral factors as well, namely tobacco use, sexual behaviors, and immunosuppression, but not alcohol use. Oral HPV infection can be added to the ever-expanding litany of maladies associated with tobacco use. The odds of oral HPV infection increase significantly in a dose-dependent fashion with increasing measure of current use of tobacco products.[177,273,274,279] Lifetime history of smoking, however, is not independently associated with the presence of oral HPV infection. Furthermore, smoking tobacco appears to have a stronger association with oral HPV infection for women than for men.[177] Similar to other sexually transmitted infections, the odds of oral HPV infection increase significantly with increased sexual exposures. Ever having performed oral sex, early oral and vaginal sexual debut, lack of barrier use, deep tongue kissing, increasing lifetime oral and vaginal sex partners, and ever having had vaginal and anal sex are all significantly associated with oral HPV infection.[177,273–276,279–281] Although many analyses have consistently demonstrated significant associations between oral HPV infection and these sexual behaviors, these behaviors are known to occur together (i.e., collinear), and thus the independent contribution of each behavior to increased oral HPV infection risk is unknown.[272]

It is interesting to note that, unlike human immunodeficiency virus (HIV) type 1, which has a higher prevalence in men who have sex with men (MSM) than in heterosexual males,[282–286] the literature does not suggest a similar relationship for oral high-risk HPV16 infection.[177,287,288] Conversely, one cohort study of HIV-infected men from Spain reported heterosexual men to have a higher prevalence (7.8 vs. 3.7%, $p < .05$) and incidence (adjusted OR 3.2; 95% CI, 1.1–9.5) of oral HPV16 infection than MSM.[287] This observed higher risk in heterosexual males is consistent with other analyses that have demonstrated that performing oral sex on a woman may confer a higher risk of oral HPV infection than performing oral sex on a man.[289] The odds of oral HPV infection are significantly increased in immunosuppressed patients, as is the case with many viral infections. Patients with HIV, lower CD4 count,[273,276,290] or iatrogenic immunosuppression[291] are more likely to have oral HPV infection. A risk factor whose absence is worth highlighting is alcohol use; its association with oral HPV infection loses significance after adjustment for sexual behavior.[177]

The natural history of oral HPV infection has not yet been fully elucidated. An observational cohort study of HIV-negative men from North America suggested that most oral HPV infections with high-risk types are cleared within 1 year, with a median duration of infection of 6.3 months (95% CI, 6.0–9.9).[292] Factors associated with persistence of oral HPV infection include current tobacco use, age above 44 years, CD4 count below 500 cells per cubic millimeter[272] and increased incidence secondary to sexual behaviors and exposure frequency.[288,292,293] A recent U.S.-based longitudinal cohort study followed both HIV-infected and at-risk HIV-uninfected individuals semiannually for 3 years to examine oral HPV transmission and persistence. The group reported 2-year cumulative incidence of oral HPV infection of 34% in HIV-infected persons and 19% in HIV-uninfected persons, with many of these infections clearing over the 2-year period. Risk factors for increased persistence included male sex, older age, and current smoking status.[294]

It is interesting to note that epidemiology of HPV infection appears to differ by anatomic site. There is a lower prevalence of sexually transmitted infections in the oral cavity than in the cervix. It is known that the immune microenvironment of the oral cavity is histologically characterized by high levels of dendritic cells and T cells,[295,296] whereas in the cervix, antigen non-specific polymorphonuclear cells are more prevalent.[297] In addition, a recent study has demonstrated markedly different immune marker profiles between these two environments, which may help explain the observed lower burden of sexually transmitted infections in the oral cavity than in the cervix.[298] The natural history of oral and anogenital HPV infection appears to have some overlap, yet distinct differences do exist, although further research confirming these findings is necessary.[288,293]

Association Between Oral Human Papillomavirus Infection and Oropharyngeal Cancers

A causal relationship between HPV and OPSCC has been established through epidemiologic and molecular studies, with HPV16 responsible for at least 90% of HPV-HNSCCs. High-risk virus types HPV18, HPV31, HPV33, and HPV35 are also responsible for a subset of HPV-HNSCCs.[299]

HPV-HNSCC arises most commonly in the oropharynx, primarily from the lingual and palatine tonsils.[300,301] Studies have estimated the prevalence of HPV-positive tumor status in OPSCC to be 60–70%, and this figure is projected to be growing.[302–306] However, HPV tumor positivity in other anatomic sites is estimated to be less frequent. For example, prevalence estimates in other anatomic HNSCC sites include nasopharynx 31%, larynx 24%, sinonasal tract 21%, and oral cavity 6–20%.[307,308] This is an area of current investigation. Thorough, gold standard investigations of nonoropharyngeal HNSCCs have not been completed to date.

HPV-OPSCC is more likely than its HPV-negative counterpart to present as a metastatic cervical nodal disease with an occult primary site.[300,309] Conversely, a large proportion of unknown primary disease originates from oropharyngeal malignancies, in which HPV prevalence is about 90%.[309,310] In fact, the tumor HPV positivity in cervical metastases with an unknown primary site is a strong biomarker of oropharyngeal origin and allows the search for the primary site to be focused on the oropharynx, whereas historically the entire aerodigestive tract was under scrutiny.[310–312]

The premalignant entity in the oropharynx due to oral HPV infection has not yet been identified, although undoubtedly such a condition exists. Detection of HPV DNA in tumor tissue is necessary but not sufficient to attribute the cause of the lesion's transformation to the virus.[299] The sequence of HPV-induced oncogenesis leading from oral infection to oropharyngeal malignancy, briefly, comprises expression of HPV oncoproteins encoded by the *E6* and *E7* genes, which degrade, respectively, tumor suppressor proteins p53 and retinoblastoma (pRb). Without these two cell cycle regulators functioning properly, proliferation is disinhibited and mutations accumulate, leading to malignant transformation.[313] The degradation of pRb leads to overexpression of a cyclin-dependent kinase inhibitor, p16, whose detection in p16-based assays conveniently serves as a histologic marker of oncogenic HPV activity.[314] Antibodies to the oncogenic protein E6 detected in healthy individuals are greatly associated with the development of OPSCC in the future (OR 275; 95% CI, .110–.681). In fact, patients who ultimately developed OPSCC were E6 seropositive up to 10 years before diagnosis.[315] Although screening for E6 as primary prevention for OPSCC is not recommended at this time, there is hope that continued investigation in this area may lead to an effective population-level screening program.

Incidence Trends for Human Papillomavirus–Positive Oropharyngeal Squamous Cell Carcinoma

The incidence of HNSCC overall in the United States has fallen,[316] a reduction that appears to correlate with declining tobacco use owing to the successful tobacco cessation campaign.[317,318] However, this decreasing incidence is not observed for all HNSCC sites. Both in the United States and in many developed countries around the world, the incidence of HNSCC within the oropharynx has risen, specifically that of HPV-related disease.[4,44,302,319] The IARC estimated 130,296 new cases (81.5% in males) of oropharyngeal cancer worldwide in 2002. For the same year, the age-standardized incidence rate of oropharyngeal cancer worldwide per 100,000 males was 3.8.[320] The most current report from the IARC estimates this same figure in 2012 to range from 4.7 in more developed areas to 2.8 in less developed areas.[321] For the United States alone, the American Cancer Society estimated 13,510 new cases (79.9% in males) of oropharyngeal cancer in 2012.[322]

Worldwide, tumor HPV prevalence has been shown to be higher among studies from North America compared with Europe and Asia.[272] Regional differences in sexual behaviors and tobacco use appear to underlie the geographic variance in HPV-OPSCC prevalence. The prevalence estimates of oropharyngeal tumor HPV positivity in the United States has increased from less than 20% in the early 1980s to just over 70% in contemporary analyses.[4,300,302–305] This, coupled with the falling rates of HPV-negative OPSCC, has led to sharply increasing proportions of OPSCC that are HPV positive.[4] This shifting epidemiologic trend is no doubt multifactorial, but changing sexual practices since the sexual revolution of the 1960–1980s—namely, increased exposure to oral HPV infection—is thought to be contributory.[278] This increase in HPV-OPSCC is so dramatic that by the year 2020, HPV, a virus whose current association to the lay public is chiefly with cervical cancer in women, is estimated to cause more OPSCC than cervical cancer in the United States.[4]

Demographic Profile of Human Papillomavirus–Positive Oropharyngeal Squamous Cell Carcinoma

The emergence of HPV-HNSCC has produced a population of patients with a unique demographic profile distinct from HPV-negative HNSCC (Table 1.9). This population of patients is on average younger, more likely to be male, white, and of higher socioeconomic status. HPV-OPSCC patients are on average 4–10 years younger than HPV-negative OPSCC patients at diagnosis,[303,323–328] which may explain the observed increased incidence of OPSCC in younger patients in developed countries.[4,44] This younger population has been shown to be healthier than its HPV-negative counterpart with improved performance status on many scales, including Eastern Cooperative Oncology Group (ECOG)[303–305] and WHO,[329] with fewer

TABLE 1.9 Major Differences Between Head and Neck Squamous Cell Carcinomas (HNSCCs) by Human Papillomavirus (HPV) Status

	HPV-Positive HNSCC	HPV-Negative HNSCC
Risk factors	High-risk sexual practices	Cigarette and alcohol use
Tumor size	Lingual and palatine tonsils	Nonoropharyngeal sites
Histopathology	Basaloid, nonkeratinizing, poorly differentiated	Keratinizing, moderately differentiated
Molecular Genetic Alterations		
P53 pathway disturbances	Degradation of wild-type p53 by E6	*TP53* mutations, 17p LOH
Rb pathway disturbances	Degradation of wild-type Rb by E7	*P16*^{INK4A}-promoter hypermethylation, 9p LOH
Relative responsiveness to chemoradiation	Better	Worse
Relative prognosis	Improved	Worse

From Pai SI, Westra WH: Molecular pathology of head and neck cancer: implications for diagnosis, prognosis and treatment. *Annu Rev Pathol Mech Dis* 4:49–70, 2009.
LOH, Loss of heterozygosity; *Rb,* retinoblastoma.

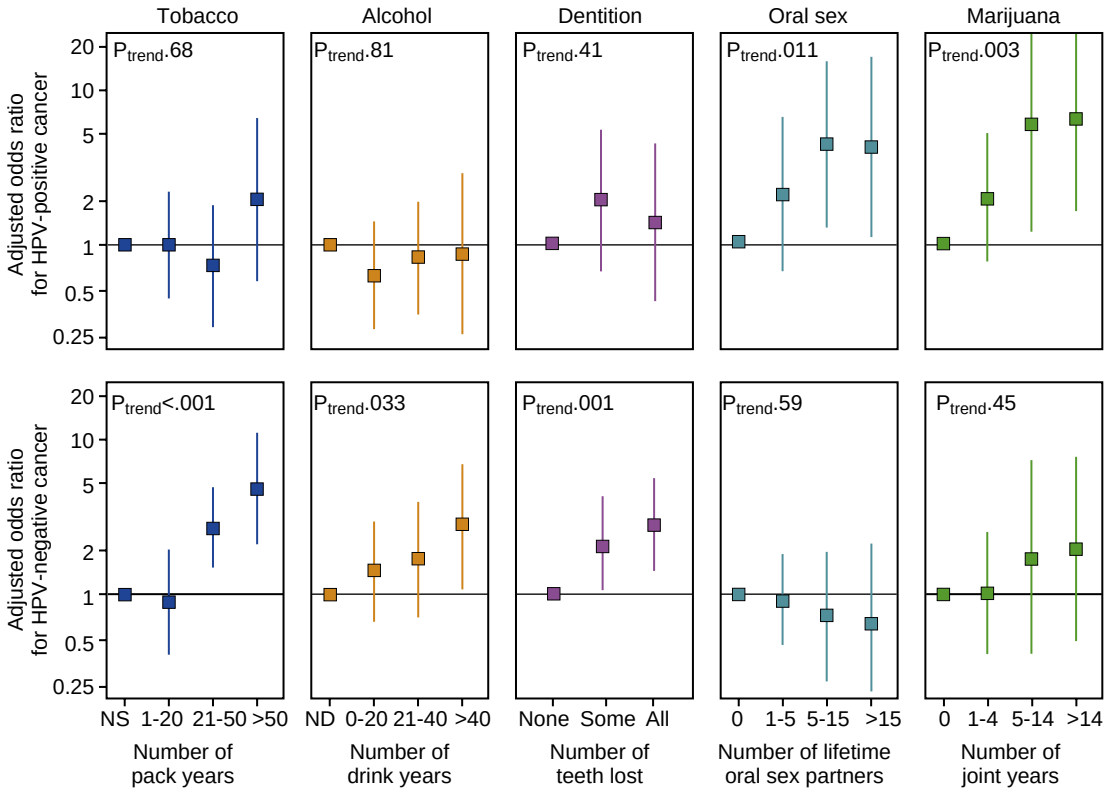
comorbidities.[303,304,324] Patients with HNSCC of all types are more likely to be male, but when comparing HPV-OPSCC and HPV-negative OPSCC, a significantly higher proportion of patients with HPV-positive tumors are male.[4,327,330,331] In fact, for men in the United States, HPV-related malignancies are more likely to be found in the oropharynx than any other anatomic site.[332] HPV-HNSCC has been demonstrated to have an overwhelmingly higher incidence in white than black patients. Studies analyzing HNSCC tumors for HPV status report tumor HPV positivity in 29–34% of white patients, but only in 0–4% of black patients.[333,334] Analyses of oropharyngeal tumor HPV positivity in white patients have reported finding HPV-positive and HPV-negative tumors in 92–97% and 75–78% of cases, respectively.[303,305,333] This racial difference in OPSCC extends to incidence rates, which have increased in white but decreased in black patients, most likely driven by higher rates of HPV-OPSCC in whites.[332] Surveys of HPV-OPSCC patients report more years of education, higher income, and greater likelihood to be married than HPV-negative OPSCC patients.[300,324]

It is important to recognize that the HPV-HNSCC patient population, in addition to having a unique demographic profile, presents a unique challenge to the head and neck surgeon in counseling patients who receive a cancer diagnosis coupled with the diagnosis of a sexually transmitted infection. This is a largely unexplored domain of inquiry whose importance has only recently come under scrutiny.[335] Continued research into the natural history and psychosocial implications of HPV-related oropharyngeal cancer is required.

Risk Factors for Human Papillomavirus–Positive Oropharyngeal Squamous Cell Carcinoma

Sexual behaviors are among the risk factors for HPV-OPSCC and closely resemble those for oral HPV infection, including having ever performed oral sex, increased lifetime number of oral and genital intercourse partners, history of casual intercourse, younger age at both oral and vaginal sexual debut, lack of barrier use during oral intercourse, and a positive history of sexually transmitted infection.[170,300,336] Despite these strong associations, the sexual history, even a comprehensive one, cannot reliably predict tumor HPV status.[337] HIV infection has been shown to be independently associated with high-risk oral HPV infection, with one study of MSM population from the Netherlands reporting detection of oral HPV infection with oncogenic types in 24.8% of HPV-infected but only 8.8% of HIV-negative MSM ($p < .001$).[338] Long-term sexual partners of patients with HPV-OPSCC, however, have not been shown to have increased rates of oral HPV infection over that of the general population.[339]

Before the era of HPV, the risk factors most importantly associated with HNSCC were heavy use of tobacco and alcohol, which when present together are synergistic.[340] Together, alcohol and tobacco are responsible for approximately 75% of all HNSCC cases.[341,342] HPV-OPSCC appears to have different risk factor profile than its HPV-negative counterpart. The rates of lifetime tobacco use for HPV-positive and HPV-negative OPSCC have been stated to be 65% and 74%, respectively.[303] Although the odds of HPV-negative OPSCC significantly increase with increasing lifetime tobacco exposure with a dose-response relationship, an inverse relationship is observed for HPV-positive disease.[300] Although tobacco exposure does confer additional risk for developing HPV-OPSCC, it is unknown whether tobacco use and oral HPV infection together modulate risk in a synergistic fashion. Alcohol use similarly increases the risk for developing HPV-negative OPSCC in a dose-dependent manner,[300] but is less prevalent among patients with HPV-OPSCC.[300,343,344] Heavy alcohol use, defined as more than 21 drinks per week, increases the odds of developing not only HPV-negative lesions, but HPV-OPSCC as well.[345] It is worth emphasizing that alcohol does



• **Fig. 1.29** Risk factors for human papillomavirus (HPV)–related and HPV-unrelated oropharyngeal cancer. (Adapted from D'Souza G, Agrawal Y, Halpern J, Bodison S, Gillison ML: Oral sexual behaviors associated with prevalent oral human papillomavirus infection. *J Infect Dis* 2009;199[9]:1263–1269.)

in fact increase the risk for HPV-OPSCC despite not being an independent risk factor for oral HPV infection. The extent to which alcohol use modulates risk both independently and in association with oral HPV infection or tobacco exposure remains to be fully elucidated. It is also possible that alcohol use is a surrogate for sexual exposure.

A unique risk factor for HPV-HSNCC not observed for HPV-negative HNSCC is marijuana use. Patients with HPV-HNSCC are more likely to report a history of marijuana use than are patients with HPV-negative HNSCC. For HPV-positive OPSCC, increasing duration and intensity of marijuana use is associated with increasing odds of malignancy.[300] It is interesting to note that, in contrast to its risk for development of an oropharyngeal cancer, one study demonstrated that marijuana may actually attenuate the risk of developing an oral tongue cancer (adjusted OR, 0.47; 95% CI, 0.29–0.75).[346] This also highlights that HPV-positive OPSCC is a distinct entity with distinct risk factors (Fig. 1.29).

Clinical Implications for Human Papillomavirus Tumor Status

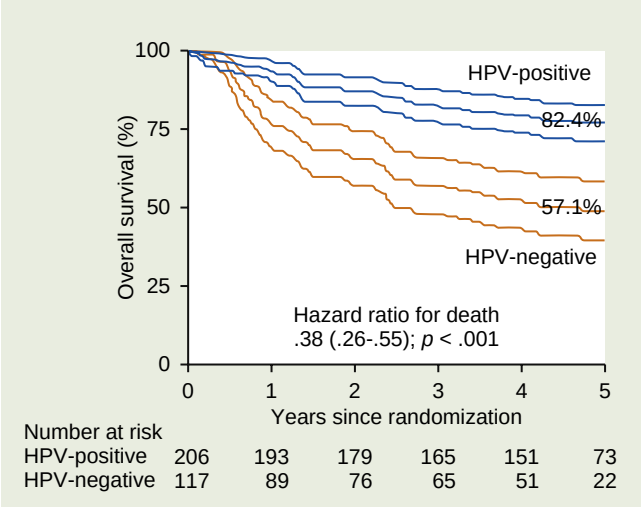
Prognosis

Before the era of HPV the prognosis for OPSCC was quite poor, with a 5-year OS of 44%.[347] A subset of HNSCC patients with a more favorable prognosis was first demonstrated in single-institution retrospective analyses to include patients with HPV-positive HNSCC, especially that originating in the oropharynx. These findings were observed for disease detected with variable tumor HPV interrogation methods and with heterogeneous treatment strategies.[323,324,330,348,349] Tumor HPV status has since been demonstrated to be the strongest independent prognostic factor for OPSCC,[350,351] with meta-analysis reporting HPV-OPSCC to have an OS rate that is 53% improved over that of HPV-negative OPSCC (hazard ratio [HR] 0.47; 95% CI, 0.35–0.62)[352] (Fig. 1.30). For nonoropharyngeal sites, it is unknown whether tumor HPV status has any impact on prognosis.[307]

The American Joint Committee on Cancer (AJCC) stage is a reasonable surrogate for prognosis and is used clinically to guide therapy for HPV-negative OPSCC.[353] HPV-OPSCC is more likely to present with smaller primary tumors (lower T stage), but more advanced nodal disease (higher N stage),* which results in an overall more advanced AJCC stage.[354,357–359] Even though HPV-OPSCC patients have more advanced AJCC staged disease on presentation, their response to therapy, progression-free survival, and OS are higher than those of their HPV-negative counterparts.[303,323,348,357,360]

Patients with HPV-HNSCC appear to have improved responses to treatment when compared with patient with HPV-negative cancers. Gillison and colleagues in 2000 demonstrated

*References 300, 304, 314, 323, 324, 354–356.



• **Fig. 1.30** Overall survival according to HPV status. (From Ang KK, Harris J, Wheeler R, et al: Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 363[1]:24–35, 2010.)

in a retrospective analysis of a large cohort of patients with HNSCC from all sites that tumors originating from the oropharynx were strongly associated with tumor HPV positivity and that when compared with HPV-negative HNSCC, HPV-positive disease carried a better prognosis. Patients with HPV-HNSCC from all sites had a 40% reduction in all-cause mortality (95% CI, 0.35–1.0, p = .07) and a 59% reduction in disease-specific mortality when adjusted for age, nodal disease, and alcohol consumption (95% CI, 0.20–0.88, p = .02).[348] Since then, these observations of improved survival in HPV-positive disease have been reproduced in several robust, collaborative, prospective analyses. The first multi-institutional (ECOG 2399) prospective evaluation of how tumor HPV status affects survival demonstrated significantly improved response to induction chemotherapy (82% vs. 55%, p = .01) and concomitant chemoradiotherapy (84% vs. 57%, p = .007) for patients with HPV-positive tumors as compared with those with HPV-negative tumors. The study included follow-up 2 years after treatment and reported a sustained favorable response with a significantly lower risk of progression (HR 0.27; 95% CI, 0.10–0.75) and death (HR 0.36; 95% CI, 0.15–0.85) for patients with HPV-positive disease after adjusting for age, tumor stage, and ECOG performance status.[305] In a retrospective analysis of the Radiation Therapy Oncology Group (RTOG) 0129 phase III trial, which evaluated concurrent cisplatin and standard or accelerated-fractionation radiotherapy in 323 patients with OPSCC, positive tumor HPV status was associated with an improved 3-year OS (82% vs. 57%, p < .001) and a 58% reduction in all-cause mortality (HR 0.42; 95% CI, 0.27–0.66).[303]

Additional phase III clinical trials have since corroborated these results, demonstrating that positive HPV tumor status confers improved prognosis after a variety of treatment regimens.[304,329,354] Analyses of OPSCC treated with platinum-based induction chemotherapy regimens have demonstrated improved response of HPV-positive compared with HPV-negative disease.[305,327] Several analyses have uniformly demonstrated that HPV-OPSCC responds better than HPV-negative OPSCC to radiation therapy, independent of the radiation regimen, addition of radiation sensitizers,[304,361] and addition of chemotherapy.[303,349,354] The U.S. population-based SEER data demonstrate a greater survival difference between HPV-related and HPV-unrelated OPSCC (using anatomic site as proxy for HPV tumor status) for patients treated with radiation therapy than for those not treated with radiation.[4] Positive HPV tumor status is significantly associated with more favorable prognosis over HPV-negative disease even for patients treated with surgery alone, although the evidence is limited to small, single-institution series.[362]

The consistently demonstrated improved survival of the OPSCC patient with positive HPV tumor status is only partially explained by this population's younger age, decreased tobacco exposure, fewer comorbid conditions, and higher performance status, as the prognostic advantage persists in multivariate analyses that adjust for these confounders.* Indeed, these confounders explain only 9% of the difference in overall and progression-free survival, which suggests that a fundamental difference in tumor biology underlies the survival advantage seen in patients with HPV-positive HNSCC.[303,352] Proffered explanations are increased radiosensitivity, increased response to chemotherapy, fewer second primary tumors, and a more favorable tumor biomarker profile, including for epidermal growth factor receptor (EGFR), p53 mutations, and survivin.[314,348,363–366] Extranodal extension, too, despite carrying a poor prognosis for patients with HPV-negative OPSCC, may have different prognostic implications for patients with HPV-OPSCC; however, this is an area of current investigation and therefore remains a poor index of prognosis until prospective data are available.[367–371] In addition to reduced risk of cancer progression when compared with HPV-negative oropharyngeal cancer after primary therapy, HPV-positive tumor status is also a strong independent predictor of reduced death after progression of disease (HR 0.48; 95% CI, 0.27–0.84).[372]

Currently, histologic tumor testing includes in situ hybridization (ISH) for HPV DNA and immunohistochemistry for p16, which is a surrogate for HPV tumor status[373]; p16 immunohistochemistry is a reliable surrogate for HPV-positive tumor status only in oropharyngeal squamous cell cancers. The role for p16 immunohistochemistry in nonoropharyngeal cancers is limited. Clinical detection relies on these methods as well as use of PCR-based methods in some clinical centers. These methods used to detect HPV within established disease are unfortunately not adaptable for preventative screening, and effective screening strategies have not yet been developed.

Survival Modifiers

In addition to affecting the risks of acquiring oral HPV infection and developing HPV-OPSCC, tobacco exposure also negatively influences response to treatment and survival.[374,375] Tobacco use is not only an independent prognostic factor for HPV-OPSCC, but it is also an independent risk factor for

* References 303, 304, 314, 323, 324, 329, 348, 349, 354.

both cancer progression and death in a dose-dependent manner.[303,376,377] One study of patients with OPSCC demonstrated that after adjustment for HPV tumor status and other factors, tobacco increases the risk of cancer progression and death by 1% per pack-year and the risk of developing a second primary tumor by 1.5% per pack-year.[376] Smoking while receiving radiotherapy doubles the risk of death.[376] Ang and colleagues proposed risk-stratifying patients by HPV tumor status, smoking status (defined as ≤10 pack-years), and tumor and nodal stage into three distinct clinical risk categories with progressively lower 3-year OS. Low-risk OPSCC comprises patients with HPV-positive tumors who are either nonsmokers with any stage disease or smokers with N0–N2a disease (3-year OS, 93%; 95% CI, 88.3–97.7). Intermediate risk includes patients with HPV-positive tumors who are smokers with N2b–N3 disease and patients with HPV-negative tumors and T2–T3 disease (3-year OS, 70.8%; 95% CI, 60.7–80.8); high risk includes patients with HPV-negative tumors who are either nonsmokers with T4 disease or smokers with any T or N stage (3-year OS, 46.2%; 95% CI, 34.7–57.5). Of note, this schema classifies HPV-OPSCC as low risk unless the patient is a smoker or has at least N2b nodal disease and classifies HPV-negative OPSCC as high risk unless the patient is a nonsmoker.[303] This analysis provides strong evidence for informing clinical trials designed to measure clinical progression and treatment response.

Nonmodifiable factors that may affect survival in HPV-OPSCC include sex and race. One study of patients with OPSCC, of whom only 12 were female, demonstrated female sex to be associated with worse prognosis independent of HPV tumor status and smoking.[326] Other studies have reported that positive HPV tumor status is associated with improved prognosis for males, but that HPV tumor status has no impact on survival for females.[330,378] Whether sex does in fact affect prognosis of patients with HPV-OPSCC requires continued investigation with analyses powered to detect sex-specific survival differences. Race, too, has emerged as a potential survival modifier for HNSCC, with some analyses demonstrating a dramatic survival difference with the mortality of black patients twice that of white patients.[333,379,380] However, this survival disparity may largely be explained by the higher prevalence of HPV-HNSCC in whites. When analyses exclude HPV-related malignancies, the survival difference is considerably attenuated.[333,380,381] Owing to the natural scarcity of black patients with HPV-positive disease, there is a paucity of literature comparing the survival of white and black patients with HPV-OPSCC, and efforts to investigate potential differences in epidemiology or tumor biology that could account for such unequal rates of HPV-positive disease by race should be strongly encouraged.

Therapeutic Considerations

Deintensification of Therapy

Although they are effective oncologic tools, it is well established that both chemotherapy and radiotherapy of the head and neck carry substantial morbidity with significant impact on quality-of-life measures. Chemotherapy, especially with platinum-based agents, risks systemic sequelae, such as renal, otologic, hematologic, neurologic, and gastrointestinal toxicities.[382] Radiation to the head and neck has been associated with high rates of dysphagia.[383,384] The risk of late-onset, severe dysphagia rises with increasing radiation dose, the volume of pharynx radiated, and the addition of concurrent chemotherapy.[385,386] One meta-analysis of three RTOG trials reported that 43% of patients treated with chemoradiation developed severe late toxicity, predominantly related to swallowing dysfunction.[385]

Because HPV-OPSCC has been consistently demonstrated to respond much better to treatment and its population has a demographic profile that is younger and has improved performance status compared with patients with HPV-negative OPSCC, treatment deintensification has emerged to lessen both acute toxicity and long-term sequelae with the hope of improving overall quality of life without compromising oncologic outcomes. Many single- and multi-institutional phase II and III trials investigating survival outcomes after attenuated doses of chemotherapy or radiation are ongoing, including trials investigating deintensification of therapy for advanced HPV-OPSCC cases.[387] The phase III RTOG 1016 trial is evaluating non-inferiority of cetuximab compared with cisplatin with concurrent standard-dose radiotherapy. The phase II ECOG 1308 trial will assess outcomes of reduced radiation dose when patients are treated with induction chemotherapy followed by a response-based dose of radiation. Transoral surgical approaches are also being explored in the context of therapeutic deintensification (see later discussion). Because therapy deintensification has the potential to compromise oncologic outcome, it is strongly recommended that it take place only under carefully designed, controlled clinical trials.[388]

Notably, with the exception of clinical trials, current OPSCC treatment guidelines do not change with HPV tumor status. Presently there are no additional treatment recommendations for patients with HPV-negative OPSCC despite clearly having a poorer prognosis.[388] A randomized phase II clinical trial (RTOG 1221) was initiated to assess survival in patients with HPV-negative OPSCC undergoing radiotherapy and cisplatin with or without transoral surgical resection; however, it was closed owing to low accrual.[389]

Primary Transoral Surgery

Though there are limited data that directly compare surgery and postoperative radiation with chemoradiation therapy for the initial treatment of patients with advanced stage OPSCC, concurrent chemotherapy has increasingly been favored by oncologists since the landmark Veterans Affairs trial.[390] Trials of patients with advanced-stage OPSCC demonstrate that patients treated with concurrent chemoradiation have 20% improvement in locoregional control and survival over patients who receive radiation alone, whose outcomes are historically comparable to those of surgery and postoperative radiation.[391–404] To date, these analyses have provided sufficient evidence to offer chemoradiation to patients with advanced stage OPSCC, despite the absence of randomized controlled trials comparing these two treatment modalities.

The emergence of alternatives to the traditional external, invasive surgical approaches, including transoral robotic surgery (TORS) and transoral laser microsurgery, have brought about a renewed interest in primary surgery concomitant with interest to deintensify therapy.[387] These newer techniques allow improved surgical access to anatomic sites of interest (e.g., base of tongue and tonsil) that are challenging to access without morbidity or external incisions. TORS is theorized to have advantages over radiation alone and chemotherapy, although these hypotheses have not been evaluated with prospective, long-term analyses. With initial surgical treatment for OPSCC, the need for adjuvant chemotherapy and radiation is determined by tumor stage, margin status of the resection, and the presence of nodal disease with extracapsular extension.[387,405] One case series of OSPCC patients receiving primary surgical treatment reported that criteria using these factors allowed 38% of patients to avoid chemotherapy and spared 11% of patients from receiving adjuvant chemoradiation.[406] Primary surgical treatment may also potentially allow attenuation of the volume and dose of radiation delivered to the pharyngeal constrictors and surrounding healthy aerodigestive tissue,[405] which could minimize the dysphagia and xerostomia that many patients experience after radiation therapy.[384] Prospective cooperative group clinical trials investigating the role of TORS in the treatment of OPSCC are currently under way.

Disease Progression

Despite clearly improved locoregional control with HPV-OPSCC, these improved outcomes were previously thought to not extend to distant recurrence.[303,304,329,407] However, RTOG 0522 demonstrated that p16 expression in patients with OPSCC is significantly associated with decreased distant metastasis at 5 years (HR 0.37; 95% CI, 0.18–0.76).[408] At the time of disease progression, there was previous thought that progression in HPV-OPSCC occurred in atypical sites and after longer intervals than with HPV-negative tumors.[409,410] However, recent data suggest that the distribution of disease recurrences is similar for HPV-OPSCC and HPV-negative OPSCC.[372] In addition, timing to recurrence was shown to be similar in clinical trials, but different in academic institutions.[372,410]

Salvage Surgery

Historically, it was thought that salvage was unlikely to be successful for OPSCC patients who experience tumor recurrence. These historic analyses demonstrate that for OSPCC overall, fewer than 20% of patients who experience recurrence are candidates for salvage surgery, which is associated with median survival of less than 1 year and an increased complication rate.[392,398,411–413] These previous analyses did not account for HPV tumor status. More recent analyses, however, have begun to challenge this belief. An analysis of patients with stage III or IV OPSCC enrolled into RTOG 0129 or RTOG 0522 demonstrated a reduced risk of death after disease progression with both p16-positive tumor status (HR 0.48; 95% CI, 0.31–0.74) and receipt of salvage surgery (HR 0.48; 95% CI, 0.27–0.84).[372] In a multi-institutional analysis of patients with recurrent OPSCC, Guo and colleagues reported surgical salvage to be independently associated with higher OS when compared with nonsurgical treatment for patients with both locoregional (aHR 0.15; 95% CI, 0.04–0.56) and distant metastatic (aHR 0.19; 95% CI, 0.05–0.75) disease recurrence. When stratifying patients by HPV tumor status, the survival advantage was even stronger for patients with HPV-negative disease.[410]

Preventive Implications

The observed epidemiology of OPSCC in the United States and around the world, as well as the dramatic reduction in cervical cancer after a successful public health campaign comprising Pap testing and HPV detection, highlights the question of prevention of this malignancy. The vaccine protecting against HPV has not been evaluated in the context of oral HPV infection. Primary prevention would be the ideal prevention mechanism at a population level, but prospective evaluation is needed. The data to date suggest that the vaccine may have efficacy in reducing oral HPV infection.[414,415] Another potential strategy is secondary prevention—that is, early detection of disease as was done with cervical Pap testing and HPV detection. An important limitation to developing an oropharyngeal Pap test equivalent is the absence of cytologic evidence of dysplasia among high-risk individuals.[414]

Future Directions

HPV-HSNCC is a growing epidemic with distinctive demographic profile, epidemiologic trends, and treatment response. The effects of sex and race on HPV-OSPCC prognosis await studies adequately powered to ascertain these differences. Efforts are under way to develop screening tools that can identify premalignant oropharyngeal lesions before malignant transformation. Whether and how the HPV vaccine will affect the epidemiology of oral HPV infection are unknown, though HPV-OPSCC incidence trends may improve if it does induce a similarly protective effect.[415,416] The etiology behind the improved response to treatment observed in HPV-OSPCC is an active area of research. With this younger, healthier population, head and neck oncologists must increasingly emphasize reduction of treatment-related morbidity while optimizing survival. The emergence of TORS and other advances in surgical technique may allow oncologists to better achieve this balance, and further research is required to delineate this role. Finally, immunologic or other therapies that exploit the unique pathophysiology underlying HPV-OPSCC is an exciting new chapter in therapy and has the promise to improve on observed outcomes.

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2

Cellular and Molecular Pathology

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The head and neck region is one of the most complex parts of the body, not only in its anatomy and function, but also because of the great variety of neoplasms it may host that can be daunting for even the most experienced pathologists. Some neoplasms are unique to this region, such as salivary gland neoplasms and odontogenic tumors, while others, such as melanoma, soft tissue and bone sarcomas, and hematologic malignancies, are not site specific. It is the task of the pathologist to provide accurate diagnoses to guide treatment and to assess prognosis. It is also the task of the clinician to understand the clinical implications of the ever-enlarging repertoire of diagnoses, and to make treatment decisions accordingly. Effective communication between pathologists and clinicians, especially for complex resection specimens, is thus not only helpful but is often essential.

Like all fields of medicine, the field of pathology is also rapidly evolving. The classification of neoplasms has been made more accurate by the aid of immunohistochemistry (IHC) and molecular studies. As new therapeutic modalities develop, such as targeted therapies and immunotherapies, the practice of pathology is also rapidly evolving to include novel biomarkers to aid patient selection.

This chapter focuses primarily on epithelial malignancies and their pathologic characters relevant to prognosis and treatment. The selected neoplasms are included either because of prevalence, aggressive biologic behavior, or the novelty of their characterization. Distinctive molecular characteristics of these head and neck neoplasms are also discussed. For a more comprehensive account of head and neck pathology, the readers are referred to head and neck pathology textbooks.[1,2]

Squamous Cell Carcinoma and Variants

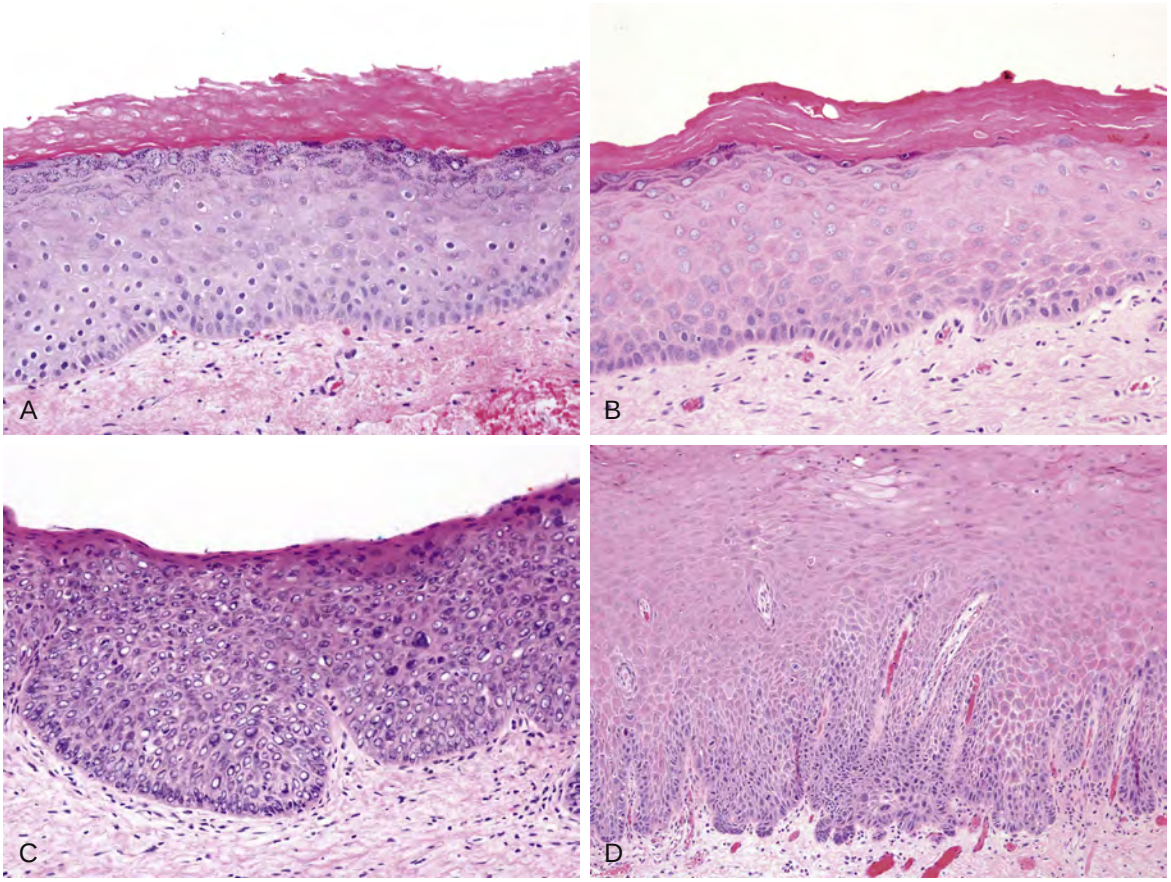
Squamous Dysplasia

Squamous dysplasia is a microscopic alteration of squamous epithelium conveying an increased risk of progression to squamous cell carcinoma. Squamous dysplasia may present as clinically identifiable lesions, allowing for early detection and surveillance. Macroscopic lesions that may harbor dysplasia include leukoplakia (white patch), erythroplakia (red patch) and speckled lesions. Erythroplakia and speckled lesions demonstrate a stronger association with microscopic dysplasia, compared to leukoplakia.

Microscopically, the dysplastic epithelium shows both cytologic and architectural atypia (Fig. 2.1). Variability of nuclear size and significantly enlarged nuclei are often seen. The nuclei may show irregular contour, with hyperchromatic coarse chromatin or vesicular chromatin. The keratinocytes show architectural disarrangement with irregular maturation. True dysplasia is sometimes difficult to distinguish from reactive atypia, especially when acute inflammation, ulceration, or infection is present.

In the head and neck region, keratinizing squamous dysplasia is the most common type of dysplasia. The grading system adopts the dysplasia grading scheme established in the nonkeratinizing epithelium of the lower genital tracts. As the dysplasia arises in the basal layer of the epithelium and extends, with progression, to the upper epithelial layers, the scheme classifies mild dysplasia as involvement of the lower third of the epithelium only, moderate dysplasia as extension to the middle third, and severe dysplasia as extension to the superficial third of the epithelium. Although this grading system works well for nonkeratinizing dysplasia, it appears to be somewhat problematic in keratinizing dysplasia. Unlike nonkeratinizing dysplasia, full-thickness involvement of epithelium by dysplasia is not required for invasion in keratinizing lesions (see Fig. 2.1D), as it is well known that invasive carcinoma may develop even when dysplasia is present only in basal layers. To properly convey the variable risk factors, practicing pathologists often grade dysplasia by incorporating both the degree of cytologic atypia and the architectural atypia in a conventional three-tier grading system, with the result being somewhat subjective, leading to moderate to poor inter- and intraobserver reproducibility.[3-5] A binary grading system distinguishing only low- and high-grade dysplasia shows more reproducibility compared to the three-tier grading and is therefore strongly advocated.[6,7]

Despite being an imperfect system, grading of dysplasia is currently the best predictor of cancer progression. Keratotic epithelium with dysplasia overall carries a 3 to 5 times increased risk of cancer development compared to keratosis with no dysplasia.[8] Severe dysplasia has approximately 30% risk of progression to cancer, compared to the 6% risk of progression seen for mild dysplasia. Mild dysplasia and even moderate dysplasia



• **Fig. 2.1** Squamous dysplasia. **A,** Benign keratosis. The squamous epithelium is thickened with a surface keratin layer (orthokeratosis). This lesion may present clinically as leukoplakia. The basal cells are regular in size and shape, and the keratinocytes show orderly maturation toward the epithelial surface. There is no morphologic evidence of dysplasia. **B,** Mild dysplasia. Cells in the basal layers are hyperchromatic and show irregularity in size and shape. The superficial portion of the epithelium still demonstrates maturation. Changes of mild dysplasia may be subtle, and distinguishing them from reactive changes can be subjective. **C,** Severe dysplasia. Marked nuclear size and shape variability is seen. There is also significant architectural disorder; the cells are haphazardly placed and demonstrate no maturation. **D,** This squamous epithelium shows dysplastic changes only in the basal portion, with intact surface maturation. However, the dysplastic cells are seen extending downward toward the stroma, making an attempt to invade. Frankly invasive carcinoma is seen adjacent to this area. Invasive carcinoma "dropping off" from basal layer without surface involvement is a well-known phenomenon in keratinizing squamous epithelium.

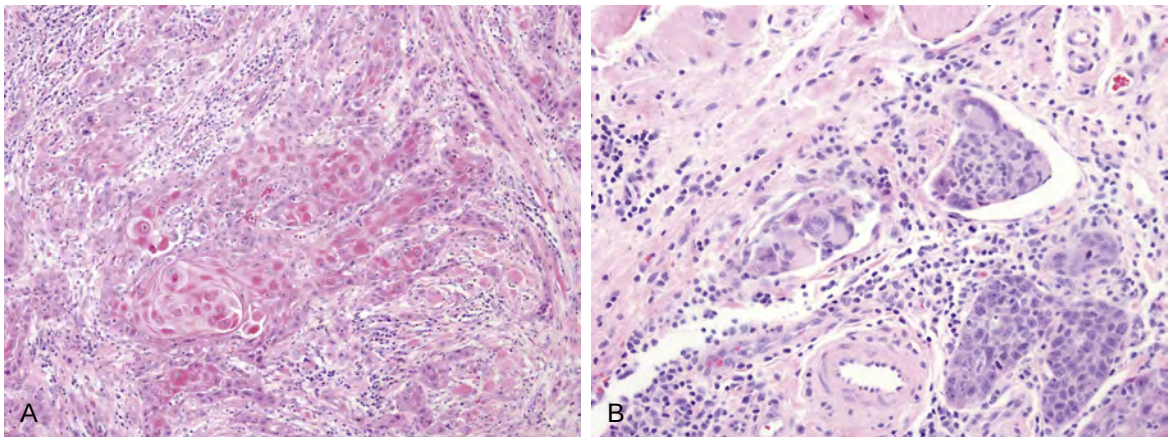
may sometimes regress. Other than morphologic evaluation, biomarkers for predicting cancer genesis of squamous epithelium have garnered significant research interest,[9,10] but none is currently conducive to clinical practice.

Conventional Squamous Cell Carcinoma

Conventional squamous cell carcinoma (SCC) is the most common malignancy in the head and neck region and the prototypical cancer type arising from keratinizing dysplasia (Fig. 2.2). Smoking and alcohol are major risk factors. Chewing betel nut is a major risk factor in the Southeast Asian population. Genetic factors may also play a role in carcinogenesis.

SCC is graded into well differentiated, moderately differentiated, and poorly differentiated by the degree of squamous differentiation. Well-differentiated carcinoma resembles its benign keratinizing epithelium counterpart, demonstrating prominent keratinization, keratin pearls, and intercellular bridging. Poorly differentiated carcinoma shows anaplasia, abundant mitosis, and rare or no keratinization. Occasionally, IHC markers (p63/p40 or keratin 5/6) are needed to confirm the presence of squamous differentiation. Tumor grading is not a major prognosticator but may have some prognostic value for earlier stage carcinomas.[11]

Essential parts of the pathology report for SCC resection specimens include TNM staging, margin status, and evaluation of other prognosticators, including lymphovascular invasion, perineural invasion, and extranodal extension of metastatic nodal disease. Synoptic reporting using a checklist template to ensure the inclusion of all the essential elements is currently the standard practice for resection of invasive cancer. Most of these elements are straightforward to evaluate, but controversies exist. Enface margins allow for assessment of a large margin area, but their use is restricted to situations where the margins are far away from the tumor, or for the purpose of intraoperative evaluation. Perpendicular margins are required to evaluate the distance of



• **Fig. 2.2** Conventional squamous cell carcinoma. **A,** Typical appearance of a squamous cell carcinoma showing infiltrative growth and abundant keratinization. **B,** Tumor cells are present in the lymphatic space in a carcinoma with only superficial infiltration of tumor nests. Despite the shallow depth of invasion, this tumor should not be classified as superficially invasive carcinoma.

tumor to margins, usually measured in millimeters. A margin of over 5 mm is commonly considered optimal for head and neck invasive SCC. Significant tissue shrinkage does occur in the resected specimens, and surgeons need to allow approximately 20–25% extra distance to achieve the desired pathology margins. Tumor thickness/depth of invasion is another critical parameter with some reporting variability. The current College of American Pathologists (CAP) guideline suggests reporting tumor thickness, using the distance from the tumor surface to the deepest point of invasion, excluding the surface keratin layer. On the other hand, the depth of invasion measures the distance of furthest invasion to the epithelial basement membrane. This measurement is sometimes difficult because of the frequent obliteration of basement membrane in the tumors, but may be more relevant to invasive behavior compared to tumor thickness. Perineural invasion as well as extranodal extension of the metastatic nodal disease have significant prognostic and therapeutic relevance and thus should be carefully assessed.

Superficially invasive carcinoma needs to be differentiated from severe dysplasia/carcinoma in situ and from deeply invasive carcinoma. Invasion may occur without full-thickness dysplasia. When invasion occurs, the invasive tumor nests are seen extending beyond the basement membrane, showing irregular borders and dyskeratosis. There is usually a stromal response, including inflammation and desmoplastic changes. Intrastromal isolated squamous cells and keratin granulomas are also signs of invasion. The definition of superficial invasion varies among authors, ranging from 2 to 5 mm from the basement membrane. The presence of lymphovascular invasion excludes a diagnosis of superficially invasive carcinoma regardless of the depth of invasion. Superficially invasive carcinoma clinically behaves similarly to carcinoma in situ and in general can be managed as such. Biologically, superficially invasive carcinoma has potential access to lymphovascular channels, so that metastasis can occasionally occur, most frequently in locations with abundant lymphatic supply, such as the supraglottic larynx.[12]

For early-stage cancers, pathology parameters are critical for decision making regarding elective nodal dissection and multimodality treatment. Tumor depth and grade are found to be two main prognostic factors for nodal metastasis. In one study, the authors found a cutoff value for depth of invasion at 2 mm, or 4 mm for the floor-of-mouth location, that separated patients with or without nodal metastasis.[13] Brandwein-Gensler and colleagues studied a large cohort of oral SCC patients for the significance of histologic parameters in local recurrence and overall survival.[14] Perineural invasion, lymphocyte infiltrate at the interface, and aggressive pattern of tumor invasion were found to be significant and independent predictors in early cancer. Brandwein-Gensler and colleagues proposed a risk model based on the histologic parameters, as a modification of previous models proposed by Jakobsson and Bryne.[15,16] The risk model aims to identify a high-risk group among early cancer patients for multi-modality treatment, in addition to traditional factors such as high tumor stage, perineural invasion, and inadequate margins. The model is being validated by independent groups and may have prognostic value,[14,17] but it is labor intensive and not yet widely used in pathology practice.

Overall survival most closely correlates with TNM tumor staging. Major prognostic factors include presence of locoregional metastasis, vascular or lymphatic invasion, positive surgical margins, and extracapsular spread of tumor cells from involved lymph nodes into the adjacent soft tissue of the neck.[18] Also, synchronous and metachronous secondary cancers are a significant threat to disease survival, as surviving patients have a 3–7% risk per year of developing a second cancer,[19-21] arising from clonally independent cells affected by field cancerization.[20,21]

Human Papillomavirus–Associated Head and Neck Squamous Cell Carcinoma

In recent decades, human papillomavirus (HPV) has become a major risk factor for head and neck squamous cell carcinomas (HNSCCs), with the oropharynx (base of tongue and palatine tonsil) being the most common site, comprising about 70%

of oropharyngeal SCC (OPSCC) in North America.[22-24] The rapidly rising incidence of HPV-HNSCC has changed the demographics of HNSCC,[23] and its incidence has surpassed that of cervical cancer in the United States. HPV-HNSCC tends to occur in white patients who are 4 to 10 years younger than HPV-negative HNSCC patients. The tumor afflicts men more often, correlating with a significantly higher prevalence of oral high-risk HPV infection in men.[24] This patient population also reports higher income and educational status and is more likely to be married and show fewer comorbid illnesses compared to the HPV-negative patients.[23] Known risk factors include a history of oral sex, a high number of lifetime sexual partners, younger age of sexual debut, oral HPV infection, and a history of marijuana use.[23] HPV-related HNSCC has a different mechanism of tumorigenesis, and its biologic behavior is distinct from that of conventional SCC. In OPSCC, HPV status is the single most significant prognostic factor for better outcomes.[25] In a retrospective study cohort at Mayo Clinic, the disease-specific survival (DSS) and recurrence-free survival rates were 100% and 90.9% at 3 years.[25,26] Because of the excellent therapeutic response, multiple clinical trials are underway evaluating the de-escalation of treatment for HPV-related OPSCC in order to minimize side effects and toxicity.

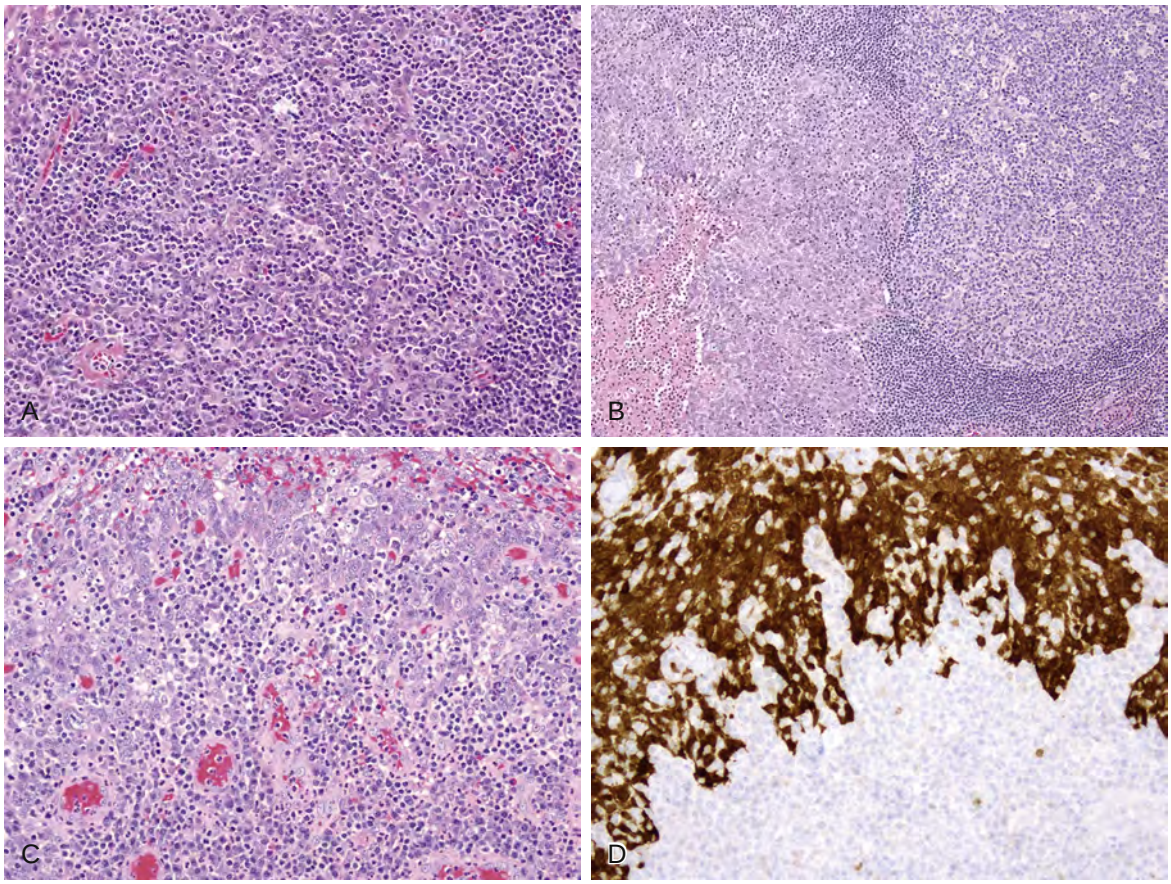
HPV-associated OPSCC often metastasizes early when the primary tumor is small, and a significant subset of patients present with a nodal metastatic neck mass from an unknown primary site. Microscopically, the tumor typically shows nonkeratinizing basaloid cells with hyperchromatic nuclei and scant cytoplasm (Fig. 2.3). The cells often grow in solid nests, cords, or trabeculae, without significant desmoplastic stromal response. Single-cell apoptosis and sometimes comedo-type necrosis can be seen. Keratinization may be present and is usually focal and abrupt, although rarely the tumor may also appear as a keratinizing SCC. Some morphologic features overlap with those of basaloid SCC in other head and neck sites but are not associated with aggressive behavior. The tumor often shows cystic features in nodal metastases and sometimes simulates a possible branchial cleft cyst in the neck area. Such tumors should be treated as metastatic SCC rather than malignant transformation of branchial cleft cysts, as the latter is at best exceedingly rare and of debatable existence.

In the past, HPV-HNSCC has been commonly graded as poorly differentiated because of the lack of keratinizing differentiation. Grading of HPV-HNSCC has, however, no prognostic significance and therefore is no longer recommended. It is hypothesized that HPV-HNSCC arises from the nonkeratinizing crypt epithelium of the tonsil and the grading scheme for keratinizing type SCC simply does not apply. The lymphoepithelium in the oropharyngeal area lacks basement membrane and has an abundant supply of lymphatic channels; thus even intraepithelial tumor carries a metastatic potential. It is recommended that all primary tumors be regarded as invasive carcinoma, regardless of whether histologic features of invasion are seen. Unlike the equivalent HPV-associated carcinoma in the cervix where Pap smears are effective for surveillance of premalignancy, premalignant stages of HPV-associated OPSCC have not yet been identified.

The current guidelines (Cancer Care Ontario Recommendations, last reviewed October 2014, and CAP 2016) recommend all adult OPSCC to be routinely tested for HPV status. Neck nodal tissue harboring metastatic SCC of unknown primary should also be routinely tested for HPV status, and positive HPV is strongly suggestive of oropharyngeal primaries. Multiple testing modalities exist, including p16 IHC, in situ hybridization of viral DNA or RNA, polymerase chain reaction (PCR) for viral DNA, or rt-PCR for viral RNA. HPV in situ hybridization for DNA and p16 IHC are currently the most widely used tests. As a surrogate marker, p16 IHC has a sensitivity approaching 100%, but relatively lower specificity, especially for non-oropharyngeal tumors. In situ hybridization has high specificity, approaching 100%, but is slightly less sensitive than p16 IHC. PCR for HPV DNA is very sensitive but tends to have more false-positive cases and should be avoided as the sole testing method. P16 IHC is accepted as the initial testing method. Further testing by validated PCR or in situ hybridization for high-risk HPV is needed when p16 IHC yields an equivocal result. Validation is also warranted when a tumor shows atypical morphology for HPV-HNHCC, such as extensive keratinization. P16 IHC is considered positive only if the staining is strong and diffuse, and with both nuclear and cytoplasmic staining. At least 70–75% of cells need to be positive,[27] with most cases in practice showing staining in virtually all the cells. Focal or weak staining should be interpreted as a negative result. P16 staining may be useful also for cytology specimens.[28] However, interpretation needs to be applied with caution, especially when the sample amount is limited, as there is no official guideline on how to determine positivity.

HPV involvement is also seen in some SCC of non-oropharyngeal sites, including about 20–25% of sinonasal tumors and 3–5% of tumors from the oral cavity, larynx, and nasopharynx.[29-36] HPV is implicated in some distinctive tumor types, such as papillary SCC. A newly discovered rare SCC variant, HPV-related carcinoma with adenoid cystic like features, is a sinonasal carcinoma with favorable prognosis.[37] HPV is also associated with Epstein-Barr virus (EBV)-negative nasopharyngeal carcinoma and conveys a prognosis similar to that for the EBV-positive group. For tumor sites with low HPV prevalence, p16 IHC lacks specificity and is not a satisfactory surrogate marker for HPV infection.[38] In addition, there is no evidence that HPV-HNSCC in non-oropharyngeal sites shows significant prognostic differences compared to the HPV-negative counterparts.[39] Apart from the specific HPV-related morphologic variants, routine testing for HPV status on non-oropharyngeal tumors is not encouraged.

Despite favorable prognosis for most HPV-OPSCC, a small subset of tumors show a highly aggressive behavior.[40] Some of these aggressive SCCs contain a small cell carcinoma component. HPV-associated small cell carcinoma retains its aggressive behavior,[41,42] and such patients should not be considered for de-escalation therapy. There is an ongoing research effort aiming to identify reliable markers to identify other subgroups of HPV-HNSCC with aggressive behavior. Clinically, HPV-HNSCC in smokers has intermediate risk compared to conventional SCC and HPV-HNSCC with no smoking history.



• **Fig. 2.3** Human papillomavirus (HPV)–associated squamous cell carcinoma. **A,** Benign squamous epithelium of deep tonsil crypts shows no distinctive basement membrane and a close association with lymphoid tissue. Squamous epithelium here lacks keratinization and has a basaloid appearance. **B,** Squamous cell carcinoma is seen at the bottom left, with focal necrosis. A germinal follicle is seen at the upper right corner and may show similar appearance to nonkeratinizing carcinoma, especially on frozen section slides with cautery artifact. **C,** Nonkeratinizing carcinoma is seen in the top half of the picture, showing a close association with lymphoid tissue. The tumor cells are larger than normal and have increased mitotic activity, but the overall morphologic appearance is not distinctive from benign epithelium in **A**. **D,** A p16 immunostain highlights HPV-associated carcinoma and can be used as a detective tool to identify carcinoma in difficult cases.

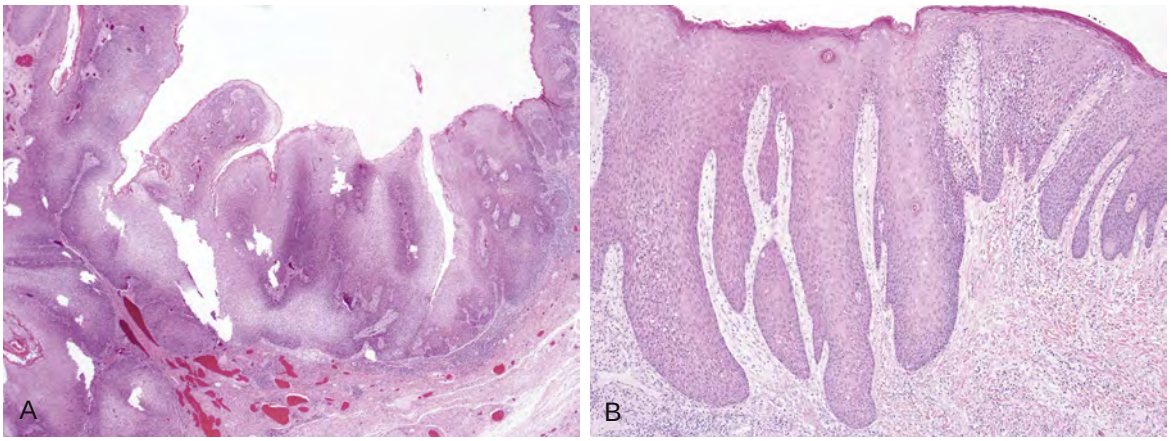
Verrucous Carcinoma

Verrucous carcinoma (VC) is a warty variant of well-differentiated SCC that is non-metastasizing and shows excellent prognosis. It usually affects older people and is most commonly seen in the oral cavity and larynx. VC presents as slow-growing and well-circumscribed, thick, broad-based firm masses with a papillary or warty appearance. VC is strongly associated with smoking and smokeless tobacco. Association with HPV infection in the past had been controversial and is not supported by recent studies.[43,44]

Microscopically, VC shows a warty or papillary architecture, with well-differentiated epithelium demonstrating no or minimal cytologic atypia (Fig. 2.4). Abundant surface keratosis is characteristic. Mitoses are infrequent and only observed in the basal or suprabasal layers. The rete ridges of the carcinoma are broad-based and push into the underlying stroma, lacking an infiltrative growth pattern. The underlying stroma commonly shows prominent lymphoplasmacytic inflammation. By definition, there is no perineural or lymphovascular invasion. The diagnosis of VC is extremely difficult on small biopsies because of the lack of cytologic atypia. Clinical presentation is often more impressive than the histologic appearance, and clinicopathologic correlation, therefore, can be quite useful. The best area to biopsy is the transition between the normal background mucosa and the carcinoma. A deep biopsy at this location helps to demonstrate the downward-pushing pattern beyond the adjacent normal epithelial-stromal border.

VC can be locally aggressive and destructive but has no metastatic potential. Areas of conventional infiltrative SCC may be seen, sometimes very focally, in a VC-like lesion. It is important to identify these areas because of their potential to metastasize. Instead of being diagnosed as VC, these tumors should be classified as SCC, SCC with verrucous features, or hybrid VC/SCC and managed similarly to conventional SCC.

Differential diagnosis includes papillary SCC, verruca vulgaris, squamous papilloma, and verrucous hyperplasia. The lack of significant cytologic dysplasia distinguishes VC from



• **Fig. 2.4** Verrucous carcinoma. **A,** This low-power view of verrucous carcinoma shows a warty squamous proliferation with intact maturation. A downward-pushing growth pattern is seen, but no infiltrating carcinoma is present. Some lymphocytic response is present in the adjacent stroma. A superficial biopsy of this tumor will closely resemble benign hyperplasia. **B,** At the junction of verrucous carcinoma and benign mucosa, the rete ridges of verrucous carcinoma *(left)* are seen extending deeper, beyond those of the adjacent benign mucosa *(right).*

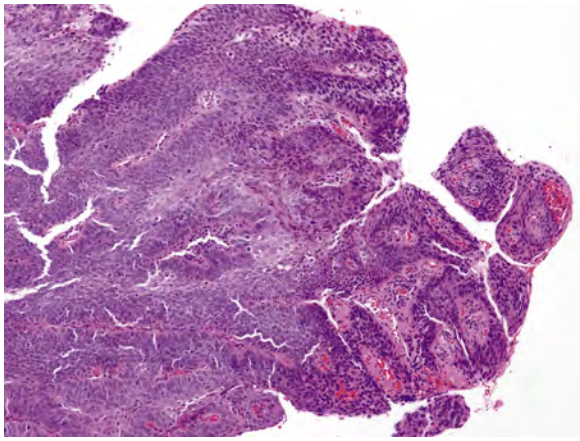
exophytic or papillary SCC. Differentiation from benign lesions is more problematic. A biopsy of VC may appear entirely benign on histology. Adequate tissue sampling with the demonstration of a pushing invasive pattern is essential to distinguish VC from verrucous hyperplasia. Verruca vulgaris shows a more prominent granular cell layer. Squamous papilloma shows a more complex architecture and lacks the bulbous rete ridges of VC.

Surgical resection of the lesion with clear margins is the preferred treatment modality and, if achieved, results in an excellent prognosis.[45] VC may recur locally if incompletely excised.

Papillary Squamous Cell Carcinoma

Papillary squamous cell carcinoma (PSCC) is an uncommon variant of SCC with a favorable outcome. It is most often seen in the larynx and the hypopharynx, but it may also occur in other head and neck regions. It affects predominantly male patients in the sixth and seventh decades. Smoking and alcohol are known risk factors. Approximately 30% of non-oropharyngeal tumors are HPV-related,[46,47] and the figure goes higher in OPSCC.[46,48] PSCC usually develops de novo, and malignant transformation from papilloma rarely occurs. Clinically, PSCC presents as a soft, friable, exophytic or papillary tumor. Common presenting symptoms include hoarseness, airway obstruction, and dysphagia.

Microscopically, PSCC shows well-formed papillary structures with thin fibrovascular cores (Fig. 2.5). The lining epithelium shows marked atypia resembling those of severe dysplasia/carcinoma in situ in the flat epithelium. Cells are usually basaloid, and keratinization is uncommon. Foci of necrosis and hemorrhage are frequently present. Noninvasive components predominate in PSCC. Stromal invasion, if seen, is usually superficial. Invasion is identified only in a small percentage of biopsies[47] and consists of single cells or small infiltrative nests. Regardless of whether the stromal invasion is identified



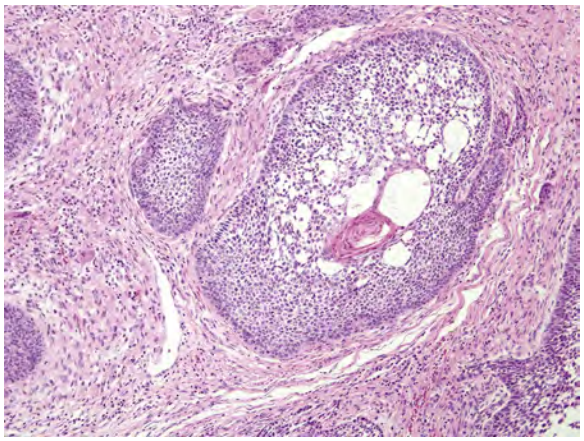
• **Fig. 2.5** Papillary squamous cell carcinoma. The tumor shows complex papillary architecture lined by nonkeratinizing squamous epithelium. Unlike verrucous carcinoma, significant dysplastic changes are present in the lining epithelium, resembling carcinoma in situ. Even though no stromal invasion is seen, this tumor should be regarded as invasive rather than in situ carcinoma.

histologically, the complex architecture of PSCC by itself is considered invasive and associated with basement membrane disruption. The differential diagnosis includes squamous papilloma and verrucous carcinoma.

PSCC usually presents at a low clinical stage, and the prognosis is favorable, likely due to a paucity of invasive components.[49,50] HPV-related tumors show a trend toward better survival.[48] Nodal metastasis may be seen in a small percentage of cases.[47] Complete excision of the lesion with follow-up is adequate treatment for most cases.

Basaloid Squamous Cell Carcinoma

Basaloid squamous cell carcinoma (BSCC) is a rare, aggressive variant of high-grade squamous cell carcinoma that occurs in various anatomic sites. This variant has a predilection for the



• **Fig. 2.6** Basaloid squamous cell carcinoma (SCC). Infiltrative tumor nests are seen composed of basaloid cells with peripheral palisading. Focal abrupt keratinization is present in one large tumor nest. The appearance is similar to some human papillomavirus (HPV)-associated SCC in the oropharynx.

base of tongue, supraglottic larynx, and pyriform sinus. Like SCC in general, BSCC affects mostly older patients, with a male predominance. Smoking and alcohol abuse are strong risk factors. BSCC commonly presents at an advanced clinical stage and shows frequent regional lymph node (64%) and distant (44%) metastasis.[51] Clinically, BSCC may show prominent deep and lateral submucosal soft tissue infiltration, mimicking a salivary gland or soft tissue tumor.[52]

By definition, the tumor is biphasic and composed of both basaloid and squamous components (Fig. 2.6). The basal cells are densely packed small cells with hyperchromatic nuclei and scant cytoplasm, and they tend to show nuclear palisading at the periphery. The cells are often set in a hyalinized, basement membrane–like stroma. The cells classically grow in a solid pattern with a lobular configuration. Other growth patterns include cribriform, pseudoglandular, and trabecular patterns. Comedo-type necrosis is frequently present, especially in large cell nests. Unlike other SCC variants, microcystic structures can be seen containing PAS and Alcian blue positive material. The squamous cell component shows individual cell keratinization, intercellular bridging, and keratin pearl formation. The SCC component can be either in situ or invasive, in the superficial portion of the tumor or within the basaloid tumor islands. Transitions between the two components are usually abrupt. The biphasic pattern is often retained in metastasis, but either component may metastasize alone.

Diagnosis may be difficult on small biopsies, especially when only one component is present. For difficult cases, IHC may be helpful to differentiate BSCC from other morphologically similar lesions, such as adenoid cystic carcinoma (AdCC). AdCC does not show squamous differentiation and shows both myoepithelial and ductal differentiation by IHC.

BSCC often presents at advanced clinical stages. The prognosis may be worse compared to conventional SCC even when matched stage for stage.[53,54] In recent years, many groups have reported that a large percentage of oropharyngeal BSCCs are HPV related and show better prognoses than the conventional SCC.[55-57] Fritsch and colleagues analyzed large population-based data using the Surveillance, Epidemiology, and End Results Program (SEER) database and concluded that BSCCs behave worse than conventional SCCs in the larynx but better in the oropharynx.[58-60] This is likely due to a large amount of HPV-associated cancers in the oropharyngeal site being reported as BSCC because of their overlapping morphologic features.

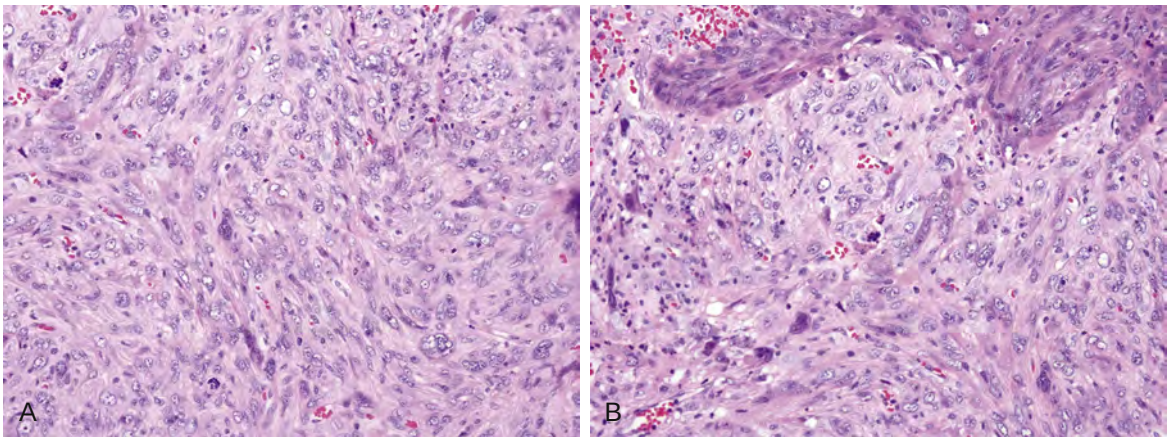
Spindle Cell Squamous Cell Carcinoma

Spindle cell SCC is a biphasic tumor with both a conventional SCC component and a malignant spindle cell component mimicking a mesenchymal malignancy. The spindle cell component usually predominates, and the conventional SCC may be difficult to identify. Alternative names for this variant include sarcomatoid carcinoma, carcinosarcoma, collision tumor, and pseudosarcoma. Instead of true collision tumors, the mesenchymal and SCC components are proven to be clonally related, with evidence supporting the evolution of the sarcomatoid component from the epithelial component.[61] The tumors may be seen in any site of the upper aerodigestive tract, with the larynx being the most common location, especially in the glottic area. Spindle cell SCC often presents as an exophytic, polypoid or pedunculated mass. An ulcerated lesion with infiltrative growth may also be seen. Metastases to the cervical nodes may show either an epithelial component or a spindle cell component, or both.

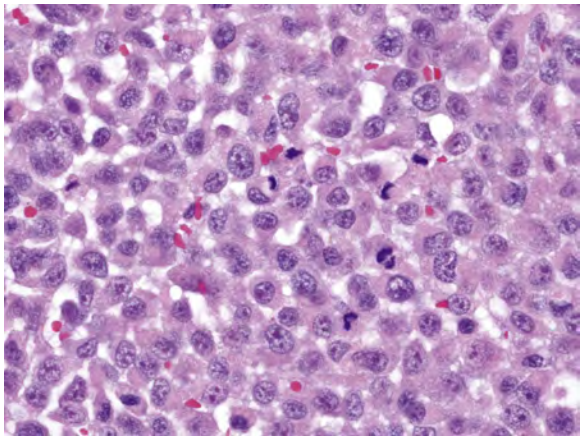
Histologically, the conventional SCC component could be in situ or invasive. The spindle cell component may show various growth patterns. The cells are pleomorphic with hyperchromatic or vesicular nuclei and are mitotically active. The appearances most often resemble high-grade fibrosarcoma, but may also show chondroid, osseous, or muscle differentiation (Fig. 2.7). The two components often abut directly against each other, but a gradual transition may also be seen.[62] By IHC, most tumors show focal staining of epithelial markers in the spindle cell component. The spindle cells also express vimentin and may be positive for other mesenchymal markers, including smooth muscle actin, desmin, and S100.[62]

The diagnosis is relatively straightforward when both the conventional SCC and sarcomatous components are identified, as long as the sarcomatous component can be differentiated from reactive stromal cell atypia. The diagnosis can be difficult when only a spindle cell component is present. IHC for pancytokeratins and p63/p40 may highlight the cells and support a diagnosis of spindle cell SCC. Up to a third of tumors show no evidence of epithelial differentiation even by IHC. A definitive diagnosis of spindle cell SCC may be difficult for such cases, but a spindle cell carcinoma is still favored in the correct clinical setting.

The prognosis depends on the tumor stage and tumor site. Polypoid tumors show better prognosis than infiltrative tumors. Tumors arising in the glottis show a better prognosis than non-glottic tumors (5-year DSS of 84.0% vs. 51.9%).[63] T1 glottic tumors can be cured by polypectomy alone. In the oral cavity and oropharynx, the prognosis for spindle cell SCC is worse compared with conventional SCC.[64]



• **Fig. 2.7** Spindle cell squamous cell carcinoma (SCC). **A,** This tumor shows a malignant spindle cell proliferation with pleomorphic nuclei, resembling a high-grade sarcoma morphologically, and may lose all the epithelial markers on immunohistochemistry. **B,** A component of conventional SCC is present in the upper right corner, confirming that the tumor is indeed a spindle cell SCC.



• **Fig. 2.8** Sinonasal undifferentiated carcinoma. Sheets of neoplastic cells are seen showing robust mitotic activities. There is no glandular or squamous differentiation. Immunohistochemistry is needed to confirm the epithelial origin and to rule out other non-epithelial malignancies.

Sinonasal and Nasopharyngeal Neoplasms

Sinonasal Undifferentiated Carcinoma

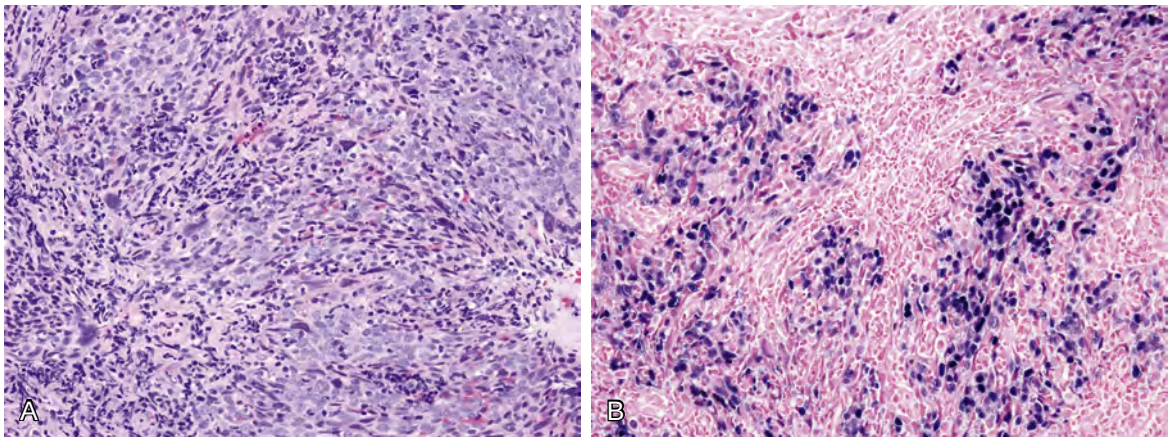
Sinonasal undifferentiated carcinoma (SNUC) is a rare, clinicopathologically distinctive carcinoma affecting adults with a broad age range. There is a male predominance of 3:1. Pathologically, it is a high-grade malignant epithelial neoplasm that displays neither squamous nor glandular differentiation. Clinically, it shows a locally aggressive and destructive tumor with a rapid clinical onset (weeks to months). The latter feature is a helpful diagnostic clue. SNUC is likely a heterogeneous entity. Recently, two new cancer entities have been defined that were previously classified under the SNUC umbrella, thanks to their unique molecular alterations. These two cancers, INI-1 deficient carcinoma of the sinonasal tract[65] and NUT midline carcinoma,[66] comprise approximately 15–20% of previously diagnosed SNUCs.

As the name implies, SNUC displays undifferentiated cells with a high nuclear to cytoplasmic ratio, coarse chromatin, and often prominent nucleoli (Fig. 2.8). The cells can be monomorphic or pleomorphic, with medium to large nuclei. Growth pattern varies, and the cells may form solid sheets, nests, ribbons, or trabeculae. SNUC often demonstrates easily detectable mitoses, extensive vascular invasion, and involvement of mucosal glands. In situ carcinoma may be present. Immunohistochemically, the tumor cells are positive for pancytokeratins, CK8 and sometimes keratin 7 (50% of cases), and negative for keratin 5/6 and p40. Mucin stains are negative. EBV is absent. Tumor cells may rarely express neuroendocrine markers such as chromogranin and synaptophysin. SNUC should be differentiated from other specific (differentiated) carcinomas including poorly differentiated SCC or adenocarcinoma, undifferentiated nasopharyngeal carcinoma, and neuroendocrine carcinomas, as well as non-epithelial tumors with epithelioid cells.

The standard treatment is aggressive multimodality therapy. Most tumors present at T4 stage, and complete local resection is difficult to achieve. The prognosis is very poor, although survival has been improved over the years with combined therapy.[67,68] Recently, Gray ST. et al. reviewed 19 SNUCs and found a high prevalence of p16 positivity (78.6%) and HPV DNA (64.3%) by PCR.[69] This was higher than the previously reported rates of 10–34.5% p16 positivity and 6.5% HPV DNA positivity. Interestingly, the p16-positive cohort showed a significantly better outcome with a 5-year overall survival of 61.9% compared to 0% for the p16-negative cases, suggesting that p16 IHC may serve as a useful prognostic marker, a surprising finding in need of independent confirmation in additional studies.

Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma (NPC) is a type of squamous cell carcinoma arising in the nasopharyngeal mucosa. There is a strong association with EBV infection (Fig. 2.9). HPV is a contributing factor in EBV-negative tumors. Other contributing factors include race, genetics, and environmental agents. NPC shows a striking geographic distribution and is common



• **Fig. 2.9** Nasopharyngeal carcinoma. **A,** An example of nonkeratinizing nasopharyngeal carcinoma showing basaloid neoplastic cells intermixed with abundant lymphocytes. **B,** Nonkeratinizing nasopharyngeal carcinoma is strongly associated with Epstein-Barr virus (EBV) infection. In situ hybridization of EBV-encoded RNA (EBER) is positive in neoplastic cells with an intranuclear distribution.

in southern China, Southeast Asia, and Northern Africa. The incidence in the non-Asian population in the United States is low. NPC is seen over a wide age range, and there is a 2–3:1 male predominance. The most common presentation is enlargement of unilateral or bilateral upper cervical lymph node. Half of patients have nasal symptoms including epistaxis, nasal obstruction, and discharge.

NPC is divided into two major categories: keratinizing squamous cell carcinoma and nonkeratinizing carcinoma. The latter is further divided into differentiated and undifferentiated types. Carcinoma with associated lymphoid stroma (lymphoepithelioma) is considered a variant of nonkeratinizing undifferentiated carcinoma. It is not uncommon to see mixed morphologic features, and in such a case, the tumor is classified based on the predominant type. The keratinizing type is similar to conventional SCC of the other head and neck sites and is more likely to be seen in non-Asians. Smoking is a risk factor for this type, and the association with EBV is weak. The keratinizing type is a more aggressive subtype, is less frequently metastatic (30%), is not radiosensitive, and has a 5-year survival of 40%. The two nonkeratinizing subtypes, differentiated and undifferentiated, have overlapping histologic features, with the subclassification failing to convey significant survival or therapeutic differences. The nonkeratinizing types have the propensity to metastasize, are radiosensitive, and have a 5-year survival of approximately 60%.[70]

Histologically, the keratinizing NPC is morphologically similar to conventional SCC of other sites, demonstrating intercellular bridges and keratinization. The nonkeratinizing differentiated subtype shows distinct cell borders and evidence of maturation within the tumor cords. This subtype mimics the morphologic appearance of transitional cell carcinoma. The nonkeratinizing undifferentiated subtype shows a syncytial growth pattern with indistinct cell borders. The cells are larger, with scant cytoplasm, vesicular nuclei, and prominent nucleoli. The nonkeratinizing subtypes evoke no desmoplastic response to tumor invasion. One diagnostic pitfall is that the tumor cells may be rather inconspicuous in the background of lymphoid stroma and sometimes may mimic germinal center cells. Both keratin IHC and EBV in situ hybridization can help highlight these tumor cells.

The clinical stage is the most important prognostic factor in NPC. Nonkeratinizing NPCs are radiosensitive, and radiotherapy has been the staple of therapy. The keratinized type is less sensitive to radiation and may require surgical resection. Concurrent chemoradiotherapy improves outcome and decreases the incidence of metastasis.[71,72]

Salivary Gland Neoplasms

Salivary gland neoplasms are overall uncommon but consist of more than 30 recognized benign and malignant entities. The small sample size poses a challenge to defining tumor grading criteria and finding prognostically significant morphologic traits. Many of the salivary gland malignancies are not graded, and the individual diagnosis by itself indicates low- or high-risk clinical behavior (Table 2.1). However, if high-grade transformation is seen in a low-risk tumor, the information needs to be clearly conveyed in the pathology report. Two carcinomas that need to be graded are mucoepidermoid carcinoma (MEC) and adenoid cystic carcinoma, and their tumor grade is both prognostically and therapeutically relevant.

There is significant morphologic overlap between different salivary gland neoplasms, both cytologically and architecturally, creating a diagnostic challenge. In addition, many low-grade salivary gland malignancies are separated from their benign counterparts by their invasive behavior, which may be only focally present and not seen on small biopsy specimens. A definitive diagnosis may not be possible on biopsies or cytology specimens. Nonetheless, these specimens are helpful in separating high-grade malignancies from low-grade and benign neoplasms, providing initial critical information for subsequent treatment.

The outcome largely depends on tumor type, grade, and stage and the primary site. Tumors arising in the parotid and submandibular glands tend to behave better than those arising

TABLE 2.1 Risk Stratification of Salivary Gland Malignancies (85)

Low Risk	High Risk
Acinic cell carcinoma	Sebaceous carcinoma and lymphadenocarcinoma
Low-grade mucoepidermoid carcinoma*	High-grade mucoepidermoid carcinoma*
Epithelial-myoepithelial carcinoma	Adenoid cystic carcinoma†
Polymorphous low-grade adenocarcinoma	Mucinous adenocarcinoma
Clear cell carcinoma	Squamous cell carcinoma
Basal cell adenocarcinoma	Small cell carcinoma
Low-grade salivary duct carcinoma (low-grade cribriform cystadenocarcinoma)	Large cell carcinoma
	Lymphoepithelial carcinoma
Myoepithelial carcinoma	Metastasizing pleomorphic adenoma
Oncocytic carcinoma	Carcinoma ex pleomorphic adenoma (widely invasive or high-grade histology)
Carcinoma ex-pleomorphic adenoma (intracapsular/minimally invasive or with low-grade histology)	Carcinosarcoma
Sialoblastoma	Adenocarcinoma and cystadenocarcinoma, NOS, high grade*
Adenocarcinoma NOS and cystadenocarcinoma, low grade*	

*Intermediategrade variants of these tumors are controversial in the assignment of risk. For mucoepidermoid carcinoma this may depend on grading scheme used. For adenocarcinoma NOS, there is little data, but what is present suggests that intermediate grade should be placed in the high risk group.
†Adenoid cystic carcinomas are all considered high risk in terms of local recurrence, but only solid adenoid cystic carcinoma (ie, high pattern grade) is considered high risk for nodal metastasis.
NOS, Not otherwise specified.
From Seethala RR. An update on grading of salivary gland carcinomas. *Head Neck Pathol*. 2009;3(1):69–77.

in the sublingual and minor salivary glands. Treatment of salivary gland tumor is based on a combination of the histologic type and clinical stage.

Pleomorphic Adenoma and Carcinoma Ex-pleomorphic Adenoma

Pleomorphic adenoma (PA) is the most common salivary gland tumor. It most frequently occurs in the superficial lobe of the parotid gland, presenting as a solitary, slow-growing, painless mass. It may also arise in minor salivary glands throughout the head and neck region. In the major salivary glands, PA usually is well circumscribed and encapsulated. PA arising in minor salivary glands lacks encapsulation. Microscopically, PA characteristically displays vast morphologic diversity. Tumors are composed of epithelial and myoepithelial cells with significant variability in the proportion of the associated mesenchymal components. Cellular PA may contain a minimal amount of distinctive chondromyxoid stroma, mimicking myoepithelial neoplasms, adenoid cystic carcinoma, or epithelial-myoepithelial carcinoma, especially on biopsies.

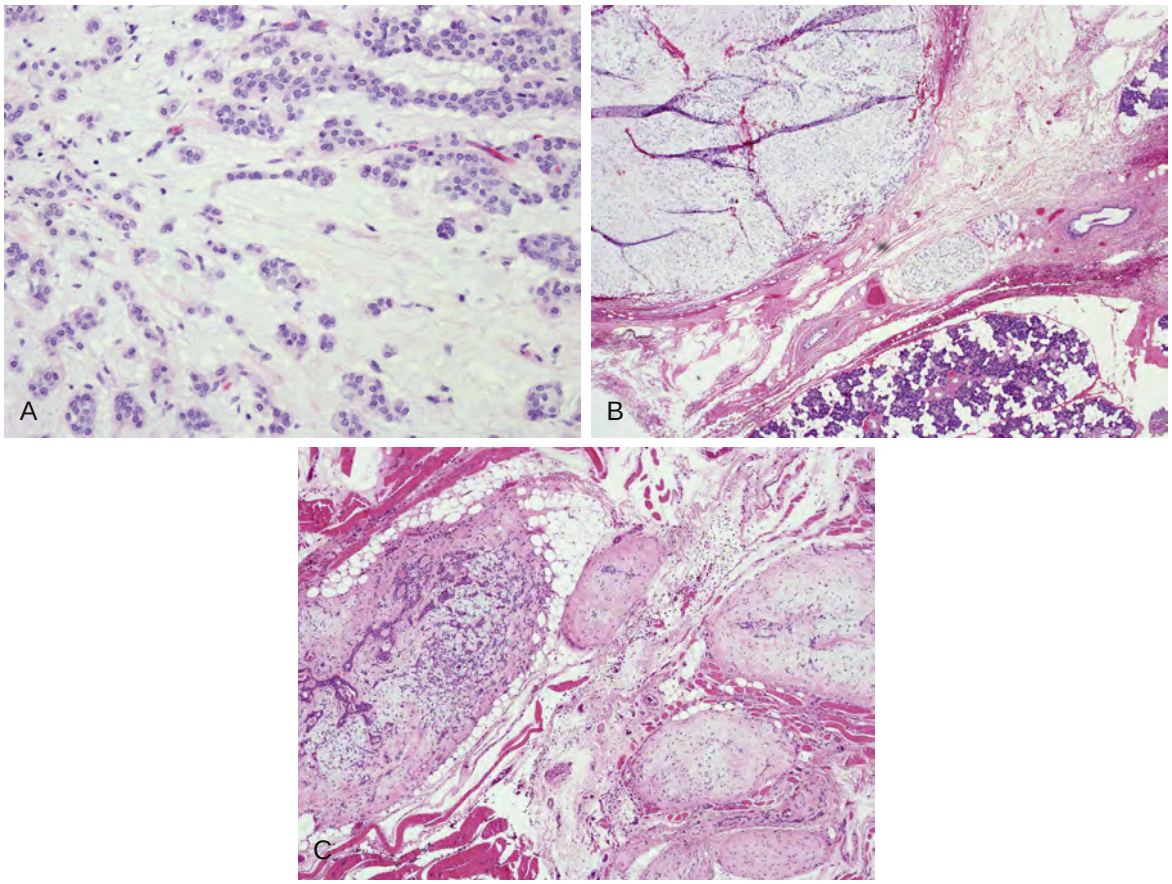
Although macroscopically encapsulated, PA frequently shows incomplete capsule, capsule penetration, pseudopodia, or satellite nodules microscopically[73,74] (Fig. 2.10). As a result, an enucleation procedure may leave tumor tissue behind and carries a significant risk of recurrence. Recurrent tumor tends to be multinodular, and the subsequent risk of secondary recurrence is higher than for primary PA.[75,76] Intravascular tumors are present in a small percentage of PAs and do not appear to affect the overall outcome or cause metastasis. Metastasizing PA does, however, occur sometimes, often developing after multiple local recurrences. Metastasizing PA is histologically benign but shows a malignant clinical behavior and may result in death.

Malignant transformation involves approximately 6% of PA, often presenting as a rapid growth of a long-standing mass. Based on the extent of invasion, carcinoma ex PA is classified as intracapsular carcinoma, minimally invasive (≤1.5 mm from capsule) carcinoma, and invasive carcinoma. Tumors belonging to the prior two categories show indolent behavior similar to benign PA. Most of the invasive carcinomas ex-PA are high-grade malignancies with aggressive behavior. Salivary duct carcinoma is the most frequent malignancy, but any type of salivary gland carcinoma may arise in a preexisting PA. Low-grade varieties make up approximately 15% of total cases and show relatively indolent behavior.[77] Given the prognostic and therapeutic implications, both histologic type and extent of carcinoma should be reported for carcinoma ex-PA.

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (AdCC) is a slow-growing salivary gland malignancy seen most often in the parotid gland, submandibular gland, and minor salivary glands. It is the most common malignancy in the submandibular gland. Although AdCC shows an initially indolent course, it is considered a high-grade neoplasm because of its protracted clinical course and frequent late recurrence/metastasis, resulting in dismal long-term survival. AdCC is also known for the tendency to invade nerves. Pain may develop before a tumor mass is evident and is a common and important diagnostic clue.

Although AdCC may appear grossly well circumscribed, microscopically this is a highly infiltrative tumor. AdCC consists of two cell populations, basaloid ductal and myoepithelial cells. The cells are monomorphic with hyperchromatic angulated nuclei and scant cytoplasm and are organized into three defined growth patterns: tubular, cribriform, and solid. The tubular pattern shows well-formed bilayered ducts and tubules. The cribriform pattern is the classic pattern for AdCC, showing "Swiss cheese"–like tumor islands with punched-out spaces



• **Fig. 2.10** Pleomorphic adenoma. **A,** An area of pleomorphic adenoma showing nests of epithelial cells in a background of myxoid stroma. Although pleomorphic adenoma shows significant morphologic pleomorphism, the epithelial cells are consistently bland and benign appearing. **B,** A well-circumscribed pleomorphic adenoma *(upper left)* arising in the parotid gland *(lower right).* Two small satellite nodules are seen away from the main tumor. A resection close to the tumor capsule will create a negative-appearing margin but leave tumor tissue behind. **C,** Recurrent pleomorphic adenoma tends to be multinodular. Numerous tumor nodules are seen here scattered in adipose tissue and skeletal muscle.

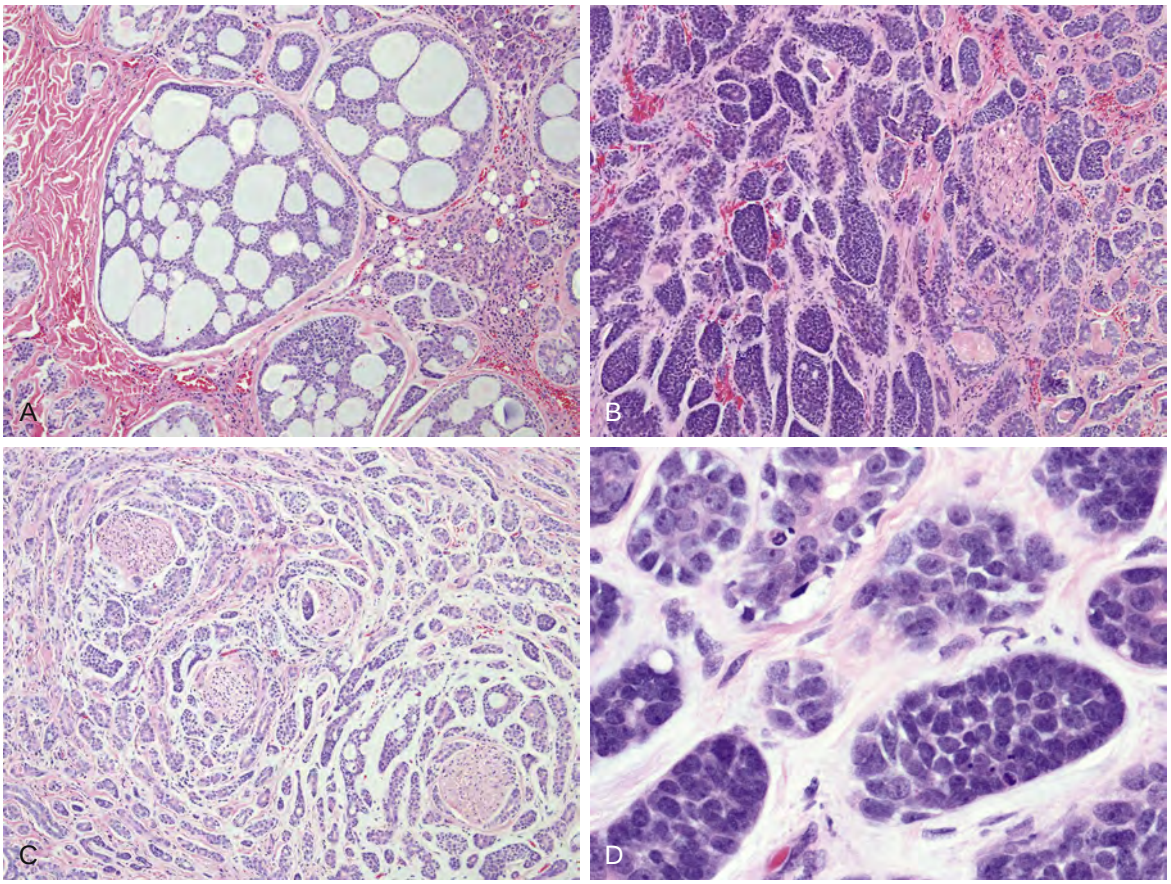
containing mucoid or myxoid material (Fig. 2.11). The solid pattern shows sheets or islands of tumor cells with no tubular or microcystic formation, and it may also have increased mitosis and focal necrosis. A mixture of these patterns is frequently present, and tumors are graded according to the dominant component. Increased percentage of solid pattern is associated with a poor outcome, and a 30% solid component is typically used as a cutoff for high-grade tumors.

The diagnosis can often be made by the characteristic histologic appearance alone, although this may be difficult for small samples and often impossible on cytology specimens. The characteristic cribriform pattern may also be seen in other salivary gland tumors, including pleomorphic low-grade carcinoma, basal cell adenoma/carcinoma, and pleomorphic adenoma.

The standard treatment is radical excision with negative margins and radiotherapy. A true negative margin is difficult to achieve, given the tendency of tumor to grow along the nerves. Frozen section of the nerve tissue often requires many levels or even exhausting of the tissue, as perineural tumor growth may appear discontinuous. It is often not practical to chase the perineural tumor, considering the high morbidity that may ensue. Also, the efficacy of radiotherapy is debatable and difficult to evaluate because of a combination of low incidence and protracted clinical course. Neck dissection is performed only for clinically positive nodes, because the frequency of occult nodal metastasis is low relative to the rate of distal metastasis. Recently, some authors proposed neck dissection due to a reported positive nodal rate of 10–15%,[78,79] but the long-term benefit of the procedure is still debatable. Recent treatment modalities, molecular targets, and ongoing clinical trials have been reviewed.[80,81]

Acinic Cell Carcinoma

Acinic cell carcinoma (ACC) is a low-grade malignant salivary gland tumor showing serous type acinar differentiation. The tumor has a wide age range distribution and is the second most common malignant salivary gland tumor in the pediatric age group. Three percent of ACC occurs bilaterally. ACC typically presents as a slow-growing tumor, with or without pain, and is not fixed to the surrounding tissue. Most ACCs arise in the parotid glands, with a small percentage arising in minor salivary glands. The incidence in the submandibular glands and sublingual glands is low. Many non-parotid tumors previously



• **Fig. 2.11** Adenoid cystic carcinoma. **A,** The classic "Swiss cheese" appearance of adenoid cystic carcinoma showing cribriform architecture with punched-out spaces containing mucoid material. This cribriform pattern is intermediate grade regarding biologic aggressiveness. **B,** Solid growth pattern with nests and islands of basaloid cells and no or minimal glandular spaces. This is the aggressive pattern, and the carcinoma is classified as high grade when the solid pattern represents more than 30% of the tumor. **C,** Extensive perineural infiltration is seen and is characteristic of adenoid cystic carcinoma. **D,** High-power view of adenoid cystic carcinoma with solid growth pattern. The cells are basaloid, hyperchromatic, and monomorphic. Scattered single-cell apoptosis is present.

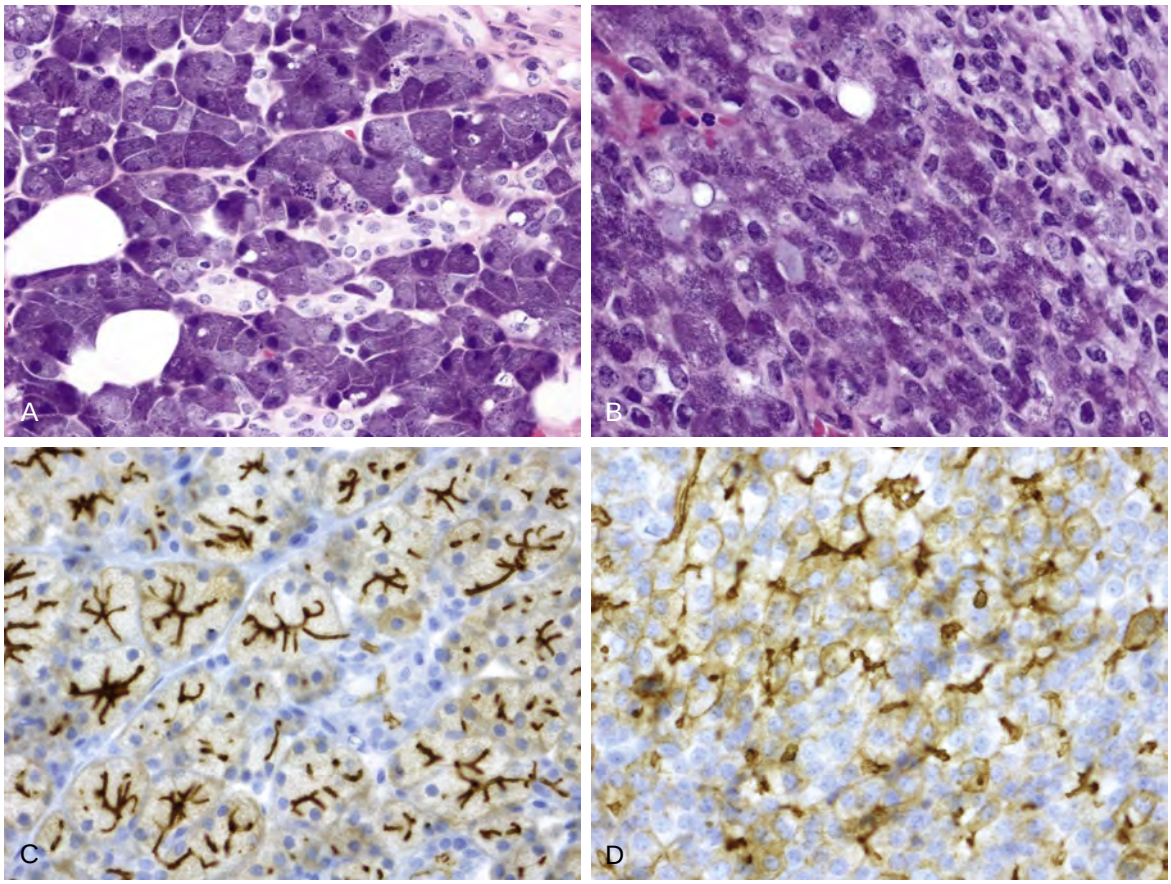
classified as ACC are found to represent secretory carcinoma, a recently defined ACC mimic.[82]

The histologic appearance of ACC is highly variable, with diverse growth patterns and cell types. Common growth patterns include solid, microcystic, papillary-cystic, and follicular. The characteristic cells are the acinar cells with low nuclear-to-cytoplasmic ratio and basophilic cytoplasmic zymogen granules (Fig. 2.12). Intercalated duct cells, clear cells, and vacuolated cells can also be seen but contain no mucin. When the acinar cells are not apparently present, a PAS with diastase stain may be used to highlight the cytoplasmic granules. Two relatively recently developed immunostains, discovered on GIST 1 (DOG-1) and sox-10, have been found to be useful for diagnosing ACC, with DOG-1 being more specific for the acinar cell differentiation. There is no benign counterpart for acinic cell carcinoma, and a diagnosis can be made in well-circumscribed and sometimes encapsulated tumors. The differential diagnosis includes benign salivary gland acinar tissue, which can be problematic in fine-needle aspiration and small biopsies. The key diagnostic morphologic feature in this situation is that ACC lacks the normal ductal cells that are seen in benign salivary gland aspirates and biopsies. Another diagnostic pitfall of ACC is that the tumor may sometimes show abundant lymphoid infiltrates, and this should not be interpreted as metastasis in a lymph node. On the contrary, such tumors are shown to have a relatively indolent behavior.

Complete surgical resection is the treatment of choice. Nodal dissection is not indicated unless nodal metastasis is present. Radiotherapy is controversial and is sometimes used for control of local disease. Up to one third of cases may recur locally, and the metastasis rate, including nodal and distal, is approximately 10–15%. The outcome is determined by tumor staging rather than histologic features. Tumors arising in minor salivary glands are typically less aggressive.

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC) is the most common salivary gland malignancy in both adults and children. It occurs in both major and minor salivary glands and often presents as a slow-growing asymptomatic mass. Clinically, it may mimic a pleomorphic adenoma in major glands or a mucocele in minor



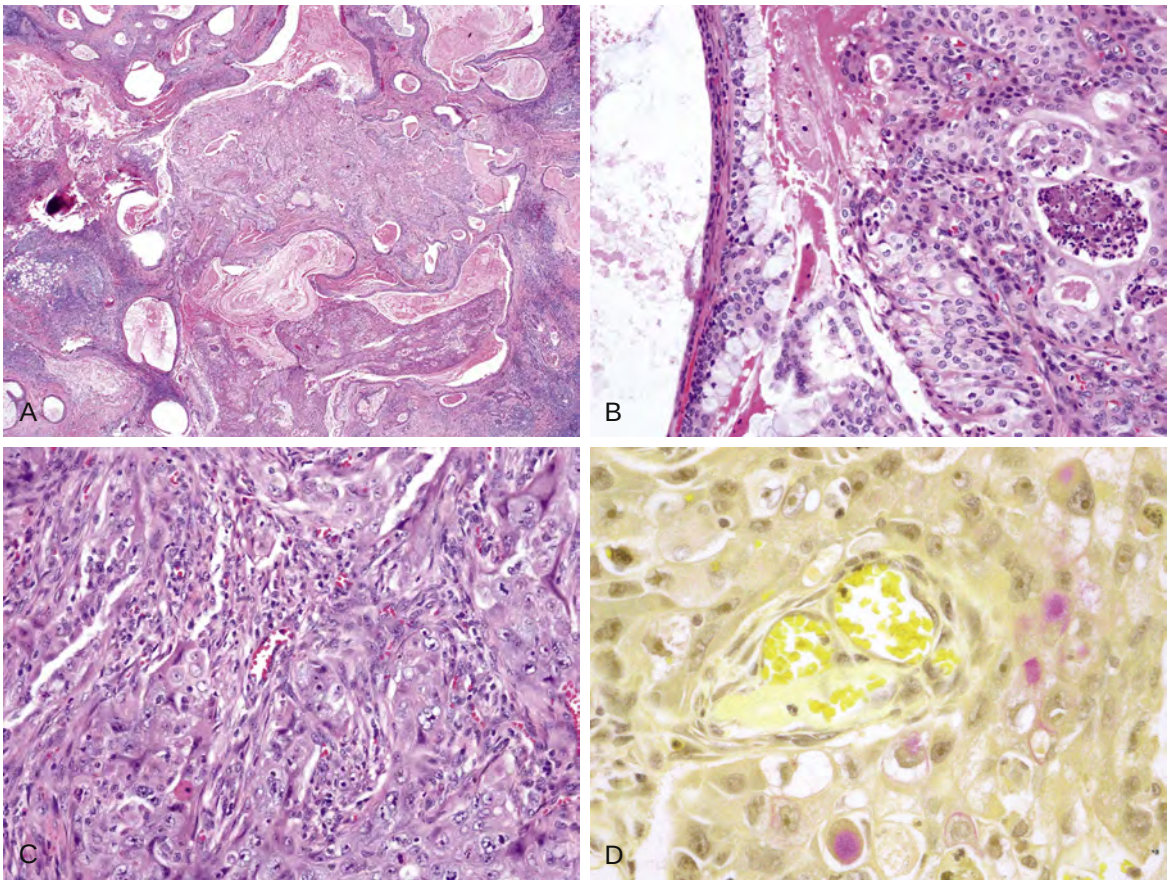
• **Fig. 2.12** Acinic cell carcinoma. **A,** Benign parotid gland showing dark-staining serous acini and scattered benign ducts. **B,** Acinic cell carcinoma showing dark-staining cells with a serous appearance. The characteristic cytoplasmic zymogen granules are conspicuous in this case even on the hematoxylin and eosin stain. **C,** An immunostain for Dog-1 is specific for acinar differentiation and highlights the luminal borders of the serous acini in the benign salivary tissue. **D,** The Dog-1 immunostain in an acinic cell carcinoma recapitulates the apical/luminal staining pattern of serous acini.

salivary glands with a bluish cystic appearance. Pain is unusual but may be seen in high-grade tumors. Radiation exposure is a known etiologic factor.

Microscopically, three major cellular components are present in varying proportions: mucous cells, epidermoid cells, and intermediate cells. The mucous cells contain intracellular mucin, which can be highlighted by a mucicarmine stain (Fig. 2.13). The epidermoid cells show abundant eosinophilic cytoplasm and occasional keratin production. Significant keratin pearl formation, however, is not a feature of MEC. Intermediate cells are frequently the most abundant cell type and may appear as small basophilic cells or clear cells. They are believed to be the precursor cells that may differentiate into either mucous or epidermoid cells. As a result, three cell types are intimately associated with each other. This feature may be useful in distinguishing MEC from adenosquamous carcinoma, which shows distinctive areas of glandular and squamous differentiation. Association with lymphoid infiltrate is common and is not to be confused with metastatic tumor in lymph nodes.

Tumor grading is a major prognostic indicator for MEC and important for treatment decisions. Whereas surgical resection is usually sufficient for low-grade tumors, high-grade tumors require tumor resection, radiation, and neck dissection. Management for intermediate-grade tumor is controversial. Tumor grading is based on cystic components, neural invasion, mitotic activity, necrosis, and cellular atypia. There are multiple grading schemes, but as yet no uniformly accepted grading system. The two currently most recognized grading methods are AFIP and Brandwein. When the clinical outcome is examined, the AFIP system appears to downgrade tumors and risks undertreatment, whereas the Brandwein system appears to upgrade tumors and risks overtreatment.[83] These grading systems are cumbersome, are difficult to apply, and lack interpersonal consensus.[84] As a result, many pathologists frequently use an intuitive grading without well-defined criteria, defining predominantly cystic ones as low-grade tumors, and those with necrosis, increased mitoses, and significant atypia as high grade. A standard scheme is still recommended for more objectivity.[85]

The clinical course is highly variable depending on the tumor grade, site, clinical stage, and adequacy of surgery. Radiation therapy has little overall impact on survival but is appropriate for high-grade tumors or tumors with positive margins. It should be noted that MEC arising in the submandibular gland have an aggressive behavior regardless of grade and should be treated accordingly.



• **Fig. 2.13** Mucoepidermoid carcinoma. **A,** A representative section of low-grade mucoepidermoid carcinoma showing prominent cystic configuration. The lining cells are a mixture of mucous cells, epidermoid cells, and intermediate cells. **B,** A high-grade mucoepidermoid carcinoma is morphologically similar to squamous cell carcinoma, although no overt keratinization should be seen. **C,** Mucous cells are infrequent, and special stains are sometimes needed to identify them. **D,** A mucicarmine stain highlights intracellular mucin (*pink* globules) in mucous cells of this high-grade mucoepidermoid carcinoma.

Salivary Duct Carcinoma

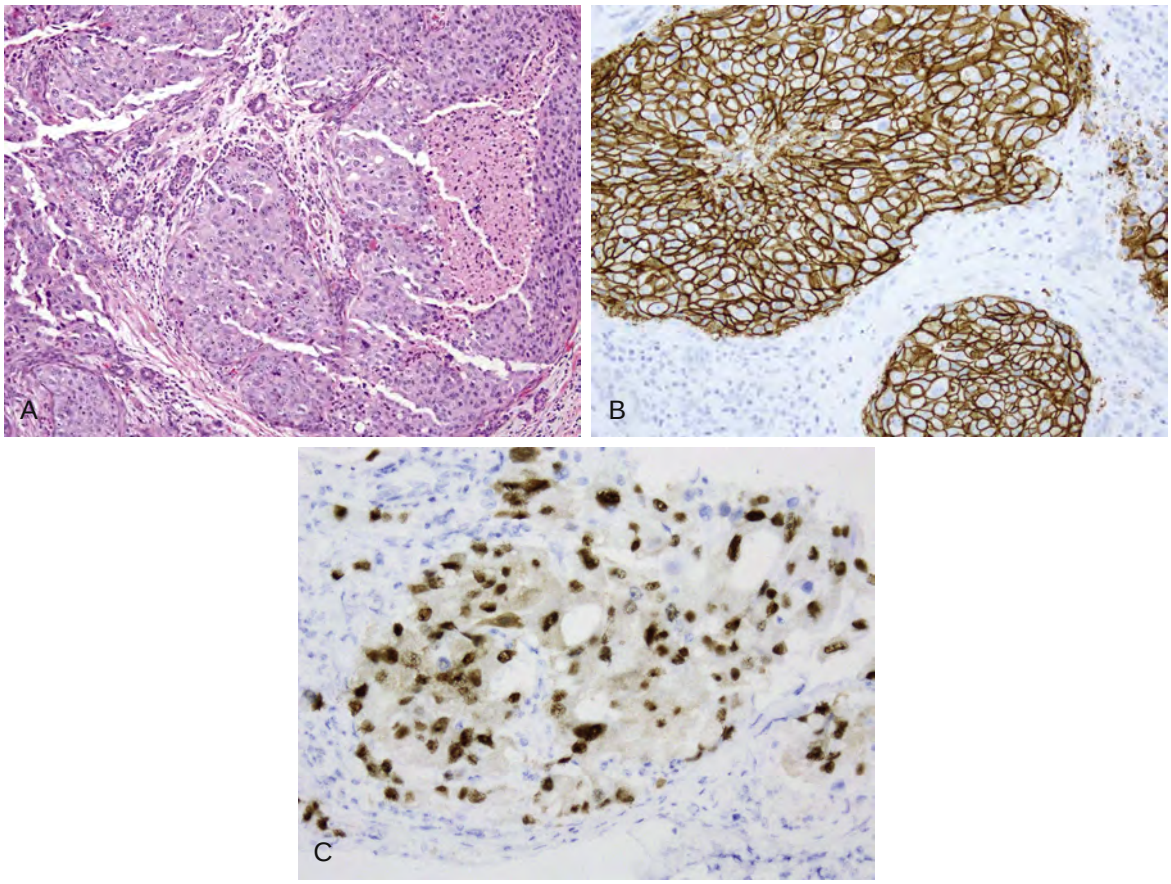
Salivary duct carcinoma (SDC) is one of the most aggressive high-grade salivary gland cancers. The tumor has been underrecognized in the past and has often been labeled as adenocarcinoma not otherwise specified (NOS). Making the diagnosis today is more clinically relevant as it carries potential therapeutic implications.[86] SDC typically presents as a fast-growing tumor of a major salivary gland, especially the parotid gland, and frequently involves the facial nerve.[87] SDC may arise de novo as well as in a previously existing PA.[88] Men are affected more often, with a 4:1 men-to-women ratio.

The typical histology is that of high-grade adenocarcinoma similar to ductal carcinoma of the breast (Fig. 2.14). Both intraductal and invasive components may be seen.[87] The cells show large nuclei with prominent nucleoli and eosinophilic cytoplasm. Necrosis is commonly present. The intraductal component may show cribriform architecture and comedo-type necrosis, similar to ductal carcinoma in situ of the breast. Perineural and lymphovascular invasion is common. Less common morphologic variants are also reported, including papillary, micropapillary, mucin-rich, sarcomatoid, and oncocytic, as well as pure in situ carcinoma without invasion.[87] On IHC, the carcinoma expresses high- and low-molecular-weight keratins and is negative for myoepithelial markers. Various markers of breast carcinoma may stain positive in SDC, such as gross cystic disease fluid protein (GCDFP-15) (>80%). Unlike most breast carcinomas, SDC is estrogen-receptor and progesterone-receptor negative. The vast majority of cases are androgen-receptor positive.[89,90]

The prognosis is poor, with the 5-year survival ranging from 35–64%.[91-94] Nodal and distant metastases are common. Nodal metastasis is common even for tumors at the early T stage.[95] Of SDCs, 15–30% show increased *HER2* expression[96-100] and are potential responders to target therapy with trastuzumab (Herceptin). An early result of clinical trials shows promising therapeutic response,[101-104] and *HER2* testing is recommended for SDC. Androgen receptor antagonist has also been proposed as a potential therapeutic agent, given the widespread expression of androgen receptors in these tumors,[105,106] and clinical trials are ongoing.

Newly Defined Head and Neck Neoplasms

Tumor morphology has been the basis of disease classification for neoplastic lesions, and historically new entities were often rare tumors. With molecular tools, more and more tumors are now being redefined by their distinct molecular signatures. Tumor classification serves as a basis for further investigation, but it



• **Fig. 2.14** Salivary duct carcinoma. **A,** The carcinoma shows an appearance of high-grade adenocarcinoma similar to some breast carcinomas. Compared to the small benign ducts in the center, the carcinoma cells are significantly larger, with open chromatin, conspicuous nucleoli, and frequent mitoses. The large tumor island to the right shows comedo-type tumor necrosis. **B,** An immunostain for Her-2 is positive in the tumor with strong membranous staining. Treatment of such tumors using trastuzumab (Herceptin) is experimental. **C,** An immunostain for androgen receptor shows nuclear staining in tumor cells. A vast majority of salivary duct carcinomas express androgen receptor.

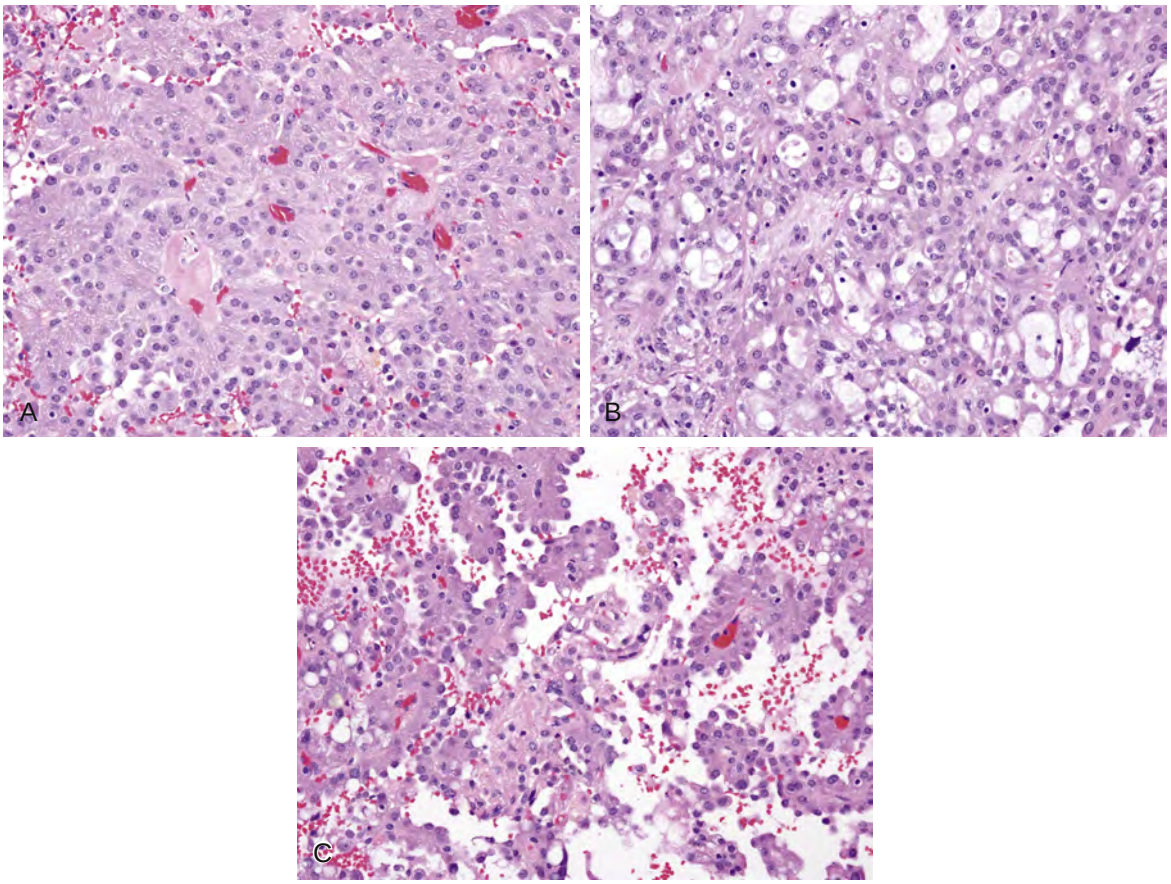
is only meaningful if the diagnoses indicate defined biologic behavior and treatment options. Here we discuss a few recently recognized head and neck malignancies. Some are known by their unique genetic alterations; others are found to have different behavior from the parental group due to a viral association. Standard treatment guidelines are not yet available. Recognizing these new entities is mostly for the prognostic purpose currently, although understanding molecular pathways of these tumors may provide targets for future alternative therapies.

Secretory Carcinoma

Secretory carcinoma (previously known as mammary analog secretory carcinoma) is a salivary gland carcinoma first described in 2010 as a tumor reminiscent of secretory carcinoma of the breast.[107] Secretory carcinoma not only shares similar morphologic and immunohistochemical properties with the breast equivalent, but also carries the same characteristic *ETV6* gene arrangement. Secretory carcinoma most frequently arises in the parotid glands, but it may also be seen in minor salivary glands. There is a strong male predominance.

Morphologically, the tumor shows a lobulated growth pattern composed of bland eosinophilic cells forming microcystic or small glandular spaces (Fig. 2.15). Prominent hobnailing is sometimes seen in cells lining the cystic spaces. Rarely, tumor cells may show intracellular mucin, mimicking MEC. In the past, this tumor was most often classified as acinic cell carcinoma, adenocarcinoma, or low-grade cystadenocarcinoma. Although secretory carcinoma does show some morphologic similarity to acinic cell carcinoma, true zymogen granules are not present. Immunostains are a useful tool to differentiate secretory carcinoma from other mimickers. Secretory carcinoma is typically positive for epithelial markers, vimentin, S100, mammaglobin, and other breast markers.[107,108] For difficult cases, fluorescence in situ hybridization (FISH) for *ETV6* gene rearrangements can confirm the diagnosis. Retrospectively, many of the prior diagnosed zymogen-poor acinic cell carcinoma and most of the non-parotid "acinic cell carcinoma" represent misclassified secretory carcinomas.[82,109]

Secretory carcinoma is considered a low-grade salivary malignancy, although there is a potential for high-grade transformation. Approximately 20% of cases develop nodal metastasis, and a small percentage of patients die from the disease. Overall, secretory carcinoma has a slightly poorer prognosis compared to acinic cell carcinoma.[107,109,110]



• **Fig. 2.15** Secretory carcinoma. **A,** A secretory carcinoma demonstrating monomorphic cells with low-grade cytologic appearance. The tumor morphology is similar to acinic cell carcinoma, but the cells do not contain true zymogen granules. **B,** A different area of the same tumor showing microcystic architectural configuration. Eosinophilic secretions can be seen in the luminal spaces. **C,** Another area in the same tumor showing a papillary configuration and lining cells with a hobnail appearance.

NUT Midline Carcinoma

NUT midline carcinoma is a rare and highly aggressive variant of SCC that occurs in all age groups. The median survival is 6.7 months, and the tumor is not responsive to conventional chemotherapy.[111] The tumor is defined by rearrangement of the nuclear protein in testis (*NUT*) gene, often by forming a *BRD4-NUT* or *BRD3-NUT* fusion oncogene. This tumor is underdiagnosed because of a lack of specific morphologic features, as the diagnostic molecular tests are often not performed. Of NUT midline carcinomas, 35% arise in the head and neck region near the midline. The diagnosis is important because of the presence of emerging NUT-targeting drugs that may affect the clinical course.[112]

Morphologically, NUT midline carcinoma shows small to medium monotonous cells with high nuclear-to-cytoplasmic ratio. One characteristic finding is focal and abrupt squamous differentiation, as gradual squamous differentiation is not present in NUT midline carcinoma. The key for correct diagnosis is a high suspicion when SNUC or poorly differentiated carcinoma with the above features are seen. A FISH test for *NUT* gene rearrangement has shown high sensitivity and specificity.[113] A more practical NUT antibody for IHC is also available and has been reported to show 87% sensitivity and 100% specificity.[114] Although the incidence of NUT carcinoma has increased annually because of increasing awareness, it is still fortunately a rare tumor. In a retrospective analysis of primary sinonasal carcinomas,[115] only 2% turned out to be NUT midline carcinomas. Two of these were previously classified as SNUC, comprising 15% of SNUC in the studied cohort.

There is no standard therapy. Retrospective study shows that surgical resection and radiotherapy independently improve survival,[111] whereas chemotherapy does not. There are reports showing a temporary response to aggressive chemotherapy, but tumors usually relapse quickly.[116,117] Targeted drugs are currently undergoing clinical trials (clinicaltrials.gov).

HPV-Related Carcinoma With Adenoid-Cystic–Like Features

HPV-related carcinoma with AdCC-like features is an HPV-related carcinoma that shows peculiar morphologic features resembling AdCC of the salivary glands.[118] It occurs more often in women than men and may involve the nasal cavity as well as paranasal sinuses. HPV 33, the most frequently

involved HPV type, is not present in most commercially available HPV testing menus. Morphologically, the tumor shows features similar to AdCC, with basaloid cells forming solid and cribriform architecture. There is often a lobular or nested growth pattern. Both myoepithelial and ductal cells are present, with ductal differentiation typically a minor component. Unlike AdCC, in situ surface squamous dysplasia is often present. The tumor also lacks the MYB gene rearrangement frequently seen in AdCC. P16 IHC is a sensitive surrogate marker for HPV involvement in this tumor but is not entirely specific. Currently, the tumor appears to be unique for the sinonasal area, as AdCC studied in other areas of head and neck does not show HPV involvement.[119]

The reported tumors were treated by surgery with or without postoperative radiotherapy or chemoradiation therapy. Limited follow-up data are available with a median follow-up length of 15 months.[37] The prognosis is favorable, with all reported patients being alive at follow-up, although some had already developed recurrent disease.

INI-1 Deficient Sinonasal Carcinoma

INI-1 (SMARCB1) deficiency has been implicated in a variety of carcinomas and sarcomas and was recently found to be also present in some sinonasal carcinomas. By IHC, loss of INI-1 expression is identified in 6% of sinonasal carcinomas.[65] The tumors were previously classified as non-keratinizing SCC, SNUC, non-intestinal adenocarcinoma, and carcinoma, NOS. Tumor cells commonly show a characteristic rhabdoid morphology. Most cases demonstrate an aggressive clinical course. INI-1 deficiency is a potential target for future therapy.

Staging of Head and Neck Cancer

The American Joint Committee on Cancer (AJCC) TNM system is the most widely adopted scheme for pathologic cancer staging. The most recent 2017 edition (8th edition)[120] will be implemented beginning January 1, 2018. The 8th edition has made significant changes to the AJCC TNM staging 7th edition for the head and neck cancers, with the aim of achieving better and more reproducible discrimination of stage groups. Major changes include a newly added TNM staging algorithm for nasopharyngeal cancer and HPV-associated OPSCC, in recognition of their unique biology and etiology. The new edition also recognize cutaneous malignancies of the head and neck as a distinctive group, now separated from cutaneous malignancies of other sites. Major modifications have been made to the staging of oral cancer, with the depth of invasion used as an additional T (primary tumor) characteristic and with extranodal extension (ENE) introduced as a novel N (lymph node) feature. Pathologic ENE is further divided into microscopic ENE (≤2 mm, ENEmi) and gross ENE (>2 mm, ENEma). When in doubt, it is recommended to classify ENE into the lower category. In addition, novel prognostic factors have been recognized as helpful in guiding clinical care, including among others a worse pattern of invasion, defined as a tumor dispersion of 1 mm or more between invasive tumor satellites.

Molecular Pathology of Head and Neck Tumors

Molecular Pathology of Head and Neck Squamous Cell Carcinomas (HNSCC)

High-risk types of HPV, an epitheliotropic, double stranded, circular DNA virus from the papovavirus family,[121] have been detected in about 20–25% of HNSCC and in up to 60% of the oropharyngeal squamous cell carcinomas (OPSCC). HPV's oncogenic protein E6 and E7 lead to disruption of key tumor suppressor genes *p53* and *Rb,* resulting in cell cycle deregulation and genomic instability. *Rb* degradation also translates into the overexpression of p16, a tumor suppressor protein, and a hallmark of HPV-16-positive cancer of the oropharynx. In the Cancer Genome Atlas (TCGA) datasets, HPV+ tumors showed clear evidence of viral host genome integration, but failed to demonstrate evidence of recurrent viral integration sites or of recurrent gene transcription across the viral-human integration locus, and were associated with loss of TNF receptor-associated factor 3 (TRAF3), amplifications in E2F1, and helical domain PIK3CA mutations, resulting in the aberrant activation of NF-κB, cell cycle, and other oncogenic pathways.[122] Expression of viral proteins E6 and E7 was also identified, consistent with TP53-mediated and direct cell-cycle control interference,[122] with the loss of *p53* function in HPV-positive HNSCCs through the expression of the viral oncoprotein E6 possibly negating selective pressures for gaining TP53 mutations. The higher survival rate among HPV-positive patients has been in part attributed to the achievable greater locoregional control due to higher sensitivity to radiation or to better radiosensitization by cisplatin-based chemoradiation strategies, possibly due to an intact TP53.

Smoking-related HNSCCs are distinguished by loss-of-function mutations in TP53 and by the inactivation of CDKN2A (which encodes the p16 protein) by mutations, loss of heterozygosity, and/or promoter hypermethylation. Additional recurrent alterations are frequent copy number changes of 3q26/28 (a region including transcription factors TP63, SOX2, and signal molecule PIK3CA, genes implicated in homeostasis of epithelial stem cells and differentiation) and 11q13/22.[122] Recurrent focal amplifications in receptor tyrosine kinases (for example, EGFR, ERBB2, and FGFR1) also predominate in HPV$^-$ tumors.[122]

Three rarer genomic subgroups were also identified in the TCGA datasets: a subset of oral cavity tumors with favorable clinical outcomes with infrequent copy number alterations in conjunction with activating mutations of HRAS or PIK3CA coupled with inactivating mutations of CASP8, NOTCH1 and TP53; a subset characterized by infrequent copy number alterations and by the presence of loss-of-function alterations of the chromatin modifier NSD1, WNT pathway genes AJUBA and FAT1; and a last subset characterized by the activation of oxidative stress factor NFE2L2, mainly seen in laryngeal tumors.[122]

Amplicon-based next-generation sequencing (NGS) with hotspot-focused NGS panels has so far essentially confirmed the TCGA findings, revealing additionally that at least 3% of our samples harbored sequence variants in genes that were not previously implicated in HNSCC pathogenesis, such as BRAF, ABL1, AKT1, KIT, MET, FGFR2, and FGFR3, and for which therapeutic agents are currently available or under development.[123-125] Interestingly, mutations in AKT1, BRAF, CTNNB1, FGFR3, HRAS, KIT, NOTCH1, PTEN, PTPN11, SMAD4, and STK11 were also found to be risk factors for poor survival.[125]

Molecular Pathology of SMARCB1/INI-1 Deficient Tumors

SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1 (SMARCB1, also known as INI-1) is a tumor suppressor gene member of the SWI/SNF chromatin-remodeling complex that regulates transcription and is ubiquitously expressed in the nuclei of all normal tissues at various levels. Inactivation of SMARCB1/INI1 in cancer, initially discovered in malignant rhabdoid tumors, has subsequently been seen in a variety of different cancers (e.g., epithelioid sarcoma, renal medullary carcinoma) characterized by rhabdoid or basaloid morphologic features.[126] Mechanisms for the SMARCB1 inactivation typically involve deletions, intragenic mutations, or epigenetic silencing. Although SMARCB1-deficient carcinomas represent only a small subset of primary sinonasal carcinomas, they accounted for 14% of those tumors that had been originally diagnosed as sinonasal undifferentiated carcinoma.[65] The ability to detect SMARCB1 loss by immunohistochemistry should facilitate a better classification of poorly differentiated sinonasal carcinomas[65] and potentially enable the development of targeted therapies.[127]

Molecular Pathology of Translocation-Associated Head and Neck Tumors

Carcinomas, such as the HNSCC discussed earlier, are generally associated with the accumulation of sequential multiple genetic alteration events altering pathways essential for the fully malignant phenotype and are thought to occur in a multistep fashion during carcinogenesis.[9,10] In contrast, hematopoietic and mesenchymal malignancies are often characterized by translocation-associated fusions of oncogenes resulting in chimeric proteins thought to be interfering with early differentiation pathways and resulting in a maturation arrest. Despite the validity of this conceptual framework, several subtypes of rare epithelial malignant tumors with specific translocations have also been recently described, suggesting the possible presence, in epithelial cells, of alternative genetic shortcuts to classical gradual multistep epithelial carcinogenesis and capable of directly leading to an invasive metastatic phenotype.[128] These recent discoveries in head and neck cancers also offer new modalities for improved diagnosis, as many fusion oncogenes have also been shown to be tumor-type specific, indicating new opportunities for the development of targeted therapies.

NUT Midline Carcinoma

A subset of poorly differentiated carcinomas, previously classified as poorly differentiated SCC or SNUC, has been found to harbor activating translocations involving the *NUT* gene (i.e., NUT midline carcinomas).[129] Although NUT midline carcinomas affect the head and neck in one third of cases, they are not restricted to any specific organ system and can affect a variety of midline regions such as the mediastinum. The rearrangements most often take the form of a BRD4-NUT fusions, and in a minority of cases, of a BRD3-NUT or of other NUT-partnered chimeric variants. The normal function of the NUT protein is to bind and activate the histone acetyltransferase (HAT) of p300, leading to increased histone acetylation. The fusion protein may sequester p300 to localized regions of chromatin, suppressing a variety of genes, including those associated with squamous differentiation, resulting in global transcriptional repression and blockade of differentiation and ultimately supporting tumor growth.[130]

Adenoid Cystic Carcinoma

Adenoid cystic carcinoma (AdCC), the second most common salivary gland malignancy, is an aggressive slowly growing cancer with an often fatal outcome. The presence of a cytogenetically recurrent t(6;9)(q22-23;p23-24) translocation in AdCC has led to the identification of a balanced translocation of the v-myb avian myeloblastosis viral oncogene *(MYB)* with homolog-nuclear factor I/B (MYB-NFIB).[131,132] MYB-NFIB rearrangements lead to the production of chimeric transcripts containing MYB and NFIB and to the deregulation of the *MYB* gene. The latter is now considered to be an essential molecular event in AdCC oncogenesis, with available data indicating that at least 80–90% of ACCs have MYB activation either by gene fusion or by other mechanisms, leading either to the overexpression of MYB-NFIB fusion proteins or to an apparently normal MYB oncoprotein.[133,134] MYB plays an important role in the control of cell proliferation, apoptosis, and differentiation, being highly expressed in immature, proliferating cells and downregulated as cells become differentiated.[135] Alternative described mechanisms of MYB overexpression include, among others, translocations of *NFIB* enhancer elements upstream or downstream of *MYB.* Rearrangements involving a second MYB family gene, *MYBL1,* have also been recently described in AdCC.[136]

Secretory Carcinoma

Secretory carcinoma (or mammary analogue secretory carcinomas of the salivary glands) is a recently described subtype of salivary gland carcinoma, with strong histologic and immunohistochemical resemblance to secretory carcinoma of the breast.[107,137] In addition to the morphologic similarities, the two entities also share a t(12;15)(p13;q25) chromosomal

translocation, resulting in an identical ETV6-NTRK3 gene fusion.[107] The ETV6- NTRK3 fusion gene encodes a chimeric tyrosine kinase that activates two major effector pathways, the Ras- MAP kinase (MAPK) mitogenic pathway and the phosphatidylinositol-3-kinase (PI3K)-AKT pathway, both of which seem to be required for ETV6-NTRK3 transformation.[138]

Mucoepidermoid Carcinoma

Mucoepidermoid carcinoma (MEC), the most common salivary gland carcinoma, is characterized by a unique and recurrent t(11;19)(q21-22;p13),[139] resulting in a fusion gene composed of exon 1 of *CRTC1* linked to exons 2-5 of *MAML2* (CRTC1-MAML2).[140] The CRTC1-MAML2 fusion preferentially occurs in low/intermediate-grade MECs with a favorable prognosis and represents a useful biomarker that distinguishes true MECs, most of which have an excellent prognosis, from fusion-negative MEC-like tumors with a more aggressive biologic behavior.[141] A second translocation, leading to a chimeric EWSR1-POU5F1 protein, has been identified in MECs with a more immature morphology and consists of the N-terminal domain of EWSR1 linked to the DNA-binding domain of the transcription factor POU5F1, a gene important during the early stages of development to maintain the pluripotent status of embryonic stem cells.[142]

Hyalinizing Clear Cell Carcinoma of the Salivary Glands

Hyalinizing clear cell carcinoma of the salivary glands (HCCC), a rare salivary gland carcinoma, has recently been shown to have in 80% of cases a t(12;22)(q13;q12) translocation resulting in EWSR1-ATF1 gene fusion.[143] HCCC is a low-grade carcinoma with distinctive clear-cell morphology and a pattern of hyalinization often associated with focal mucinous differentiation. The gene fusion is not detected in any of the morphologic mimics and represents a potentially useful diagnostic biomarker. Interestingly, EWSR1-ATF1 fusions have been described in clear cell sarcomas of tendons and aponeurosis and other soft tissue tumors with a clear cell morphology, supporting the association of the EWSR1-ATF1 fusion with clear cell tumors across epithelial and mesenchymal neoplasms.

Pleomorphic Adenoma

Cytogenetic studies of pleomorphic adenomas (PA) have shown the presence of recurrent translocations or intrachromosomal rearrangements resulting in a gene fusion involving the transcription factor genes *PLAG1* and *HMGA2.*[144] *PLAG1* encodes a developmentally regulated DNA-binding zinc finger protein that is part of a family of cell cycle progression–related proteins. PLAG1 deregulated expression[145] leads to the deregulation of downstream PLAG1 target genes and to the activation of IGF-II signaling.[146] The PLAG1 and HMGA2 fusions identified in PA have not been encountered in any other histopathologic subtypes of salivary gland neoplasms and are therefore a useful biomarker in diagnostically difficult cases.

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3

Molecular Biology

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Head and neck squamous cell carcinoma (HNSCC) is the sixth most common form of cancer. Each year, HNSCC is diagnosed in more than 600,000 people worldwide, with 50,000 new cases and more than 10,000 deaths occurring in the United States alone.[1,2] HNSCC encompasses tumors of a variety of subsites, including the oral cavity, oropharynx, larynx, and hypopharynx, and each subsite has unique features of its anatomy, function, lymphatic drainage, etiology, and morphology. Although the etiology may vary somewhat from subsite to subsite, most HNSCC has traditionally been associated with tobacco exposure (either smoking or chewing tobacco) and to a lesser extent alcohol use. Other exposures such as betel nut chewing in Southeast Asia are also significant contributors to the development of HNSCC. In recent years the increasing incidence of human papillomavirus (HPV)-associated HNSCC in the oropharynx has been recognized, often in patients without significant prior exposure to alcohol or tobacco. A small minority of cases is related to other causes, such as Fanconi anemia, and there exists a subset of young patients in whom HNSCC develops in the absence of any known risk factors.

Current treatment algorithms for HNSCC focus on surgical excision, radiation therapy, and cytotoxic chemotherapy. Even though there have been many advances in these treatment modalities that have improved treatment-related sequelae, the overall 5-year survival rate for non–HPV-related HNSCC has remained around 50%.[2] Patients with HPV-related HNSCC fare much better, likely due to the unique biology of this tumor subtype and its sensitivity to treatment.[3] Further advances in the treatment of HNSCC likely lie with the development of targeted therapeutics that specifically address the molecular causes of a patient's tumor while minimizing treatment-related side effects. The epithelial growth factor receptor (EGFR) monoclonal antibody cetuximab is the first such targeted therapy approved for use by the U.S. Food and Drug Administration (FDA) in HNSCC, and many more are currently under development. Thus, an understanding of the molecular pathogenesis of HNSCC is critical for clinicians who treat HNSCC.

Since the completion of the Human Genome Project in 2003, significant attention has been given to "personalized medicine," or the ability to tailor therapy based on a patient's unique genetic profile. However, the initial promised revolution in medical treatment has not yet occurred, due to the enormous expense and effort required to undertake genotyping, as well as the additional levels of genomic complexity, such as epigenetic regulation, that are not easily evaluated by sequencing. However, over the past decade advances in technology such as next-generation sequencing that allow for massively parallel sequencing, advances in data management and computing technology, and further understanding of genomic regulation have greatly reduced costs and brought the goal of personalized medicine closer. Since 2011, several studies using whole exome sequencing and integrated genomic analysis were published that have greatly expanded our knowledge of the molecular details contributing to the development of HNSCC. These studies revealed specific alterations in elements of cell cycle control, squamous differentiation, mitogenic signaling, and epigenetic regulation that appear to drive the progression of HNSCC (Table 3.1). Based on these findings, therapies that target these alterations are now being developed and currently range from benchtop testing to large-scale clinical trials. This chapter focuses on the major molecular pathways that have been identified as contributors to the pathogenesis of HNSCC and discusses a few of the most promising therapies in development.

Alteration of Cell Cycle Control: *TP53*

TP53 is by far the most commonly mutated gene in HNSCC, with more than 50% of tumors harboring some form of genetic alteration.[4] Recent exome sequencing studies have confirmed this finding, demonstrating a mutation rate of 47–69% in HNSCC.[5-8] *TP53* is mutated in a wide range of cancers, and plays a central function in cell cycle control, DNA repair, and apoptosis. Given the critical tumor suppressor function of p53 in a range of cancer types, it is commonly referred to as "the guardian of the genome." In an unstressed state, constitutively expressed p53 is inhibited by MDM2 and ubiquitination leading to degradation. However, in the presence of cellular stress such as DNA damage or oxidative stress, a variety of sensor kinases phosphorylate p53,

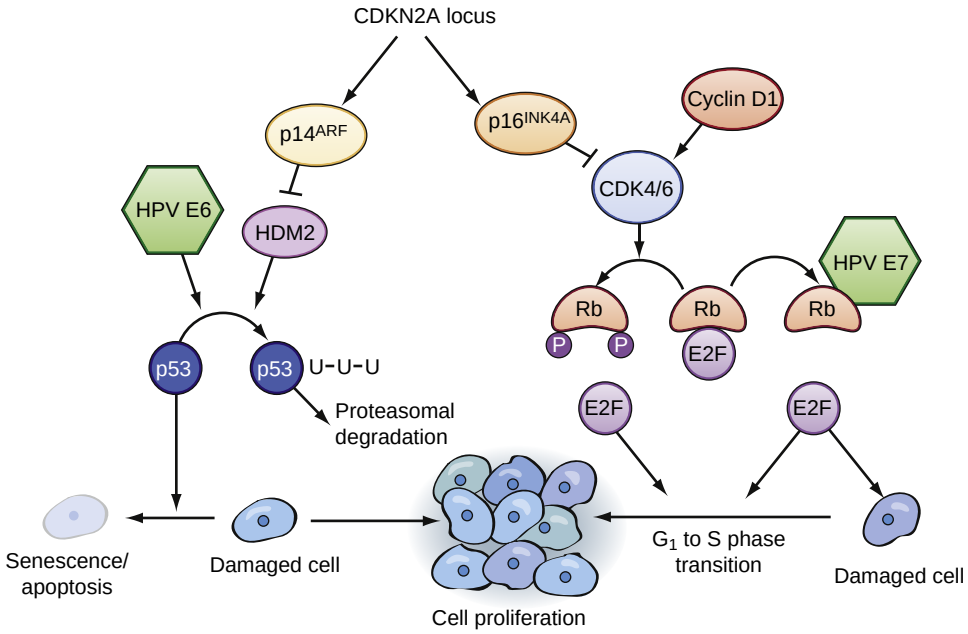
TABLE 3.1 Results of Major Exome Sequencing Studies in HNSCC

Study		Stransky et al[8]	Agrawal et al[5]	Pickering et al[7]	Lui et al[63]	Kandoth et al[6]
No. of tumors analyzed		74	32	38	151	306
Mean mutation rate (HPV–)		4.83 mut/Mb	20.6 mut/Mb	NR	NR	NR
Mean mutation rate (HPV+)		2.28 mut/Mb	4.8 mut/Mb	NR	NR	NR
Cell cycle regulation/ genomic integrity	*TP53*	62% (73% of HPV–)	47% (78% of HPV–)	66%	NR	69.8%
	CDKN2A	25%	9%	74%	NR	21.3%
	TP63	7%	NR	9%	NR	
Squamous differentiation	*NOTCH1*	11%	15%	9%	NR	19.3%
	NOTCH2/3	11%	NR	9%	NR	9.8%
	SYNE1	20%	28%	NR	NR	21%
Mitogenic signaling	*HRAS*	5%	4%	9%	4.6%	3.3%
	PIK3CA	8%	6%	11%	12.6%	20.6%
	PTEN	7%	NR	NR	13.6%	1.3%
Epigenetic regulation	*MLL2*	11%	NR	11%	NR	17.9%
	MLL3	9%	NR	NR	NR	7.3%
	EZH2	5%	NR	NR	NR	0.3%
	NSD1	9%	NR	9%	NR	10.6%
	PRDM9	11%	NR	NR	NR	6.5%
Other	*TGFBR2*	3%	NR	NR	NR	3%
	SMAD2	NR	NR	NR	NR	1%
	SMAD4	NR	NR	9%	NR	2%
	FAT1	12%	NR	30%	NR	23.5%
	CASP8	8%	NR	10%	NR	9%
	FBXW7	5%	5%	6%	NR	5%

leading to stabilization, tetramerization, and nuclear translocation. A variety of pathways may activate p53, including ATM, CHK2, p14, and ATR.[9] Once in the nucleus, p53 is then able to influence the expression of downstream genes (such as p21) that control cell cycle arrest and DNA repair; at higher levels of p53 activation, pro-apoptotic genes, such as *PAX* and *PUMA,* are upregulated. If DNA damage cannot be repaired, further p53 accumulation may inhibit BCL2 or BCL-x, leading to apoptosis.[9]

Most mutations (50–63%) within *TP53* found in HNSCC are missense mutations, primarily in the DNA binding domain.[5,8] The remaining mutations in this gene are a mix of nonsense, insertions/deletions, and splice site mutations. The effects of various mutations on the function of p53 are complex. Many mutations are completely inactivating, as would be expected for a tumor suppressor gene, whereas others may only downregulate the action of p53 on some downstream effectors but not others. Furthermore, some mutations alter the three-dimensional structure of p53 and alter its protein-protein interactions, which may cause disruption of other protein functions. This phenomenon may actually lead to downregulation of other proteins, thereby giving "gain of function" and causing *TP53* to behave more like an oncogene than a tumor suppressor.[10-13] In tumors with wild-type p53, the function of this protein is often reduced via other mechanisms, such as HPV-associated E6 protein action, amplification of MDM2, or deletion of CDKN2A.[14-16] Thus, alteration of the p53 pathway in some manner is nearly universal in HNSCC.

Mutations in *TP53* have also been identified as an early driver of HNSCC development, present in 15–27% of dysplastic lesions of the upper aerodigestive tract.[17,18] The presence of *TP53* mutations in dysplastic lesions is associated with a high risk of progression to malignancy, and incidence of *TP53* mutations increases as the severity of dysplasia increases.[17,19] Based on these and other findings, the "patch-field" progression model of HNSCC has been proposed. In this model, HNSCC develops within a field of abnormal mucosa with genetic abnormalities arising from expansion of a stem cell harboring a mutation in *TP53*.[20] Subsequent tumors may



• **Fig. 3.1** Regulation of the cell cycle and genomic integrity by CDKN2A and p53.

also arise within this field of mucosa with *TP53* mutations, although in other cases different *TP53* mutations have been detected in tumors and adjacent mucosa, suggesting the presence of different clonal populations harboring mutations.[21] Tobacco and alcohol exposure are associated with increased rates of *TP53* mutation, suggesting that these well-known risk factors for HNSCC may lead to *TP53* mutation.[22]

TP53 mutations have also been identified as a prognostic marker for HNSCC. In particular, mutations that truncate or disrupt the function of p53 are associated with decreased survival regardless of treatment modality, while patients with either wild-type or nondisruptive mutations fare better.[4,23,24] Several studies have also shown that *TP53* mutations predict resistance to chemotherapy,[25,26] locoregional recurrence after primary radiation therapy,[27,28] and failure after surgical excision and adjuvant radiotherapy.[29,30] However, use of *TP53* mutation as a prognostic marker remains controversial due to variability in testing techniques and inadequate sensitivity and specificity of various methodologies. However, newer sequencing protocols appear far better than previous techniques for detecting *TP53* mutations,[31] and may be promising for future clinical application.

Given the weight of evidence supporting the central role of the p53 pathway in the pathogenesis of HNSCC, restoration of normal p53 function is a potential therapeutic strategy for HNSCC. To this end, several viral vectors harboring wild-type p53 have been developed. Phase I clinical trials have shown these to have an excellent safety profile,[32] and phase II results demonstrated efficacy.[33,34] A phase III trial of Advexin (Introgen Inc, Austin, Texas.) that compared intratumoral injection of this adenovirus-based therapy to methotrexate demonstrated that patients with wild-type *TP53* showed a better response to Advexin, while those with *TP53* mutations showed a better response to methotrexate.[35] Further trials of therapies targeting the p53 pathway are pending, and one adenovirus-based vector, ONYX-015 (Onyx Pharmaceuticals, San Francisco, Calif.) has been approved for clinical use in China.[36]

Alteration of Cell Cycle Control: CDKN2a (P16) and the Rb Pathway

The Rb (retinoblastoma) pathway is a critical regulator of cell cycle progression. In G_1 phase, the Rb protein binds to E2F, a transcription factor, and arrests cell cycle progression. However, this block can be overcome by the action of the cyclin-dependent kinases CDK4 and CDK6, which phosphorylate Rb and lead to release of E2F.[37,38] Action of CDK4 and CDK6 is regulated by cyclin D1, which binds these proteins and effectively serves as the regulatory subunit of the protein complex. Action of this cyclin D1/CDK4/6 complex allows the cell to progress to the S phase, and ultimately cell division. This protein complex is itself inhibited by p16/INK4A (encoded by the *CDKN2a* gene), which binds the cyclin D1/CDK4/6 complex and prevents it from phosphorylating Rb. Thus, *p16* is a potent tumor suppressor gene (Fig. 3.1).

In HNSCC, the Rb pathway is most frequently altered, either via loss of p16 or via upregulaton of CCD1 (cyclin D1). In exome sequencing studies, 9–21% of tumors harbored mutations in the *CDKN2a* gene.[5,6,8] Loss of heterozygosity and deletions of the *CDKN2a* locus are observed in another 20–30% of tumors. When genetic alterations are combined with epigenetic silencing, such as promoter DNA

hypermethylation, nearly 80% of HNSCC tumors exhibit loss of p16 function.[39,40] Cyclin D1 upregulation has also been observed, with amplification of the chromosomal region containing the *CCND1* gene (which encodes cyclin D1) occurring in 30–35% of HNSCC[41,42] and overexpression of cyclin D1 occurring in up to 80% of HNSCCs.[43] When considered together, mutations of *CDKN2A* and/or amplification of *CCND1* were found in 94% in HNSCC,[7] making this a near universal abnormality in HNSCC. This pathway is also directly affected by HPV E7 protein, which binds the Rb protein directly, thereby circumventing the regulation of this pathway by p16/INK4A.

CDKN2A alterations are likely an early event in the development of HNSCC, because leukoplakia lesions with loss of heterozygosity at the 9p21 locus harboring *CDKN2A* have an increased risk of malignant transformation.[44,45] However, *CDKN2A* mutations alone do not appear to be sufficient to induce tumor formation; alterations of this gene have also been identified in benign lesions with minimal potential to transform into malignancy.[46] Nevertheless, low p16 levels and high cyclin D1 levels are independent predictors of poor outcomes in patients with HNSCC.[47,48] Given the ubiquity of Rb pathway abnormalities in HNSCC, attempts have been made to target this pathway therapeutically. Restoration of p16 levels with adenoviral vectors have been attempted,[49] and early phase I trials are currently under way with CDK4 inhibitors.[50]

Human Papillomavirus

HPV infection has recently been recognized as the primary causative agent for most oropharyngeal carcinoma. From 1984 to 2004, the proportion of oropharyngeal SCC related to HPV infection increased from 16% to 72%, and its incidence continues to rise.[51] This double-stranded DNA virus was first identified as a cause of cervical and anogenital cancer; however, by 2020 it is projected that HPV-related oropharyngeal cancer will surpass the annual incidence of cervical cancer. More than 100 subtypes of HPV are known, but the vast majority of oropharyngeal cancers are related to HPV-16, with a handful of other subtypes such as HPV-18, HPV-31, and others accounting for the remainder.

HPV drives tumorigenesis through the actions of two primary proteins, E6 and E7. These proteins downregulate p53 and Rb, respectively, and thus recapitulate two primary pathways previously described in HPV-negative HNSCC (see Fig. 3.1). HPV E6 causes ubiquitination of p53 and eventual degradation, thereby inactivating p53 in the absence of mutations or other genetic alterations.[52] HPV-E7 targets Rb for degradation via interaction with the cullin 2 ubiquitin-ligase complex, thereby releasing the E2F protein to drive cell cycle progression into the S phase. Unlike HPV-negative cancers that frequently downregulate Rb via loss of p16, HPV-associated HNSCC continues to express p16, thus this protein is often used as a marker for HPV infection.[53] Despite the obvious parallels between HPV pathology and SCC pathogenesis, HPV is a relatively ubiquitous infection that most people clear without difficulty; only a small subset go on to develop HPV-related SCC.

Patients with HPV-associated HNSCC generally represent a different demographic from the traditional HNSCC patient.[54] The primary risk factor for HPV-associated HNSCC is sexual history, in particular lifetime number of orogenital contacts.[55,56] Patients with HPV-associated HNSCC tend to be significantly younger than patients with non–HPV-associated tumors and tend to have less prior exposure to tobacco or alcohol.[56] Multiple studies have also shown that patients with HPV-associated HNSCC have a much better prognosis and improved treatment outcomes compared to patients with non–HPV-associated HNSCC.[3,57-60] The progression of HPV-positive HNSCC also appears distinctly different from HPV-negative disease; while HPV-positive HNSCC tends to present with larger, bulky cervical disease, cervical neck metastases do not necessarily bode poorly for patient outcomes, and current literature demonstrates that the current TNM staging scheme has little prognostic value for HPV-positive patients.[61,62]

Given the strikingly different demographics, treatment response, and prognosis between HPV-positive and HPV-negative HNSCC, it is logical to conclude that the underlying molecular pathology of HPV-positive and HPV-negative HNSCC is significantly different. Evidence for this was provided by exome sequencing studies of HNSCC, which demonstrated a lower mutation frequency in HPV-positive HNSCC compared with HPV-negative HNSCC.[5,8] Although these studies reported significantly different mutation rates due to differences in technique and data analysis, in both studies the mutation rate observed in HPV-negative tumors was between two and four times that seen in HPV-positive tumors, and this effect was independent of tobacco exposure. Additional differences were noted when the mutational profile of HPV-positive and HPV-negative tumors was compared, particularly in regard to *TP53* mutations. Mutations in *TP53* were not seen in HPV-positive tumors, while they are present in a majority of HPV-negative tumors (found in 73–78% of tumors[5,8]). Furthermore, additional analysis of the PI3K pathway demonstrated that a subset of HPV-positive tumors exists where the only mutations present are found in the PI3K pathway,[63] suggesting that in some tumors alteration of this pathway alone in combination with the oncogenic effects of HPV infection is sufficient to initiate tumor formation.

These recent findings are consistent with the known biology of HPV infection, and appear to confirm that the primary driver of carcinogenesis in HPV-positive HNSCC is the oncogenic effect of the HPV E6 and E7 proteins. Only a small number of additional mutations are needed to develop cancer in the face of p53 and Rb inhibition by HPV, whereas HPV-negative tumors require a far larger number of genetic alterations in multiple pathways to occur. This may explain the improved treatment response of HPV-positive tumors relative to HPV-negative tumors, in that mutations in multiple pathways in HPV-negative tumors may confer additional mechanisms of resistance to therapy that are not present in HPV-positive tumors. Further characterization of the genetic alterations in greater numbers of HNSCC tumors should shed further light on the unique biology of HPV-positive tumors and suggest new avenues for specific treatments.

Abnormal Squamous Differentiation and the Notch Pathway

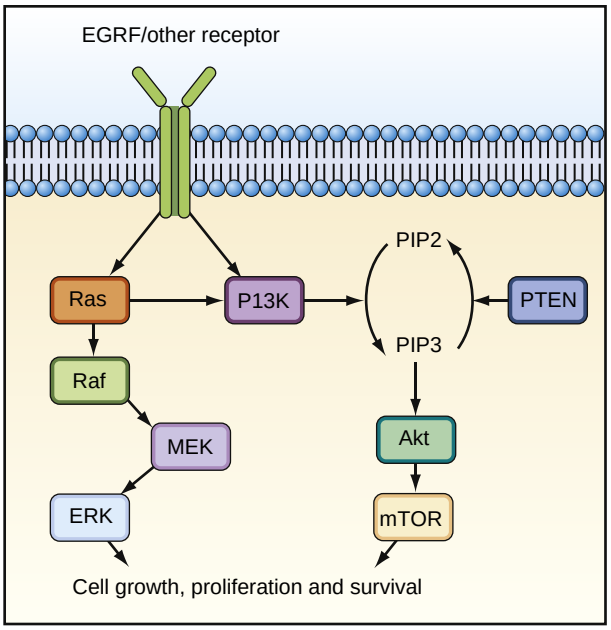
In recent years the Notch pathway has emerged as a significant mechanism in the development of HNSCC. The Notch pathway is a regulator of cell fate, influencing proliferation and differentiation through extracellular interactions.[64] The Notch family consists of four transmembrane receptors (Notch 1-4). Binding of one of five known ligands (Jagged 1 and 2, Delta 1, 3, and 4) leads to cleavage of the intracellular domain, allowing it to translocate to the nucleus. Once in the nucleus Notch leads to alterations in target gene expression by transforming a ubiquitous repressor into a transcriptional activator.[65]

Notch signaling has been shown to be responsible for a variety of regulatory functions, including cell cycle control and differentiation.[66,67] In squamous epithelium, Notch signaling promotes terminal differentiation, but may also suppress HPV E6 and E7 expression.[68] Notch was previously implicated as oncogenic in T-cell acute lymphoblastic leukemia, chronic lymphocytic leukemia, and diffuse large B-cell lymphoma due to the presence of activating mutations and translocations.[69-73] However, it appears to function as a tumor suppressor in HNSCC, in that recent reports have primarily described Notch1 mutations that would be predicted to cause missense mutations in ligand-binding domains or nonsense mutations that would cause truncated proteins lacking transcriptional activity.[5,8] Furthermore, restoring activated or wild-type Notch1 to HNSCC cell lines harboring *NOTCH1* mutations significantly inhibited cell growth, validating the role of Notch1 as a tumor suppressor in HNSCC.

Although not previously implicated in HNSCC pathogenesis, whole-exome sequencing studies of HNSCC revealed that the *NOTCH1* gene harbored mutations in approximately 10–15% of tumors, making it the second-most commonly mutated gene after *TP53*.[5,7,8] This was confirmed by analysis of the Cancer Genome Atlas, which showed a mutation rate of 19%.[6] Further characterization of the Notch pathway found that up to two thirds of tumors harbored a mutation in some component of the signaling pathway, demonstrating its central role in HNSCC pathogenesis.[7]

Exome sequencing studies also identified mutations in the *TP63* tumor suppressor gene in 8.5% of HNSCC tumors.[7,63] Additionally, copy-number amplification of *TP63* was identified in 26% of tumors in a further study.[7] This gene has been implicated in cell fate and cell survival,[74-77] and appears to function in opposition to Notch signaling. In squamous epithelium, Notch1 downregulates p63 expression, while p63 inhibits Notch1 expression[73] and antagonizes the ability of Notch1 to promote differentiation.[78] Overall, this suggests that disruption of a balance between Notch activity and p63 leads to alteration of normal squamous epithelial differentiation, cell cycle disruption, and eventually to the development of HNSCC.

Despite the central role of Notch signaling to HNSCC, therapeutic modulation of this pathway may be problematic. Given that Notch may function as either an oncogene or tumor suppressor depending on the cell type, it is possible that altering Notch activity in one tissue could lead to the development of a tumor in another tissue. Recent development of gamma-secretase inhibitors allows for the inhibition of Notch pathway activation[79] and has been used in trials for leukemia and breast cancer. A phase III trial of a gamma-secretase inhibitor in Alzheimer's was halted due to an increased incidence of skin cancer.[80] Thus, potential targeting of this pathway may be fraught with unintended consequences.



• **Fig. 3.2** Mitogenic signaling pathways: Ras and PI3K.

Cell Growth and Survival: EGFR, Ras, and PI3K Pathways

The regulation of cell growth and survival is a complex process controlled by multiple interacting signaling pathways. Not surprisingly, many of these pathways are altered in HNSCC. The EGFR signaling pathway is perhaps the best known; activation of EGFR initiates a signaling cascade that may lead to downstream signaling via the Ras/Raf/MAPK signaling pathway or the PI3K pathway (Fig. 3.2). EGFR is a tyrosine kinase receptor and member of the ErbB protein family. Binding of epithelial growth factor leads to homodimerization of EGFR or heterodimerization with other ErbB family members, autophosphorylation, and activation of downstream pathways. Overexpression of EGFR in HNSCC was first reported more than 20 years ago[81] and may be overexpressed in up to 90% of HNSCC.[82,83] However, the number of EGFR activating mutations is relatively small, and variable amounts of EGFR copy number amplification.[7,84,85] Multiple EGFR-targeting drugs are currently FDA approved, and one, cetuximab, is indicated for treatment of HNSCC. To date, HNSCC has demonstrated a relatively modest response to

EGFR inhibitors,[86,87] and response to treatment does not necessarily correlate with EGFR overexpression status. It is likely that EGFR inhibition may be overcome by downstream alterations in signaling pathways or alternative signaling via other receptors.

The primary downstream pathway for EGFR signaling involves Ras signaling via Raf/MEK/ERK or the PI3K pathway. Ras is frequently mutated in cancer and comprises a family of three genes: HRAS, KRAS and NRAS. While KRAS mutations are most common in all cancer types, HNSCC mutations occur nearly exclusively in HRAS[88] Mutations in HRAS occur in 4–5% of HNSCCs[5,8] and generally function to lock Ras in the active guanosine diphosphate–bound state, thereby promoting cell growth and survival. Activated Ras may trigger Raf activation, leading to MEK and subsequent ERK phosphorylation; ERK then may trigger a number of downstream effects, including proliferation, differentiation, morphology, and survival. An analysis of the overall Ras/Raf/MEK/ERK pathway found that mutations in this pathway occur in 8% of HNSCCs,[63] and *HRAS* mutations account for the majority of these. Thus, while this pathway is not a major driver of HNSCC pathogenesis, selective inhibition may be useful in a subset of patients.

The PI3K pathway is another major signaling pathway involved in cell growth, differentiation, and migration. PI3K may be activated by Ras or via receptor tyrosine kinases. While EGFR does not directly bind PI3K, it can heterodimerize with other receptors, such as ErbB3, that can directly activate PI3K.[89] PI3K is a dimer composed of a catalytic subunit (encoded by the *PIK3CA* gene) and a regulatory subunit. This dimer functions to phosphorylate phosphatidylinositol (4,5) biphosphate into phosphatidylinositol (3,4,5) triphosphate; this in turn leads to activation of Akt and PKB kinases. The entire signaling cascade is negatively regulated by the action of PTEN, which dephosphorylates phosphatidylinositol (3,4,5) triphosphate. *PIK3CA* mutations have been identified in 6–8% of HNSCCs by exome sequencing,[5,8] while analysis of the Cancer Genome Atlas found more than 20% of HNSCCs harboring *PIK3CA* mutations.[6] Gene copy gains of *PIK3CA* have also been identified in 9% of HNSCCs.[7] The negative regulator PTEN is also often disrupted,[90,91] with PTEN mutations occurring in approximately 5% of HNSCCs, and gene copy loss occurring in another 8% of tumors.[63] Examination of the entire PI3K signaling pathway identified mutations in more than 30% of HNSCCs,[63] making this one of the more frequently altered pathways in HNSCC. As noted previously, a small subset of HPV-positive tumors has also been identified in which PI3K pathway mutations are the only known mutations, suggesting that these tumors are primarily driven only by the action of HPV E6, E7, and PI3K pathway activation.[63] Furthermore, the presence of multiple mutations within the PI3K pathway is associated with advanced stage tumors. These results indicate that the PI3K pathway is a significant contributor to HNSCC pathogenesis in a large number of patients.

In addition to its significance to at least a large percentage of HNSCC, the EGFR/Ras/PI3K signaling pathways have the potential to be more easily targeted by therapeutic interventions than some other pathways. As described previously, cetuximab is an EGFR inhibitor approved for use in HNSCC, and other EGFR inhibitors have also been studied in HNSCC clinical trials.[92,93] While EGFR inhibitor resistance is a clinical issue, this may potentially be overcome by targeting multiple points along the signaling pathway. Ongoing clinical studies include targeting both Met and Akt signaling (NCT01476137), EGFR and ErbB2 signaling (NCT01184482), mTOR signaling (NCT00854152), and PI3K activity (NCT01737450, NCT01252628, NCT01602315). Future use of these inhibitors may rely on proper patient selection and tumor genotyping. Early pilot studies have demonstrated good responses to PI3K pathway inhibitors and mTOR-targeted therapies in patients with *PIK3CA* mutations or PTEN loss,[94,95] suggesting that the application of PI3K pathway inhibitors may be most effectively aimed at the subset of patients that harbor abnormalities in these signaling pathways.

Epigenetic Phenomena

In recent years, epigenetic changes have gained significant attention as a major contributor to cancer pathogenesis. Through the modulation of chromatin structure, which is primarily affected through histone modification and CpG island hypermethylation, gene expression may be upregulated or downregulated by making it relatively more or less accessible to the transcription machinery. This is a potent mechanism for altering gene expression separate from mutation, chromosomal deletion, or copy number amplification. Epigenetic changes have been found to occur in virtually all cancers, and HNSCC is no exception. Aberrant methylation of numerous genes related to HNSCC pathogenesis, including *CDKN2A*, *p14*, *cadherin 1-type1*, *death associated protein kinase (DAPK)*, *runt-related transcription factor 3 (RNX3)*, *adenomatous polyposis coli (APC)*, and *beta-catenin*[96] Distinct profiles of DNA hypermethylation have been identified in oral dysplasia, carcinoma in situ, and HNSCC, suggesting a progression of chromatin remodeling during the development of HNSCC.[97]

Given the significant role that epigenetic modification may play in carcinogenesis, it is not surprising that mutations and other aberrations have been observed in genes regulating chromatin structure. Histone modifier genes have been found to be mutated in a significant number of HNSCCs. These genes (and respective percentage of mutations seen) include *MLL2* (11–17.9%), *MLL3* (7.3%), *NSD1* (10.6%), and *EZH2* (0.3–5%).[6,8] Most of the mutations observed in these genes represented inactivating mutations, suggesting that these genes serve as tumor suppressor genes in HNSCC. In contrast, Bmi1, a mediator of chromatin structure and regulator of epigenetic silencing, is overexpressed in oral tongue SCC and is associated with cervical metastasis and decreased survival.[98] Thus, other histone modifying genes appear to function as oncogenes. This is not surprising, in that these individual proteins may modify the overall expression of broad sets of genes; some may contribute more to growth and survival, while others may skew toward senescence or apoptosis.

In light of the significant role that these genes regulating global gene expression patterns may have in cancer progression, they may provide opportunities for therapeutic interventions. Several drugs are currently FDA approved that target the epigenetic machinery. The DNA methyltransferase inhibitors azacitidine and decitabine are approved for use in myelodysplastic syndrome, while the histone deacetylase inhibitors vorinostat and romidepsin are approved for the treatment of cutaneous T-cell lymphoma.[99] While these and other similar drugs have shown efficacy in clinical trials, primarily as chemosensitizers, questions remain regarding their use. At this point it is unclear whether their action on chromatin structure itself is critical for their anticancer properties, along with the durability of their treatment effects and long-term toxicities. While the effects of any particular drug on its target enzyme are clear, it is less well understood what downstream effects these drugs have on the transcriptional profile of targeted cells. Thus, while the further development of more selective inhibitors of DNA methyltransferase and histone-modifying enzymes is important, this needs to be coupled to a more detailed understanding of epigenetic pathways and their effects on global gene expression.

Additional Pathways

In addition to the major pathways described, several other genes have been implicated in the pathogenesis of HNSCC. The TGF-β pathway is an important regulator of cellular proliferation and differentiation. In the squamous epithelium, TGF-β signaling controls epithelial-mesenchymal transition; this promotes invasion, metastasis, and resistance to chemotherapy and radiation. Deletion of chromosome 18q, which harbors several genes in the TGF-β pathway, has been shown to occur in many cancer types, including HNSCC.[100] Mutations in the TGF-β pathway proteins TGFBR2, SMAD2, and SMAD4 have been identified in HNSCC,[101,102] although mutations were not identified in recent exome sequencing studies.[5,7,8] These mutations appear to be a low-frequency event, in that analysis of the Cancer Genome Atlas showed mutations in TGFBR2, SMAD2, and SMAD4 in 3%, 1%, and 2% of HNSCC, respectively.[6] Given the complex interactions and functions of the TGF-β pathway, further work is needed to fully understand the role of this pathway in HNSCC pathogenesis.

Another gene implicated in HNSCC pathogenesis is *FAT1*, a member of the cadherin family of cell membrane proteins. Cadherins play an important role in cell-cell adhesion, cell polarity, and signaling, and *FAT1* has been shown to regulate developmental programs as well as squamous epithelial invasion and migration.[103-105] *FAT1* mutations have been identified in 12–30% of HNSCC,[7,8] and focal deletions of this gene were also seen in a number of tumors, bringing the total *FAT1* inactivation rate to approximately 46%.[7] Mutations in other cell polarity and adhesion proteins have also been found in HNSCC,[106] suggesting that disruption of cell-cell adhesion and polarity is a common step in the acquisition of invasiveness by HNSCC.

Alteration of the apoptotic signaling cascade may also be important for the development of HNSCC. Caspase 8 is a proapoptotic enzyme responsible for proteolysis during programmed cell death. Mutations in *CASP-8* have been identified in 8–10% of HNSCCs.[7,8] Cell lines harboring *CASP-8* mutations appear more aggressive in xenograft animal models.[7] CASP-8 mutations also appear to be correlated with *HRAS* mutations, suggesting a functional link between the Ras pathway and Caspase-8 in some tumors.[7]

Implications of Recent Findings

Historically, most patients with HNSCC have been treated with some combination of surgical resection, radiation, and cytotoxic chemotherapy. While many advances have occurred over the past several decades that in many ways have reduced the significant side effects of these therapies and made this aggressive multimodality treatment easier for patients to tolerate, the overall survival rate for HNSCC has not significantly changed in 30 years.[107] The one significant increase in survival among head and neck cancer has been for cancers of the oropharynx; however, this is likely due to the increasing incidence of HPV-related HNSCC and its improved response to therapy, rather than any true improvement in therapy. Thus, there is an acute need for a new paradigm for treatment of HNSCC.

Recent genomic analyses of HNSCC provide significant insight into the pathogenesis of HNSCC and potential avenues for new treatments. Perhaps the most striking finding of these genomic studies is the wide heterogeneity in mutations and other genetic alterations present in HNSCC. Even the most common genetic events, p53 inactivation (either through mutation or inactivation by HPV) and disruption of the *CDKN2A/CCND1* axis, are not universal. Somewhere between 10% and 30% of HNSCCs do not have any demonstrable alteration in p53 function. The next most common mutations and expression changes, in pathways such as Notch signaling, mitogenic signaling pathways, or *FAT1*, occur in between 45% and 66% of tumors.[7] A wider variety of pathways are affected in anywhere between 5% and 20% of tumors. Thus, no two tumors are exactly alike, implying that there is unlikely to be any sort of one-size-fits-all targeted therapy. Future studies aimed at specific pathways implicated in HNSCC pathogenesis will likely require tumor sequencing for patient selection to best enrich the study population for patients most likely to respond to the drug in question.

The second major discovery from genomic analysis of HNSCC is that most mutations and genetic alterations in HNSCC appear to be related to loss of tumor suppressor genes (e.g., p53), rather than activation of oncogenes. This is a critical point for the development of therapeutics, because it is far easier to design a drug to inhibit the activity of an oncogene than it is to restore the function of a tumor suppressor that has been inactivated. While a variety of selective inhibitors of various proteins, particularly signaling kinases, are either available or in trials, there are no systemic therapies currently available that restore the function of a mutated or deleted gene. Even so,

most HNSCC had been shown to harbor one or more unique genomic events such as copy gain or activating mutations that may be targetable with current drug therapies. In all 80% of HNSCC had at least one targetable event, and 54% had two or more.[7] A majority of these genetic alterations were targets of agents that are currently approved for use in cancer, including *TNK2*, *PTK2/FAK*, and SRC-family kinases. Several additional genetic alterations were seen that could be targeted by agents currently in clinical trials, including aurora family kinases and members of the PI3K signaling cascade. Thus, despite complexity and heterogeneity present in HNSCC, there exist many promising candidate molecules that may be efficacious in at least select subsets of patients with HNSCC.

While an enormous advance has occurred in our understanding of the molecular pathogenesis of HNSCC over the past decade, a significant amount of work remains. For example, the role of many genes implicated in HNSCC (e.g., *NOTCH1*, *FAT1*, and *CASP8*) and their contribution to the pathogenesis of HNSCC have not been fully elucidated. Furthermore, much of the in vitro work on the mechanisms of various proteins and preclinical testing of potential therapeutic agents is carried out in established HNSCC cell lines due to the ease of manipulation and testing. However, many of these lines have not yet been characterized for their genomic alterations; in the absence of these data, it is difficult to assess which cell line may be the best model system for elucidating the functional consequences of various mutations or testing a new therapeutic agent. Furthermore, it is well established that tumors are not a monoclonal population of cells, but harbor many different cell types and microenvironments. The roles for cancer stem cells, stromal cells, immune cells, microvasculature, and other cells within a tumor and the unique genetic profiles of these cell types have not been examined with current sequencing studies. A better understanding of the variety present within a particular tumor will be necessary to craft effective targeted therapies with a durable response.

Conclusion

Many significant advances have occurred recently that have greatly expanded our knowledge of the molecular pathogenesis of HNSCC. Although there is significant heterogeneity in the genomic landscape of HNSCC, several key genes and pathways, such as p53, CDKN2A/CCND1, Notch signaling, and the EGFR/Ras/PI3K pathways, appear to be major contributors to the development of HNSCC. Many of these same pathways are also affected in HPV-related HNSCC, through a combination of genomic changes (albeit at a significantly lower rate than in HPV-negative HNSCC) and the direct action of the HPV E6 and E7 proteins. These advances in the understanding of HNSCC pathogenesis have identified many potential opportunities for future targeted therapeutics. Further definition of the molecular underpinnings of HNSCC development and genomic characterization of individual patients will be needed to advance the goal of individually tailored and effective therapy for HNSCC.

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Oncoviruses

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Viruses are the second leading cause of human cancers. Approximately 12% of all human cancers are caused by only seven viruses, specifically Epstein-Barr virus (EBV), human papillomavirus (HPV), hepatitis B and C viruses (HBV and HCV), human T-cell lymphotropic virus-1 (HTLV-1), Kaposi sarcoma herpesvirus (KSHV or HHV8), and Merkel cell polyomavirus (MCPyV).[1] Human cancers caused by oncoviruses share several common features: (1) the viral infection is often necessary but not sufficient for tumorigenesis; (2) persistent viral infection precedes cancer development; (3) chronic inflammation associated with the viral infection sets the stage for subsequent adaptive mechanisms of host immune evasion used by the cancer cell.[1,2]

Following a brief history of the discovery of oncoviruses, the four viruses with associated clinical manifestations in the head and neck region, specifically, HPV, EBV, MCPyV, and HHV8 (KSHV), are discussed. With each of these viruses, clinical presentation and viral biology with concomitant oncogenic mechanisms and immune evasion strategies are reviewed (Box 4.1).

Historical Background

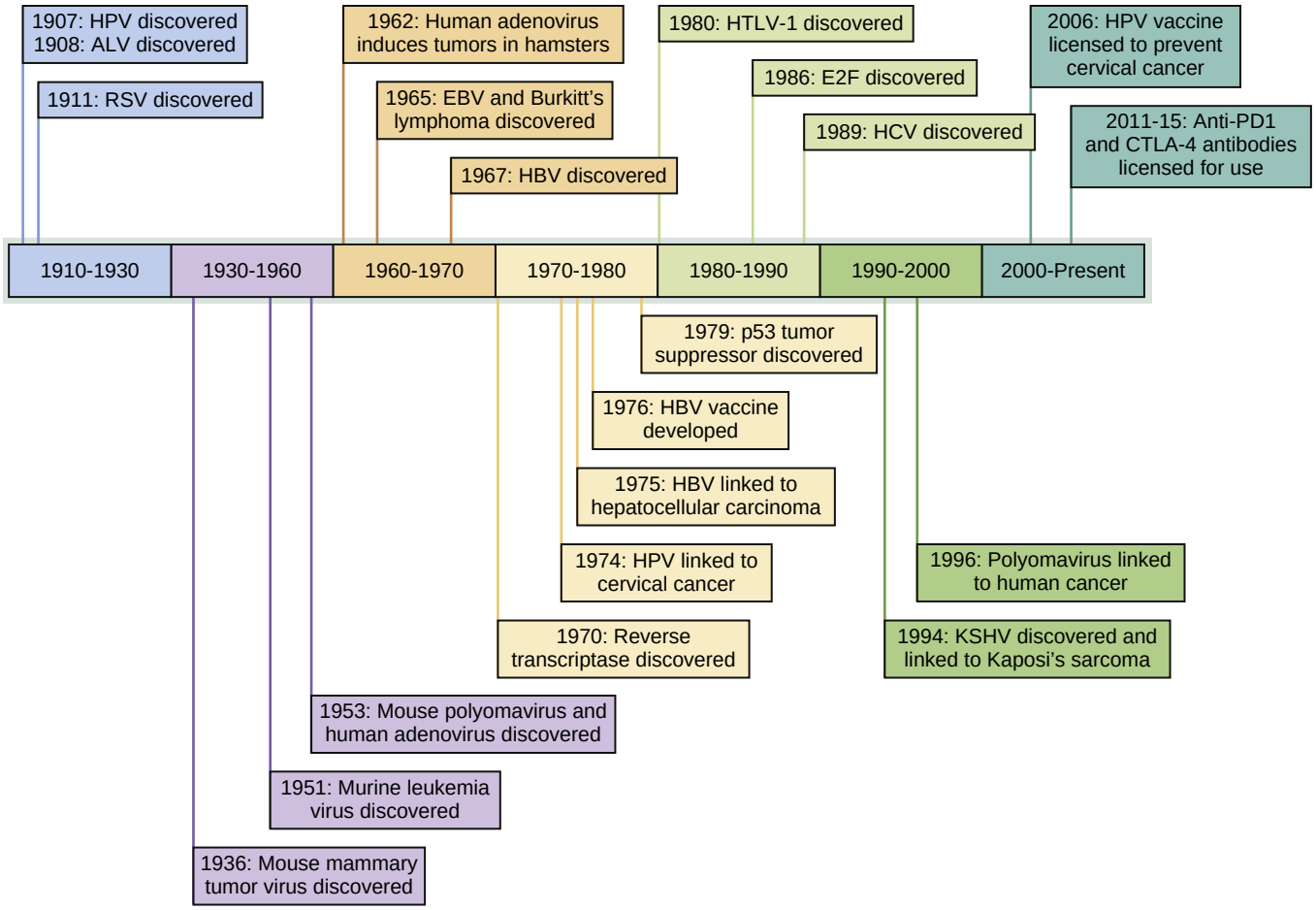
Cancer has been recognized as a disease since early Egyptian, Greek, and Roman times. The first written reports of cancer can be found in ancient Babylonian and Chinese texts and these findings led initial investigations into how lymph, blood, and, later, cells could underlie tumorigenesis and metastasis.[3] Advances in cell theory, an improved understanding of human pathophysiology, and the discovery of viruses in the early 20th century paved the way for the establishment of the field of tumor virology (Fig. 4.1). The person who pioneered the concept that viruses can cause tumors was Francis Peyton Rous. In 1911, Rous, while at the Rockefeller Institute, prepared a cell-free filtrate from a spindle cell sarcoma isolated from a chicken and injected the cell-free filtrate into healthy hens. He discovered that the recipients developed the same tumors as the donors. From this observation, he hypothesized that a virus was the agent responsible for transmission.[4] Later termed Rous sarcoma virus (RSV), it was the first known RNA virus and represented one of the first carcinogenic agents able to induce malignant solid tumor formation in mammals.[5] Subsequently, Rous received the Nobel Prize in Physiology or Medicine in 1966 for his discovery of tumor-inducing viruses.

The 1930s to 1960s became the primary period of mammalian tumor virus discovery. In 1935, Francis Rous and Joseph Beard identified that a papillomavirus, then the first known DNA tumor-inducing virus, could cause warts that progressed to skin carcinomas.[6] In 1936, Johns Bittner showed that a mouse mammary tumor virus present in the milk of cancer-afflicted mice could transmit the disease to her offspring. This work, built upon by Ludwik Gross, identified two additional RNA viruses, murine leukemia virus in 1951 and murine polyomavirus in 1953.[7-10]

The 1960s and 1970s marked the discovery of human tumor viruses, namely EBV, HBV, and HPV. In 1965, Tony Epstein and Yvonne Barr established the first cell lines derived from Burkitt lymphomas and visualized intracellular particles resembling herpesvirus by electron microscopy. Following this discovery, Gertrude and Werner Henle proved that the herpes-like virus was biologically active but phenotypically distinct from other herpesviruses, classifying EBV as the first human tumor virus.[11,12] Work by Baruch Blumberg, who identified the Au antigen that later was proved to be the surface antigen of HBV, established the necessary background to link chronic HBV infection to hepatocellular carcinoma (HCC).[13] Similar to EBV-induced lymphomas, the incidence of HCC is strongly correlated with the length of HBV infection and exposure to other environmental agents, such as aflatoxin from peanuts. Work by Maurice Hilleman and colleagues at Merck resulted in production of the HBV vaccine based on the HBV surface protein discovered by Blumberg, effectively representing the first patent for a cancer vaccine that aimed to prevent chronic HBV infection and subsequent development of HCC.[14]

• Box 4.1 Major Mechanisms of Immune Evasion Employed by Oncoviruses

Restriction of viral protein expression
Molecular mimicry
Disruption of antigen presentation on major histocompatibility complex class I or II molecules
Disruption of cytokine and chemokine signaling
Increased expression of PD-L1



• **Fig. 4.1** Timeline of key events in cancer immunology and immunotherapy.

Building on early work on papillomaviruses in the 1950s, Harald zur Hausen proposed that HPV could be the causative agent of cervical cancer. zur Hausen demonstrated that HPV DNA was present in cervical cancer cells and that two types in particular, HPV16 and HPV18, were responsible for the majority of cervical cancer cases.[16-18] Later epidemiologic work established that these high-risk HPV types were also linked to anogenital cancers and a subset of head and neck cancers. Fueled by success in developing an HBV vaccine and early work by Ian Frazer and others, clinical trials with commercially developed virus-like particle vaccines that protected against HPV16 and HPV18 infection demonstrated efficacy in preventing HPV infection and the development of HPV-associated anogenital lesions.[19]

Viruses have contributed not only to our understanding of oncogenesis but also to our understanding of basic cellular biology. Pioneers Howard Temin and David Baltimore continued to work through the 1970s to prove that the RNA virus, RSV, depended on DNA replication and DNA-dependent RNA synthesis, eventually receiving the Nobel Prize in Physiology or Medicine in 1975 for their discovery of reverse transcriptase.[20,21] Building on their work, Michael Bishop and Harold Varmus postulated that RSV captured a cellular oncogene, in their work on *src,* through its reverse transcriptase-dependent life cycle.[22] Later studies on retroviruses such as murine leukemia virus showed that tumorigenesis was caused by insertional mutagenesis of the viral genome into the host cell nuclear DNA.[23] The discovery of p53 by Lane and Levine in 1979 and retinoblastoma (Rb) in 1971 by Alfred Knudson helped establish new paradigms for tumor progression and began to provide a vision of how viruses might interact with specific genes to cause tumorigenesis.[24-26]

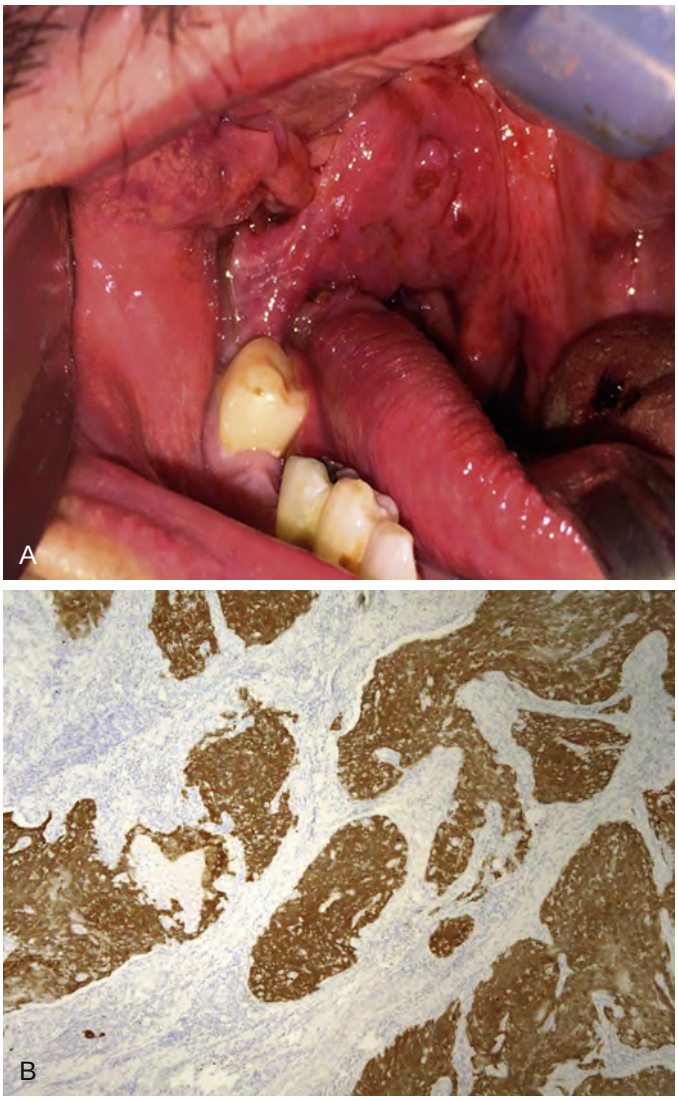
Since the 1980s, additional human tumor viruses, such as human T-cell leukemia virus type 1 (HTLV-1), HCV, and Kaposi sarcoma virus, have been identified. HTLV-1, identified by Robert Gallo and colleagues in 1980, was the first discovered human retrovirus and was linked to adult T-cell leukemia by Yorio Hinuma and colleagues.[27,28] After the identification of HCV as a flavivirus, Houghton and colleagues reported a link between HCV and HCC, which was similar to the link seen between HBV and HCC, noting long-term infection with HCV as a major risk factor for the development of HCC.[29] Additionally, during the early to late 1990s, a second tumorigenic human herpesvirus was discovered, called Kaposi sarcoma virus. After the association between acquired immunodeficiency syndrome (AIDS) and a more aggressive version of Kaposi sarcoma was noted,

Yuan Chang and colleagues discovered a new virus distantly related to EBV, named Kaposi sarcoma herpesvirus or human herpesvirus type 8 (HHV8).[30] While the mechanisms by which human immunodeficiency virus (HIV) potentiates HHV8-mediated tumorigenesis are not completely understood, current research suggests that HHV8 replication may be increased in the presence of HIV. In 2008, a new polyomavirus was described to cause Merkel cell carcinoma (MCC), a rare but particularly aggressive form of human skin cancer derived from neuroendocrine cells.[31]

Human Papillomavirus

Overview

HPV are non-enveloped DNA viruses that contain a double-stranded genome of approximately 8 kilobases (kb). HPV types are often clinically categorized into either low- or high-risk groups, based on their predilection to induce cancers in their host. The majority of the 200 different HPV types that have been characterized to date are in the low-risk category for malignant transformation. The low-risk HPV types 6 and 11 cause recurrent respiratory papillomas within the upper aerodigestive tract. In contrast, the high-risk HPV types 16 (HPV16) and 18 (HPV18) can cause squamous cell carcinomas.[32,33] In the United States, up to 80% of oropharyngeal (tonsil and base of tongue) cancers are caused by HPV infection. Depending on the location of the epicenter of the tumor, patients with HPV-related head and neck squamous cell carcinoma (HPV-HNSCC) may present with tonsil asymmetry, throat pain, dysphagia, referred otalgia, halitosis, or weight loss (Fig. 4.2). Because HPV-HNSCCs originate in the crypts of tonsils, rather than the surface epithelium as is the case for tobacco-related tumors, there also may be no detectable mass or abnormality at the primary tonsil site, and patients may present with an asymptomatic neck mass. In addition to causing cancer in the oropharynx, HPV can cause cancers at other sites within the head and neck region, including the sinonasal tract.[34]

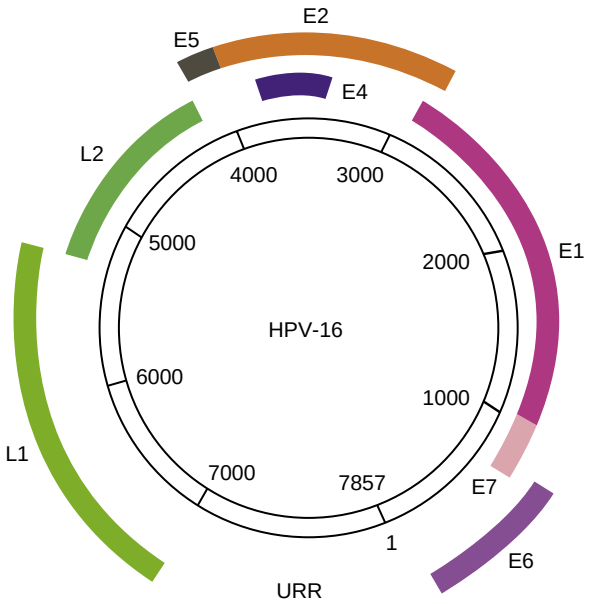


• **Fig. 4.2** **A,** Squamous cell carcinoma of the right tonsil which extends into the soft palate. **B,** Staining of the cancer for p16 by immunohistochemistry and its location in the oropharynx suggests an HPV etiology. (B from Duncan LD, Winkler M, Carlson ER, et al: p16 immunohistochemistry can be used to detect human papillomavirus in oral cavity squamous cell carcinoma, *J Oral Maxillofac Surg* 71:1367-1375, 2013.)

Genomic Organization and Life Cycle

HPV replicates only one of its two circular DNA strands and the 8 kb genome can be divided into a 4 kb early (E) region that encodes primarily nonstructural proteins, a 3 kb late (L) region that encodes two viral capsid proteins, and a 1 kb noncoding region (long control region, LCR) that contains *cis*-acting elements that control viral replication and gene expression from the E and L regions[35] (Fig. 4.3). Based on our understanding of the cervical mucosa, HPV has a tropism for the basal cell layer within stratified squamous cell epithelium. The virus links its life cycle to the differentiation program of the stratified squamous epithelial cells as the infected epithelial cells migrate through the various cell layers.[36] While the mechanism of cellular invasion has not been completely characterized, $\alpha_4\beta_6$ integrin has been postulated to play a crucial role.[37] Similarly, the events leading to intracellular viral coat shedding and nuclear import of the HPV genome remain largely uncharacterized.

Based on the cervical model, the HPV genome is primarily held to a low copy number as the infected basal epithelial cells undergo differentiation into squamous keratinocytes. Once the keratinocytes have terminally differentiated, the virus replicates to high copy number, expresses the L genes, and produces progeny virions.[38] HPV proteins E1 and E2 have been shown to have key roles in viral DNA replication. E2 is a transcription factor that interacts with the consensus motif $ACCN_6GGT$ in the viral LCR, acting primarily as a transcription activator.[39] However, E2 can also act as a transcriptional repressor of viral gene expression, such as E6 and E7, as the basal epithelial cell undergoes its differentiation process to become a keratinocyte.[40] E2 also associates with the viral DNA helicase E1 to ensure accurate and precise gene promoter recognition.[41]



• **Fig. 4.3** The human papillomavirus (HPV) genome. Late (L) expressed genes *L1* and *L2* encode two viral capsid proteins, whereas early (E) expressed genes *E1-7* encode primarily nonstructural proteins. E1 and E2 play key roles in viral DNA replication, whereas E5 has been discovered to activate receptor tyrosine kinases in a ligand-independent manner. *E6* and *E7* are the main oncogenes in HPV and are known to inactivate p53 and Rb, respectively. (From Riemer AB, Keskin DB, Zhang G, et al. A conserved E7-derived cytotoxic T lymphocyte epitope expressed on human papillomavirus 16-transformed HLA-A2+ epithelial cancers. *J Biol Chem.* 2010; 285: 29608-22.)

In contrast, the viral E4 protein has been shown to interact with the keratin intermediate filaments in the keratinocyte, to destabilize their quaternary architecture, and to allow for the release of new virions.[42]

Integration of the HPV genome seems to be biased toward genic regions, and integrations are associated with alterations in DNA copy number, mRNA levels, and chromosomal rearrangements. Additionally, cancers that have integrated HPV genomes appear to have different patterns of DNA methylation and gene expression.[43] In general, the viral E6 and E7 genes are consistently maintained during viral genome integration, while other genes, such as E1 and E2, are often lost.[44] Maintenance of E6 and E7 expression is necessary for sustaining the tumorigenic phenotype. Loss of E2 has been shown to support a growth advantage in keratinocytes, in that E2 has the chance to become reactivated and suppress E6 and E7 expression in some clonal populations.[45] Additionally, E5, a viral protein that activates receptor tyrosine kinases (RTKs) in a ligand-independent manner, is also lost upon host cell genome integration. Studies have shown, however, that maintenance of E5 expression in the infected keratinocyte is not necessary for oncogenesis.[46]

HPV E6 and E7 Oncoproteins

The oncogenic potential of high-risk HPV16 and HPV18 is driven by the expression of the viral oncoproteins E6 and E7. In the cervical model, keratinocytes that express high levels of E6 and E7 have been shown to display histopathologic characteristics of high-grade squamous intraepithelial lesions and show increased genomic instability.[47,48] E6 and E7 have been shown to inactivate p53 and Rb tumor suppressors, respectively.[49] Additionally, E6 can activate human telomerase reverse transcriptase (hTERT) transcription, allowing for the maintenance of telomere length and, thus, immortalization of the keratinocyte.

The HPV E7 protein consists of 100 amino acids and contains no characterized enzymatic activity but has been shown to associate with complexes of other intracellular proteins. E7 interacts with Rb through LXCXE conserved motifs within conserved region 2 that is similar to the adenovirus E1A protein. The LXCXE pocket regulates the activity of the E2F transcription factor family that is responsible for controlling cell cycle transitions, primarily the G_1/S-phase transition.[50-52] In addition to binding Rb, E7 helps challenge the growth-arrest capabilities of cyclin dependent kinase inhibitors, such as p21 and p27. The resulting inhibition of p21 and p27, coupled with unrestrained activity of the E2F transcription factor, allows for continual expression of genes necessary for DNA replication, transcription, and translation to produce viral progeny.[53-55] Recent reports have also shown that E7 may interact with transcriptional co-activators, such as p300 and CREB binding partner (CBP), leading to increased rates of viral E6 and E7 transcription.[56,57]

The HPV E6 protein is also a low molecular weight protein of 150 amino acids that contains two CXXC motifs. As E7 induces unrestrained cellular and viral DNA synthesis by inactivating Rb, inhibiting p21 and p27, and activating p300 and CBP, the keratinocytes typically initiate apoptotic pathways that are dependent on p53 expression and activity.[58] Thus, HPV E6 abrogates this p53 response by forming a complex with the keratinocyte E6-AP protein that is necessary for p53 activation. Part of the HECT (homology to E6 C terminus) family of E3 ubiquitin ligases, E6-AP does not interact with p53 in the absence of E6, rather E6 retargets E6-AP to ubiquitinate p53, targeting it for proteasomal degradation.[59-62] Further research has shown that E6 proteins interact with factors other than p53, such as p300 and ADA3 (a transcriptional co-activator).[63,64] Additionally, the PDZ binding domain on E6 may allow for scaffolding of additional transduction pathways that may include interferon regulation and other kinase activities.[65]

Cellular life spans are highly dependent upon the length of cellular telomeres and activation of p53-dependent pathways when these telomeres are shortened below a critical length. As each round of DNA replication leads to progressively shorter telomeres, cancer cells must find a mechanism of maintaining telomere length. HPV E6 has been shown to induce hTERT transcription, leading to telomere maintenance and immortality.[66]

Genomic Instability

HPV E6 and E7 combine to inactivate tumor suppressors Rb and p53, which are responsible for cellular checkpoints that

monitor cell size, nutritional status, and most importantly, DNA quality. E6 and E7 cooperate to induce defects in chromosomal separation during mitosis, resulting in aneuploidy, primarily resulting from centrosome abnormalities.[67] E7 expression induces centrosome and centriole duplication errors in normal cells, increasing the chance that an error will occur in chromosomal separation.[67] Errors in chromosome separation lead to gain or loss of chromosomes or other genomic stabilities that can increase the malignant potential of the cell. E6 and E7 may also synergize to cause anaphase bridges that lead to double-stranded DNA breaks.[68] Furthermore, multiple mitotic checkpoints are subverted in cells that express HPV E6 and E7, leading to tetraploidy or sub-chromosomal loss.[69,70] Common mutations in HPV-HNSCC include helical domain changes in *PIK3CA*, amplification of *TP63* and *SOX2*, loss of *TRAF3,* genomic amplification of the gene *E2F1,* and retention of *CDKN2A* that is commonly lost in HPV negative cancers.[71]

Mechanisms of Immune Evasion

Modulation of the host innate and adaptive immune systems by HPV facilitates its evasion of natural killer (NK) and $CD8^+$ T cells acting upon infecting keratinocytes. HPVs are non-lytic and non-enveloped, replicate their genomes in the host nucleus, and do not have a blood-borne phase of infection. The low profile maintained by HPV, preferred codon usage, molecular mimicry, modulation of major histocompatibility complex (MHC) class I and II antigen presentation, and interference with interferon (IFN) production and signaling combine to allow HPV to escape detection by the host immune system.

Regulated Expression of Immunogenic Viral Protein

As the life cycle of HPV is non-lytic and does not contain a blood or lymph-borne phase of infection, HPV does not elicit pro-inflammatory signals that would activate dendritic cells (DCs) or Langerhans cells (LCs) in the microenvironment. Very low levels of immunogenic HPV proteins E6 and E7 are expressed during keratinocyte differentiation, and those that are expressed are primarily contained in the nucleus of the infected cells.[72] Thus, availability of exogenous viral antigens to be presented on MHC class II molecules in antigen-presenting cells (APCs) is low. Additionally, because HPV does not infect DCs or LCs, robust presentation of viral antigens on APC MHC class I molecules is also impaired. The redundancy of codons to encode the same amino acid and the number of tRNA molecules that recognize a particular codon differ among viruses and mammalian cells. HPV uses codons not commonly employed by mammalian cells, allowing an additional level of control of expression of early and late genes.[73] This additional level of control suppresses E6 and E7 expression during basal keratinocyte differentiation and contributes to the lack of available epitopes displayed on MHC class I and II molecules.[73]

Molecular Mimicry

Molecular mimicry is exemplified when the structural properties of a foreign molecule closely resemble an endogenous host molecule. The molecular mimicry between HPV E7 and several human proteins may allow HPV to harness the host process of self-tolerance to inhibit recognition of viral epitopes. HPV E7 shares common amino acid sequence motifs with proteins involved in DNA excision repair, namely, XPGC (xeroderma pigmentosum group G complementing protein) and RBP-1 (retinoblastoma binding protein-1).[74-76] A cell-mediated process that targets these epitopes would cause dysregulation of genome repair and lead to abnormalities in the key G_1/S-phase cell cycle checkpoint. Thus, HPV may have evolved to mimic epitopes to which the adaptive immune system is centrally tolerant.

Alterations in Antigen Presentation Machinery

A key evasion mechanism used by HPV is the modulation of antigen presentation on MHC class I molecules. $CD8^+$ cytotoxic T lymphocytes recognize infected cells by interacting with viral peptides bound to MHC class I on the surface of infected cells. HPV prevents antigen presentation of proteasome subunits low molecular weight peptide 2 and 7, LMP2 and LMP7, and of the transporter associated with antigen processing 1 and 2, TAP1 and TAP2, through a variety of mechanisms, including reduced expression of selective class I proteins.[77] The E7 protein has been shown to repress the promoter for MHC class I heavy chain expression and represses the activity of a bidirectional promoter that regulates transcription of the TAP1 and LMP2 genes.[78] HPV E7 may also inhibit the ATP-dependent transport of peptides into the endoplasmic reticulum (ER) via TAP1/TAP2.[79]

In addition to HPV E7, HPV E5 acts to inhibit degradation of epidermal growth factor in human keratinocytes and prevents acidification of endosomes by interacting with the pore-forming subunit of the vacuolar H^+-ATPase.[80] MHC class I complex stability is dependent upon pH. E5-modulated alkalization of endosomes and the Golgi apparatus disrupts intracellular trafficking of proteins, including MHC complex I.[81] Additionally, E5 has been shown to downregulate the specific surface expression of HLA-A and HLA-B, both of which are responsible for presenting class I–restricted viral epitopes to $CD8^+$ T cells. Surface expression of HLA-C and HLA-E remains normal, allowing HPV-infected keratinocytes to evade NK cell scanning.[81] In addition to modulating MHC class I expression, E5 may also impact MHC class II epitope presentation. The invariant chain (Ii) is required to chaperone and stabilize MHC class II and is degraded in endosomal compartments to allow for epitope placement in the class II binding cleft. Because E5 prevents acidification of endosomes, Ii degradation is hindered and the formation of peptide-charged mature MHC class II molecules is inhibited. Thus, HPV E5 may also inhibit $CD4^+$ T cell recognition by downregulating MHC class II molecules.[82]

Alterations in Pro-inflammatory Cytokines

Type I IFN, which is produced by virally infected cells, primes infected cells and the neighboring cells for antiviral activity. Additionally, type I IFN has immune stimulatory activity that can chemoattract neutrophils, macrophages, NK cells, and

DCs.[83,84] HPV has evolved to circumvent the antiviral properties of type I IFN by using E7 to inhibit IFNα-mediated signal transduction. HPV E7 binds IFN-regulatory factor (IRF)-9, preventing it from translocating to the nucleus and activating the ISRE (IFN-stimulated response element) that transcribes factors involved in antiviral defense and immune system responsiveness.[85,86] E7 also binds IRF-1 and inhibits IRF-1–mediated activation of the IFNβ promoter. The E7/IRF-1 complex recruits histone deacetylase to the IFNβ promoter, preventing transcription of the locus.[87] Reduced availability of IRF-1 also leads to downregulation of IRF-1 target genes, including *TAP1* and *MCP-1* (monocyte chemoattractant protein-1).[88] HPV E7 may also reduce binding of NF-κB to its consensus DNA sequences, further dampening the immune response.[89] In addition to HPV E7, the E6 oncoprotein also interacts with the IFN pathway. E6 binds IRF-3, inhibiting transcription of the IFNβ gene.[90] Additionally, E6 interaction with the kinase Tyk2 prevents Tyk2 from associating with IFNα-1R, further impairing JAK/STAT signaling that contributes to the IFNα transduction cascade.[91] E6 may also inhibit expression of IFN-responsive genes such as interleukin (IL)-8 and IL-18, which serve as $CD8^+$ T-cell chemoattractants and activators, respectively, as well as NF-κB and cell cycle regulation loci.[57,92,93]

Immune Checkpoint Activation

HPV-HNSCC localizes to the lingual and palatine tonsils—lymphoepithelial organs that represent a first line of defense against oral infections. Paradoxically, despite oncogenic HPVs expressing foreign viral antigens that are capable of eliciting robust immune responses, the viruses are nonetheless able to escape immune clearance. Localized expression of programmed cell death ligand-1 (PD-L1) within the reticulated epithelium of the crypts of the tonsils, which are the sites of origin of these virus-related cancers, suggests that the reticulated epithelium of the tonsillar crypts may represent a distinct immune microenvironment relative to the surface epithelium.[94] The deep invaginations of tonsil crypts make them susceptible to collection of bacteria and foreign material. Thus, the resident lymphohistiocytes are chronically exposed to high concentrations of foreign antigen. It is therefore possible that, even in the absence of overt chronic tonsillitis, there is ongoing basal immune activation in the crypts that drives PD-L1 expression. Given the selective expression of PD-L1 within the deep crypts, this region may consequently represent an immune-privileged site, in which effector function of virus-specific T cells is downmodulated, thereby facilitating immune evasion at the time of initial HPV infection and subsequent virus-induced malignant transformation.

Epstein-Barr Virus

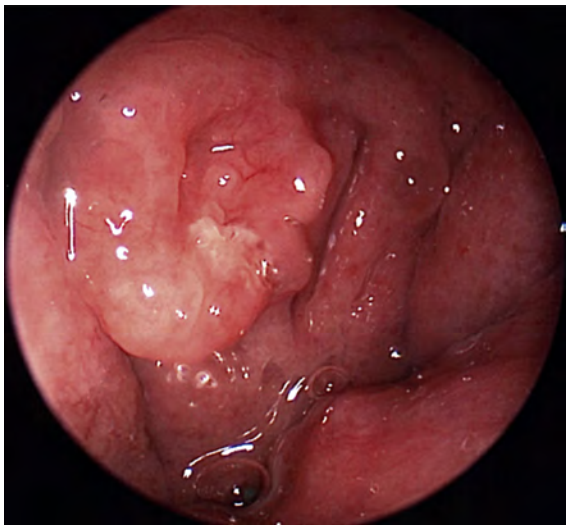
Overview

EBV is a prototypic member of the herpesvirus family and has a linear DNA viral genome encased within a nucleocapsid and a viral envelope.[95] Greater than 90% of the world's population is infected with EBV, often from an early age, and EBV transmission is postulated to occur by salivary exchange.[96] Primary infection with EBV is typically asymptomatic, although if infection is delayed until adolescence, EBV may present as infectious mononucleosis, which is characterized by prominent cervical lymphadenopathy, pharyngitis, and fever.[97] Patients typically shed high viral titers from the lytic infection occurring in the oropharynx and have a characteristic IgM response. Latent infection in memory B cells can cause lymphomas in immunosuppressed individuals, including Hodgkin and Burkitt lymphomas. Of particular importance to otolaryngologists, malignant transformation associated with epithelial infection with EBV is associated with nasopharyngeal and certain salivary gland carcinomas[98] (Fig. 4.4).

Genomic Organization and Life Cycle

EBV infects both B cells and epithelial cells of the oropharynx, posterior nasopharynx, parotid gland, and tonsils. Infection of B cells establishes a latent infection in memory B cells through binding of its major envelope glycoprotein, gp350, to CD21 (also known as complement 2 receptor and complement C3d receptor) on the surface of B cells.[95] In addition, MHC class II molecules on the surface of the B cell function as a co-receptor for a second EBV glycoprotein, gp42, which is necessary in concert with glycoproteins gH and gL to permit EBV entry into B cells.[99] Additionally, EBV infection of epithelial cells has been noted through the detection of EBV DNA within cells lining the parotid duct and EBV DNA and mRNA in sloughed oropharyngeal epithelial cells and tonsillar lymphoid cells.[100] Because epithelial cells do not express MHC class II molecules characteristic of APCs, EBV attaches to epithelial cells through another glycoprotein, gH, and entry into epithelial cells is mediated by gH/gL complexes.[101,102]

The 18-kb double-stranded linear DNA molecule consists largely of genic regions interspersed with direct tandem repeats and is replicated by a virally encoded DNA polymerase[103]



• **Fig. 4.4** Squamous cell carcinoma of the right nasopharynx with an etiologic origin from Epstein-Barr virus infection.

(Fig. 4.5). Within latently infected cells, the viral genome is held in multiple copies as an extrachromosomal episome that is replicated by host DNA polymerases.[104] After cellular entry, the linear DNA molecule circularizes by virtue of the direct tandem repeat sequences at the termini of the DNA.[105] Viral gene expression is tightly controlled during latent infection in order to limit recognition of infected cells by cytotoxic $CD8^+$ T cells. Six EBV nuclear antigens (EBNAs 1, 2, 3A, 3B, 3C, and LP) and three membrane proteins (LMP 1, 2A, and 2B) are expressed at low levels during latency.[97] Additionally, two small noncoding RNAs, *EBER1* and *EBER2,* are consistently expressed but their function remains poorly characterized.[97] The nuclear antigens appear important for maintenance and replication of the episomal EBV genome and the latent membrane proteins function in oncogenesis by inducing cell-surface adhesion molecules and upregulating the expression of anti-apoptotic proteins. EBNA1 interacts with viral promoters to regulate the transcription of the EBV nuclear antigens and LMP1, while EBNA2 interacts with DNA-binding protein RBP-Jκ (Jκ-recombination-binding protein) to activate *CD23* and *LMP1* and *LMP2A.*[106,107] EBNA-LP additionally interacts with EBNA2 to allow for efficient cellular growth and transcriptional activation of histone deacetylase 1 and cyclin A, and is modulated by interactions with various EBNA3 family members.[108-111] The oncogenic role of the EBV-encoded latent membrane proteins is discussed here.

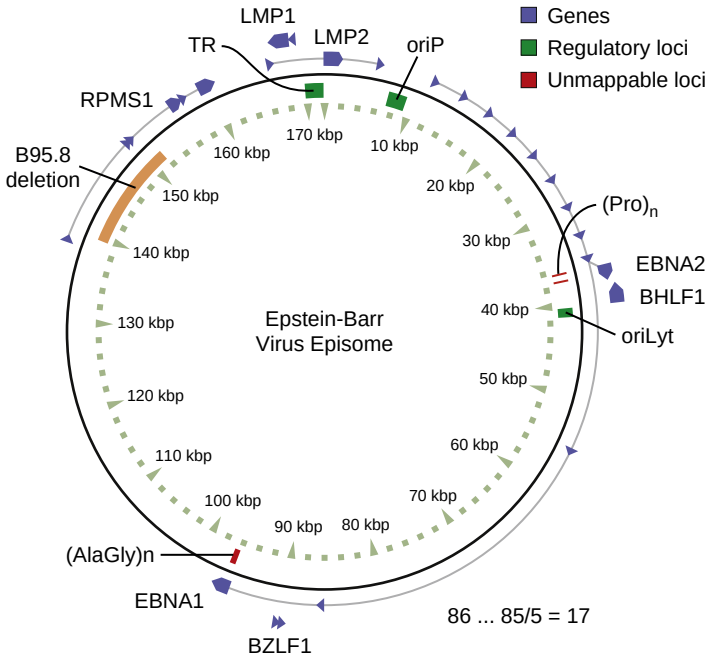
EBV Latent Membrane Oncoproteins

LMP1 is the main oncogenic protein of EBV. Studies on rodent fibroblasts showed that LMP1 expression is both necessary and sufficient for EBV-induced B-cell transformation and that LMP1 functions as a constitutively active member of the tumor necrosis factor receptor family, driving numerous signaling cascades, including the NF-κB, JNK, and MAPK pathways, regardless of the presence or absence of TNF ligand.[112,113] Additionally, LMP1 shares sequence similarity with CD40, allowing it to serve as a partial agonist receptor to allow for transmission of growth and differentiation signals to B cells.[114] LMP1 ligand-independent signaling also induces the expression of cell-surface adhesion molecules and upregulates numerous anti-apoptotic proteins, including BCL2. [115]

LMP2A transforms epithelial cells and modulates their adhesion and motility, potentially through activation of the PI3K-AKT pathway and increases in nuclear β-catenin.[116,117] In B cells, LMP2A also drives proliferation and survival of undifferentiated B cells, allowing those cells without immunoglobulin on their surfaces to migrate to peripheral lymph nodes and lymphoid organs such as the spleen and Peyer patches.[118] Additionally, LMP2A has been shown to induce the expression of genes involved in cell-cycle progression and prevention of apoptosis in Reed-Sternberg cells in Hodgkin lymphoma.[119,120]

Mechanisms of Immune Evasion

EBV encodes two key proteins, BCRF1 and BARF1, which provide robust mechanisms for escape from the adaptive immune system and persistence of infection. The cytokine and chemokine receptor BCRF1 shares significant sequence similarity with IL-10, allowing it to inhibit IFNγ synthesis by



• **Fig. 4.5** The Epstein-Barr virus (EBV) genome. The EBV genome is held as an extrachromosomal episome in latently infected cells and encodes a mix of EBV nuclear antigens (EBNAs) and latent membrane proteins (LMPs). EBNA1 is known to regulate the transcription of other EBNAs and *LMP1*, while EBNA2 has been shown to activate transcription of *LMP1* and *LMP2*. *LMP1* is the main oncogene of EBV and drives numerous signaling cascades, including NF-κB, JNK, and MAPK pathways. LMP1 also upregulates anti-apoptotic *BCL2*. LMP2 activates the PI3K-AKT pathway and increases nuclear β-catenin.

blood mononuclear cells. Decreased levels of IFNγ prevent activation of antiviral programs in neighboring epithelial and adaptive immune system cells.[121] In contrast, EBV BARF1 functions as a soluble decoy receptor for colony-stimulating factor 1 (CSF-1). Because CSF-1 typically increases expression of IFNα by mononuclear cells, BARF1 expression prevents the antiviral actions of IFNα, including induction of proteases and nucleases that control viral DNA replication and capsid production.[122] Additionally, EBV-infected cells typically downregulate the expression of proteins necessary for antigen presentation and processing on MHC class I molecules that are important for recognition of viral peptides of $CD8^+$ T cells, including TAP1/2 and MHC class I.[123]

Recent studies have shown that PD-1 expression is upregulated on tumor-specific cytotoxic $CD8^+$ T cells in nasopharyngeal carcinoma and EBV-associated lymphoma.[124,125] PD-1 overexpression was correlated with shorter overall survival, disease-free survival, and recurrence-free survival and was shown to be an independent risk factor for treatment failure by traditional chemotherapy and radiation therapy.

Merkel Cell Carcinoma Polyomavirus

Overview

Discovered in 2008 by Patrick Moore and Yuan Chang, MCPyV is a non-enveloped, icosahedral, double-stranded DNA virus with a genome of around 5 kb.[126] Merkel cell carcinoma (MCC), a malignancy of neuroendocrine cells, is diagnosed in approximately 1,500 patients per year, although annual incidence has been increasing by 5–10% in recent years.[127-129] MCC typically presents as an asymptomatic skin lesion that expands rapidly and is more prevalent in immunosuppressed, older, and fair-skinned people[130,131] (Fig. 4.6). MCC most commonly presents in sun-exposed areas, primarily on the head and neck, although cases are also seen on the upper and lower limbs.[127] Although MCC is relatively rare, it represents an aggressive subset of skin cancers, with a mortality rate approaching 30% or higher.[129]



• **Fig. 4.6** Merkel cell carcinoma in a sun-exposed area of the face. Differential diagnoses can include basal cell carcinoma, epidermoid cyst, or amelanotic melanoma.

Epidemiologic studies suggest that a combination of immunosuppression, ultraviolet light exposure, and infection with MCPyV creates the ideal setting for development of MCC. Serology-based antibody testing for MCPyV capsid proteins demonstrates that 80% of the adult population is seropositive and is most likely asymptomatically infected with the virus during early childhood.[132] Viral DNA has been found in the respiratory tract, saliva, lymphoid tissues, and gastrointestinal tract, although the skin is the primary residence of the virus.[31] However, current understanding of the complete viral life cycle and route of transmission is limited by a lack of laboratory-based experimental systems in which MCPyV can be propagated.

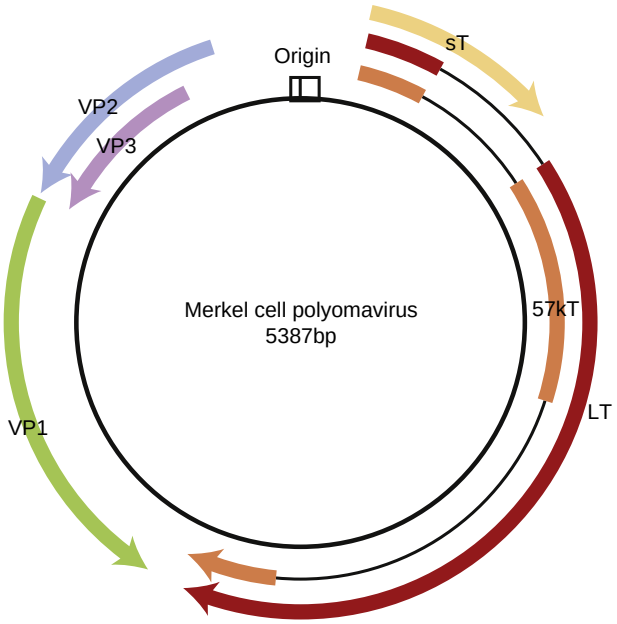
Genome Organization and Life Cycle

As mentioned, a comprehensive understanding of the MCPyV life cycle is limited by a lack of cell line models that can propagate MCPyV in the context of MCC. Recent reports suggest that MCPyV infects Merkel cells by initially binding glycosaminoglycans, including heparan sulfate, then associating with sialic acid, which functions as a co-receptor for gene transduction.[133] The 5.4-kb, circular, double-stranded DNA genome has a similar architecture to other polyomaviruses and contains bidirectional early and late coding regions[134] (Fig. 4.7). The three genes—large T antigen (LT), small T antigen (sT), and 57kT antigen (57kT)—allow for viral DNA replication, while the late genes—virus proteins 1 and 2 (VP1 and VP2)—encode the structural components of the virus capsid.[135] The early gene products are primarily responsible for modulating cell cycle progression and tumor formation in MCC.

MCPyV LT has numerous protein domains that have the potential to contribute to MCPyV oncogenesis, including a nuclear localization sequence, an Rb-binding domain, a DNA origin-binding domain, and a helicase domain.[136] The sT protein contains a protein phosphatase 2A (PP2A) binding site that has been shown to be important in virus-induced cellular transformation to MCC.[137]

Oncoproteins

The exact role of LT and sT in MCPyV oncogenesis is tenuous, with conflicting data; some groups suggest that MCP requires MCPyV T antigen proteins for pathogenesis, and other groups suggest that T antigens may play a role in initial oncogenesis but are not required after initial transformation.[138-141] Knockdown of LT and sT has been shown to increase cell death and decrease proliferation of MCC, with sT most likely serving as the main oncogenic protein. sT antigens have the ability to bind PP2A to allow for unregulated cell cycle progression. sT preserves the hyperphosphorylated status of transcription factor eIF4E-binding protein 1 (4E-BP1), allowing eIF4E to associate with the 5′ cap on processed mRNA and promote active translation.[137] Additionally, the Rb-binding motif of LT may sequester Rb and allow for unregulated progression through the G_1/S-phase



• **Fig. 4.7** The Merkel cell polyomavirus (MCPyV) genome. The three genes, large T antigen (LT), small T antigen (sT), and 57kT antigen (57kT), function to allow for viral DNA replication, while the late genes, virus proteins 1 and 2 (VP1 and VP2), encode the structural components of the virus capsid. LT and sT are thought to be the main oncogenes of MCPyV by sequestering Rb and encoding a protein phosphatase 2A (PP2A) binding site to preserve hyperphosphorylated 4E-BP1, respectively.

cell cycle checkpoint.[138] Tumor-specific mutations that truncate LT allow for the retention of the DnaJ domain that binds heat shock proteins and the Rb-binding domain, but remove the origin-binding and helicase domains necessary for transcription of viral DNA to produce virions.[142] Thus, MCPyV-positive MCC often does not produce mature virus via a lytic cycle.

Interestingly, MCPyV-positive MCCs overwhelmingly lack p53 mutations, although high copy numbers of MCPyV viral DNA are associated with p53 expression in as few as 7% of MCPyV-positive tumors.[143] Thus, while overexpression of mutated p53 likely does not contribute to oncogenesis, it is unclear how MCPyV inactivates the p53 pathway. Recent work has suggested that the LT antigen can bind to the DNA-binding domain of p53 to inhibit p53-dependent transcription of cell cycle arrest and pro-apoptotic genes.[144,145]

Mechanisms of Immune Evasion

Given the lack of a model system to culture MCPyV-positive MCC, the mechanisms of immune evasion employed by MCPyV remain uncharacterized.

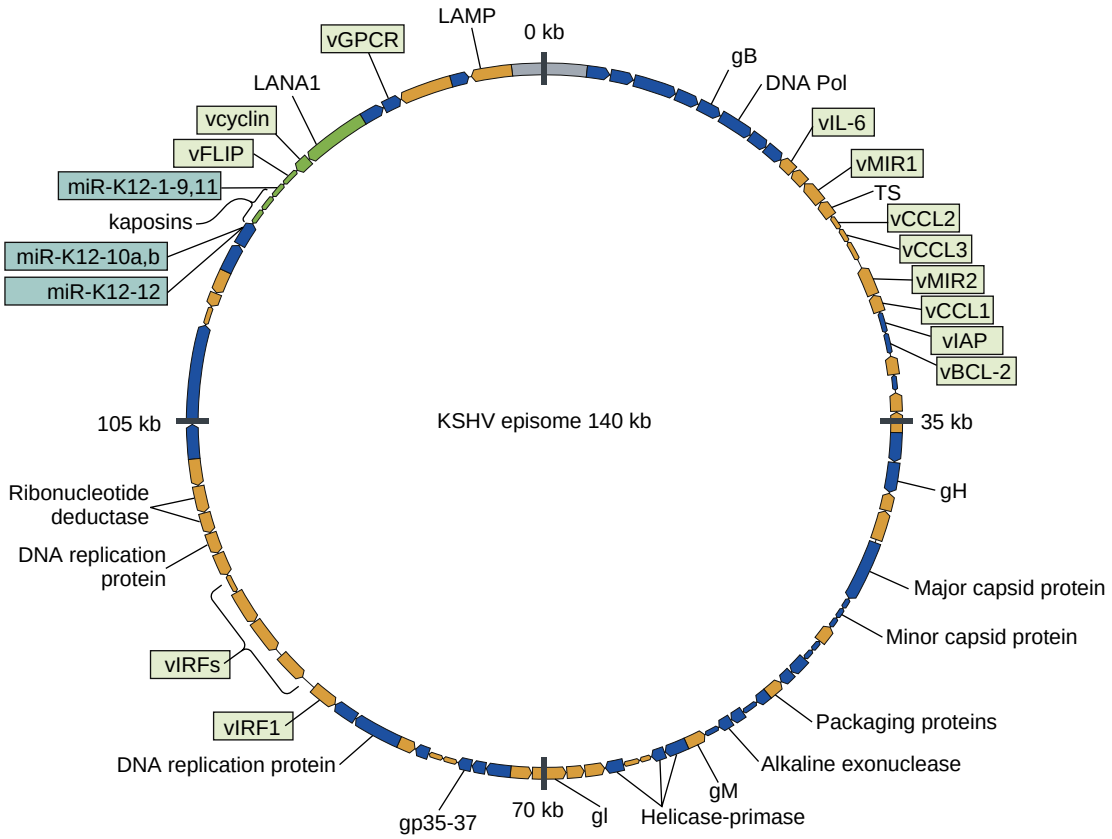
Kaposi Sarcoma Herpesvirus

Overview

Kaposi sarcoma was first discovered in 1872 by Moritz Kaposi and was initially recognized to affect Mediterranean and Eastern European men in their late 60s. During the acquired immune deficiency syndrome (AIDS) epidemic, however, KS became associated with one of the most aggressive AIDS-associated cancers that presented with lymphadenopathy and cutaneous dark purple lesions[148,149] (Fig. 4.8). The lesions are highly angiogenic, contain numerous T and B cells, and are dominated by a mixture of erythrocytes and endothelial cells that have the characteristic spindle morphology of KSHV-infected cells.[150] KSHV, the etiologic cause of Kaposi sarcoma, can be classified into five major serotypes, primarily corresponding to different geographic distributions, and can be associated with four epidemiologic forms, including sporadic KS, African KS, HIV-associated KS, and immunosuppressive-associated KS.[148] KSHV infects and remains latent in up to 50% of sub-Saharan Africans, while seroprevalence rates in Europe, Asia, and North America are less than 5%.[151] Its 165 kb linear DNA genome



• **Fig. 4.8** **A,** Kaposi sarcoma involving the oral mucosa. A confluence of several raised, nodular lesions involve the right oropharynx and the soft and hard palate, crossing the midline to involve the contralateral oropharynx. **B,** An isolated exophytic lesion involving the mucosa overlies the left mandible. Kaposi sarcoma can invade the bone and cause tooth mobility.



• **Fig. 4.9** The Kaposi sarcoma virus (KSHV/HHV8) genome. The linear DNA genome of KSHV encodes numerous glycoproteins gB, gH, gL, gM, and gN necessary for cellular attachment and entry. Latent phase gene expression is restricted to *latency-associated nuclear antigen (LANA), cyclin D, vFLIP,* and *Kaposin*, which are the four genes thought to drive KSHV oncogenesis. LANA is important for maintaining the viral episome during latency and represses cellular Rb and p53 activity. Viral cyclin-D (vCyclin) drives unrestrained cell cycle progression, while vFLIP activates the NF-κB pathway. Kaposin has been shown to increase cytokine release. Upon lytic phase reactivation, various inflammatory proteins, cytokines, and chemokines are expressed from the viral genome, including vIL6, vCCL2, vCCL3, and vIRFs. Anti-apoptotic vBCL-2 is also expressed, in addition to a number of regulatory micro-RNAs (miRs) that increase tumorigenesis.

is similar to other herpesviruses and becomes episomal upon host cell entry. Characterized by both latent and lytic portions of its life cycle, latent infection is relatively quiescent and shows limited production of virions and other immunogenic viral particles. The DNA sequence of latent cycle genes shows homology to human cellular genes and may contain excised copies of the human genome that were acquired as the virus evolved to maintain a proliferative advantage and avoid detection by the immune system.[152,153]

Genome Organization and Life Cycle

The KSHV genome is organized as linear dsDNA that is enclosed in a viral capsid and envelope[154] (Fig. 4.9). KSHV primarily infects endothelial cells and gains entry to the cell in two different phases: attachment and membrane fusion and/or endocytosis. KSHV encodes numerous glycoproteins necessary for cellular attachment, including those conserved with other herpes viruses, including gB, gH, gL, gM, and gN.[155,156] Additionally, KSHV has been shown to bind heparan sulfate, the integrin $\alpha_3\beta_1$, and DC-SIGN, a marker found on dendritic cells.[157-160] After attachment to the endothelial cell surface, KSHV likely enters the cell by fusion of the viral envelope and cellular plasma membrane and/or endocytosis via a clathrin-mediated mechanism.[161-163]

The latent phase of the KSHV life cycle is restricted to expression of a few viral proteins, including latency-associated nuclear antigen (LANA), cyclin D, viral FLICE-inhibitory protein (vFLIP), and Kaposin.[164-167] Low levels of protein expression are maintained by hypoacetylation of promoter histones and methylation of DNA. LANA seems to be the key protein necessary for persistence of the KSHV episomal viral genome during latency by affixing it to the host cell nuclear chromatic structure, primarily through histone H3 and H4 association.[168] Other proteins function in maintaining an oncogenic state and are discussed herein later. In contrast, systematic expression of viral capsid and envelope proteins, identified as immediate early, early, and late genes, characterize the lytic cycle. Cells that undergo stochastic lytic reactivation express macrophage inflammatory protein-1, viral IL-6, viral Bcl-2, and various miRNAs.[169,170] The immediate early genes tend to activate downstream genes responsible for

making the host cellular environment suitable for viral replication. The RTA protein is the best characterized among immediate early genes and serves as the key protein necessary for latent to lytic cycle progression. RTA binds the pluripotent transcription factor Oct-1, in combination with RBPJκ, to drive transcription of lytic cycle genes but is repressed by the key latent protein LANA.[171,172] The early gene subsets are characterized by the expression of Kaposin and viral IL-6.[173] Kaposin encourages the export of intron-lacking viral RNA from the nucleus, although the mechanism is poorly defined. KSHV also encodes a viral version of IL-6 that is activated during the lytic phase to promote proliferation and survival of B cells and upregulates expression of a viral G-protein coupled receptor (GPCR) to contribute to tumor angiogenesis.[174] Late gene expression is primarily focused on the production of viral capsid and envelope components.

Oncoproteins and miRNAs

Four key latency-associated proteins, LANA, vCyclin, vFLIP, and Kaposin B, along with a cluster of miRNAs, are known to contribute to KSHV oncogenesis. LANA is the protein required for establishing and maintaining KSHV latency in proliferating endothelial cells by tethering the circular viral DNA to host chromosomes during mitosis.[175] LANA also interferes with Rb and p53 function through its E3 ubiquitin ligase activity, leading to unrestrained cell cycle progression and a hampered DNA repair response.[176,177] Nuclear sequestration of GSK-3β (glycogen synthase kinase 3β) also prevents β-catenin phosphorylation and degradation, leading to increased transcription of TCF/LEF-regulated genes that have been shown to be involved in cellular differentiation.[178] LANA may also epigenetically silence the TGF-β locus, further contributing to oncogenesis.

The viral cyclin shares significant homology with cellular cyclin D, although it has been shown to interact with a broader repertoire of cyclin-dependent kinases and is less sensitive to cyclin-dependent kinase inhibitors, such as p21.[179-181] vCyclin drives unrestrained cell cycle progression, leading to activation of the p53-mediated DNA damage response. However, LANA inhibition of the p53 response allows for robust progression and continued mitosis. In contrast, vFLIP has been proved to be a potent activator of the NF-κB pathway, leading to increased expression of NF-κB-regulated cytokines and driving an inflammatory local tumor microenvironment.[182-184] Kaposin B also increases cytokine release, specifically of IL-6, by blocking the degradation of cytokine mRNAs through its interaction and activation of MK2 (MAPK-associated protein kinase 2).[185]

A cluster of latency-associated 12 miRNAs has been shown to be highly active in KSHV-associated cancers.[186] One of the miRNAs, miRNA-k12-11, mimics the host oncogenic miRNA-155 that is important in immune regulation and lymphocyte differentiation.[187] miRNA-k12-11 downregulates the expression of BACH-1, a transcriptional repressor of hypoxia, and associated genes like HIF1α to further modulate KSHV-associated tumorigenesis.[188]

Mechanisms of Immune Evasion

KSHV interferes with both the adaptive and innate immune system to avoid detection and elimination of KSHV-infected epithelial cells, including interfering with IFN signaling, altering the host cell chemokine repertoire, inhibiting complement, and escaping NK and cytotoxic T-cell responses. Upon infection of epithelial cells with KSHV, the cytoplasmic protein IRF3 becomes phosphorylated and is translocated to the nucleus to induce the expression of IFNβ. However, KSHV encodes viral IRF genes that are structurally similar to host IRFs but lack key tryptophan residues that are necessary for DNA binding.[189] Thus, the vIRFs inhibit the production of type I IFN genes by acting as dominant inhibitors of cellular IRFs. vIRF1 has also been shown to bind and sequester p300, a key transcriptional co-activator required for efficient transcription of viral response genes, while vIRF3 interacts with IRF7 to prevent the DNA-binding activity of IRF7 and thus blocking the production of IFNα.[190,191]

KSHV modulates the host chemokine response by encoding three viral chemokine homologs, vCCL1, cCCL2, and vCCL3, that function as either agonists or antagonists of host chemokine receptors in order to skew the antiviral immune response toward an immunosuppressive T_H2 phenotype instead of an immunostimulatory T_H1 phenotype.[192] vCCL1 acts as an agonist for CCR8, while vCCL2 agonizes CCR3 and vCCL3 agonizes CCR4. These CCR3, CCR4, and CCR8 receptors are expressed preferentially on T_H2 lymphocytes.[150,193-195] Additionally, vCCL2 is immunosuppressive and can antagonize a wide variety of host cytokine and chemokine receptors found primarily on T_H1 cells. By skewing the immune response toward a T_H2 phenotype, virally infected cells can avoid attracting cytotoxic $CD8^+$ T cells.[192,196] Myeloid-derived cells such as macrophages can also be suppressed by a virally encoded homolog of CD200 that provides an inhibitory signal to cells that produce T_H1 cell-associated cytokines.[197]

The complement system that culminates in the formation of the membrane attack complex and results in cell death can be activated by antibody binding, recognition of pathogen surfaces, or recognition of carbohydrates on the microbial surface.[198] KSHV has evolved to interfere with the pathways of complement activation by encoding host regulators of complement activation.[199] The lytic protein KCP (KSHV complement control protein) enhances decay of the classic C3 convertase, prevents C3b deposition on virally infected cells, and serves as the necessary co-factor for inactivation of C3b and C4b.[200]

Similar to other oncoviruses, KSHV downregulates MHC class I expression, primarily through two lytic cycle gene products, K3 and K5.[201] K3 and K5 increase ubiquitination of cell surface MHC class I molecules, leading to rapid internalization and lysosomal degradation.[202] This prevents expression of viral proteins on MHC class I molecules, leading to a less robust activation of the cytotoxic T-cell response. However, downregulation of MHC class I molecules is usually a signal for NK cells to recognize and lyse virally infected cells. K5 has been shown to downregulate cell surface molecules ICAM-1

and B7-2, two co-stimulatory molecules that are necessary for NK cell activation, through increased ubiquitination and lysosomal degradation.[203,204] Downregulation of ICAM-1 prevents NK cells from binding tightly enough to virally infected cells to recognize a lack of MHC class I molecules, and lack of B7-2 prevents robust activation by not providing a necessary co-stimulatory signal.[202]

Conclusion

Virally induced malignancies serve as a model system in which to understand mechanisms of oncogenesis and immune evasion. Viruses induce oncogenesis by modulating the cellular biology through oncogene capture, insertional mutagenesis, and genome instability,[32] while simultaneously employing mechanisms to escape host immune recognition and clearance. A robust understanding of both of these mechanisms can provide a foundation upon which to build a growing understanding of cancer development as well as better direct efforts in the development of novel treatment strategies for virally associated cancers.

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5 Diagnostic Imaging

BRONWYN HAMILTON

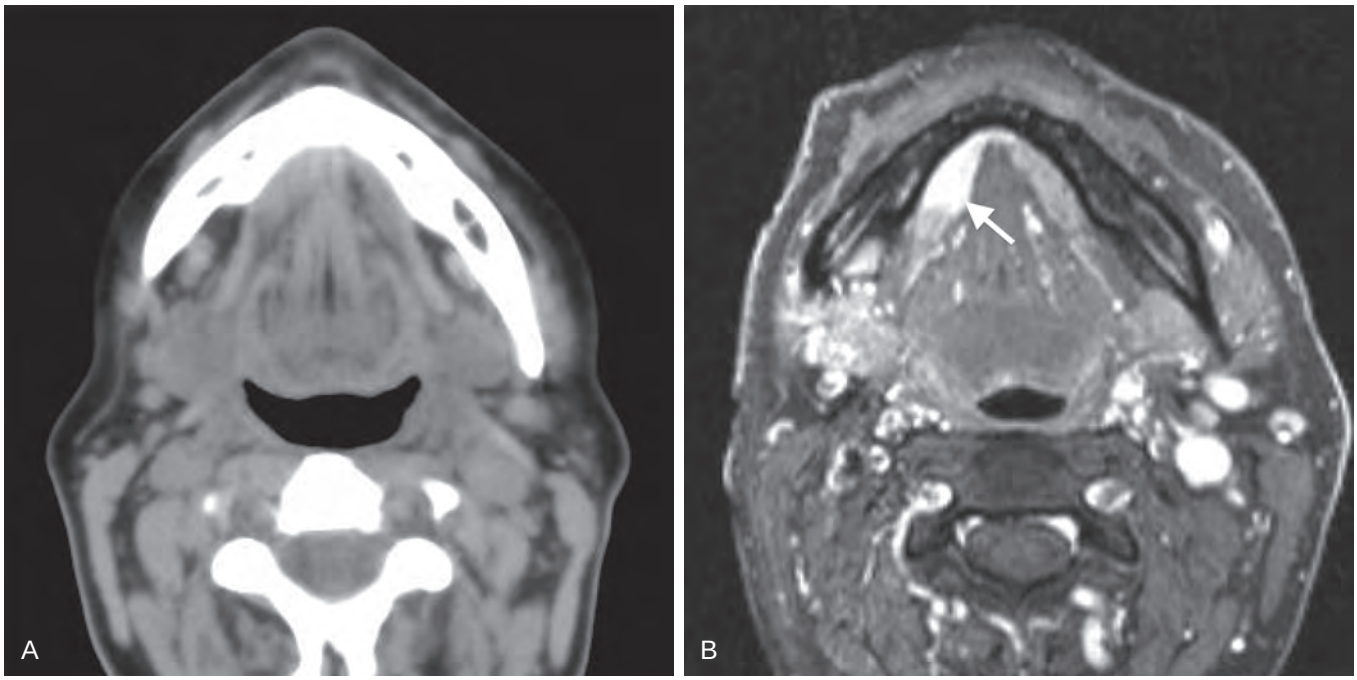
Anatomic Imaging: Computed Tomography and Magnetic Resonance Imaging

Anatomic imaging has become an indispensable tool in the clinical evaluation and staging of head and neck squamous cell carcinoma. Enhanced neck computed tomography (CT) is the modality of choice for most institutions for work-up of new head and neck cancer because of its widespread availability, short scan times, excellent multiplanar reconstruction capabilities, and familiarity among clinicians.

Enhanced magnetic resonance imaging (MRI) offers several advantages over CT; however, MRI is mainly limited by long scan times. MRI is particularly well suited to specific anatomic locations, such as the paranasal sinuses, salivary glands, and oral cavity, because motion artifacts are less problematic there. Dental amalgam artifacts are also typically much smaller on MRI than CT, allowing for better visualization of oral cavity primary lesions. Soft tissue contrast is better with MRI even in patients without technical artifacts, allowing for more sensitive detection of subtle lesions (Fig. 5.1). Hypopharynx and larynx cancers may be better imaged with good quality MRI, particularly for cartilage invasion. However, patients with issues related to managing secretions and motion or claustrophobia are better imaged with CT.

Imaging is helpful in initial cancer work-up to evaluate local spread of disease that may be inaccessible to clinician evaluation, and it has the potential to upstage primary and nodal status. Anatomic imaging with CT and MRI can also be helpful for preoperative identification of variant anatomy that may be at risk (Fig. 5.2), particularly during trans-oral robotic surgery.

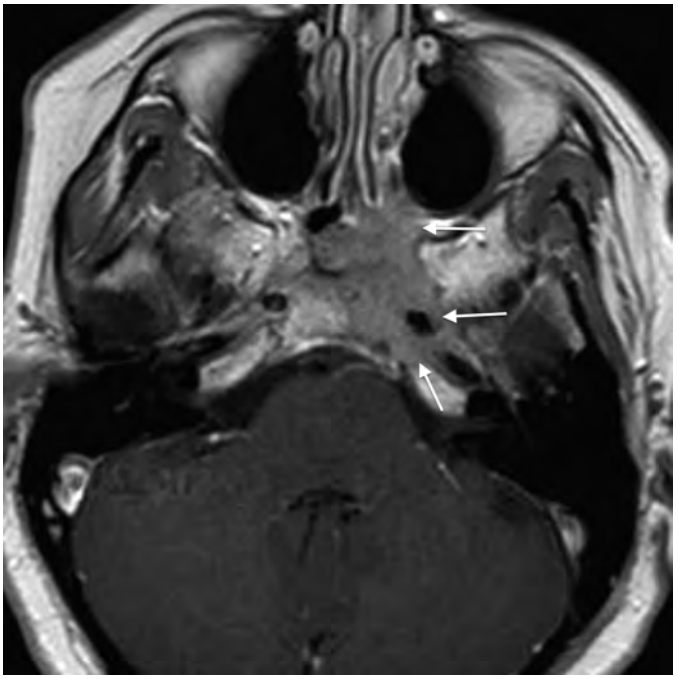
Imaging can benefit evaluation of the post-therapy neck because patients may have indurated difficult-to-palpate necks or abnormalities involving deep non-palpable structures in the neck. Examples include retropharyngeal nodal metastasis,



• **Fig. 5.1** Axial non-contrast CT **(A)** performed in a 53-year-old woman with fullness in the anterior floor of mouth shows no convincing abnormality. Reason for lack of contrast is unclear. Axial T1-weighted post-contrast MRI with fat saturation **(B)** performed at the same time as **A** shows excellent delineation of a right sublingual gland enhancing mass *(arrow),* later proven to be adenoid cystic carcinoma.



• **Fig. 5.2** Axial contrast-enhanced CT demonstrates medial deviation of the left internal carotid artery *(arrow).* This anatomic variant is a relative contraindication to oropharyngeal trans-oral robotic surgery resection, because of the risk for vascular injury.



• **Fig. 5.3** Axial T1-weighted post-contrast MRI reveals extensive perineural tumor spread in the pterygopalatine fossa and spreading along V2 with invasion of the cavernous sinus and skull base *(arrows)* in a patient previously treated for left parotid adenoid cystic carcinoma. Tumor had originated from the auriculotemporal nerve.

perineural tumor spread, and localized involvement of bone, cartilage, or marrow.

For many institutions, CT is a much simpler and easier tool for initial cancer evaluation. MRI is most useful to evaluate the paranasal sinuses and salivary glands and to evaluate cases of suspected skull base, intracranial and/or orbital spread of disease, intracranial involvement, and perineural tumor spread (Fig. 5.3). Any tumor that involves osseous structures, and in particular the skull base, may benefit from both CT and MRI characterization because of inherent and complementary advantages (CT for early cortical erosion and osseous destruction and MRI for marrow involvement and better soft tissue detail).

Primary Site Evaluation by Imaging

The goal of primary site imaging is for surgical planning and to improve clinical staging by detection of deep spread of disease that may not be clinically accessible to evaluation (Fig. 5.4). Some primary neoplasms, particularly those involving salivary glands, are nearly invisible on CT and may only be well demonstrated on MRI (Fig. 5.5). Some examples of improved preoperative staging through imaging include the paraglottic fat invasion, which may upstage a clinical T2 laryngeal carcinoma to T3 (Fig. 5.6) and spread of retromolar trigone carcinomas to the masticator space or skull base. Cartilage assessment is best performed by reviewing bone window views of neck CT. Sclerosis is a non-specific imaging finding (Fig. 5.7); however, destruction adjacent to enhancing neoplasm is predictive of invasion (Fig. 5.8). Identifying subtle cartilage destruction on CT is more challenging than on MRI because of variations in normal cartilage ossification. Overt extralaryngeal extension provides definitive evidence of cartilage destruction and upstages laryngeal cancers to T4, however. Invasion of the carotid sheath or prevertebral muscles by the primary site or nodes may not be easily evaluated clinically, but may be detected on CT or MRI, allowing for correct staging to T4c.

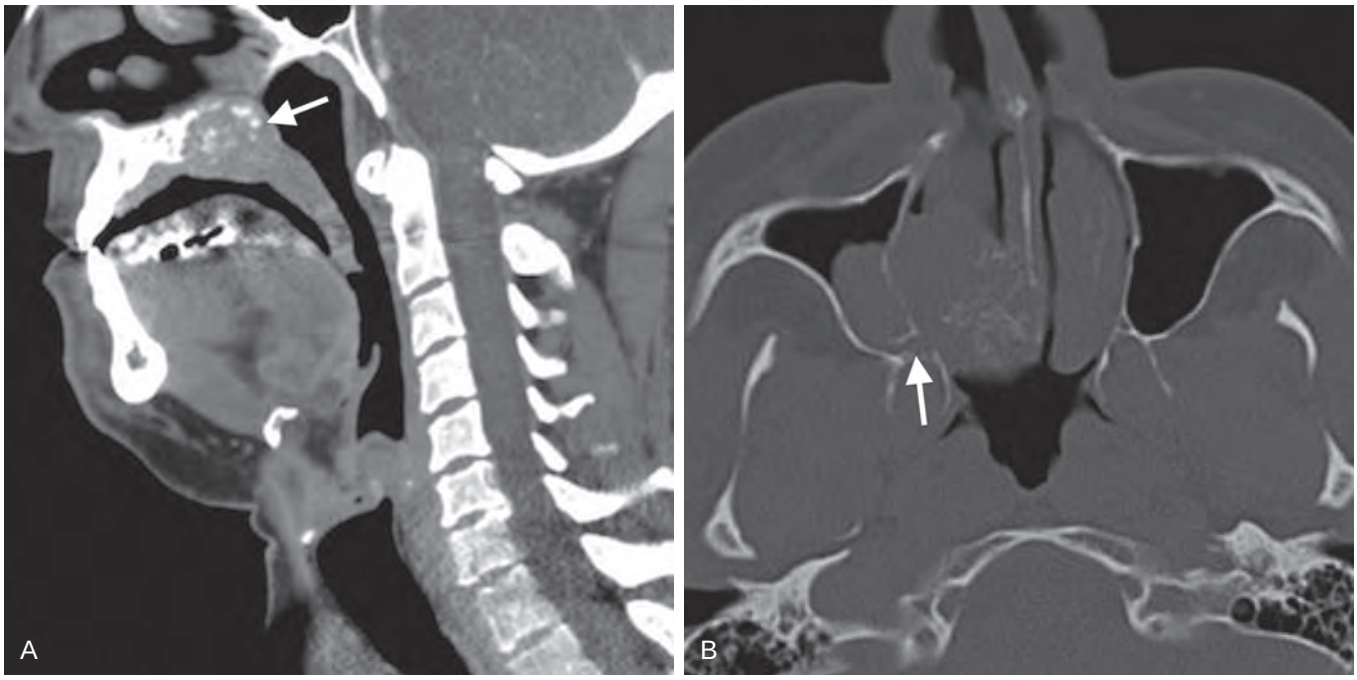
Evaluation of submucosal disease can be aided by imaging, particularly for tumors of cartilage origin. Although MRI can be somewhat useful, CT for chondroid tumors of the larynx is most characteristic and nearly pathognomonic (Fig. 5.9).

Lymph Node Evaluation by Imaging

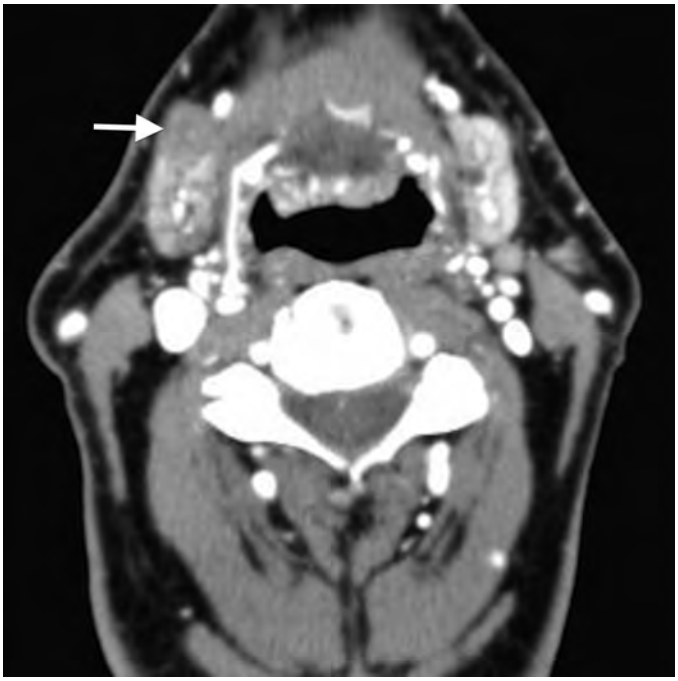
Imaging evaluation of lymph nodes is neither sufficiently sensitive nor specific for accurate staging, usually necessitating formal neck dissection and histologic confirmation. Adding CT was shown to improve the detection rate of cervical adenopathy from 75% using physical examination alone to 91% using both CT and physical examination in one comparative study.[1] The following criteria are commonly accepted standards for pathologic or malignant lymph nodes on imaging:

1. Size >1.5 cm in levels I and II*
2. Size >1 cm in remaining nodal levels
3. Imaging evidence of necrosis
4. Rounded nodal shape/morphology
5. Intense and/or heterogeneous enhancement

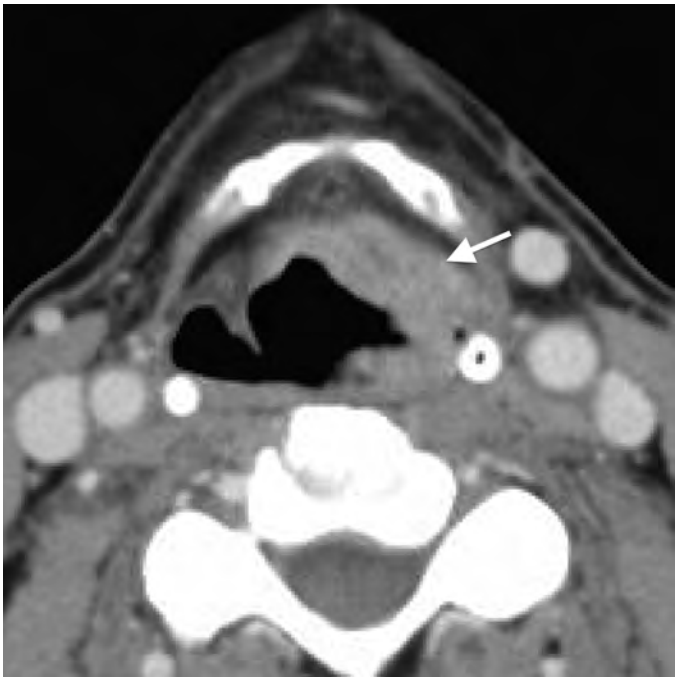
*There is some controversy regarding the choice of short versus long axis for nodal measurement, with resulting impact on relative sensitivities and specificities.



• **Fig. 5.4** Sagittal multiplanar reconstruction **(A)** from a contrast-enhanced CT demonstrates a soft tissue mass with internal calcifications eroding the hard palate *(arrows).* Biopsy disclosed mucoepidermoid carcinoma. Axial bone windows **(B)** in the same patient show invasion into the right greater palatine foramen *(arrow).*



• **Fig. 5.5** Axial contrast-enhanced CT shows a subtle mass in the right submandibular gland *(arrow)* in a patient with upper aerodigestive tract squamous cell carcinoma and fludeoxyglucose-avid nodule (positron emission tomography [PET] not shown) in right level I suspicious for metastatic adenopathy. This was biopsy-proven pleomorphic adenoma. Salivary gland masses can be nearly occult on enhanced CT, and MRI is better to evaluate. Note that primary salivary neoplasms are an occasional source of false-positive studies for metastatic carcinoma with PET. Careful correlation with anatomic imaging is required for correct diagnosis.



• **Fig. 5.6** Axial contrast-enhanced CT shows soft tissue invasion into the pre-epiglottic fat *(arrow),* a clinically inapparent finding that upstages this supraglottic cancer to T3.



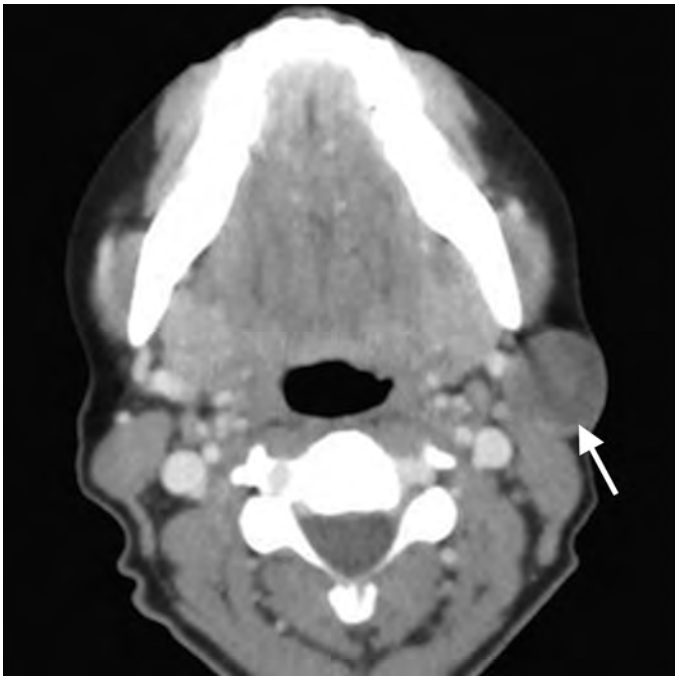
• **Fig. 5.7** Axial contrast-enhanced CT in a patient with small primary squamous cell carcinoma in the left post-cricoid hypopharynx adjacent to marked left cricoid sclerosis *(arrow).* Sclerosis is common and not a reliable indicator of cartilage involvement, in that it may be reactive.



• **Fig. 5.9** Axial contrast-enhanced CT in a 53-year-old man with vocal cord paralysis and submucosal mass lesion of the subglottis demonstrates enlargement of the cricoid cartilage *(arrow),* with smooth margination and relatively low attenuation. No destructive changes are evident. Imaging characteristics are nearly diagnostic for laryngeal chondroid neoplasm.

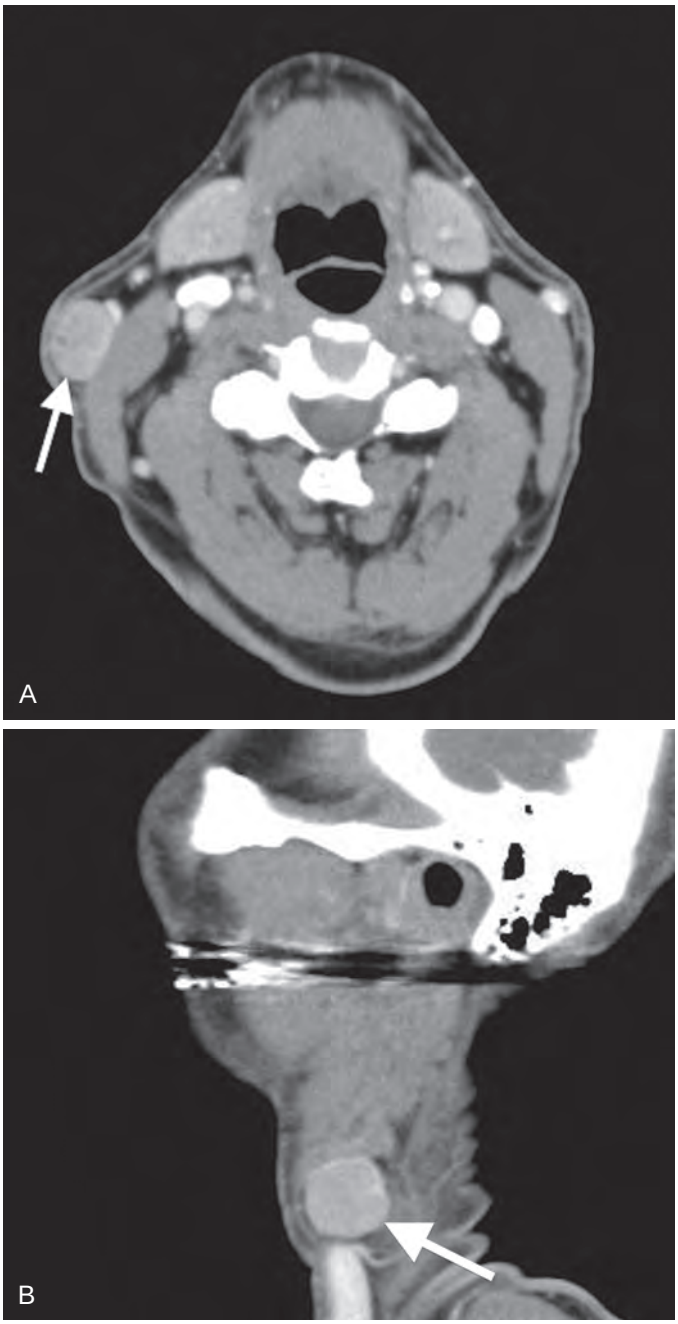


• **Fig. 5.8** Axial contrast-enhanced CT shows erosion of the cricoid *(arrow)* consistent with invasion of adjacent squamous cell carcinoma.



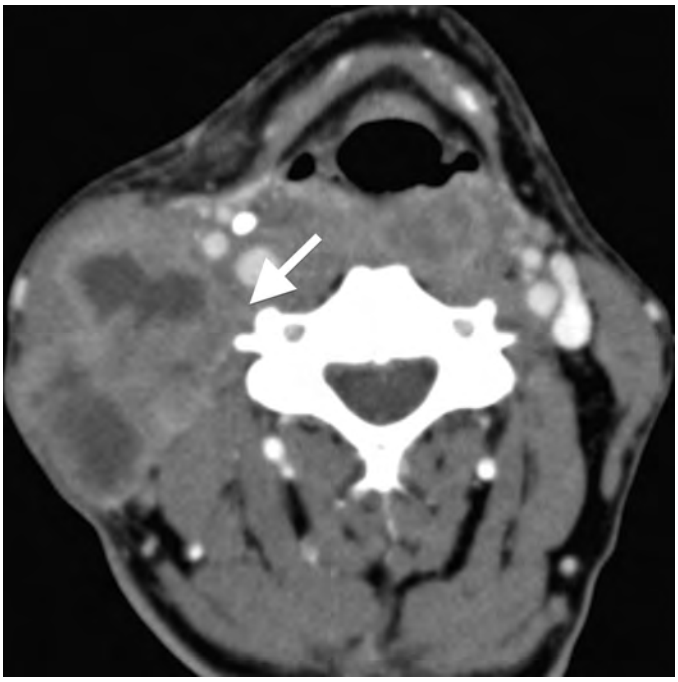
• **Fig. 5.10** Axial contrast-enhanced CT in a 24-year-old woman with palpable left level II cystic mass *(arrow)* mimicking branchial cleft cyst. This was metastatic papillary thyroid carcinoma. Metastatic adenopathy in thyroid cancer is frequently cystic and may have calcifications. Human papillomavirus–positive squamous cell carcinoma is also known to result in cystic level II adenopathy that can mimic branchial cleft cyst if no obvious mucosal primary is evident.

New neck masses in a young adult should be considered malignant until proven otherwise. A common error is assuming that cystic level II region masses are misdiagnosed as branchial cleft cysts, when malignant adenopathy is a far more common cause of cystic masses in this location (Fig. 5.10). The rise in human papillomavirus–positive cancer has contributed



• **Fig. 5.11** Axial contrast-enhanced CT **(A)** and sagittal multiplanar reconstruction **(B)** demonstrate a mass between the sternocleidomastoid and platysma muscle *(arrows).* This localizes to the parotid tail, suggesting primary parotid neoplasm; however, in this case biopsy confirmed melanoma metastasis to an intraparotid lymph node. Skin cancers of the ear and scalp usually metastasize first to the parotid lymph nodes, being that they are the first order nodal basin. Skin or systemic cancers may metastasize here, and it is common for patients to under-report a history of skin cancers that may be a helpful clue to diagnosis.

to the prevalence of cystic nodal metastasis as a common clinical presentation for unknown primary head and neck cancer.[2] Other interpretive errors include misinterpretation of masses at the angle of mandible as level II metastasis, which may be of parotid tail in origin. Masses here favor primary parotid neoplasms or metastases from skin malignancies (Fig. 5.11).

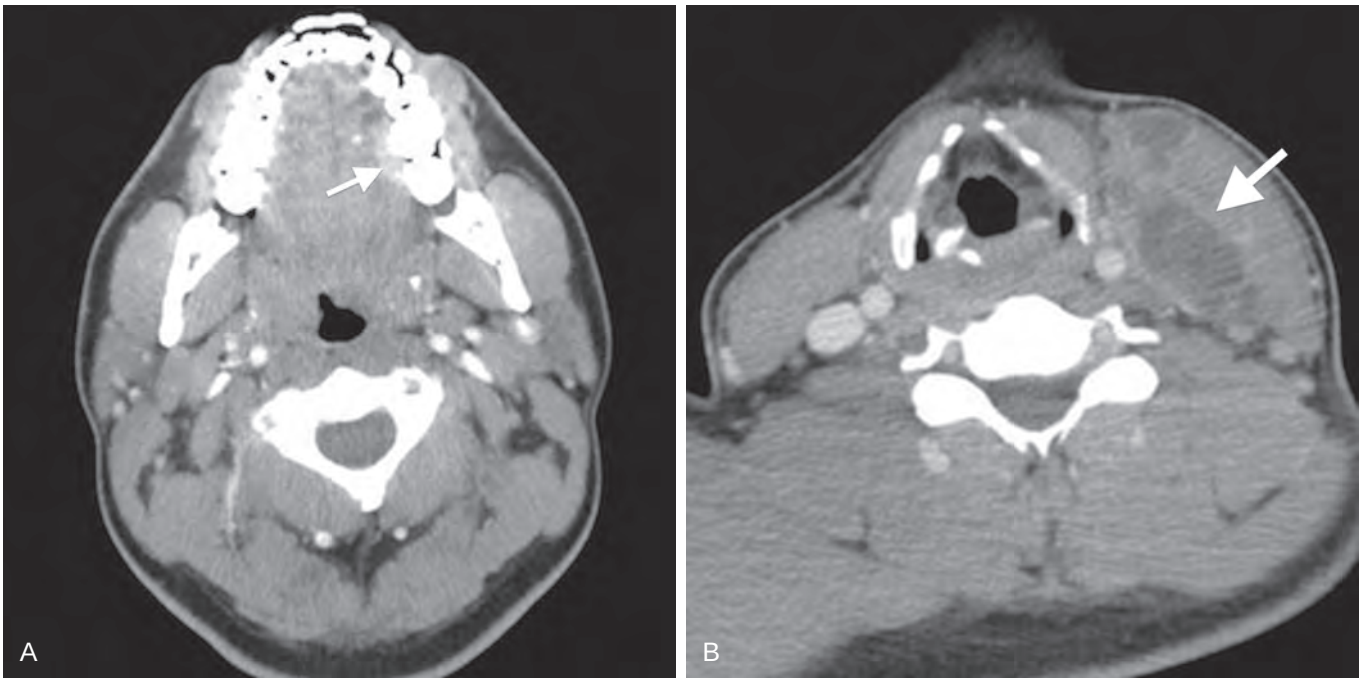


• **Fig. 5.12** Axial contrast-enhanced CT in a 60-year-old man with hypopharyngeal squamous cell carcinoma is suspicious for invasion of the prevertebral muscles, although this was not documented clinically. Extensive metastatic adenopathy is also present *(arrow),* with margins inseparable from the lateral aspect of the carotid sheath and perivertebral space, suspicious for invasion and extracapsular extension *(arrow).* Gross radiologic evidence of extracapsular extension correlates with worse prognosis. This patient also had a synchronous lung cancer identified at presentation (not shown).

Nodal extracapsular extension (ECE) increases the rate of locoregional failure and is an indication for adjuvant chemoradiation therapy. CT evidence of ECE includes ill-defined or irregular nodal borders and adjacent soft tissue invasion (Fig. 5.12). Although studies evaluating imaging prediction of ECE have shown low sensitivity overall, there is good specificity when there is invasion of adjacent normal structures.[3,4] Radiographically detected ECE has little predictive impact on locoregional control, but is a predictor of distant control failures and lesser survival, independent of formal pathologic staging.[5]

Imaging the N0 Neck

Imaging is a helpful adjunct to evaluation of the clinically node-negative neck. The choice of modality is usually dependent on institutional expertise. Evaluation of various modalities has shown no significant difference in diagnostic accuracy for CT, MRI, positron emission tomography (PET), or ultrasound (US). Based on meta-analysis data, pooled estimates for sensitivity were 52%, 65%, 66%, and 66%, for CT, MRI, PET, and US, respectively. Pooled estimates for specificity were 93%, 81%, 87%, and 78% for CT, MRI, PET, and US, respectively.[6] Disadvantages of US include a technical inability to detect deep lymph nodes such as retropharyngeal lymph nodes and operator dependence, although technical artifacts on CT, MRI, and PET such as those due to metallic



• **Fig. 5.13** Axial contrast-enhanced CT **(A)** in a patient with clinically low-risk T1 N0 M0 oral tongue cancer *(arrow)* showed no adenopathy. This patient underwent sentinel lymph node sampling to avoid cervical lymph node dissection. Contrast-enhanced CT **(B)** and positron emission tomography (not shown) performed 13 months later showed massive left nodal recurrence in levels II through IV *(arrow)*.

implants can also distort or limit image quality. Selected patients may be able to avoid diagnostic cervical lymph node dissections given low pre-test probability and imaging-negative nodal evaluation.

Sentinel Lymph Node Evaluation

Sentinel lymph node evaluation is a more recently adopted strategy to avoid the risks of cervical lymph node dissection in low-risk cancer patients. The draining lymph node identified scintigraphically can be selectively removed, and if cancer-free, has been used to justify avoidance of prophylactic and diagnostic cervical lymph node dissection.[7] Data to support this approach are limited, however, and even low-risk patients may have nodal failures (Fig. 5.13).

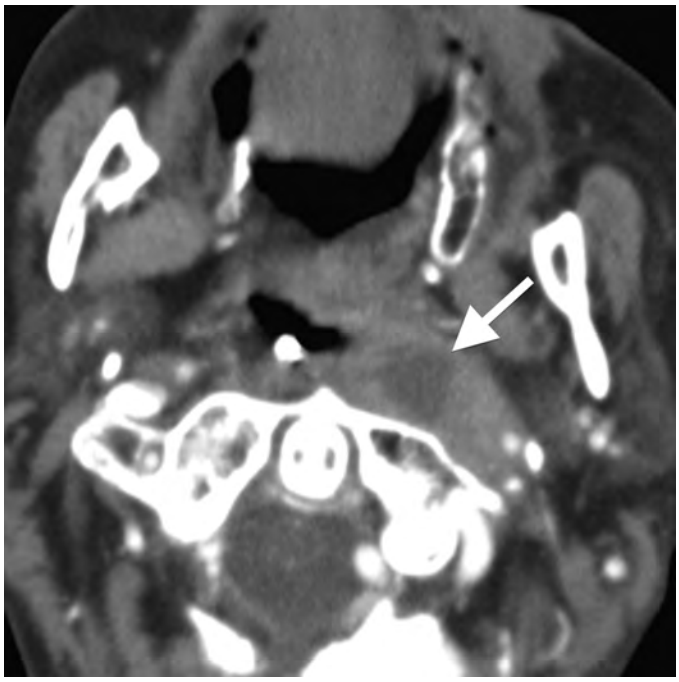
Imaging Nodal and Metastasis Staging Impact on Treatment Planning

Identification of lymph nodes not removed by a cervical neck dissection is important for radiation treatment planning. Small sub-centimeter lymph nodes may be non-palpable but morphologically abnormal on CT, allowing for correct characterization (Fig. 5.14). Retropharyngeal lymph nodes are not clinically palpable and can easily be overlooked on imaging (Fig. 5.15). Although uncommon, these are present in about 10% of oropharyngeal and 8% of hypopharyngeal squamous cell carcinomas, and confer worse outcomes in terms of disease recurrence, distant relapse, and survival.[8,9] Recognition is important because retropharyngeal adenopathy represents an important cause of treatment failure if not included in the radiation field.[10,11]



• **Fig. 5.14** Axial contrast-enhanced CT in a patient with a large supraglottic squamous cell carcinoma demonstrates a small necrotic right level III lymph node *(arrow)*, which is pathologic given its necrotic appearance. Small nodes like this may be non-palpable and can impact N staging.

PET can also be a helpful adjunct to determine nodal metastasis, although it is also limited by a number of factors. First, small lymph nodes (<5 mm) may be a source of false-negative results. Nodal cystic or necrotic change is a frequent source of false-negative PET studies because the centrally necrotic



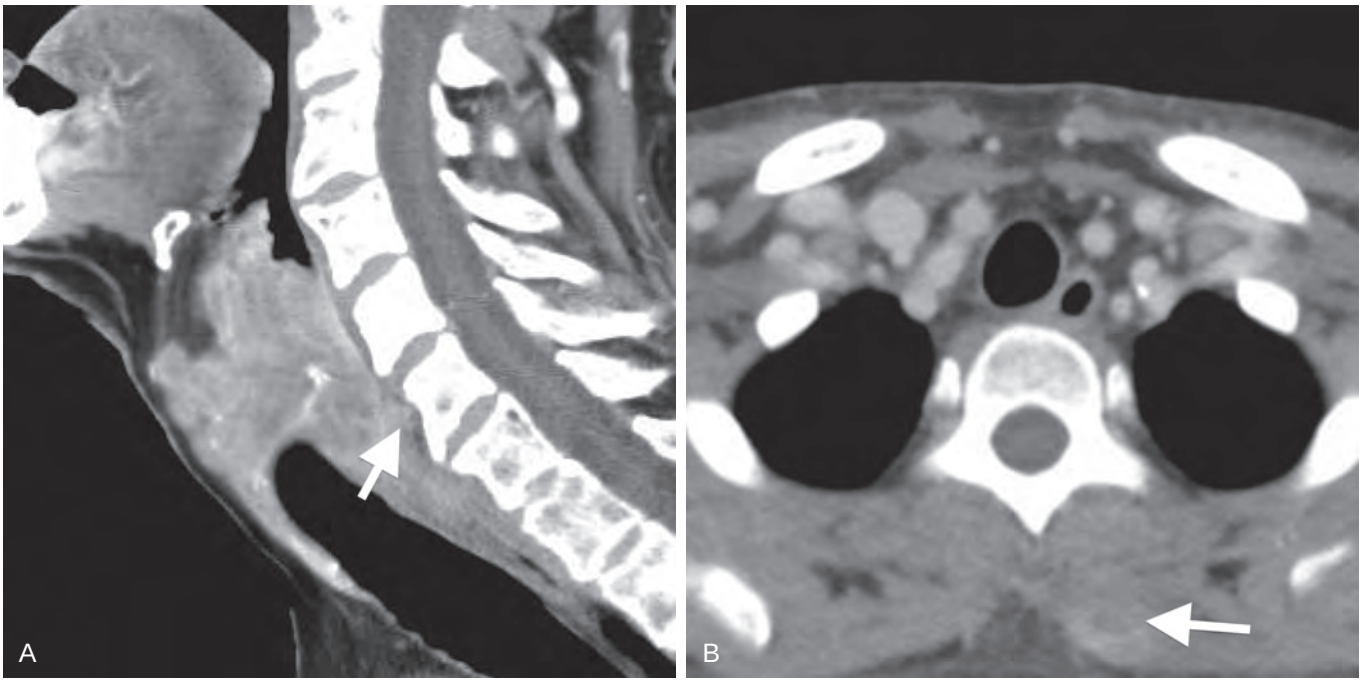
• **Fig. 5.15** Axial contrast-enhanced CT in a 63-year-old man with oropharyngeal cancer. An irregularly marginated rim-enhancing nodule in the left retropharyngeal space *(arrow)* was an atypical site of metastatic adenopathy. This occurs in about 10% of oropharyngeal carcinomas and is important to include in the radiation treatment plan.

portion is not metabolically active and therefore does not take up radionuclide. Notable sources of radiographically false-positive lymph nodes on PET include inflammatory and infected lymph nodes, recent intervention (biopsy and/or radiation), and interpretive errors (normal morphologic uptake misinterpreted as adenopathy). Many sources of potential errors can be minimized with knowledge of normal variant uptake and a dedicated contrast-enhanced neck CT for co-localization.

Detection of synchronous or metachronous primary carcinomas and metastatic disease is aided by either CT or PET/CT. Some abnormalities can be easily missed with imaging, but may be aided by directed clinical history and physical examination. These include uncommon locations of head and neck cancer metastatic disease dissemination, such as dermal and muscle metastases (Fig. 5.16), and metastases to brain and spinal cord. Dedicated brain and spine MRI best detects metastases to the neuraxis, although the metastases are sometimes incidentally detected at the top of the field of view on routine neck CT surveillance (Fig. 5.17).

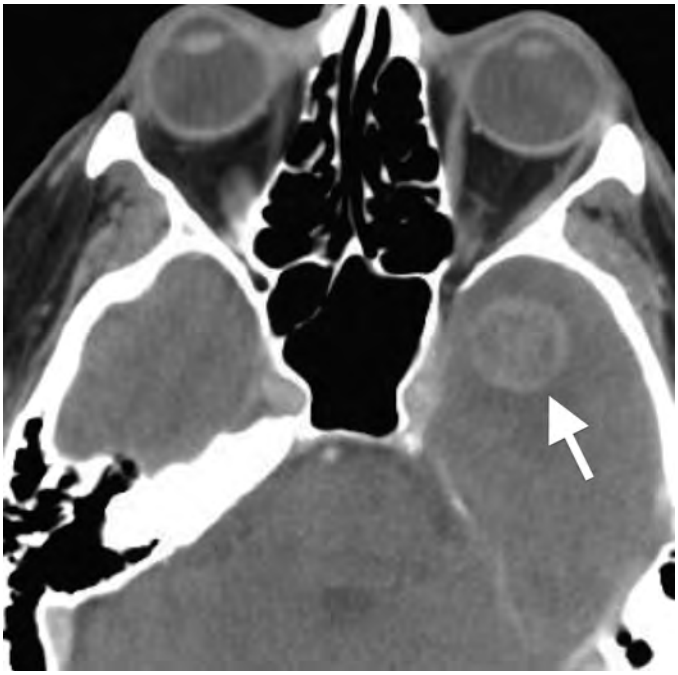
Physiologic Imaging: Positron Emission Tomography

PET has also become commonplace in head and neck cancer, although its use is limited geographically by reimbursement



• **Fig. 5.16** Sagittal multiplanar reconstruction **(A)** from a contrast-enhanced CT in a 56-year-old man with stage IV squamous cell carcinoma of the larynx demonstrates enhancing soft tissue invading the prevertebral muscles *(arrow),* suspicious for perivertebral space invasion. Axial contrast-enhanced CT **(B)** in a 29-year-old woman with squamous cell carcinoma shows a subtle enhancing mass in the left paraspinal muscles *(arrow).* The mass was initially missed until the patient brought this area, which was painful, to clinical attention. This was biopsy-proven metastatic carcinoma.

issues. The primary indication for PET at initial presentation is to assess for distant metastatic disease, to evaluate for potential primary sites in the setting of the unknown primary cancer (Fig. 5.18), and/or to evaluate physiologic activity within borderline cervical adenopathy.[12]

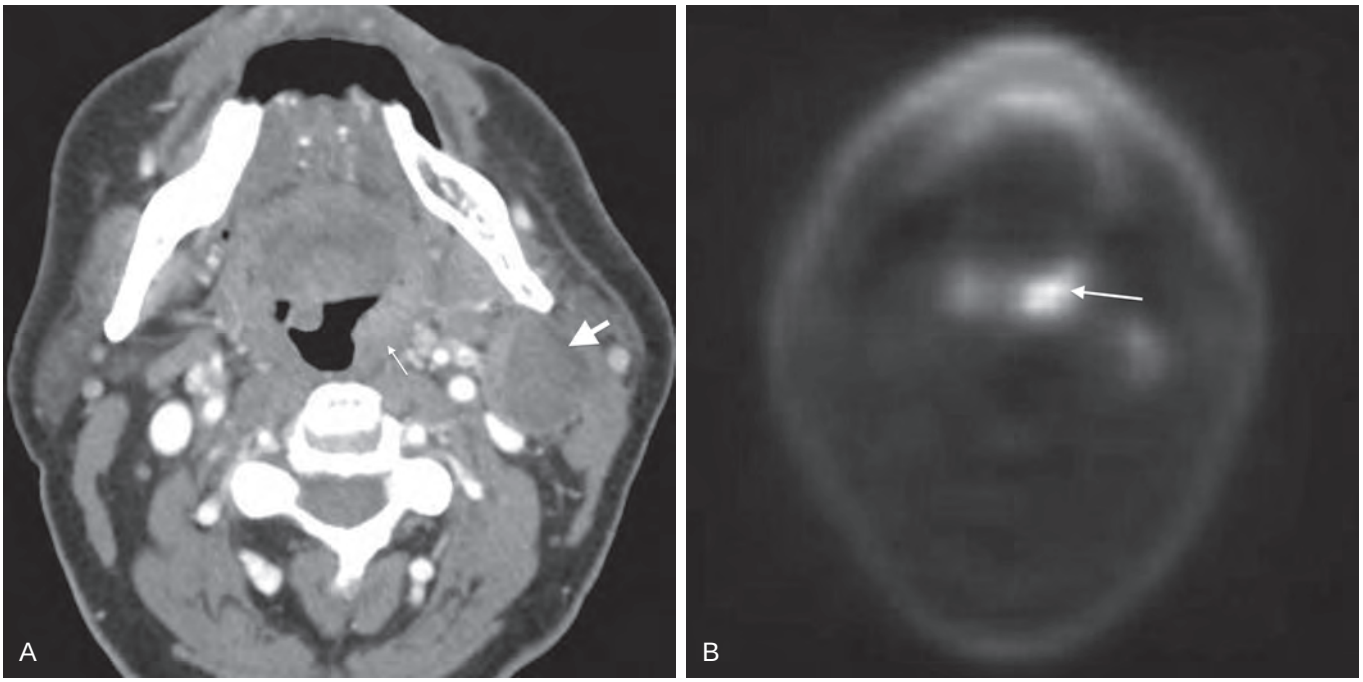


• **Fig. 5.17** Axial contrast-enhanced CT reveals a metastatic lesion to the brain *(arrow)* in a patient with recurrent laryngeal cancer. These finding prompted a change in treatment plan to palliation.

PET is useful in the post-treatment setting to evaluate for local and distant disease recurrence. The main limiting factors with post-treatment PET are surgical and particularly radiation therapy changes that cause increased uptake due to inflammation that can mimic tumor recurrence. Delaying PET for 12 weeks after treatment minimizes this confounder.

Some cancers are non–fludeoxyglucose (FDG)-avid tumors, particularly small and/or necrotic tumors, but also those with low metabolic activity. These can be sources of false-negative PET studies, but can be resolved with enhanced CT/cross-sectional imaging. PET is not helpful for discriminating recurrent tumor from inflammation and infection, including radionecrosis, which can be PET avid. Background avidity can obscure malignant disease, such as brain metastasis, but this is often easily resolved with dedicated anatomic imaging. Interpretive errors include mis-registration errors (motion during scan results in inappropriate localization of FDG-avid tissue) and muscle uptake, which can be resolved by review of non–co-registered images. Finally, salivary uptake in infectious, inflammatory, and benign neoplastic processes can mimic metastatic disease (Fig. 5.19).

Most PET studies are co-registered to a CT performed concurrently. Ideally, this should be a contrast-enhanced study of diagnostic quality similar to other CT scans; however, at many institutions only a low-dose non-contrast CT is obtained because of reimbursement limitations. This makes interpretation more challenging. In the future, PET/MRI holds promise as an evolving modality in head and neck cancer because it combines functional and molecular information with anatomic imaging, but there is a paucity of data on its utility in that it is currently primarily a research tool.



• **Fig. 5.18** Axial contrast-enhanced CT **(A)** shows necrotic level II adenopathy *(thick arrow)* in a patient with unknown primary squamous cell carcinoma. Subtle left palatine tonsillar asymmetry *(thin arrow)* might suggest a possible primary source although concurrent positron emission tomography **(B)** is more convincing, given the focal hypermetabolism *(arrow),* and helps guide directed biopsy.

Post-therapy Imaging: Recognizing Normal Postoperative Changes

Given the wide variety of surgical treatment options available to patients, it is helpful to be familiar with the normal appearance of the postsurgical neck, particularly if seen by a surgeon or radiation oncologist other than the primary treating physician. Flaps, lymph node dissections, and denervation changes all change the appearance of the neck on imaging in recognizable ways. Surgical flaps that incorporate bone and fat do not result in interpretive dilemmas; however, the incorporation of muscle and other soft tissue structures can make differentiation from tumor challenging. Obtaining a baseline imaging study can help improve the ability to detect recurrent cancer in this setting. Other than detection of new enlarging soft tissue abnormalities compared with the postsurgical baseline examination, the most useful imaging clue to recurrent neoplasm is the presence of abnormal enhancement. Variations in contrast enhancement, dose, and timing can influence detection rate, however. Stomal and suture line recurrences are frequent sources of local treatment failures, as is cervical adenopathy (Fig. 5.20).

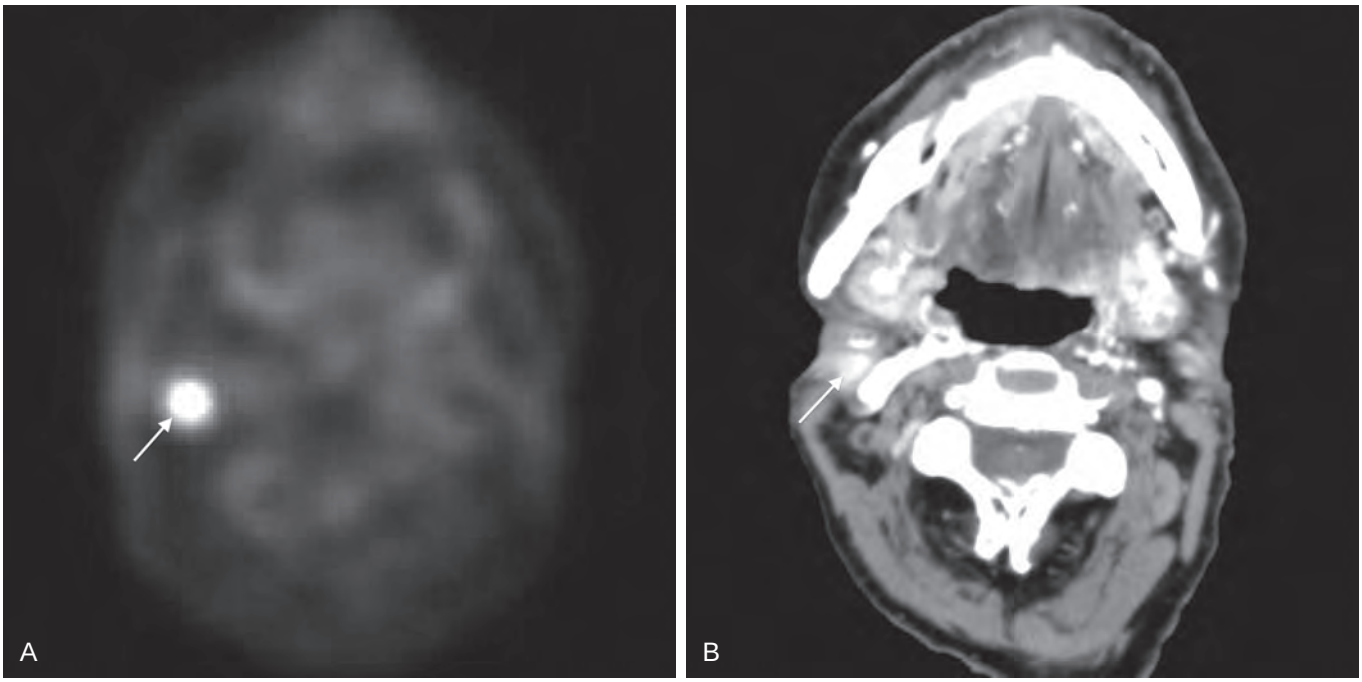
Patients undergoing small bowel grafts for aerodigestive tract reconstruction normally incorporate mesenteric lymph nodes that can mimic malignant adenopathy (Fig. 5.21). This should be recognized as a normal postoperative appearance; however, if there is persistent concern, negative metabolic imaging with PET and/or short interval follow-up to document stability can be useful adjuncts to confirm a suspected benign nature.

Post-therapy Imaging: Imaging of Radiation-Induced Inflammatory Changes

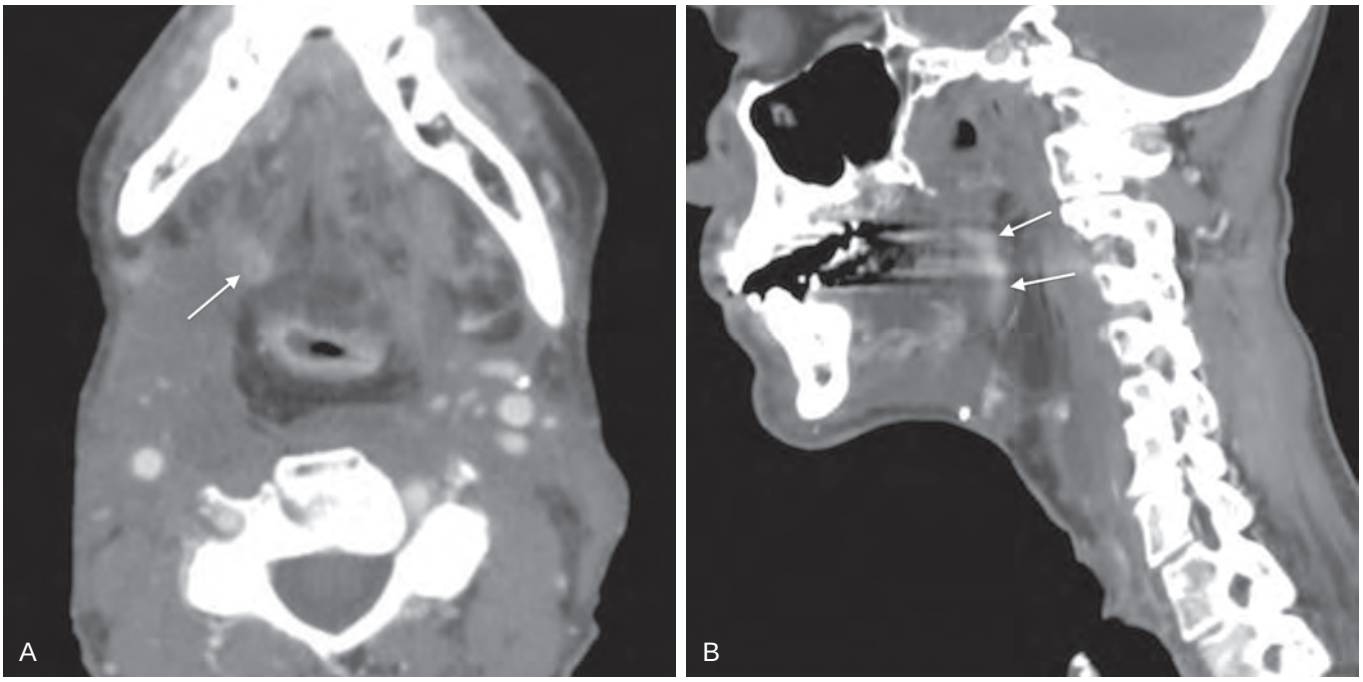
Imaging is determined by the location involved. New brain enhancement after radiation therapy for upper aerodigestive tract carcinomas can be confirmed by review of the radiation fields and dosimetry charts. Perfusion-weighted MRI can be a helpful confirmatory test if needed (Fig. 5.22).

The hallmark findings of radionecrosis include soft tissue gas, bony and/or cartilaginous fragmentation, and lack of normal enhancement. Exposure of bone or cartilage may be seen clinically and/or radiographically and helps in diagnosis. Although mandibular involvement is most frequently encountered, other sites of involvement, such as laryngeal cartilage and vertebral radionecrosis, can be more clinically challenging due to their deep and inaccessible locations. Imaging can improve characterization of radionecrosis in these areas if gas and fluid collections are observed in areas where no recent instrumentation has been performed (Fig. 5.23). Superimposed infection is very common. Osseous or cartilaginous fragmentation and destructive changes are also typical findings.

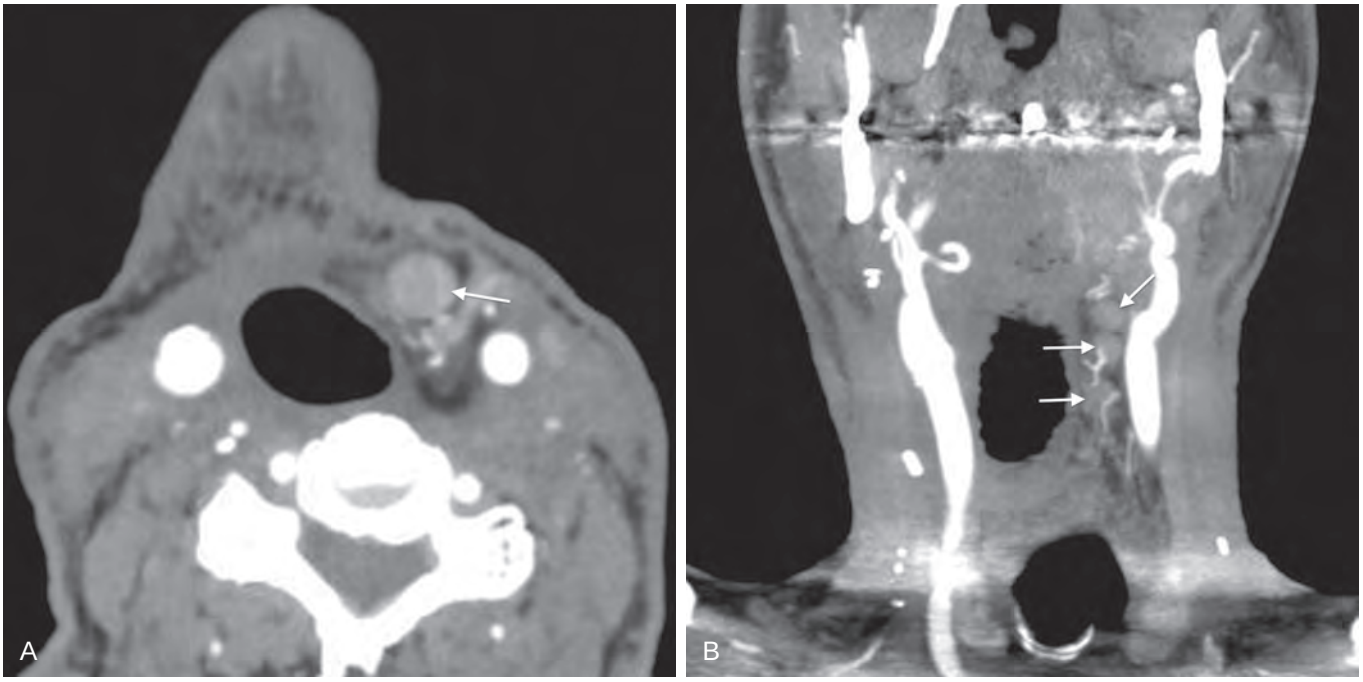
PET is frequently positive in radionecrosis and thus does not serve to distinguish this from tumor recurrence. Although biopsy or surgical resection is the gold standard for diagnostic confirmation, it can aggravate radionecrosis and should be avoided if feasible. Some cases of laryngeal chondronecrosis are successfully treated with antibiotics and hyperbaric oxygen, although many cases may require complete total laryngectomy. Hyoid necrosis is a finding that should warrant particular caution, because it can herald future carotid "blow-out," given the



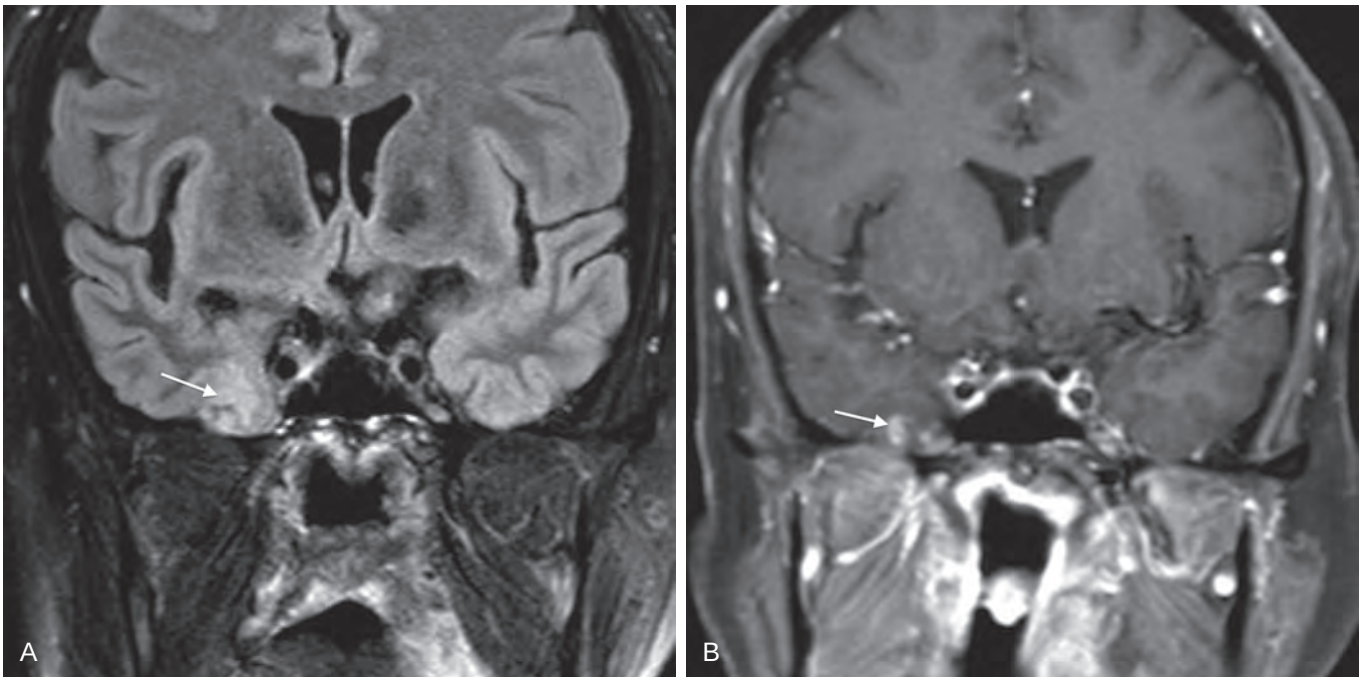
• **Fig. 5.19** Axial positron emission tomography image **(A)** raises concern for metastatic adenopathy in right level II *(arrow)* in this patient with primary squamous cell carcinoma. Axial contrast-enhanced CT **(B)** properly localizes this mass to the right parotid gland. Fine-needle aspiration showed pleomorphic adenoma *(arrow)*.



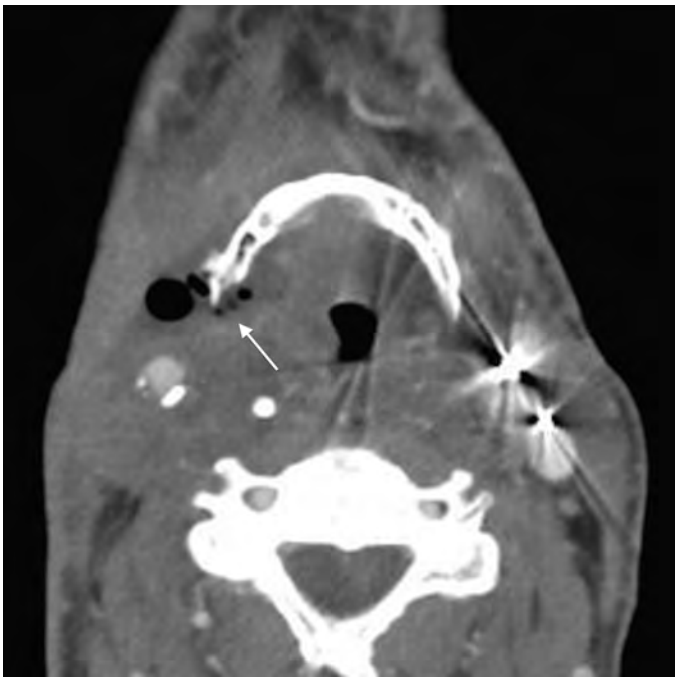
• **Fig. 5.20** Axial contrast-enhanced CT **(A)** and sagittal multiplanar reconstruction **(B)** in a 70-year-old man with a history of base of tongue squamous cell carcinoma status post neck dissection and chemoradiation many years earlier. He recently underwent total laryngopharyngectomy and flap reconstruction for new cancer of the right oropharynx and subglottis. Early stomal recurrence is noted *(arrows).* Focal enhancing nodules, particularly along flap margins, should raise concern for recurrent disease.



• **Fig. 5.21** Axial contrast-enhanced CT **(A)** and coronal multiplanar reconstruction **(B)** in a patient after laryngopharyngectomy with jejunal flap reconstruction shows rounded lymph nodes *(arrows)* included as part of the normal mesenteric free flap transfer. This should not be confused with malignant adenopathy.



• **Fig. 5.22** Coronal fluid attenuation inversion recovery imaging **(A)** and coronal T1 post-contrast MRI **(B)** in a patient status post radiotherapy for tonsil cancer shows edema and enhancement in the medial right temporal lobe *(arrows)* that is typical for radionecrosis. Correlation with the dosimetry maps and perfusion weighted imaging, along with short interval surveillance imaging, can help confirm the diagnosis and ensure image resolution and differentiation from developing central nervous system neoplasm or infection.



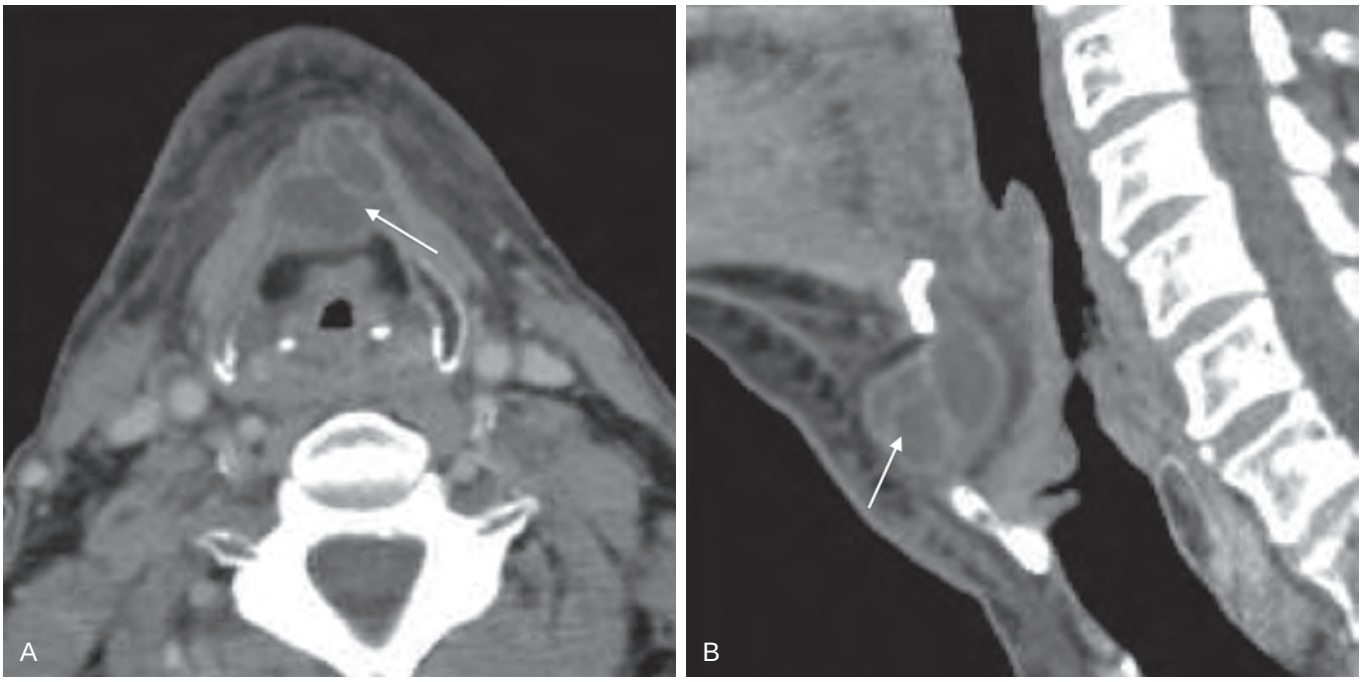
• **Fig. 5.23** Axial contrast-enhanced CT in a 62-year-old man after re-irradiation for recurrent base of tongue cancer reveals a rim-enhancing fluid collection with pockets of gas surrounding a fragmented and eroded hyoid bone *(arrow)*. These findings are consistent with radionecrosis and the clinician should be wary of a higher risk for future carotid "blow-out"; the internal carotid artery is in close proximity, also surrounded by low-density phlegmon and/or abscess.

proximity of the carotid artery (thus assuming a similar radiation dose) to the hyoid.

A benign finding occasionally seen after radiation therapy is cystic transformation of a preexisting thyroglossal duct cyst or remnant.[13] Such remnants are not uncommon, and they may be small and underappreciated on the pretreatment study. Because the remnants may enlarge and cystic change may develop, during radiation treatment, they can mimic malignant level VI adenopathy (Fig. 5.24). Comparison to the pretreatment scan can usually identify the lesion and confirm this benign entity. Surveillance imaging will show regression of the lesion after inflammation has subsided.

Conclusion

Imaging has become a useful tool in the work-up of patients with head and neck cancer. Although many institutions vary with regard to preference in modality, contrast-enhanced neck CT is the most practical and widely used modality because it is less susceptible to motion and many technical artifacts. Despite limitations, PET is particularly helpful in M staging (distant metastatic disease), helping guide directed biopsies in unknown primaries, and to further characterize clinically and/or radiographically indeterminate disease. MRI is the preferred modality for detecting perineural spread of disease and for assessing the potential of sinonasal, orbital, and intracranial spread of disease.



• **Fig. 5.24** Axial **(A)** and sagittal multiplanar reconstruction **(B)** images in a patient with cystic transformation of a preexisting thyroglossal duct cyst *(arrows)* developing after radiation therapy for squamous cell carcinoma. Routine surveillance imaging showed regression.

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6

Endoscopic Evaluation of the Upper Aerodigestive Tract

JAMES PHILLIP THOMAS

A patient may come in to the office with a complaint that resembles a diagnosis, such as "I have a cancer." However, more commonly a patient arrives with a symptom, one that requires an examination to determine the cause—and the more accurate the examination, the more accurate and precise the diagnosis. Symptoms that most commonly trigger an endoscopy of the upper aerodigestive tract are:

- A voice problem
- A breathing problem
- A swallowing problem
- A neck mass

For these symptoms, endoscopy can play many roles:

- Finding a lesion
- Visibly identifying what the lesion is likely to be
- Defining the margins of the lesion
- Defining the functional impairments of the lesion
- Predicting which functional impairments are likely after treatment of a lesion

Although there are times when even an average physician can place a mirror in the back of the throat and identify a cancer, standard endoscopy can go far beyond the simple indirect mirror assessment of the larynx. Standard-definition endoscopy can identify the major structures of the larynx (Fig. 6.1).

Standard endoscopy still has some significant limitations. From the typical endoscopic viewpoint (see Fig. 6.1), only non-subtle masses are identifiable and many problems with breathing and phonation are missed.

Goals of advanced endoscopy include:

- *For hoarseness:* Determine what pathology impairs vocal cord vibration.
- *For dyspnea:* Determine if a change in anatomy is creating a fixed airway obstruction between the upper pharynx and the carina or determine if a change in vocal cord movement functionally obstructs the airway.
- *For dysphagia:* Determine if there is a mass along the pathway of the esophagus. Determine if there is a change from normal in laryngeal elevation, laryngeal closure or epiglottic inversion during a functional evaluation of swallowing.
- *For a neck mass:* Determine if there is a subtle primary lesion in the pharynx or larynx.

Advanced endoscopic evaluation of the pharynx and larynx is the combination of technology (equipment) and technique (expertise) leading to a precise diagnostic view of both the structures and the function of this anatomic region. *High-definition technology* for imaging the pharynx and larynx, including the vocal cords, currently includes:

- Chip-on-tip endoscopes
- High-definition cameras
- Stroboscopic lighting
- Digital recording
- High-definition monitors
- Selective color filters

Additional technologies will likely continue to be developed and added to the clinical examination as they become available and understood.

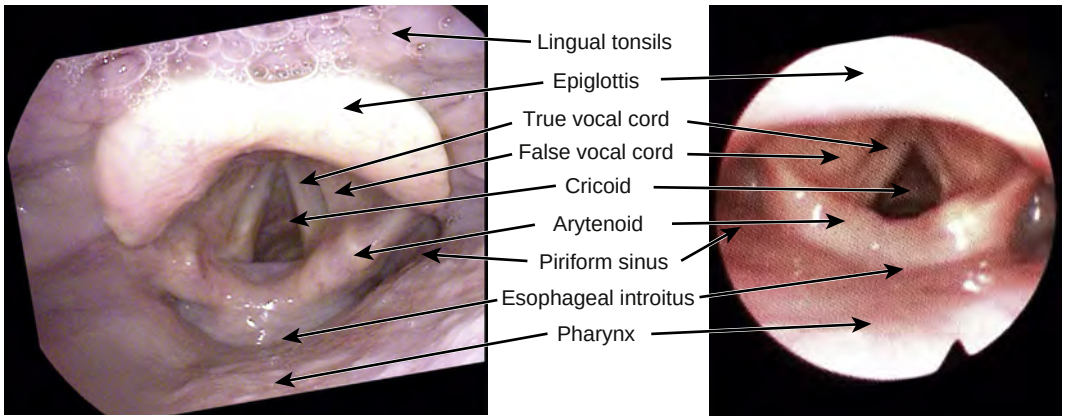
High-definition techniques allow the examiner to optimize images, regardless of whether they are obtained with high or low technology or even lower quality equipment. An optimum combination of equipment and technique leads to a cost-effective, high-yield, and accurate diagnosis. It can lead to a detailed conversation with the patient about diagnosis, treatment, and future function.

High-definition techniques include:

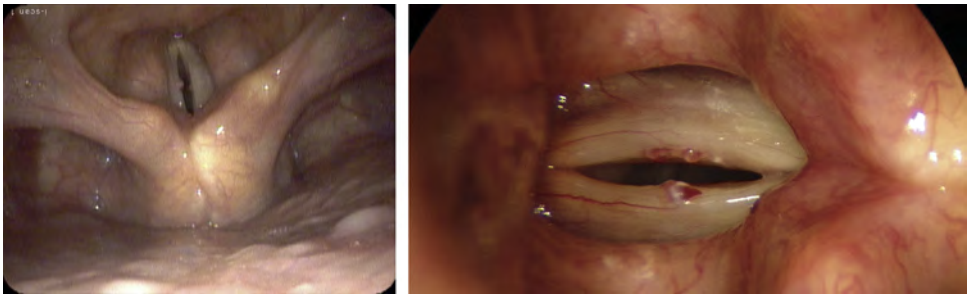
- Moving the endoscope close to the area of pathology
- Using lidocaine to pass obstructions
- Using both rigid and flexible endoscopes for improved perspective

Low-definition laryngeal endoscopy is where examiners may have high-technology equipment and even a high-technology education, but they:

- Do not realize where to aim the endoscope given the symptom
- Do not take the time to record quality images of the area of pathology
- Do not understand the need for using low technology wisely to bring the area of pathology into focus
- Do not review for mistakes to learn from them



• **Fig. 6.1** Standard or typical endoscopic view of larynx. General structures including lingual tonsils, epiglottis, false vocal cords, true vocal cords, arytenoids, anterior cricoid cartilage, esophageal inlet, piriform sinuses and pharyngeal walls are visible. *Left,* Chip-on-tip endoscopic view. *Right,* Flexible fiber-optic view.



• **Fig. 6.2** Flexible endoscope wide field of view compared with a rigid endoscopic narrower field of view. Images taken on the same day, at the same approximate pitch and same approximate phase of stroboscopy. The camera is positioned at approximately the tip of the epiglottis. *Left,* Standard definition (640 × 480) chip endoscope has a wide field of view, and the vocal cords appear in the distance. *Right,* High-definition (1080i) rigid endoscope (camera oriented horizontally to fill more of the frame) has a narrower field of view, and the vocal cords appear larger viewed from the same distance with the camera at the tip of the epiglottis.



• **Fig. 6.3** Flexible endoscope tip curvature. The more uniform the curve and the closer the articulation to the tip, the more maneuverable the endoscope will be within the confines of the larynx. *Left,* Less flexible articulation. *Right,* More flexible articulation.

Endoscopy Laboratory

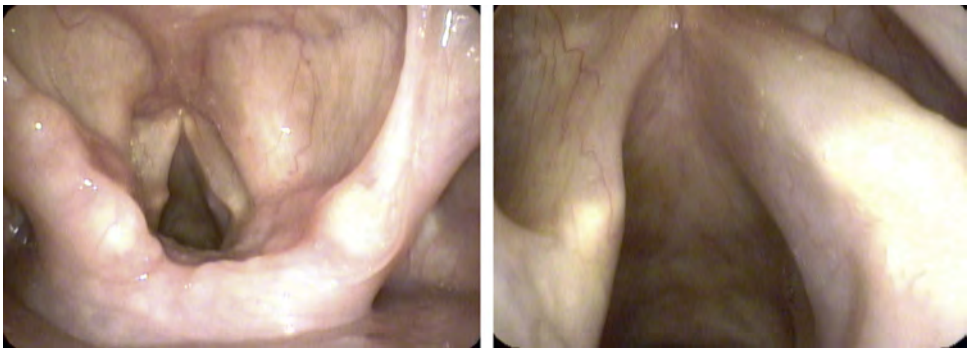
A voice laboratory might contain some or all of the following:

- Endoscopes (rigid and/or flexible [fiber-optic or chip-on-tip])
- Camera and processor (integrated or external, possibly with color selectivity)
- Bright light source
- Stroboscope
- Hardware and software for recording and reviewing video with simultaneous audio
- High-definition monitors

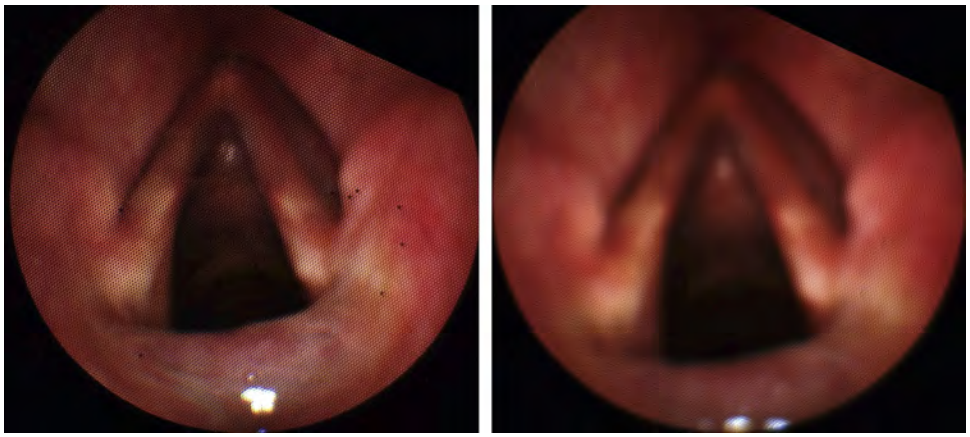
Flexible Endoscopes

There are a number of variations in the equipment available for flexible laryngoscopy. The main difference is between fiber-optic technology, where the camera is mounted onto the eyepiece, and chip-on-tip technology, where the camera is integrated into the tip of the endoscope. The flexible aspect of these technologies allows the endoscope to be passed through the nose, which typically reduces the gag reflex during the examination (compared to a transoral mirror examination). The endoscope can easily be passed close to the vocal cords and even beyond the structures of the larynx. Most laryngeal function is retained during a flexible endoscopic examination.

Flexible endoscopes have a wider-angle lens than rigid endoscopes, enabling a wider-angle perspective than the human eye. Consequently, close objects appear relatively larger than objects farther away (Fig. 6.2). With bright light, there is high depth of field, so much of the image can be in focus at a given time. Endoscopes with an even curve in their distal articulation and with the articulation located close to the tip of the endoscope are easiest to maneuver in the confines of the pharynx and larynx (Fig. 6.3). One of the most valuable features of flexible endoscopes with a tight curve is the ability to change



• **Fig. 6.4** Angle of view. *Left,* Vocal cords viewed from above. The left true vocal cord is bowed and there is atrophy of the left false vocal cord. *Right,* With the endoscope oriented nearly parallel to the vocal cords, the left vocal cord's thyroarytenoid muscle atrophy becomes more apparent compared directly with the mass of the right vocal cord.



• **Fig. 6.5** Fiber-optic endoscope view. Fiber-optic light fibers are visible as circles. *Left,* Broken fibers are black dots. *Right,* Intentionally defocused image reduces the effect of pixilation at the expense of clarity.

perspective or the angle of view within the confines of the airway. A modified view of the vocal cords provides additional perspective on the same area of pathology (Fig. 6.4).

Fiber-optic Endoscopy

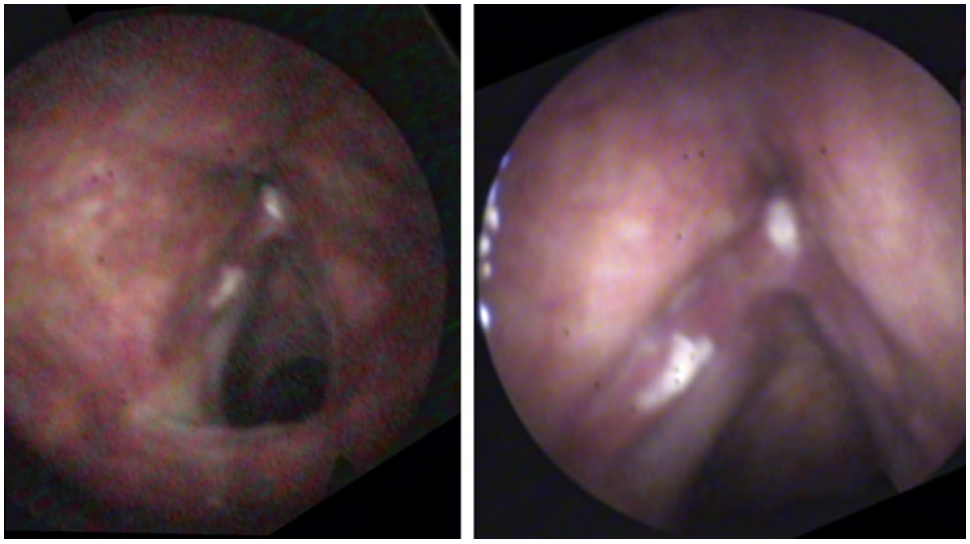
Typically the flexible fiber-optic endoscope is attached to a light source and to a separate camera. The predominant appeal for fiber-optic technology is the relative low expense compared to newer chip-on-tip technology.

Although an attached camera can be updated from standard definition to high definition, the images provided by fiber-optic technology are of inherently limited quality because after the glass fibers carry light to the interior of the larynx, they transmit the image of the larynx back through the fibers to the camera, which is attached externally. These relatively large glass fibers are visible in any image produced. When the image is recorded, the pixilation of the glass fibers may interact with the pixels on the recording device to create a moiré effect. Attempts to diminish the honeycomb quality in the image and moiré effect often involve a loss of resolution by blurring the image either physically or electronically. Ultimately when glass fibers break over time, light absorption becomes complete and leads to a black spot in the image (Fig. 6.5).

Reflected light decreases greatly with distance from the camera processor. Technology built into camera processors may compensate for inadequate light through electronic amplification or video gain, which comes at the expense of digital noise. Digital noise is particularly evident when the endoscope is relatively far away from the pathology. For example, with the endoscope at the level of the tip of the epiglottis, there is significant loss of light at the level of the vocal cords, several centimeters distant. Because most users have the auto-gain function turned on, electronic amplification of the image occurs without the examiner even sensing degradation of the image. As electronic gain increases, more pixels in the image are assigned colors that don't actually exist. The image becomes more pixelated. Additionally, as capillaries become blurred, the image becomes more apparently red (Fig. 6.6).

Chip-on-Tip Endoscopy

Chip-on-tip technology derives its name from miniaturizing the electronic sensor or chip and then placing this chip camera (which was previously attached to the endoscope eyepiece) onto the tip of the endoscope, transmitting images electronically through the flexible scope to an external processor. Because the image no longer passes through light fibers, moiré effect is eliminated and the images are much clearer (Fig. 6.7).



• **Fig. 6.6** *Left*, Automatic light gain by the camera processor adds dots of varying colors through interpolation when the endoscope is relatively far away from the tissue being imaged. Striping is the moiré effect created by interaction between the discrete light fibers in the scope and the pixels in the camera chip. *Right,* By moving the endoscope closer to the structures, the pathology fills more pixels, more light is reflected from the tissue, and automatic gain is reduced with a reduction of digital noise.



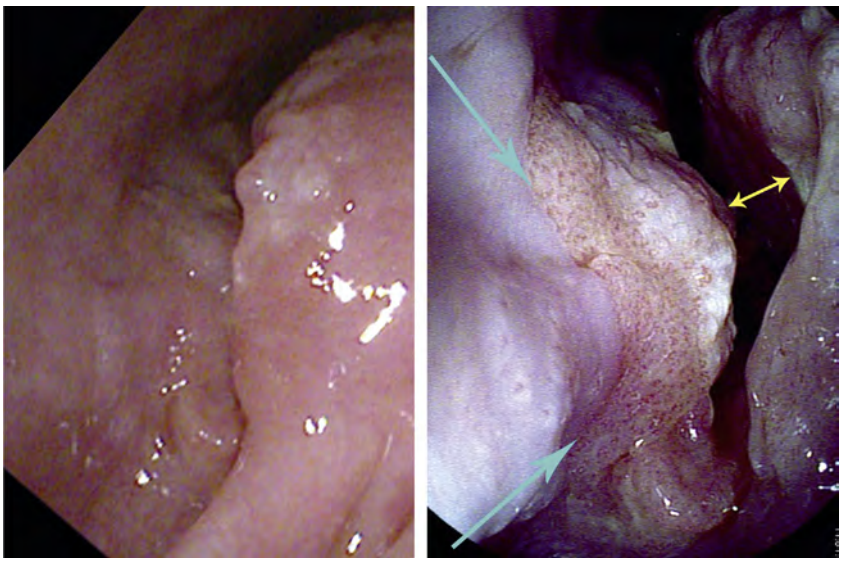
• **Fig. 6.7** Flexible endoscopes. Examination on the same day as Fig. 6.6. *Left,* Fiber-optic endoscope—Fibers visible, particularly broken fibers as black spots, digital noise present as speckling and redness, moiré effect as yellow and red striping. *Right,* Chip-on-tip endoscope—clearer image.

As chips become smaller, higher resolution chips lead to higher definition images and/or smaller endoscopes. When topical anesthesia of the larynx is not used, smaller endoscopes can generally be moved closer to the laryngeal structures before gagging or laryngeal irritation occurs. Additional processing of the image such as selective light absorption can perceptually alter the information in the images (Fig. 6.8).

Rigid Endoscopes

Rigid transoral laryngeal endoscopes (Hopkins rod) tend to come in two configurations based on the angle of view: 70-degree and 90-degree endoscopes (Fig. 6.9). Sometimes a quick focus ring is added, although the claim is made that this absorbs some light. In general, the glass transmitting the image through a rigid endoscope carries more light than flexible endoscopes.

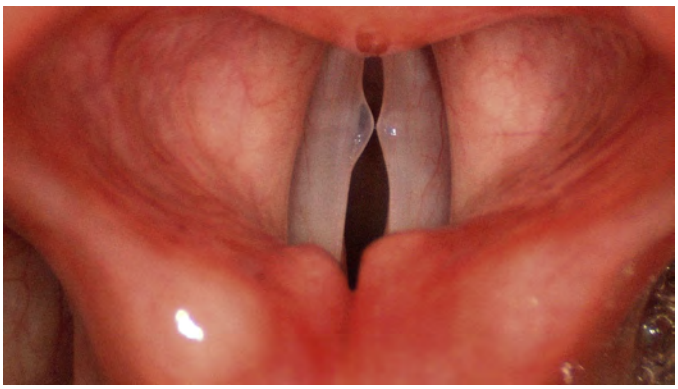
The benefits of the rigid endoscope are that it provides a high-clarity image, it can be attached to a standard-definition camera, and it may be upgraded with a high-definition camera later. Because attached cameras can be physically larger than chip-on-tip cameras, higher definition cameras are typically available for rigid endoscopes; 4K cameras are currently being released. Rigid transoral endoscopes are particularly valuable for the perpendicular view of vibrating-margin (mucosal-edge) lesions of the vocal cords. When attached to a stroboscope, mucosal lesions on the margin of the membranous vocal cord stand out in high contrast



• **Fig. 6.8** Selective color imaging. *Left,* Standard light. *Right,* Using the trumpet maneuver to insufflate the piriform sinus spreads the laryngeal tissue away from the lateral pharyngeal wall *(yellow double-headed arrow)*, and the selective color lighting highlights the vascularity of this tumor and clearly differentiates the tumor margin (*blue arrows* point to tumor margin).



• **Fig. 6.9** 70-degree and 90-degree rigid endoscopes. The 70-degree endoscope *(above)* typically depresses the tongue, bringing the tip closer to the vocal cords than the 90-degree endoscope *(below)*. The 90-degree endoscope has a quick-focus ring.



• **Fig. 6.10** Rigid endoscope viewpoint. Perpendicular orientation of the rigid endoscope highlights the vocal cord margins. Opaque, mid-right vocal cord vibratory margin swelling and translucent left vocal cord polyp clearly defined.

against the background of the dark trachea (Fig. 6.10), making it most useful for lesions of the mucosal margin.

The potential pitfalls of the rigid endoscope are that it usually provides only a single perspective view, various anatomic structures can obstruct the image (uvula, base of tongue, epiglottis, posterior pharyngeal masses, supraglottic squeeze), gagging may preclude an examination altogether, and it has a relatively shallow depth of field. Functional evaluation is limited, because the tongue is often stabilized by the examiner's hand.

Camera and Processor

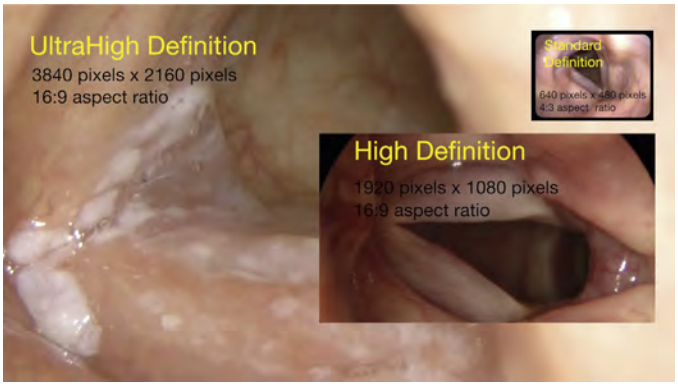
In the video world, what is meant by "high definition"?

Although any combination of x by y dimensions could be used, the video broadcast industry settled on a relatively few standardized sizes and ratios. The most popular, based originally on television formatting, has been labeled standard definition (SD). When televisions were still analog, the standard called NTSC consisted of 525 lines, the aspect ratio was 4:3 (horizontal:vertical), and the images were recorded at almost 60 frames per second (exactly 60 frames led to interference from 60-cycle current). Each frame consists of two fields, which are interlaced and leave an artifact in single frames of moving objects (Fig. 6.11). As digital technology took over this standard, the 4:3 aspect ratio turned into 640 × 480 pixels used to record the same image (some of the additional vertical lines were used for other things during the analog era). Newer developments include 60 frames per second recorded in some cameras with only 1 field per frame (progressive), which eliminates interlacing artifact. Many other compromises have been made over time for technical as well as commercial reasons. Technology has not stood still, and silicon means an increasing number of pixels can be processed and stored. Various compromises have led to higher definition

Video format classification shorthand represents: vertical resolution + frequency/frame rate
SD (480i29.97) = 640 by 480 pixels + interlaced scan (29.97 images/second with 2 interlaced fields per frame)
HD (720p30) = 1280 × 720 pixels + progressive scan (30 images/second with 1 field per frame)
FHD (1080i29.97) = 1920 × 1080 pixels + interlaced scan (29.97 images/second with 2 interlaced fields per frame)



• **Fig. 6.11** Interlacing. Jagged edge effect when vocal cords are recorded using stroboscopy with interlaced video recording. Even lines are from one field and odd lines are from a field taken 1/30th of a second later.



• **Fig. 6.12** Number of pixels. Relative sizes of standard-definition (SD), high-definition (HD 1080i), and ultrahigh-definition (UHD 4K) video when viewed at the same resolution.

video recording standards, and a 16:9 aspect ratio was settled on for theater viewing. Some of the shorthand used to express video recording is as follows:

UHD is also known as 2K for the almost 2000 (1920) horizontal pixels. UHD also includes sizes beyond 2K and is designated by the horizontal component such as 4K (3840 horizontal pixels) (Fig. 6.12).

As computer monitors evolved, many other pixel dimensions and aspect ratios have been developed. Listed are some of the more common sizes.

Graphic Format Classification

VGA (equivalent to SD)	640 × 480 pixels
SVGA	800 × 600 pixels
SXGA	1280 × 1024 pixels
WUXGA	1920 × 1200 pixel

Determining the video output of the endoscope's camera processor affects the resolution that should be captured. Capturing at a higher resolution than the video output results in wasted hard disk storage. Capturing at a lower resolution than the video output results in loss of image resolution.

Light

Camera and processor are usually sold as a package. Often the light source is integrated into the processor. However, for laryngology, separating the light cable from the camera allows for switching from a continuous light source to a stroboscopic light source. Xenon, halogen, and LED lights are being used for laryngeal endoscopy. Each colors the image in a slightly different way. Even the camera used for recording and the screen used for viewing the video recording alter the perceived color of the laryngeal tissues.

A detailed comparison of two major producers of laryngeal endoscopes, Olympus and Pentax, is available at http://voicedoctor.net/blog/review-high-definition-laryngoscopes-olympus-vs-pentax. Even when the resolution of the cameras is identical, videos of an individual larynx appear different depending on the camera used to obtain the images.

Transmission

Carrying audio and video signals along a cable requires a format. The terms used include:

- DVI: Digital video interface (carries analog or digital signals, SD or HD, but no audio)
- HDMI: High-definition multimedia interface (SD, HD, video, audio)
- SDI: Serial digital interface (single cable)
- HD-SDI: High-definition serial digital interface
- FireWire 800
- Thunderbolt (Apple)
- USB: Universal serial bus; USB-3 and USB-C are fast enough to carry video

Conversion

What comes out of the camera may not be compatible with what a computer is able to capture. Unless one manufacturer designs the entire system, the user may need to do a conversion between the output from the camera and the input on the computer. Also, because each level of higher definition video consists of geometrically *(x × y)* more data, most conversion processes require hardware to do a conversion quickly enough so it does not lose frames from the video. The cable usually comes out of the medical camera processor carrying video to a hardware converter, which may combine the audio

with video and convert the video to a format designed for digital capture.

Capture

Capturing video on an Apple laptop computer is easy when using various software programs that can grab live video. For example, using a hardware conversion box that encodes the video for Apple's QuickTime video format allows quick capture of high-resolution video. QuickTime seems to have remained a stable "wrapper" over the past 15 years, and although the codecs within QuickTime have changed over time, one can still view older video files easily.

Video files can be viewed directly on the desktop or in various software programs (iMovie, Final Cut Pro, Adobe Premiere, and others). Various medical manufacturers' custom software might allow for only forward and reverse viewing of the captured video. However, a general video-editing program is very useful. For example, Apple's Final Cut Pro video program or Adobe's Premiere video editing program allow keywording, labeling of individual frames, exporting of selected frames or clips, slow motion, fast motion, or frame-by-frame review. They can render and display a given interlaced frame completely on a high-resolution graphics monitor.

Storage

It is not necessary to store every pixel that comes out of an endoscope. There are various compression and storage formats for video called *codecs.* Some of the current common codecs and wrappers include:

- MPEG-4
- MPEG-2
- H.264
- WMV (Windows media video)
- Apple ProRes 422
- DV
- .mov (QuickTime)

It is possible to have a mix of formats on a hard drive. For example, older digital files may be formatted in DV when they were recorded on digital tape. Recent files may be high-definition videos using Apple ProRes 422 and standard definition videos in H.264. Hospital operating room cameras and endoscopes may variously capture video in MPEG-4 and WMV formats, and the formats change every few years.

The memory capacity of a laptop can rapidly fill up with high-definition video files. A large external RAID hard drive can store many video files and it can be configured to retain two copies of each video (in the event that one hard drive dies, the video will still exist elsewhere on the set of RAID drives). Storing another copy of all the video files on a separate hard drive, kept at a different physical location, is excellent insurance against data loss. Redundancy is a key word for managing digital data.

Slow Motion

Video is typically captured at about 60 images per second, whereas almost all vocal cord vibratory movement occurs at more than 80 cycles per second. Therefore, blurred images are almost guaranteed. Although after watching enough video recordings, the viewer develops an ability to infer from these blurred images what might be happening to the vocal cords in real time, there are two methods for capturing clearer images of moving vocal cords. Each method has trade-offs.

A significant improvement on standard video occurs with a stroboscope. An audio sensor detects the pitch of the voice and triggers a strobe light to flash at one or two beats more per second than the vibration of the vocal cords. The video then records slow, apparent motion of the vocal cords. A trade-off with stroboscopy is that when there is diplophonia, the strobe light cannot track two separate pitches and will flash irregularly. This artifact may create a false impression of the actual physical movement of the vocal cords. A second trade-off is the common interlaced video format in which almost all images of vibrating vocal cords will appear disjointed on standard video recordings played on video monitors (see Fig. 6.11).

High-speed video records several thousand frames per second, thus recording actual vocal cord motion. Some of the trade-offs with this technique are that it requires a large amount of storage; it can be difficult to capture actual pathologic movement of the vocal cords because you have to record in short, several-second bursts; and it can take a long time to review this video to find the pathologic motion. As a newer technology, it is also relatively more expensive than stroboscopy.

Selective Color Imaging

Because video images consist of red, green, and blue channels, it is possible to selectively filter out some of the light on the individual color channels. Both Olympus and Pentax equipment electronically filter certain bands of light in the blue and green wavelengths, which are absorbed by hemoglobin. Blood, normally viewed as red in video images, then appears dark or black in the video recordings, adding additional contrast to vasculature compared with the surrounding tissue.

The capillary vasculature of the larynx *pops out* in these images. Although the capillaries are visible using the normal lighting algorithms, emphasizing capillaries tends to lead the eye to various laryngeal conditions. In particular, hemorrhage and dilated capillaries occur with trauma and infections, but most notably capillaries are dilated and generate specific patterns as tumors grow and require or induce an increased vascular supply for their metabolic needs (see Fig. 6.8).

Recording and Reviewing Video

Ultimately, many events in the larynx happen very quickly, and sometimes pathology may be visible and recognizable on only a single frame of a video recording. This means that during live recording, the problem might be present but not be visually recognized. Even during a quick overview of the recording performed while the patient is in the examination room and during an explanation of the problem to the patient, it is possible to slip through the video to the most pertinent pictures already noticed in order to describe the problem. On a regular basis, though, at a later time the video should be reviewed again

while developing a report on the patient. Try to find optimal individual frames of the video that demonstrate the pathology. During this detailed review, as the video is played frame by frame, additional findings may become more noticeable.

After surgery, or intervention, or even just the passage of time, if something does not turn out as expected, it is a good idea to return to earlier videos and review them in light of the new video information. This review may reveal details missed on prior viewings. Consequently, the video is valuable not only for finding the immediate problem, but it is also useful for discovering the significance of audio and visual findings that might have been missed initially.

Low Technology

Low technology is really the most valuable part of an advanced endoscopic examination. The detailed image obtained does not necessarily depend on expensive equipment. It depends on the examiner's knowledge, skill, and patience. No matter what definition the endoscope records at, pathology hidden when an endoscope is placed at the level of the epiglottis (a common location for many endoscopic laryngeal recordings) is essentially zero definition. Applying topical anesthesia and maneuvering an endoscope, sometimes beneath arytenoids, between compressed false vocal cords, into a collapsed piriform sinus, around the inferior extent of a growth, or even between the vocal cords will give a high-definition perspective to a lesion (Fig. 6.13).

Here are some selected ways that low technology can be used to carry out a high-definition laryngeal examination.

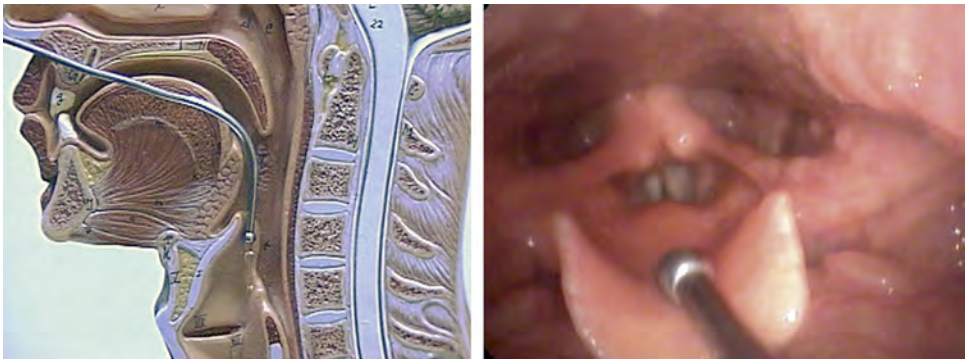
Closeness

Occasionally the endoscope can be maneuvered close to the larynx if a patient can tolerate it, or if a sensory nerve injury allows the endoscope to actually touch the larynx without triggering a gag or initiating a laryngospasm. Sometimes it is possible to maneuver the endoscope in between the vocal cords during inspiration and abduction, and back it out during expiration, as the vocal cords tend to adduct. Smaller endoscopes can be positioned closer to the larynx without touching the supraglottic structures, which avoids triggering a gag reflex.

More typically though, topical anesthesia is the laryngologist's best friend. With the addition of ~4 mL of topical 4% lidocaine, typically dripped on the vocal cords in 1-mL aliquots over 1 or more minutes with an instrument such as an Abraham cannula (Fig. 6.14), the larynx can be completely anesthetized and an endoscope can usually be maneuvered anywhere within the larynx or trachea.[1] The first aliquot of



• **Fig. 6.13** Zero-definition endoscopy. *Left,* Viewed from the level of the tip of the epiglottis, the vocal cords appear "paralyzed" (and that was the diagnosis of several examiners, to the point where they injected botulinum toxin trying to "relax" the vocal cords—this treatment made her airway obstruction worse from Bernoulli effect). *Right,* After topical anesthesia, the flexible endoscope passed beneath the arytenoids reveals a scar band bridging and fixing the vocal processes of the arytenoid cartilages.



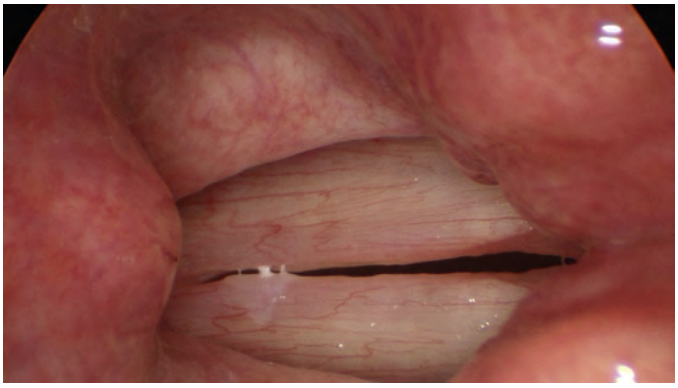
• **Fig. 6.14** Topical anesthesia. One method for applying topical anesthesia directly onto the vocal cords using an Abraham cannula and dripping lidocaine while the patient says /i/. *Left,* profile view of cannula use. *Right,* endoscopic view of cannula use.

anesthetic makes the patient cough and distributes medication around the entire larynx, pharynx, and subglottis. Asking the patient to phonate while adding more topical lidocaine generates a laryngeal gargle as the lidocaine bubbles on the superior surface of the vibrating vocal cords. After the fourth milliliter is dripped and vocally gargled, topical anesthesia is complete.

Camera Orientation

Rigid

Although the image captured by endoscopes is typically round, there is enough transmission of light with rigid endoscopes to mechanically zoom some cameras, without abundant loss of light and resolution. When combined with the newer high-definition ratio of 16:9, vibrating vocal cord anatomy nicely aligns with this horizontal visual field in terms of length:width ratio, using more of the pixels available on the camera. Compared to a typical placement of the camera on a flexible fiber-optic endoscope or the orientation of the camera chip on integrated chip endoscopes, this rotation of the external camera attached to the rigid endoscope 90 degrees aligns the vibrating edges of the vocal cords horizontally on the stretched, high-definition video monitor. It has the potential to fill more pixels with vocal cord pathology (see Fig. 6.2 and Fig. 6.15).



• **Fig. 6.15** Camera orientation. Orienting the camera at 90 degrees to the rigid scope eyepiece aligns the vocal cords along the longest axis of the video recording. More pixels are available for viewing the vocal cord margins, the primary site of sound production and the most likely location to identify the causes of hoarseness.

Laryngeal Maneuvers

Choose a Vowel

Because most consonants are produced at the level of the palate, tongue, and lips, it is typically not necessary to visualize connected speech during a laryngeal examination for voice symptoms. Vowels are produced in the pharynx, so they also are largely irrelevant during an assessment of voice. The vocal cords are primarily responsible for the production of sound, and they primarily modulate frequency and volume. Consequently, if we eliminate words (the variation of consonants and vowels) during our examination, we reduce inadvertent movement of the flexible endoscope by palatal and tongue movement. We want to keep the pharynx as open as possible and the epiglottis as far forward as possible to optimally visualize the vocal cords. The vowel /i/* provides for this maximal pharyngeal opening (Fig. 6.16).

Alter Pitch

We can record our examination at both low and high pitch. In fact, if we identify a particular pitch during the vocal capabilities pattern-matching portion of our examination that triggers dysphonia, we should make an attempt to record that same pitch during our endoscopic examination. Apart from finding a specific pitch that triggers dysphonia, high pitch activates the cricothyroid muscle to lengthen the vocal cord and the thyroarytenoid muscle to intrinsically tension the vocal cord. As the vocal cords lengthen, any lesion along the vibratory margin will tend to be pushed out into the field of view, particularly from the rigid endoscope's vertical viewpoint. At high pitch, the vocal cords are also reaching their maximum tension, which will aggravate any preexisting stiffness and make vibratory impairment from stiffness more visible (Fig. 6.17).

Recording at low pitch removes any inadvertent or obligate compensation by the cricothyroid muscle. Activation of the cricothyroid muscle may occur in nonorganic voice disorders. It almost always occurs in neurologic disorders involving paresis of either the thyroarytenoid muscle or the lateral cricoarytenoid muscle.

As the patient reduces pitch, this natural or intrinsic compensation by the cricothyroid muscle for a weakened thyroarytenoid muscle disappears, allowing the weak vocal cord to

* /i/ is the phonetic symbol for the sound of "e" as in the word "we."



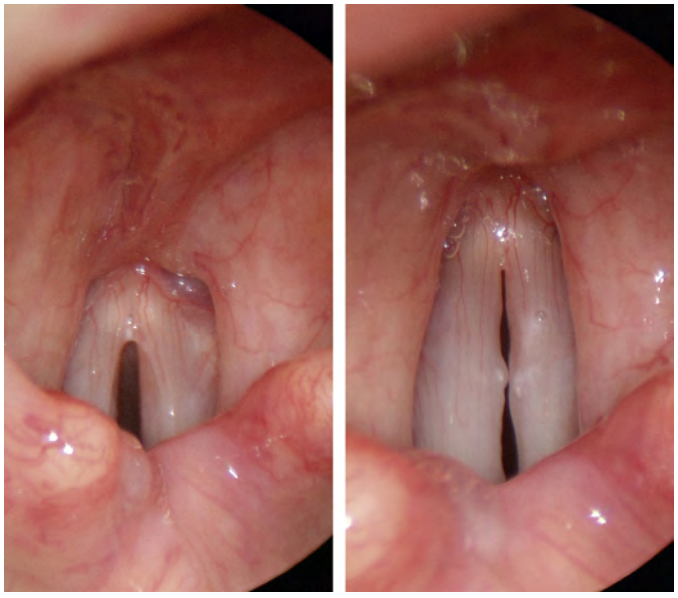
• **Fig. 6.16** Vowels. *Left,* Vocal cords are more difficult to see completely during the /a/ sound as the epiglottis and tongue base push posteriorly. *Right,* Phonation with an /i/ vowel opens the pharynx widely.

oscillate more laterally (Fig. 6.18), and sometimes, with enough difference in tension, the vocal cords will break synchrony and the weak cord will flutter.

With the removal of intrinsic compensation by the cricothyroid muscle, a weakened lateral cricoarytenoid muscle leaves the vocal process canted laterally, creating a large and obtuse angle between the vocal process and the membranous vocal cord (Fig. 6.19).

Another inadvertent compensation is that typically, yet surprisingly, patients do not want to sound abnormal during an examination for a hoarse voice, even though abnormal voice is the reason for their office visit. This is particularly true for singers. They often convince themselves that abnormal vocal sounds are the results of poor technique. In order to avoid audible impairments in their upper vocal range, they increase both their vocal cord tension and their subglottic pressure and consequently their volume. The increased subglottic pressure overcomes small gaps, small elevations, and minor stiffness. By eliciting low-volume sound production from the patient, smaller vocal impairments can be visually discovered during the examination.

Eliciting higher volumes, especially at low pitch, can augment neurologic and muscular weakness visual findings by causing the weakened vocal cord to vibrate abnormally. A nontense thyroarytenoid muscle may break up into two or more oscillatory segments, generating the appearance of flutter on stroboscopy, and also may oscillate lateral to its axis, creating an infinite open phase on stroboscopy.



• **Fig. 6.17** Changing pitch. *Left,* At low pitch, vocal cords are short and loose—marginal lesions disappear into the vocal cord mucosa. *Right,* At high pitch, vocal cords are long and tense—marginal lesions are pushed into the central glottic opening as a silhouette.

Tools for the Endoscopist

Alter Pitch

- High pitch
  - Highlights vocal margin
  - Augments stiffness
- Low pitch
  - Highlights weakness
  - Typically removes compensation from superior laryngeal nerve (cricothyroid muscle)

Alter Volume

- Low volume
  - Highlights gaps, stiffness, elevations
- High volume
  - Highlights weakness

Quiet Observation

Monitoring the vocal cords closely during quiet respiration can detail subtle neurologic findings. Fasciculations are often noticed during quiet breathing when the larynx is relatively still. These can be seen on the arytenoids relatively easily. They are also visualized within the laryngeal ventricle on the superior surface of the vocal cord in a denervated thyroarytenoid muscle.

The timing of abduction and adduction is also assessed during quiet respiration. During expiration, partial adduction typically occurs, whereas during inspiration, partial abduction occurs. The degree of abduction and adduction should



• **Fig. 6.18** Low-pitch evaluation of thyroarytenoid muscle. *Left,* At high pitch, the vocal cords are tensioned by both the thyroarytenoid and cricoarytenoid muscles, and it is difficult to perceive much difference between the vocal cords. *Right,* At low pitch, cricothyroid muscle compensation is removed, and the lack of tension and mass within the right vocal cord becomes very apparent on stroboscopy, here captured during the open phase.

be symmetric. With acute denervation, the range or degree of motion is less on the injured side. Later in the healing process, as varying amounts of synkinetic reinnervation occur, the timing of motion can become asynchronous. Additionally, with synkinetic reinnervation, the resting position of the vocal process may become more medial.

Height differences between the vocal processes can really only be appreciated well when the flexible endoscope is placed between the arytenoids, nearly parallel to the axis of the vocal cords. From this posterior view, oriented along the axis of the vocal folds, the mass of each thyroarytenoid muscle can also be compared (see Fig. 6.4).

Sniffing augments abduction, lengthening the vocal cords while they are pulled further apart than during expiration or even quiet inspiration, and an atrophic vocal cord will thin even further. This finding is most prominent when deep inspiration occurs immediately after phonation (Fig. 6.20).

The same inference may be visualized in a negative way. During deep inspiration, the ventricle on the side of thyroarytenoid muscle atrophy appears to enlarge relative to the other side. This may be easier to visualize in the sense that both thyroarytenoid muscle atrophy and false vocal cord atrophy contribute to the size of the laryngeal ventricle (see Fig. 6.20).

Trumpet Maneuver

Asking the patient to blow against his or her closed lips, much as if trying to play a trumpet, can insufflate the pharynx exposing the external aspect of the larynx within the piriform sinuses and at the esophageal introitus (see Fig. 6.8).

Perception

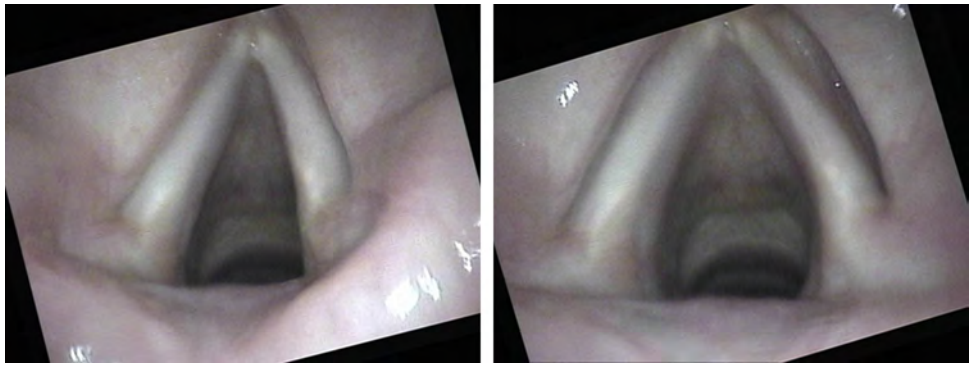
Sometimes the obvious is not recognized easily. For an example of the difference between looking and perceiving, consider a fungal infection where a very thin white film from *Candida albicans* on the vocal cords can be more readily perceived as an obscuring of the expected normal capillary architecture, which should typically be clearly visible beneath mucosa (Fig. 6.21).

Summary

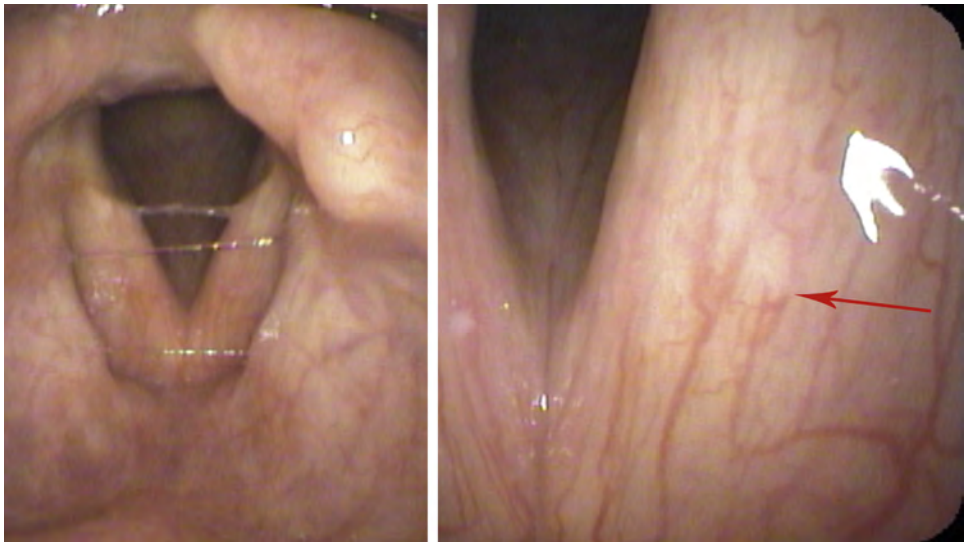
When you have the money, spend it for new high technology. Whether you do or don't have money, use what you have better.



• **Fig. 6.19** Low-pitch, close evaluation of the lateral cricoarytenoid muscle with the endoscope beneath the arytenoids. *Left,* At high pitch the cricothyroid muscle pulls the weak left vocal process toward the midline. *Left inset,* Distant view suggests an almost parallel position. *Right,* At low pitch, the right vocal process pushes across the midline, while the left vocal process remains unrotated and extremely lateral with a large glottic gap. *Right inset,* Supraglottic squeeze tends to hide the true vocal cord positions.



• **Fig. 6.20** Respiration quiet and active. *Left,* During quiet respiration, the thyroarytenoid muscles are relaxed and the vocal cords and ventricles appear similar in size. *Right,* During deep inspiration (sniffing), the right vocal cord thins and the right ventricle appears to enlarge, suggesting atrophy and paresis of the right thyroarytenoid muscle.



• **Fig. 6.21** Perception. *Left,* Typical endoscopic laryngeal view of an individual with hoarseness; a general "redness" may be perceived. *Right,* Moving the endoscope close to the vocal cords, the dilated capillaries on the anterior vocal cord (which create the "redness" in the left photo) disappear beneath a white film as they pass posteriorly (arrow defines approximate transition point). This film, from fungus, stiffens the vocal cords. The absence of clearly visible capillaries best defines the pathology.

Reference

1. Thomas JP. Topical anesthesia for office based laryngeal interventions. In: Oswal V, Remacle M, Jovanvic S, et al., eds. *Principles and practice of lasers in otorhinolaryngology and head and neck surgery*. 2nd ed. Amsterdam: Kugler; 2014.

7

Virtual Surgical Planning

JOHN T. STRANIX, CASIAN MONACO, TOMER AVRAHAM, LAWRENCE E. BRECHT, JAMIE P. LEVINE, DAVID L. HIRSCH

Surgical management of head and neck oncology often requires composite resection with full-thickness bony extirpation of the affected maxillofacial skeleton. The high functional and aesthetic demands of this complex anatomic region necessitate meticulous planning and precise execution by a multidisciplinary surgical team. Advancements in computer-assisted design (CAD) software have been applied to high-resolution 3D imaging technology to generate powerful tools for planning complex craniofacial resections and reconstructions.[1-8] These virtual surgical plans can then be precisely translated into surgical aids through the process of computer-assisted manufacturing (CAM). Virtual surgical planning (VSP) and the CAD/CAM surgical modeling process has significantly impacted modern head and neck surgery, with demonstrated benefits in a broad range of applications.[1,2,7] The soft tissues of the head and neck region are dependent on the underlying skeletal framework to maintain appearance and contour, which makes precise bone positioning essential for reconstruction.

CAD/CAM: Virtual Surgical Planning and Execution

Operative Planning

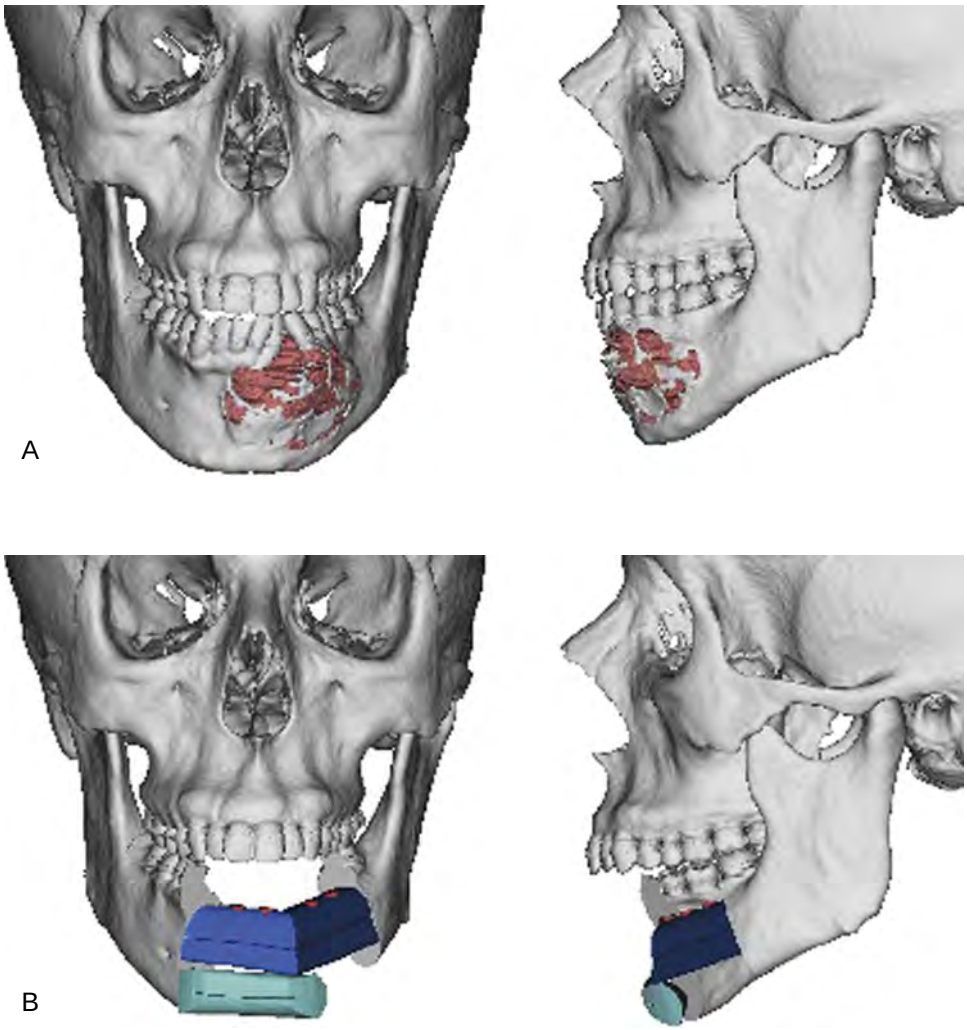
Planning starts with a high-resolution computed tomography (CT) of the patient's craniofacial skeleton. To improve the accuracy of preoperative modeling, scans are obtained with the patient wearing fiducial markers on the face for reference. If the anticipated bony defect following tumor resection will require free tissue transfer of a vascularized bone flap, a high-resolution CT of the flap donor site is also obtained to get an exact understanding of the vascular and bony anatomy.

For resections with a dentoalveolar component that will affect occlusion and orthognathic relationships, laser scanned occlusal molds or topographic occlusal imaging is obtained as well. Soft tissue imaging and simulation software have been shown to be accurate enough for clinical relevance,[9] and may be used as an aid in treatment planning to anticipate the postoperative facial appearance resulting from the planned skeletal changes.[10] These files are then forwarded to a commercial vendor and are converted into interactive 3D virtual models of the facial soft tissue, cranio-maxillofacial skeleton, and flap donor site. The pitch, yaw, and roll recorded by the fiducial markers in natural head position are used to adjust the 3D CT scan coordinates and digital head position accordingly.

An online meeting is coordinated among the engineers from the modeling company and the ablative, reconstructive, and prosthodontic teams. Using the virtual model, resection margins are determined and the engineer marks the desired cutting paths for the osteotomies. Following virtual resection of the diseased segment, the virtual image of the vascularized bone flap is superimposed on the ablative defect in the desired vascular and soft tissue orientation. Virtual osteotomies are then designed to fit the flap precisely into the idealized reconstruction with optimal bony apposition[11] (Fig. 7.1). The engineers use the geometry of the resected segment or mirror the contralateral disease-free skeleton to re-create the native bony structure and restore occlusal relationships. These techniques are also useful for secondary reconstructions wherein the resection or injury has already occurred and symmetry has been lost. The virtual surgery approach allows for a greater number of segmental osteotomies to be planned and multiple osteotomy combinations to be tried until the optimal permutation is identified to restore the craniofacial skeleton. Recent reports suggest reduced operative times may be achieved using these technologies, despite increased reconstructive complexity.[12,13] Once the ablative and reconstructive plan is completed, all teams approve the presurgical design plan.

Modeling Phase

Based on the surgical plan developed by the ablative, reconstructive, and prosthodontic teams in conjunction with the engineers from the vendor, stereolithographic manufacturing of the necessary components is performed. A model of the native craniofacial skeleton is produced for intraoperative reference. Custom cutting guides are manufactured that fit flush onto the facial skeleton and osseous flap to ensure the osteotomies precisely match those from the virtual surgical plan



• **Fig. 7.1** Three-dimensional virtual models for surgical planning. **A,** Preoperative anatomy. **B,** Planned reconstruction.

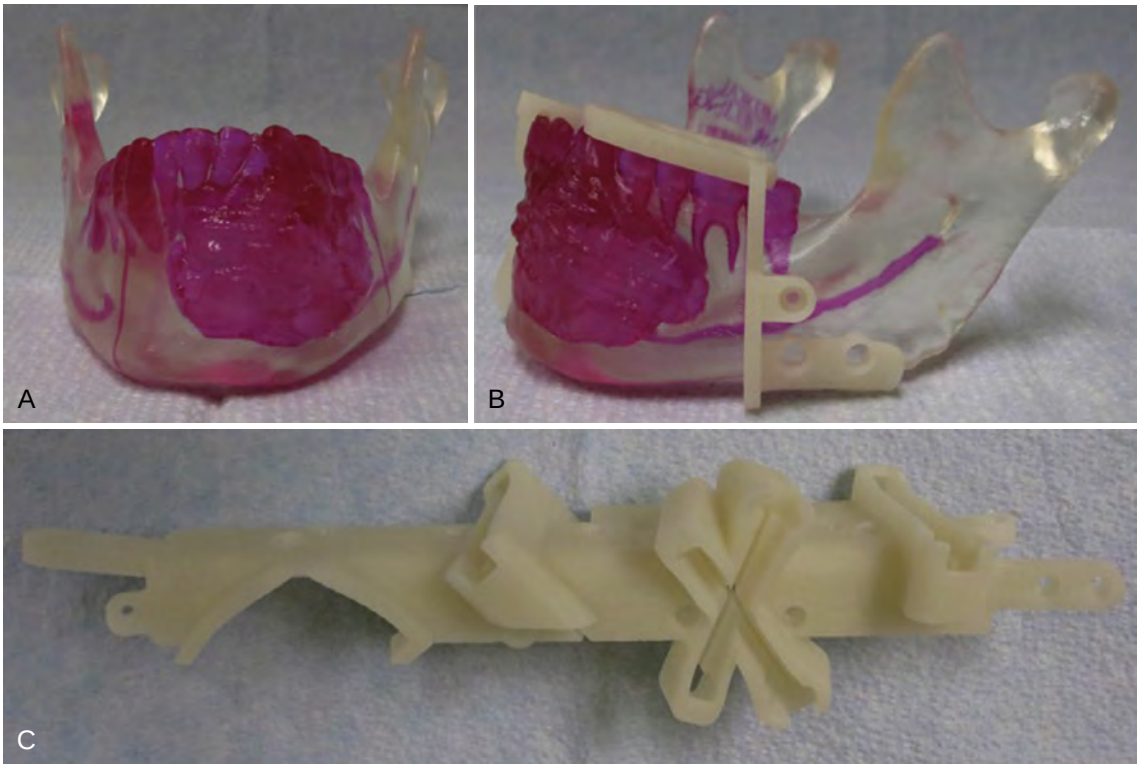
(Fig. 7.2). These models and cutting guides facilitate the osteotomy process and allow for seamless integration between the ablative and reconstructive portions of the operation.

To ensure precise and stable intraoperative occlusal relationships, splints may also be designed and fabricated that enable alignment of the maxillary-mandibular segment to the cranial base in all degrees of freedom.[14-16] These intraoperative guides establish bony landmarks outside of the resection margins to relate and secure the osteotomized segments of the maxillofacial skeleton into the desired final position. This orthognathic positioning system eliminates the need for intraoperative placement of peripheral reference markers, ensures maintenance of condylar positioning in centric relation, bypasses the traditional time-consuming process of mock surgery on mounted dental models, and obviates the need for fabrication of guiding intermediate splints. This process can allow for complex and multipart jaw movements that combine orthognathic repositioning and ablative reconstruction with maximal accuracy.

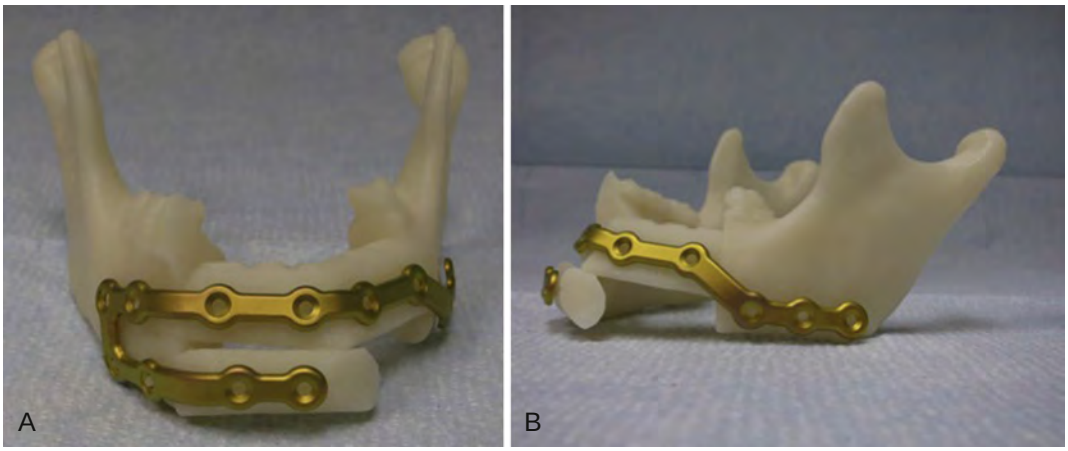
To facilitate skeletal plating after resection, a reconstruction plate template can be generated to allow for bending of the titanium plate preoperatively. Recent advances in milling processes have also made it possible to custom manufacture reconstruction plates for each individual reconstruction based on the virtual surgical plan (Fig. 7.3). Titanium plate contour and fixation points are designed to optimize bony apposition, minimize periosteal stripping, avoid damage to nearby vulnerable structures (e.g., inferior alveolar nerve), and provide appropriate structure for implant positioning. Use of "predictive holes" allows for repurposing of screw holes initially used for fixation of the ablative cutting guide, for securing the reconstruction plate (Fig. 7.4). In addition to dental implant planning for delayed prosthodontic denture rehabilitation, certain cases can be designed with both the customized alloplastic implants and denture for immediate placement, which allows for the creation of a "jaw in a day."[17] This can be designed to obtain optimal soft tissue changes for very individualized reconstructions.[10,18]

Surgical Phase

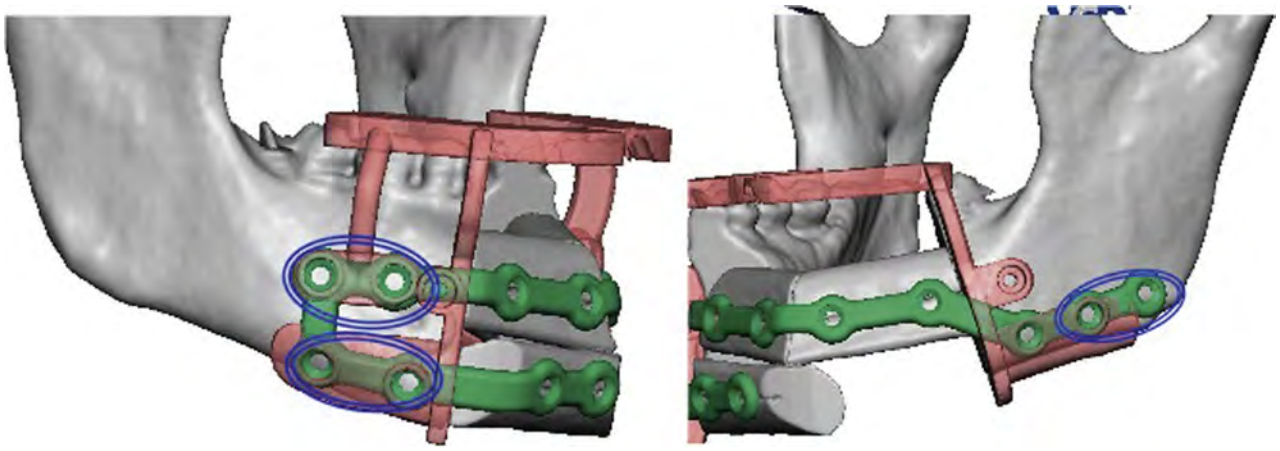
Oncologic resection proceeds in typical fashion with incisions based on the location and severity of the tumor and need for neck dissection. If necessary, virtual modeling can also be linked with intraoperative navigation programs for even greater precision.[14] After access is obtained, it is necessary to ensure the maintenance of maxillo-mandibular relationships. For mandibular resections, this is most commonly accomplished



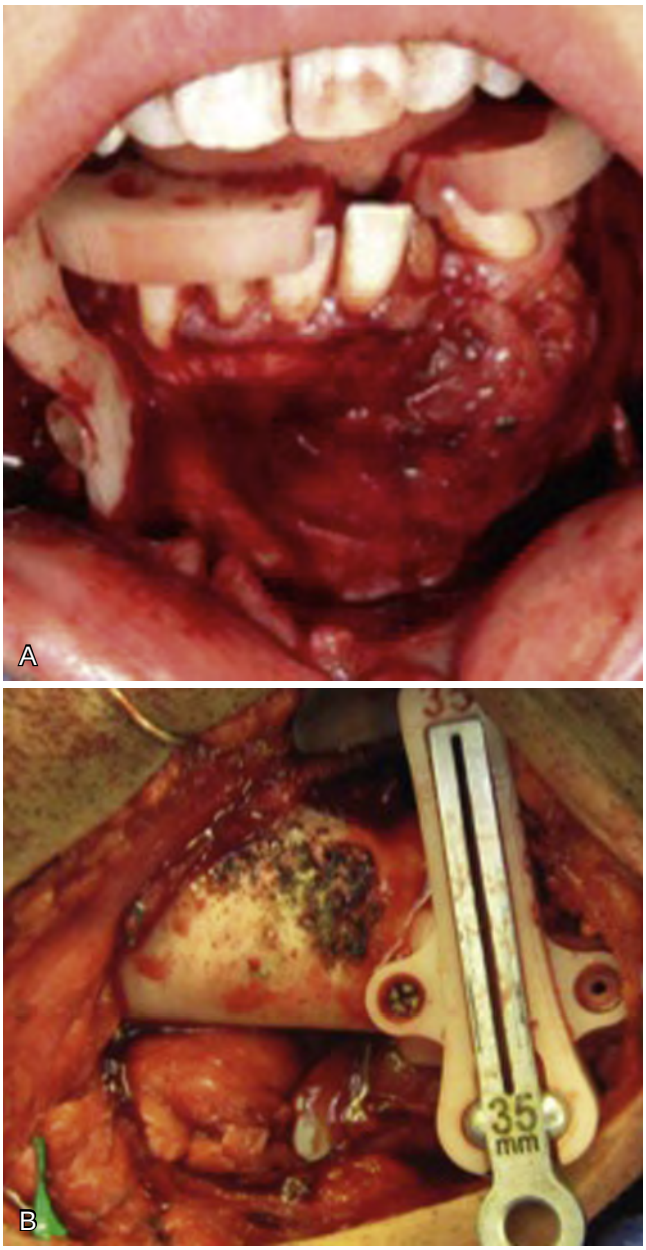
• **Fig. 7.2** Computer-assisted manufacturing allows the virtual surgical plan to be precisely translated into the operating room. **A,** Stereolithographic model of the diseased mandible. **B,** Mandibular cutting guide in place on the model demonstrating proper splint orientation and path of the inferior alveolar nerve. **C,** Linear cutting guide for the fibula osteotomies.



• **Fig. 7.3** Stereolithographic model of the planned reconstruction with the custom manufactured reconstruction plate fitting precisely into the anticipated position. **A,** Anterior. **B,** Lateral.



• **Fig. 7.4** Drill sites outlined in double circles indicate the locations of predictive holes that are repurposed for securing the custom reconstruction plate after the osteotomies are performed.



• **Fig. 7.5** Intraoperative examples of custom mandibular cutting guides secured in place before the designed osteotomies. **A,** Intraoral view of the mandibular cutting guides shown in Figs. 7.1 to 7.4. **B,** The cutting guide can be reinforced with a metal insert to prevent inadvertent damage to the plastic splint with the saw and subsequent deviation from the planned osteotomy orientation.

with an external plate attached to the proximal and distal bone outside the surgical margins. Other techniques include lingual pre-plating, placement of the dentate patient into maxillo-mandibular fixation (MMF), and the Luhr technique of attaching the proximal mandible to the maxilla.[19] Using a CAD/CAM orthognathic positioning system, however, intraoperative splints that maintain the maxillo-mandibular relationships without the need for peripheral reference markers to measure desired skeletal movements can be manufactured.[14-16] This has simplified the process of maintaining precise occlusal position between the resection and reconstructive phases.

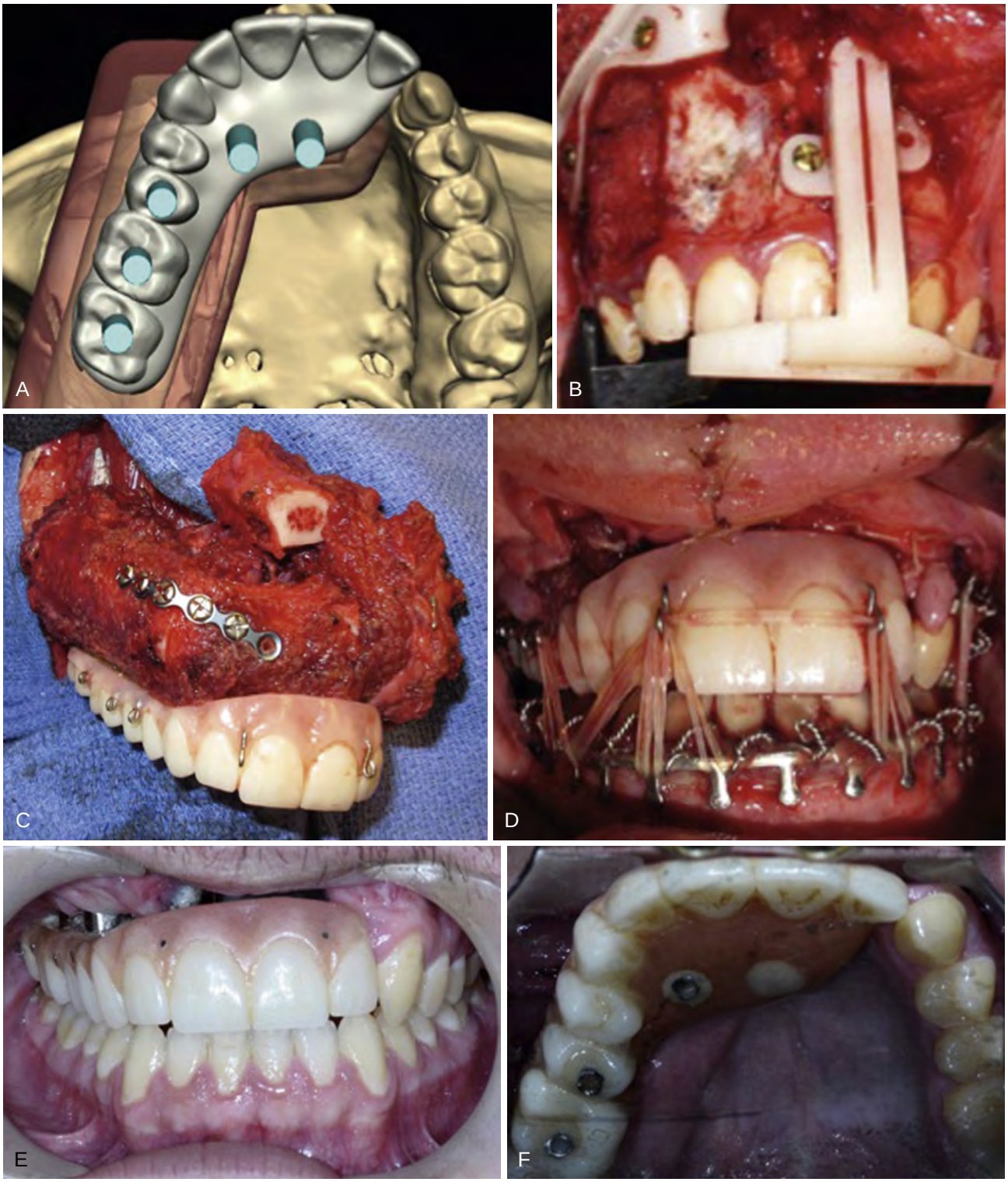
The prefabricated cutting guides for the resection are introduced into the field and secured in place (Fig. 7.5). It is important when planning the placement of these guides that they be small enough not to encroach on soft tissue margins. If an external fixator is used, its location must also be taken into account so that it does not impede cutting guide placement. Once the cutting guides are secured, the resection is completed using a sagittal saw to exactly duplicate the angles of osteotomy planned on the computer model.

Resection ideally occurs simultaneously with harvest of the planned free flap to be used for reconstruction using a two-team approach. Flap harvest proceeds in standard fashion and incorporates the bony and soft tissue components required for structural support and coverage of the oncologic defect. Before division of the vascular pedicle, the prefabricated cutting guides for the osseous component of the flap are applied and the planned osteotomies are performed (Fig. 7.6). These virtually planned osteotomies not only streamline the transition from resection to reconstruction, but also allow multiple reconstructive considerations to be taken into account. The cutting jigs are designed to optimize soft tissue location and orientation, maximize vascular pedicle length, leave sufficient bone at the donor site, and provide ideal alignment for functional dental rehabilitation. Close communication must be maintained between the ablative and reconstructive teams, specifically regarding any alterations to the preoperative plan. If the surgical plan is implemented without major intraoperative changes, the procedures can proceed independently to maximize operative efficiency and minimize anesthesia time.

The resulting bony segments are then secured to the custom reconstruction plate, creating the exact shape required to fill the osseous defect. It is also possible to accurately place dental implants and even dental prostheses into the osseous segment at this time (Fig. 7.7). If dental implants are being



• **Fig. 7.6** Prefabricated linear cutting guide secured to the osteocutaneous fibula free flap.



• **Fig. 7.7** Single-stage complete reconstruction of a maxillary defect with a fibula free flap, alloplastic implants, and immediate dental prosthesis placement. **A,** Virtual plan for immediate dental prosthesis placement. **B,** Cutting guides secured in place for the resection. **C,** Complete fibula construct assembled while still attached to its vascular pedicle on the leg. **D,** Immediate result following flap inset and microvascular anastomoses. Occlusion **(E)** and fixed **(F)** prosthesis at 18 months postoperative follow-up.

placed, they are drilled before performing the osteotomies so that accuracy of placement is not compromised. Once assembled, the pedicle is divided and the flap is inset. First the flap-plate combination is fixed in place, typically with minimal need for trimming to obtain flush bony apposition due to the cutting guide precision. The microvascular anastomoses then take place with subsequent inset of the soft tissue flap components and closure.

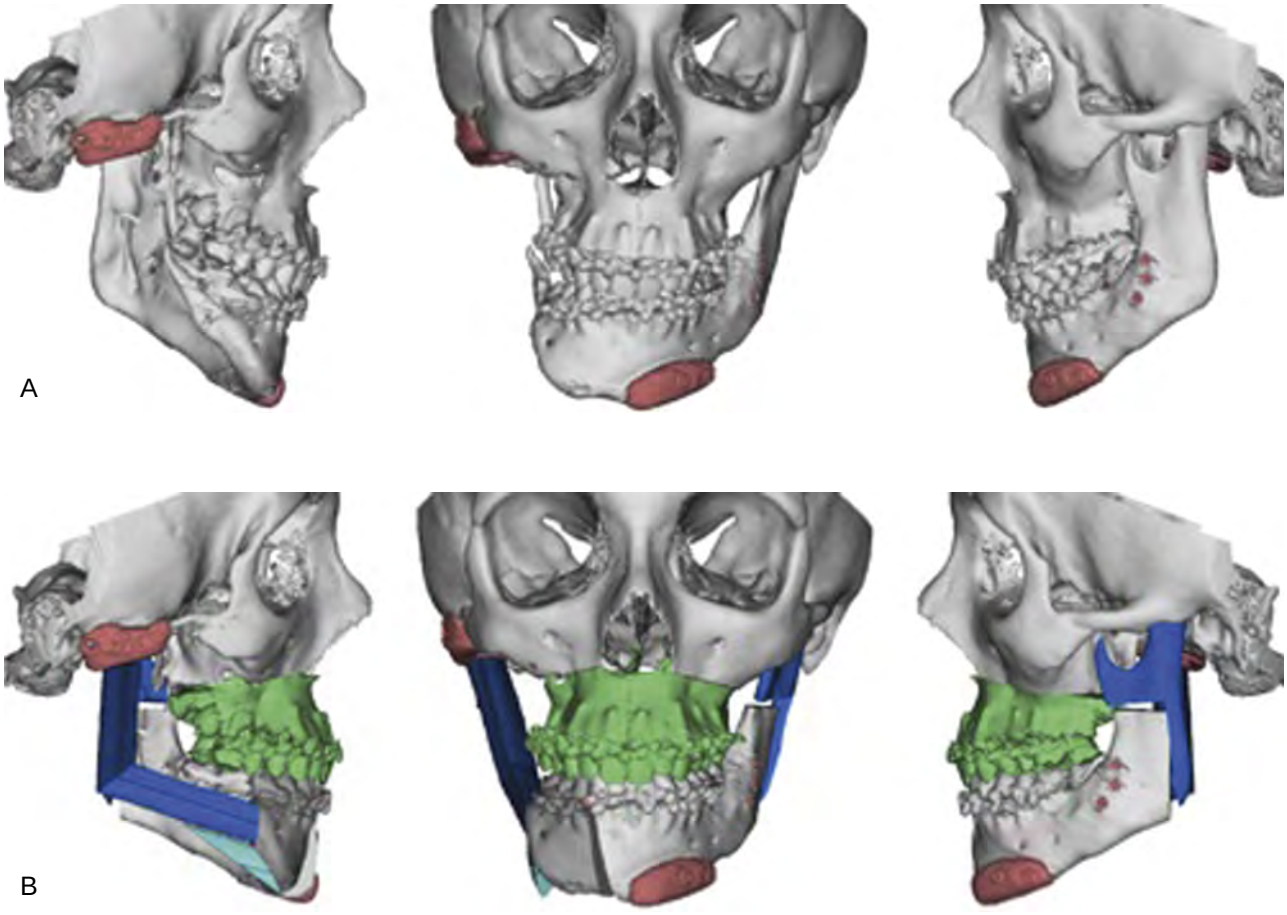
Case Examples

Case 1: Refractory Pruzansky Class III Hemifacial Microsomia

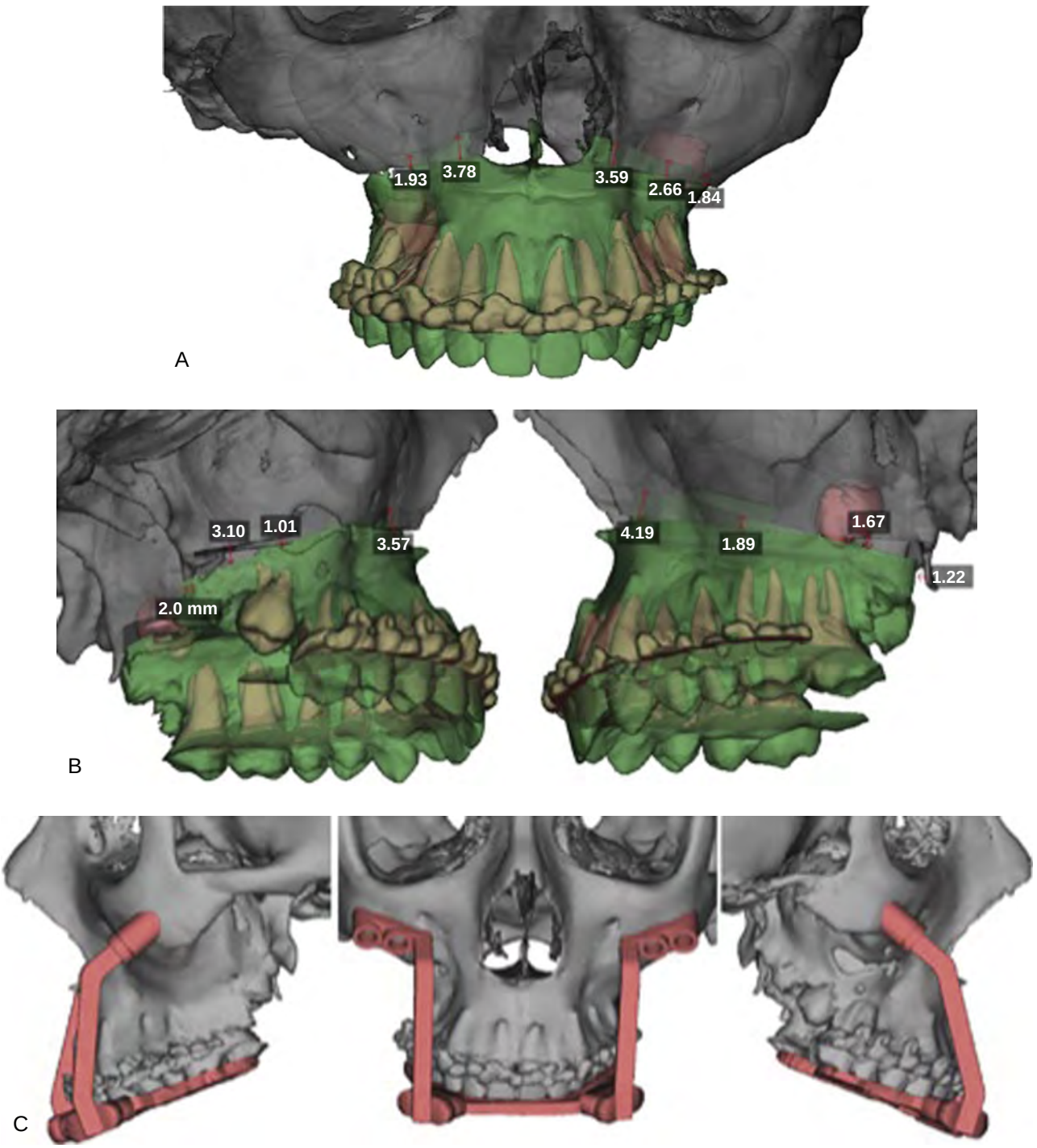
The patient was an otherwise healthy 19-year-old woman with a history of right hemifacial microsomia, Pruzansky class III. She had near complete absence of her right mandible with associated functional deficits. Before her initial presentation, she had undergone six maxillofacial surgeries, including right temporomandibular joint (TMJ) prosthesis placement. All previous interventions had essentially failed and the patient was referred for evaluation and possible virtually planned orthognathic reconstruction.

Preoperatively, it was noted that the patient would require Le Fort I osteotomy with impaction of the maxilla, an inverted L osteotomy of the "normal" left ramus, and a parasymphyseal osteotomy in addition to creation of a neomandible on the right side (Fig. 7.8). The identification of the proper occlusal positioning was facilitated by the use of customized orthognathic positioning splint (OPS) technology (Fig. 7.9).

Attention was first brought to the maxilla and the preoperatively planned Le Fort I osteotomy. Virtually determined measurements dictated a 5-mm anterior maxillary impaction. Le Fort osteotomy was performed in standard fashion until preparations were made for the downfracture. At this point, the patient was placed into a prefabricated splint secured to the maxillary dentition via wire fixation. The anticipated forward rotation was guided by splint arms that were secured to the superior maxilla and medial zygoma in locations dictated by OPS measurements (Fig. 7.10). The free maxilla was then secured in this location using four mid-face miniplates.

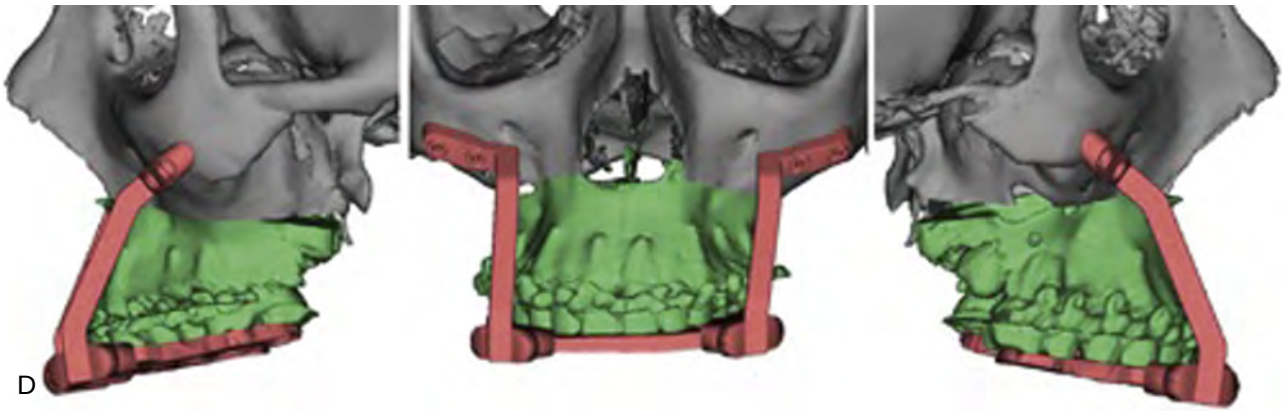


• **Fig. 7.8 CASE 1. A,** Preoperative CT reconstruction demonstrating previously placed implants and hypoplastic right mandible. **B,** Virtual surgical representation of proposed Le Fort I osteotomy with impaction of maxilla, inverted L osteotomy on left mandible with right parasymphyseal osteotomy and right neomandible from the free fibula graft.



• **Fig. 7.9 CASE 1.** **A,** Virtual representation of the Le Fort I maxillary movement to attain ideal position and occlusion. **B,** Inferolateral views. **C,** Orthognathic positioning splints. These are secured to the stable zygomas to serve as the fixation points for orthognathic reference.

Continued





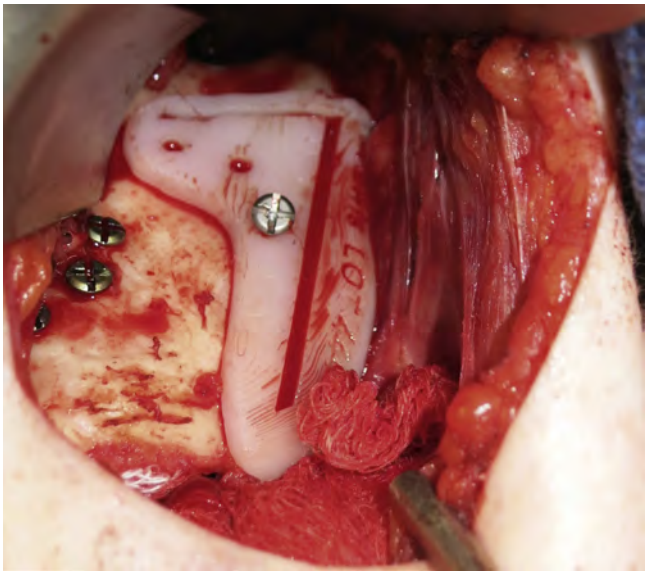
• **Fig. 7.9, cont'd CASE 1. D,** After the completed osteotomy. **E,** Sandwich splint in place, upon which the mandible positioning is later based.







• **Fig. 7.10 CASE 1. A,** Intraoperative view of maxillary component advanced into the ideal pre-planned position using the orthognathic positioning splint. Splint is secured to the right **(B)** and left **(C)** zygomas.



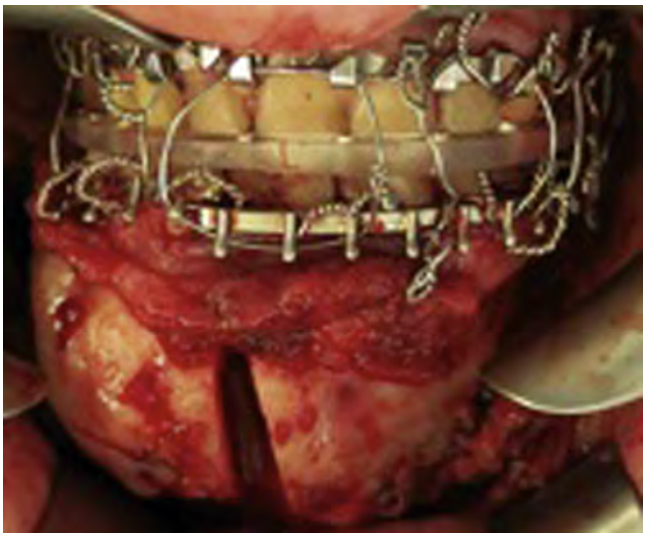
• **Fig. 7.11 CASE 1.** Cutting guide for inverted L osteotomy on left mandible.



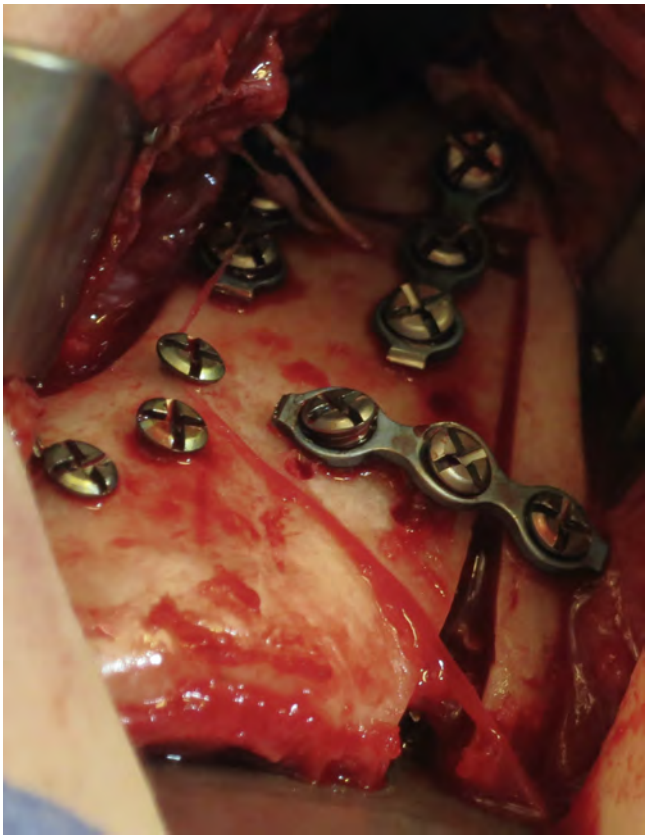
• **Fig. 7.12 CASE 1.** Cutting guides on the right parasymphyseal segment for the midline osteotomy and right segmental mandibulectomy.

Once the maxilla was fixated in its correct location in relation to the skull base, the mandible was then exposed. An inverted L osteotomy on the left-hand side was performed using a virtually determined cutting guide (Fig. 7.11). The midline osteotomy was also performed at this time to allow for lateral rotation of the left mandible.

A segmental mandibulectomy on the right side was then performed to remove the abnormal bone. A prefabricated cutting guide dictated the locations of both the midline and right parasymphyseal osteotomies (Fig. 7.12). The patient was then placed in MMF using a prefabricated splint and 26-gauge wires



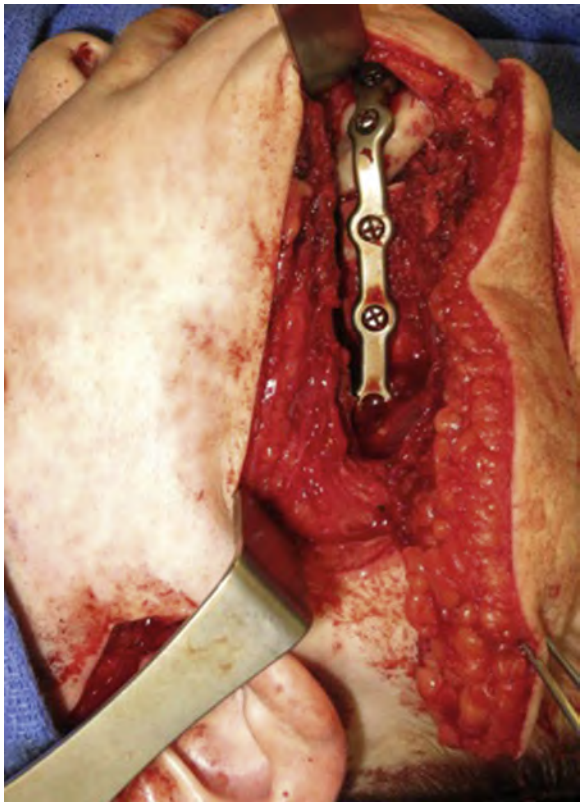
• **Fig. 7.13 CASE 1.** Patient placed in maxillo-mandibular fixation with prefabricated splint, ensuring maintenance of ideal occlusion with the now stable maxilla.



• **Fig. 7.14 CASE 1.** Left mandible inverted L osteotomy secured with miniplates after determination of ideal orientation.

(Fig. 7.13). The left inverted L osteotomy was then adjusted to the orientation that accomplished normal occlusion and was fixated with miniplates (Fig. 7.14).

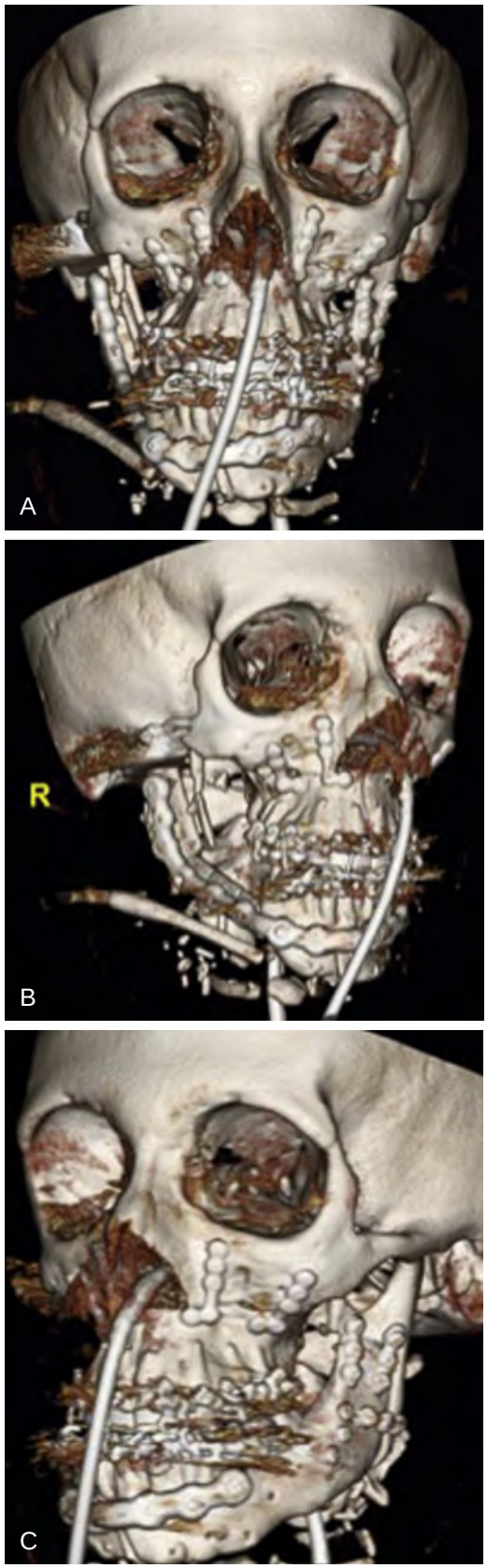
Following the plating of the left inverted L, the patient was kept in MMF and the right preauricular incision was planned in order to facilitate placement of the neo-condyle on the proximal fibula segment. Full exposure was obtained up to



• **Fig. 7.15 CASE 1.** Neo-mandible with free fibula flap secured in position to the custom reconstruction plate.

the previously placed right TMJ prosthesis. The custom reconstruction plate was then secured to the native left mandible with excellent contour adaptation. After this was performed, the right parasymphyseal segment separated by the midline osteotomy was secured in a location dictated by both the orthognathic splint and reconstruction bar.

While the head and neck team was working, the plastic surgery team simultaneously harvested the osteocutaneous free fibula flap. A 5- × 10-cm skin paddle was included to account for soft tissue swelling and allow for closure of the right modified Risdon incision. Before division of the pedicle, a virtually planned cutting guide was secured to the fibula and the pre-planned osteotomies were performed. The two-segment fibula flap was then brought up to the head and neck field. The neo-condyle was fashioned by burring the proximal bony component into a semicircular shape. The flap was then introduced into the defect with the neo-condyle seated into the previously created glenoid fossa implant, and this proximal fibula segment was secured to the reconstruction plate. The body segment of the fibula was subsequently positioned to maximize bony contact with both the neo-ramus and right parasymphyseal segment (Fig. 7.15). Postoperative CT scans demonstrate accurate positioning with good bony apposition and occlusion (Fig. 7.16). Preoperative and 3-month postoperative photographs (Fig. 7.17) illustrate the significant improvement in facial symmetry, projection, and occlusion.



• **Fig. 7.16 CASE 1. A-C,** Postoperative CT scans demonstrating adherence to the virtual surgical plan.



• **Fig. 7.17 CASE 1.** Comparison of preoperative appearance to the result 3 months postoperatively. **A,** Preoperative, patient in repose. **B,** Postoperative, patient in repose. **C,** Preoperative smile. **D,** Postoperative smile. **E,** Preoperative profile in repose. **F,** Postoperative profile in repose.

Case 2: Locally Invasive Tumor of the Hard Palate Requiring Subtotal Maxillectomy

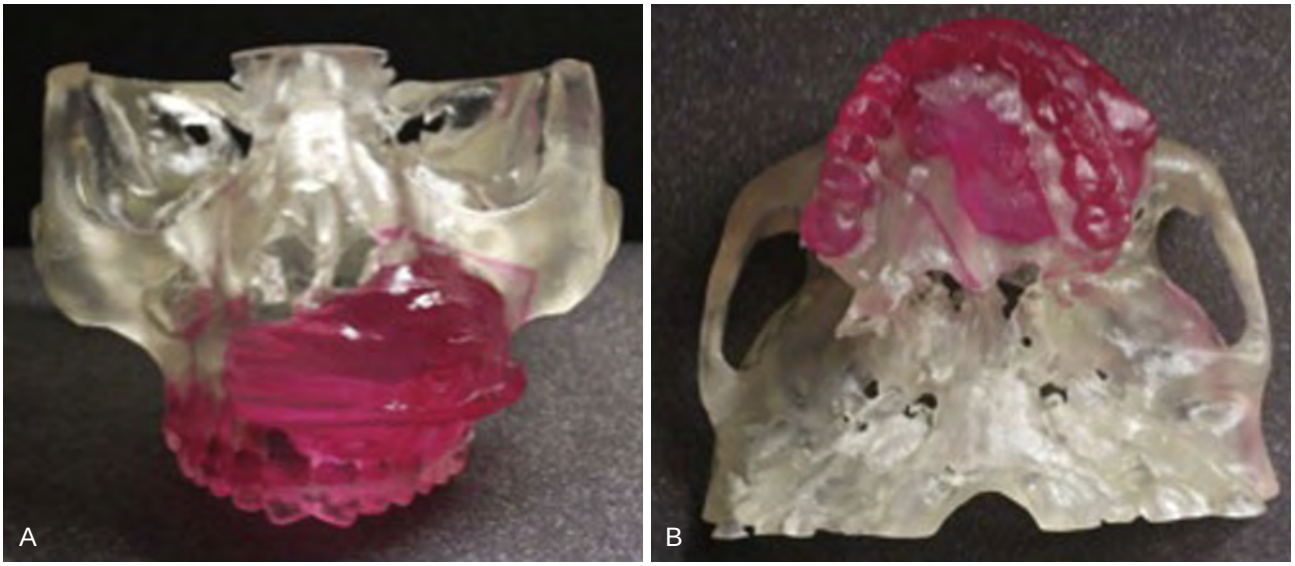
A 54-year-old woman presented with a locally advanced desmoplastic ameloblastoma involving the entire left maxilla and alveolus with extension to the right first molar. Preoperative CT scans were obtained, from which stereolithographic models were created (Fig. 7.18). Virtual planning was performed highlighting the significant pathology, necessary resection margins, and optimal method of reconstruction.

A virtual surgical resection and reconstruction using vascularized fibula were performed (Fig. 7.19). The planned resection margins included a significant proportion of the left zygoma body posteriorly and extended anteriorly toward the upper third of the piriform rim. It was noted that tooth number 4 would have to be extracted in order to accommodate a posterior osteotomy margin on the right to be carried anteromedially to the piriform. Virtual reconstruction indicated that a three-segment fibula graft would be needed for the alveolar defect with an additional fourth piece to account for the zygoma resection. Six primary endos-teal implants were also planned, positioned in locations that would optimize occlusion once dental rehabilitation was completed.

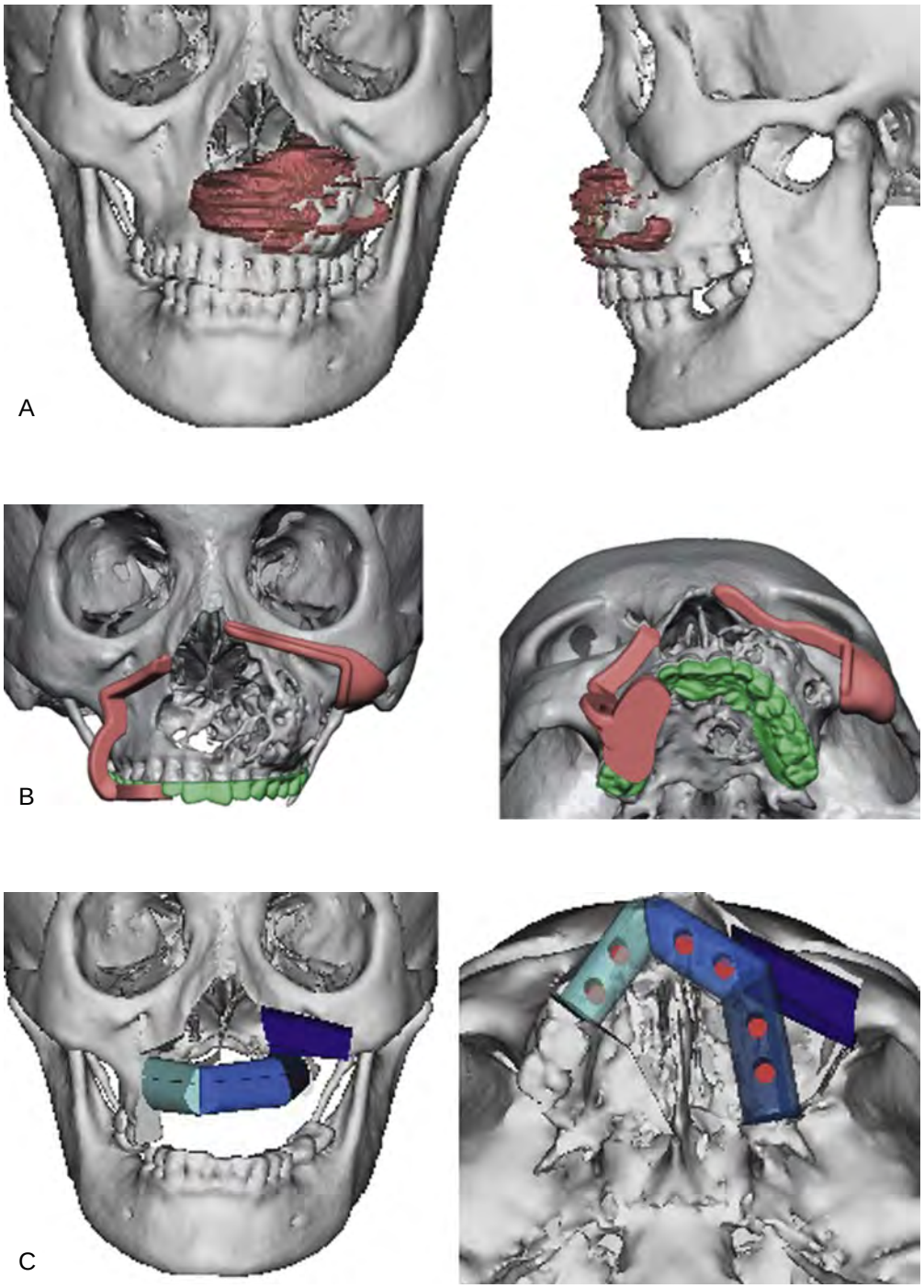
With the anticipated resections and reconstructions determined, stereolithographic models (Fig. 7.20) and cutting guides were manufactured to facilitate precise complementary cuts and implant placement in three dimensions. These included a linear cutting jig for the fibula (Fig. 7.21), maxillary resection guides (Fig. 7.22), and a temporary construct to guide the assembly of the neo-maxilla (Fig. 7.23).

The head and neck resection proceeded as planned, starting at the left zygoma. Subperiosteal dissection exposed the resection margins, and osteotomies proceeded medially toward the piriform. The nasal mucosa was dissected free for maximal preservation. On the right side, tooth number 4 was extracted and mucoperiosteal flaps developed. Subperiosteal dissection exposed the anterior maxillary wall for planned osteotomy toward the piriform. Again, nasal mucosa was preserved as much as possible. The palate was then exposed, dissecting free the palatal mucosa in a subperiosteal plane. Osteotomies were then completed on the posterior and medial aspects of the palate, connecting with the left-sided osteotomies in the retropalatine pterygoid region. With the resection completed as planned, the specimen was removed and the resulting defect examined (Fig. 7.24). Upon completion of the midface resection, the left facial artery, facial vein, and external jugular vein were dissected out to serve as recipient vessels for microvascular anastomosis.

Elevation of a free fibula osteomyocutaneous flap from the left leg was simultaneously performed by the plastic surgery team. This was done in the standard fashion with a skin paddle included for palatal coverage (Fig. 7.25). With the fibula flap isolated on its vascular pedicle, the linear cutting jig was applied to the fibula and correct orientation was confirmed before securing the jig with monocortical screws. Six endosteal implants were then placed in the specified locations on the jig (Fig. 7.26). The wedge osteotomies were then performed on the fibula, and the three alveolar segments were positioned into the prefabricated guide to align the neo-maxilla (see Figure 10-23, *B*). Of note, all three alveolar segments were in line distal to the circulation. The fourth piece for the zygoma was proximal on the fibula, coming off of the periosteal sleeve. A 2-mm reconstruction plate was then contoured to the three-segment neo-maxilla seated in the temporary guide and secured with monocortical screws (Fig. 7.27).



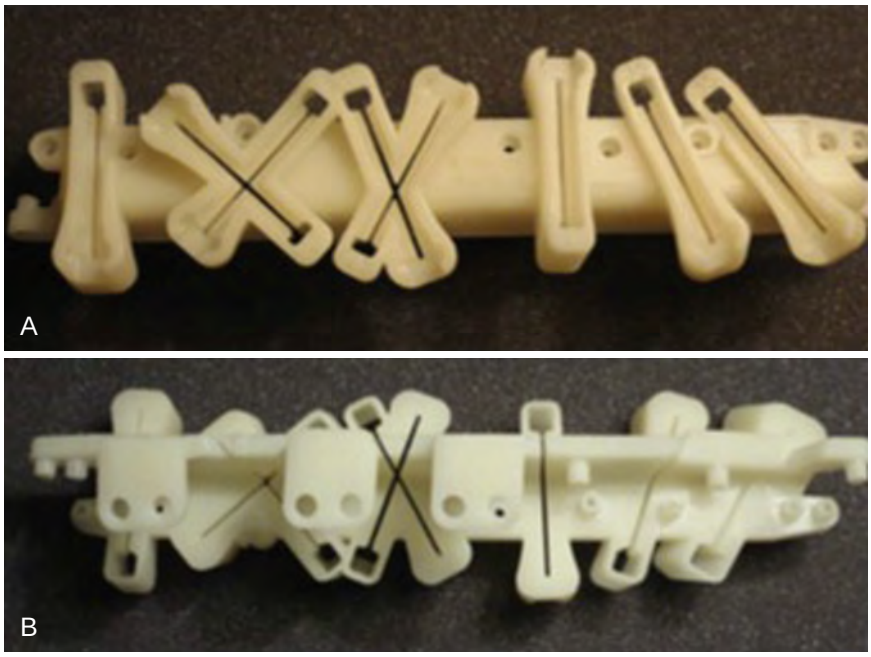
• **Fig. 7.18 CASE 2.** Stereolithographic model of planned maxillary resection with pathology highlighted in pink. Note the proposed osteotomy lines. **A,** Anterior. **B,** Inferior.



• **Fig. 7.19 CASE 2.** **A,** Preoperative 3D anatomy from CT data for virtual surgical planning. **B,** Planned resection osteotomies with custom cutting guides designed for stereolithographic printing and intraoperative use. **C,** Virtual reconstruction of the midface defect with a free fibula flap.



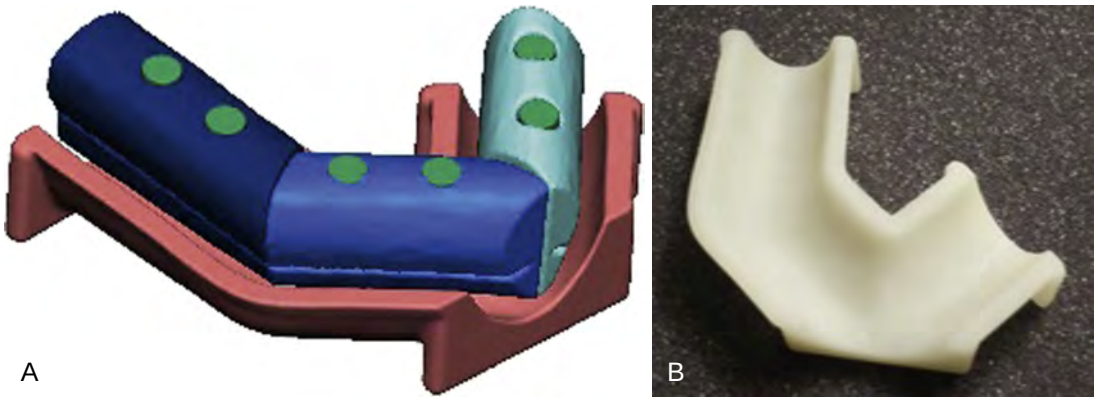
• **Fig. 7.20 CASE 2. A,** Planned resection osteotomies and subsequent reconstruction performed on a model. Note the simulated free fibula flap in place with three segments composing the neo-alveolus and a fourth segment reconstituting the left zygomatic defect. **B,** Inferior view demonstrating the locations of six endosteal implants. **C** and **D,** Reconstruction with mandible in place.



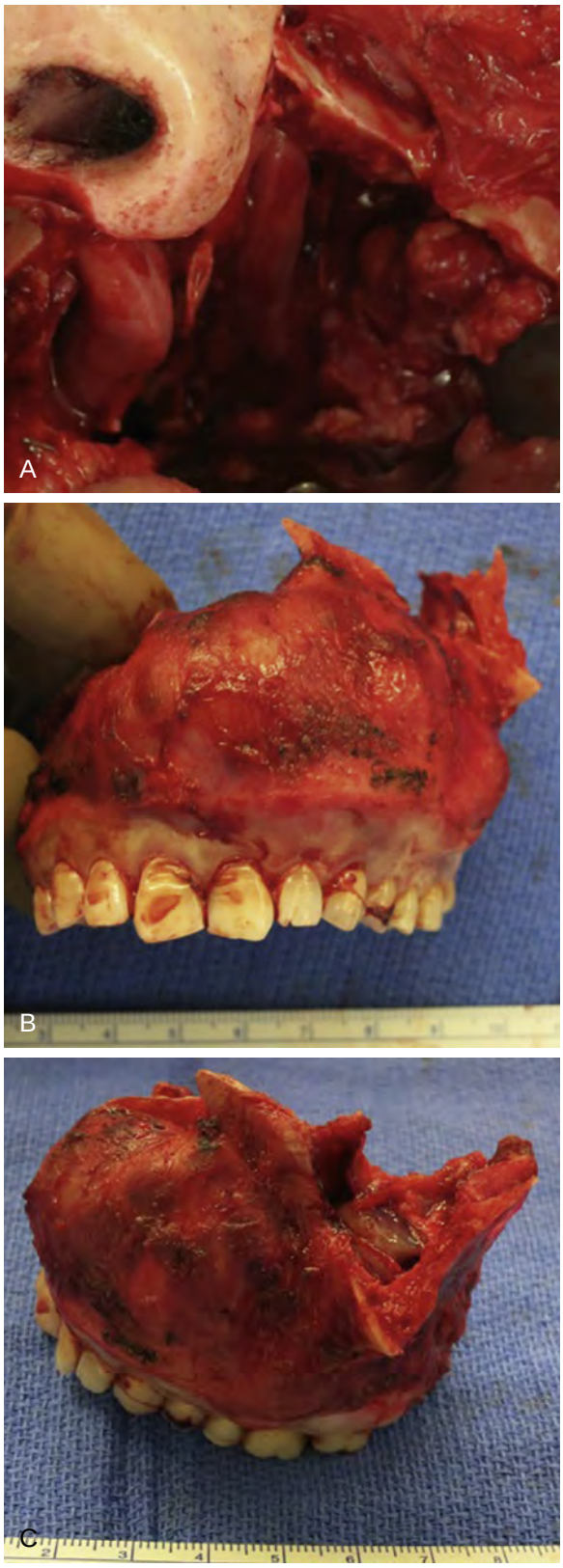
• **Fig. 7.21 CASE 2.** Fibula jig, which included cutting guides for the osteotomies **(A)** and holes to drill for implant placement **(B)**.



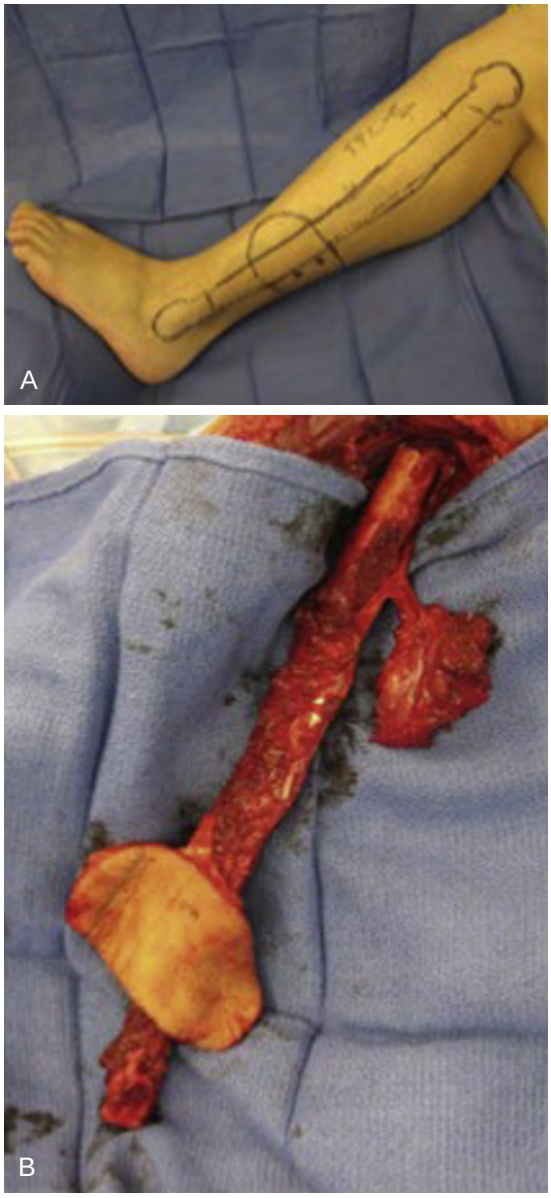
• **Fig. 7.22 CASE 2.** Cutting guides for maxillary resection.



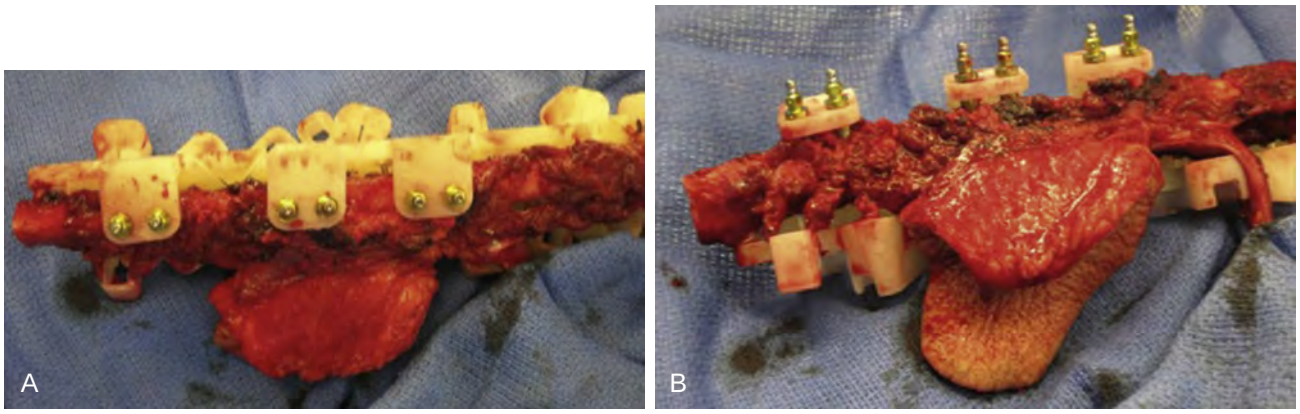
• **Fig. 7.23 CASE 2.** Virtual design **(A)** and intraoperative construct guide **(B)** for the fibula segments intended to create the neo-maxilla.



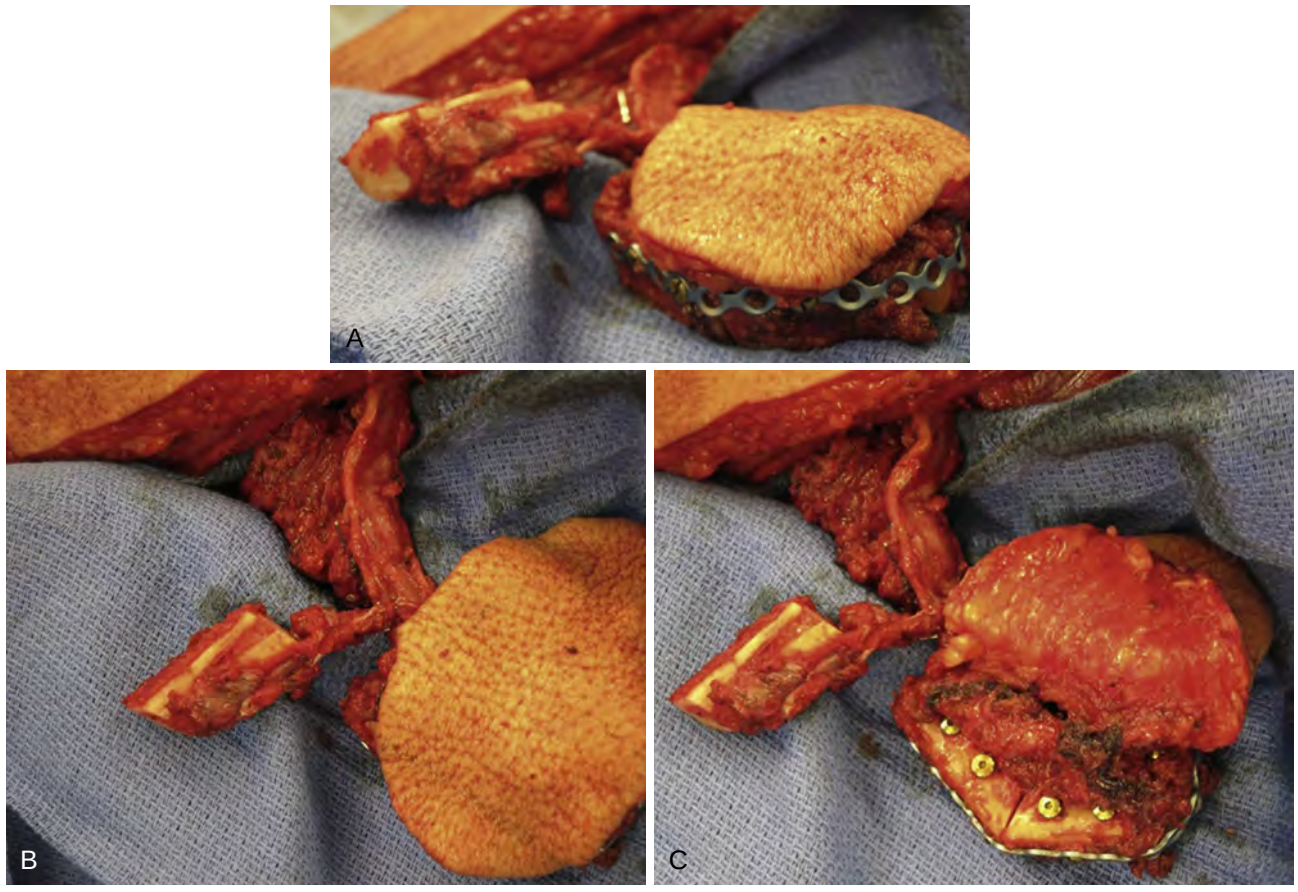
• **Fig. 7.24 CASE 2.** Post-ablative defect **(A)** with anterior **(B)** and left lateral **(C)** views of the extirpated specimen.



• **Fig. 7.25 CASE 2. A,** Standard markings for free fibula flap. **B,** Fibula graft raised, with skin paddle defined, still attached to pedicle.



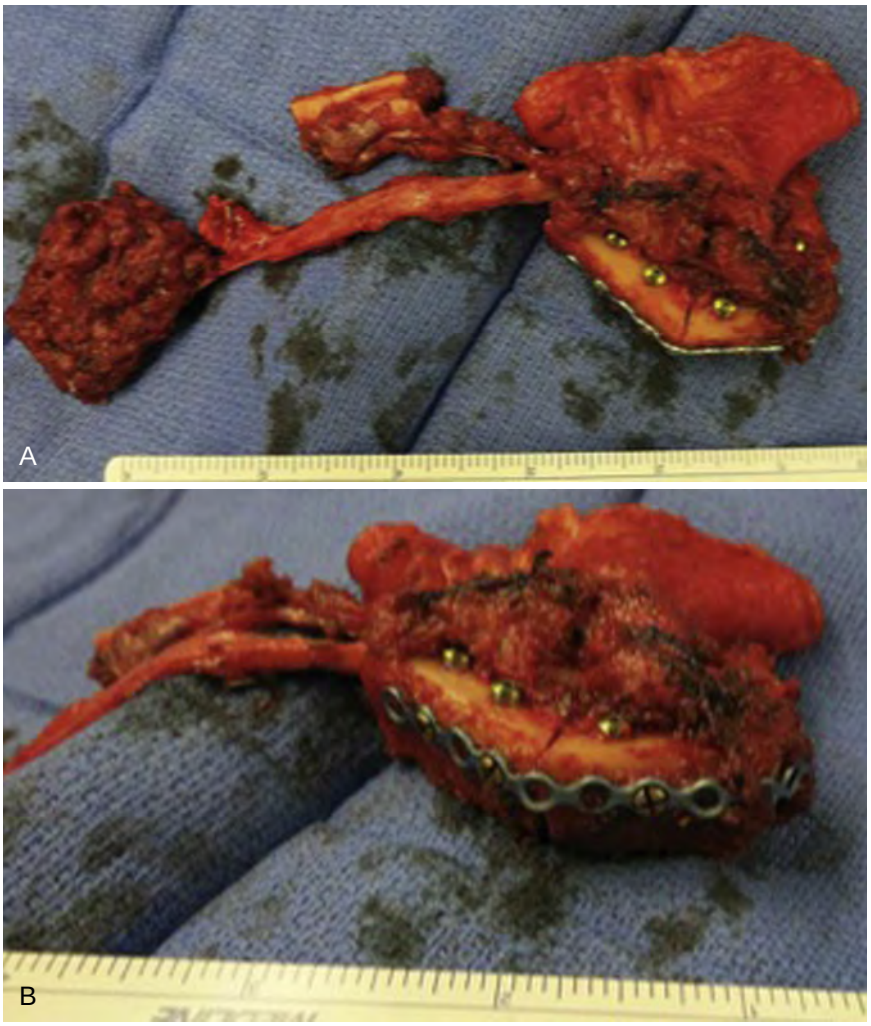
• **Fig. 7.26 CASE 2.** **A,** Custom jig secured to fibula with implants placed while still attached to pedicle. **B,** Lateral view demonstrating implant placement guided by jig.



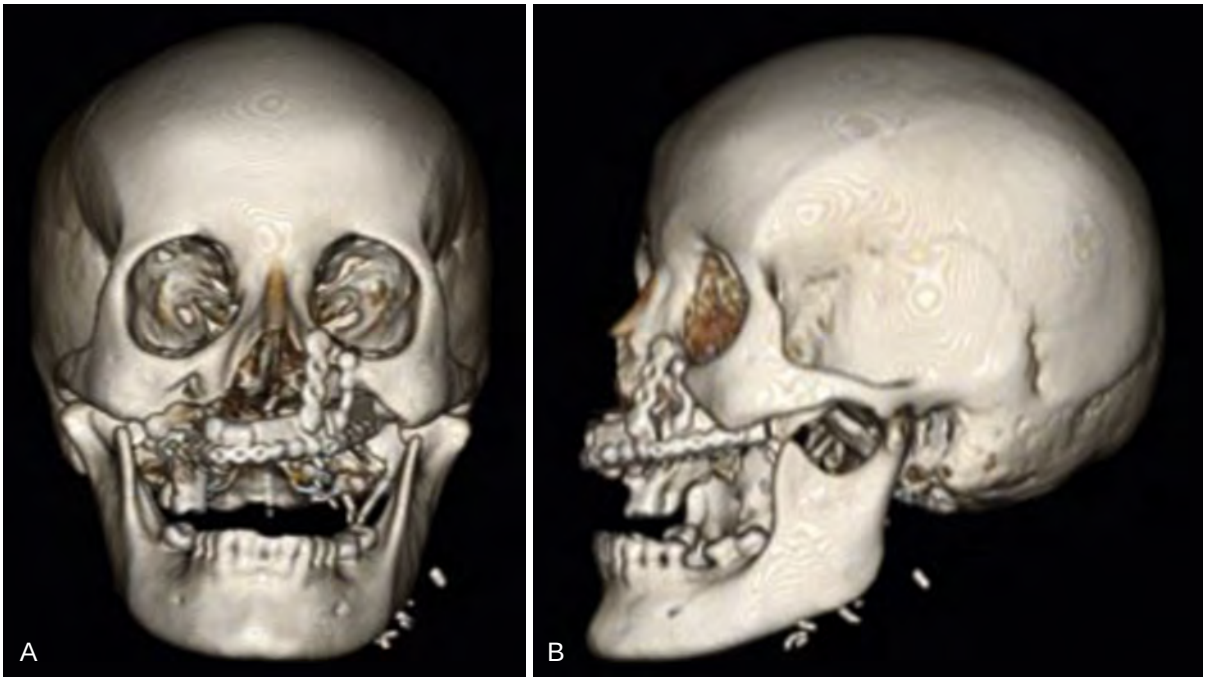
• **Fig. 7.27 CASE 2.** **A,** The alveolar fibula segments are secured to reconstruction bar. **B,** Note the skin paddle oriented over the dental implants on what is to become the new palatal surface. **C,** Segments secured to reconstruction bar with skin flap retracted, demonstrating implants. Note the fourth bone segment, intended to reconstruct the zygoma defect, coming off the most proximal aspect of the flap.

The assembled free flap construct was then divided from the peroneal vessels and brought up to the head and neck (Fig. 7.28). Bony fixation was performed first, securing the three-segment neo-maxilla to the remaining zygoma. The fourth, longitudinally osteotomized segment was then positioned into the left zygoma defect and secured with a lag screw and miniplate. Once bony fixation was completed, the microvascular anastomoses were performed. A vascular tunneler was used to bring the vessels to the submandibular region where the facial vessels and external jugular vessels were exposed, and microvascular anastomoses were successfully completed. The soft tissue components were then inset with the flap skin paddle sutured into the remaining palatal mucosa in order to close down this region posteriorly. Anteriorly, the skin paddle was wrapped around the bone to cover the reconstruction plate. The most anterior aspect of the skin paddle was de-epithelialized, tucked below the lip, and sutured to nasal mucosa.

A CT scan obtained on postoperative day 4 demonstrated accurate construct placement with excellent bony apposition (Fig. 7.29).



• **Fig. 7.28 CASE 2.** Osteomyocutaneous flap immediately after pedicle division. **A** and **B,** Note all dental implants and the reconstruction plate have already been placed.



• **Fig. 7.29 CASE 2.** Postoperative CT result 4 days after surgery: **(A)** anterior, **(B)** left lateral.

Case 3: Complex Orbitomaxillary Defect Due to Recurrent Rhabdomyosarcoma

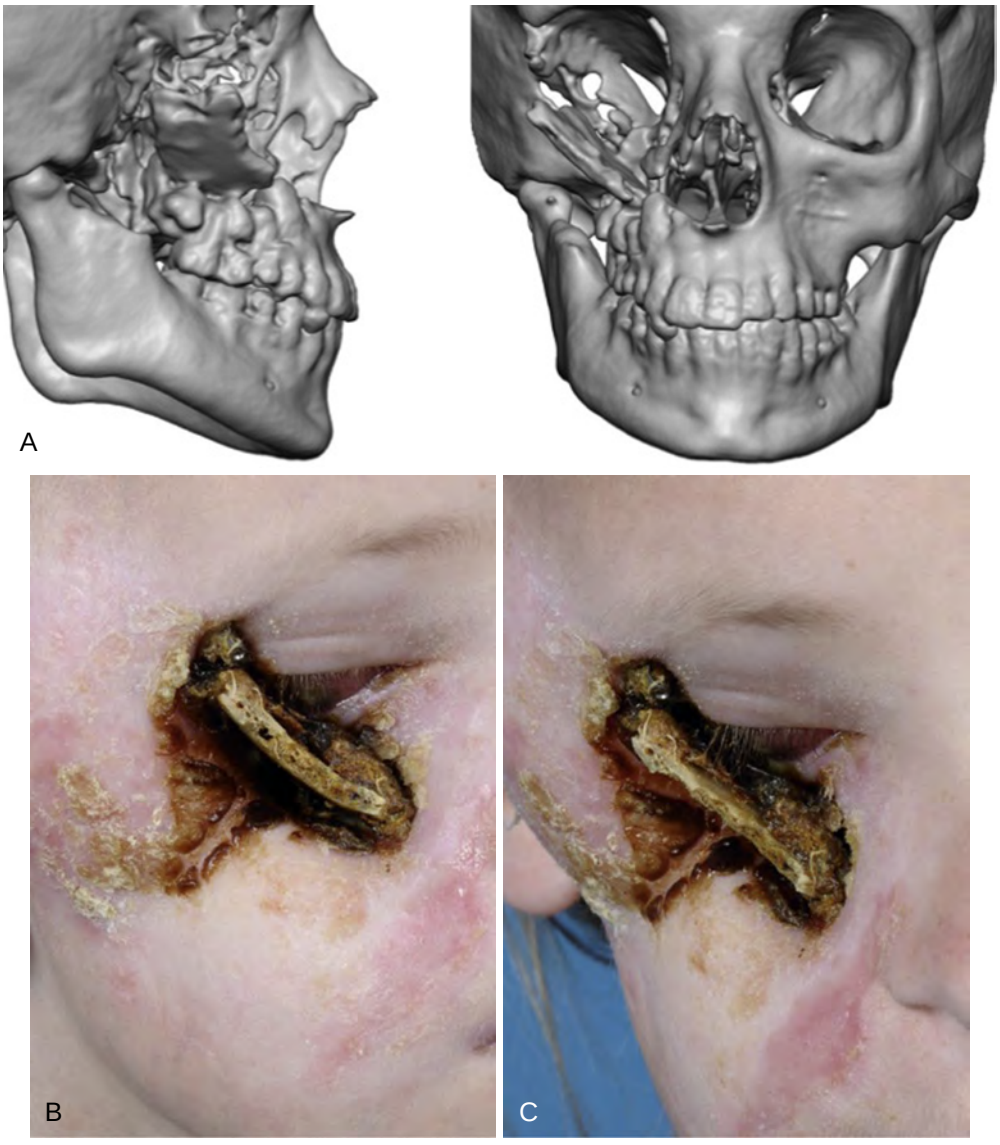
A 12-year-old girl presented with a complex defect involving the right orbit and cheek. Five years earlier she had been diagnosed with orbital rhabdomyosarcoma, which was treated with chemotherapy and radiation. Two years later there was a recurrence, which was resected and reconstructed with free rectus flap and calvarial bone graft. She then underwent an additional course of radiation therapy, after which a non-healing wound developed. This wound was present for more than a year at presentation. Physical examination demonstrated a non-functional globe, soft tissue defect communicating with the orbit and maxillary sinus, severe radiation-induced changes to surrounding skin, including the lower lid, and loss of malar projection (Fig. 7.30).

CT with 3D reconstruction demonstrated near complete loss of her lateral orbital rim and zygomatic arch. Her orbital floor was constituted by attenuated bone graft from her previous reconstructive procedure (Fig. 7.31). The patient underwent enucleation along with composite resection of damaged and nonviable soft tissues and bone, as guided by the virtual modeling session, which was attended by engineers, the ablative team, the reconstructive team, and the maxillofacial prosthodontist (Fig. 7.32).

A fibula flap with a skin paddle and a cuff of flexor hallucis longus was harvested in standard fashion. Preoperative imaging was used to plan a reconstruction of the inferior orbital rim and zygomatic arch. A prefabricated cutting jig allowed for precise placement of end osteotomies and a single wedge osteotomy. Additionally, a separate jig was fabricated to allow a splitting osteotomy of the fibula. This permitted elevation of a bony segment supplied by periosteal circulation for lateral orbital rim reconstruction (Fig. 7.33). All osteotomies were performed before ligation of the flap pedicle on the leg. A stereolithographic model of the recipient site was used to facilitate flap inset with miniplates. Microsurgical anastomosis was performed in the neck to the external carotid and jugular systems. The muscular portion of the flap was used to obliterate dead space and the skin paddle to line the cheek and lower lid (Fig. 7.34). Postoperative CT imaging demonstrated the bony construct in position with excellent anatomic reproduction (Fig. 7.35), thus facilitating the fabrication of an appropriately formed orbital prosthesis to complete the reconstruction (Fig. 7.36).



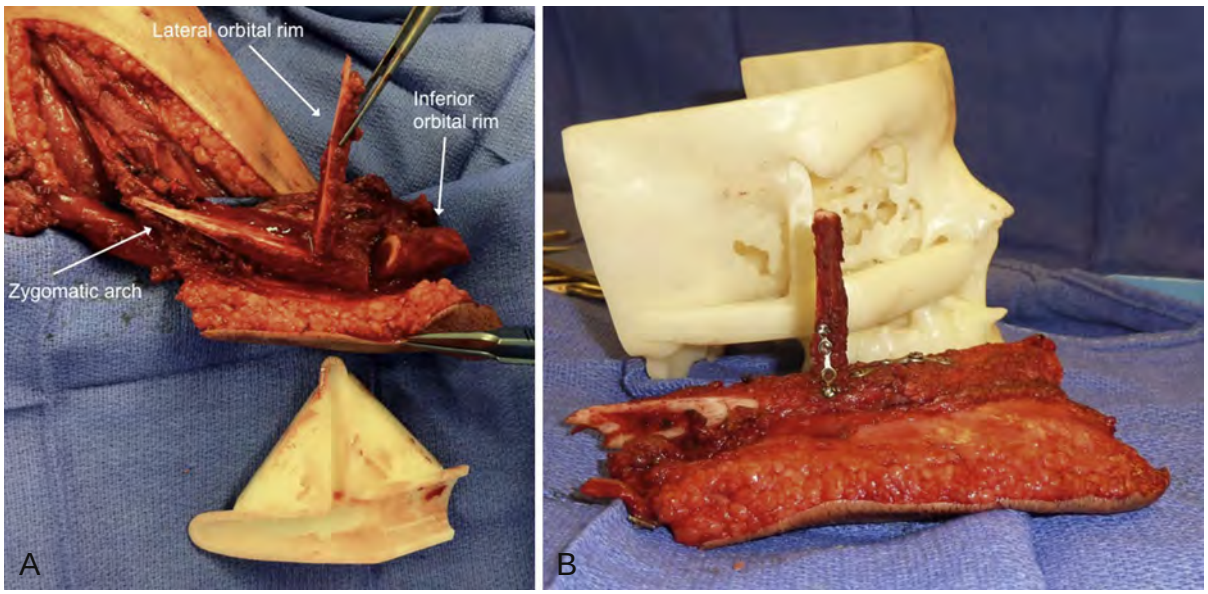
• **Fig. 7.30 CASE 3.** Preoperative photography demonstrating a non-functional globe, soft tissue defect communicating with the orbit and maxillary sinus, severe radiation changes to surrounding skin including lower lid, and loss of malar projection. **A,** Anterior. **B,** Lateral. **C,** Inferior.



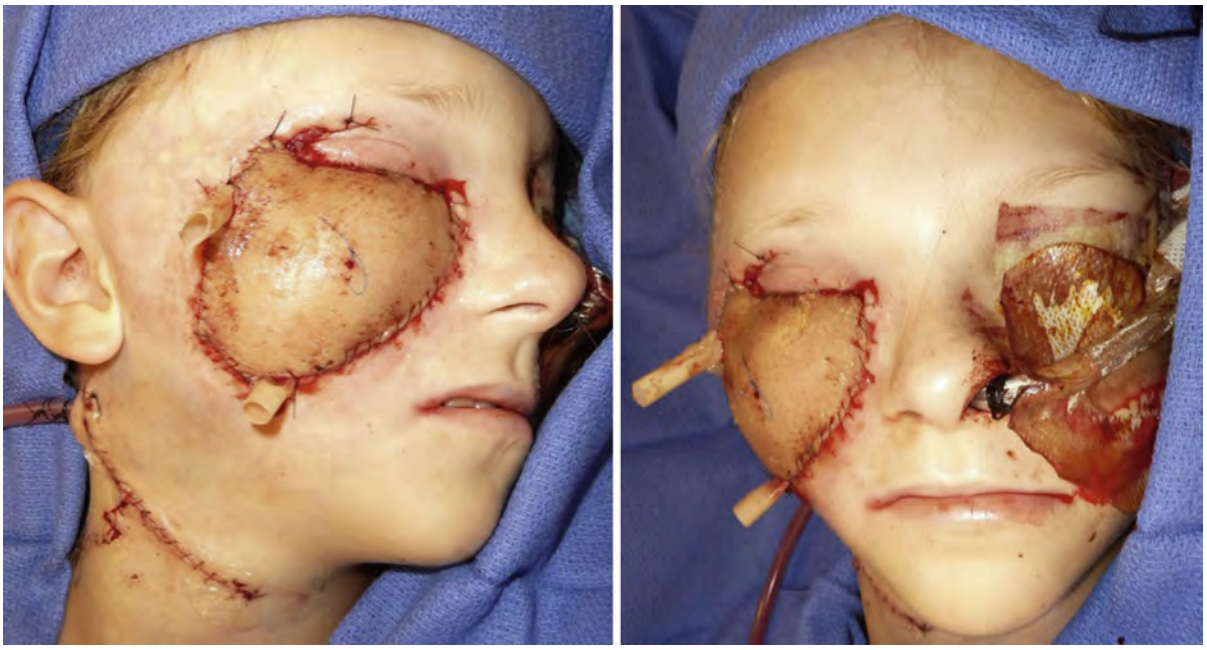
• **Fig. 7.31 CASE 3.** **A,** CT with 3D reconstruction demonstrating near complete loss of the lateral orbital rim and zygomatic arch. **B** and **C,** The orbital floor is constituted by attenuated bone graft from a previous reconstructive procedure.



• **Fig. 7.32 CASE 3.** Intraoperative photo demonstrating the composite defect and neck dissection for vascular access.



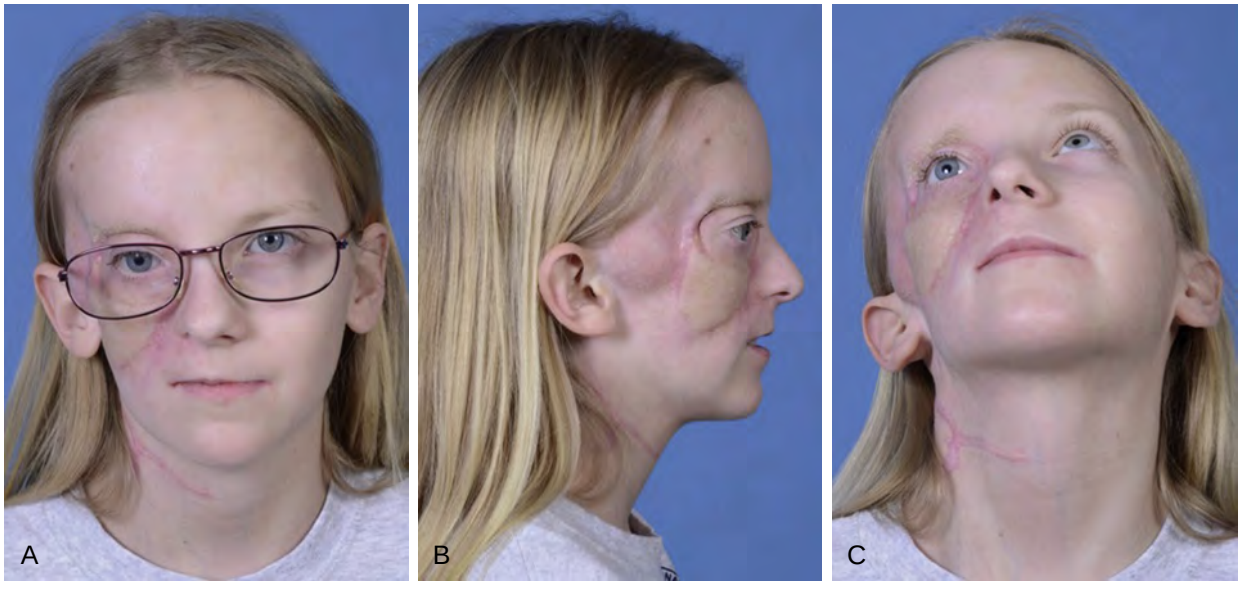
• **Fig. 7.33 CASE 3.** **A,** Osteotomized flap construct while still perfused on the leg. Various bony segments used to reconstruct specific anatomic structures are labeled. **B,** The construct, following harvest, next to a stereolithographic model used to guide inset.



• **Fig. 7.34 CASE 3.** The patient following fibula flap inset. The skin paddle was used to resurface the cheek and lower lid.



• **Fig. 7.35 CASE 3.** Postoperative CT demonstrating bony construct in excellent position. *Black arrow* indicates Penrose drain.

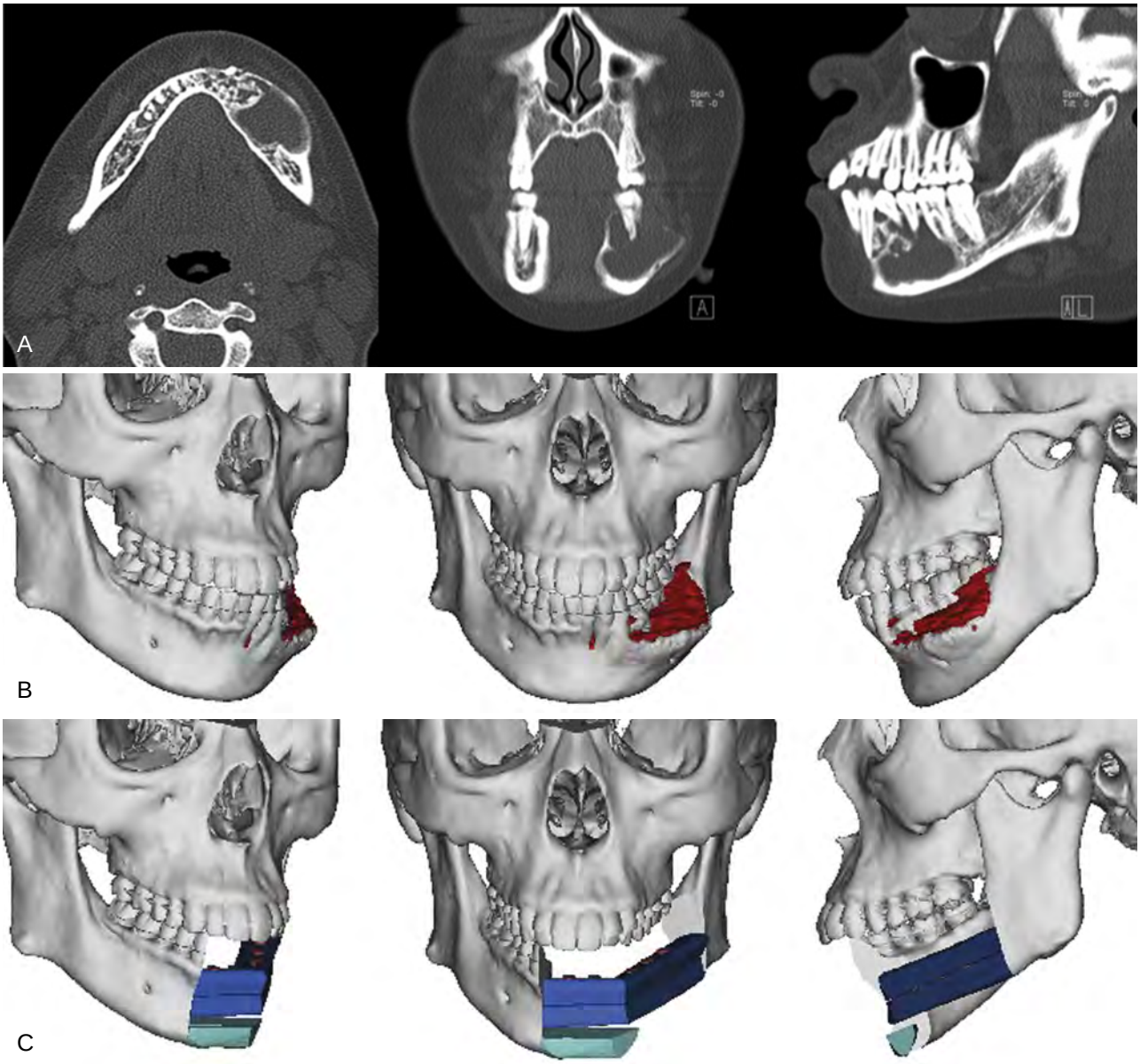


• **Fig. 7.36 CASE 3.** Nine-month postoperative result with right orbital prosthesis in place. **A,** Anterior. **B,** Lateral. **C,** Inferior.

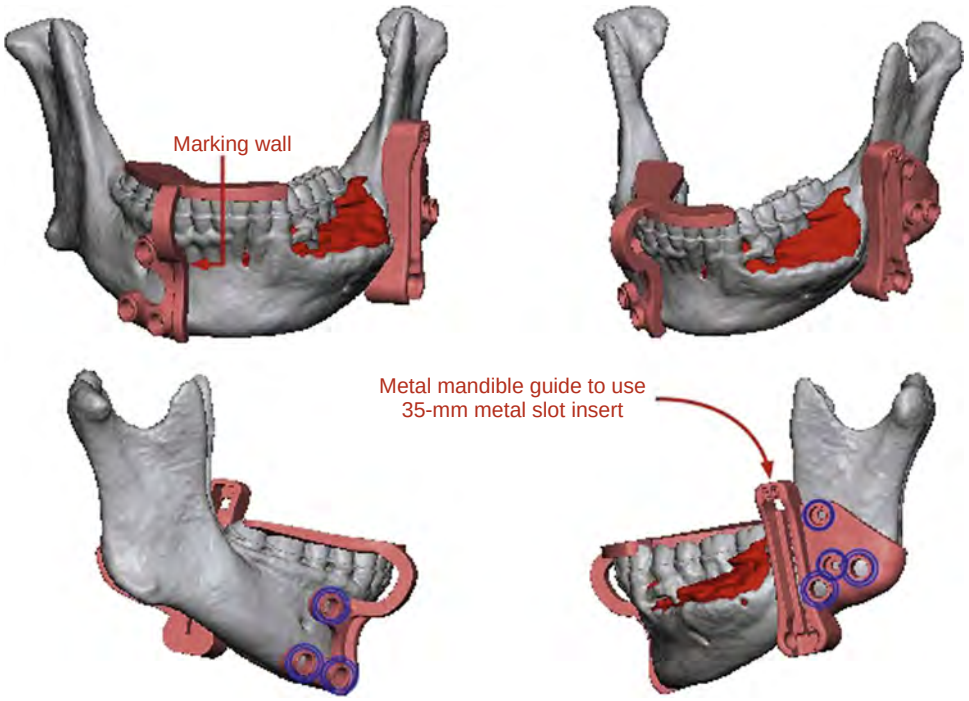
Case 4: Giant Ameloblastoma of the Mandible

A 33-year-old woman with no past medical history initially presented to her dentist with the chief complaint of left-sided mouth swelling and discomfort. Work-up revealed a large follicular ameloblastoma extending from the symphysis menti to the body of the left mandible with root involvement of the incisors, canines, and both premolars. The decision was made to proceed with a left segmental mandibulectomy and immediate reconstruction with a fibula free flap, dental implants, and placement of a prosthesis. Preoperative work-up included a high-resolution non-contrast CT scan of the mandible and a CT angiogram of the bilateral lower extremities. The CT data were then used for VSP to design the required ablative mandibular osteotomies and the right fibula osteotomies necessary to reconstruct the defect (Fig. 7.37). A customized reconstruction plate was manufactured in addition to the cutting jigs and guides designed during the VSP meeting (Figs. 7.38 through 7.40). Positioning of five dental implants was incorporated into the reconstructive design and a fixed dental prosthesis was also fabricated preoperatively.

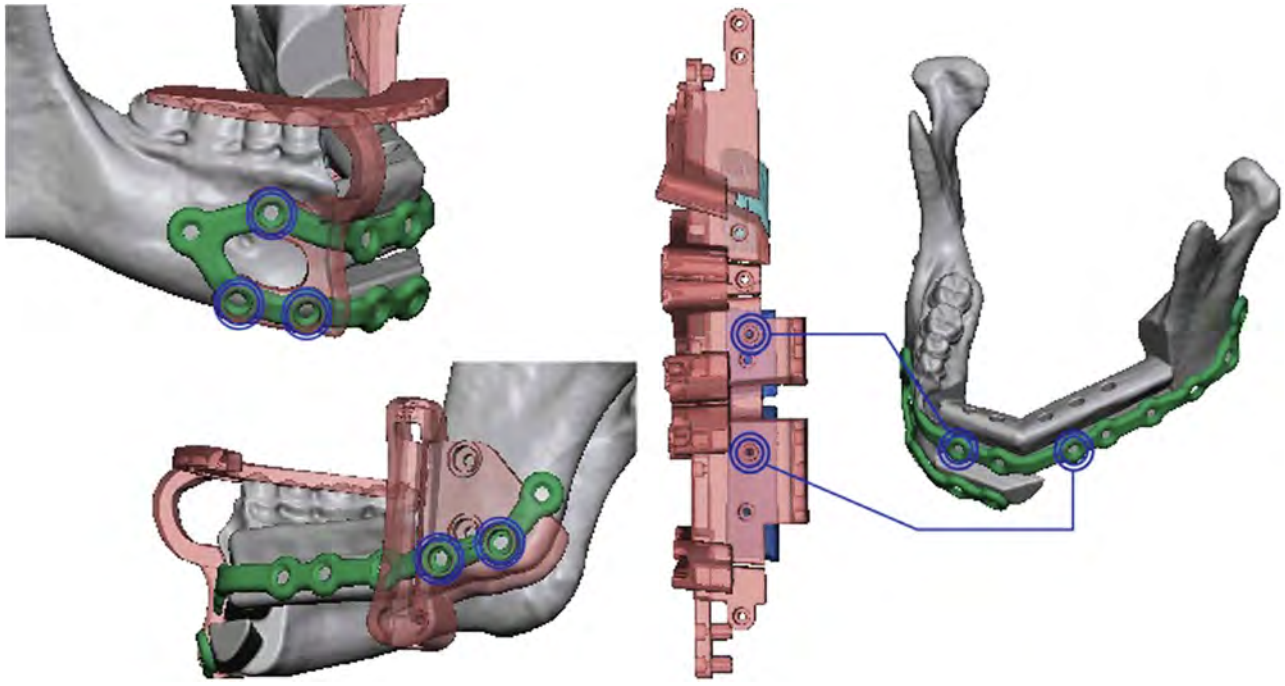
The procedure began with uncomplicated tracheostomy placement. The extirpative portion of the operation was performed using combined extra-oral and intra-oral approaches with dissection proceeding until the entire tumor was isolated. At this point, the prefabricated cutting guides were fixated to the mandible (Fig. 7.41), predictive holes for the future plate were drilled, and osteotomies were created using a sagittal saw. Following removal of the specimen (Fig. 7.42), the patient was placed in MMF using screws and the prefabricated occlusal splint. The custom reconstruction



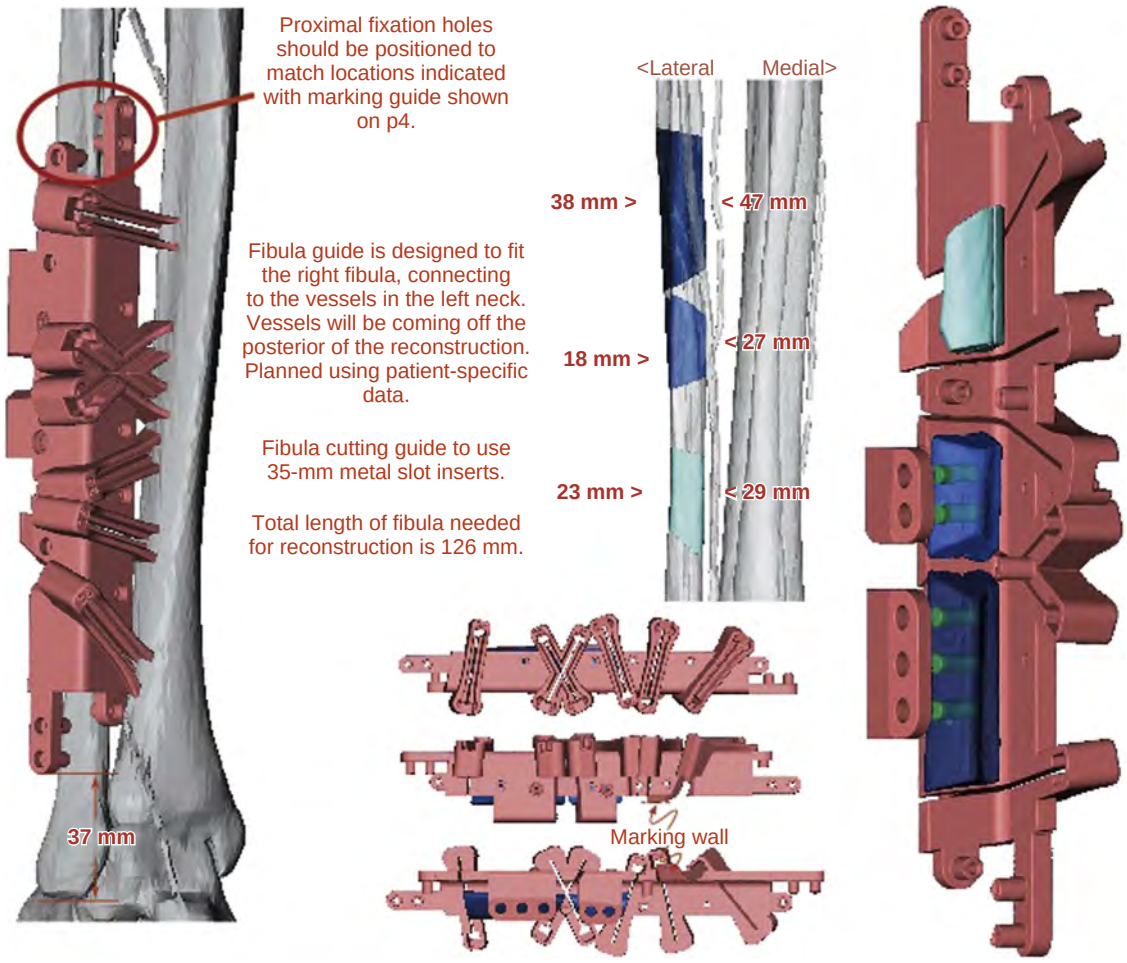
• **Fig. 7.37 CASE 4.** Three-dimensional models are generated from patient CT imaging data for virtual surgical planning. **A,** Preoperative CT scan. **B,** Virtual model of preoperative pathologic anatomy. **C,** Virtual model of anticipated reconstruction result.



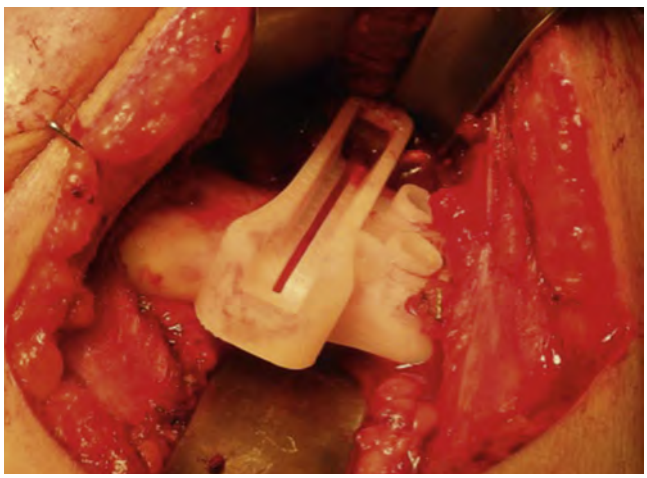
• **Fig. 7.38 CASE 4.** Virtual cutting guide designs for the mandibular resection. The right mandibular guide incorporated an orthognathic splint component. The drill holes marked with double circles indicate predictive holes for subsequent reconstructive plate placement following the osteotomies.



• **Fig. 7.39 CASE 4.** Virtual representation of the reconstructive plate orientation with regard to the cutting guides. Note that the plate is designed to travel around the right mental foramen and spare the right mental nerve.



• **Fig. 7.40 CASE 4.** Virtual plan for the fibular osteotomies and dental implant placement.



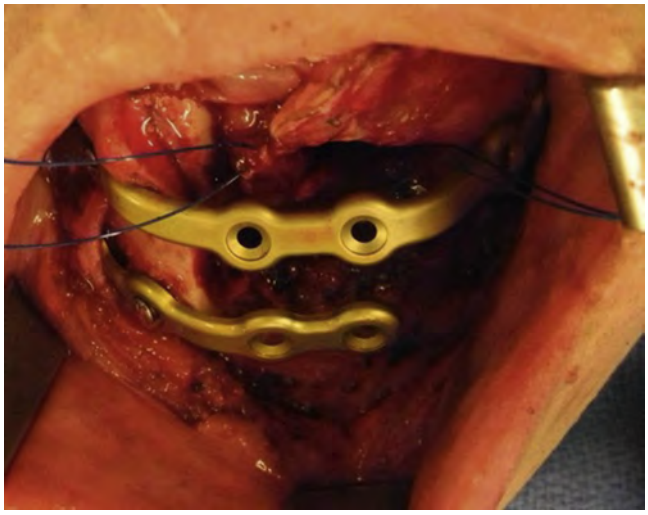
• **Fig. 7.41 CASE 4.** Cutting guide secured in place before the left mandibular body osteotomy.



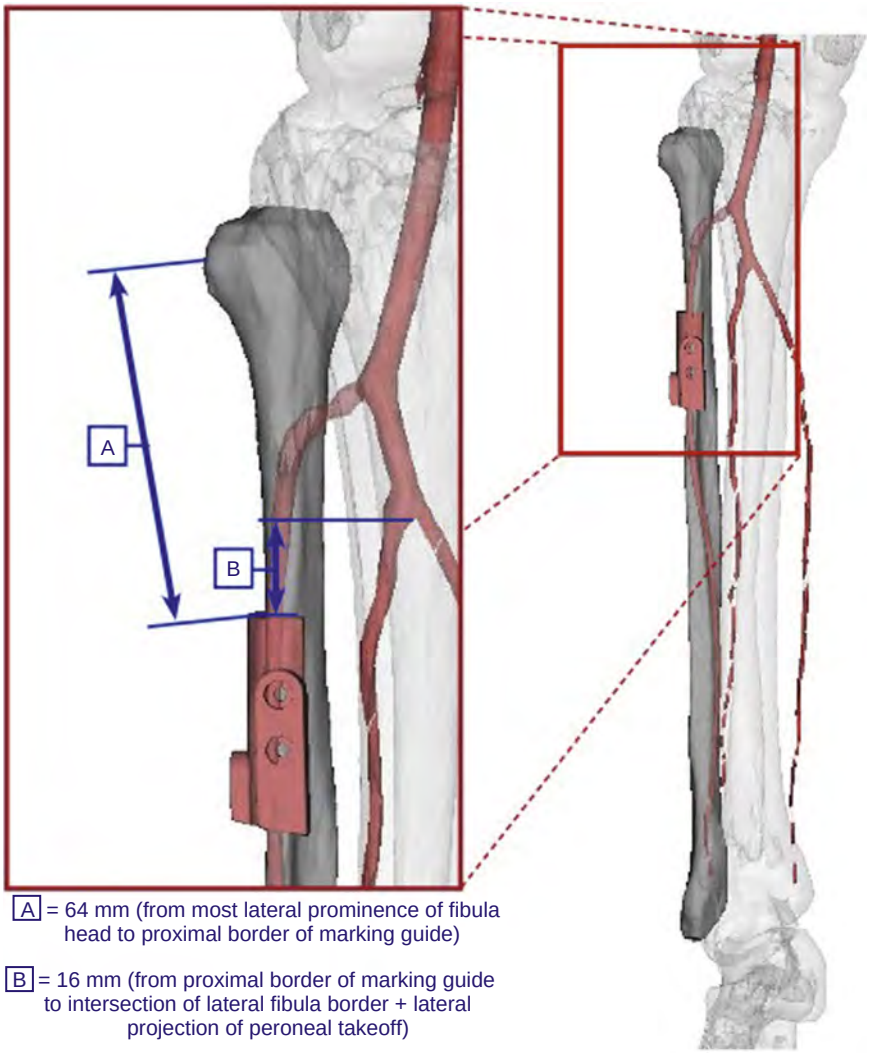
• **Fig. 7.42 CASE 4.** Diseased segment of left mandible following resection.

plate was then fixated in place with excellent apposition and wrapped around the right mental nerve as designed (Fig. 7.43).

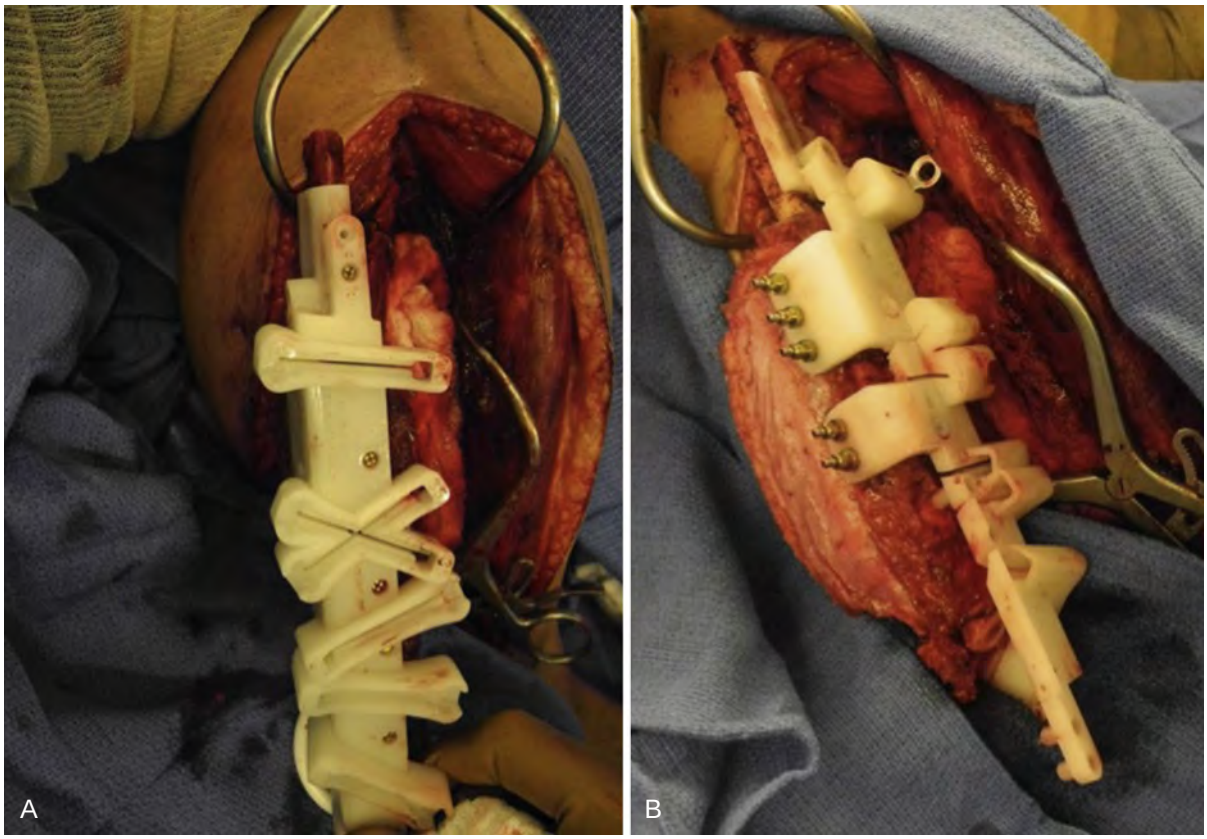
Preoperative VSP determined that a three-segment, double-barrel fibula free flap would provide the optimal reconstructive outcome. The planned fibula osteotomies accounted for the location of the peroneal vascular pedicle in order to ensure adequate segment perfusion and optimal pedicle length (Fig. 7.44). Simultaneously with the mandibular resection, the plastic surgery team harvested the right fibular free flap in standard fashion. Completion of the resection without deviation from



• **Fig. 7.43 CASE 4.** Anterior intraoral view following mandibular resection demonstrating the reconstruction plate in place and secured with screws drilled into the predictive hole locations.



• **Fig. 7.44 CASE 4.** Peroneal artery anatomy obtained from preoperative lower extremity CT angiogram is incorporated into the virtual design of the fibula flap to ensure adequate perfusion to each osseous segment while optimizing pedicle length.



• **Fig. 7.45 CASE 4.** Intraoperative view of the linear fibula cutting guide in place while the fibula is still attached to the vascular pedicle. **A,** Guide secured in place with monocortical screws. **B,** Following placement of five dental implants.

the preoperative plan was confirmed with the head and neck team. The linear cutting jig was then oriented along the fibula in the desired position and secured using monocortical screws (Fig. 7.45). The dental implants were then placed and the osteotomies performed in the exact orientation designed preoperatively. The three fibula segments were then bent into the appropriate orientation and the implants were noted to fit the prefabricated dental prosthesis quite well with excellent bony segment apposition (Fig. 7.46). At this point, long abutments were placed onto the implants and the dental prosthesis was secured using acrylic.

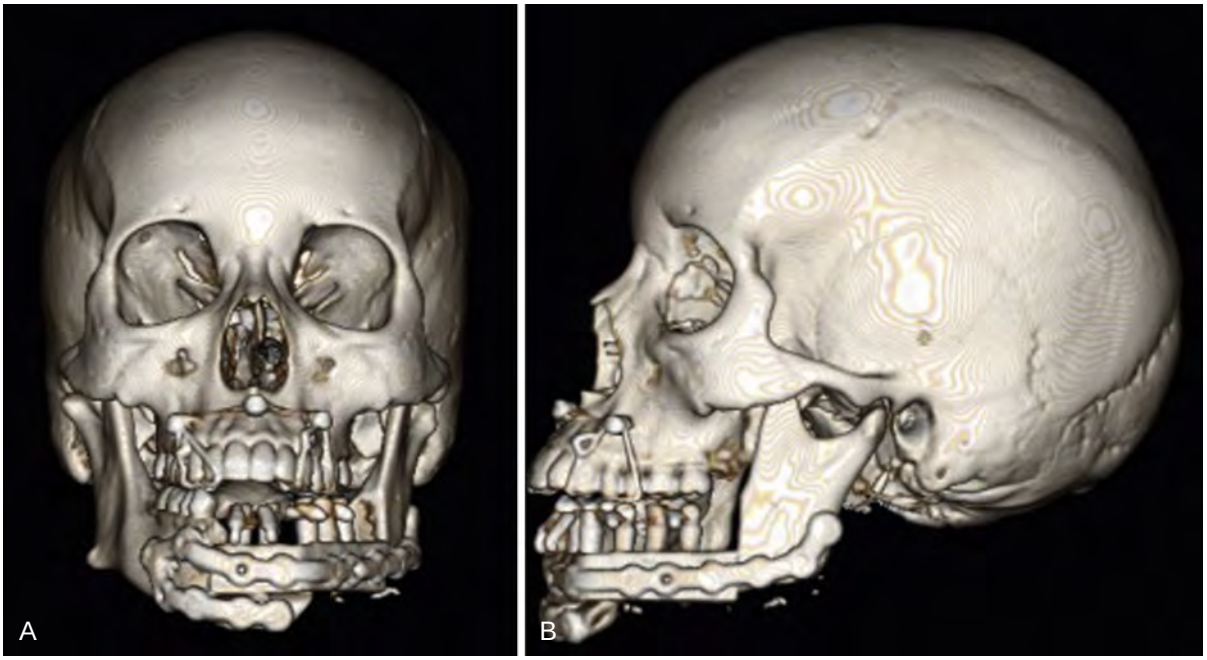
With the mandibular resection completed and the fibula construct isolated on its vascular pedicle, the vascular supply to the flap was divided at the leg and transferred into the mandibular defect. The fibula construct was noted to fit precisely into the mandibular space with excellent apposition to the remaining mandible and reconstruction plate (Fig. 7.47). Release of MMF demonstrated good occlusion, and the dentition was subsequently guided into an occlusal splint and stabilized with MMF rubber bands. The microvascular anastomoses were then performed successfully to the left facial artery and vein. Postoperative CT scan demonstrated excellent congruence between the preoperative virtual modeling and the anatomic reconstruction achieved (Fig. 7.48).



• **Fig. 7.46 CASE 4.** Complete fibula construct with dental prosthesis in place before division of the peroneal vessels.



• **Fig. 7.47 CASE 4.** Anterior intraoral view of the fibula construct immediately before closure. The flap appears well perfused and demonstrates excellent bony apposition and occlusion.



• **Fig. 7.48 CASE 4.** Postoperative CT demonstrating precise execution of the preoperative virtual surgical plan. **A,** Anterior. **B,** Left lateral.

Discussion

Oncologic ablation and reconstruction ideally require a multidisciplinary surgical team including head and neck surgeons, plastic and reconstructive surgeons, oral and maxillofacial surgeons, and prosthodontists. Computer-assisted operative planning facilitates communication and understanding among the teams involved to produce a comprehensive oncologic treatment plan tailored to each individual patient. The operative plan developed on the virtual model is implemented in the operating room through CAM of precise surgical cutting guides, anatomically exact stereolithographic models, and precisely pre-milled plating hardware.

The cohort of patients with head and neck cancer tend to be some of the most debilitated patients with significant comorbidities. Intraoperative accuracy and efficiency are necessities in order to accomplish complete oncologic ablation and functional reconstruction while minimizing operative time and anesthesia requirements. Computer-assisted surgery improves operative accuracy and efficiency by minimizing the amount of intraoperative guesswork and fine-tuning that is traditionally required. This technique allows for the assembly of a complex multisegment osseous component that precisely matches the reconstructive needs without interruption of perfusion or intraoperative measuring. Consequently, both the reconstructive operative time and duration of flap ischemia are reduced significantly.[12,13,20,21] This is significant, in that increased flap ischemia duration has been associated with increased postoperative flap complications.[22,23]

In addition to improving surgical planning and coordination, this powerful technique has a much shallower learning curve compared to traditional approaches. Tumor resections and reconstructions are simplified into their component parts to make even the most complex operations understandable and approachable. This also serves to improve surgical resident education and facilitates better patient comprehension of their planned procedure.

At present, incremental cost associated with computer-assisted techniques is approximately $3000 to $5000 per case. For complex operations, however, this is often easily offset by the reduction in operative time,[20] decreased flap complications from shorter ischemia times,[12,13,21] and improvement in functional outcomes with higher rates of dental rehabilitation.[12] Also, in patients who are receiving either intraoperative implant placement alone or implant placement with single-stage denture placement, there is a significant cost savings related to decreasing the surgical staging that would normally be required for the patient to obtain a completed reconstruction. The time to complete oral and dental reconstruction is also significantly decreased by using these modeling techniques. Reduction of anesthesia requirements for this cohort of patients may also decrease their operative morbidity and risk for postoperative complications. The potential benefit of minimizing the need for later operative revisions also exists due to initial imprecision of a reconstruction that was not virtually planned.

Summary

Computer-assisted surgical planning and modeling allows for accurate operative design with reliably predicted results. Surgical teams are now able to create single-staged ablative/reconstructive procedures all the way through to prosthetic dentition and expected soft tissue outcomes. These procedures are then translated to the operating room where they are carried out with unparalleled precision and efficiency. The selected cases illustrate the power and versatility of this technique for diagnosing, treating, and reconstructing complicated defects of the head and neck.

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8

Intraoperative Navigation

GIDO BITTERMANN, MARC C. METZGER, RAINER SCHMELZEISEN

Cancer of the head and neck requires a multidisciplinary approach in order to obtain a balance between tumor control and quality of life. Locally advanced head and neck squamous cell carcinoma is commonly treated by a combination of surgical resection, local reconstruction, and radiotherapy. Due to the complex anatomy of the head and neck regions, the challenge of complete tumor resection and adequate organ preservation with good postoperative function is often difficult. Given the involvement of multiple disciplines, precise communication is indispensable and also a challenge. To optimize tumor therapy, computer-aided surgery (CAS) and navigation procedures were introduced in craniomaxillofacial surgery (Fig. 8.1). The idea of intraoperative navigation is based on the neurosurgical development of a stereotactic frame more than 100 years ago. The goal of this method was to guide surgical instruments targeted to specific anatomic regions by using a coordinated anatomic atlas. CAS in oral and maxillofacial surgery was started more than 20 years ago and has developed as a standard procedure for head and neck surgery.[1-11]

3D Imaging

Computed tomography (CT) was invented by Allan M. Cormack in 1964, and the first prototype was developed by N. Hounsfield in 1973. Advances in software technology have resulted in the ability to produce 3D computer images of the facial skeleton. This development of 3D imaging provided the basis for medical 3D surgical planning. The generated layers may be converted to a volumetric dataset and a 3D reconstruction of the anatomy can be created.[12-14]

Computer-Aided Surgery Systems

Frameless CAS systems were subsequently developed and are commonly used in neurosurgery, orthopedics, and craniomaxillofacial surgery[15-17] (Fig. 8.2). CAS generates a precise 3D "virtual patient" and allows for simultaneous visualization of an operative site and surgical instruments with correlation to the patient's preoperative planning or treatment.[18,19] Surgical navigation systems have become an established technique in the removal of skull base tumors and has applications in foreign body removal, implantology, and orthognathic surgery.[20-24] Anatomic reconstruction of complex facial defects and planning for reconstruction creates a difficult challenge. Therefore, surgeons have applied CAS to assist in restoration of facial symmetry. This system can be used for both presurgical planning (i.e., osteotomies, mirroring of symmetric bone segments) and intraoperative navigation, as well as for postoperative data processing.[25-28] Virtual computer-assisted preoperative planning is an appropriate tool for complex reconstruction strategies with autologous grafts or alloplastic implants.[15] Until now, CAS has been practiced as part of the surgical routine in post-traumatic orbital and mid-face reconstructions as well as tumor surgery.[16,18,29-31] CAS procedures mainly consist of five steps:

1. Data acquisition
2. Preoperative planning
3. Intraoperative registration
4. Surgical navigation procedures
5. Postoperative data processing



• **Fig. 8.1** Computer-aided surgery navigation system by Brainlab, Feldkirchen, Germany. Optical registration sensor is fixed to the patient's head on the left side.

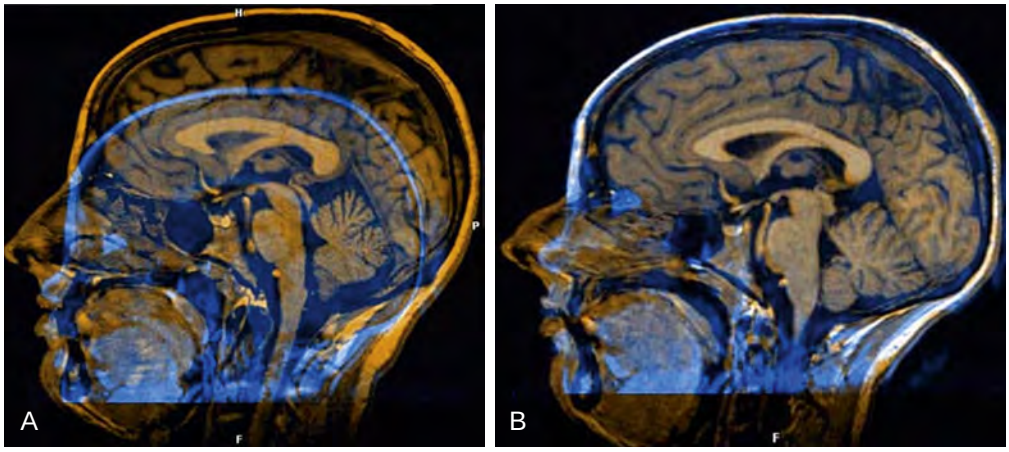


• **Fig. 8.2** Optical registration sensor and optical reference markers to triangulate the patient's location and location of surgical instruments in space. To avoid registration errors due to displacement of the optical reference sensor, it should be invasively secured to a patient's head using a bony anchored device. An additional referencing transmitter is located on the surgical instrument.

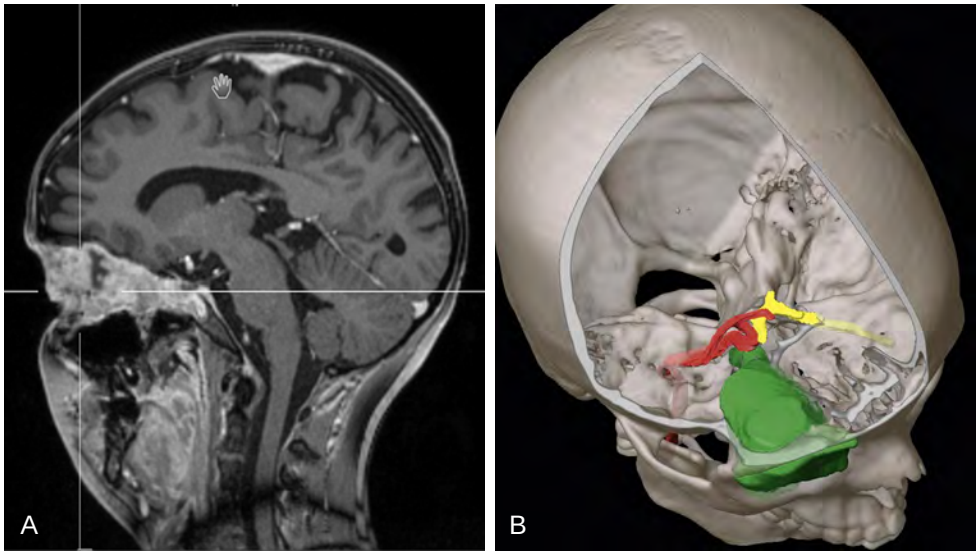
Data Acquisition

CAS systems require a 3D dataset to create a "virtual patient." The 3D representation of soft tissue and bony structures provides a precise condition for the planning of surgical therapy.[32] Commonly, 1 to 2 mm CT slices are required in CAS procedures.[33] The fusion of CT and magnetic resonance imaging (MRI) data has been shown to be helpful when soft and hard tissues are being examined.[34] With regard to diagnosis, treatment, and follow-up of head and neck cancer, CT and MRI have been considered the standard imaging modalities.[28,35] Information gathered from positron emission tomography can be added to preoperative data.[36-38] The fusion of these multiple image modalities is an optimal method for comparing and matching the obtained information (Fig. 8.3). In this way the tumor and its associated destruction are delineated in three dimensions.[39]

Furthermore, it is possible to use cone beam CT (CBCT) for intraoperative navigation. In addition, the representation of the vascular system can be integrated in the preoperative



• **Fig. 8.3** Example of an image fusion: CT and MRI dataset before fusion **(A)** and after fusion **(B)** procedure.



• **Fig. 8.4** **A,** Rhabdomyosarcoma of the right orbital cavity sagittal MRI. **B,** 3D reconstruction of CT dataset. Segmentation of the internal carotid artery *(red),* the optical nerve *(yellow),* and the tumor *(green)* and representation after image fusion of MRI and CT.

dataset (Fig. 8.4). After importing the 3D dataset, atlas-based segmentation is performed automatically in a so-called data pre-processing procedure.[40]

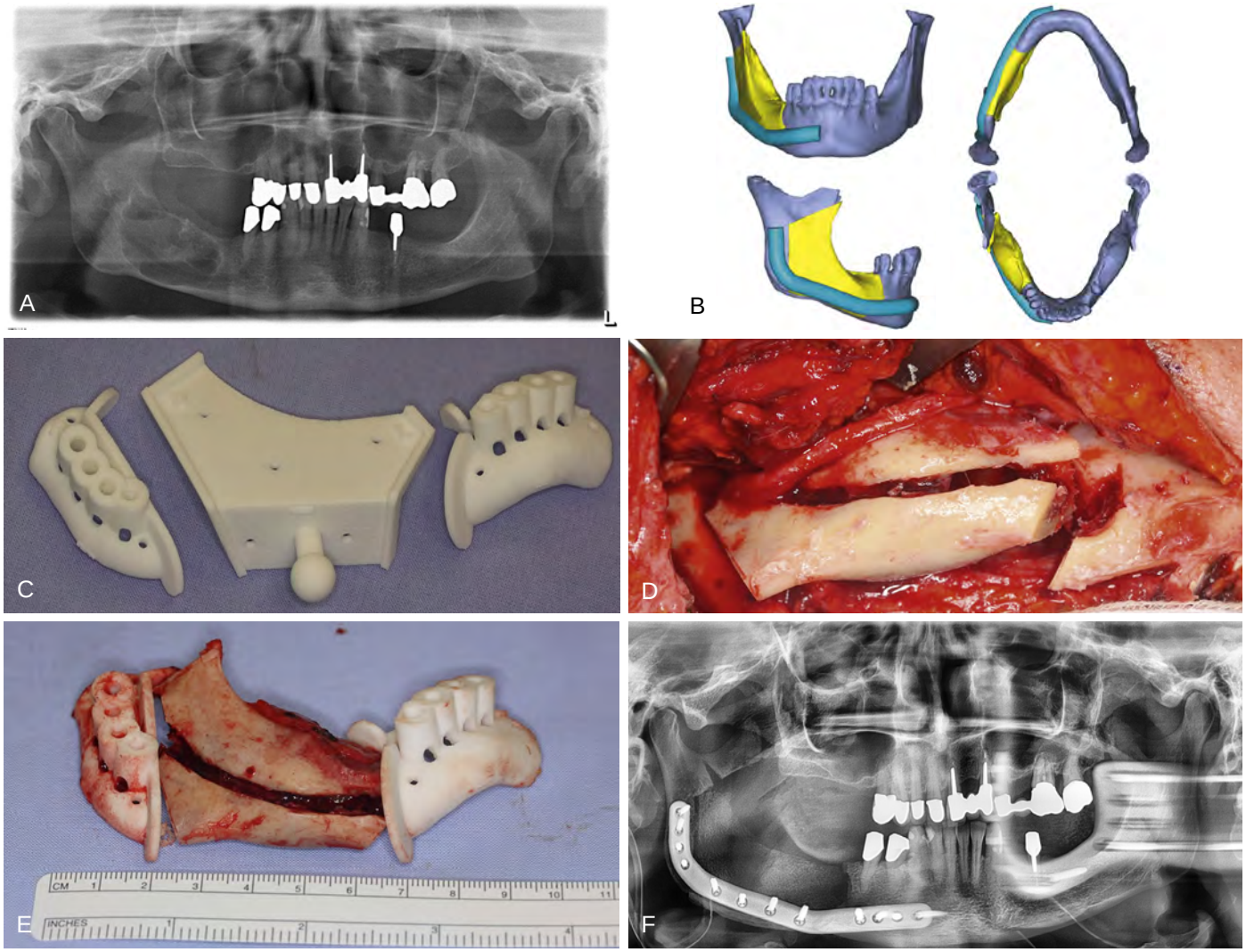
Further Use of Acquired 3D Data

Considering the large amount of 3D DICOM (digital imaging and communications in medicine) data that are acquired and stored on a daily basis, cephalometric and topographic analysis of anatomic mean shapes are possible. Specific algorithms, such as the principal component analysis, allow entire surface shapes and dimensions to be analyzed. Recently, this technique has been used to generate standardized anatomic forms clustered by different sizes, thus allowing for the production of osteosynthesis plates and implants that provide a better fit and improved biomechanical characteristics[41-47] (Fig. 8.5).

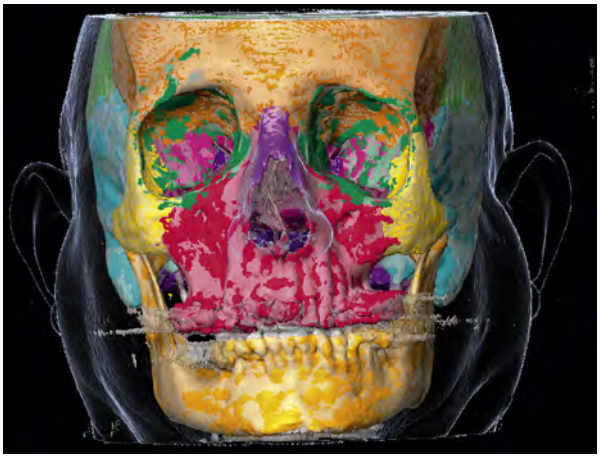
Preoperative Planning

Segmentation

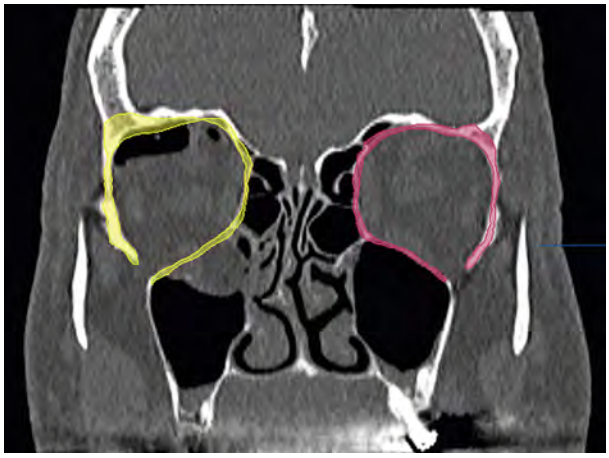
For preoperative planning, different tissues must be marked using a segmentation procedure. In the field of oral and maxillofacial surgery, precise methods for segmentation of bony structures are essential.[48] This is performed by selecting different Hounsfield units (e.g., bone can be selected and labeled). In former times, this act was time consuming in that it required the marking of each axial slice. Today, an automatic data pre-processing procedure is state-of-the-art. After importing DICOM data into the software, an algorithm performs the bony segmentation process automatically for the whole skull, including all anatomic subregions[40] (Fig. 8.6). The latest development in this field is an automatic segmentation of the soft tissue and most importantly, the vascular system. After



• **Fig. 8.5** **A,** Ameloblastoma of the right mandible. **B,** Surgical plan for mandible resection and reconstruction *(yellow)* with an autologous bone graft. Patient-specific reconstruction plate was designed after mirroring of the unaffected left to the right side. **C,** Cutting guides for planned resection with fixation holes and trocar guide cylinders. **D,** Intraoperative view of the right mandible after osteotomies and lateralization of the mandibular nerve. **E,** Cutting guides after complete tumor resection. **F,** Postoperative radiologic control after reconstruction with autologous bone graft and patient-specific reconstruction plate.



• **Fig. 8.6** Automatically segmented skull.



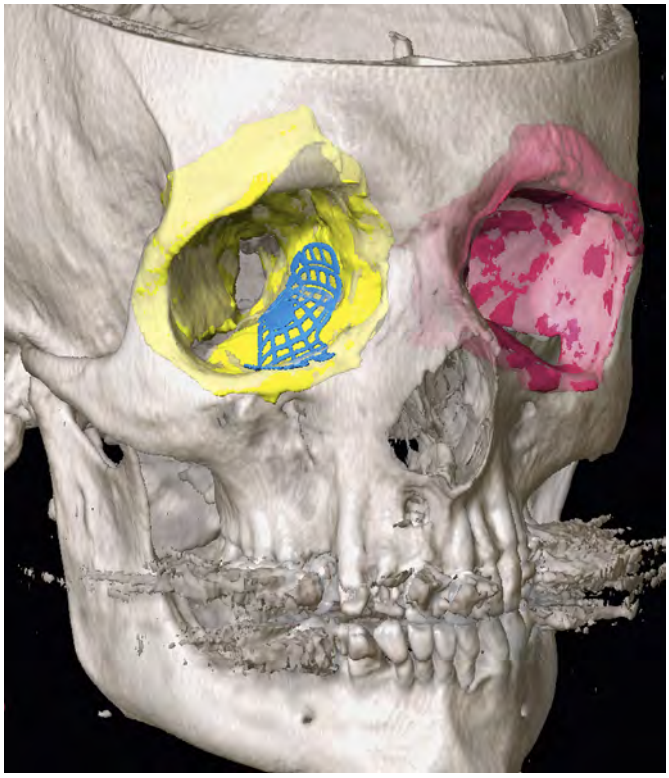
• **Fig. 8.7** Patient with orbital floor fracture on the right side. Mirroring procedure in a coronal CT view; left *(red)* unaffected side is mirrored to the injured side *(yellow)*.

integration of this additional information in the planning software, a precise delineation of the tumor in relation to the arterial and venous system is possible.

Mirroring—Advanced Planning

Graphic processing programs allow 3D cephalometric measurements, interactive transection and repositioning, simulations of osteotomies, and optical reflection of bone segments.[49] A standard procedure for advanced planning is mirroring of the uninjured side. After segmentation of the unaffected side, this image is mirrored into the affected side (Fig. 8.7), allowing for a relatively simple generation of an optimal virtual model.[16,26] Manual alignment may be necessary due to existing asymmetries of the skull. However, the use of this procedure has been limited to unilateral defects. Bilateral defects still remain a major challenge for preoperative planning. Additionally in bilateral orbital defects, special virtual implant models from standard CT datasets can be inserted, controlled, and used for size determination (Fig. 8.8).

Alloplastic Implants for Mid-face and Orbital Floor Reconstruction. The purpose of bony mid-face and orbital



• **Fig. 8.8** 3D reconstruction with insertion of a virtual orbital floor template *(blue)* to reconstruct the fractured orbital cavity *(yellow)*.



• **Fig. 8.9** Preformed orbital floor and medial wall titanium implant in an artificial orbital cavity.

floor reconstruction is the anatomic true-to-original 3D reconstruction of the affected area with regard to shape and volume.

Indications for covering or bridging the defect are necessary in order to avoid soft tissue displacements.[47] Therefore, the insertion of alloplastic material for the support of the soft tissue and to reshape the cavity is often required.[47] In recent years, the use of preformed titanium meshes has been established for internal orbital floor reconstruction (Fig. 8.9). They are

biocompatible and rigid enough to cover large defects, which allows for adaptation to the individual patient's anatomy.[50-58] Autologous bone grafts such as calvarium, iliac crest, or microvascular bone offer a possibility for rebuilding and augmenting orbital contours, especially after tumor resection. They are often used when radiation is planned. Bone grafts cannot be correctly anatomically shaped, and reduction of the bone volume occurs. Alternatively, alloplastic materials such as titanium and porous polyethylene are used; however, these materials, except titanium, occasionally cause some complications and a true to original reconstruction of the demanding 3D anatomy of the orbital walls is rarely achieved.[10,31,47,56,59-67] In addition, the use of patient-specific implants offers satisfactory results in mid-face reconstruction and may be considered part of the preoperative planning (Fig. 8.10).

Delineation of Tumor, Safety Margins, and Important Anatomic Structures

Complex mid-face fractures as well as ablative tumor surgeries require major planning of procedures with regard to the multitude of regions of interests that will be involved for functional reconstruction. It is essential to evaluate the extension of the entire defect respective to the tumor volume and the intended resection limits, and then to prepare this information for intraoperative navigation (Fig. 8.11). In this way, the tumor extension and its associated destruction as well as important anatomic structures are delineated in three dimensions. The different tissues can then be marked by simulated segmentation for the planning of resection and reconstruction.[11]

Once a decision for surgery is made, the next important step is precise communication between the surgeon, the radiologist and pathologist, and the radiation oncologists regarding tumor volume, orientation, and location, as well as the need for any additional biopsies.[11,25] To achieve this communication, a virtual CAS-based interdisciplinary interface is necessary (Fig. 8.12).

Intraoperative Registration

A key component and a frequent challenge for intraoperative navigation is the registration procedure of the patient into the 3D treatment plan. For intraoperative registration, CAS systems require a headset with an incorporated transmitter to be placed on the patient. In order to allow movements of the patient's head during surgery and while using intraoperative navigation, the reference sensor must be attached to the skull. To avoid registration errors due to displacement of the optical reference sensor, the sensor should be invasively secured to a patient's head using a bony anchored device.

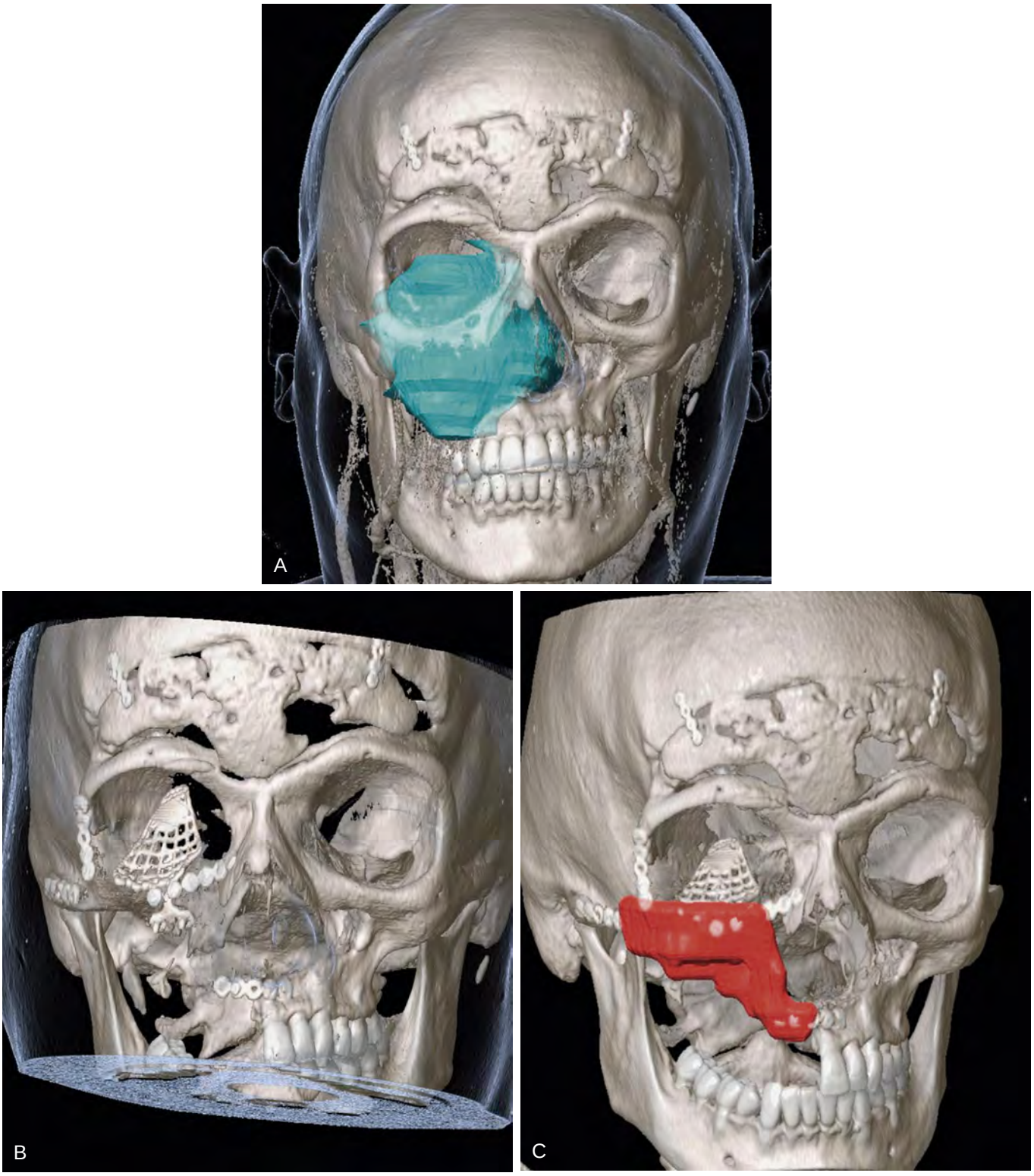
Reference Marker

An additional referencing transmitter is located on the surgical instrument. The optical detection allows the computer to integrate the spatial information of the actual patient (Cartesian coordinates x, y, z) to a virtual patient (Cartesian coordinates x′, y′, z′) for a precise localization of the patient and surgical instruments in the space.[18,68,69] This is accomplished by identification of specific fiducial markers on the CAS monitor (i.e., virtual patient). Fiducial markers provide the CAS systems with landmarks to triangulate and localize the entire facial skeleton. Fiducial markers are stable landmarks that can be identified on both the virtual and real patients, and are used for intraoperative registration. Markers can be divided into two types, invasive and non-invasive (Fig. 8.13). The fiducial markers are identified by a surgical probe on the real patient. With each new point, the CAS system is able to more accurately triangulate the patient's location in space.

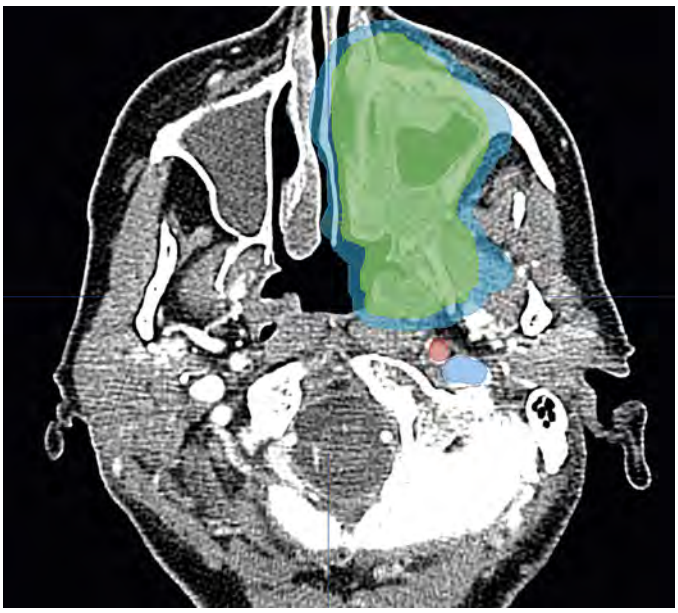
Invasive fiducial markers (e.g., titanium screws) are rigidly fixated to the skull before the preoperative CT scan and remain in place until the procedure is completed.[70,71] Non-invasive fiducial markers can be subdivided into three types: adhesive markers, dental splints, and anatomic landmarks (i.e., bone and skin surface).[70,72,73] Adhesive markers and dental splints must be applied to the patient before acquiring the CT dataset and may be not available following the operation. Anatomic landmarks are inherently present. The optimal placement of these landmarks was described by West and colleagues.[74]

- Fiducial markers placed in a straight line provide little 3D information. Therefore, the markers should be placed whenever possible in a non-linear and non-planar fashion to offer as much 3D information as possible.
- The "center point" of the fiducial markers should be the surgical target area. The ideal fiducial locations would be in a sphere around the surgical field. This is not always possible. However, an attempt should be made to spread the location of the fiducial markers around the target surgical area to provide the most accurate registration possible. Fiducial placement patterns that are located on one side of the surgical field will have reduced accuracy when compared with those with a spherical placement.
- Distances chosen between markers should be as large as possible. Fiducial markers that are spaced farther apart provide a larger zone of accuracy.
- The number of fiducial markers should be as many as possible. Each fiducial marker provides more information and helps triangulate exact patient location. Therefore, the more points provided, the more accurate the registration.[74]

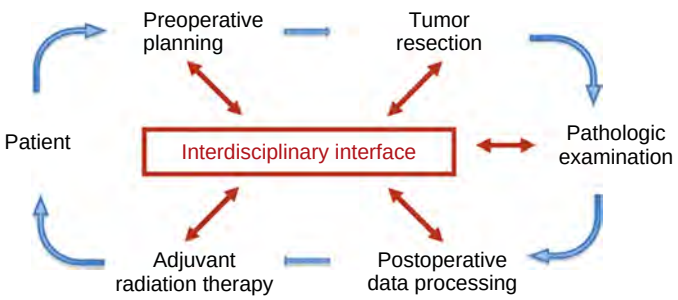
Several studies have evaluated the accuracy of different registration procedures in CAS procedures.[34,75-81] The accuracy of the navigation system is defined by the difference, in millimeters, between the virtual and real coordinates. It may be enhanced by localization of fiducial markers around the area of interest. Registration errors cause inaccuracies when superimposing the virtual patient onto the actual patient.[72,82,83] Metzger and colleagues[68] evaluated four different CAS registration strategies in the maxillofacial skeleton and concluded that invasive fiducial markers are most accurate. Skin surface landmarks, bony landmarks, and intraoral splints provide a registration error between 2 and 3.8 mm.[68] However, each method has distinct advantages and disadvantages.



• **Fig. 8.10** **A,** Second recrudescence of a chondrosarcoma of the right maxillary sinus. 3D reconstruction of the tumor borders *(blue)*. **B,** Situation after third operation with hemi-maxillectomy and reconstruction of the orbital floor. **C,** Planned reconstruction of the right zygoma with patient-specific Polyetheretherketon (PEEK) implant *(red)*.



• **Fig. 8.11** Representation of the tumor extension *(green)* and planned resection borders with security margin *(blue)*. Additionally the internal carotid artery and jugular vein on the left side are marked.



• **Fig. 8.12** Computer-aided surgery procedures and an interdisciplinary interface could improve the communication between surgeons, radiologist, pathologists, and radiation oncologists.

Invasive Marker

Invasive fiducial markers offer a high degree of precision because they are small and rigidly fixated, and a large number of markers can be placed in any stable bone around the surgical area of interest. The area of accuracy has been found to be excellent for maxillofacial reconstruction, except in the mandible. The target registration error was between 0.4 and 1.9 mm in several studies.[34,76,84,85] Unfortunately, the invasive nature of these markers causes more difficulties for placement and they may not be tolerated well by patients. A further disadvantage is that the fiducials must be placed before the CT scan is performed. This may necessitate a second 3D scan before surgery or during surgery.[68] A novel development is the intraoperative fusion of marked subvolume gained by CBCT scan with an initial markerless CT dataset. Enhancing an initially performed dataset with a registration marker by using a marked subvolume could improve the workflow for CAS, a step in the procedure that is made possible by the availability of CBCT technology.[86]



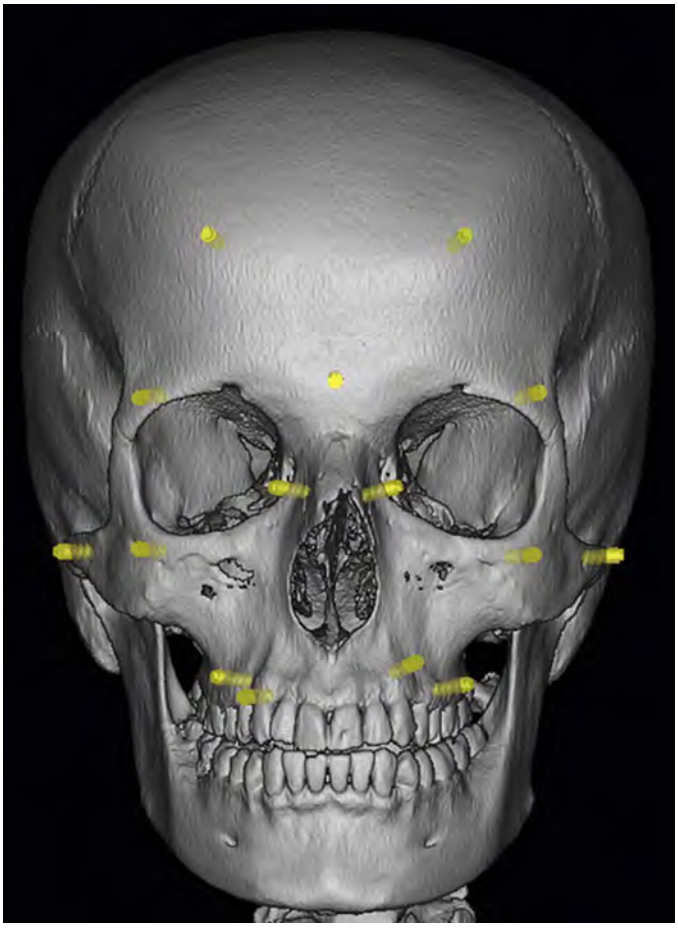
• **Fig. 8.13** Non-invasive marker (dental splint in situ). The intraoral splint offers excellent results with a low difficulty of application. Specialized techniques are necessary for fabrication and the zone of accuracy is limited. Surgical navigation of the lower jaw remains difficult. The mobility of the lower jaw complicates its synchronization with the rest of the cranium.

Non-invasive Fiducial Marker

Skin surface matching for registration has become a standard procedure of care for optical CAS systems used in endoscopic sinus surgery. Marmulla and colleagues performed investigations on this technique in maxillofacial surgery.[83,88-90] Most navigation systems offer this option. Skin surface, non-invasive fiducial markers do not require a second CT scan before surgery. Furthermore, 100 to 150 marker points can be collected in approximately 20 to 30 seconds. The collection of marker points can be performed using a surgical probe or a laser scanner. The major disadvantage here is that any change of surface constitution, for example by increased facial swelling, requires a current CT scan for registration.

Registration by bony landmarks has many similarities to skin surface matching.[68] The fiducials are present on all patients, and an indefinite number of points can be chosen. The zone of accuracy is relatively small but localized to the central midface. A major disadvantage of using bony landmarks is that it requires bone exposure for registration. While large regions of the facial skeleton may be exposed for complex maxillofacial reconstruction, isolated procedures such as orbital reconstruction would offer a small region of exposed bone. Other options to compensate for the lack of bony exposure include transcutaneous registration with a sharpened surgical probe. Another possibility is the combination of skin surface registration and bony landmarks[68] (Fig. 8.14).

Registration using dental splints is an extremely easy way to register landmarks. The splint can be applied and the patient is rapidly registered. Should a further registration be necessary, the splint is readily available. The disadvantages of this method are the need for specialized skills and time delay for splint fabrication and possible need for a second CT scan with the splint in place. Furthermore, the technique is not applicable for edentulous patients and patients with palatal fractures. In addition,



• **Fig. 8.14** Registered skull showing the use of bony landmarks. The bony landmarks are present on all patients, and an indefinite number of points can be chosen.

localization of fiducial markers is limited to a small region in the lower facial skeleton. The resultant region of greatest accuracy is therefore localized to the lower portion of the facial skeleton.[68]

Although the aforementioned registration methods have been successfully applied in practice, there is still no ideal registration method.[69] All of the described registration strategies have specific advantages and disadvantages. Invasive fiducial markers are the most accurate method, but require a surgical procedure to place the markers and additional 3D imaging to obtain the necessary data. Skin surface registration offers excellent application without the need for repeat CT scans; however, any surgical intervention or resultant facial edema may require repeat scans to obtain accurate datasets. Using bony landmarks has similar advantages to skin surface matching. The intraoral splint also offers precise results with a low difficulty of application, but specialized techniques are necessary for fabrication and the zone of accuracy is limited.[68]

Registration of the Mandible

Numerous studies confirmed an accurate registration in the area of the craniofacial skeleton.[34,68,76,77,79] The accuracy and reliability of intraoperative navigation are highly acceptable for procedures on the cranial vault, upper and middle facial thirds, and the skull base.[91,92] Surgical navigation of the lower jaw remains difficult. The mandible moves separately from the rest of the cranium and thus complicates its synchronization with the preacquired imaging data during surgery. This disadvantage can result in inaccuracies during navigation.[93] The mobility of the lower jaw, and consequently the problems with the registration procedure and its synchronization during surgery with the preacquired 3D treatment plan, has induced the development of specific mandibular registration methods.[19,93,94] Bouchard and colleagues[19] described a technique using an electromagnetic reference sensor attached rigidly to a tooth of the mandible with dental composite material.[19] For pig cadaver measurements of osteotomies of the mandible, they could demonstrate a mean difference between 3D planning and the osteotomy of 2.4 ± 1.4 mm. Casap and colleagues[93] evaluated the accuracy of two navigation systems for surgery of the lower jaw. An image-guided implantology system presented a navigational error of less than 0.5 mm. A second system designed for ear, nose, and throat surgery revealed an error between 3 and 4 mm. This indicates that improved registration techniques should improve the overall system performance.

Intraoperative Navigation

Based on the preoperative treatment plan and the identification of all fiducial markers on the CAS monitor, the optical detector allows the computer to integrate spatial information from the actual patient with a virtual one. This allows precise localization of the patient and surgical instruments on and in the patient.

Intraoperative Imaging

The concept of computer-aided maxillofacial surgery includes the presurgical planning software,[30,31,95,96] intraoperative navigation,[21,27,31,97] and intraoperative CT.[98,99] Therefore, the final reconstruction and the surgical result may be controlled. There are two different possibilities for intraoperative CT scanning: fan beam and CBCT scanners. Both modalities are fast and result in a sufficient bone resolution. Fan beam scanners operate in a manner similar to conventional CT. They use a collimator and a series of detector arrays to compile a data volume. Cone beam scanners use a flat panel image intensifier with a moving radiation source to collect a volume of data and present them in a 3D format. C-arm devices offer the same function (Fig. 8.15). Intraoperative CT or cone beam scanners are the most helpful for maxillofacial procedures requiring precise postoperative symmetry with limited intraoperative visualization. CBCT provides significantly more information for the clinician than conventional radiologic imaging, and it involves less radiation than conventional CT. Furthermore, CBCT allows visualization of precise location and sufficient screw fixation with less metal artifactual distortion.[100] In addition, the use of intraoperative CBCT enables visualization of the reduction of the condylar process and condylar head fractures of the mandible in all three planes. Unsatisfactory reduction can be detected during



• **Fig. 8.15** C-arm device for an intraoperative cone beam scan. A flat panel image intensifier with a moving radiation source is used to collect a volume of data for presentation in a 3D format.

the operation and immediately corrected. This provides the surgeon with the required anatomic visualization in the intraoperative setting and allows for a revision if necessary. This can improve surgical results, spare the patient additional surgery, and reduce postoperative complications.[101] Portable CT technology is now a practical and easily accessible option for many maxillofacial surgeons. It allows for rapid analysis of a surgical repair and reduces the threshold for revision of a poorly placed implant or reduction.

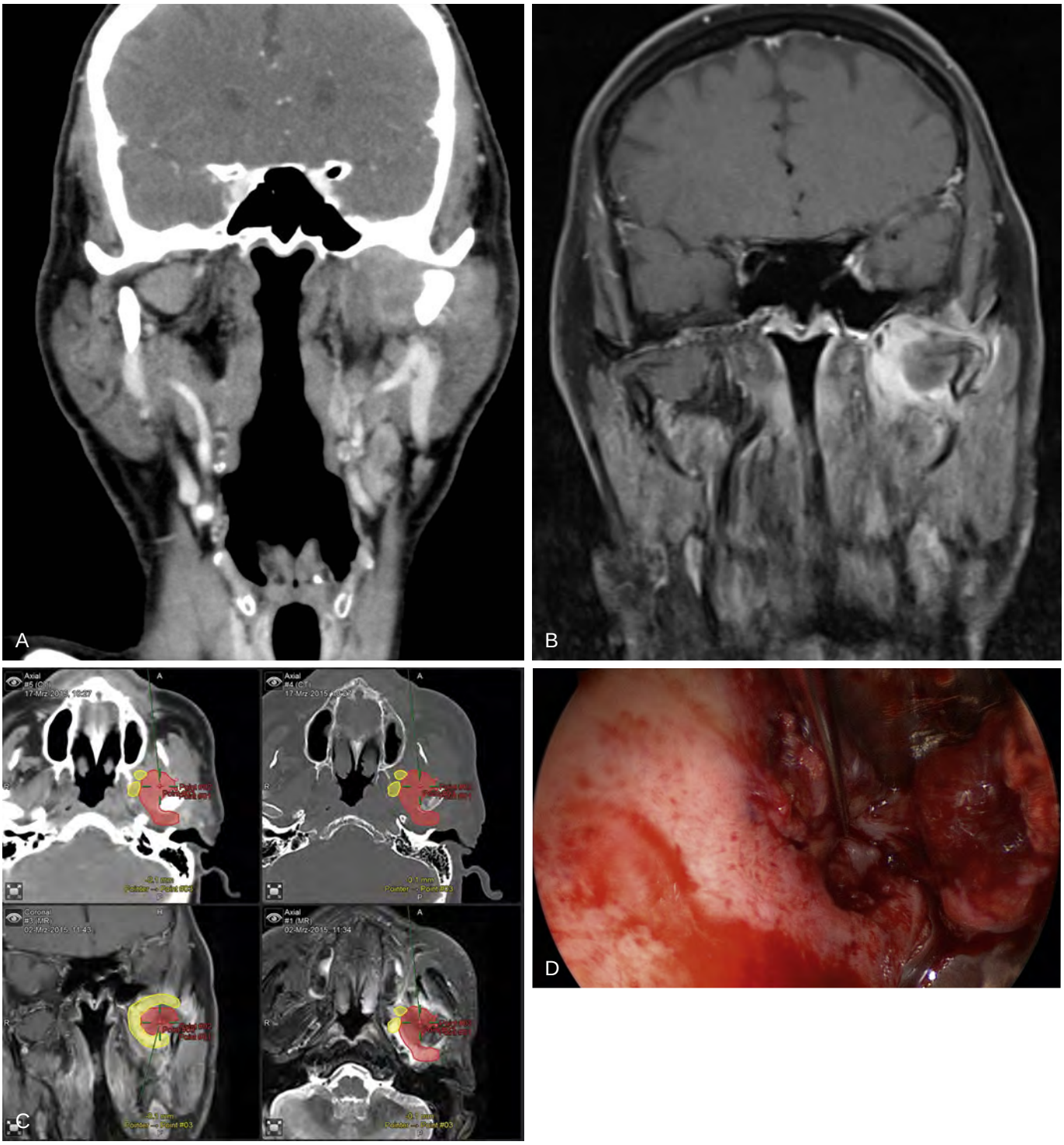
Navigation Allows for Control of the Treatment Plan

The transformation of preoperative planning into a precise surgical outcome using CAS depends on location, surgical approach, and type of reconstruction. The surgical resection, borders, or osteotomy may be controlled by use of a navigation pointer during the trauma reconstruction, surgical repositioning, or tumor resection.[26] This instrument allows one to compare the preoperative 3D planning and the intraoperative findings using a virtual model (Fig. 8.16). A precise surgical resection based on the preoperative planning has been successfully performed.

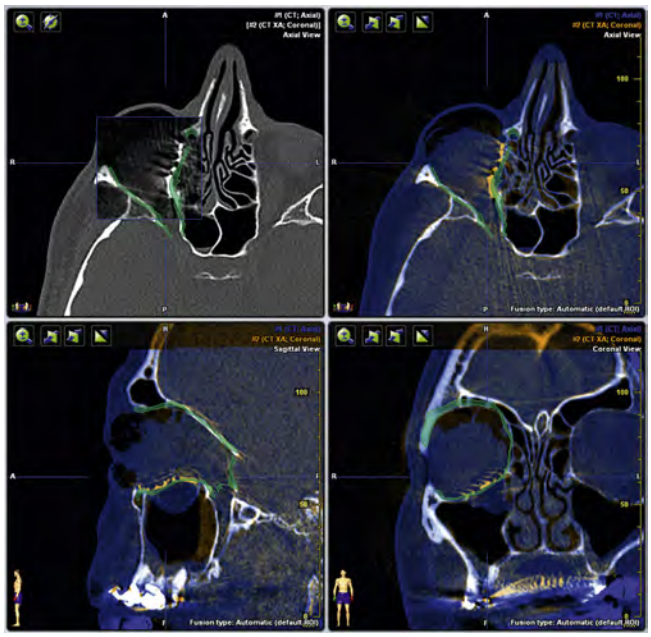
Until now, CAS has been established as part of the surgical routine in post-traumatic orbital reconstructions.[16,29] After mirroring of the unaffected orbital cavity to the affected side and development of a treatment plan, reconstruction of the orbital floor and placement of the orbital floor implant could be controlled in real time. The introduction of mobile CBCT devices in the operating theater has made the intraoperative radiologic control option available, which has shown better outcomes in that surgical revisions could be avoided[100,102-115] (Fig. 8.17). An implementation of this technology into existing virtual planning and navigation methods is simple due to the standardized DICOM data format and allows for the development of new possibilities with regard to patient registration and simulation.[106,108,109,116-119]

Navigation Enables Collection of Surgical Information and Improves Interdisciplinary Communication

Because cure is the desired goal in cancer surgery, a complete resection of the tumor is crucial. Patients with positive or close tumor resection margins show a significantly poorer surgical outcome.[120] It is becoming more and more common to send frozen section biopsies for analysis intraoperatively. The method of labeling these biopsies is language dependent and individual to the surgeon.[11] The processing pathologist receives a specimen and a label with a minimal idea of its orientation. From this a simple response of "positive" or "negative" is sought. If a positive result is returned, it falls upon the memory of the surgeon to locate precisely where the sample was obtained, ultimately affecting the final resection margin.[11] When collecting frozen sections, the site of the biopsy could be marked and mapped by the navigation probe and this precise localization data stored (Fig. 8.18). The labeled frozen sections and the dataset with coordinates could then be transmitted to the pathologist who can color code the positive and negative results on the virtual image.[11] These can then be incorporated into the 3D treatment software. Further resection in this color-coded area is carried out and when examined histopathologically shows complete resection.[11] This ultimately improves the communication between the surgeon and the pathologist. In addition, the tumor resection margins could be marked with the navigation pointer to allow a precise delineation of the reconstruction volume.[25]



• **Fig. 8.16** Metastasis of lung cancer medial of the left condyle in a CT **(A)** and MRI **(B)** dataset. **C,** Intraoperative navigation probe for biopsy in the central part of the tumor *(red)*. **D,** Corresponding clinical view. The biopsy probe can be controlled by the use of a navigation pointer during the surgery.



• **Fig. 8.17** Intraoperative image fusion of preoperative CT scan and intraoperative cone beam CT with planned and mirrored right orbital cavity and orbital floor implant in situ.

Postoperative Data Processing

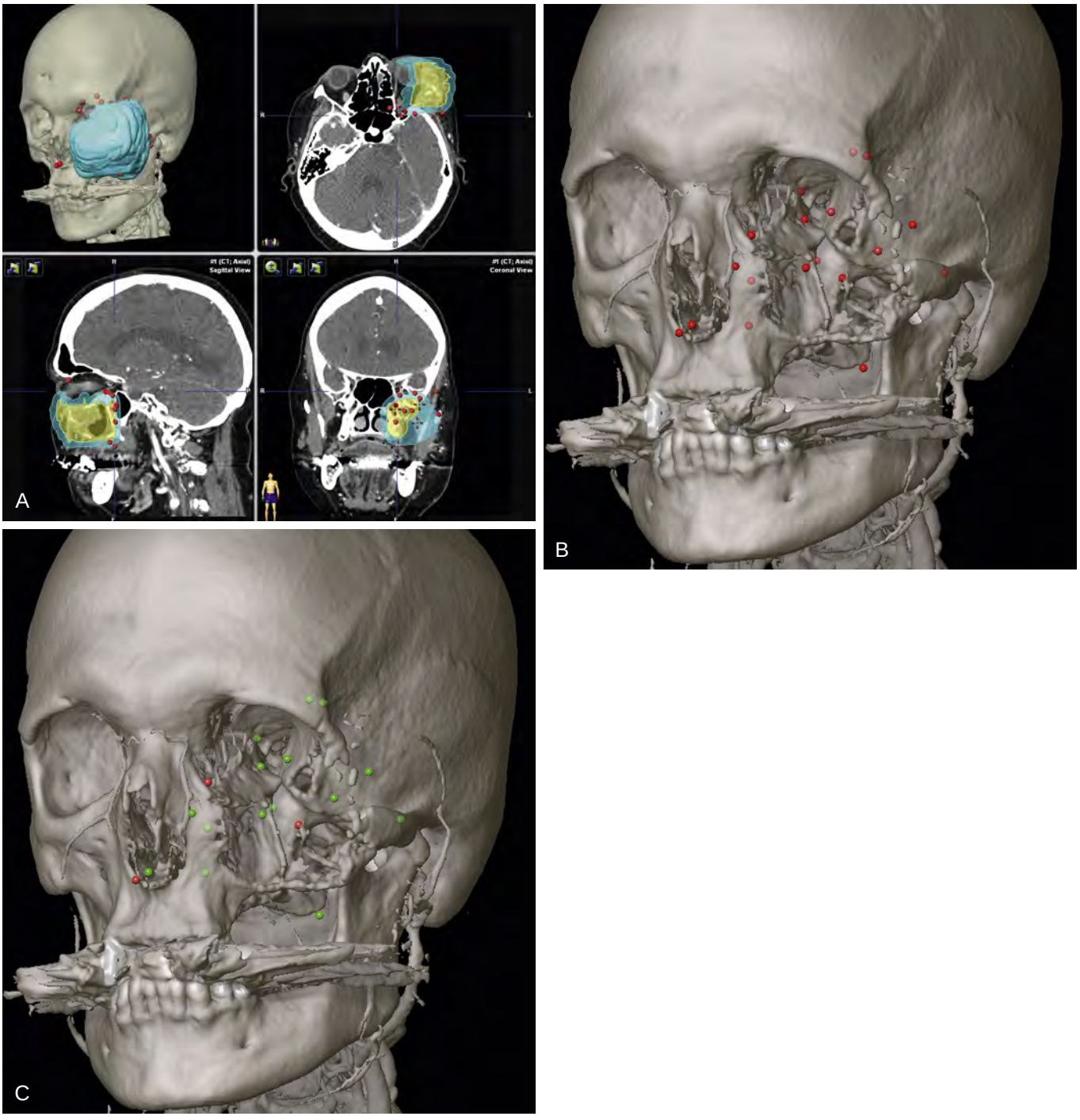
The combination of surgery and postoperative radiotherapy for the treatment of advanced head and neck squamous cell carcinoma was developed in an empiric manner due to the poor locoregional control rates achieved with either modality alone.

The tissue defect often requires reconstruction. Uncertainty still exists regarding a precise radiotherapy target volume definition.[121] Therefore, precise correlation of resection borders and graft reconstruction becomes important. For many years, tumor resection margin localization has been carried out both clinically and by using a combination of preoperative and postoperative information, such as radiologic imaging and surgical and pathologic annotations. In theory, tumor resection margins can be delineated using the interface between native tissue and graft tissue. The detectability of free flap grafts on CT scans alone does not allow a precise localization of the former tumor resection margin, and delineation of reconstructed tissue from resection margins on postoperative CT scans is often difficult in the majority of patients.[122,123] Various refinements in the field of CAS have been implemented in order to improve marking of resection margins.[18,25]

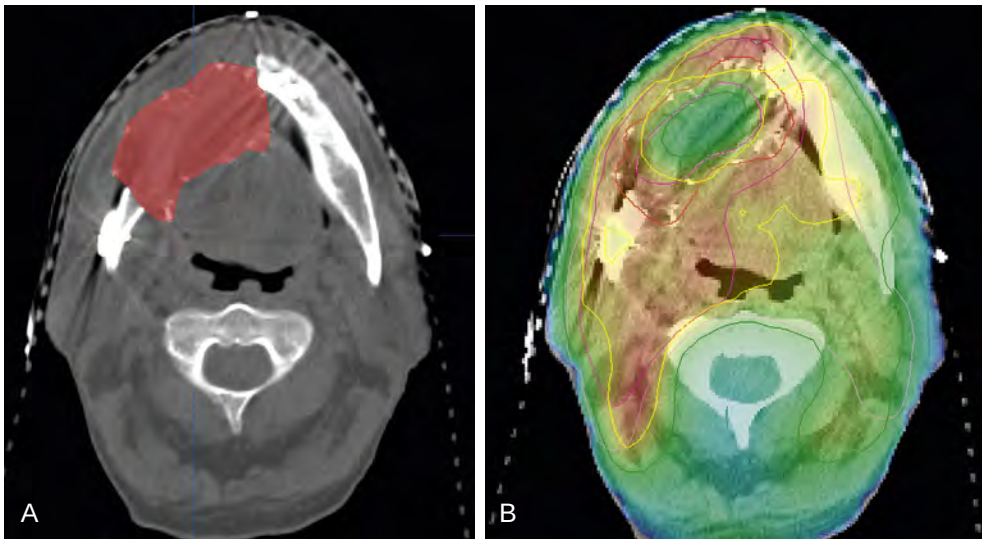
Anatomic areas of clinical interest, for example the resection margins, can be defined by precise coordinates. 3D virtual marking and mapping of resection margins enable a precise delineation of skull base and mid-face tumor margins.[11,91,123]

Although the accuracy and reliability of the navigation workflow are generally accepted for mid-face and cranial vault operations, intraoperative navigation of the mandible and adjacent soft tissue structures, such as the tongue or the floor of mouth, is still challenging.[11,92] This is either the result of the mandible's independent movement from the rest of the cranium or the soft tissue shifts that result from gravity and swelling. An additional marking of the tumor resection margins by titanium ligature clips can overcome these difficulties (Fig. 8.19). If a radiation boost treatment is to be used to secure improved local control, it would seem reasonable that efforts should be made to ensure that it is delivered accurately to the tissue at greatest risk for local recurrence, while sparing other tissue. Marking of resection margins either by clip insertion or CAS procedures can modify radiotherapy field borders to focus irradiation on former tumor resection margins and consequently reduce the target volume and decrease the risk for recurrence and complications (Fig. 8.19B). The navigation provides very accurate delineation of the target tissue margins upon which the oncologist can focus adjuvant radiation, thus reducing the exposure of the free vascular flap reconstruction.

Surgical navigation has become an established technique in the field of head and neck surgery, but it is important to keep in mind that navigation landmarks only mark single points within the surgical bed, requiring observers to interpolate the border of the cavity. This can contribute to inaccuracy in tumor resection margin delineation. Integration of histologic information in a navigation-assisted multidisciplinary network can overcome these difficulties. A close collaboration between surgeons, radiation oncologists, and pathologists in a multidisciplinary approach is supplemented by a visuospatial orientation aid and can lead to a significant improvement in cancer treatment and the patient's quality of life. In future development, robot-controlled surgery may become an additional resource in the field of CAS. In combination with planning software, these resources may be used to the advantage of both the surgeon and the patient.



• **Fig. 8.18** **A,** 3D reconstruction of tumor delineation *(yellow)* with planned safety margin *(blue)*. Intraoperative navigation and labeling of frozen sections *(red)*. **B,** Dataset will be transmitted to pathologist with all virtual marked landmarks *(red)*. **C,** 3D reconstruction after intraoperative labeling of frozen sections and after perioperative pathologic examination. Incomplete resection: green points, negative; red points, positive frozen sections.



• **Fig. 8.19** **A,** Delineation of radial forearm flap *(red)* with titanium clips after complete tumor excision of a floor of mouth squamous cell carcinoma. **B,** Radiotherapy planning: intensity modulated radiation therapy was delivered as step-and-shoot technique with Oncentra Masterplan software version 4.3 (Nucletron, The Netherlands). A dose reduction was performed at the center of the reconstructive flap based on the titanium clip delineation. The calculated radiation dose: red, 63.6 Gy; yellow, 56.4 Gy; green, 47.5 Gy; light blue, 29.7 Gy.

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9 Management of the Neck

KRISHNAKUMAR THANKAPPAN, MONI ABRAHAM KURIAKOSE, PETER E. ANDERSEN

PART 1: NECK DISSECTION

The status of the cervical lymph nodes is the single most important prognostic factor affecting the survival of patients with head and neck squamous cell carcinoma.[1] The management and staging of disease in the neck are of vital importance in treating patients with head and neck cancers.

Patterns of Nodal Metastasis by Site of Primary Tumor

The lymph nodes in the neck are classified based on a modification of the original Memorial Sloan Kettering Cancer Center classification adopted by the American Head and Neck Society and Committee for Head and Neck Surgery and Oncology of the American Academy of Otolaryngology–Head and Neck Surgery. The lymph nodes in the neck are subdivided into specific anatomic subsites and are grouped into seven levels[2] (Table 9.1 and Fig. 9.1).

Level I nodes include lymph nodes in the submental and submandibular triangles; level II, III, and IV nodes are deep jugular nodes in the upper, middle and lower portions of the neck; and level V nodes are those in the posterior triangle of the neck. Level II is further subdivided into IIA and IIB by the course of the spinal accessory nerve. Level V is also subdivided into VA and VB by an imaginary horizontal line at the level of the cricoid cartilage (Fig. 9.2).

Some of the earliest experiments that led to understanding of the patterns of lymph node drainage in the neck were conducted by Ugo Fisch in the 1960s.[3-6] Fisch performed studies using cervical lymphography to map the lymphatic drainage pathways in the neck. He injected oil-based contrast media into the postauricular lymphatics, and the drainage pathway was studied using lymphography. Fisch noted that after the injection of contrast in this region, the flow of contrast was from the postauricular lymphatics to nodes just behind the angle of the mandible (levels IIB and VA nodes), which he termed "junctional" nodes. Contrast flowed from these junctional nodes to nodes along the spinal accessory nerve posteriorly and along the jugular nodes anteriorly. Fisch also noted that contrast flowed from the spinal accessory nodes to the jugular nodes anteriorly, but it did not move in the opposite dissection. This finding perhaps explains the finding that involvement of levels IV and V nodes in the absence of disease in levels I, II, and III is an extremely uncommon occurrence.

Understanding the patterns of lymph node metastasis is important in identifying the lymph node groups at highest risk for metastasis from a primary tumor. This understanding of the orderly and predictable spread allows us to treat the lymph node groups that are at highest risk for disease while minimizing morbidity by unnecessary dissection of lymph node groups at low risk.

Work by Shah and Lindberg[1,7] helped to map the lymph node levels most at risk based on location of the primary tumor sites. The lymph node groups at highest risk for harboring lymph node metastasis from primary tumors of the oral cavity are in levels I, II, and III.[1,7] Lymph nodes in level II, III, and IV are at the greatest risk of harboring metastases from primary tumors from cancers in the oropharynx, hypopharynx, and larynx[1,7] (Fig. 9.3).

Indications for Neck Dissection

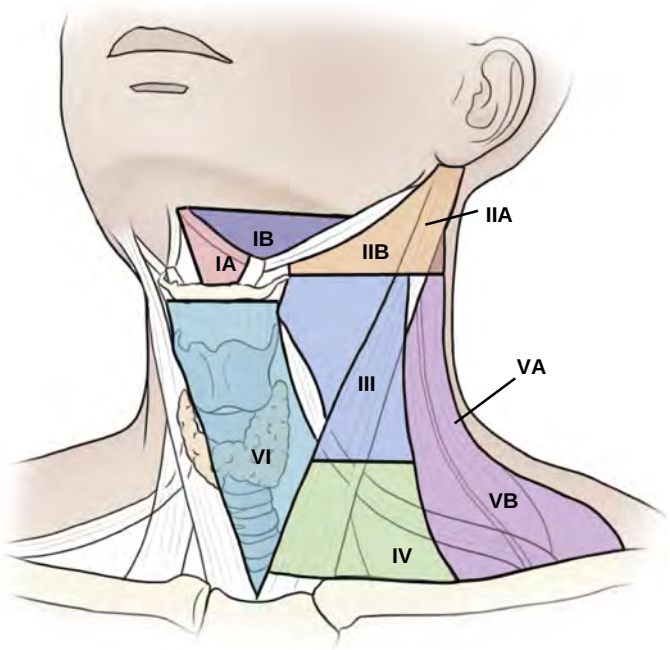
Elective Neck Dissection

Performing a neck dissection when there is no clinical or radiologic evidence of disease has been a historically controversial topic. Neck dissection carries significant morbidity, with up to 70% of patients complaining of shoulder pain and 33% having significant neck pain after surgery.[8,9] Ideally, surgery should be avoided in patients who do not need it. The risk of occult nodal metastases is, however, significant. In the literature, occult nodal metastases occur in 26–33% of head and neck cancer patients.[1,10] Breaking this down by the location of the primary tumor, occult nodal metastases occur in 34–45% of oral cavity cancers, 31–39% of oropharyngeal cancers, 17–56% of hypopharyngeal cancers, and 26–30% of laryngeal cancers.[1,10,11] A strategy of elective neck dissection in all patients would, however, mean doing an unnecessary operation in about 70% of these clinically N0 patients, subjecting them to unnecessary risks and morbidity.

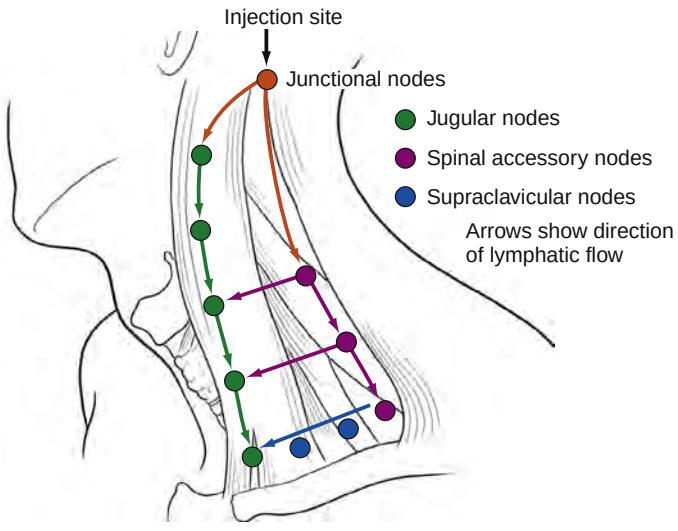
Surgical options for management of patients with clinically N0 disease include either an elective neck dissection, usually performed concurrently with the surgical resection of the primary tumor, or close surveillance with a therapeutic neck

TABLE 9.1 Anatomic Boundaries of the Seven Levels and Sublevels of Cervical Lymph Nodes

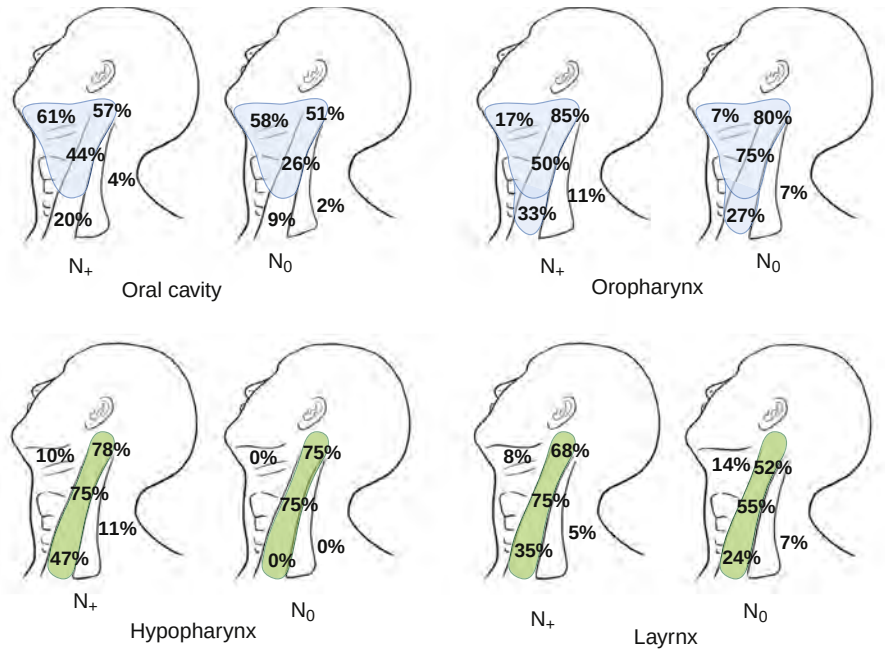
Level	Borders			
	Superior	Inferior	Anterior (Medial)	Posterior (Lateral)
IA	Symphysis of mandible	Body of hyoid	Anterior belly of contralateral digastric muscle	Anterior belly of ipsilateral digastric muscle
IB	Body of mandible	Posterior belly of muscle	Anterior belly of digastric muscle	Stylohyoid muscle
IIA	Skull base	Horizontal plane defined by the inferior border of the hyoid bone	Stylohyoid muscle	Vertical plane defined by the spinal accessory nerve
IIB	Skull base	Horizontal plane defined by the inferior border of the hyoid bone	Vertical plane defined by the spinal accessory nerve	Lateral border of the sternocleidomastoid muscle
III	Horizontal plane defined by the inferior body of the hyoid	Horizontal plane defined by the inferior body of the cricoid cartilage	Lateral border of the sternohyoid muscle	Lateral border of the sternocleidomastoid muscle or sensory branches of cervical plexus
IV	Horizontal plane defined by the inferior border of the cricoid cartilage	Clavicle	Lateral border of the sternohyoid muscle	Lateral border of the sternocleidomastoid or sensory branches of cervical plexus
VA	Apex of the convergence of the sternocleidomastoid and trapezius muscles	Horizontal plane defined by the lower border of the cricoid cartilage	Posterior border of the sternocleidomastoid muscle or sensory branches of cervical plexus	Anterior border of the trapezius muscle
VB	Horizontal plane defined by the lower border of the cricoid cartilage	Clavicle	Posterior border of the sternocleidomastoid muscle or sensory branches of cervical plexus	Anterior border of the trapezius muscle
VI	Hyoid bone	Suprasternal notch	Common carotid artery	Common carotid artery
VII	Suprasternal notch	Innominate artery	Common carotid artery	Common carotid artery



• **Fig. 9.1** Lymph node sublevels of the neck. From Edge SB: *AJCC Cancer Staging Manual,* ed 7, New York, 2009, Springer.



• **Fig. 9.2** Patterns of lymphatic flow based on Fisch experiments. (From Givi B, Andersen PE: Rationale for modifying neck dissection, *J Surg Oncol* 97(8):674-682, 2008.)



• **Fig. 9.3** Distribution of nodal metastasis by primary site. (From Shah JP: Patterns of cervical lymph node metastasis from squamous carcinomas of the upper aerodigestive tract, *Am J Surg* 160(4):405-409, 1990.)

dissection for patients who go on to develop evidence of nodal metastases. For oral cavity cancers, a third option of using sentinel lymph node biopsy in selected cases[12,13] exists, and this is discussed in the second part of this chapter.

The decision to perform an elective neck dissection is guided by an assessment of the risk of occult metastasis to the nodal basin. Weiss and colleagues performed a decision tree analysis and concluded that patients could be safely observed if the probability of occult cervical metastasis was less than 20%; if the risk was greater than 20%, elective treatment of the neck was warranted.[14]

Oral Cavity

Other than sentinel lymph node biopsy, depth of invasion by the primary tumor is currently the best predictor of occult nodal metastasis.[15-17] In a study by Spiro and colleagues,[15] tumors with a depth of invasion less than 2 mm had neck metastases in 7.5% of cases, tumors with a thickness between 3 and 8 mm had a 34.3% rate of nodal metastasis, and tumors with thickness 9 mm or more had a 41.2% rate of nodal metastasis. Close surveillance of the neck is a reasonable strategy for tumors where the depth of invasion is 2 mm or less, given that the rate of lymph node metastasis is extremely low. A recent randomized controlled trial by D'Cruz and co-workers has shown that performing elective neck dissection in patients with early T1/T2 tongue tumors in N0 patients improved both overall and disease-specific survival compared with observation of the neck with therapeutic neck dissection used for salvage therapy. In the series by Shah and colleagues,[1] 0.1% of the patients undergoing elective neck dissection had disease in level IV and 0.52% had disease in level V. The Brazilian Head and Neck Cancer Group performed a multicenter prospective trial comparing the efficacy for elective supraomohyoid neck dissection to modified radical neck dissections in patients with T2-4N0 oral cancers.[18] There was no significant difference in recurrence rate or survival in both groups. Thus an elective neck dissection including levels I, II, III, and IV appears to be adequate for the majority of patients.

Oropharynx

In the Shah and colleagues series,[1] only 2.1% of patients undergoing elective neck dissection had level I involvement, and only 2.1% of patients had level V involvement. An elective neck dissection clearing levels II, III, and IV would have been adequate in clearing all diseased nodes in 95.8% of patients.

Larynx

The various subsites of the larynx have different lymphatic drainage patterns, and this has important implications for treatment. The supraglottis drains bilaterally into lymphatics along the superior laryngeal artery and drains into the jugular chain of nodes. More than half of patients with supraglottic cancers will have nodal involvement, and bilateral nodal involvement is not uncommon even in early tumors. The subglottis drains into lymphatics that travel along the inferior thyroid artery and into the pretracheal lymph nodes. The glottis has relatively sparse lymphatics that drain to the jugular chain of nodes, and it is uncommon for early-stage glottin cancers to have nodal involvement. An elective neck dissection usually involves bilateral II, III, and IV neck dissections for tumors of the supraglottis and glottis, and levels II, III, IV, and VI for patients with supraglottic tumors.

Hypopharynx

In the series by Shah and colleagues,[1] the metastatic nodes seen in patients undergoing elective neck dissection were all confined to levels II and III. There were no patients in that series

with involvement of level I or level V. Thus a selective neck dissection clearing levels II, III, and IV is adequate to treat most patients with hypopharyngeal tumors with N0 disease.

Elective Neck Irradiation

Performing a neck dissection carries the benefit of more accurate nodal staging as well as avoidance of the short-term and long-term side effects of radiation therapy. Elective neck irradiation, however, gives lymph node failure rates of less than 5% when the primary lesion was adequately controlled.[19-21]

Therapeutic Neck Dissections

A therapeutic neck dissection is done when there is clinical evidence of nodal involvement. Practically speaking, this usually means finding enlarged nodes on either physical examination or imaging studies, or a positive biopsy result. Positron emission tomography with computed tomography (PET-CT) scans are increasingly being used to detect occult nodal disease. ^{18}F-Fluorodeoxyglucose (^{18}FDG) PET has been shown to be superior to CT or magnetic resonance imaging (MRI) for detecting lymph node metastasis, with sensitivity and specificity of 90% and 94%, respectively, compared with 82% and 85% for CT, 80% and 79% for MRI, and 72% and 70% for ultrasonography.[22]

As previously discussed, the most significant prognostic factor for patients with head and neck squamous cell carcinoma is the presence of regional nodal metastasis. Moreover, prior to the advent of radiation therapy, radical surgical resection represented the only available treatment option and chance for cure. In keeping with the established principles of surgical oncology, the earliest pioneers of neck dissection described and championed en bloc extirpation of all cervical nodal groups from the mandible to the upper clavicle. This philosophy remained popular throughout the early to mid-20th century, as the surgical management of head and neck cancer in many ways mirrored the evolution of surgical cancer treatment as a whole. Perhaps the most well-known advocate of what is now known as the classic *radical neck dissection* was Hayes Martin, who strongly advocated the sacrifice of the sternocleidomastoid muscle (SCM), internal jugular vein (IJV), and spinal accessory nerve (SAN) as crucial to the effective surgical management of HNSCC.[23] However, with improved understanding of the disease process and advances in multimodality therapy, there has been a resulting change in the surgical management of regional nodal disease in HNSCC. In addition to removal of disease, the surgeon must also be highly cognizant of the functional impacts of a given operation and must balance the need for effective oncologic treatment with minimizing undue surgical morbidity. However, the fundamental question of which operation to perform based on the risk and extent of nodal metastasis remains, and it is crucial for the head and neck surgeon to understand the foundational basis and evidence for modifying the classic neck dissection.

Since the original description of the radical neck dissection by Crile in 1906,[24] there has been a steady evolution toward more focused and less radical procedures. This has been due in large part to increased awareness and appreciation for the postoperative morbidity associated with radical en bloc resections. Beyond the cosmetic deformity that can result, sacrifice of the SAN with the subsequent denervation and atrophy of the trapezius muscle frequently results in a debilitating "shoulder syndrome" characterized by significant shoulder pain and restricted range of motion.[25] This was the primary impetus for contemporary surgeons to develop modified surgical procedures that reduced morbidity while still maintaining equivalent oncologic outcomes.

Although Crile proposed preservation of the spinal accessory nerve in patients who were clinically N0,[24] Suarez was the first to describe the "functional neck dissection" and to promote the preservation of non-lymphatic structures normally sacrificed during radical neck dissection (RND). This de-radicalization subsequently led to what can best be termed *modified radical neck dissection* (MRND) in which involved and/or at-risk nodal groups are removed while preserving the SCM, IVJ, and/or SAN unless they are grossly involved with disease. Over time, more selective procedures targeting specific at-risk nodal basins have become more widely used, especially in clinically negative necks or in cases of limited nodal burden. However, until recently comprehensive MRND remained the preferred approach for the majority of N+ cases. Contemporary thought has now challenged this dogma and demonstrated the utility and efficacy of more selective surgery even in patients with gross nodal disease.

In general terms, neck dissection is performed in three clinical scenarios: elective neck dissection, which is performed at the time of the primary surgery in patients without clinically evident nodal disease; therapeutic neck dissection, which is performed in patients with known nodal disease; and as a salvage procedure following definitive radiation or chemoradiation therapy. In the case of elective surgery for N0 disease, the safety and efficacy of selective neck dissection has been well established.[26-28] Furthermore, although some controversy remains regarding the survival benefit of elective neck dissection for early-stage, clinically N0 tumors, a recent randomized trial by D'Cruz and co-workers demonstrated significantly higher overall survival (OS) in patients undergoing upfront elective neck dissection versus those who were treated with therapeutic dissection once they developed clinically apparent nodal disease (80% vs. 67.5%).[29]

For patients presented with clinically N+ disease, the evolution from traditional RND to less aggressive modified procedures have been more convoluted. Although it would seem intuitive to presume that disease will always be present in clinically positive nodes (i.e., those found to be enlarged on clinical exam or imaging), several studies have refuted this presumption.[1,30,31] This then raises an important question: Does every patient with clinical evidence of lymph node metastasis need radical neck dissection, and, if not, what is the extent of surgery that is appropriate to limit unnecessary morbidity while not sacrificing oncologic outcomes?

Several studies have effectively demonstrated the benefits and oncologic efficacy of MRND in the management of clinically evident nodal disease. Andersen and colleagues[32] specifically demonstrated that both survival and recurrence rates were

not adversely affected by the routine preservation of the spinal accessory nerve. Similar findings were reported by Byers,[33] who showed an overall recurrence rate of around 6% following functional node dissection with the use of appropriately selected adjuvant radiation. These studies, in turn, opened the door for acceptance of MRND as a viable option for patients with N+ disease, and it has now become generally accepted that MRND is equivalent to RND in the setting of nodal disease. Moreover, an overarching theme of these studies is that a concerted effort should be made to preserve non-lymphatic structures that are not grossly involved by disease, as this does not appear to compromise oncologic outcome and significantly reduces the associated morbidity of more radical neck surgery.

Although more controversial, the next logical progression was in the use of selective neck dissection (SND) in cases of N+ disease. While some authors have argued that SND is not adequate and increases the risk of recurrence,[34] there is also a preponderance of evidence that suggests that in appropriately selected N+ patients, SND is comparable to more extensive procedures. Previous work by Byers[33] and Medina[35] effectively demonstrated that SND followed by appropriate adjuvant radiation therapy can be a reasonable approach to patients with N1 and N2 disease. These results have been validated by several additional studies, such as that by Traynor and colleagues,[36] who reported a 4% regional failure rate and no recurrences in the operated neck in 207 patients with N1 and N2 disease undergoing SND. Similar findings were reported in a 10-year retrospective review by Andersen and co-workers.[37] In their series of 106 previously untreated patients with primarily N1 and N2 disease, only six patients failed in the ipsilateral neck (94.3% regional control). It should be noted that, as with many of the previous studies, the majority of patients received adjuvant radiation therapy, and the authors stressed the importance of prudent patient selection. Based on the results of these and other studies, there would appear to be an expanded role for selective node dissection in treatment of the node-positive neck. However, although SND seems to offer similar oncologic results to more comprehensive approaches, it is important to realize that there remains an overall paucity of prospective randomized data on this subject and in fact, the outcomes of SND versus MRND for N+ disease have never been prospectively compared.

There are very important considerations that must be taken into account regarding the use of SND as a part of a therapeutic strategy. Many of the aforementioned series have strict criteria in selecting patients for SND, including evidence of minimal neck disease on preoperative evaluation, lack of poor prognostic factors in the tumor, and lack of obvious extranodal spread and invasion of adjacent structures noted intraoperatively. SND may be appropriate in patients with disease limited to N1 and N2 and confined to first and possibly second echelons of nodal drainage. Whatever approach is to be used, a comprehensive physical exam and review of diagnostic studies are essential requirements in order to offer the best surgery for a particular patient. Moreover, the head and neck surgeon must be able to adapt the surgical plan intraoperatively as dictated by the appearance, behavior, and burden of the disease, so as to provide the best oncologic outcome with the lowest possible risk of recurrence.

The Role of Salvage Neck Dissection Following Radiation and Chemoradiation Therapy

Following the landmark VA Laryngeal Cancer Study, organ preservation protocols emphasizing primary radiation and chemoradiation therapy have become widely used in the treatment of HNSCC.[38] A thorough discussion of the indications and rationale for selecting patients for primary, non-surgical therapy is beyond the scope of this chapter and is provided elsewhere in this text. However, it suffices to say that for even more advanced-staged HNSCC of the oropharynx, larynx, and hypopharynx, upfront radiation, and chemoradiation therapy have become commonly used with good results in many centers. As a result, surgical intervention including neck dissection is often used for salvage treatment following chemoradiation. The role and performance of neck dissection after definitive radiation with or without chemotherapy is one of the less studied uses of this operation. In general, neck dissection can be used in two clinical scenarios: The first includes neck dissection after chemoradiation without any evidence of persistent or recurrent disease in the neck; and the second involves surgery for persistent and/or recurrent disease following chemoradiation therapy.

Although the surgical principles are similar, salvage neck dissection is a unique operation with its own specific considerations. The decision to perform surgery following chemoradiation therapy is rarely straightforward, and the indications are not as well defined. The first issue is the relative unreliability of traditional imaging and diagnostic tools in assessing the neck following radiation and chemoradiation. Numerous studies have demonstrated that clinical exam is not reliable or accurate in the detection of persistent or recurrent disease. In fact, only 39–46% of patients deemed to have incomplete clinical response were found to have residual disease following salvage neck dissection across several series.[39-41] The addition of post-treatment and surveillance imaging undoubtedly improves this diagnostic accuracy but is far from infallible. For instance, Ojiri and colleagues demonstrated a false-positive rate of over 57% with post-radiation CT.[42] Other studies have shown similar discordance between CT and MRI findings and the presence of residual disease on final surgical pathology.[43-45] PET-CT has seen increased use in post-treatment staging and surveillance, and it has demonstrated improved sensitivity and negative predictive value for detecting residual and recurrent disease.[46,47] A recent study by Kim and associates comparing PET-CT with CT-MRI found that PET-CT was superior in detection and localization of recurrent disease. Based on correlation with final surgical pathology, PET-CT had an overall accuracy of 89% in demonstrating residual and recurrent disease versus 78% with CT and MRI.[48] At present, a negative PET-CT is perhaps most useful, as it may allow the surgeon to confidently spare a patient from unnecessary salvage surgery.

Another important consideration in the decision to perform salvage neck surgery is the increased rate of postoperative complications and morbidity. Post-treatment neck dissection can prove to be a difficult endeavor because of diffuse soft tissue fibrosis and inflammation, obliteration of normal fascial planes,

and vascular friability that can be present. Moreover, because of the deleterious effects of radiation on the surrounding tissue, it is generally accepted that the risk of complications with salvage neck surgery is higher overall compared with primary surgery—as high as 50%, based on some series.[49] Although the majority of postoperative issues involve poor wound healing,[50] other major complications including fistula, chyle leaks, and even life-threatening vascular rupture can also occur with increased frequency. Many surgeons choose to perform reconstruction with rotational myocutaneous flaps in these settings, especially if the major neck vasculature is at risk because of sacrifice of overlying soft tissue.

A final important consideration when committing to perform post-treatment salvage neck dissection is determining the extent of surgery. The key factors that influence this determination are the stage of the neck prior to treatment as well as the clinical and imaging assessment before and after treatment. In cases of no (N0) and low burden neck disease (N1), the general consensus is to observe the neck unless there is clinical evidence of residual disease (i.e., persistent PET-CT uptake) or later nodal recurrence. However, the management of patients with N2-N3 disease remains controversial, especially in cases of good treatment response. There are strong advocates on both sides of this argument. Based on several prior studies, Pellitteri and colleagues in 2006 recommended planned neck dissection for patients with N2-N3 disease regardless of apparent clinical response.[51] The group's recommendation was based on the risk of occult nodal disease despite apparent clinical response, the poor prognosis associated with gross nodal recurrence, and a lack of proven pathologic correlation with post-treatment imaging including PET. However, a recent prospective, randomized trial reported by Mehanna and co-workers calls into question the need for planned, post-treatment neck dissection for all cases of advanced nodal disease.[52] The authors evaluated 564 patients with advanced nodal disease (N2-N3). Of these, 282 underwent surveillance PET-CT at 12 weeks, with neck dissection performed only if PET-CT showed an incomplete or equivocal response, and 282 received planned neck dissection. Their results showed no statistically significant difference in survival between the two groups, while surveillance PET-CT was associated with fewer surgeries and lower overall cost per patient. Although this is the largest randomized trial to date, it is perhaps important to note that 75% of the patients in this study presented with p16+ oropharyngeal carcinomas, which could affect its generalizability.

The extent of salvage neck dissection also remains an area of controversy. Although many authors have traditionally recommended at least a comprehensive, MRND involving all major nodal basins,[53] this too has recently been called into question. Again it is a matter of balancing the goal of a complete oncologic resection with the increased morbidity of more aggressive surgery in the post-radiation setting. The rationale for performing more selective surgery even in salvage cases is based on advancements in radiation techniques, more accurate imaging technology, and the improved response to chemoradiation seen with p16+ disease. Moreover, a more restrained surgical approach is also supported by emerging clinical evidence. Several studies have shown selective salvage neck dissection to be an effective approach in a majority of cases with a low risk of subsequent neck failure.[54-56] However, more comprehensive surgery may still be warranted in some circumstances, such as in patients with multiple involved levels prior to treatment, those with residual disease in level V, and/or those presenting with recurrence in previously uninvolved nodal levels.[57-59] Regardless of the extent of salvage surgery, it is generally performed within 6 to 8 weeks post-treatment, and the surgeon must be mindful of and prepared for its increased difficulty and potential complications.

Conclusion

Because of its significant impact on the overall prognosis of the patient, staging and management of cervical nodal disease is of utmost importance in the management of patients with head and neck cancer. Recent advancements in our understanding of the disease process and new technologies will help us manage these patients adequately while minimizing morbidity.

PART 2: SENTINEL LYMPH NODE BIOPSY

Management of node-negative neck in oral cavity squamous cell carcinoma (OSCC) is controversial. There are differences of opinion about choosing an elective neck dissection versus a "watch and see" policy.[60,61] The incidence of occult neck metastasis ranges between 10–50%.[62-64] This results in overtreatment in about 70% by doing an elective neck dissection resulting in avoidable morbidity. Presently, pathologic evaluation is the most reliable method of staging cervical nodes.[65] As in the case of many solid tumors,[66,67] sentinel lymph node biopsy (SNB) is emerging as a potential method for staging of lymphatic metastasis in OSCC. This chapter will review the current understanding of the mechanism of lymphatic metastasis, concept of SNB, evolution of the concept, current status of SNB in OSCC, technique of isolation of the sentinel lymph node (SLN), intraoperative assessment of sentinel nodes, and pathologic evaluation of the SLN, including the histologic and molecular markers in identifying occult disease in sentinel nodes. This section also reviews studies reporting the outcomes in SNB, the morbidity of the technique compared to selective neck dissection the controversies, and latest developments.

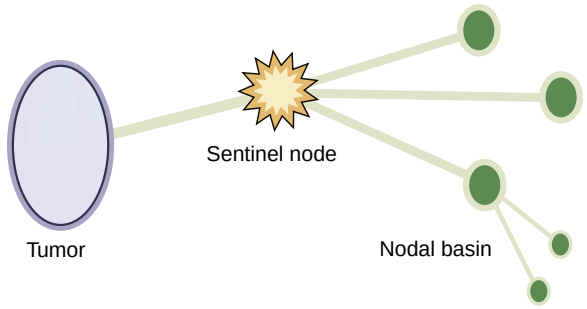
The Concept of SNB

Tumor cells enter the lymphatic system through the peritumoral lymphatics.[68] The absence of basement membrane and the large number of gap junctions between the endothelial cells assists the access of tumor cells to the lymphatics. The tumor emboli are then disseminated in the lymphatic system in an orderly fashion, beginning with the SLN and then to the remaining lymph nodes within the nodal basin[69] (Fig. 9.4). The lymph nodal basins in oral cavity cancer are well characterized.[70,71] The basis of the concept is that the status of the sentinel node predicts the presence of metastasis in the rest of the nodes within the nodal basin. After filtering through

the sentinel node, the tumor emboli exit through the efferent lymph vessels located at the hilum to other nodes within the nodal basin. The pattern of growth of tumor emboli filtering through the SLN is well established, starting as isolated tumor cells (ITCs), then micrometastasis and macrometastasis.[72]

The Evolution

In 1955, Seaman and Powers[73] demonstrated for the first time the concept of the first echelon node and nodal basin using radioactive colloid gold. Gould and colleagues[74] subsequently coined the term *SLN* in a case of malignant parotid tumor. Cabanas[75] established the basis of SLN theory. In penile cancer, he showed that a specific node in each groin received lymphatic drainage, and the pathologic status of this SLN can be used as a guide to determine the need for lymph node dissection. In 1992, Morton and co-workers[76] demonstrated the clinical feasibility of the SNB in cutaneous malignant melanoma using isosulfan blue dye. They were able to identify the SLN in 82% of patients. Alex and Krag[77] proposed the use of lymphoscintigraphy and a handheld gamma probe for intraoperative identification of the SLN in cutaneous malignant melanoma. With a handheld gamma probe, they were able to identify SLNs in 90% of the cases. Morton and co-workers[78] later concluded in a randomized clinical trial that blue dye and lymphoscintigraphy is superior to blue dye alone in cutaneous malignant melanoma. With the combined technique, the SLN could be identified in more than 95% of patients. These studies have demonstrated that when the SLN is negative for metastasis, the remaining nodes within the nodal basin are also negative.[79] SNB has become the standard of care in melanoma[66,80] and cancer of the breast.[67,81] SNB for early-stage oral cavity cancer continues to gain acceptance worldwide as an effective alternative to elective neck dissection for staging the N0 neck.[82]



• **Fig. 9.4** Concept of sentinel node biopsy.

Technique

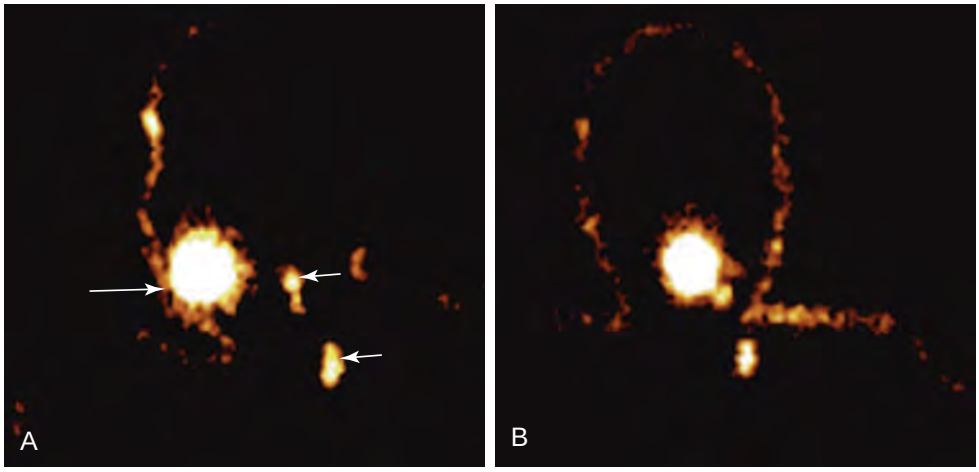
SNB consists of two steps: identification of the SLN, and its pathologic evaluation. SLNs can be identified by three techniques: blue dye, preoperative dynamic lymphoscintigraphy, and intraoperative static lymphoscintigraphy.

Blue Dye Technique

Isosulfan blue dye is used commonly. The dye is injected submucosally around the tumor. The SLNs are stained blue 15 to 45 minutes after the injection. The technique needs visualization, and hence it is essential to expose the entire nodal basin, thereby increasing the invasiveness of the procedure. Moreover, blue dye consists of small particles with a very poor retention in the sentinel lymph node. This is probably because of the fast lymphatic drainage in the head and neck area. Staining of the mucosa around the tumor may make the surgical excision of the primary tumor difficult. This technique is no longer preferred for identification of the SLN.

Lymphoscintigraphy

Preoperative dynamic lymphoscintigraphy involves the injection of radiolabeled colloid at the periphery of the tumor. The flow of radiolabeled dye from the primary tumor to the sentinel nodes can be visualized in real time using a gamma camera operating in a continuous mode in both the anteroposterior and lateral views (Fig. 9.5). The position of the nodes where the



• **Fig. 9.5** Preoperative dynamic lymphoscintigraphy: lateral **(A)** and frontal **(B)** views (*long arrow* indicates primary tumor and *short arrows* indicate sentinel lymph nodes). (From Kuriakose MA, Trivedi NP: Sentinel node biopsy in head and neck squamous cell carcinoma, *Curr Opin Otolaryngol Head Neck Surg* 17(2):100-110, 2009.)



• **Fig. 9.6** Sentinel nodes marked on the neck.



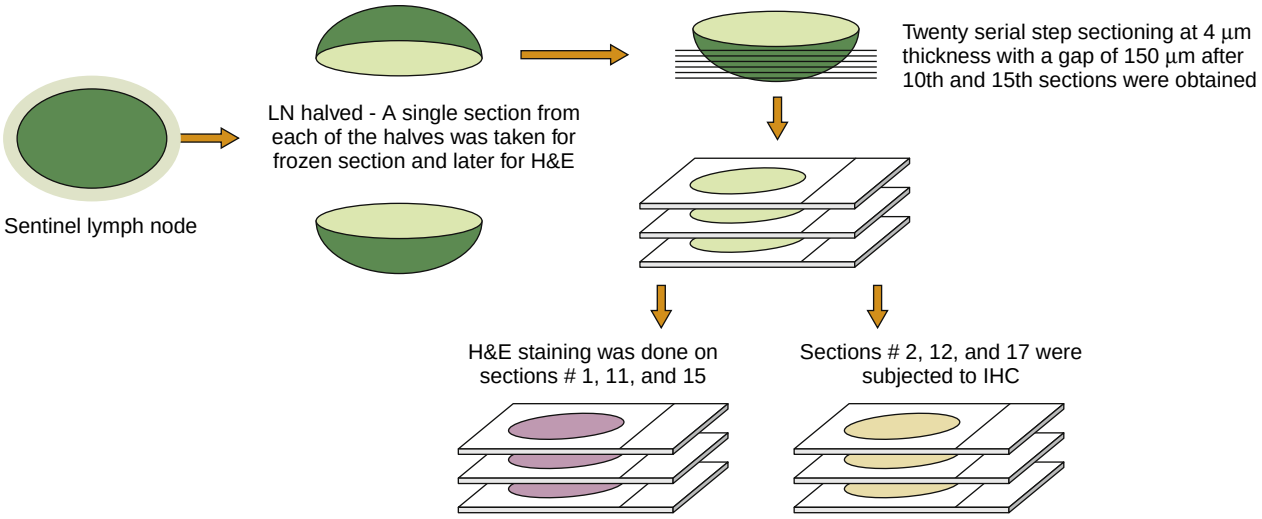
• **Fig. 9.7** Intraoperative handheld gamma probe localization of the sentinel lymph node. (From Kuriakose MA, Trivedi NP: Sentinel node biopsy in head and neck squamous cell carcinoma, *Curr Opin Otolaryngol Head Neck Surg* 17(2):100-110, 2009.)

radioactivity localizes can be marked on the skin. Intraoperative static lymphoscintigraphy involves identifying the nodes with the highest radioactivity using a handheld gamma probe. An incision is made at the region of the nodes marked by the preoperative dynamic lymphoscintigraphy (Figs. 9.6 and 9.7). It is important that the incision be planned in such a way that it may be extended to do a neck dissection, should it be required. There is no threshold radioactivity value for the SLN. It varies by the time of injection, quantity of radioisotope used, and location of the lesion. The nodes with the peak radioactive reading, as well as any adjacent nodes that are more than 10% as hot as the SLN, are removed. After removal, nodes must be checked for radioactivity. The surgical bed should not have radioactivity higher than the background reading. The 10% rule was developed on the basis of the observation that about 13% of metastatic nodes are not those that are the hottest node.[83] There is controversy about the number of SLNs to be biopsied for accurately determining the pathologic nodal status.[84] This question was addressed by Werner and colleagues.[85] They performed SNB in 90 patients with clinically N0 head and neck cancer. Up to three SLNs were biopsied in these patients. Overall, 23 of the 90 patients (25.6%) showed evidence of occult metastasis. It was observed that if only the node with the strongest tracer uptake had been biopsied, the histologic evidence of metastasis would have been missed in 9 of 23 (39%) patients. This study clearly suggested that the node with highest radioactivity may not be the pathologically positive SLN, and more than one SLN needs to be harvested for accurate pathologic evaluation.[86,87] Detection of the SLN at level I become difficult at times due to the "shine-through" effect of the primary tumor. This is especially true in case of a primary tumor in the floor of the mouth. In this scenario, it is recommended that the primary tumor be removed first before localizing the SLN.[88-90]

Radioisotopes

Gold-198 was the first material used for the purpose. This had a particle size of 5 nm. Although this material has greater and faster uptake than any other subsequently developed radioisotopes, the high dose of radiation thwarted its broader clinical use.[91] Iodine-131 and ^{99m}Tc were later introduced for lymphoscintigraphy. The ^{99m}Tc attached to sulfur colloid is now the most widely used for lymphoscintigraphy. The advantages of ^{99m}Tc sulfur colloids are that they emit only gamma rays and have low radiation exposure, the half-life of ^{99m}Tc is only 6 hours, and it has a peak energy emission peak of 140 keV. This is within the detection range of most gamma camera and handheld gamma probes. The particle size and the attached molecules are the primary factors that determine the rate of uptake into the lymphatics and the filtration within the sentinel node. The optimal particle size of radioisotopes is between 5 and 10 nm.[92] A particle smaller than 5 nm may be taken up by the vascular system. The radioisotopes may be used as either filtered or unfiltered forms. Filtration allows control of particle size to a specific range (15-50 nm). Unfiltered nanocolloids have a particle size ranging from 5 to 1000 nm.[91,92] The dose of radioisotope used also varies from 0.5 to 0.8 mCi. Using a ^{99m}Tc sulfur colloid in cutaneous lesions, the transit time to the lymph node is less than 1 hour. The radioactivity may be retained in the lymph node for an additional 3 to 6 hours. However, for mucosal head and neck tumors, the transit time is less than 30 minutes. The radioactivity can be detected for 3 to 6 hours after the injection. Ideally, the injection, dynamic scintigraphy, and intraoperative gamma probe localization should be done on the same day.

Tilmanocept is a new agent. It is a ^{99m}Tc-labeled non-particulate radiotracer that contains multiple mannose moieties with high affinity for the CD206 receptor found on macrophages and dendritic cells, enhancing targeting to these cells within the SLN. Studies in breast cancer and melanoma have shown that tilmanocept may have improved clearance from the site of the primary tumor and enhanced retention within the



• **Fig. 9.8** Schema for pathologic evaluation of sentinel lymph node. *H&E,* hematoxylin and eosin; *IHC,* immunohistochemistry; *LN,* lymph node.

sentinel node when compared to sulfur colloid.[93,94] Because of the rapid clearance and prolonged retention within the sentinel nodes, patients could be injected preoperatively from immediately prior to surgery up to 30 hours preceding surgery. A single institution reported their experience as part of this larger multicenter trial in their initial report of 20 clinically node-negative patients.[95] The NPV was 100% for five patients with floor-of-mouth tumors. Complete results of the multicenter Phase III trial are yet to be published.

Pathologic Evaluation

The identified SLNs can be subjected to different pathologic investigations with varying stringency, sensitivity, and clinical utility. This includes frozen section, imprint cytology, standard histopathology, serial step sectioning (SSS), standard histopathology and SSS, and immunohistochemistry (IHC). Of these, frozen section and imprint cytology can be used for intraoperative evaluation.

Frozen Section

Intraoperative detection of metastatic deposits in sentinel node biopsy is important to avoid a staged second procedure. Recent studies have shown reasonable negative predictive value with frozen section analysis (83%).[96-98] Intraoperative evaluation with frozen section was accurate in detecting macrometastasis, but was not effective in detecting micrometastasis and isolated tumor cell deposits.[99] Moreover, if smaller deposits (mainly isolated tumor cells)[96] are located within the tissue used for frozen section analysis, it would be missed in eventual analysis for micrometastasis.

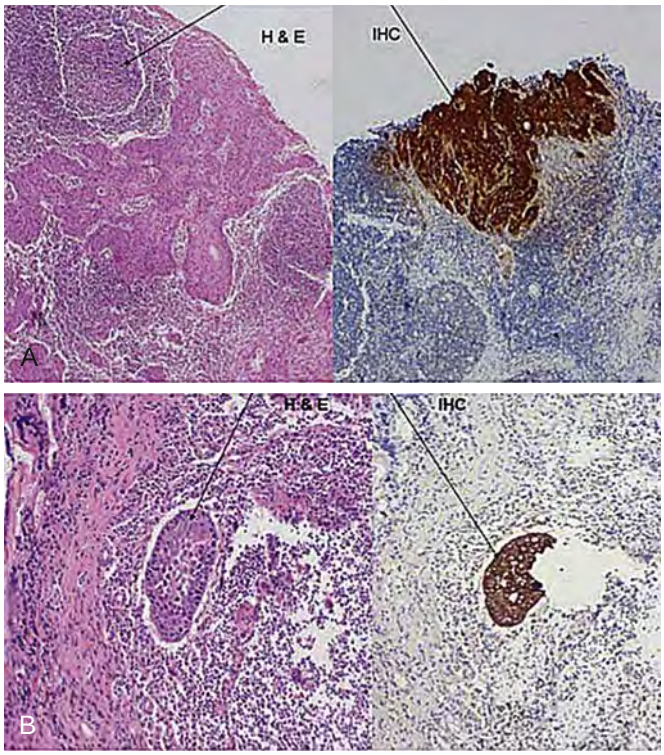
Imprint Cytology

Imprint cytology as an alternative to frozen section analysis of lymph nodes has been reported.[100] In the study by Trivedi and colleagues,[99] the detection rates of imprint cytology and frozen section were identical. As in frozen section, imprint cytology failed to detect micrometastasis and isolated tumor cells.

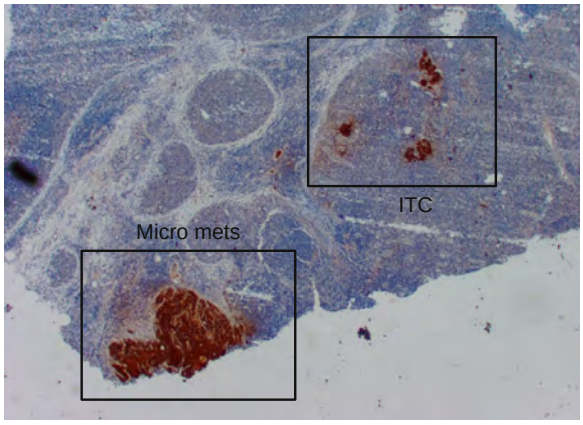
Routine Histopathologic Evaluation and Serial Step Sectioning

Routine pathologic evaluation of a neck node consists of identifying each individual node, bisecting the node at its center, and then staining one or two sections to find light-microscopic evidence of metastatic deposits.[101] This, in reality, is an incomplete examination. If deposits were small and present in other regions of the node, they would be missed. Studies have shown that routine evaluation misses up to 21% of disease nodes in breast cancer.[102] It has been shown that SSS with hematoxylin-eosin (H&E) stain and IHC and molecular methods identify smaller metastases more accurately. Nelson[103] has reported that H&E staining with step sections identifies 1 cancer cell among 10,000 normal cells. IHC identifies 1 tumor cell among 100,000 normal cells. RT-PCR is the most sensitive of all. It identifies 1 cell among 1 million normal cells. In clinical practice, SSS with H&E staining upstages the tumor in 10%, whereas IHC further upstages it up to 10% more.[104,105] In the study by Trivedi and colleagues,[99] routine pathologic evaluation detected occult metastasis in 16.2% but missed metastasis in 8.7% of cases. SSS with H&E stain and IHC identified the metastasis in 25% and hence further upstaged the neck by about 9%. Other studies[104,105] also reported similar results. SSS was necessary to detect micrometastatic deposits. Routine pathologic evaluation was not sufficient to detect this metastasis. IHC was needed only to identify isolated tumor cells. The clinical significance of these smaller foci of metastasis is not established.

There is now a standard recommendation for pathologic evaluation of the SLN.[106] The node is dissected free of any fat and bisected through its long axis. If each half of the node is more than 2.5 mm wide, they are then further sectioned longitudinally so that each section is not more than 2.5 mm. SSS is then carried out at 150-µm intervals. At each step, four sections are obtained. One section will be stained by H&E and the other by IHC for cytokeratin (Fig. 9.8). If any cytokeratin-positive cells are identified, they are compared with the adjacent H&E section to confirm that the positivity was due



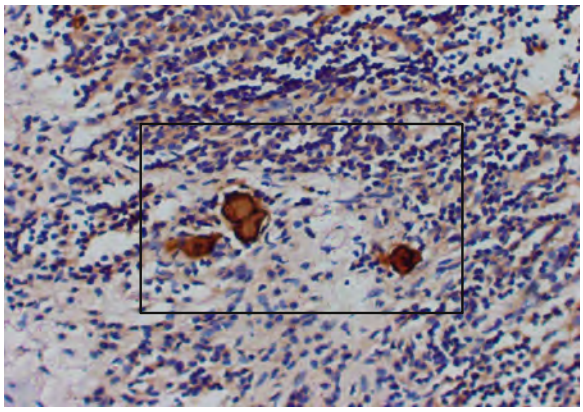
• **Fig. 9.9 A,** Macrometastasis (original magnification 40). **B,** Micrometasis (original magnification 200). *H&E,* hematoxylin and eosin; *IHC,* immunohistochemistry (B from Trivedi NP, Ravindran HK, Sundram S, et al: Pathologic evaluation of sentinel lymph nodes in oral squamous cell carcinoma, *Head Neck* 32(11):1437-1443, 2010.)



• **Fig. 9.10** Micrometastasis and isolated tumor cells (ITC). (From Kuriakose MA, Trivedi NP: Sentinel node biopsy in head and neck squamous cell carcinoma, *Current Opinion in Otolaryngology & Head and Neck Surgery,* 2009, 17:100–110.)

to tumor cells. A standard and uniform reporting of the SLN needs to be adopted to compare results.[106]

Histologically detected metastases are termed as occult metastases, which can be further categorized based on histopathologic criteria. Hermanek and colleagues[107] proposed histopathologic classification of occult metastasis for breast cancer into macrometastasis, micrometastasis, and isolated tumor cells. A widely used staging scheme for breast cancer formally defines macrometastasis (Fig. 9.9) as metastatic deposits more than 2 mm in diameter. Micrometastasis is a metastatic deposit between 2 mm



• **Fig. 9.11** Isolated tumor cell. (From Trivedi NP, Ravindran HK, Sundram S, et al: Pathologic evaluation of sentinel lymph nodes in oral squamous cell carcinoma, *Head Neck* 32(11):1437-1443, 2010.)

and 0.2 mm in diameter (Fig. 9.10). Deposits less than 0.2 mm are defined as isolated tumor cells[108] (Fig. 9.11). This can be either single cell deposits or a cluster of tumor cells. Unlike in breast cancer, there is no uniform histopathologic staging available for occult metastases in head and neck cancer. Some studies have included 3 mm as the upper limit of size of micrometastasis,[109] but these studies do not always mention lower limits for micrometastasis. Most studies, though, use 2 mm as the upper limit and 0.2 mm as the lower limit for micrometastasis.[110] Metastatic deposits less than 0.2 mm are generally defined as isolated tumor cells.[107,108,111,112]

Diagnostic Efficacy

SNB has to be evaluated in three aspects: first, the feasibility of the procedure to identify sentinel lymph nodes; second, the extent to which metastasis can be detected within those nodes; and third, the accuracy of the procedure in determining the status of the neck.

Sentinel Lymph Node Identification

The technical feasibility of SNB is ascertained by the probability of identifying sentinel lymph nodes with preoperative lymphoscintigraphy and intraoperative detection using a handheld gamma probe. High rates of sentinel lymph node identification in oral cancer have been reported, suggesting that the procedure is feasible. Pilot studies from 20 centers were collectively analyzed.[113] Among 379 patients with clinically N0 disease, sentinel lymph nodes were identified in 366 patients, with an identification rate of 97%. A systematic review and diagnostic meta-analysis of all published literature on SNB in oral cancer through 2003 were performed by Paleri and colleagues.[114] The analysis included 301 patients with oral cavity primary tumors from 19 studies. The study reported an overall sentinel lymph node identification rate of 97.7%. The 5-year results of a European multi-institutional study[90] showed that, of the 227 SNBs reported, 134 were performed on early-stage (T1-T2) oral cavity cancer. In these patients, sentinel nodes were correctly identified in 93% (124 of 135) of patients. The ability to identify the sentinel node was less in patients with

floor-of-mouth tumors compared to all other subsites (88% vs. 96%, P = 0.138). The meta-analysis by Govers and colleagues[115] had 847 cases of early-stage oral cavity or oropharynx cancer in total. At least one sentinel node was detected in almost all patients included from the studies, and an SNB could thus be performed in 835 patients. The sentinel node detection rates ranged from 91% to 100%.

Detection of Occult Metastasis

The next step in evaluating SNB lies in determining the extent to which occult metastases are identified. The finding of occult metastasis within the sentinel node on pathologic evaluation results in upstaging of the node-negative N0 neck. The rate of upstaging by SNB must be compared with that by elective neck dissection, which is currently the best available method of detecting occult metastasis. Pathologic evaluation of specimens stained with H&E and elective neck dissection upstages approximately 30% of patients. In the Canniesburn trial,[104] where the sentinel lymph nodes were examined by a routine H&E staining, serial sectioning, and immunohistochemical analysis for cytokeratin, upstaging of disease occurred in 34% of cases. Nodal metastasis was identified by H&E staining alone in 26% of cases and by additional pathologic means in 11% of cases. Therefore, although the extent to which SNB upstages the neck by traditional pathologic methods seems similar to that with elective neck dissection, the use of additional pathologic methods results in perhaps an even greater level of detection of disease. Additional pathologic methods, such as serial sectioning and immune-histochemical analysis, may increase the identification of micrometastasis. The identification of micrometastases creates a problem for the current staging system for oral cancer. Patients with micrometastatic disease found by additional pathologic methods and with no additional disease in the neck specimen are upstaged from clinically N0 to a new classification of pNmi, or pathologic nodal micrometastasis, for which the prognosis is unknown.

Accuracy of Sentinel Node Biopsy

Many single-institution series have published the results of sentinel lymph to accurately stage the neck compared to elective neck dissection.[110,116-128] In the European multi-institutional study,[31] with a minimum 5-year follow-up, the overall sensitivity of the procedure was 91%. The patients with floor-of-mouth tumors demonstrated lower negative predictive values (NPV) compared to other oral cavity sites (88% vs. 98%). These findings led the authors to recommend the use of SNB as a reliable staging procedure in all oral cavity sites with the exception of the floor of the mouth. The American College of Surgeons Oncology Group (ACSOG) trial,[129] a multi-institutional trial from the United States (Z0360), included 140 patients with early-stage (T1-T2) oral cavity cancer. SNB was performed, followed by immediate elective lymph node dissection. The negative predictive value for SNB in this study, which consisted primarily of oral tongue and floor-of-mouth carcinomas, was 94% (95% confidence index [CI]: 0.88-0.98) on routine histologic analysis, with improvement to 96% with immunohistochemical staining. SNB appeared to perform slightly better for smaller lesions, with NPV of 100% for T1 lesions compared to 94% for T2 lesions. The similar conclusions of these multiple published experiences support SNB as an accurate procedure for staging the neck in early-stage oral tongue cancer. In the meta-analysis by Paleri and colleagues including 301 patients with oral cavity squamous cell carcinoma as well as a smaller subset of 49 patients with oropharynx cancer,[114] the pooled sensitivity of SNB for the study group was 0.926 (95% CI: 0.852-0.964) using a random effects model, with individual ranges of 0.75 to 1. A more recent meta-analysis examining the diagnostic accuracy of SNB in head and neck cancer[130] included 766 patients in 26 studies between 1970 and 2011, in which the pooled NPV was 96% (95% CI: 94–99%). In the subset of 593 patients with early-stage cancer (T1-T2), consistency of the findings across the multiple studies included in these meta-analyses demonstrates that the accuracy of SNB is reproducible. As with most procedures, however, surgeon experience does seem to affect the results. In the ACOSOG trial, increased surgeon experience with SNB correlated with a higher negative predictive value when compared with surgeons with less experience (100% vs. 95%).[129] In yet another meta-analysis by Govers and colleagues,[115] 21 studies (847 patients) could be included. Most of these patients had OSCC. The pooled data showed an overall sensitivity of 0.93 (95% CI 0.90-0.95). Negative predictive values ranged from 0.88 to 1. Subgroup analysis showed no significant differences in subgroups. As with most procedures, however, surgeon experience does seem to affect the results. In the ACOSOG trial,[129] increased surgeon experience with SNB correlated with a higher negative predictive value when compared with surgeons with less experience (100% vs. 95%). A single-center study of 79 patients with clinically N0 early oral cancer (after ultrasound-guided fine-needle aspiration cytology) found a sentinel lymph node detection rate of 99%, a sensitivity of 91%, and a negative predictive value of 90%.[131] This study showed evidence that the previously reported promising short-term results can be sustained through long-term follow-up. In summary, based on the sensitivity and specificity of SNB in early-stage oral cancer, it seems that the accuracy of SNB is similar to that of elective neck dissection.

Recurrence and Survival Outcomes

Oncologic outcomes can be results regarding nodal recurrences or survival outcomes. There can be comparison between SNB versus SND in the management of the N0 neck, or between SLN-negative versus -positive groups of patients. In a retrospective study by Fan and colleagues, 82 patients underwent elective neck dissection (n = 52) or SNB (n = 30) for cT1-2N0 oral cancer. The use of SNB was not associated with a difference in either 10-year recurrence-free (72.3% vs. 73.3%; p = 0.81) or overall survival (43.3% vs. 44.2%; p = 0.83) when compared to elective neck dissection.[122] Alvarez and co-workers, in a study of 63 patients with floor-of-mouth carcinoma, reported no significant differences in disease-specific survival (DSS) or disease-free survival (DFS) for patients undergoing SNB compared to a standard cohort of elective neck dissection and observation.[110] There is a similar paucity of studies comparing SNB-positive and negative patients. In a European

multicenter trial,[90] no significant difference between SNB-positive and SNB-negative patients could be shown. There was a numeric reduction in locoregional DFS in the SNB-positive patients. However, no significant difference was demonstrated in survival between patients undergoing SNB-assisted neck dissection and SNB alone.

Hernando and colleagues[132] compared 32 patients who underwent SNB and 41 who underwent elective neck dissection (END) (levels I-III). Seven regional recurrences were recorded in the END group. Three neck recurrences occurred in the SNB group. No significant differences were found in DFS or OS between the groups. Fan and colleagues reported a retrospective review of 82 patients with cT1-2N0 oral tongue SCC. Thirty patients underwent SNB, and 52 patients underwent END. There was a significant difference between the SNB and END groups in the incidence of occult cervical lymph node metastasis in initial specimens (30% vs. 11.5%; p = 0.037). However, there were no significant differences between the groups for 10-year overall and cervical recurrence-free survival rates and 10-year OS rate. They concluded that. SNB is superior to END for the prediction of cervical lymph node metastasis in patients with cT1-2N0 oral tongue SCC. Neck dissection may be avoided in SLN-negative patients, owing to the comparable prognosis of SNB.

In a Dutch multi-centric trial by Flach and associates,[133] patients were consecutively enrolled from 4 institutions, with T1/T2 oral cancer and cN0 neck based on palpation and ultrasound guided fine-needle aspiration cytology. SLN negative patients were carefully observed, SLN positive patients were treated by neck dissection, radiotherapy or a combination of both. Twenty of 62 patients (32%) had positive SLNs. Macrometastases were found in 9 patients, micrometastases in 8, and isolated tumor cells in 3 patients. Median follow-up was 52.5 months. Of the 42 SLN negative patients, 5 developed a regional recurrence of which 4 patients could be successfully salvaged. DFS, OS and DSS of SLN negative patients were 72.0%, 92.7% and 97.4%, and for SLN positive patients these numbers were 73.7%, 79.7%, 85.0%, respectively (DFS: p = 0.916, OS: p = 0.134, DSS: p = 0.059, respectively). Neck control rate was 97% in SLN negative and 95% in SLN positive patients. They concluded that SNB is able to reduce the risk of occult lymph node metastases in T1/T2 oral cancer patients from 40% to 8%, and enables excellent control of the neck.

Morbidity Related to SNB

The morbidity of elective neck dissection is well studied. Common problems are shoulder dysfunction, pain, paresis/paralysis of the marginal branch of the facial nerve, scar, postoperative sensory deficits. SNB is described as a minimally invasive procedure. It is assumed to be a less morbid procedure. Schiefke and colleagues[134] reported a cross-sectional retrospective study. The study measured 24 patients who had SNB for oral cavity cancer and 25 patients who underwent elective neck dissections of levels I-III for oral cavity, oropharyngeal, and 1 hypopharyngeal cancer. Data were taken for health related and disease-specific QOL measurements, depression and anxiety scales, as well as functional measurements relating to shoulder function, hypoglossal and facial nerve function, scarring, sensory function, and lymphedema. Reduced shoulder dysfunction, sensory disturbance, and impairment from cervical scars were noted in the SNB cohort. QOL measurements indicated similar health-related QOL but a reduction in swallowing subscales on the disease-specific measurements in patients who underwent elective neck dissection. A similar decrease in functional morbidity was noted in a study by Murer and co-workers,[135] comparing 62 patients undergoing SNB alone (n = 33) versus elective neck dissection for a positive SNB (n = 29). Reductions in shoulder function, increased postoperative complications, and longer incisions were noted in patients undergoing neck dissections compared to those undergoing SNB alone. Hernando and colleagues,[132] in a recent study, compared postoperative morbidity in patients who had undergone SNB and END. Seventy-three consecutive patients were included. Shoulder function, length of surgical scar, and degree of cervical lymphedema were assessed. Neck hematoma and the presence of oro-cervical communication were also analyzed. Thirty-two patients underwent SNB and 41 underwent an END (levels I-III). There were statistically significant differences between the groups in shoulder function and average scar length, favoring SNB. However, differences in degree of lymphedema were not statistically significant. Neck hematomas and oro-cervical communications occurred only in the END group. The findings from these limited studies show that SNB is less morbid than a selective neck dissection.

Advantages of SNB

The key advantages of SNB over SND are decreased morbidity, improved identification of "skip" metastases, and improved histologic evaluation of surgical specimens. The decreased morbidity relates to a more limited dissection, placing fewer structures at risk while still providing adequate diagnostic material. The ability to identify "skip" metastases and unpredictable lymphatic drainage patterns is another advantage of SNB. In 2006, Civantos and colleagues[136] showed that 14 of 103 (13.6%) cases revealed sentinel nodes outside expected lymph node basins. They comment that these nodes would not have been dissected with standard neck dissection. A third advantage of SNB is related to the pathologic handling of the specimen. Although SND examines more lymph nodes, the specimen is embedded and sectioned in total, but only single sections are studied. Missed micrometastases often occur. In contrast, step sectioning of the entire sentinel lymph node(s) followed by systematic staining with H&E and immunohistochemistry can be performed for the small numbers of nodes harvested with SLN biopsy, thus enhancing identification of microscopic disease.[129]

Disadvantages and Limitations of SNB

There are five main limitations of SNB:

1. *Lack of confirmatory data.* Apart from few prospective trials, much of the data are single-center retrospective studies.
2. *Weakness in assessing floor-of-mouth (FOM) tumors.* The obvious drawback of SNB is its poor performance identifying

true sentinel nodes in patients with FOM tumors due to shine-through radioactivity caused by the close proximity in anatomy, thus masking signal from the relevant sentinel node(s).[129] This could be overcome by excising the primary tumor first. Part of the problem is also due to the properties of the radiolabeled agent. The detection of the sentinel lymph node is more difficult in patients with FOM cancers; the sentinel lymph node(s) are harvested successfully in 88% of cases, compared to 96% for tumors in other sites of the oral cavity. Likewise, sensitivity of SNB is lower for FOM tumors compared with other sites (80% vs. 97%).

3. *Surgeon's learning curve.* The success rate of identification of the SLN is dependent on the experience of the surgeon. The recommendation of cutaneous melanoma is 30 cases.[78] Ross and colleagues[104,105] noted that in experienced hands, the SLN detection rate was 96%. However, for surgeons who had performed fewer than 10 operations, the successful SLN detection rate was only 57%.
4. *Operating room logistics for performing the procedure, as well as performing the completion neck dissection if the SLN biopsy is positive.* The sulfur colloid agent injection into the primary tumor site and lymphoscintigraphic imaging of the neck must be performed within minutes to several hours. Additionally, SLN biopsy ideally is performed within 3 to 6 hours from the time of injection. This imposes challenges related to operating room management and coordination with the nuclear imaging service.
5. *Lack of spatial resolution of the gamma camera.*[137] One of the major limitations of the current single-photon emission CT (SPECT) scans used in lymphoscintigraphy is the limited spatial resolution. Novel methods for SLN detection, such as magnetic resonance lymphangiography using a carbon dye labeling technique[138] and use of SPECT-CT, are presently under investigation to improve the spatial resolution of the lymphoscintigraphy technique.[139]

Another issue is the prognostic significance of the micrometastases. Micrometastasis and molecular staging are found to have clinical significance in melanoma.[140] It has been recommended that an intensive search be undertaken for small foci of lymph node metastasis in head and neck cancer.[117] The clinical significance of occult metastasis in head and neck cancer is not well established. There is difference of opinion in literature regarding its prognostic significance. Although some studies showed no difference in outcome of patients with macro- or micrometastases,[141] a few others[142] have shown some prognostic value of micrometastases. However, larger studies with long-term follow-up are required to address this issue. If SNB is negative for micrometastasis, there is a high chance that the rest of the neck nodes will be negative as well. If SNB is positive, how many and which other neck nodes, if any, would harbor metastasis is not clearly established. For melanoma, Morton[143] showed that less than 1% of patients had disease in non-sentinel nodes when micrometastasis was present in the SLN. So in those patients, SNB only would be enough, avoiding further nodal dissection. There are no prognostic indicators available in head and neck cancer that can predict the presence of micrometastases in the rest of nodes when micrometastasis is present in the SLN.

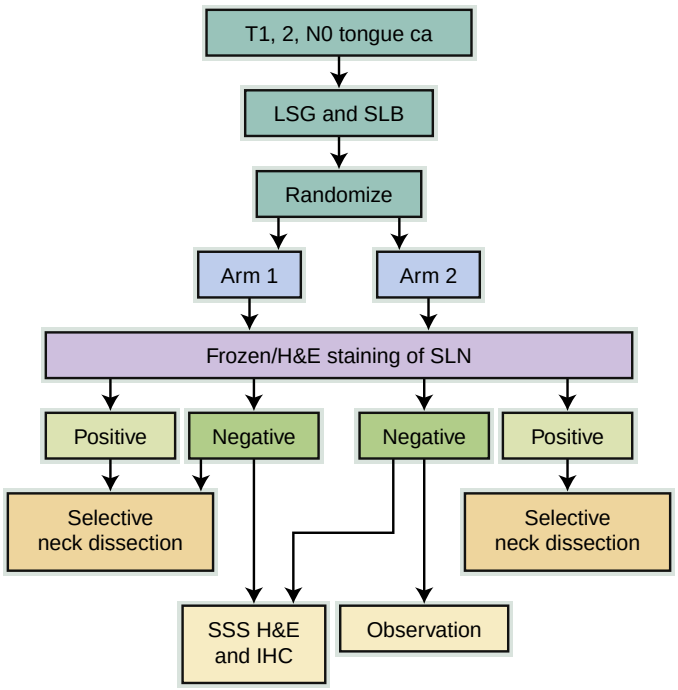
Recent Developments

A PET tracer, zirconium-89 nanocolloidal albumin, dedicated to lymphatic mapping and sentinel lymph node detection using high-resolution PET-CT was developed recently. Compared with gamma-based techniques, improved detection and precise localization of SLNs could be achieved on PET-CT in recently conducted clinical feasibility studies. PET-CT was able to identify sentinel lymph nodes close to the injection site and lymphatic vessels, which were not visualized on SPECT-CT.[144] For better use of SLN biopsy, it is essential to develop a novel technology that can detect smaller deposits in SLNs intraoperatively. Technical innovations to improve intraoperative SLN localization include intraoperative real-time imaging, freehand SPECT, and fluorescence imaging. Intraoperative real-time imaging with the portable gamma camera provides an overview of all radioactive spots and can show SLNs near the injection site by adjusting its position.[145] Also, it can provide certainty about the completeness and accuracy of SLN excision by showing the remaining activity. Freehand SPECT can determine the position of the detector relative to the patient through generated 3D images. This provides information about the direction and depth of the sentinel lymph node in relation to the probe. The possibility of generating images in the operating room after removing the sentinel lymph nodes, but before closing the wounds, may be useful for confirming harvesting of all hotspots. Promising results in patients with OSCC have been reported.[146] Near-infrared (NIR) fluorescence imaging may also be a very attractive option to facilitate intraoperative detection. The feasibility of NIR fluorescence-guided sentinel lymph node detection has been demonstrated in head and neck cancer, where indocyanine green was used as the fluorescent tracer.[147] Other tracers with improved optical properties have been tested in HNSCC in preclinical settings.[148] The clinical use of these agents is still to be evaluated.

Van den Berg and colleagues[147] reported on a small study of 14 patients with OSCC who were peritumorally injected with ICG-^{99m}Tc-nanocolloid. They concluded that combined preoperative SLN identification and intraoperative radio- and fluorescence guidance during SLN biopsies for oral cavity cancer proved feasible using ICG-^{99m}Tc-nanocolloid. The addition of fluorescence imaging was shown to be of particular value when SLNs were located in close proximity to the primary tumor. Intraoperative ultrarapid IHC and intraoperative real-time reverse transcriptase-polymerase chain reaction (RTPCR) evaluation[149] may aid in the future to improve the sensitivity of intraoperative detection of occult metastasis.

A Randomized Comparison with SND: The Need and the Hurdles

There are very few prospective studies on SNB. Of these, even fewer have specifically looked into the efficacy of SNB compared to SND. There exists a need for randomized controlled trials comparing the SNB-directed approach to that of SND. The authors have completed a randomized controlled clinical trial, and the results are expected. Fig. 9.12 shows the



• **Fig. 9.12** Randomized trial schema from authors' institution. The trial has completed accrual and the results are expected. *ca,* cancer; *H&E,* hematoxylin and eosin; *IHC,* immunohistochemistry; *LSG,* lymphoscintigraphy; *SLB,* sentinel lymph node biopsy; *SLN,* sentinel lymph node; *SSS,* serial step sectioning.

study schema of the trial. The primary objective of this trial was also to see the diagnostic efficacy of the procedure. But the oncologic efficacy was also studied, though the study was not sufficiently statistically powered to do so. The sample size limitations may be a hindrance to the ability of such a study to prove the non-inferiority of SNB to SND. To prove non-inferiority of SNB over SND, with an assumption of risk of neck failure in the standard arm (SND) as 10% and a margin of risk of neck failure in the test arm (SNB) as 5% on either side, the minimum sample size required in each arm would be 650 patients.[150]

Conclusion

There are no methods presently available that can accurately predict the negative status of neck nodes other than by pathologic analysis of SND. SNB with lymphoscintigraphy is a potential tool to stage patients with clinically N0 neck nodes. The advantage is the reduced morbidity and better cosmetic outcomes. SNB is studied most in patients with previously untreated early-stage (T1-T2) oral cavity cancer with clinical N0 stage. As in other solid tumors, existing data suggest that the status of the SLN predicts the pathologic stage of the nodal basin. The procedure is technically demanding, especially in FOM cancers. The isolated SLN should be subjected to SSS and staining by H&E and IHC. Intraoperative frozen section and imprint cytology are not sensitive enough to identify small foci of micrometastasis and ITCs within the SLN. The clinical relevance of micrometastasis and ITC needs to be established. The accuracy of SNB has been tested in multiple single-center studies and two multicenter trials. The pooled data showed an overall sensitivity of 93%. Negative predictive values ranged from 88% to 100%. There exists no randomized clinical trial with adequate power comparing SNB and elective neck dissection in oral cancer. Though established guidelines have recommended SNB for early-stage tongue cancers, confirmatory data still do not exist to support its routine use in the management of the N0 neck.

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10 Microvascular Surgery

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Defects of the head and neck present a unique reconstructive challenge given the important anatomic structures in close proximity and the functional and esthetic aspects that must be considered. These patients have to contend with the emotional and psychological issues related to their cancer diagnosis and treatment, as well as the morbidity associated with their ablative and reconstructive surgery. The importance of choosing the most appropriate reconstructive option is vitally important in head and neck cancer patients given the effect it has on the patient's self-image, ability to carry out basic life needs (nourishment, breathing, talking), and overall quality of life.

Microvascular free flap surgery was performed in the 1960s by Suarez and Jacobson, who were the first to use a microscope to anastomose two vessels.[1] Despite the availability of free tissue transfer since the early 1970s, most head and neck flap reconstructions were done using local and regional flaps until the late 1980s, as early series of free flaps sometimes reported a high risk of free flap failure, leading to the slow adoption of the procedure.[2] This changed, however, once free flaps were shown to be safe and reliable, after which microvascular free tissue transfer became widely applied for head and neck reconstruction. A major advantage of free tissue transfer arises from the ability to select a flap that has tissue characteristics that can be matched to the defect site, thereby optimizing functional and esthetic outcomes. The high success rate of modern microvascular surgery along with the versatility and functionality of the various free flaps available make this the preferred reconstructive option for many head and neck defects.

Selection of Method of Reconstruction

When considering options for management of wounds in the head and neck, surgeons have traditionally relied on a reconstructive ladder, which proceeds from least complex to most complex. Healing by secondary intention often works well for smaller defects that lie over rigid surfaces that are unlikely to become distorted through the process of scar contracture. The next step up the ladder consists of simple primary closure for wounds that can be directly reapproximated. Delayed primary closure may be used for infected wounds or wounds that need time to "declare" their full extent before closure. Continuing up the ladder, skin grafting is the next option and includes both full-thickness and split-thickness grafts. This is followed by tissue expansion, which necessitates the implantation of an expander to progressively dilate local tissue to be used in reconstruction. The next step up the ladder is local flaps, including advancement, rotation, and transposition flaps. Regional pedicled flaps are next, including the deltopectoral flap, the pectoralis major flap, the latissimus dorsi flap, the supraclavicular artery island flap, and the trapezius flap. Local and regional flaps were the workhorse methods for reconstruction of major head and neck defects from the 1960s through the 1980s. The pinnacle of the reconstructive ladder and most complex choice for defect repair involves free tissue transfer. This technique has been refined over many years and has become a reliable and effective method of reconstructing complex head and neck defects.

The choice of which method to use from the reconstructive ladder depends on several factors. The nature of the defect should be considered, and attempts should be made to replace missing tissues with like tissues. The overall health of the patient, donor site morbidity of graft sites, and patient desires must all be considered, as well. In addition, prior radiation and surgery can compromise vascular supply and limit the use of reconstructive techniques that depend on local blood supply. Given the numerous considerations involved in choosing a reconstructive method, the simplest repair is not always the best choice. This is evidenced by the increased popularity of free tissue transfer for repair of low-volume but critical defects. It is now apparent that despite their reliance on microvascular anastomoses, free flaps are often inherently more reliable than pedicled flaps owing to their more robust blood supply. As surgeons push the arc of rotation of local and regional flaps, the blood supply to the distal edge of the flap becomes more tenuous, resulting in an increased risk of distal tip flap necrosis. It is documented that the risk of partial flap necrosis for regional flaps commonly used for head and neck reconstruction often falls in the range of 10–20%.[3-7] Even though microvascular

procedures often require more time and surgical skill, they often provide superior functional and esthetic results with reduced wound-healing complications when compared with regional pedicled flaps.

Surgical Planning and Preoperative Considerations

The first step in planning microvascular free tissue repair of a head and neck surgical defect involves consideration of the nature of the defect. The characteristics of the defect should usually be the primary determinant of the flap donor site. In analyzing a defect, it is often helpful to consider the soft tissue, bone, and neurologic components of the defect, and then select a flap donor site that has characteristics that best provide compensation for or replacement of the components of the defect. In addition, selection of a flap that offers a long vascular pedicle containing large-caliber blood vessels contributes significantly to a successful outcome by increasing the reliability of the flap. Although most of the surgical planning is done before the procedure, microvascular surgeons must be prepared to make changes intraoperatively if the defect is different than anticipated.

A careful assessment of patient comorbidities should be undertaken to help stratify the risk of perioperative complications. Prior studies have shown a strong correlation between the presence of comorbidities and the risks of postoperative complications in microvascular head and neck reconstruction.[8,9]

Careful attention should especially be paid to cardiac comorbidities, as perioperative myocardial infarction has been shown to lead to a significant risk of postoperative death.[10] In some cases, less complex methods of reconstruction should be considered in patients with high levels of comorbidity, even though this may sometimes result in an increased risk of wound-healing complications and impaired functional or esthetic outcomes.

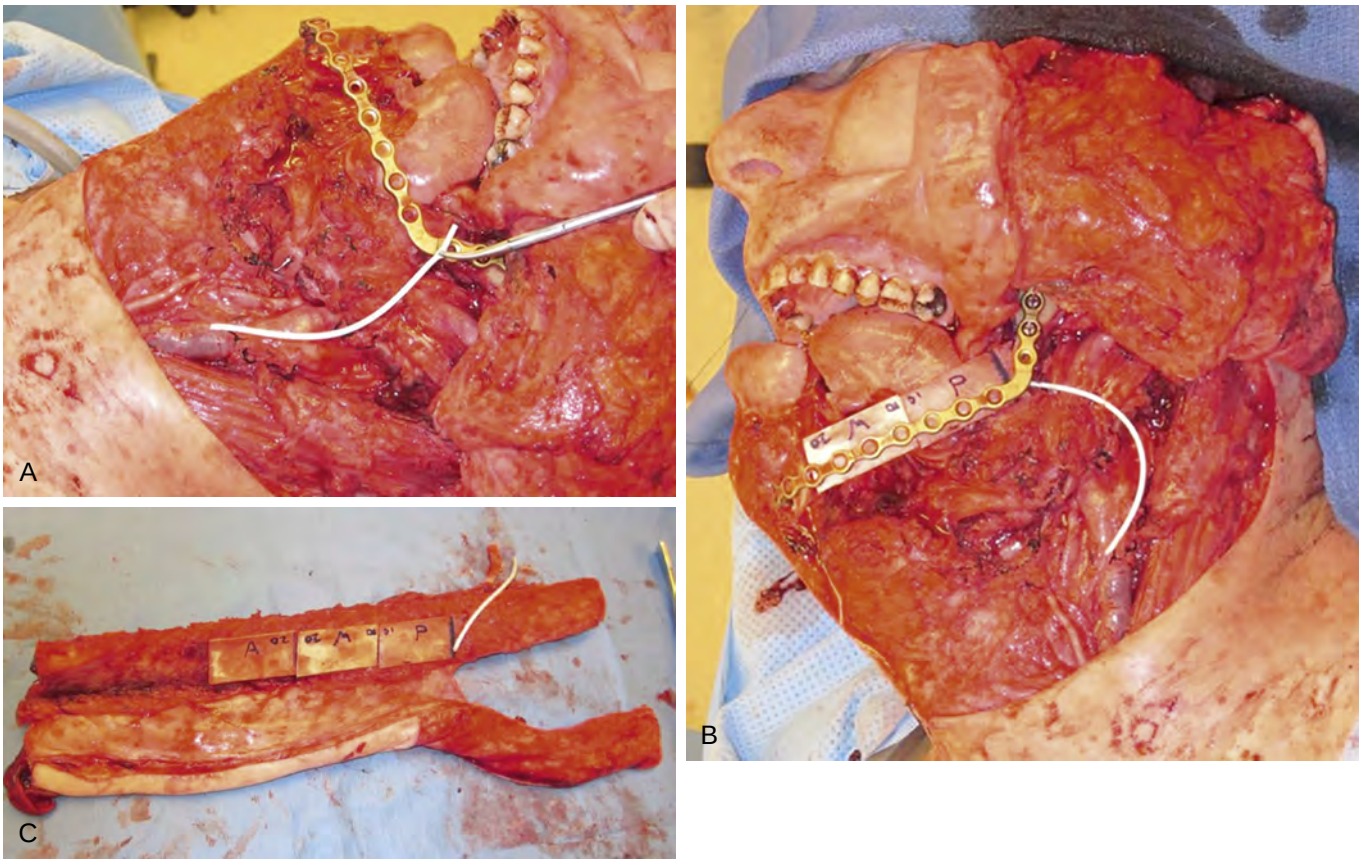
Because many patients who undergo free flap reconstruction after resection of head and neck cancer are being treated for advanced stage or recurrent cancers, it is important to consider the patient's cancer-related prognosis when considering the method of reconstructive surgery.[11] In patients with a poor prognosis who are at risk for experiencing early cancer relapse, consideration should be given to using methods of reconstruction that provide a rapid recovery after surgery. For instance, not all patients should be recommended free flap reconstruction after partial maxillectomy. When the defect is favorable for use of an obturator, consideration for prosthetic rehabilitation should be made in patients with a poor prognosis, because rehabilitation with an obturator will be completed much sooner that an osseous reconstruction with subsequent placement of dental implants.

Preoperative imaging should be obtained if indicated. Magnetic resonance angiography, computed tomography (CT) angiography, or Doppler ultrasonography is indicated for the evaluation of lower limb vasculature before fibula free flap surgery.[12,13] Congenital anomalies that result in absence of the anterior and/or posterior tibial artery are known to occur in about 5% of patients, and in these cases the perfusion territory of the absent blood vessels is usually supplied by the peroneal artery (see Fig. 10.10D). Affected patients will often have normal pedal pulses and no symptoms of peripheral vascular disease. In cases of salvage surgery after prior neck dissection, it is helpful to have a contrast-enhanced CT scan of the neck or Doppler ultrasonography to evaluate for potential recipient vessels.[14] CT imaging can also be used for virtual planning of the proposed surgery, which enables prefabrication of osteotomy cutting guides and customized hardware in cases of oromandibular and palatomaxillary reconstruction. All patients who undergo radial forearm flap reconstruction should undergo an Allen test before surgery to assess the adequacy of blood flow to the hand that is provided by the ulnar artery while the radial artery is compressed. In patients with an equivocal Allen test result, Doppler ultrasonography of the radial and ulnar artery is indicated to confirm that removal of the radial artery will not cause ischemia in the hand.

Intraoperative and Postoperative Considerations

Good communication among the surgeons, the anesthesiologists, and the nursing staff is critical to perform microvascular head and neck reconstructive surgery safely and efficiently. Two-team surgery for simultaneous tumor resection and free flap harvest is desirable, because two-team surgery can frequently shorten the overall length of surgery by a couple of hours. However, with two-team surgery, close communication between the ablative and reconstructive teams to discuss the anticipated nature of the defect and preservation of potential cervical recipient vessels is of paramount importance. Patient positioning, padding of pressure points, selection of sites for vascular access that do not interfere with flap donor site wounds, and communication regarding airway management should be discussed before the patient is brought to the operating room. Intraoperative use of warming blankets and patient temperature monitoring are important to avoid hypothermia, which might induce systemic vasospasm. Although it is important to maintain a sufficient perfusion pressure, it is traditionally recommended that intraoperative and postoperative vasopressor agents that might cause vasospasm of the flap vascular pedicle be avoided if possible, although the actual clinical impact of vasopressor agents on free flap perfusion is uncertain.[15]

Probably the most important factors that contribute to a successful outcome in microvascular head and neck reconstructive surgery arise from the use of free flap donor sites that offer large-caliber blood vessels and long vascular pedicles, combined with intraoperative considerations to achieve a favorable pedicle geometry that prevents vessel compression and kinking. The ideal vascular pedicle should be long enough to not put tension on the anastomosis, but not so long that the vessels will kink owing to redundancy. This consideration is more important for the venous pedicle, given its thinner vessel wall,



• **Fig. 10.1** **A,** Left mandibular defect with a white Vessiloop being used as a template to determine the ideal length of the fibular flap's vascular pedicle to reach the common facial side branch of the internal jugular vein, which will be used as the recipient vein to perfuse the flap. **B,** A wooden tongue depressor is used to make templates of the desired fibular bone graft segments. **C,** The Vessiloop and tongue depressor templates are used to contour the fibula flap. The Vessiloop is used to determine the location of the position of the fibula bone graft segments, thereby producing an ideal length and geometry of the flap's vascular pedicle. Repositioning the fibula bone graft segments toward the distal fibula would produce a vascular pedicle that would be too long and prone to kinking. Repositioning the fibula bone graft segments toward the proximal fibula would produce a vascular pedicle that would be too short and prone to cause tension across the microvascular anastomoses.

which is more prone to kinking. Typically this is less of a concern for the arterial pedicle, which has a thick-walled vessel that is resistant to kinking. A craniocaudal orientation of the flap pedicle is less prone to kinking than an anteroposterior-oriented pedicle when the head is turned to the left or right. In head and neck reconstruction, free flap failure most frequently results from venous thrombosis that arises secondary to poor geometry of the venous vascular pedicle, which results in kinking of the venous vascular pedicle. For this reason, sufficient flap insetting to know the location and position of the vascular pedicle after insetting should always be done before flap revascularization. In addition, we make extensive use of templates of the flap and its vascular pedicle when planning flap contouring and insetting, with the goal of achieving an optimal geometry of the flap vascular pedicle (Fig. 10.1).

Hand-sewn anastomoses are the preferred method for some microvascular surgeons; however, the introduction of the venous coupling device has led to its widespread adoption thanks to its ease of use and time savings. The device is composed of two opposing polyethylene rings embedded with stainless steel prongs. The vessels are loaded into the rings with the intima facing out and then the rings are driven together and fastened. Studies have shown that the use of such a device is both safe and effective. In addition, the use of two venous anastomoses, when the opportunity exists, leads to less risk of venous congestion and need for take-back exploratory surgery.[16,17] Given that flap failure is more likely to occur from a compromised vein than from an issue with the artery, it is important to consider this when planning the use of recipient veins in the neck.

Postoperatively the patient is followed clinically by checking the flap color, turgor, and capillary refill, and the pedicle is checked with a Doppler stethoscope to confirm venous and arterial blood flow. Any signs or symptoms of flap compromise should be acted on promptly because expedient intervention is critical when treating postoperative flap ischemia. Most commonly, vascular compromise is related to venous congestion, which results in a hyperemic, darkly discolored flap that is engorged. A flap with arterial flow disruption becomes pale with decreased turgor. The microvascular surgeon should have a low threshold for returning to the operating room for exploration if vascular compromise is suspected. The high-risk period for flap compromise is usually the first 72 hours after surgery.

TABLE 10.1 Patient Demographics

	All Patients (*N* = 1500)
Age, mean (standard deviation [SD])	61.7 (13.9)
Females, *N* (%)	506 (33.7%)
Males, *N* (%)	994 (66.3%)
Head and Neck Defect Site, *N* (%)	
Oral cavity, oropharyngeal	1176 (78.4%)
Pharyngoesophageal	125 (8.3%)
Midface, skull base, scalp	217 (14.5%)
Flap Type, *N* (%)	
Radial forearm	576 (38.4%)
Rectus abdominis	51 (3.4%)
Subscapular system	133 (8.9%)
Fibular	646 (43.1%)
Iliac crest	5 (0.3%)
Jejunal	1 (0.1%)
Anterolateral thigh	87 (5.8%)
Gracilis	1 (0.1%)

From Seth R, Razfar A, Singh RK, et al: *A simplified approach to the microvascular head and neck reconstruction: an 18-year experience with 1500 cases*. Presented to the American Academy of Otolaryngology Head and Neck Surgery Annual Meeting, Vancouver, British Columbia, Canada, September 30, 2013.

Experience With Microvascular Head and Neck Reconstruction

To make observations regarding the indications, applications, and outcomes of microvascular flap reconstruction of the head and neck, the following is a presentation of ADB's experience with 1500 free flaps performed for head and neck reconstruction from 1995 to 2013[18] in Table 10.1.

Ninety-five percent of these flaps were used to reconstruct defects arising after resection of head and neck neoplasms, with 95% of those neoplasms being malignancies. Overall, 77% of the defects involved the oral cavity and/or oropharynx. The single most common indication for free flap reconstruction of the head and neck was a segmental defect of the mandible. This indication accounted for about 40% of the cases.

Although dozens of different free flaps have been described in the medical literature, it should be noted that only five types free flaps accounted for 99% of the cases performed. These included fibular flaps, radial forearm flaps, subscapular system flaps, anterolateral thigh flaps, and rectus abdominis flaps. Anterolateral thigh flaps were adopted in 2005, and since that time the volume of rectus abdominis free flap procedures performed has dropped off precipitously. Currently, the senior author uses four different types of free flaps to reconstruct 99% of all defects that require microvascular reconstruction. These include fibular flaps, radial forearm flaps, subscapular system flaps, and anterolateral thigh flaps.

Free Flaps Commonly Used in Head and Neck Reconstruction

Fibular Free Flap

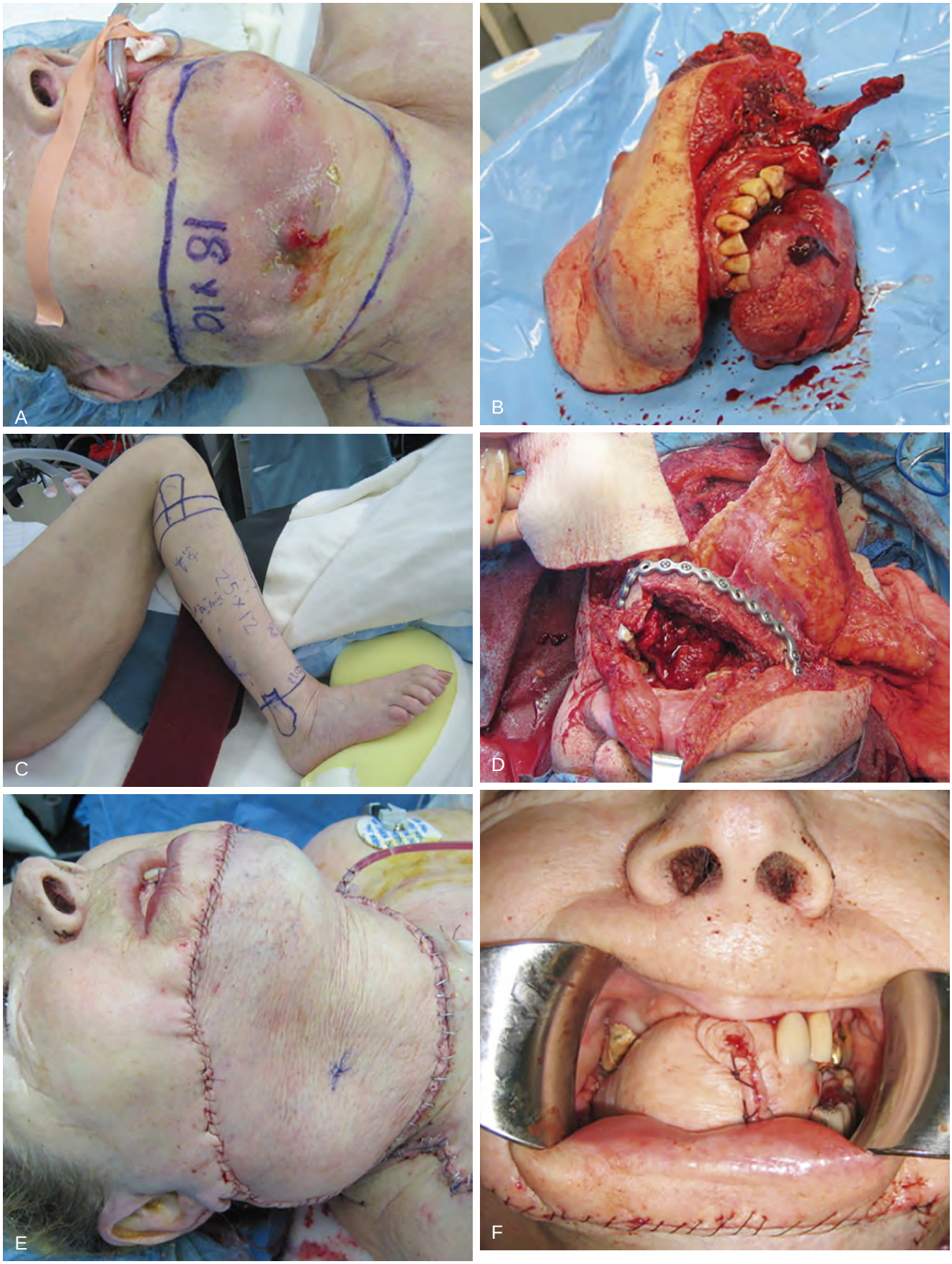
The fibular flap contains vascularized bone and has evolved to become the workhorse flap for oromandibular reconstruction, being used in about 90% of cases. It can also be used for palatomaxillary reconstruction in cases where prosthetic rehabilitation is unfavorable. Up to 25 cm of bone graft is available, depending on patient stature. The fibular flap is perfused by the peroneal artery and the paired peroneal venae comitantes. The skin paddle is perfused by cutaneous perforators for the peroneal vessels that are present in about 98% of legs. Large skin paddles and multiple skin paddles perfused by different perforators can be incorporated for reconstruction of high-volume, complex soft tissue defects (Fig. 10.2).

The advantages of the fibular flap are the availability of a long bone graft with a thick cortex that can accept dental implants (Fig. 10.3). The fibular flap has a long vascular pedicle that contains large-caliber blood vessels. In most patients, there is limited long-term donor site morbidity. The most common long-term donor site deficit is impaired great toe flexion, related to impaired function of the flexor hallucis longus muscle. Other disadvantages include a propensity for the vascular pedicle vessels to be affected by peripheral vascular disease; a hair-bearing skin paddle, especially in male patients; a relatively thin skin paddle that may lack sufficient bulk for certain high-volume soft tissue defects; and poor mobility of the skin paddle relative to the bone graft due to the relatively short cutaneous perforators.

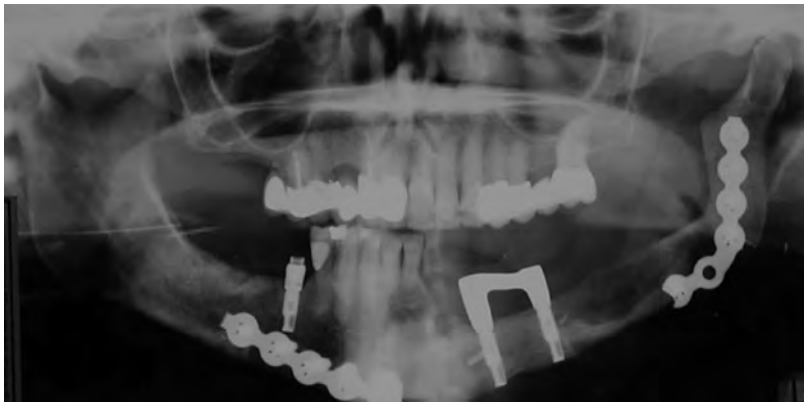
Radial Forearm Free Flap

The radial forearm flap arterial inflow is provided by the radial artery, whereas the venous outflow is provided by either the radial venae comitantes or the subcutaneous cephalic vein. The radial forearm flap is most often used as a thin fasciocutaneous flap. In the senior author's experience with 576 cases, only one osteocutaneous flap was used. Early reports indicated a significant risk of pathologic forearm fracture after harvesting of an osteocutaneous radial forearm flap that contained a monocortical segment of the radius bone. More recently, acceptable donor site morbidity has been reported after prophylactic plating of the radius bone donor site defect with a load-bearing plate.[19] But even when considering the reduced donor site morbidity with this technique, the fact remains that the thin bone graft offered by the osteocutaneous radial forearm flap is ill-suited for reconstruction of most oromandibular and palatomaxillary defects (Fig. 10.4).

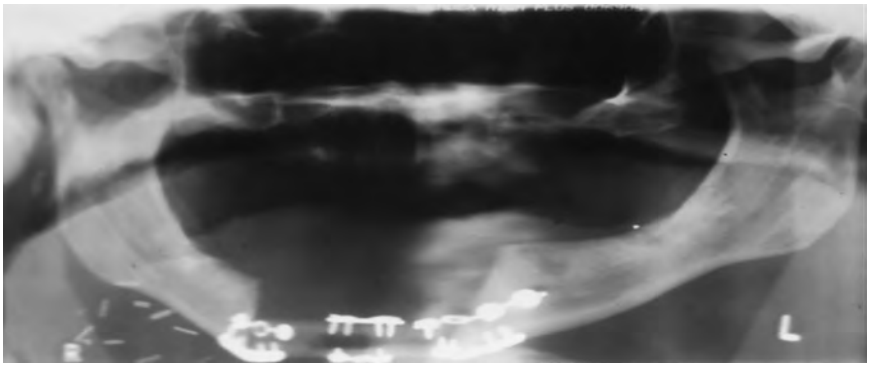
A common indication for fasciocutaneous radial forearm free flap reconstruction is for reconstruction of oral and pharyngeal defects that require a thin and pliable flap. A very common application is for reconstruction of hemiglossectomy defects, in which case the radial forearm free flap effectively restores floor-of-mouth sulcular anatomy, restores oral cavity volume, and preserves mobility of the residual tongue, thereby



• **Fig. 10.2** **A,** Advanced carcinoma of the tongue with through-and-through extension into submandibular neck and chin skin. **B,** Surgical specimen after composite resection of tongue, mandible, and neck skin. **C,** Fibular free flap is designed with a 300-cm^2 skin paddle. Three cutaneous perforators to the skin paddle were localized using a Doppler stethoscope. **D,** The fibular bone graft has been inset using a mandibular reconstruction plate. The large skin paddle had been cut into two separate skin paddles, with the distal leg skin paddle being perfused by two perforators and the proximal leg skin paddle being perfused by one perforator. **E,** The proximal leg skin paddle is used to reconstruct the excised neck skin. **F,** The distal leg skin paddle is used to reconstruct the excised portion of the tongue.



• **Fig. 10.3** Two osseointegrated dental implants have been placed into a fibular bone graft to support an implant-borne denture. Because of the relatively small height of the fibula bone graft when compared with the native mandible, a mesostructure has been placed onto the implants to bring the height of the denture up to the height of the native teeth.



• **Fig. 10.4** Postoperative panoramic x-ray study demonstrates osteocutaneous radial forearm free flap reconstruction of the mandible. Note that the radial bone graft is an extremely poor match for the resected native mandible, even in this patient with an edentulous and atrophic native mandible.



• **Fig. 10.5** Left anterolateral tongue and floor of mouth reconstruction using a radial forearm free flap helps to preserve speech articulation.

enhancing speech articulation quality (Fig. 10.5). The radial forearm flap is also commonly used as a patch or tubed flap for pharyngoesophageal reconstruction in patients who undergo total laryngectomy with partial or total hypopharyngectomy (Fig. 10.6). Overall, 85% of patients regain oral alimentation after this type of reconstruction,[20] and the quality of tracheoesophageal speech after radial forearm pharyngoesophageal reconstruction is superior to that seen after jejunal flap pharyngoesophageal reconstruction. Finally, as a sun-exposed donor site that contains thin skin, the radial forearm free flap often provides a reasonable esthetic outcome for reconstruction of facial skin defects, especially in skin cancer patients, in whom the forearm skin often has similar actinic changes as those seen in the face (Fig. 10.7).

The extreme reliability of the radial forearm flap should be considered as one of its primary advantages. In the senior author's experience with 576 cases, there was a 0% incidence of free flap failure and a 0.3% incidence of partial flap necrosis. The extremely high reliability of the radial forearm flap should be taken into account when considering "simpler" methods of reconstruction using local or regional fasciocutaneous flaps, such as the pedicled supraclavicular island artery flap and submental island artery flap, in which the risk of flap necrosis may be higher.[7] The primary disadvantage of the radial forearm free flap relates to the forearm donor site defect. The risks of skin graft failure, tendon exposure, and delayed forearm wound healing can be mitigated by performing a suprafascial dissection during flap harvest, or by covering the flexor carpi radialis

tendon using a local flexor digitorum superficialis myofascial flap. Although objective testing often reveals long-term motor and sensory disturbance in the hand after radial forearm free flap harvest, this frequently does not correlate with patient reported subjective complaints, which are generally limited.[21] Probably the most common donor site complaint relates to the esthetic appearance of the donor site wound, which can be improved by using a thick skin graft and local flexor digitorum superficialis myofascial flap during the reconstruction of the forearm donor site wound (Fig. 10.8).



• **Fig. 10.6** Total laryngopharyngectomy defect is being reconstructed using a radial forearm free flap that is being tubed over a salivary bypass tube.

Subscapular System Free Flap

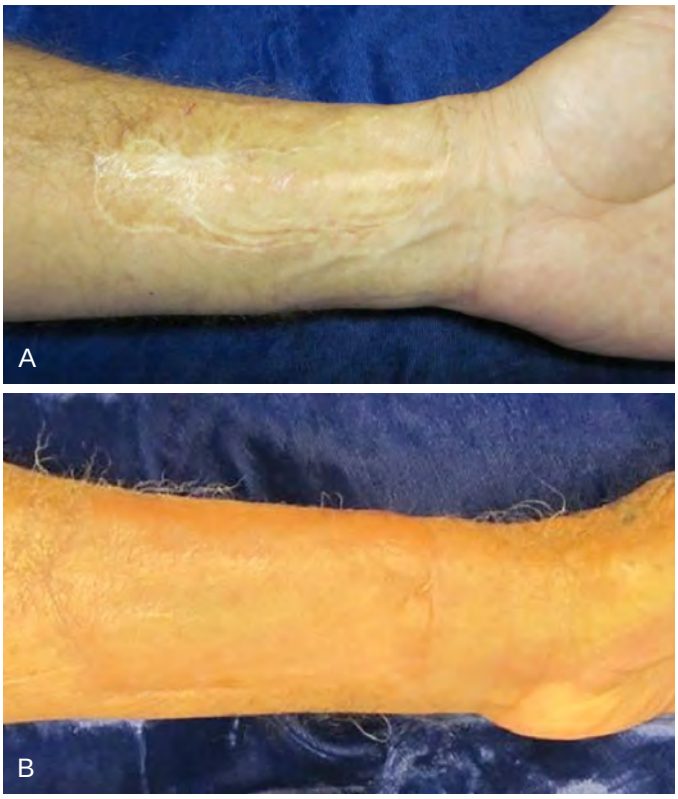
The subscapular system free flaps provide a wide variety of bone and soft tissue grafts for transfer based on a single vascular supply. Available flap components include the scapular and parascapular fasciocutaneous flaps, the latissimus dorsi myofascial or myocutaneous flap, the serratus anterior myofascial flap, the teres major myofascial flap, the lateral border of the scapula bone graft, the scapular tip bone graft, and vascularized rib bone grafts. The subscapular artery and vein are branches of the axillary artery and vein. The circumflex scapular artery arises as a posterior branch of the subscapular artery and supplies periosteal branches to the lateral border of the scapula. The distal tributaries of the circumflex scapular artery supply the scapular and parascapular skin paddles. The thoracodorsal artery arises as a descending branch of the subscapular artery. It gives off a posterior angular branch that supplies the teres major muscle and tip of the scapula bone and an anterior branch that perfuses the lower slips of the serratus anterior muscle and ribs. The terminal portion of the thoracodorsal artery supplies the latissimus dorsi muscle.

The primary indications for subscapular free flaps include (1) reconstruction of oromandibular and palatomaxillary defects, frequently in cases in which use of a fibular flap is precluded by lower extremity peripheral vascular disease[22] (Fig. 10.9); (2) reconstruction of complex three-dimensional defects that require multiple different tissue components perfused by independent peripheral branches of the subscapular vessels (Fig. 10.10); and (3) reconstruction of high-volume or large surface area defects, such as scalp defects (Fig. 10.11).

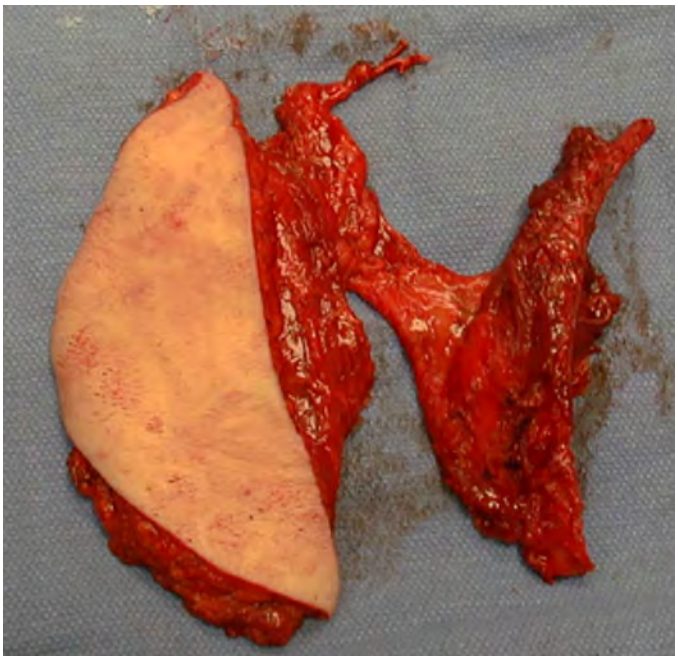
The advantages of subscapular system flaps arise from the multiple tissue components that are available, allowing for reconstruction of a large number of different types of



• **Fig. 10.7** Side-by-side comparison of cheek skin reconstructions using radial forearm and fibula free flaps. The radial forearm flap reconstruction offers a superior esthetic outcome with regard to matching the color, texture, and actinic changes seen in the native facial skin.



• **Fig. 10.8** **A,** Postoperative appearance 5 years after a radial forearm free flap donor site was reconstructed using a 0.016-inch-thick split-thickness skin graft. Note the visible scarring and prominent contour of the flexor carpi radialis tendon. **B,** Postoperative appearance 1 year after a radial forearm free flap donor site was reconstructed using a 0.020-inch-thick split-thickness skin graft and a local flexor digitorum superficialis myofascial flap was used to cover the flexor carpi radialis tendon. Note the improved scarring and inconspicuous contour of the flexor carpi radialis tendon.



• **Fig. 10.9** The latissimus dorsi serratus anterior vascularized rib flap is the senior author's most common type of free flap used for oromandibular and palatomaxillary reconstruction in patients who cannot undergo a fibula flap procedure because of lower extremity peripheral vascular disease. It contains a latissimus dorsi myocutaneous component *(left)* and a serratus anterior rib myo-osseous component *(right).* It has several advantages over use of subscapular system flaps that contain the lateral border of the scapula bone perfused by the circumflex scapula vessels, including a longer vascular pedicle, a longer available length of bone graft, and the ability to harvest the latissimus serratus rib flap while the patient is positioned supine, thereby facilitating simultaneous two-team surgery.

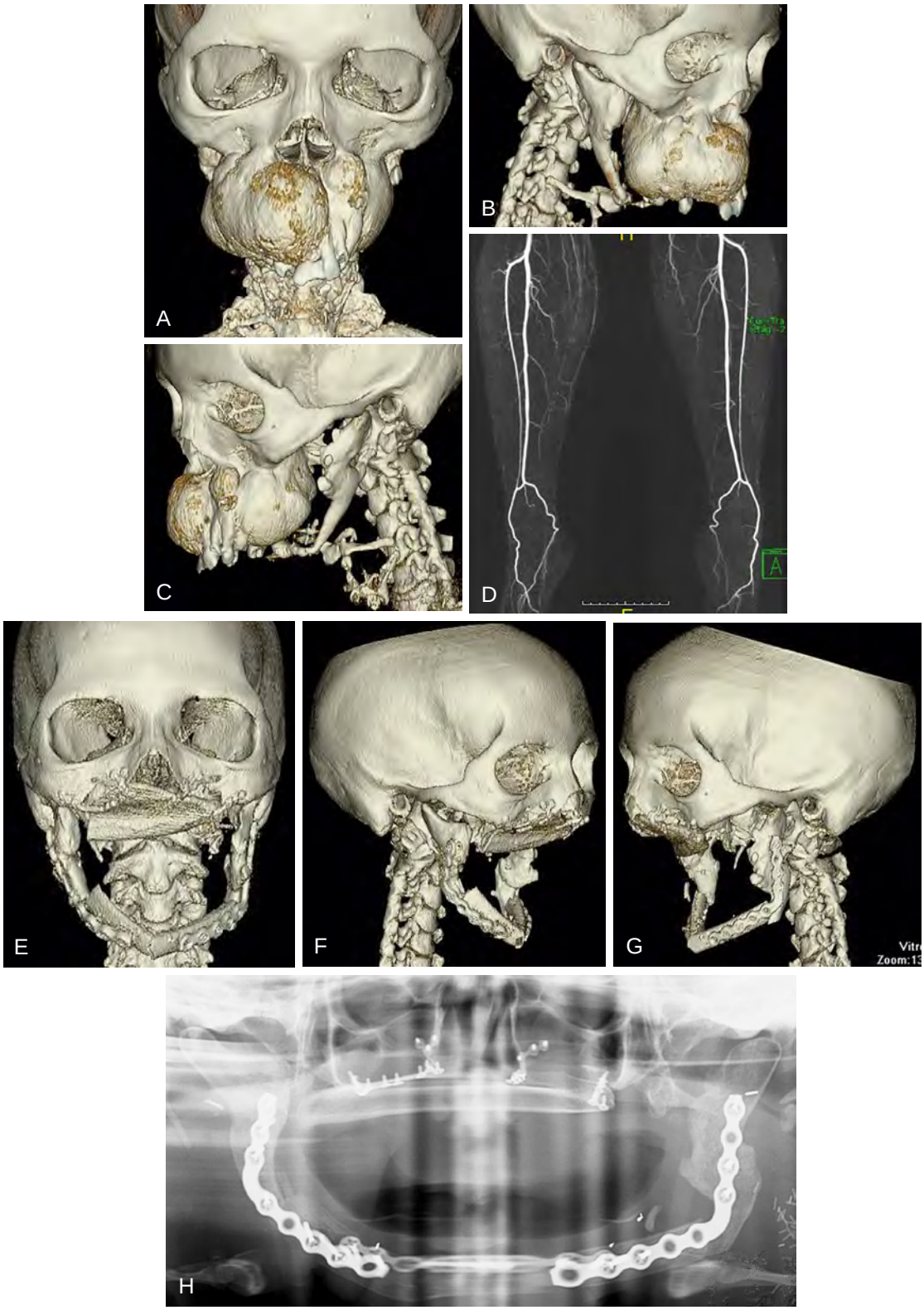
defects, very complex defects, and large defects. In addition, the subscapular vessels are rarely affected by peripheral vascular disease in patients who cannot undergo harvest of a fibular flap owing to peripheral arterial disease of the legs. Disadvantages include the need for partial lateral decubitus positioning during flap harvest, which can make the two-team approach more difficult, as well as the potential for short pedicle length for flaps that are perfused by the circumflex scapular vascular pedicle. For these reasons, flaps perfused by tributaries of the thoracodorsal vascular pedicle are used more frequently than the circumflex scapular vessels. Finally, scapular bone and rib grafts may not provide for sufficient bone stock for placement of dental implants in patients who undergo oromandibular and palatomaxillary reconstruction.

Anterolateral Thigh Free Flap

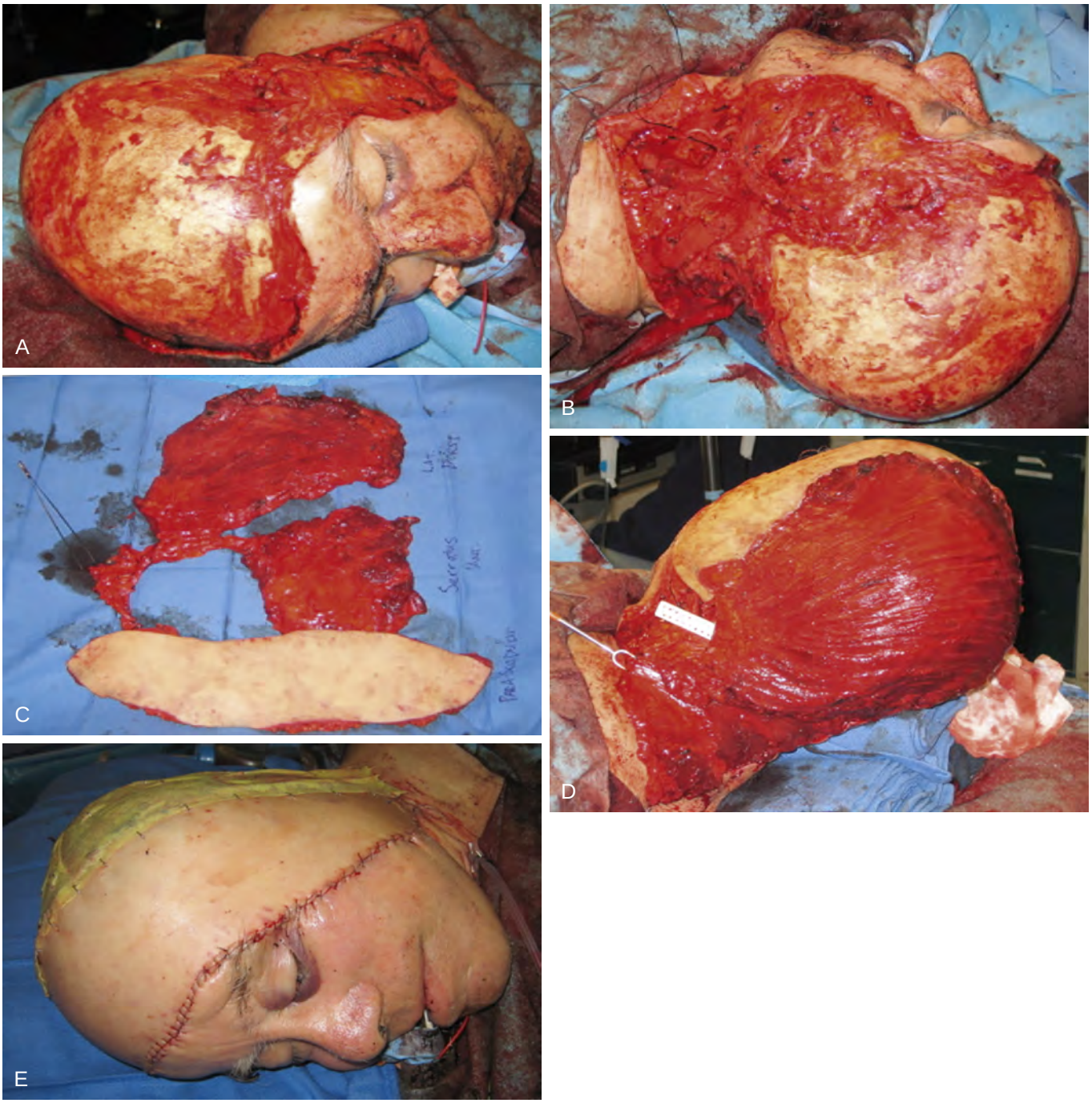
The characteristics of anterolateral thigh flaps vary considerably depending on the patient's body habitus. As a result of this flap variability, the indications and applications of anterolateral thigh flaps vary according to body habitus. In thin patients, the tissue is often thin and pliable, so in this patient population, anterolateral thigh flaps are often used in a fashion that is similar to the application of radial forearm flaps for reconstruction of the oral cavity and pharyngoesophageal defects (Fig. 10.12). Obese patients often have thicker flap tissue that is better suited for reconstruction of high-volume defects of the skull base and midface, as well as for total glossectomy reconstruction (Fig. 10.13).

The blood supply of the anterolateral thigh free flap is provided by the lateral circumflex femoral artery and vein. In 80–90% of cases, the blood supply to the anterolateral thigh free flap arises from the descending branch of the lateral circumflex femoral vessels; in 10–20% of cases the blood supply to the flap arises from the transverse branch of the lateral circumflex femoral vessels. In 80–90% of cases, cutaneous perforators to the skin paddle of the flap take a musculocutaneous course through the medial portion of the vastus lateralis muscle.

The advantages of anterolateral thigh flaps arise from the relative lack of long-term donor site morbidity. However, some patients may experience temporary leg weakness with some knee instability after flap harvest. Flaps wider then 8–10 cm may not close primarily and may require a skin graft for closure of the thigh donor site wound. Disadvantages of the flap arise from the thick dermis and pale skin color of the flap, which make it a poor substitute for replacement of facial skin. Among the flaps that are commonly used



• **Fig. 10.10** **A, B,** and **C,** Preoperative three-dimensional (3D) computed tomography (CT) scan shows a large hard palate ossifying fibroma in a patient who previously underwent an angle-to-angle mandibulectomy for a mandibular ossifying fibroma with unsuccessful nonvascularized iliac crest bone graft reconstruction. **D,** Lower extremity magnetic resonance imaging reveals bilateral congenital peroneal arteria magna, with aplasia of the posterior tibial arteries, hypoplasia of the anterior arteries, and peroneal arteries, which are the dominant blood supply to both feet, precluding use of a fibula flap. **E, F,** and **G,** Postoperative 3D CT scan after bilateral maxillectomy and simultaneous reconstruction of the maxilla and mandible using a subscapular system free flap. The hard palate was reconstructed using a scapula tip bone graft that was perfused by the angular branch of the thoracodorsal artery. The anterior arch of the mandible was reconstructed using a serratus anterior rib myo-osseous flap component that was also perfused by the thoracodorsal artery. **H,** Panoramic x-ray study 6 months after procedure reveals healing of the osteotomies.

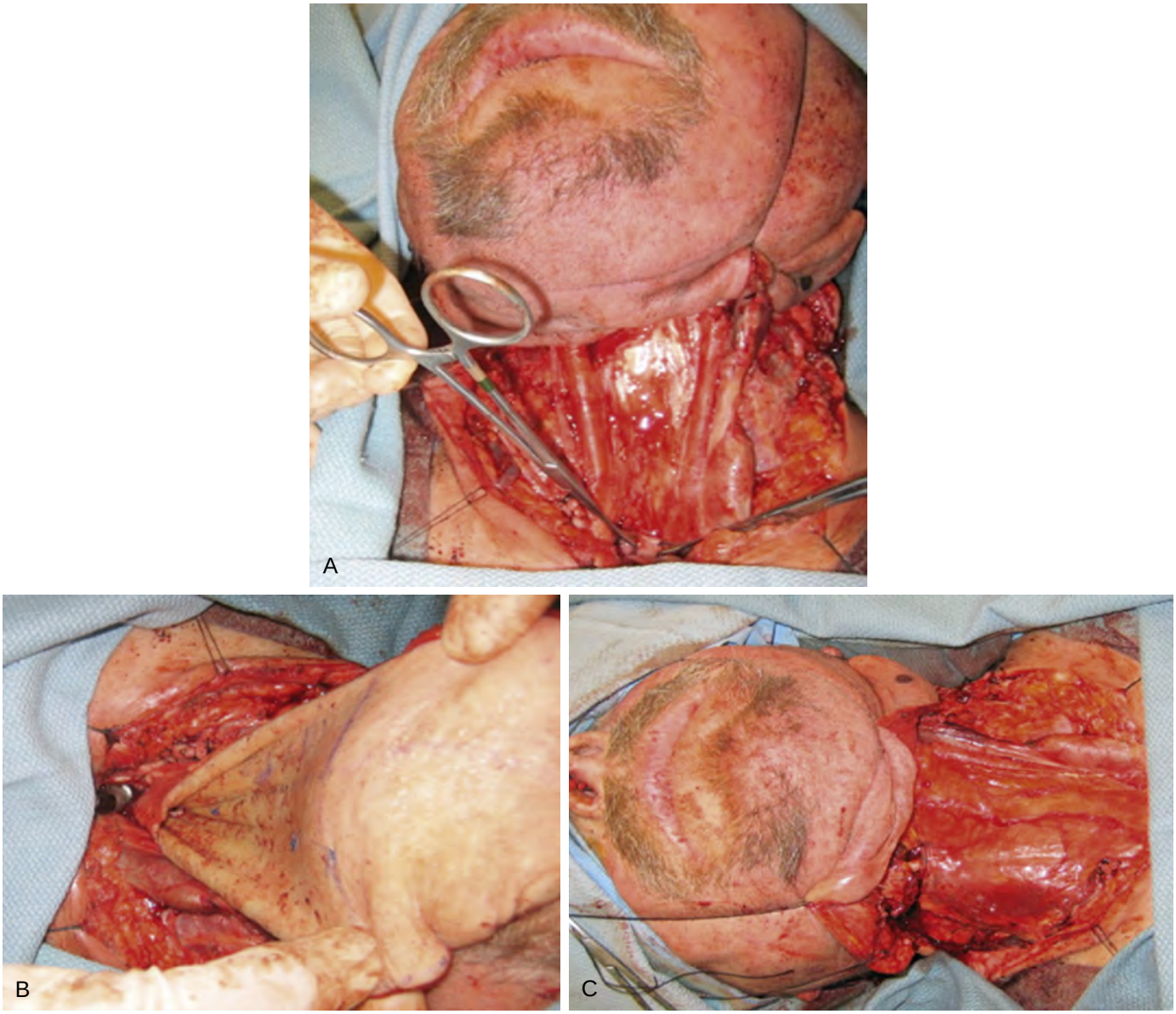


• **Fig. 10.11** **A** and **B,** Extensive defect of the face and scalp resulting after resection of a scalp angiosarcoma. **C,** A subscapular system "megaflap" has been harvested; it contains a latissimus dorsi myofascial component, a serratus anterior myofascial component, and a parascapular fasciocutaneous component. **D** and **E,** The latissimus and serratus myofascial flap components were used in conjunction with skin grafts to reconstruct the posterior aspect of the defect; the parascapular flap component was used to reconstruct the anterior aspect of the defect.

for head and neck reconstruction, the anterolateral thigh free flap is the only flap wherein normal variants of the flap's vascular anatomy are common. However, these are usually easily recognized during flap dissection. Anterolateral thigh flaps are also the only commonly used flaps for head and neck reconstruction that frequently require a musculocutaneous perforator dissection, making flap harvest slightly more challenging.

Free Flap Complications and Outcomes

In the senior author's experience with 1500 free flaps used for head and neck reconstruction performed over 18 years, the perioperative mortality was 1.3%. The overall flap success rate was 99.5% among patients who survived the postoperative period. Free flap failure occurred more frequently in fibula flaps (1.2%) versus other flaps (0%) and in women



• **Fig. 10.12** **A,** Pharyngoesophageal defect resulting after a total laryngopharyngectomy done to treat recurrent hypopharyngeal cancer after prior unsuccessful chemotherapy and radiation therapy. **B,** An anterolateral thigh flap is tubed for circumferential pharyngoesophageal reconstruction in this patient with a thin body habitus. **C,** The anterolateral thigh free flap has been inset and revascularized, thereby restoring pharyngoesophageal continuity.



• **Fig. 10.13** Postoperative appearance 2 years after total glossectomy reconstruction using an anterolateral thigh free flap.

TABLE 10.2 Microvascular Reconstruction Surgery Outcomes

Source	Institution	No. of Head and Neck Cases	Success Rate
Schusterman et al, 1994	University of Texas MD Anderson	308	94.5%
Urken et al, 1994	Mount Sinai Medical Center	200	93.5%
Jones et al, 1996	University of Pittsburgh	305	91.2%
Makitie et al, 1997	Helsinki University Hospital	313	91.5%
Simpson et al, 1996	St. James's University Hospital	150	95.0%
Chalian et al, 2001	University of Pennsylvania	156	99.4%
Disa et al, 2001	Memorial Sloan Kettering Cancer Center	728	98.6%
Wei et al, 2001	Chang Gung Memorial Hospital	1235	96.6%
Nakatsuka et al, 2003	Saitama Medical School	2372	95.8%
Yu et al, 2009	University of Texas MD Anderson	1310	98.0%
Nuara et al, 2009	Cleveland Clinic	300	99.7%
Pohlenz et al, 2012	University Medical Center Hamburg-Eppendorf	1000	94.2%
Frederick et al, 2013	University of Alabama	1051	97.3%
Beckler and Blackwell, current study	University of California Los Angeles	1500	99.5%

(1.4%) versus men (0.1%). Fourteen cases required reexploration for impaired flap perfusion, and seven cases were salvaged. The most common wound-healing complications were wound infection (4.3%), salivary fistula (4.3%), and impaired flap donor site healing (4.2%). The overall risk of partial free flap necrosis was only 0.5%, but partial flap necrosis was seen more commonly with fibula flaps (4.8%) than with other flaps. Pulmonary edema and supraventricular tachycardia were the most common medical complications occurring after free flap reconstruction. Patient comorbidity level significantly correlated with the risks for overall complications and medical complications, and wound-healing complications significantly correlated with a history of prior surgery.[2]

Microvascular Surgical Outcomes

Advances in microsurgical techniques and increased experience have made this reconstructive technique reliable and successful. Table 10.2 lists large series of microvascular head and neck reconstruction.[23-35]

This combined experience indicates that in the 21st century, free flaps have proven to be extremely reliable, having a cumulative success rate of about 97% among 9652 cases.

Summary

Microvascular surgery has advanced significantly since the first techniques were pioneered in the 1960s. Many of the older methods that were traditionally used for reconstruction of head and neck defects, including local and regional pedicled flaps, have been replaced by free flaps that contain tissue components that are much better tailored for specific defects. The evolution of microvascular surgery over the past several decades has been brought about by the expansion of training programs, refinement of technique and equipment, and the acceptance of these flaps as a reliable and successful reconstructive option, which has spurred their use. The high reliability and improved outcomes of free flaps in head and neck reconstruction bring into question the order of reconstructive techniques in the reconstructive ladder. In many cases, it is more prudent to use a free flap over a pedicled flap when reconstructing a major defect because it is better suited for the defect, provides improved functional and esthetic outcomes, and, despite the increased complexity of the technique, is likely more reliable and associated with a lower risk of wound-healing complications.

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11

Tissue Engineering

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The image of tissue engineering is that of a futuristic pristine laboratory culturing human stem cells into organs for transplantation. The reality is that tissue engineering for practical applications in jaw reconstruction is an already established procedure with a straightforward clinical methodology and a proven track record. In the form of in situ tissue engineering, which refers to the regeneration of bone in this case within the recipient site of the patient, such tissue engineering represents a standard of care along with free vascular osteocutaneous flaps and autogenous cancellous marrow grafts.

The Principles of Tissue Engineering

In situ tissue engineering is an extension of known bone science. That is, the regeneration or even the remodeling of bone requires three elements: cells, a signal, and a matrix (scaffold). These together comprise the classic tissue engineering triangle (Fig. 11.1).

The Cells

Because there is confusion concerning the use of stem cells and overuse of the term, the types of cells are defined here and the ones used in current reconstructions of the jaws are identified:

- Omnipotent stem cells: Primitive blastomere cells capable of regenerating a complete organism (cloning)[1]
- Pluripotent stem cells: Primitive cells that can form an entire organ (e.g., kidney, liver)[1,2]
- Multipotent stem cells: Renewable cells that can form several tissue types (e.g., bone, cartilage, blood vessels, connective tissue)[1-4]
- Progenitor cells: Renewable cells committed to one tissue type (e.g., bone or cartilage or blood vessels)[1-4]

For in situ tissue engineering, the cellular components are multipotent stem cells and osteoprogenitor cells. Although similar and perhaps even identical cells may reside in adipose tissue, those used for bone regeneration today are derived from bone marrow through aspiration. They are then concentrated by centrifugation. Similar cells can be obtained from blood by phlebotomy followed by centrifugation, also known as platelet rich plasma (PRP).[5,6] The multipotent stem cell associated with the greatest stimulation of bone regeneration is the $CD34^+$ cell.[7] Proven osteoprogenitor cells are the $CD44^+$, $CD90^+$, and $CD105^+$ cells.[7-9] All four cell types can be concentration derived from bone marrow or peripheral blood with the greatest concentration present in bone marrow.

The proven signal for bone regeneration in the jaw reconstruction is recombinant human bone morphogenetic protein in an acellular collagen sponge (rhBMP-2/ACS).[10-12]

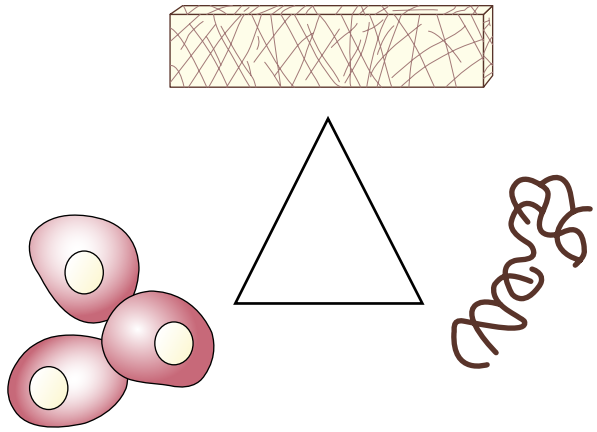
The best matrix is mineralized freeze-dried allogeneic bone because it can bind the important cell adhesion molecules of fibrin, fibronectin, and vitronectin as well as the chemoattractant protein stromal derived activation factor 1-alpha (SDAF-1-alpha).[13]

Developing the In Situ Engineering Graft at the Point of Care

The components of an in situ tissue engineering graft can be developed within 30 minutes in the operating room while the recipient site is being prepared.[14,15]

Bone marrow is aspirated from two puncture sites in each anterior ilium (Fig. 11.2). Each site will yield 30 mL of aspirate. The Harvest Technologies' bone marrow aspiration (BMA) bone marrow aspirate concentrate (BMAC) kit comes with a trocar with an oversheath for penetration of the iliac crest and aspiration for bone marrow (Fig. 11.3). The trocar, sheath, and internal barrel of two 20-mL syringes are coated with a heparin-saline solution of 2,000 units of heparin per milliliter. The trocar-sheath complex is worked into the iliac crest to a depth of 2 cm with a wrist rotation motion (Fig. 11.4). Once the trocar sheath is within the iliac crest, the sharp trocar is removed. Five milliliters are aspirated with the sheath handle being rotated 360 degrees to maximize the yield of stem cells and osteoprogenitor cells while minimizing the aspiration of circulating blood in the marrow (Figs. 11.5 and 11.6). With each 5 mL of aspirate, the sheath is withdrawn 2 to 3 mm so as to aspirate another 5 mL of bone marrow from a fresh internal site until two 15-mL syringes are obtained for 30 mL of BMA from each puncture site.

When a total of 120 mL of BMA is obtained from the four puncture sites, the contents of each syringe is placed into a blood collection bag into which the aspirating team has already placed



• **Fig. 11.1** The classic tissue engineering triangle of cells, signal, and matrix (scaffold).



• **Fig. 11.2** Two aspiration sites from each side of the anterior ilium are used. The first site should be 2 cm posterior to the anterior iliac spine.



• **Fig. 11.3** Aspiration trocar-cannula complex and 20 mL syringes.

8 mL of anticoagulate citrate dextrose A (ACD-A). This 120 mL of BMA is then drawn out into each of two 60- mL syringes to be placed into the centrifugation canisters (Fig. 11.7). The centrifugation canisters each containing 60 mL of BMA are then centrifuged into BMAC in a 14-minute twin spin cycle. The canisters



• **Fig. 11.4** Aspiration trocar-cannula in place to a 2 cm depth into the iliac crest.

are designed to selectively gain high yields of $CD34^+$ $CD44^+$, $CD90^+$, and $CD105^+$ cells from the 120 mL of BMAC obtained via their floating shelf through density gradient separation.

While the BMA is being aspirated, the rhBMP-2/ACS is dissolved in the recommended amount of sterile water provided in the Medtronic Infuse Bone Graft product and allowed to dissolve for 5 minutes. It is then placed on the acellular collagen sponge for 15 minutes before use, where 95% of the rhBMP-2 becomes bound to the ACS (Fig. 11.8). For continuity defects of the mandible, the authors have found that 1 mg of rhBMP-2 is required for every 1 cm of continuity defect.

Once these first two components are prepared, the BMAC is added to the freeze-dried mineralized allogenic bone to reconstitute it and adhere the stem cells and osteoprogenitor cells to their surface. The rhBMP-2/ACS is cut into 1- × 1-cm squares and added (Fig. 11.9). This composite graft completes the tissue engineering triangle and takes far less time and has far less morbidity than an open bone harvest required for a cancellous marrow graft or the harvest of a free vascular osteocutaneous graft.

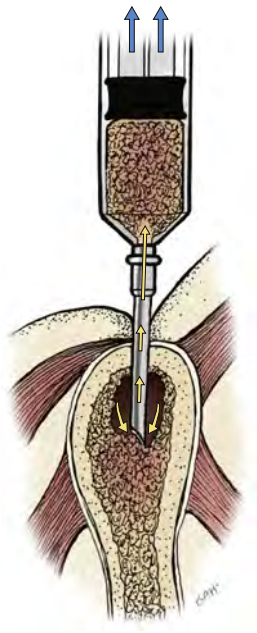
Surgical Applications of In Situ Tissue Engineering Grafts

Continuity Defects of the Mandible from Extirpation of Benign Tumors

The tissue bed that results from a benign tumor resection has not been compromised by radiation or chronic infection. Therefore, such grafts are placed as an immediate reconstruction usually with preservation of the neurovascular bundle. The technique is straightforward. The authors stabilize the defect with a titanium reconstruction plate using four bicortical locking screws in each segment. When a disarticulation



• **Fig. 11.5** Aspiration of bone marrow is 5 mL at one depth within the ilium; rotating the cannula 360 degrees maximizes the stem cell/progenitor cell yield.

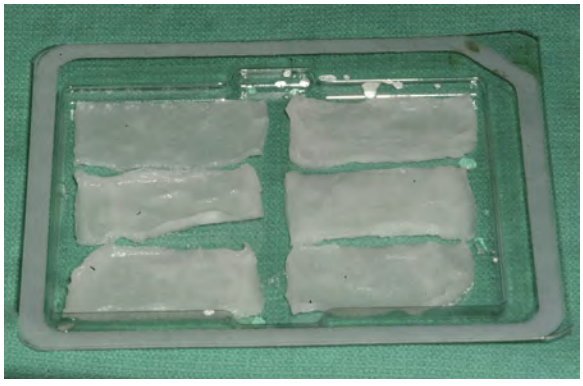


• **Fig. 11.6** The concept of bone marrow aspiration is the closed harvest of sufficient stem cells/progenitor cells to regenerate new bone.

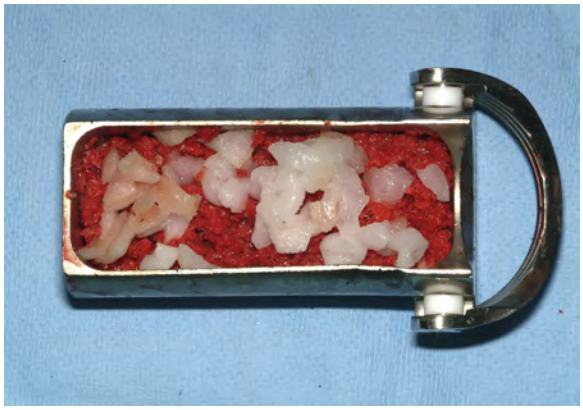
resection is required, six to eight screws on the distal segment are used together with a titanium condylar replacement against the native disc. The particulate nature of an in situ tissue-engineered graft is contained by a titanium mesh at the inferior border. Once the in situ tissue-engineered graft is in place (Fig. 11.10), the authors coat the graft with the bone marrow plasma activated with calcium chloride and thrombin, which adds structural consistency as well as additional cell adhesion molecules that are part of the matrix component (Figs. 11.11 and 11.12). The bone marrow plasma is the acellular component of



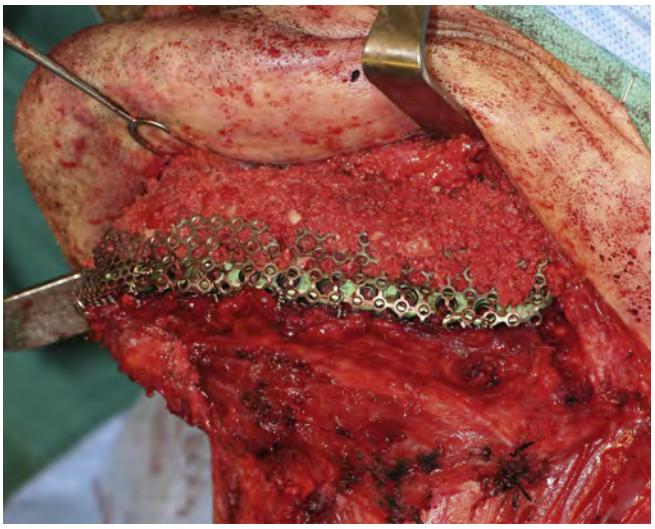
• **Fig. 11.7** The bone marrow aspirate is withdrawn from the transfer bag through a microfilter. The transfer bag was prepared by adding 8 mL of anticoagulate citrate dextrose-A.



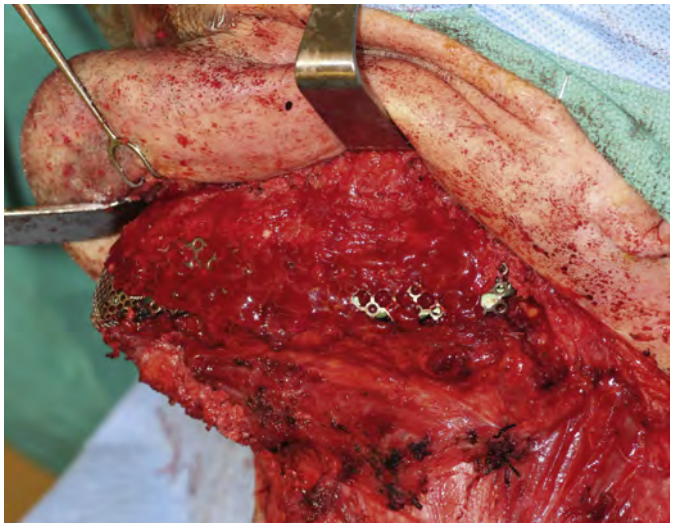
• **Fig. 11.8** rhBMp-2 wetted onto the acellular collagen sponge.



• **Fig. 11.9** It is best to evenly distribute the rhBMP-2/ACS throughout the graft by first cutting it into small squares.



• **Fig. 11.10** The composite graft of crushed cancellous allogenic bone/rhBMP-2/ACS/bone marrow aspirate concentrate in place to reconstruct a hemimandible.



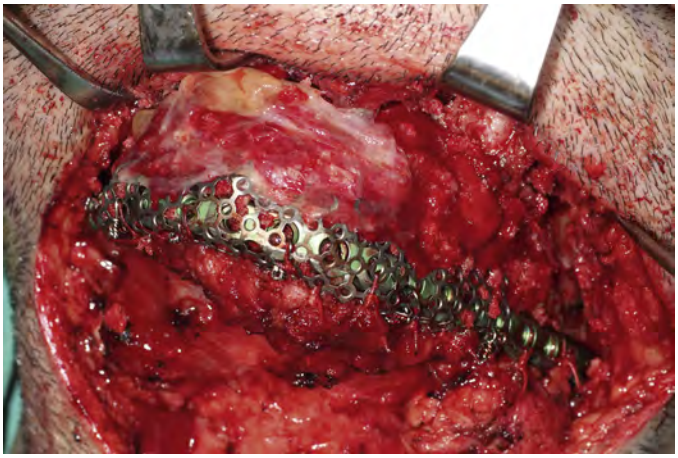
• **Fig. 11.11** The graft in Fig. 12.10 coated with additional bone marrow aspirate concentrate.

the BMAC and contains large quantities of fibrin, fibronectin, SDAF1-alpha, and numerous integrins.

Due to the rapid revascularization and osteoid synthesis of tissue-engineered grafts, the patient's oral mucosa and neck incisions heal rapidly without dehiscence and maxillo-mandibular fixation is limited to only 3 weeks. Dental implants are placed 4 to 6 months later to gain the final steps of complete functional rehabilitation (Figs. 11.13 and 11.14).

Continuity Defects of the Mandible from Gunshot Wounds or Infections

In most cases of continuity defects of the mandible from gunshot wounds or infection, the same application of an in situ tissue-engineered graft is used. However, in cases of significant soft tissue loss of either skin or mucosa, a free fasciocutaneous flap, such as a radial forearm or anterior lateral thigh flap, is required. This flap can be developed as a staged procedure



• **Fig. 11.12** The final coat of clotted bone marrow plasma adds cell adhesion molecules as additional scaffolding to the graft in addition to bioactive molecules such as SDAF-1-alpha.

before the in situ tissue-engineered graft or at the same time (Figs. 11.15 through 11.17).

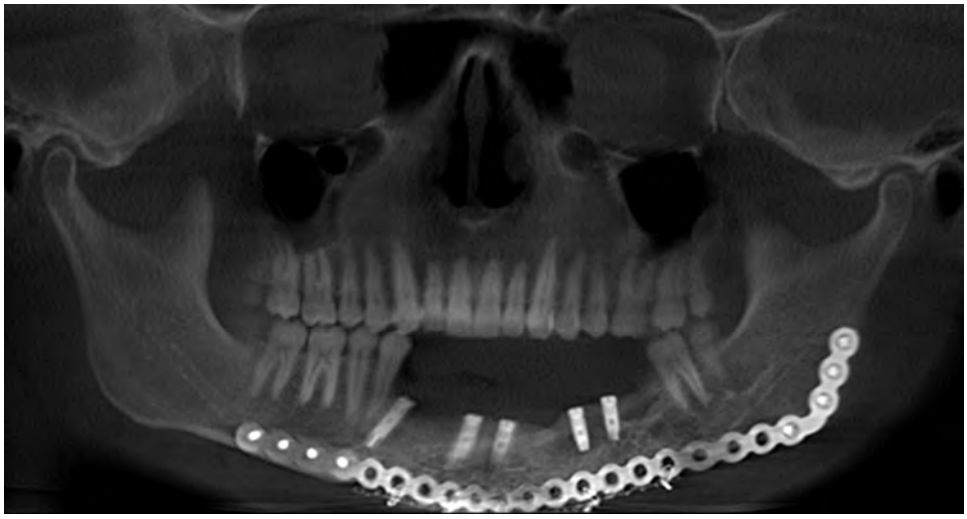
Defects in the Maxilla in a Non-radiated Tissue Bed

The dissection of the tissue bed in the maxilla must avoid a communication into the nasal cavity and must undermine the labial mucosa sufficiently to achieve a tension-free closure. The composite in situ tissue-engineered graft is placed into a titanium mesh, where it is bent and shaped to achieve the arch curvature and alveolar bone for later implant placement coordinated with the mandibular arch. The titanium mesh may be bent and shaped at the time of surgery, or sooner, using an accurate 3D generated model (Fig. 11.18). The graft material is compacted into the mesh before placement using the guideline of 0.5 mg of rhBMP-2 for every tooth missing in the defect (Fig. 11.19). The graft-loaded mesh is then placed into the maxilla and fixated with monocortical screws and the undermined mucosa closed with a mattress type closure (Fig. 11.20).

Such grafts can withstand tissue borne prosthesis due to the protective quality of a rigid mesh. In situ tissue-engineered grafts in the maxilla require 6 months for maturity, at which time the mesh is removed and dental implants with the correct trajectory for an appliance coordinated to the mandibular arch can be placed. This will allow for a precise and long-term stable prosthesis (Figs. 11.21 through 11.23A-C).

Continuity Defects of the Mandible in Malignant Tumor Extirpation Not Requiring Radiation Therapy

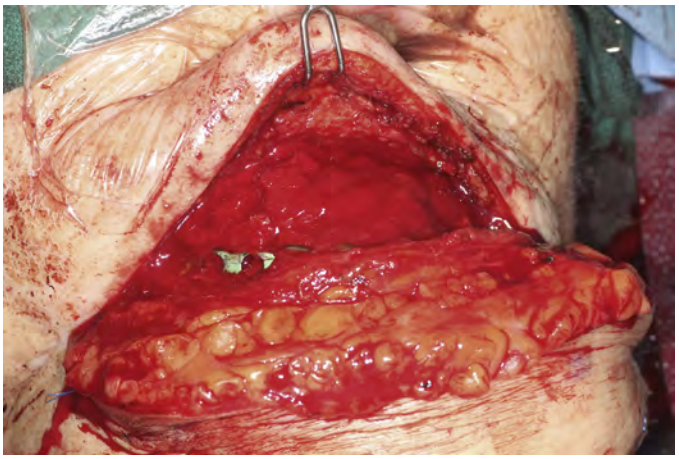
Even though reconstructing mandibular resections at the same time as cancer is resected as alluring, it presents two fundamental problems: (1) positive permanent section margins may require a return to the surgery that tears down the initial graft or compromises its blood supply; (2) postoperative radiation therapy will affect any bone graft in the radiation field. Even free vascular osteocutaneous grafts are affected and frequently result in osteoradionecrosis because its single paired vessel



• **Fig. 11.13** Consolidated in situ tissue-engineered graft with dental implants in place.



• **Fig. 11.14** Denture reconstruction such as this is a requirement of a successful graft.



• **Fig. 11.15** In situ tissue-engineered graft with anterior lateral thigh flap anastomosed and ready to cover the graft.

blood supply is even more vulnerable to radiation than native bone with collateral vasculature. Therefore, it is the authors' preference to stage a definitive reconstruction using in situ tissue-engineering or any other graft technique for 3 months.

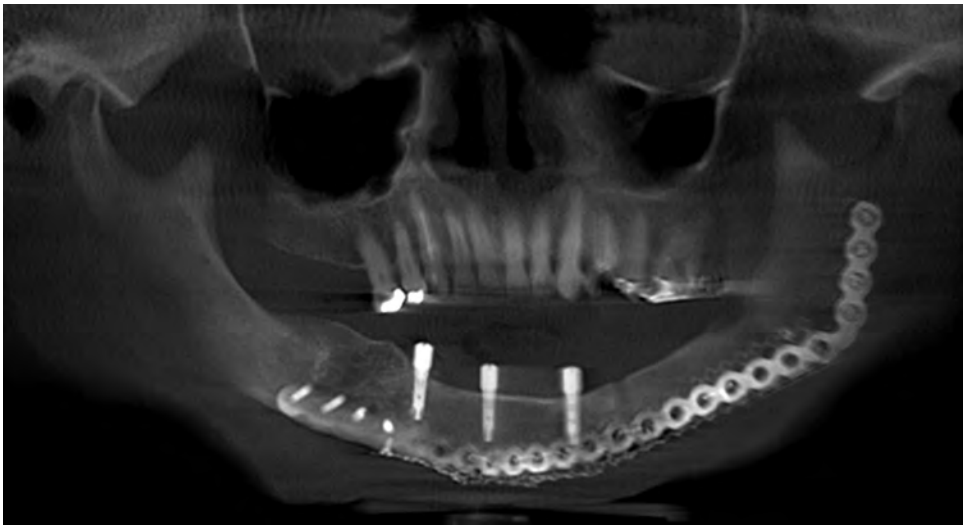


• **Fig. 11.16** Free vascular flap covering in situ tissue-engineered graft.

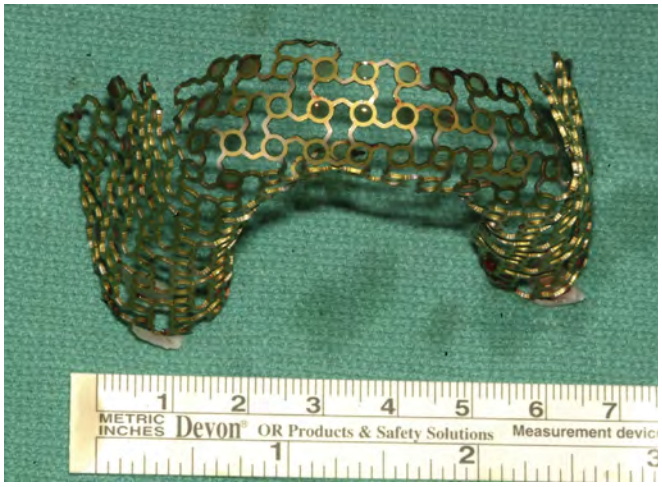
In such cases, the mandible has been initially stabilized with a titanium reconstruction plate and any soft tissue loss reconstructed with a free vascular fasciocutaneous or myocutaneous flap. At the 3-month time interval, and the assurance that margins were clear and that no radiation therapy is indicated, the titanium plate is removed, the encapsulating scar about the plate is removed, the full recipient tissue bed is developed, and the same titanium plate is returned and fixated (Fig. 11.24). As in the other grafts described, the in situ tissue-engineered composite graft of 20 mL of BMAC, 1 mg/cm defect of rhBMP-2/ACS, and mineralized freeze-dried cancellous allogeneic bone 8 mL/1 cm of defect is placed in the defect contained at the inferior border by a titanium mesh (Figs. 11.25 and 11.26).

The Biologic Sequence of Bone Regeneration in In Situ Tissue-Engineered Grafts

In contrast to free vascular osteocutaneous grafts which transfer a pre-formed adult bone with its inherent morphology and size, an in situ tissue-engineered graft regenerates new bone



• **Fig. 11.17** Consolidated in situ tissue-engineered graft seen in Figs. 11.15 and 11.16 with implants in place.



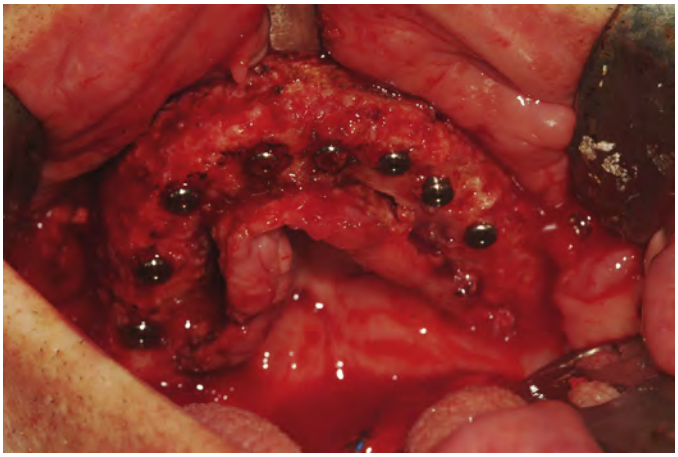
• **Fig. 11.18** A titanium mesh shaped to the contours of a maxillary ridge contains the in situ tissue-engineered graft.



• **Fig. 11.20** Titanium mesh crib loaded with graft is fixated with non-cortical screws.



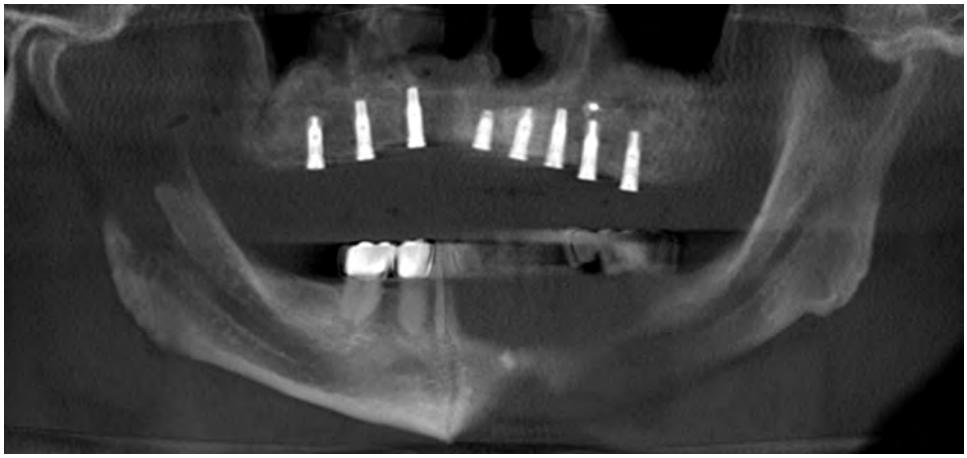
• **Fig. 11.19** In situ tissue-engineered graft compacted into the titanium mesh crib.



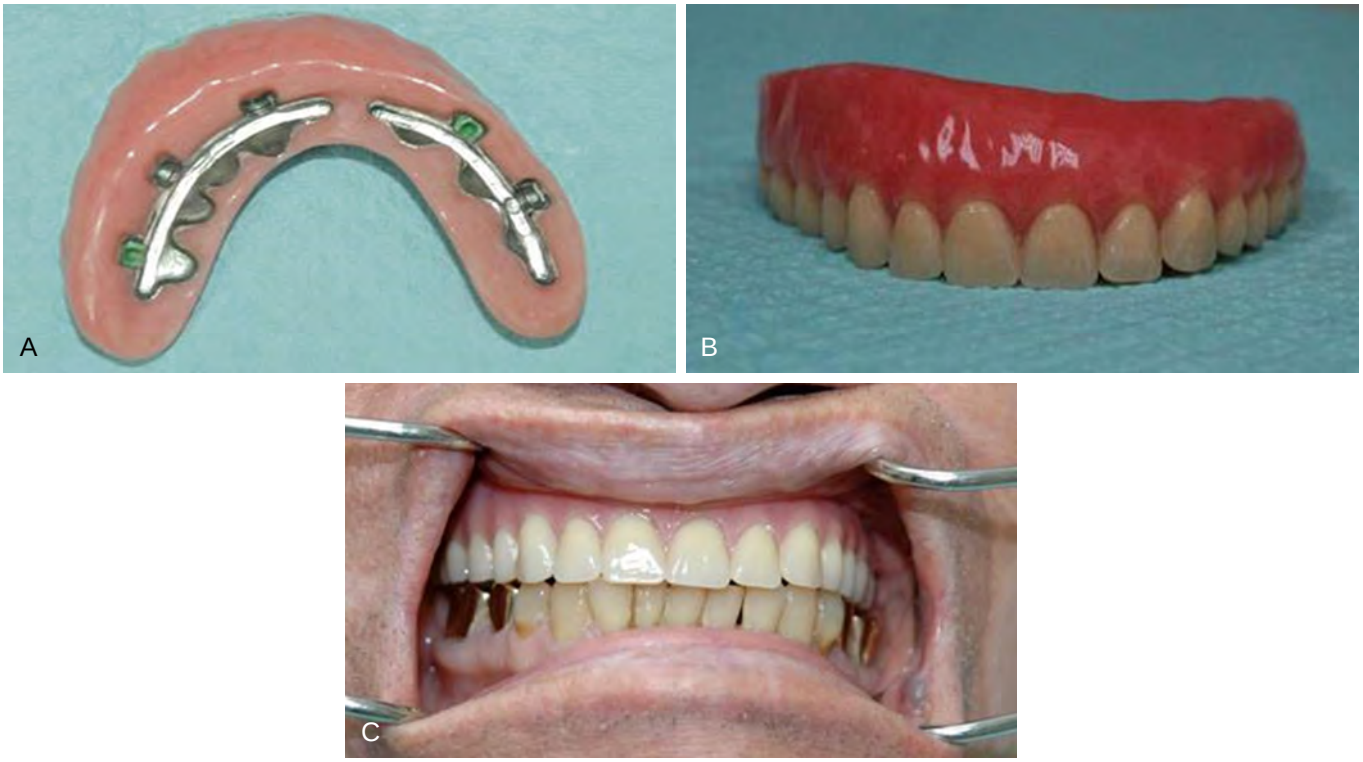
• **Fig. 11.21** Mesh removed and eight dental implants placed into in situ tissue-engineered graft.

similar to embryologically formed bone and is capable of forming bone in a shape and size most closely approximating that of the mandible or the maxilla as well as osseointegrating dental implants very well.[7,11]

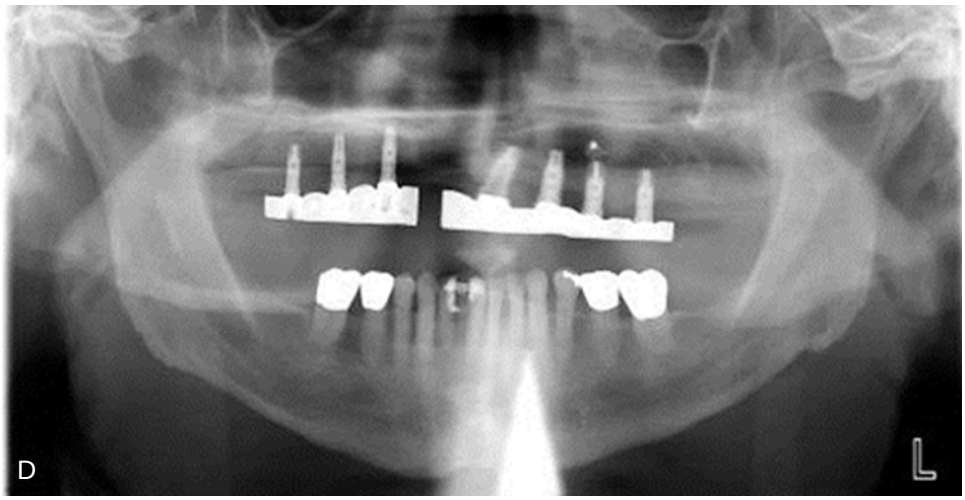
Within the graft after soft tissue closure, the cell adhesion molecules fibrin, fibronectin, and vitronectin, a host of integrins in the BMAC, and the activated bone marrow plasma coat the surface of the cancellous allogeneic bone to create a rich interlocking matrix upon which new osteoid will be deposited.[16] The multipotent stem cells and osteoprogenitor cells that have surface receptors for BMP-2 ($CD34^+$, $CD44^+$, $CD90^+$, and $CD\ 105^+$) bind the rhBMP-2 to their surface.[17] The rhBMP-2 also chemoattracts circulating stem cells and induces a proliferation of the stem cells and osteoprogenitor cells within the graft in addition to a differentiation into functional osteoblasts.[18] Moreover, the release kinetics of the ACS is such that after an initial release of rhBMP-2 it is followed by a steady release over 21 days.[19] This begins and extends a rapid new bone formation. Additionally, BMP-2 is known to upregulate the synthesis and release of vascular endothelial growth factor (VEGF),[20] which results in the rapid revascularization bone formation as well as the rapid



• **Fig. 11.22** Robust quantity of bone regenerated by in situ tissue-engineered graft.

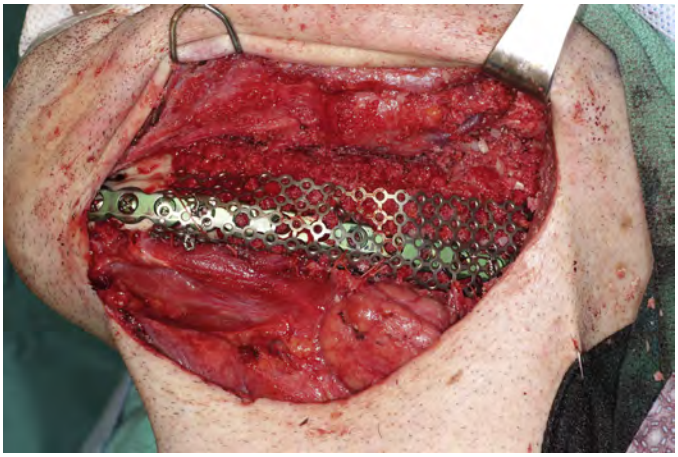


• **Fig. 11.23** Stable milled bar denture supported by implants and in situ tissue-engineered graft. **A,** Undersurface of milled bar denture. **B,** Denture ready for connection to implant bar. **C,** Maxillary denture in place with excellent occlusion.

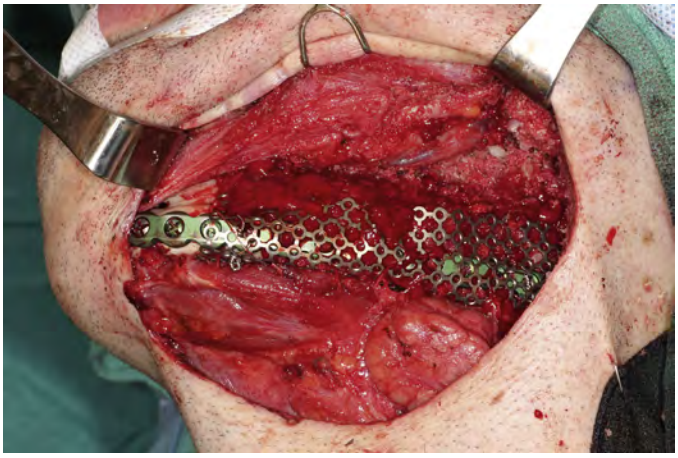




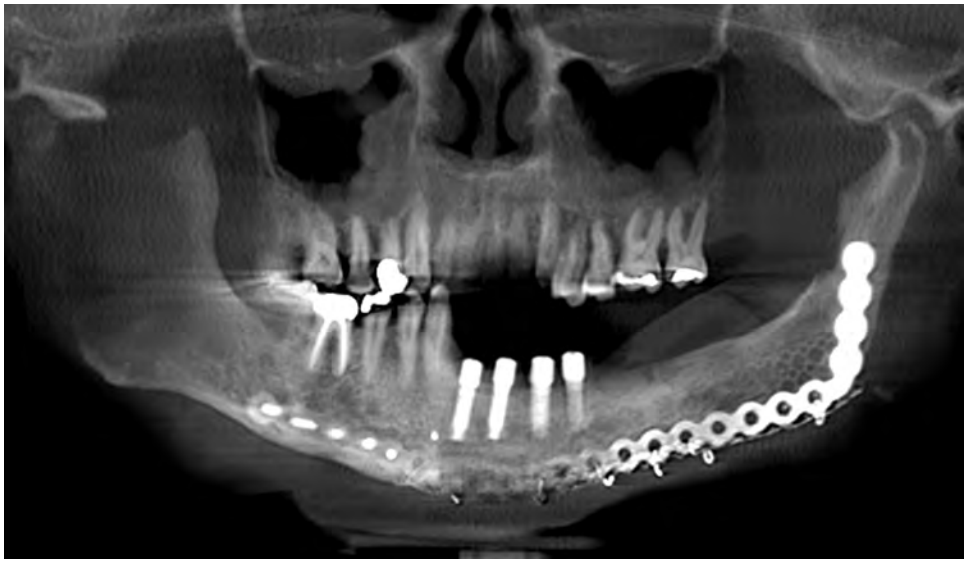
• **Fig. 11.23—cont'd** **D,** Panoramic radiograph showing seven dental implants in mature bone supporting the denture. **E,** Implant retained denture providing lip support and facial esthetics.



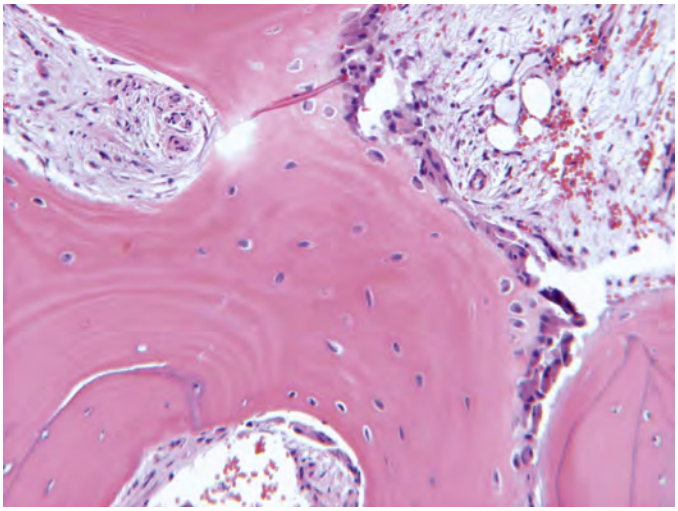
• **Fig. 11.24** In situ tissue-engineered graft stabilized with a titanium plate and mesh in a cancer patient with no evidence of disease.



• **Fig. 11.25** Graft seen in Fig. 11.24 coated with additional clotted bone marrow aspirate concentrate to make full use of all stem cells and osteoprogenitor cells. The clotted texture of an in situ tissue-engineered graft with bone marrow plasma coated not only adds cell adhesion molecules and integrins but also allows for sculpting of the graft.



• **Fig. 11.26** Consolidated in situ tissue-engineered graft and implants in a patient with a history of osteosarcoma and treated with resection and chemotherapy but no radiation.



• **Fig. 11.27** Core bone biopsy of an in situ tissue-engineered graft showing mature bone and bone marrow with osteoblastic rimming without evidence of residual non-vital allogenic bone particles.

soft tissue healing observed with in situ tissue-engineered grafts. The original stem cells and osteoprogenitor cells differentiates into new osteoblasts and become adherent on the surface of the cancellous allogeneic bone by the cell adhesion molecules and synthesize osteoid aided by the abundant perfusion from new capillaries. Therefore, over the first 21 days, new bone in the form of osteoid is rapidly deposited throughout the matrix.

Between the end of this first 3 weeks and 6 months, the new bone undergoes the normal bone 150- to 180-day resorption/new bone apposition remodeling cycle wherein a more mineralized mature bone develops.[21] During this process, the non-vital allogenic bone is completely resorbed and replaced with new bone so that none appear on the histology of bone cores taken during implant placements (Fig. 11.27).

Advantages of In Situ Tissue-Engineered Grafts

A study comparing in situ tissue-engineered grafts to the two other standards of care—autogenous cancellous marrow grafts and free vascular osteocutaneous grafts from the fibula—revealed the follow list of advantages as illustrated in Table 11.1.

1. An equal or better success rate
2. Reduced morbidity
3. Shorter hospital stay
4. No ICU requirement
5. Cost effective/cost saving
6. Does not require microvascular training
7. Fewer surgeons required to complete the surgery

Apparent in eliminating donor site morbidity is the reduced overall pain and discomfort for the patient as well as conservation of operating room time, intensive care unit time, and the length of hospital stay, translating into reduced overall cost. Not apparent is the earlier return to work and family, and lesser disability.

Disadvantages are as follow:

1. Requires an understanding of bone regeneration and tissue-engineering principles
2. Enhanced edema lasts 2 to 3 weeks. NOTE: This is due to the chemoattraction and proliferation of stem cells and osteoprogenitor cells induced by the rhBMP-2/SDAF-1-alpha and not to enhanced inflammatory cells
3. Contraindicated in patients with active cancer[22]

Special Consideration in Patients Who Received Radiation to the Recipient Tissue Bed

Irradiated tissue is the least supportive of wound healing and bone graft healing. Radiation reduces the number of resident stem cells and osteoprogenitor cells in tissue as well as the vascular supply.[23] The tissue bed becomes hypocellular, hypovascular, and hypoxic, also called "three-H tissue."[24] Moreover, irradiated tissue worsens with time in that the normal renewal

TABLE 11.1 Time and Cost Comparison of Graft Types

	In Situ Tissue-Engineered	Autogenous Cancellous Marrow	Free Vascular Osteocutaneous
Number	80	80	43
Bone regeneration	76 (95%)	75 (94%)	35 (81.4%)
Hounsfield density* 6 months	74.4	722	988
Trabecular bone area†	67%	63%	N/A‡
Donor site	0	80/80	43/43
Mean hospital stay	1.7 days	4.2 days	11.9 days
Mean operating room time	3.7 hours	5.7 hours	10.2 hours
Intensive care unit	0 days	0 days	2 days
Mean costs	$24,200	$48,300	$93,500

*A measure of graft mineralization.
†A histomorphometric measure of viable bone.
‡No implants were placed in these grafts.



• **Fig. 11.28** In radiated tissue beds, 33–50% of the graft should be openly harvested autogenous bone.

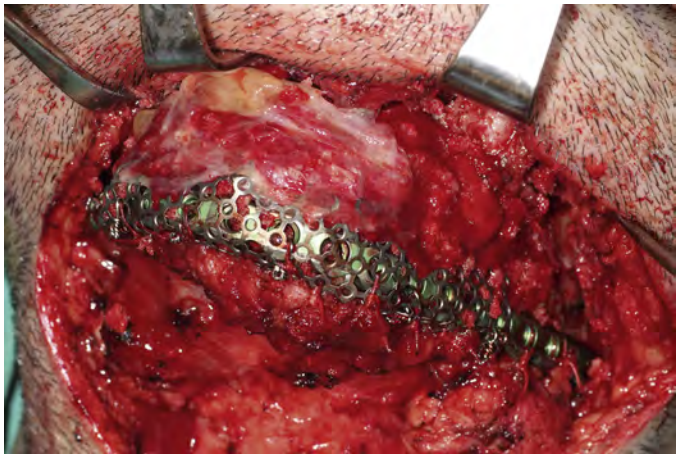


• **Fig. 11.29** In situ tissue-engineered graft containing 50% autogenous cancellous marrow in a heavily radiated tissue bed.

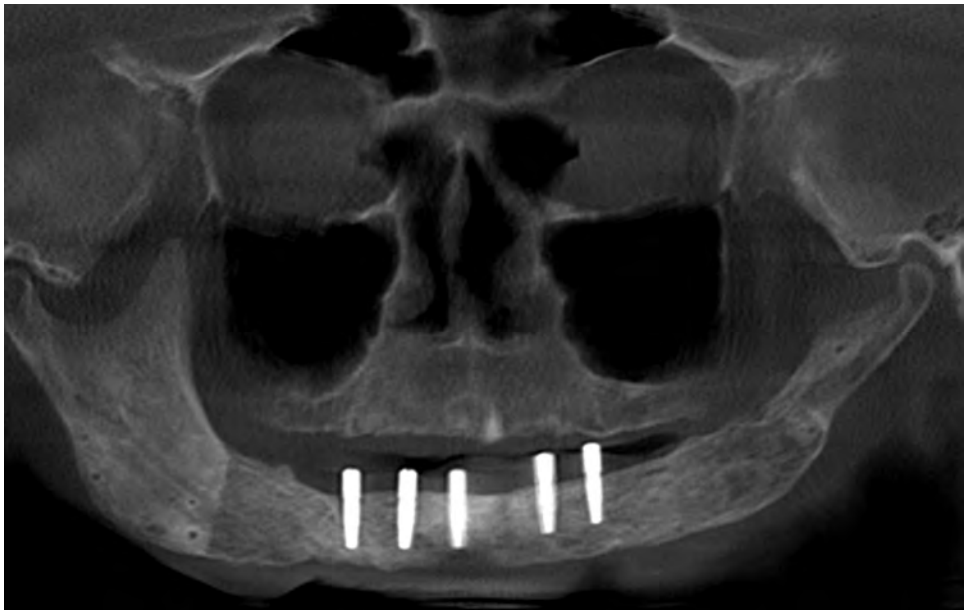
of, for example, endothelial cells, fibroblasts, osteoblasts, and periosteal cells, is impaired.[25] Radiation also damages the intimal layer of larger veins and arteries, making them more thrombogenic and thus reducing the success of free vascular transfers. Therefore, the authors use the standard protocols of hyperbaric oxygen recommended by the Undersea and Hyperbaric Medicine Society to improve the recipient tissue[26]:

- For surgery in radiated tissue without osteoradionecrosis, 20 sessions of 100% oxygen breathing for 90 minutes at 2.4 atmospheres absolute pressure (ATA) before surgery, followed by 10 sessions after surgery
- For cases of clinical osteoradionecrosis, 30 sessions of 100% oxygen breathing for 90 minutes at 2.4 ATA before surgery, followed by 10 sessions after surgery

Related to mandibular and maxillary reconstruction in such irradiated patients, the state of tissue-engineering science has not yet been able to fully reconstruct these patients without using some autogenous cancellous marrow. This is due to the limitation of stem cells and osteoprogenitor cells that can be harvested and concentrated by the current techniques discussed in this chapter. While new bone marrow aspiration protocols are being studied, as are bioreactors, to greatly expand the numbers of stem cells and osteoprogenitor cells, they are not currently validated to regenerate bone in an irradiated tissue bed. Therefore, in irradiated patients, the authors use a ratio of 33–50% autogenous bone to 50–67% mineralized cancellous allogenic bone as a modification for in situ tissue-engineering. This relatively small addition (20 to 40 mL) of fresh autogenous bone marrow provides equal outcomes as is observed with in situ tissue-engineered grafts without autogenous bone in the non-irradiated patients (Fig. 11.28). This observation underscores the great amount of untapped stem cells and osteoprogenitor cells in human bone marrow that may soon be obtainable with improved techniques (Figs. 11.29 through 11.31).



• **Fig. 11.30** As in the non-radiated patient, the graft is coated with clotted bone marrow plasma before closing.



• **Fig. 11.31** Mature graft seen in Figs. 11.28 through 11.30 with ideal height and natural mandibular morphology as well as housing dental implants.

TABLE 11.2 University of Miami School of Medicine Data of rhBMP-2/ACS vs Autogenous Bone Graft Reconstructions With 2- to 7-Year Follow-up

	rhBMP-2/ACS			Autogenous Bone Grafts		
	Number	Bone Regeneration (%)	Cancers (%)	Number	Bone Regeneration (%)	Cancers (%)
Benign tumors	52	51 (98%)	1 (1.9%)	52	50 (96%)	0
Trauma	32	30 (94%)	0	32	30 (94%)	0
Osteoradionecrosis	94	89 (95%)	3 (3.2%)	94	89 (95%)	4 (4.3%)
Primary malignant tumor extrapolation	43	40 (93%)	2 (4.7%)	43	41 (95%)	2 (4.7%)
Ridge augmentation	91	85 (93%)	1 (1.2%)	91	83 (91%)	1 (1.2%)
Sinus augmentation	84	79 (94%)	1 (1.2%)	84	76 (91%)	2 (2.4%)
Total	396	374 (94%)	8 (2.0%)	396	369 (93%)	9 (2.3%)

Use of rhBMP-2/ACS and Purported Risk for Cancer

A potential risk for cancer development with rhBMP-2/ACS in spinal fusions has been advanced by a subset of orthopedic spine surgeons.[27-29] These have been mostly cumulative uncontrolled statistical studies with no proposed mechanism of tumorigenesis. This is important because the classic work by Hanahan and Weinberg requires six survivable mutational events to occur in any cell before it becomes a cancer cell: (1) sustaining proliferative signaling, (2) evading growth suppressors, (3) resisting cell death, (4) enabling replicative mortality, (5) sustaining induced angiogenesis, and (6) activating invasion and metastasis.[30, 31] No growth factor including rhBMP-2 is mutagenic and none directly enter the nucleus of a cell. Moreover, the rhBMP-2 studies that led to FDA approval did not identify an increased cancer rate in any rhBMP-2 group compared with the control group,[12,32,33] and several independent investigators found no correlation between cancers and rhBMP-w2/ACS.[34-36]

Nevertheless, the authors have directly explored the relationship of cancer development specific to 396 head and neck reconstructive surgeries when rhBMP-2/ACS was used in doses exceeding 4.2 mg (mean dose 10.4 mg) compared with 396 reconstructive surgeries without rhBMP-2/ACS. The results are presented in Table 11.2.

There was no statistical difference in cancer occurrence between the two groups. Therefore, the use of rhBMP-2/ACS in in situ tissue-engineering poses no increased cancer risk because there is no plausible mechanism that it can induce a cancer and controlled evidence has shown that it does not. However, the authors observe and recommend that the product label relating that rhBMP-2/ACS (Infuse Bone Graft, Medtronic) is contraindicated in patients with exigent cancer (known active cancer) be observed and reserve cancer reconstruction using rhBMP-2/ACS to those who have no evidence of disease.

Conclusion

Useful bone regeneration gaining jaw continuity with ideal height and width coordinated to the opposing arch and capable of predictable dental implant osseointegration via tissue engineering, is not a futuristic thought but an already validated and practiced method. It is part of the current trend in all of medicine to produce an equal or better outcome with reduced morbidity, decreased operating room time, decreased hospital time, and lower cost to our already overstressed health care system. Today, in situ tissue-engineering gaining bone in large jaw defects is only the beginning and represents a model and stepping stone for bone regeneration on an even grander scale, as well as its applications to other tissues.

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12

Maxillofacial Reconstruction and Prosthetic Rehabilitation

FELIX SIM, LARRY M. OVER, ERIC J. DIERKS, ALLEN CHENG, ASHISH A. PATEL, R. BRYAN BELL

Over the past couple of decades, there have been great improvements in the techniques available for reconstruction of head and neck defects after ablative surgery for the treatment of cancer. With these improvements come higher end-points to achieve for both esthetic and functional outcomes. Dental rehabilitation, while feasible in only a minority of patients, should be the goal in all patients undergoing composite resection for the treatment of head and neck malignancies.

There are three major factors that have significantly influenced the ongoing progression of reconstructive surgery in the head and neck. First, the continued improvement in microvascular techniques and instrumentation has led to better outcomes of free tissue transfer, which in turn has pushed the boundaries of what is possible in ablative surgical practice. A greater emphasis on quality of life associated with head and neck cancer treatment has shifted toward a decrease in donor site morbidity, improved quality of tissue harvested, and esthetic and functional outcomes. In certain parts of the head and neck, from both functional and esthetic standpoints, free tissue transfer provides excellent outcomes that have been shown to improve quality of life after ablative surgery.[1]

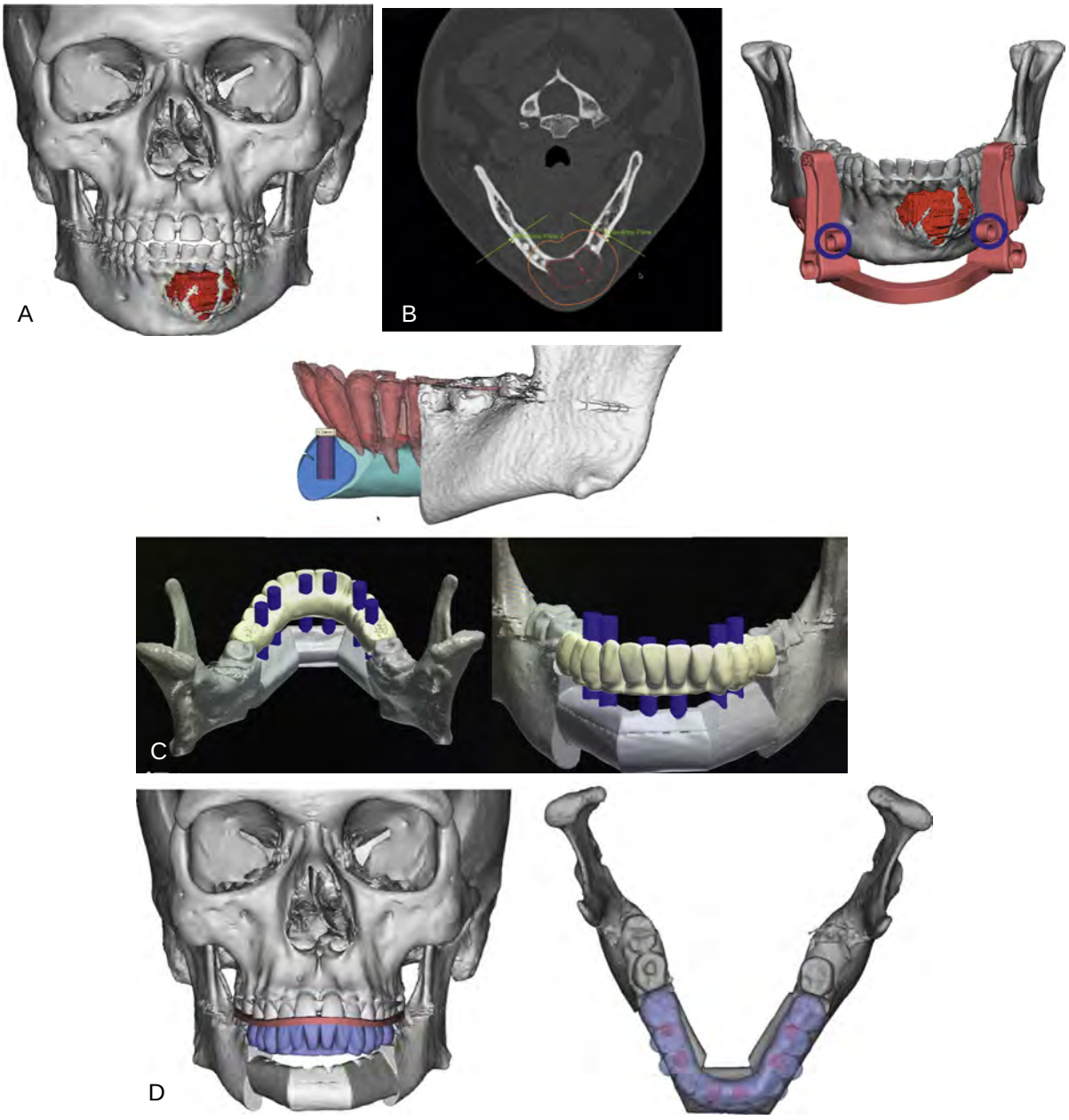
Since Per-Ingvar Brånemark introduced the concept of osseointegration in 1952, the use of osseointegrated implants has continued to gain momentum with the introduction of not only dental but also craniofacial and extremity applications.[2] Dental implants have now become the standard of care for replacement of missing dentition. Although osseointegration is highly predictable for most patients, the success rate has been continually improved by ongoing research and development, including alterations in and modifications to the implant topography, implant surface, and fixture design.[3–5] In reconstruction of tooth-bearing osseous structures such as the maxilla or mandible, osseointegrated implants placed into free vascularized bone flaps may facilitate a predictable method of dental rehabilitation in an otherwise challenging group of patients. In addition to dental rehabilitation, osseointegrated implants facilitate rehabilitation with facial prostheses. Because of the complex anatomy of the nose, ear, and eye, there is strong consensus that these facial prostheses provide a superior esthetic result when compared with autogenous reconstruction in some cases. Implant-retained prostheses provide a viable alternative to autogenous reconstruction and can achieve excellent symmetry, color, and anatomic detail.

Another factor that has helped improve outcomes and accuracy in reconstruction planning is the use of three-dimensional data obtained from computed tomography (CT) images for virtual surgical planning (VSP) and stereolithographic and rapid model prototyping.[6–10] Despite notable improvements in surgical techniques, problems remain with regard to reestablishing facial symmetry and accurately repositioning skeletal or composite tissue constructs into the preablative anteroposterior, vertical, and sagittal relationships. These relationships should ideally result in favorable facial proportions and allow for successful implant-supported prosthetic rehabilitation. The use of VSP and biomodels obtained from CT data has undoubtedly aided the assessment of patients in three dimensions, leading to improved outcomes. It has also helped to reduce intraoperative surgical time with all its associated benefits such as shorter flap ischemia time and lower operating room costs. Immediate implant placement is also feasible using VSP, with the ultimate application being the "jaw in a day" concept, introduced by Levine and Hirsch, in which tumor ablation, jaw reconstruction, implant placement, and prosthesis delivery are all performed in one operation[6] (Fig. 12.1).

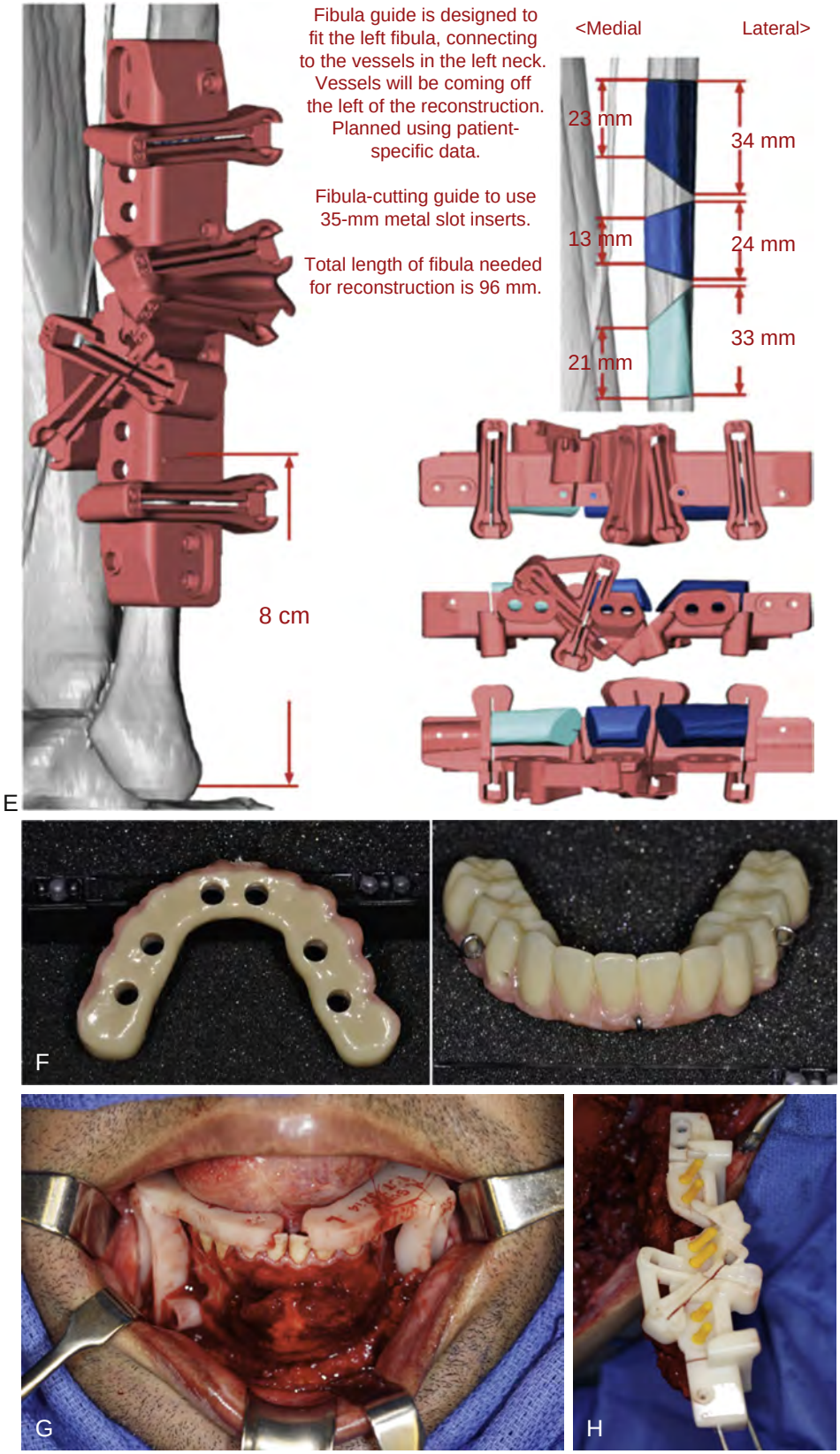
The purpose of this chapter is to illustrate the application of these various technologies in the assessment, planning, and use of implant-supported prosthetic rehabilitation of patients undergoing surgical treatment for head and neck cancer.

Virtual Surgical Planning

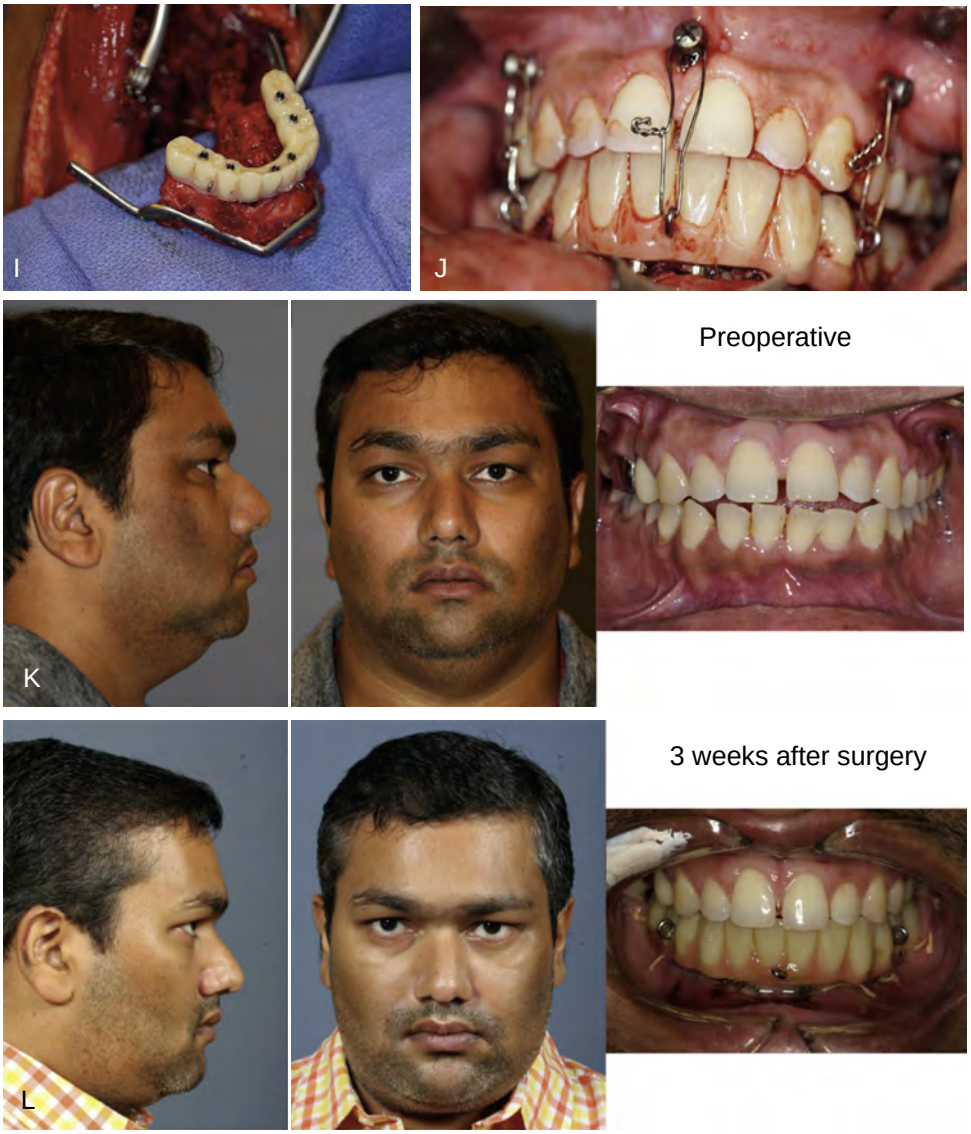
VSP has the potential for increasing predictability and accuracy in head and neck reconstruction and implant-supported prosthetic rehabilitation, by facilitating accurate positioning of neo-maxillary and neo-mandibular constructs relative



• **Fig. 12.1** Segmental resection of an anterior mandible ameloblastoma with immediate implant placement and prosthesis as in the concept of a "jaw in a day" described by Levine and Hirsch. **A,** Anterior mandible solid ameloblastoma. **B,** Resection margins planned during virtual surgical planning (VSP) based on axial CT scan determining extent of tumor. Resection cutting guide is shown in the right figure *(outlined in red).* **C,** After virtual reconstruction with the left fibula, implant placement was planned in the ideal anterior occlusion relationship with reference to the fibula. **D,** Fibula cutting guide designed to incorporate implant guides for placement of implants before osteotomy of fibula.



• **Fig. 12.1, cont'd** **E,** Temporary dental prosthesis made from custom-milled acrylic resin. **F,** Intraoperative photo of occlusal-based resection cutting guide in situ. **G,** Fibula cutting guide and implants with directional guide in place. Note that two fixtures were placed in each osteotomy segment. **H,** After osteotomy of the fibula, the temporary snap coping abutments were placed over the fixture and the prosthesis was fitted onto it before fixation of the fibula with the custom reconstruction plate. Note that the fibula is still attached to the peroneal pedicle.



• **Fig. 12.1, cont'd** **I,** The osteotomized fibula flap together with the prosthesis is then placed in the defect in the planned occlusal relationship and placed in wire intermaxillary fixation (IMF). Once the occlusion is established, the fibula is then fixated to the mandible. IMF was maintained for 2 weeks postoperatively. **J** to **L,** Preoperative and 3 weeks postoperative clinical photographs of patient showing well-maintained projection of the lower third of face and occlusion.

to the opposite jaw and with consideration of the dental arches. Three-dimensional simulation software also defines the coronal, axial, and sagittal planes to facilitate accurate implant placement with selected diameter and length according to bone availability. The protocol used for VSP at our institution was described by Hirsch and colleagues[10] as follows:

1. A preoperative high-resolution CT scan is obtained to capture the patient's facial skeleton and donor site (e.g., lower extremity CT angiogram) when applicable. The scanning protocol is outlined in Box 12.1.
2. The images are then converted to Digital Imaging and Communications in Medicine (DICOM) format and forwarded to a third-party modeling company or an in-house virtual surgical laboratory. There, the scans are uploaded into various proprietary planning software, and three-dimensional virtual reconstructions of the maxillofacial skeleton as well as the donor site are constructed.
3. A Web meeting is then held with company or laboratory software engineers and the surgical team. During this VSP session, the extent of the resection and location of bony flap placement are determined by the surgeon and marked on the three-dimensional reconstructed image. The virtual resection eliminates the diseased portion of bone from the image (Figs. 12.1B and 12.2A).
4. The three-dimensional bony flap image is then superimposed on the defect, with determination of its direction, orientation, and length. Once the bony flap is near the desired position, the virtual osteotomies are placed on the bony flap to fit the planned reconstruction (see Fig. 12.1E).

If implants are to be placed either primarily during the reconstructive phase (see Fig. 12.1C) or secondarily after any planned adjuvant therapy is completed (see Fig. 12.2), then the implant position can also be determined in relation to the opposing dentition, and the fibula position is refined to accommodate the dentition in a process called *reverse engineering*. The majority of patients in our practice undergo segmental mandibulectomy for cancer, so these predetermined positions can then be incorporated in the cutting guide of the donor bony flap or, more commonly, delayed until after adjuvant therapy.

5. Next, a prosthesis is digitally designed and modified to optimize the shape of the neo-mandible or neo-maxilla (see Fig. 12.1C).
6. The modeling phase involves additive manufacturing of the planned components designed to transfer the virtual plan into reality. Three models may be obtained. The first model is of the native facial skeleton with the diseased tissue in place; the second model is of the native facial skeleton with the reconstructed bony flap in place; and third is a template of the bony flap that has been osteotomized to fit into the defect. These models act as a guide to surgeons and can be used as an educational tool for residents and patients.
7. Next, cutting guides are produced that fit onto the native mandible or maxilla and allow the angles of resection to precisely match those created during the planning phase (see Figs. 12.2B and 12.2C).
8. Customized reconstruction plates can be prebent from stock plates with a template made by the modeling company to match the cutting guide; alternatively, the plate can also be fully customized (manufactured), depending on the surgeon's preference and the complexity of the fixation required (see Fig. 12.2D).
9. Cutting guides for the donor site are constructed when applicable. In mandibular reconstruction the use of a cutting guide greatly improves the time and accuracy in recreating the curvature of the mandible when multiple fibular osteotomies are required. A linear cutting guide is fabricated from the cut pieces of the virtual fibula, with cutting slots that are located at the appropriate lengths along the fibula and at the proper angles to re-create closing wedge osteotomies without any intraoperative measuring. When implants are to be placed primarily, then the cutting guide can also be designed to include slots where the implants should be placed. These cutting guides can be placed along either the anterior or the lateral aspect of the fibula. We prefer lateral cutting guides so that the pedicle can be better protected when the osteotomy is performed with a saw (see Fig. 12.1D).

Soft Tissue Management

Ablative surgery for oral cancer will often lead to loss of attached gingival mucosa. This tissue, which is tightly adherent to bone, provides an ideal transition point for prosthesis and fixture junction. The immobility of the attached gingiva allows ease of hygiene maintenance, which in turn leads to prevention of periimplantitis. In head and neck reconstruction, the soft tissue component of the free flap is not adherent to the underlying bone owing to the nature of the perforator blood supply to the skin paddle. The thick, mobile characteristics of this skin paddle make it a poor choice for receiving dental implants. Several techniques have been proposed to help overcome these challenges in both oral and extraoral situations.

Thinning of the Skin Paddle

Thinning of the skin paddle can be performed at any phase of surgery, although it is advisable to wait for a minimum of 6–12 months after completion of all cancer therapy to

• Box 12.1 Sample Craniomaxillofacial CT Scanning Protocol for Virtual Surgical Planning

Please keep in mind the following key points:

- Acquire scans at a high spatial resolution. Series should be acquired with thin, contiguous image slices and as small a field of view (FOV) as possible while still including the patient's external contour. Remove all removable appliances and braces before scanning. Patient must remain completely still throughout the entire scan. If patient motion occurs, the scan must be restarted.
- Image distortion from patient motion will severely compromise the accuracy of a model. Ensure that scares are free from motion artifact.
- Do not use a gantry tilt in scanning patients.
- Archive the entire study, preferably in Digital Imaging and Communications in Medicine (DICOM) format, to a removable medium such as Sony/MaxOptix optical disk, Pioneer optical disk, 4- or 8 mm DAT, or CD-R. Many of the older proprietary image formats (e.g., GE Advantage, Picker, Philips) can be supported, but the most reliable method of image transfer is DICOM format on CD-R. It is also possible to transfer image data via computer network.

Example Image Protocols for Orthopedic Study

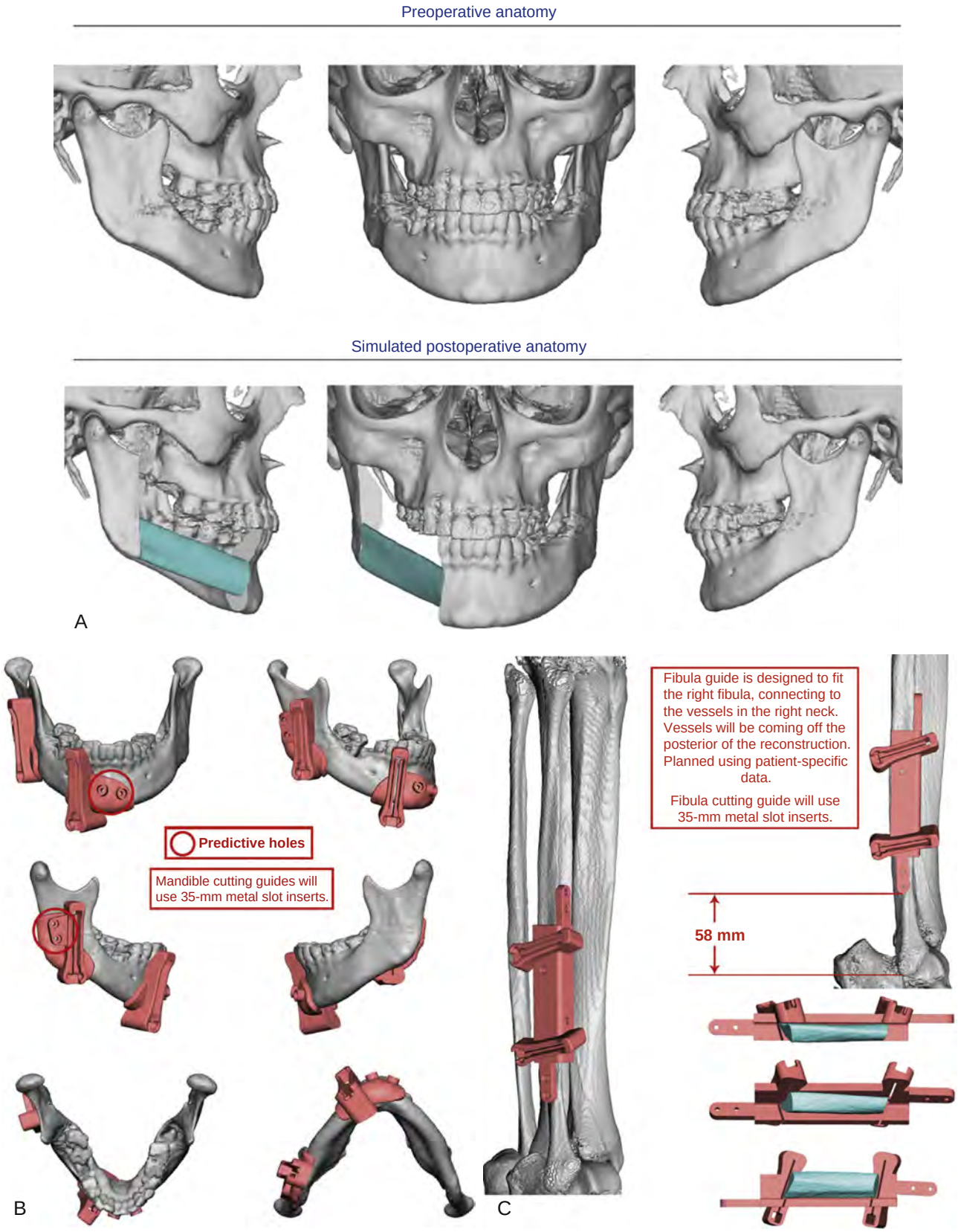
Acquisition	Helical
Field of view	20–25 cm
Gantry tilt	0 Degrees
Scan spacing	Contiguous slices
Series	Original/Primary/Axial (no recon, reformat or post process data)
Slice thickness	1.25 mm or less
Algorithm	Standard (not bone or detail)
Pitch	1:1 or 1:1.5

Variations on this example are acceptable as long as the aforementioned key points are followed. If using a multidetector scanner, reconstruct images at thin sections.

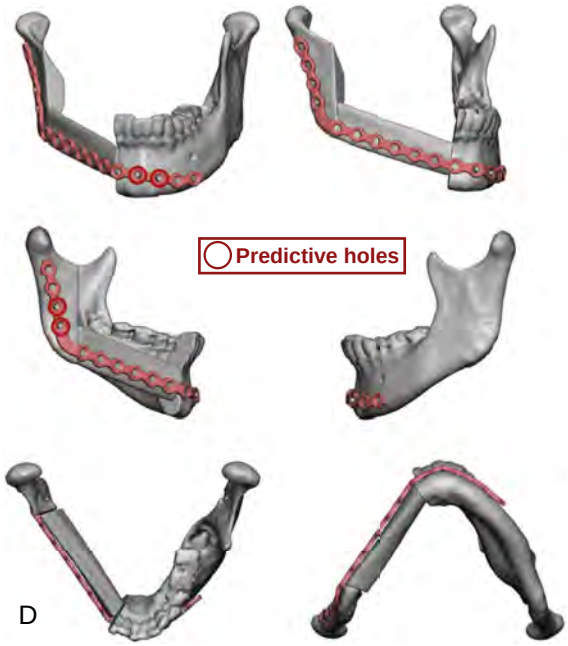
If using a single-slice scanner, do not reconstruct images to slicers that are thinner than the original acquisition. This simply interpolates between slices and does not improve the resolution of the study.

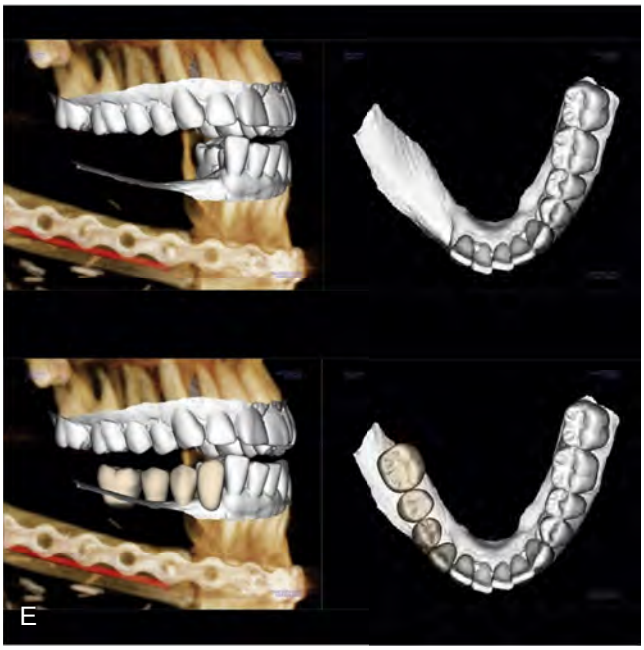
Medical Modeling can import image data from most mainstream CT scanners and PACS systems and most storage media.

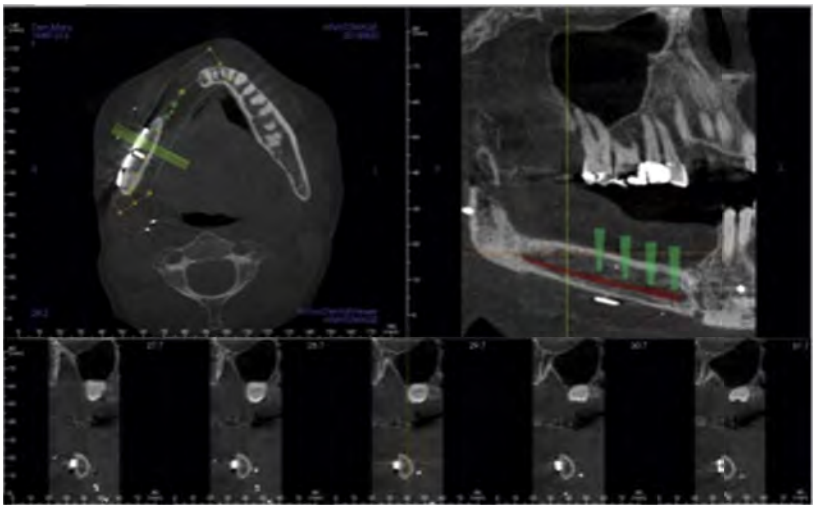
Source: http://www.medicalmodeling.com/images/documents/MM-007_Rev_R_CT_Protocol.pdf. Used with permission from 3D Systems.



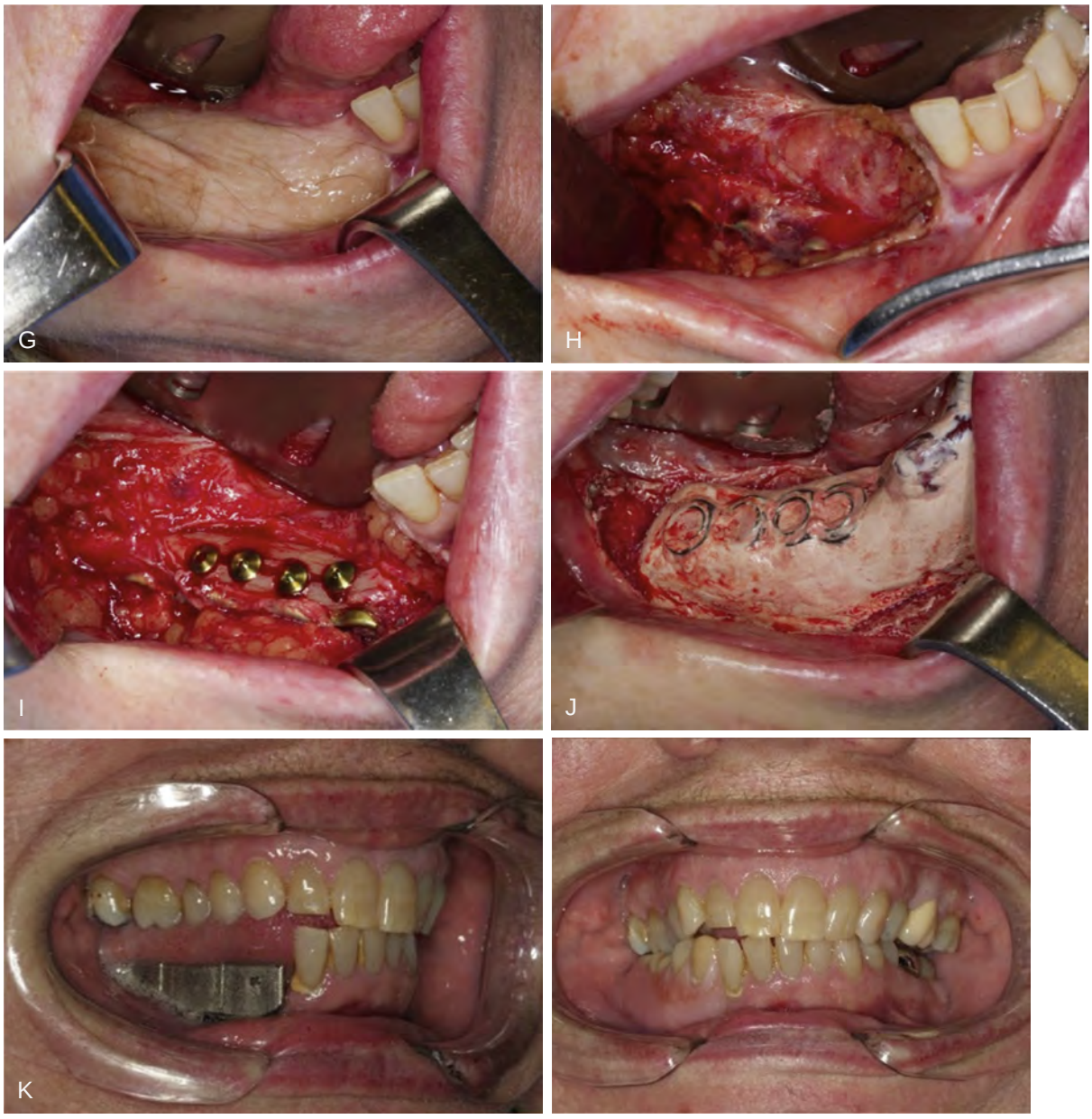
• **Fig. 12.2** Reconstruction of a right mandibular body defect with a single-segment fibula osteocutaneous free flap and delayed implant rehabilitation. **A** to **D,** cT4N0M0 right mandibular gingiva squamous cell carcinoma (SCC) with preoperative virtual surgical planning (VSP) showing resection and reconstruction plan.







• **Fig. 12.2, cont'd** **E** and **F,** Ten months after completion of adjuvant radiation, implant planning was done using postoperative scans, allowing ideal placement of fixtures in relation to fibula and opposing maxillary arch.

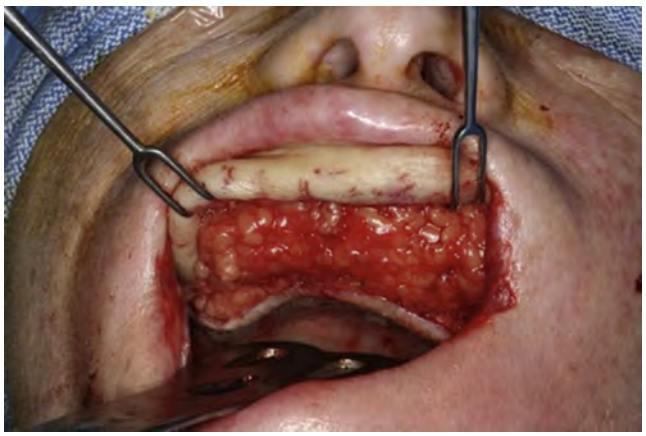


• **Fig. 12.2, cont'd** **G,** Soft tissue architecture of fibula skin paddle before implant placement. **H,** Excision of skin paddle with preservation of the underlying periosteum. **I,** Four fixtures placed with the aid of a surgical guide with minimal reflection of the periosteum to allow mucosalization. **J,** The surgical guide was used as a stent to secure the periodontal tissue dressing (Coe-Pak) overlying the periosteum and implants. **K,** Postoperative photographs of connection bar overlying the implants and final hybrid prosthesis in situ.

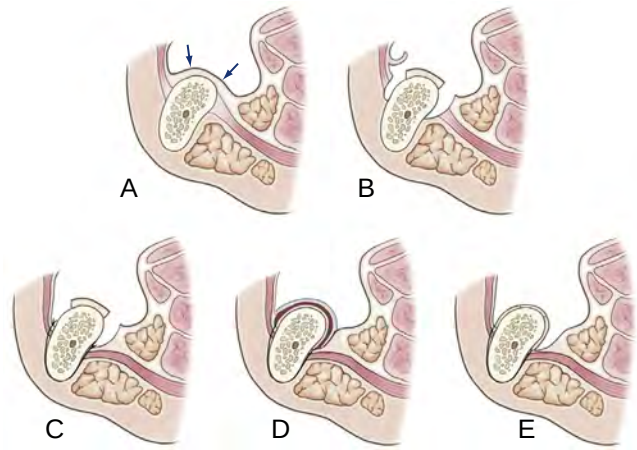
allow maximum soft tissue shrinkage and to allow the patient to progress with the initial surgical phase with no evidence of locally recurrent disease. It is customary to perform this thinning or excision of the skin paddle at the same time as implant placement. Thinning is then done by elevation of the skin paddle and subcutaneous lipectomy down to periosteum (Fig. 12.3). After implant insertion, any excess skin paddle can be excised to ensure good adherence of the skin to the fibular periosteum, and the defect can be skin grafted or allowed to mucosalize.

Vestibuloplasty

Vestibuloplasty, with or without the use of a split-thickness skin graft, can be performed at the time of second-stage surgery or as a separate procedure (Fig. 12.4). A custom splint should be applied to the wound bed for several weeks to produce a



• **Fig. 12.3** Subcutaneous lipectomy of the skin paddle after implant placement.



• **Fig. 12.4** **A** to **C**, Vestibuloplasty with mucosal incision and supraperiosteal dissection to reposition the cut mucosal edge further apically. **D** and **E**, A split-thickness skin graft or palatal mucosal graft is then placed on the periosteum and bolstered down with a stent for 5–7 days.

well-adapted mucosa that has adhered to the underlying reconstructed jaw. The flap skin paddle is usually either excised or incised and reflected labially in a subcutaneous plane to line the lip and create a neo-vestibule (see Fig. 12.4). The edges of the skin paddle are then sutured to the underlying periosteum at the base of the sulcus using non-resorbing sutures and additional anchoring sutures through the external skin to ensure secure fixation of the skin edge. Externally, along the skin, cotton roll bolsters are placed to pad the skin from the sutures. Although this procedure addresses the lack of vestibule, it does not reduce the incidence of periimplantitis. The reconstructed mandible and maxilla typically lack neurosensory proprioception, and therefore oral hygiene maintenance is less than ideal. With the many designs of prostheses, it is imperative to make the abutment-prosthesis construct easily accessible for oral hygiene to prevent growth of hyperplastic tissue. Should soft tissue hyperplasia occur, it should be excised to prevent further accumulation of plaque that can compromise the longevity of the implant.

Soft Tissue Grafting

A surgical option that can often be used to provide keratinized periimplant soft tissue is to replace the skin paddle with a split-thickness skin graft or palatal mucosal graft. This is usually done during second-stage surgery, when placement of healing abutments through the skin graft can be combined with placement of a bolster to help the graft adhere to the underlying wound bed or periosteum.

Extraoral sites similarly need to be prepared for prosthetic rehabilitation at the time of first-stage implant placement. The most common sites are the orbit, nose, and ear. Similar to techniques in the oral cavity, extraoral skin paddles or flaps should be debulked or excised and skin grafted to create a cul-de-sac in the orbit or a nasal or lateral skull base with fixed tissue adherent to periosteum.

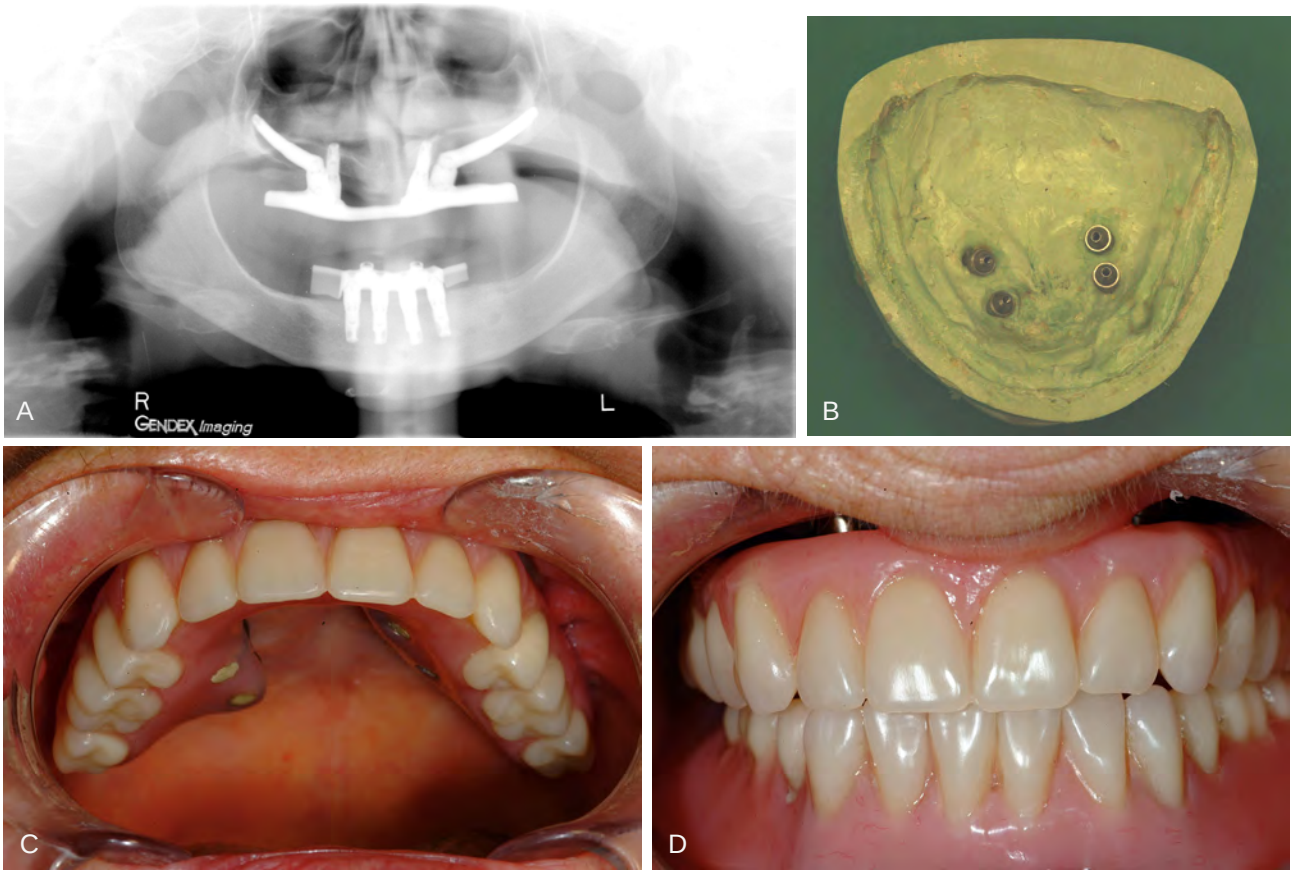
Intraoral Prosthetic Planning

It is critical that preoperative planning for either removable or implant-supported fixed prostheses involve the restoring maxillofacial prosthodontist before surgery, if at all possible. Because of the complex biomechanics associated with prosthetic design, infrastructure frame, and periimplant soft tissue, it is recommended that restoration with these prostheses be performed by maxillofacial prosthodontists or prosthodontists with subspecialty training in the area of prosthetics. The choice of either a fixed dental prosthesis or a removable dental prosthesis is dependent on several factors, such as bone quality and quantity, number and position of potential implants, quality of underlying soft tissue, manual dexterity of the patient, and hygiene maintenance.

While fixed prostheses provide superior performance and esthetics when compared with removable prostheses, choices may be limited because of difficult access to the oral cavity related to scarring or radiation-induced fibrosis. The maintenance of good hygiene is important to prevent inflammatory periimplant granulation tissue. Because of these challenges, a fixed-removable precision attachment prosthesis has been the preferred type of prosthesis in postablative oncologic cases.

The ability to remove the prosthesis is critical in cases in which visualization and maintenance of soft tissue are necessary. It is not uncommon for periimplant mucosa to require surgical debridement of hyperplastic granulation tissue. With time, owing to the lack of innervation of the flaps, muscle or fat atrophy will often necessitate relining procedures to prevent accumulation of food debris beneath the prosthesis.

Reconstruction of a complete dental arch with a fixed prosthesis will require a minimum of 4–5 conventional implants in the mandible and 5–8 conventional implants in the maxilla or a combination of zygomaticus implants with conventional implants, with the greatest spread anteroposteriorly to minimize cantilever forces along the posterior portion of the prosthesis (Fig. 12.5). As few as two implants can be used to retain a mandibular removable prosthesis. It



• **Fig. 12.5** **A** to **D,** Implant rehabilitation of a full-arch maxilla using two zygomaticus implants and two conventional anterior maxillary implants for fixation of a hybrid maxillary dental prosthesis.

is the authors' preference to fabricate a screw-retained Hader framework joining all the mandibular implants. This has the advantage of better stabilization and stress distribution of the implants. The framework provides superior retention as well as critical horizontal stability to the prosthesis. Four implants are needed to support and retain a maxillary removable prosthesis, again using the same prosthodontic principles. For unilateral arch rehabilitation, 3–4 implants are recommended. The minimum dimension of an implant is generally considered to be 3.5 mm in diameter and 10 mm in length.

Timing of Implant-Supported Prosthetic Rehabilitation

In oncologic postablative reconstruction, implants are commonly placed into the reconstructed jaws secondarily. To date, there is no consensus as to when is the best time to place these implants. Many of these patients require postoperative adjuvant radiotherapy, and delayed placement allows better assessment of postsurgical status and the patient's prognosis and surveillance for tumor recurrence. The majority of tumor recurrence generally occurs within the first 12–24 months. A longitudinal prospective study showed that 44% of cancer patients who underwent mandibular resection had recurrence within 13 months of surgery.[11] Another advantage of delaying implant placement is that it will allow preoperative planning with computer guidance, which will lead to improved localization and placement of these fixtures, resulting in improved biomechanics and longevity of the prosthesis.

Several studies have shown that implant survival was not affected by radiotherapy if the implant was placed within 6 months after completion of radiotherapy[12,13] (Tables 12.1 and 12.2). This may not always be practical, because in the majority of patients full recovery after radiotherapy can take up to 12 months due to factors such as xerostomia, dysgeusia, trismus, mucositis, deglutition. In our institution, implant placement is usually delayed for a minimum of 12 months after surgery to allow for complete osseous union of the neo-mandible or neo-maxilla, to decrease the probability of future recurrences, and to allow time to optimize nutritional status.

Classification for Reconstruction of Head and Neck Defects

Head and neck ablative defects can be broadly classified into soft tissue only or composite defects, which involve the soft tissue and underlying hard tissue (cartilage and/or bone). However, for practical purposes, we prefer that defects be classified

TABLE 12.1 Dental Implant Survival Rates in Various Non-irradiated and Irradiated Tissue

Radiation Timing and Anatomic Site	No. Placed	No. Surviving	Survival Rate
Preimplantation Radiation			
Maxilla	516	407	78.9
Mandible	2322	2166	93.3
Vascularized free flaps	366	327	89.3
Nonvascularized bone flaps	115	94	81.7
Overall			88.9
Postimplantation Radiation			
Mandible	81	79	98
Vascularized free flaps	17	17	100
Overall			92.2

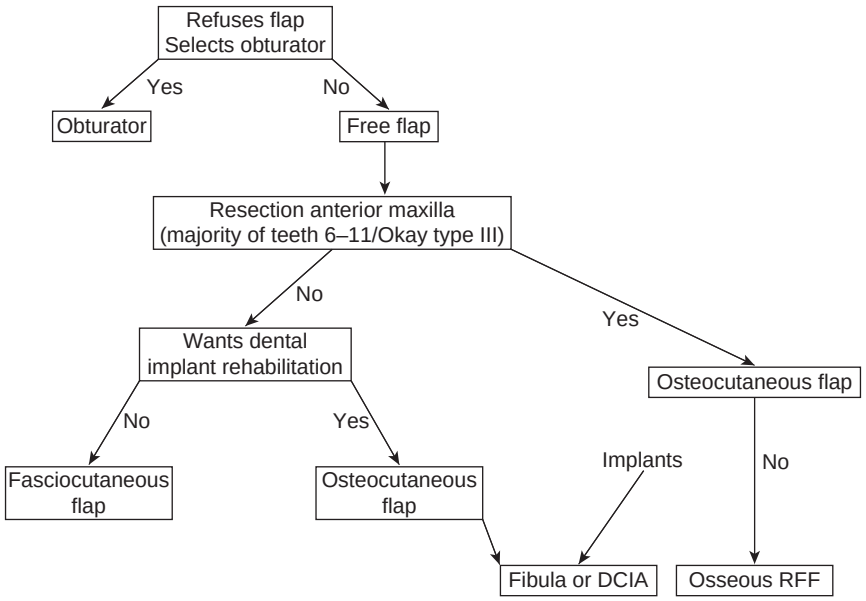
Source: Nooh N. Dental implant survival in irradiated oral cancer patients: a systematic review of the literature. *Int J Oral Maxillofac Implants.* 2013; 28(5):1233–1242.

TABLE 12.2 Odds Ratio (OR) of Factors Influencing Implant Failure Following Radiation Therapy

Evaluated Factor	OR	95% CI	*P* Value
Mandible (vs. maxilla)	3.67	2.81–4.79	< .0001
Mandible (vs. grafted bone)	1.95	1.42–2.67	< .0001
Free flap (vs. nonvascularized graft)	1.87	1.05–3.34	.0333
Native bone (vs. grafted bone)	1.37	1.02–1.85	.0376
Radiation dose <55 Gy (vs. >55 Gy)	1.47	1.18–1.82	.0005
HBO (vs. no HBO)	1.05	0.75–1.48	.7877

CI, confidence interval; HBO, hyperbaric oxygen.

Source: Nooh N. Dental implant survival in irradiated oral cancer patients: a systematic review of the literature. *Int J Oral Maxillofac Implants.* 2013;28(5): 1233–1242.



• **Fig. 12.6** Algorithm for reconstruction of maxillectomy defects. *DCIA,* deep circumflex iliac artery; *RFF,* radial forearm free flap.

as either intraoral or extraoral defects. Intraoral defects are further classified as maxillary or mandibular. Both have more detailed classification systems, as illustrated later.

Preoperative Assessment: Maxillary Defects

Our approach to maxillary reconstruction is to balance the functional and esthetic requirements of the particular defect with respect to the desires of the patient for teeth, a removable or fixed prosthesis, and suitability for free tissue transfer and prognosis (Fig. 12.6). The traditional method of using a prosthetic obturator for intraoral defects, for example, has its shortcomings, especially when being used to reconstruct large defects in which nasal escape will compromise speech quality and swallowing. Because of these disadvantages, free vascularized tissue is our preferred method for reconstructing most maxillectomy defects; this allows for immediate obturation of the defect and provides a platform for implant placement if necessary.

The disadvantage of free vascularized reconstruction is that it does not allow visualization in the defect for potential future recurrences, and the flap will most often need to be thinned before implant placement and prosthetic reconstruction.

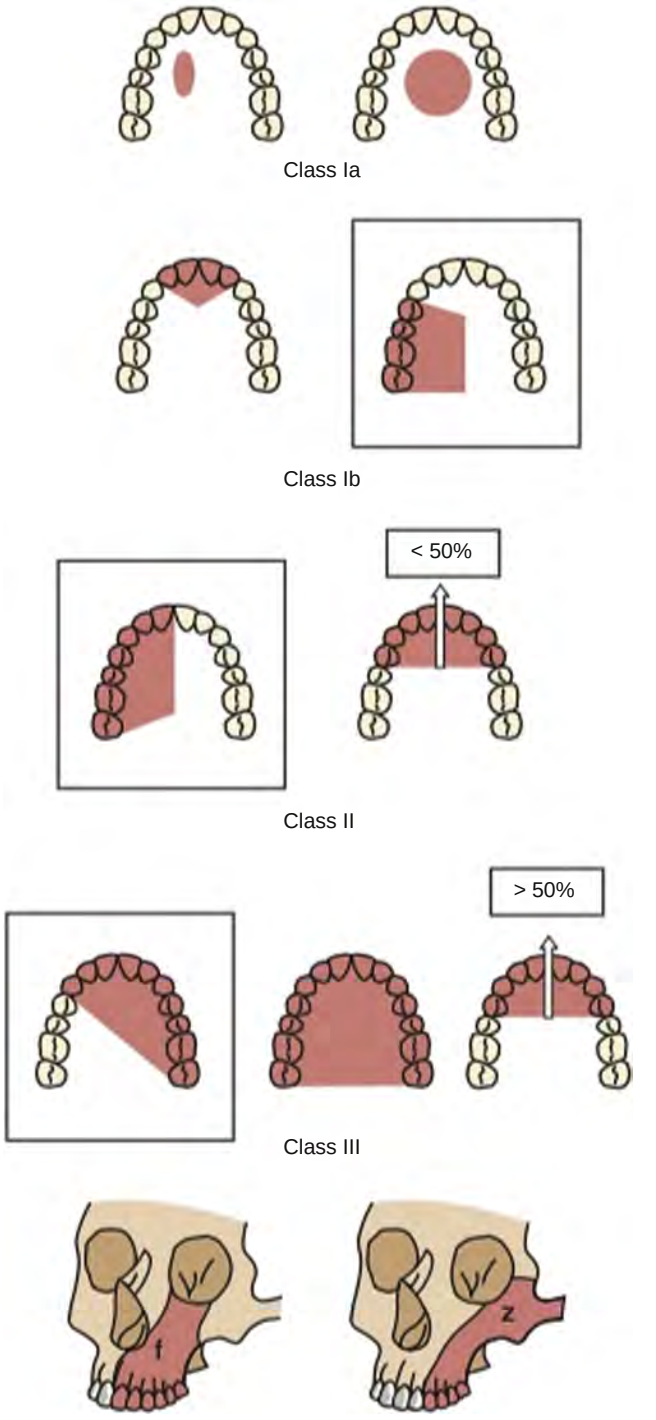
Numerous classification systems have been described to serve as a guide to maxillary rehabilitation. However, our preferred systems are those described by Okay and colleagues[14] as used to categorize the size and location of the maxillary defect, with consideration given to the prosthetic biomechanical properties that contribute to stability and function (Fig. 12.7)[14]; and Brown and Shaw[15] (Fig. 12.8), which considers the facial skeleton to a greater extent than does the Okay classification. Regardless of the classification system, it should be noted that a reduction in the dental arch and hard palatal surface is inversely proportional to prosthetic stability.

According to Okay's classification, three categories of defects describe the horizontal nature of maxillary defects. A class I defect has sufficient remaining retentive and stabilizing components to retain either a fixed or a removal prosthesis (Figs. 12.9 and 12.10). Class I defects are therefore amenable to either prosthetic obturation or surgical reconstruction with a radial forearm free flap or palatal island flap. There is sufficient remaining dental arch and palate that can be used to provide restoration of the dental arch with a tissue-borne prosthesis. In partially dentate cases, implants can be placed in the native maxilla to aid retention. A class II defect is a hemimaxillectomy defect extending to the midline (Fig. 12.11). In class II defects, the increased size of the defect and loss of the ipsilateral canine and molar dentition make the use of a vascularized bone free flap reconstruction critical if a prosthetic obturator is not used. A class III defect extends beyond the midline. The defect involves both canines and the ipsilateral molar dentition and results in a bilateral defect with almost no support for any prosthesis. As the maxillectomy defect increases in size and the remaining dentition and palate decrease in size, a vascularized bone free flap is preferred over a fasciocutaneous free flap to allow for osseointegrated implants to be placed to retain the prosthesis (Fig. 12.12). Treatment planning should involve more implants rather than the minimum number required for support of a restoration. In the event of implant failure, prosthetic success can still be achieved with a shorter restoration of the dental arch or an implant-assisted overdenture without added time or surgery.

It is important that whatever classification system the surgeon uses, a consultation with the maxillofacial prosthodontist be conducted ahead of time, with regard to tumor prognosis, potential resection size and shape, type of vascularized bone flap or osteocutaneous free flap reconstruction, grafting during or after surgery, and whether or not implants are part of the surgical plan, either at the time or surgery or at a delayed surgical procedure. Classification systems are only as good as the communication between the surgeon and maxillofacial prosthodontist, and they are to serve as a general guide to assist in the preoperative and presurgical planning.

Depending on the nature and size of the defect and the presence of the patient's dentition, the conventional obturator can function quite well as a means of restoring the dentition and separating the oral and nasal cavities. One of the often overlooked aspects of the maxillectomy in the extraction of teeth within the resected area is the removal of the entire bony alveolar housing. Ideally, after the tooth adjacent to the resected margin has been removed, the bony housing is preserved. Removing only half of the housing closest to the resection will preserve the bone next to the adjacent tooth. This will prevent mechanical

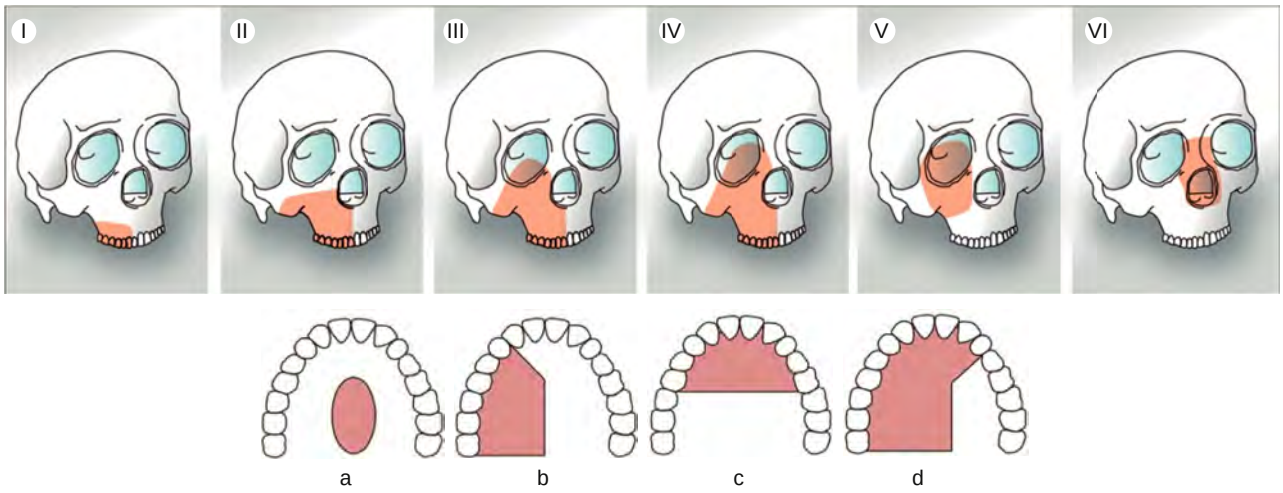
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• **Fig. 12.7** Okay classification of surgical reconstruction of palatomaxillary defects.

- Class Ia: Defects involve any portion of hard palate but not tooth-bearing maxillary alveolus.
- Class Ib: Defects involve premaxilla or any portion of maxillary alveolus and dentition posterior to canines.
- Class II: Defects involve any portion of hard palate and tooth-bearing maxillary alveolus and only one canine. Anterior margin of defect lies within premaxilla. This class includes transverse palatectomy defects that involve less than 50% of hard palate.
- Class III: Defects involve any portion of hard palate and tooth-bearing maxillary alveolus, including both canines. This class includes total and transverse palatectomy defects that involve more than 50% of hard palate.

(Redrawn from Okay DJ, Genden E, Buchbinder D, et al: Prosthetic guidelines for surgical reconstruction of the maxilla: a classification of defects, *J Prosthet Dent* 86:352–363, 2001.)



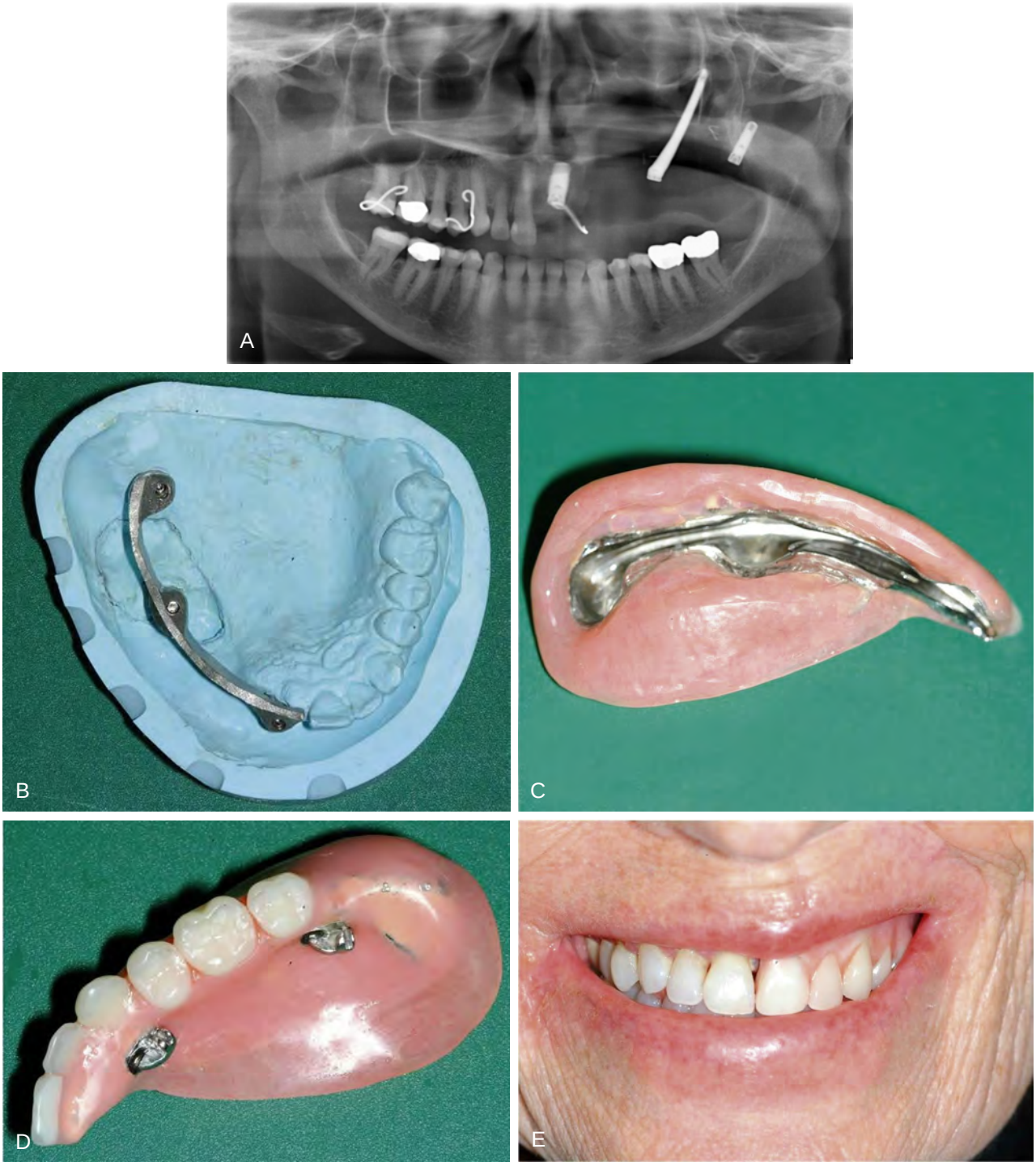
• **Fig. 12.8** Brown classification of maxilla and mid-face.
Vertical classification:
I. Maxillectomy not causing an oronasal fistula
II. Not involving the orbit
III. Involving the orbital adnexa with orbital retention
IV. With orbital enucleation or exenteration
V. Orbitomaxillary defect
VI. Nasomaxillary defect
Horizontal classification:
a. Palatal defect only, not involving the dental alveolus
b. ≤½ unilateral
c. ≤½ bilateral or transverse anterior
d. >½ maxillectomy
(From Brown JS, Shaw RJ. Reconstruction of the maxilla and mid-face: introducing a new classification. *Lancet Oncol.* 11(10):1001–100, 2010.)



• **Fig. 12.9** Reconstruction of an anterior maxillary Okay class Ib maxillary defect with an obturator. **A,** Squamous cell carcinoma (SCC) of anterior edentulous maxilla. **B,** Final results with definitive obturator.



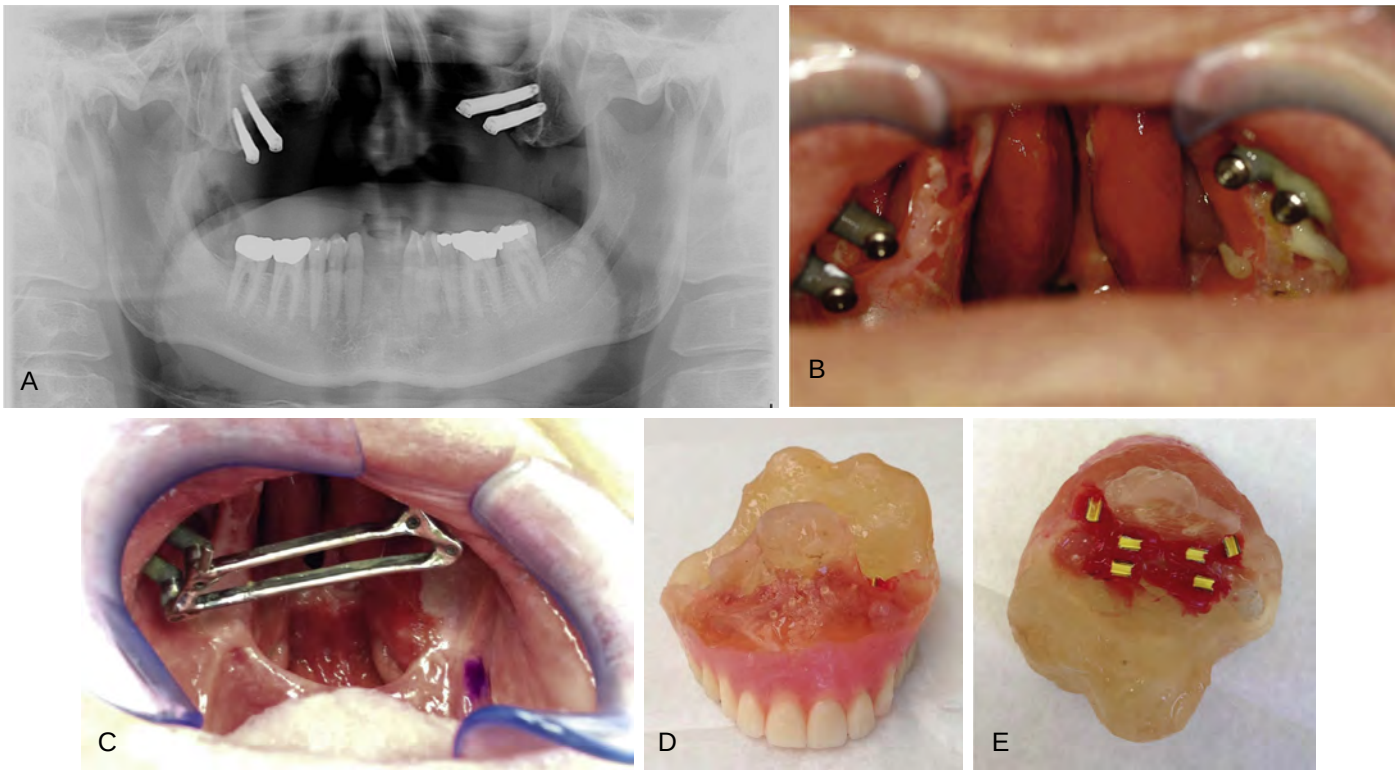
• **Fig. 12.10** Reconstruction of a posterior maxillary Okay class Ib maxillary defect with an cobalt chrome denture. **A,** Squamous cell carcinoma (SCC) of posterior left maxilla. **B,** Cobalt chrome partial denture with acrylic obturating sinus defect. **C** and **D,** Final results with definitive obturator.



• **Fig. 12.11** Reconstruction of an Okay class II maxillary defect that extended to the midline. **A,** Because of increased instability from a hemimaxillectomy defect, three implants were inserted (zygomaticus, pterygoid, and anterior alveolar) to retain a removable hybrid prosthesis. **B** to **D,** Three fixtures connected with a bar and latch denture to allow self-removal for hygiene maintenance. **E,** Final result of left hemimaxillectomy rehabilitation.



• **Fig. 12.12** Reconstruction of an Okay class III maxillary defect with a radial forearm fasciocutaneous free flap and four zygomatic implants. **A** and **B,** Loss of upper lip projection in the absence of bony support after a low-level maxillectomy. A radial forearm free flap was used to create separation between the nasal and oral cavity. **C** and **D,** Four zygomatic implants were inserted with fixture heads projecting toward the alveolus or anterior hard palate. **E,** The four fixtures connected with a bar for clip retention. **F,** Prosthesis designed with clip retention on tissue fitting surface. **G,** Final result with improved projection of upper lip and smile line.



• **Fig. 12.13** Reconstruction of an Okay class III maxillary defect without any soft tissue reconstruction and rehabilitation with only four zygomatic implants. A conventional obturator without any additional stabilization will result in poor retention and stability. **A** and **B,** Four zygomatic implants were inserted with fixture heads projecting toward the hard palate. **C,** Cross-arch stabilization of the implants with two bars. **D** and **E,** The maxillary obturator is fitted around the oronasal defect with retentive clips placed to secure the prosthesis/obturator against the crossbars, providing secure retention.

trauma and periodontal bone loss, which will lead to premature loss of this tooth. It is critical with a conventional obturator to preserve the canine or canines, if possible. The canine plays a significant role in stabilization of both the anterior and mid-posterior maxillary arch, because of the length of its root, the position of this tooth in the arch, and the large amount of bone that usually encases this tooth. Preoperative planning should, if possible, save the canine for postprosthodontic reconstruction with or without implants. In larger defects with limited dentition, implants for the maxilla can be used to aid retention of these obturator dental prostheses. Implants in the maxilla can be inserted into alveolar bone, or the bony flap of a previously reconstructed maxilla. In cases in which there is inadequate native bone, the use of zygoma implants has also been advocated to help retain these prostheses. Zygoma implants have been adapted often in combination with traditional endosseous implants for maxillary obturator support and retention.[16]

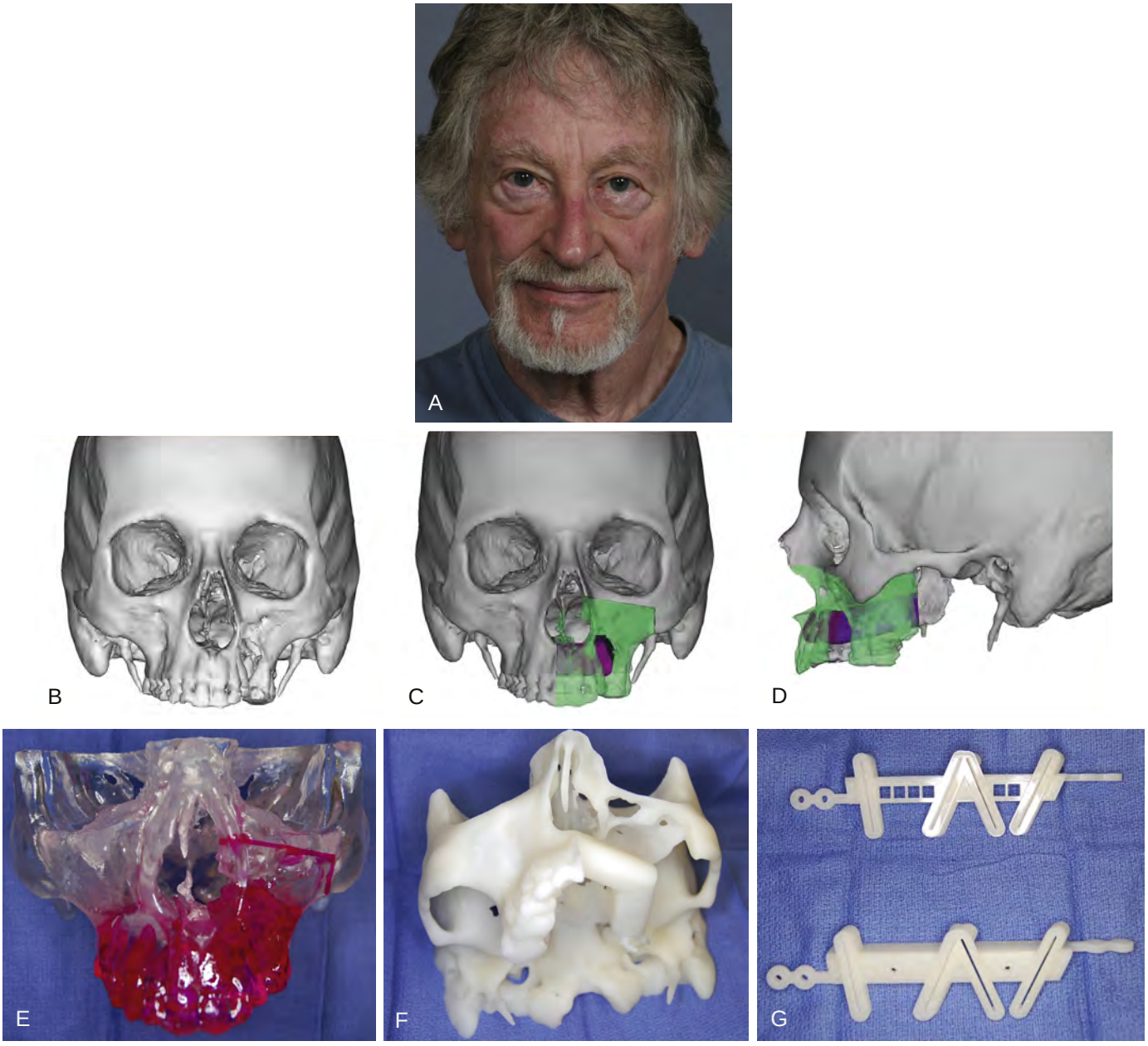
Zygoma implants should be considered if there is inadequate bone posterior to the canine region (see Figs. 12.12 and 12.13). Zygoma implants have allowed the use of distant bone stock (i.e., body of zygoma) to overcome regional bony deficiency. The use of zygoma implants to retain and support a prosthetic obturator in maxillary reconstruction has been described by Schmidt.[16] Placement of the zygoma implant is much easier if done at the time of tumor resection, because delayed placement will necessitate dissection in patients with trismus who have scarred, often irradiated tissue. Owing to the complexity of restoring zygoma implants, preoperative consultation with the maxillofacial prosthodontist is essential. The number, type, and design of implant placement will depend on the location and size of the maxillary defect, as well as the location and amount of remaining bone. Given the long lever arm and the small amount of bone integration, it is critical that these implants be placed bilaterally or, at a minimum, in combination with standard implants placed along the contralateral side to allow for rigid cross-arch stabilization and better distribution of occlusal and retentive forces.

Special Considerations for Implants in the Reconstructed Maxilla

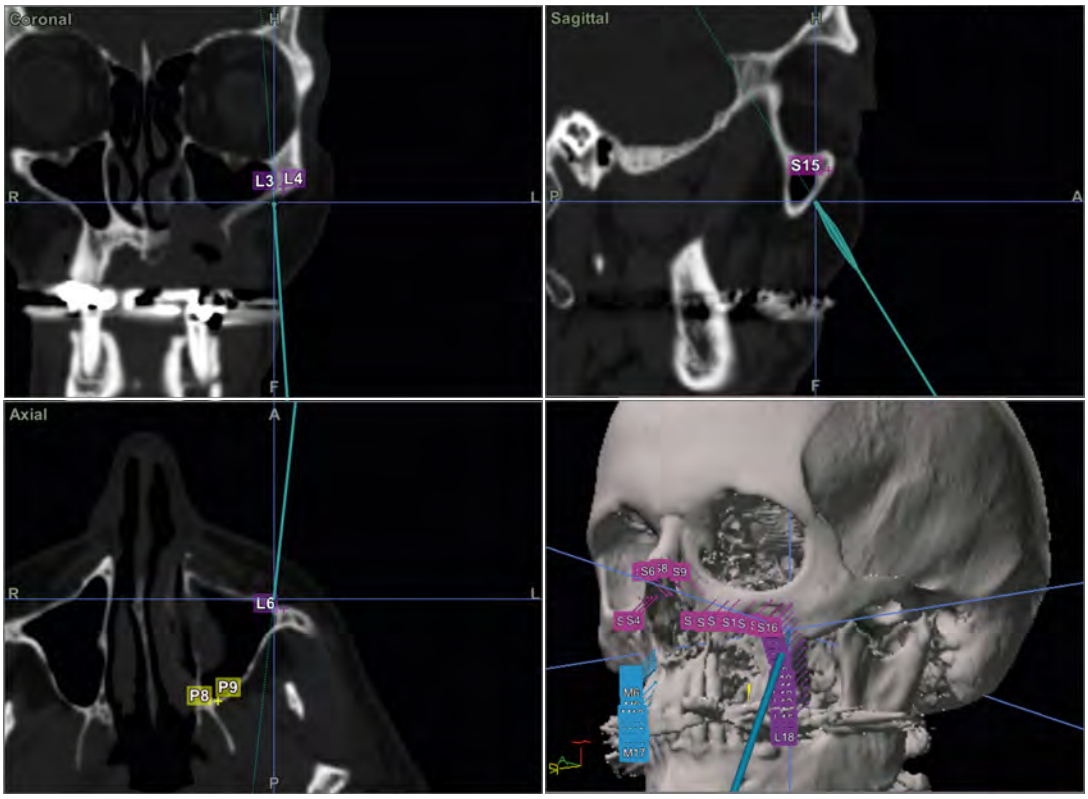
Using the maxillectomy classification as described by Okay and colleagues (see Fig. 12.7), as mentioned previously, class I defects, in our experience, can be readily managed with a prosthetic obturator, with or without a soft tissue flap A vascularized bony free flap offers the most contemporary prosthetic solution for class II and III defects (Figs. 12.14 to 12.18).

Bell and colleagues described the use of intraoperative navigation combined with custom cutting guides and guide stents to implement the virtual plan for patients undergoing maxillectomy or mid-face resection reconstruction using fibular free flaps.[9] The planned reconstruction data from patients undergoing maxillary ablation was "back converted"

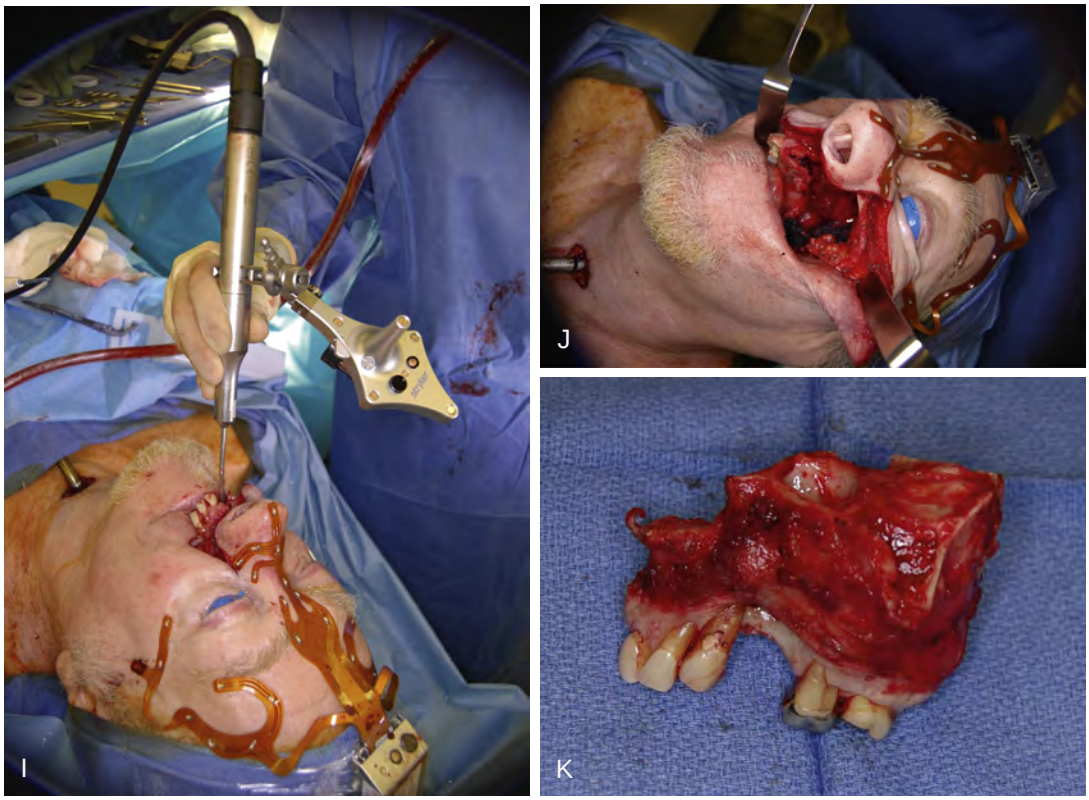
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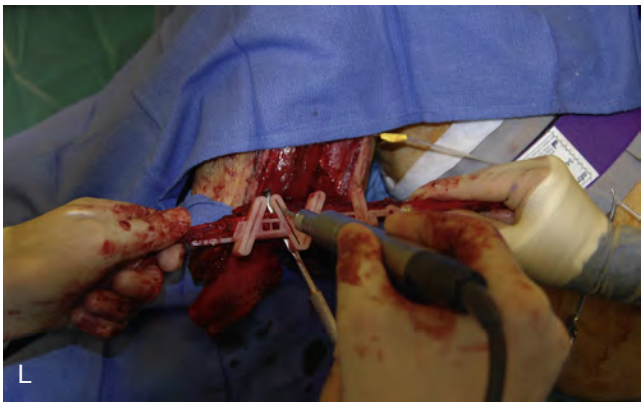
• **Fig. 12.14** Reconstruction and rehabilitation of a left subtotal hemimaxillectomy defect (Brown class IId) with a fibula free osteocutaneous flap and delayed implant placement. **A,** A 67-year-old man with cT4N0M0 left maxillary gingiva squamous cell carcinoma (SCC). **B** to **D,** Virtual surgical planning (VSP) of resection plan with preservation of the orbital floor and reconstruction with a two-segment fibula to recreate the maxillary alveolar process. **E** to **G**, Stereolithographic preoperative model with the segmented fibula to guide placement of bone. Fibula cutting guide to enable accurate osteotomies of the fibula to match the VSP.

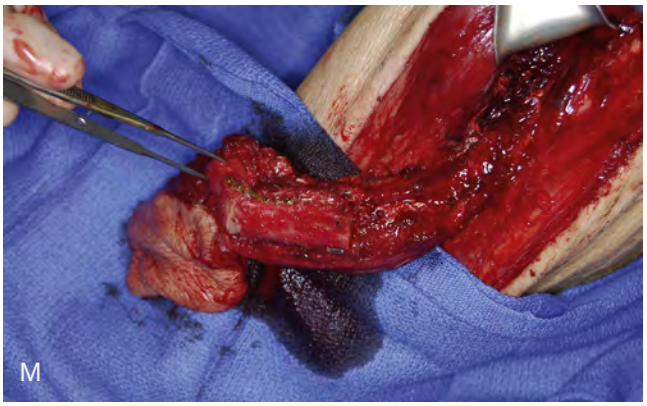


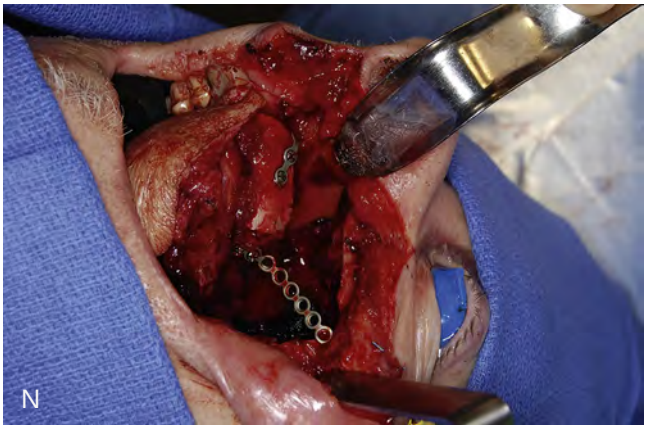
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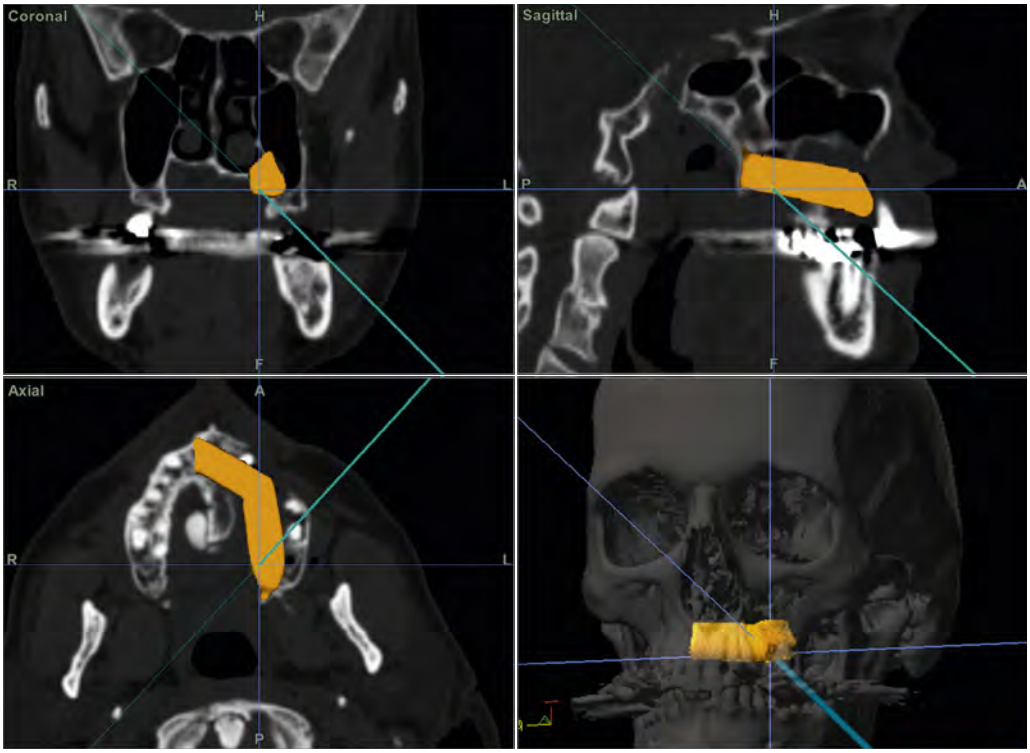


• **Fig. 12.14, cont'd** **H** to **K,** Before use of cutting guides for primary resection, intraoperative navigation was used to confirm accuracy of resection, with the planned cuts along the maxilla transferred to the CT images **(H).** With use of a saw registered with the navigation, bone cuts for the maxillectomy were able to be made according to the VSP plan **(I).** After removal of the specimen, navigation can be used to check that bony resection margins correspond to the VSP **(J** and **K)**.



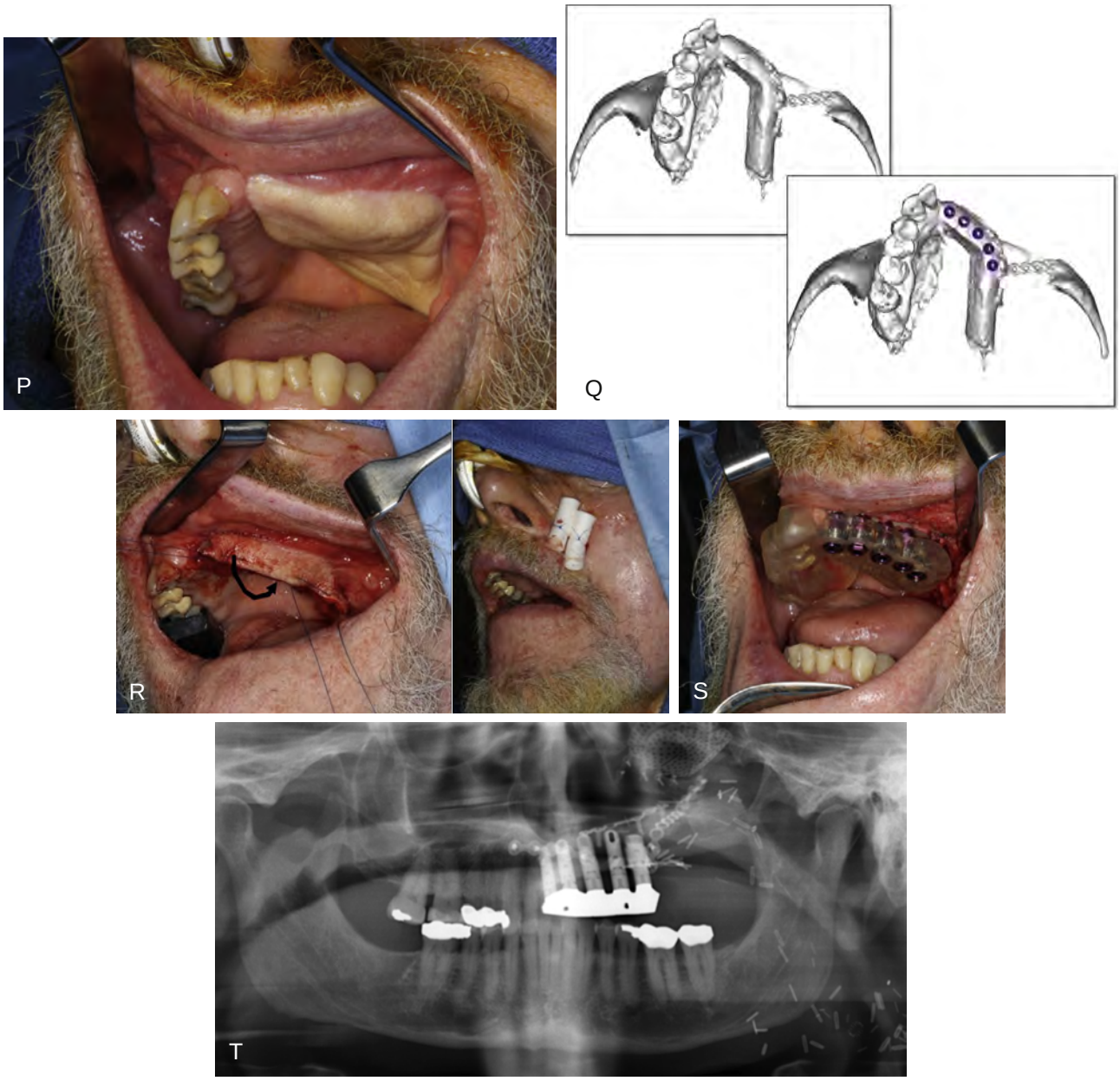






O

• **Fig. 12.14, cont'd** **L** to **O,** Fibula closing wedge osteotomies are made with the cutting guides, and the two segments are assembled and fixed with miniplates. Assembly of the two segments of fibula was aided by the three-dimensionally printed model containing the fibula bone flap (see Fig. 12.14F). This construct is then transferred to the maxillary defect and secured in place with additional miniplates. Navigation is used to guide the positioning of the fibula so that it corresponds to the virtual plan that has been exported to the navigation software **(O)**.



• **Fig. 12.14, cont'd** **P,** Appearance of soft tissue 12 months after initial reconstruction. **Q** to **S,** Planning for implant rehabilitation with overengineered infrastructure using five fixtures. Vestibuloplasty and excision of excess skin paddle were performed simultaneously during first-stage surgery for insertion of the implants. A surgical implant guide was made to aid the insertion of these fixtures.









• **Fig. 12.14, cont'd** **T** to **V,** Postoperative orthopantomogram and clinical photos with attachment bar connecting the fixtures. Note the mucosalized area from the excised skin paddle around the fixtures. **W** and **X,** Postoperative clinical photos with the dental prosthesis in situ.

from its proprietary language to the standard DICOM format, so that digital reconstruction may then be imported into a surgical navigation system (Intellect Cranial Navigation System, Stryker, Freiburg, Germany). The resection was performed under navigation guidance so that the ablative defect matched the planned fibular reconstruction. Custom guide stents were then used to recreate the fibular closing wedge osteotomies, so that the neo-maxillary construct fit the ablative defect. The entire neo-maxillary construct was then inserted under navigation guidance. Secondary implant placement was then planned with the VSP software, and custom guides for implant placement were fabricated to be used for insertion of fixtures. At the same time, vestibuloplasty was performed.

This method has been used for total maxillectomy defects, with reports by Bell[17] and Hanasono and colleagues,[8] who also described favorable results in a single patient who underwent reconstruction of a total maxillectomy defect (see Fig. 12.16). Besides providing a chance for preoperative planning, Bell and Hanasano and colleagues noted that computer-assisted preoperative planning also limits the number of incisions that have to be made on the face.

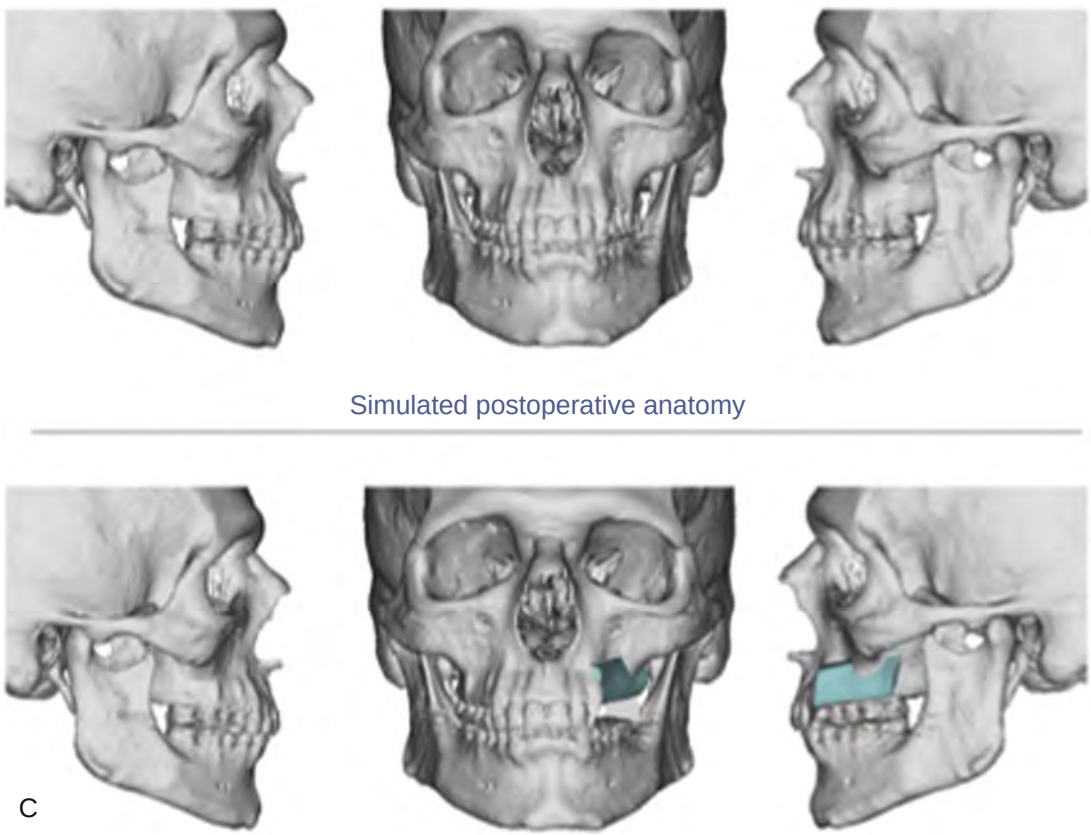
Zygoma Implants

Postablative defects in the maxilla following both malignant and benign neoplasms will often preserve the body of the zygoma, which enables its use for insertion of zygomatic implants. Zygoma implants have a length of 30–55 mm. Implant osseointegration occurs at the apex of the fixture, where it engages the dense body of the zygoma, producing an osseointegrated length ranging from 15 to 20 mm. In ideal situations, the axes of the zygoma implants lie along the zygomaticomaxillary buttress and the fixture head is situated along the region of the second premolar and first molar. Therefore the fixture head is angulated at 45–55 degrees to the long axis of the implant. Despite the good stability achieved with integration with the zygoma, the long lever arm of this fixture requires it to be used with cross-arch stabilization, whether it be in the form of another contralateral zygoma implant or conventional implants. This cross-arch stability requirement limits the use of zygoma implants for unilateral maxillectomy defects.

The use of zygoma implants provides an option for a framework to which dental prostheses can be attached.

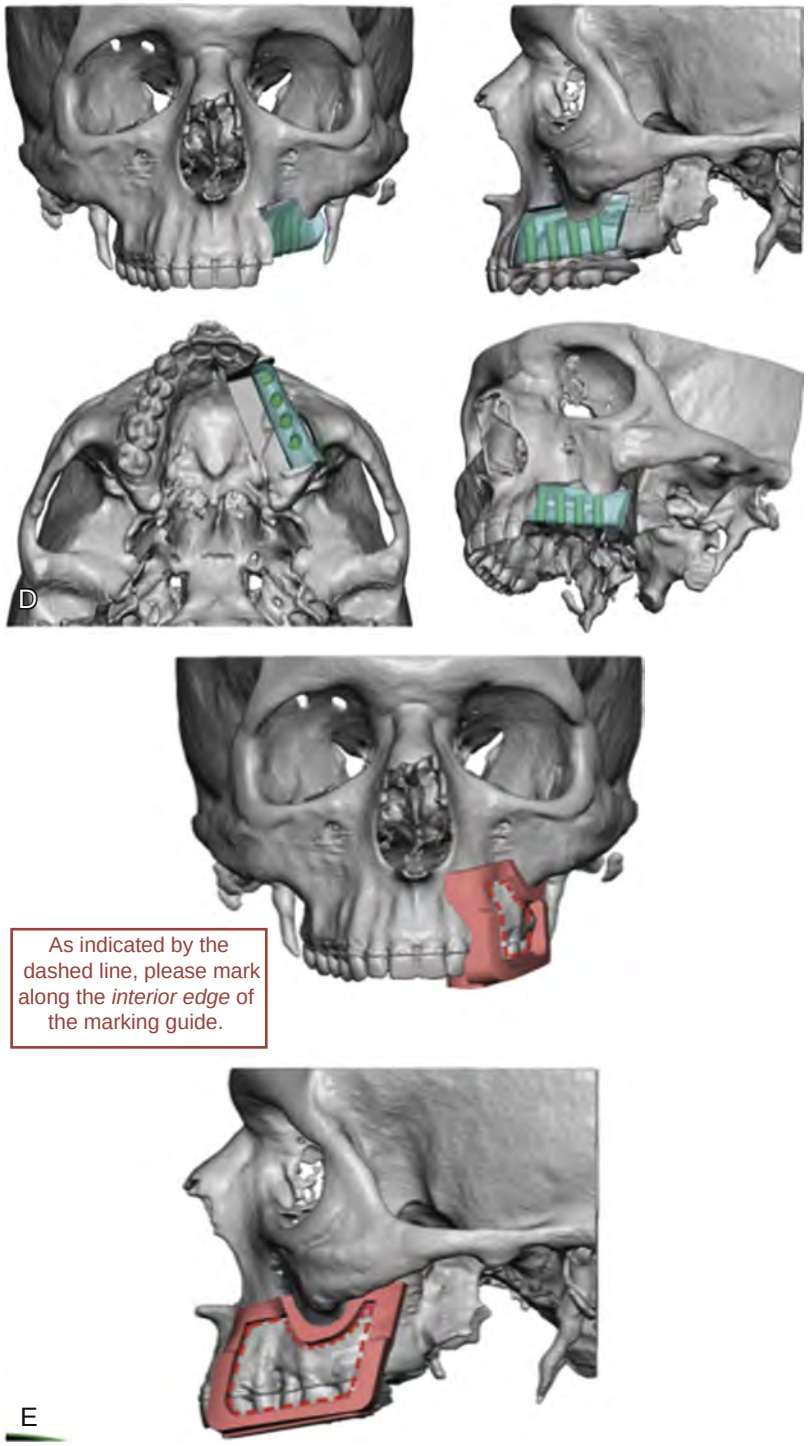
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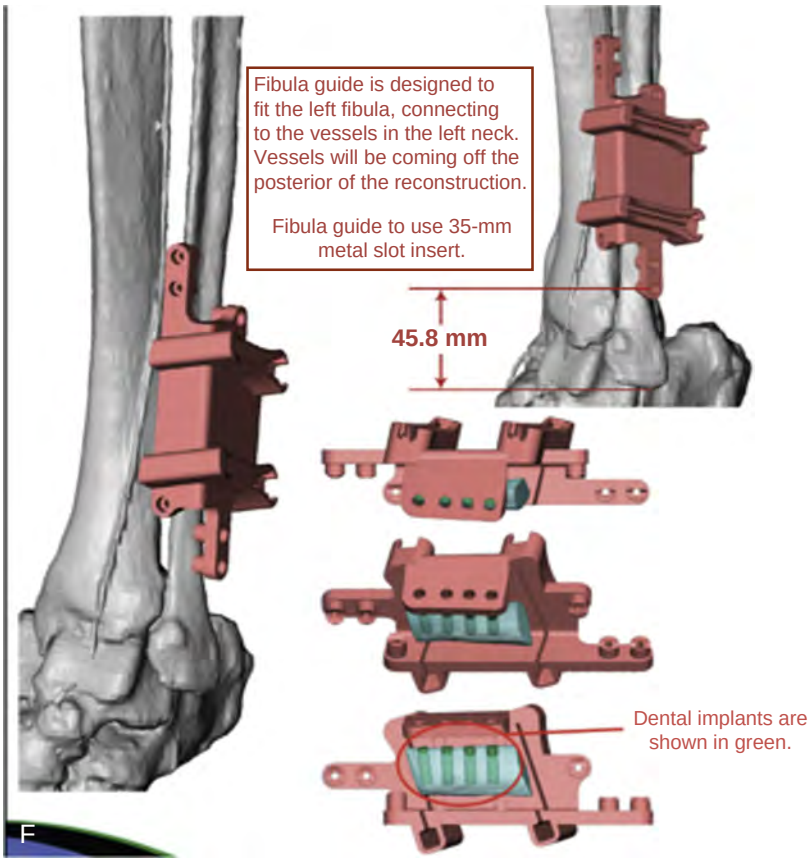


• **Fig. 12.15** Reconstruction and rehabilitation of a left partial maxillectomy defect (Okay class Ib) with a fibula free osteocutaneous flap and immediate implant placement. **A** and **B,** A 55-year-old male with a cT2N0M0 left maxillary gingiva squamous cell carcinoma (SCC). **C,** Virtual surgical planning (VSP) of the single-segment fibula reconstructing the maxillary alveolus.

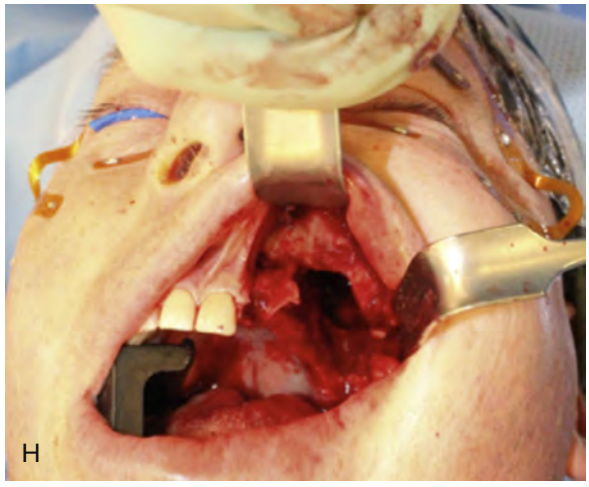
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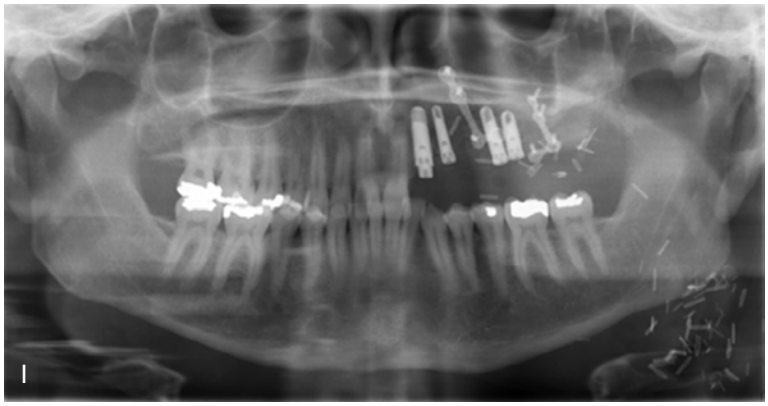


• **Fig. 12.15, cont'd** **D,** Four implant fixtures placed within the fibula. **E,** Illustration of the cutting guide to accurately reproduce the planned resection. With this cutting guide, there was less reliance on intraoperative navigation.









• **Fig. 12.15, cont'd F,** Implant guides were incorporated within the fibula cutting jig. **G,** Tumor cutting guide in place. Note that intraoperative navigation was still used to analyze the accuracy of the resection. **H,** Defect after resection of primary.





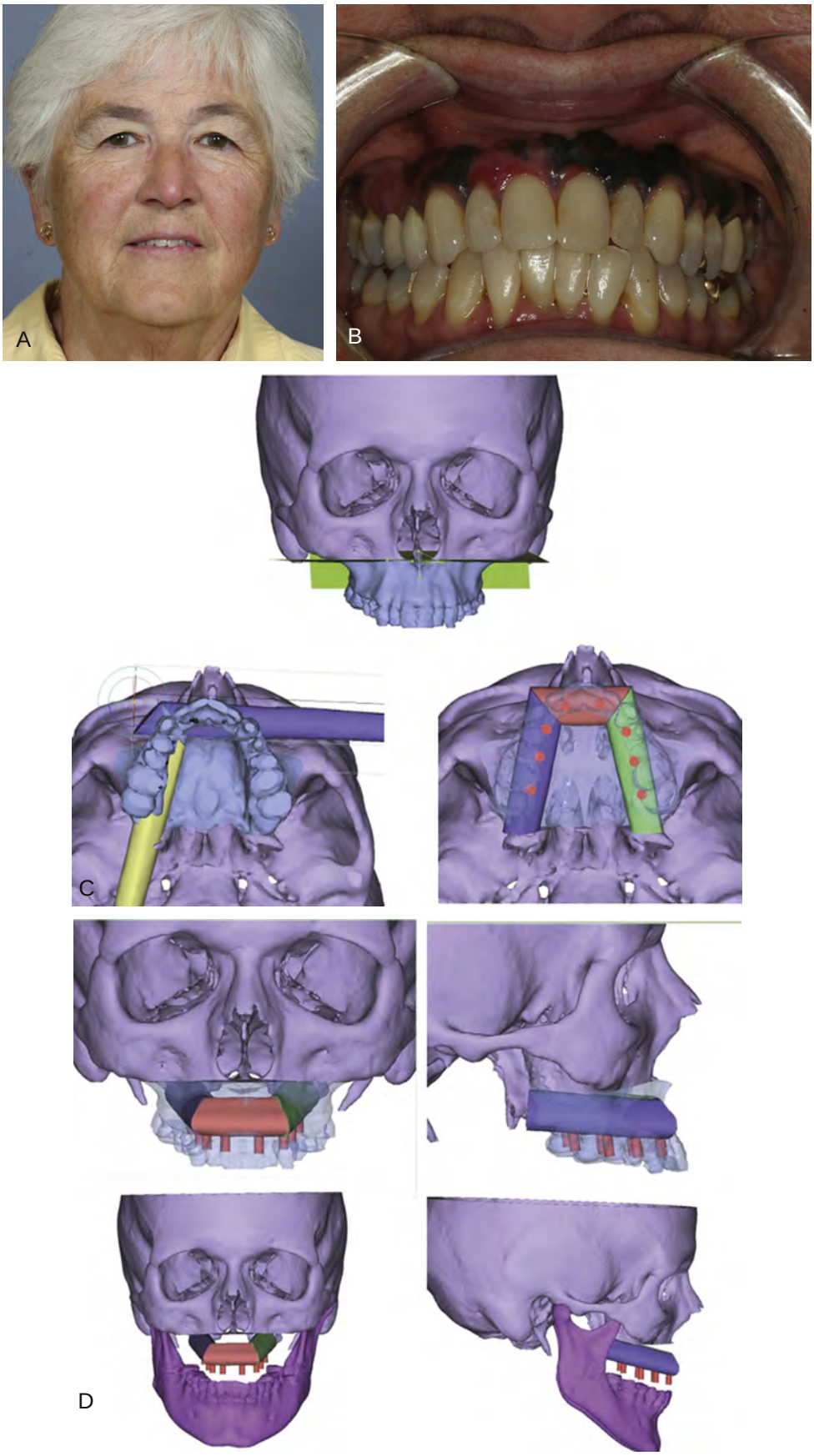
• **Fig. 12.15, cont'd** **I** to **K,** Postoperative radiograph and clinical photographs after insertion of connector bar and dental prosthesis. Note that in this case, the fibula was harvested with a small skin paddle for monitoring; this was excised during second-stage surgery.

Schmidt reported the use of bilateral, dual zygoma implants to support a total maxillary prosthesis without anterior implants.[16] Soft tissue free flaps and zygoma implants can be combined. Panagos and Hirsch reported a hybrid immediate reconstruction of a maxillary defect that used a microvascular radial forearm flap with both a zygoma implant and a pterygoid implant. The implants perforated the flap to support a maxillary prosthesis.[18] The combination of vascularized iliac crest bone with a soft tissue paddle plus zygoma and conventional implants placed at the time of ablative surgery has also been reported.[19]

In postablative cases where the defect has been reconstructed with free vascularized tissue to seal off the nasal from the oral cavity, dental rehabilitation with implants is usually done in a delayed fashion to allow shrinkage of soft tissue bulk. Even despite this, on most occasions these flaps will require some debulking and additional soft tissue surgery to optimize placement of implants and prostheses. Use of zygoma implants that can be placed at the time of ablative surgery will allow for a faster recovery toward full dental rehabilitation.

Technical considerations for planning and insertion of zygoma implants in maxillectomy defect surgery are as follows[20]:

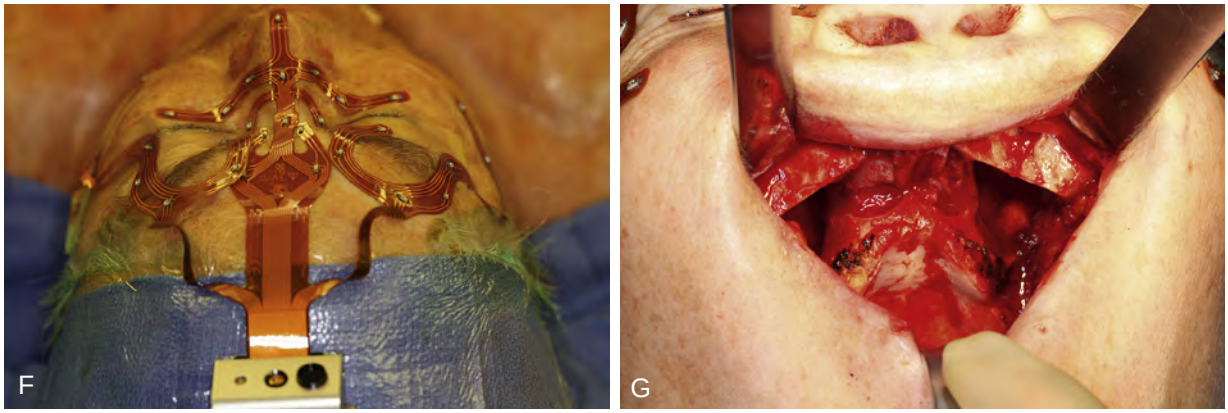
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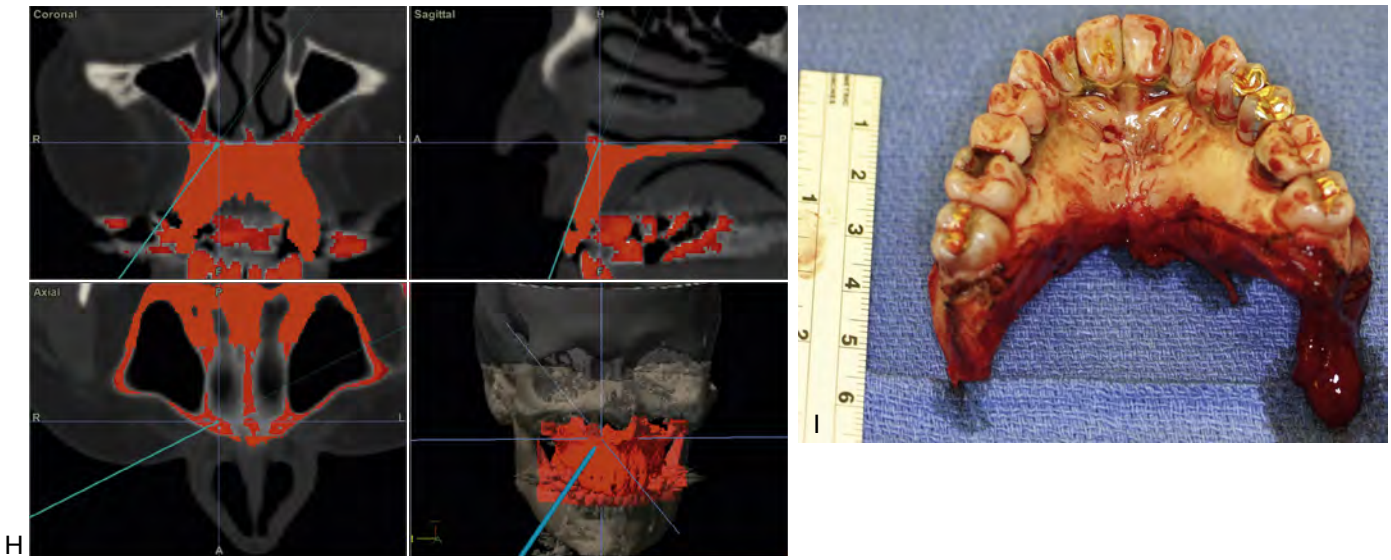


• **Fig. 12.16** Reconstruction of an Okay class III defect with a three-segment fibula osteocutaneous free flap and immediate implant rehabilitation. **A** and **B,** Malignant melanoma of labial attached gingiva. A low bilateral maxillectomy was planned, with preservation of the orbital floor. **C** to **E,** Virtual surgical planning showing before and after virtual resection and simultaneous implant insertion with the three-segment fibula used to reconstruct the whole alveolar segment. Bone graft template with guide stent for implant insertion is shown in Fig. 12.16E.

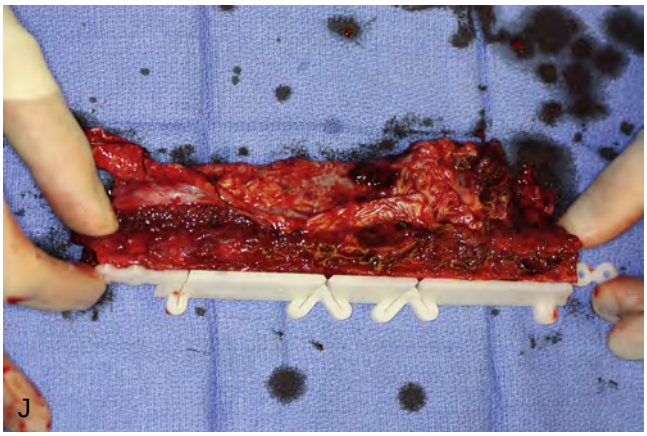
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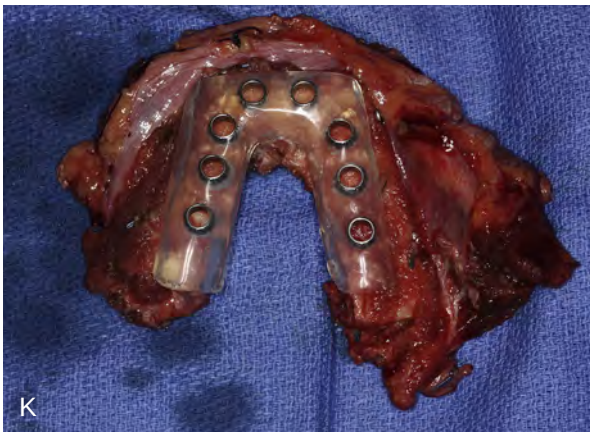


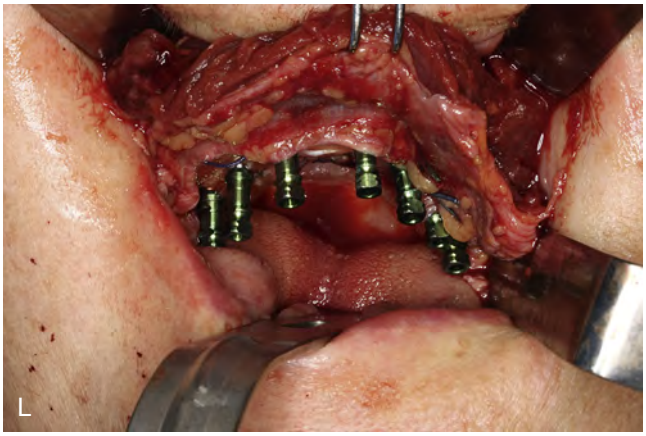


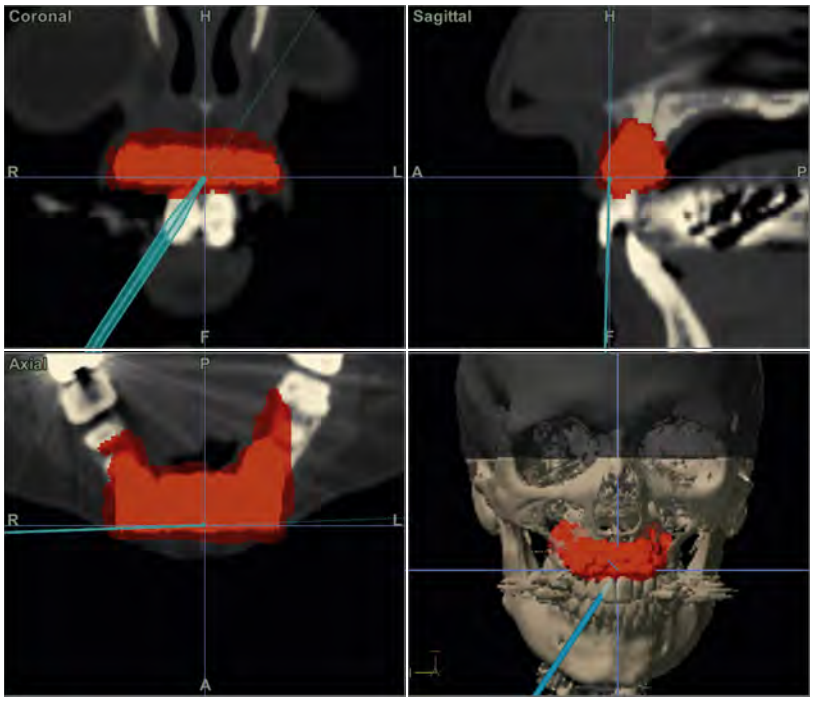


• **Fig. 12.16, cont'd** **F** to **N,** Intraoperative photos showing use of navigation for resection and the use of a cutting guide for the fibula osteotomies. Once the fibula is osteotomied and closing wedges removed, the segments are brought together and placed within the guide stent (see Fig. 12.16K) for implant placement. The navigation system is again used to guide the inset of the fibula to ensure accuracy (Fig. 12.16M).



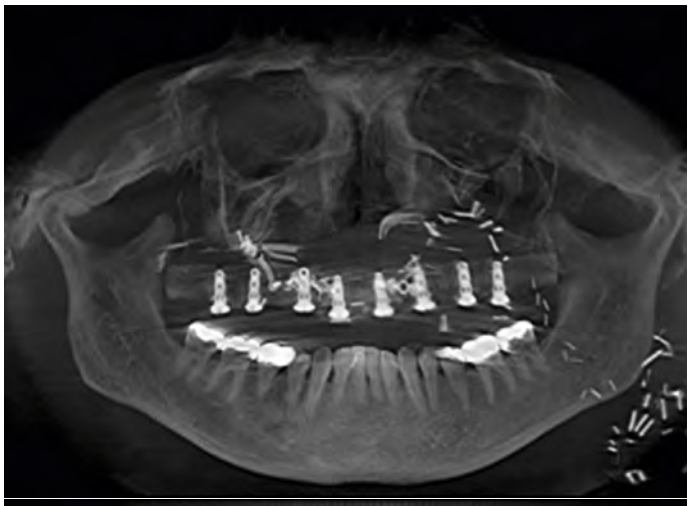


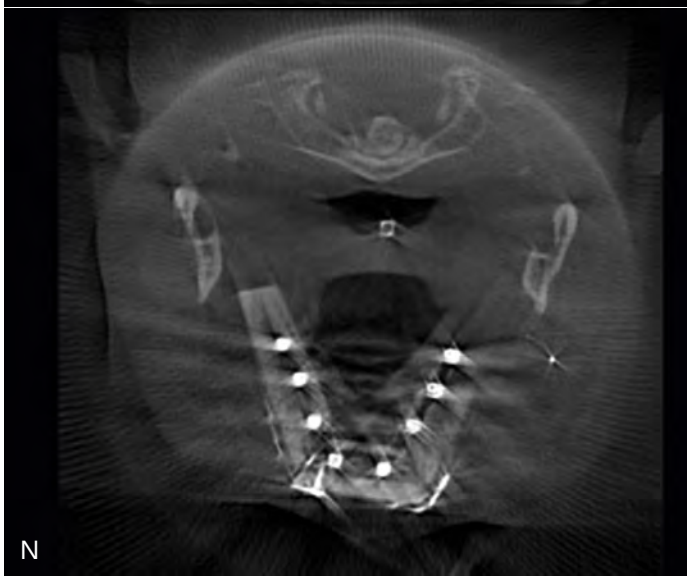




M

• **Fig. 12.16, cont'd** For legend see opposite page.







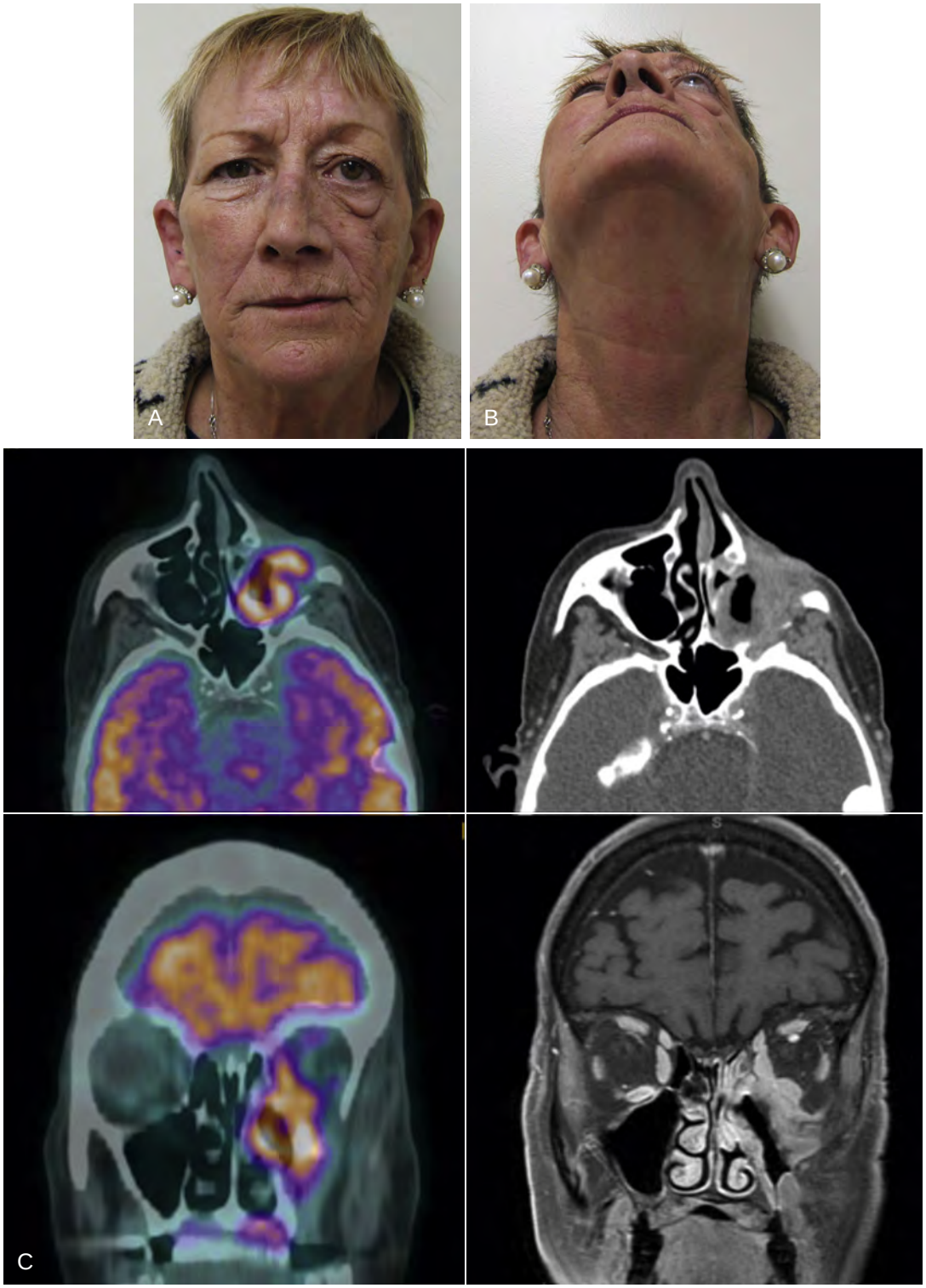






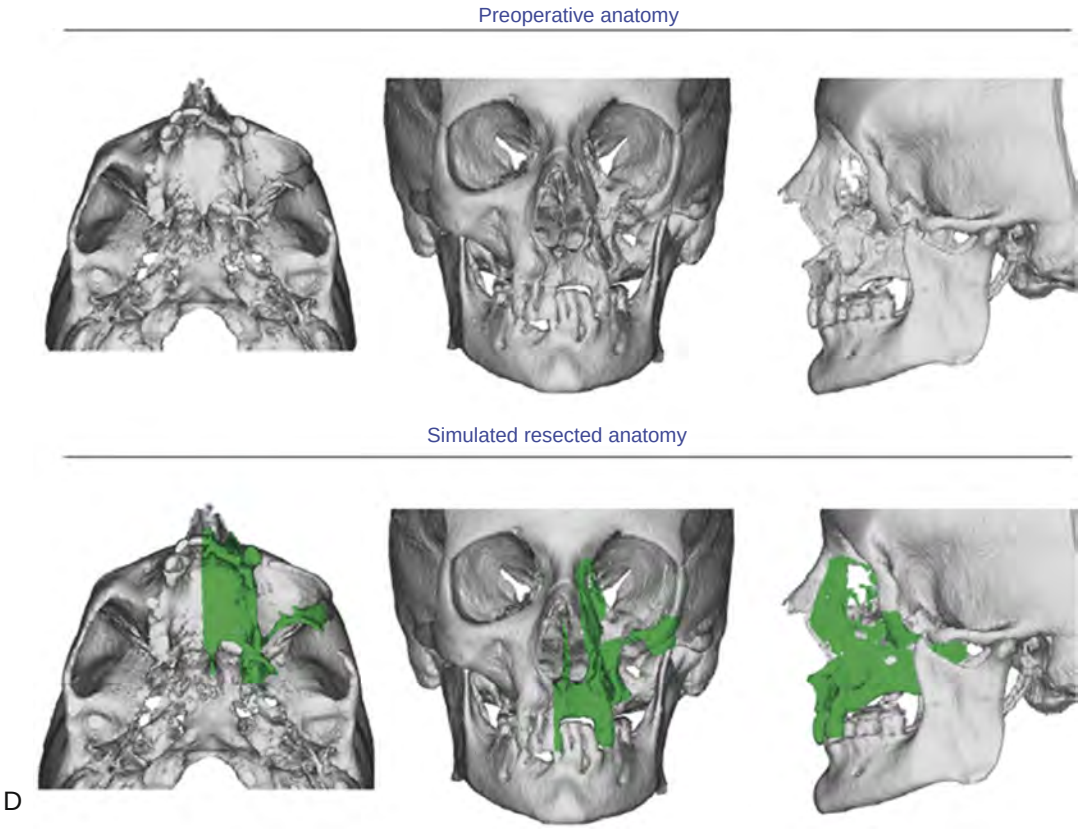


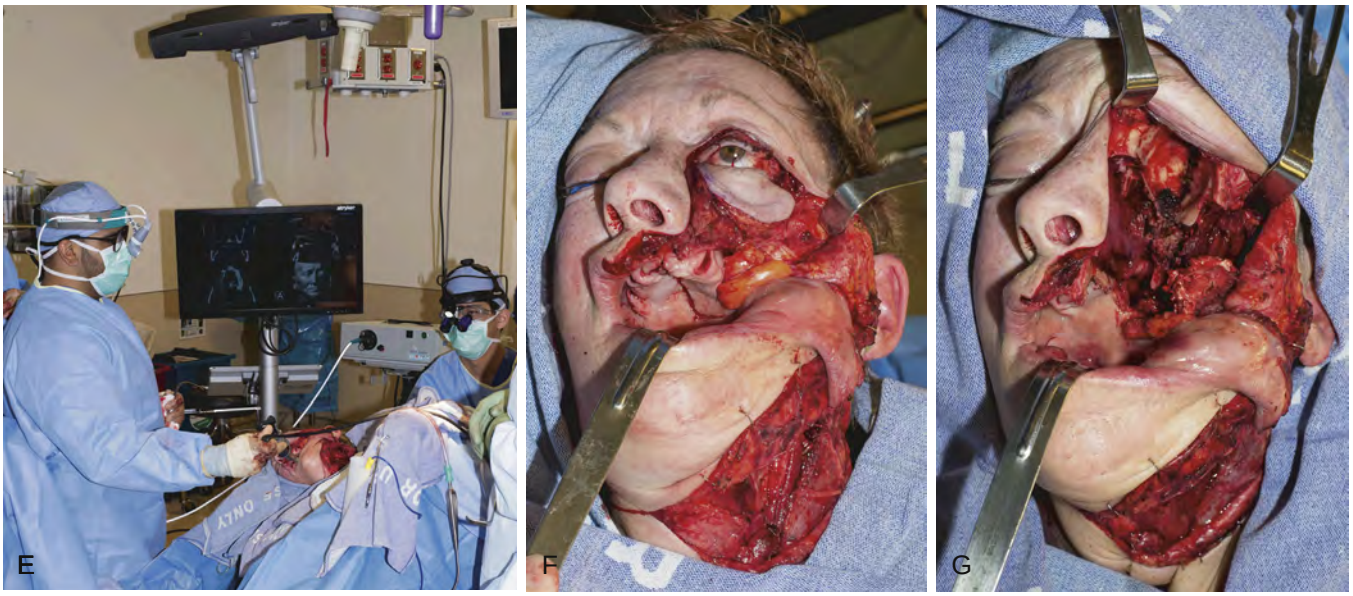
• **Fig. 12.16, cont'd** **O** to **S,** Postoperative clinical photographs and radiographic images showing position of fibula segments with implants in situ.



• **Fig. 12.17** Reconstruction of a Brown class IVd defect with a chimeric osteomyocutaneous scapula free flap and delayed implant rehabilitation for an orbital prosthesis. **A** to **C,** A 64-year-old woman with a cT4N0M0 left maxillary sinus squamous cell carcinoma (SCC) with invasion into the orbit.

Continued





• **Fig. 12.17, cont'd** **D,** virtual surgical planning (VSP) of the planned resection of left hemimaxilla and zygomatic complex. **E** to **H,** Intraoperative photos showing use of navigation and extent of hard and soft tissue defect.



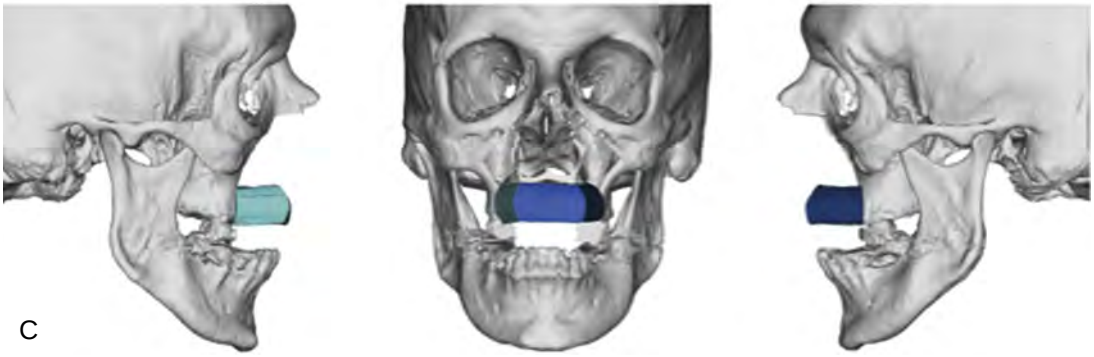
• **Fig. 12.17, cont'd I,** Chimeric scapula free flap with latissimus dorsi, scapular tip, and scapular and parascapular skin paddle. **J,** The scapula tip was used to reconstruct the anterior maxilla and mid-face; latissimus dorsi with the overlying skin was used to obturate the orbital cavity; and the scapular/parascapular skin paddles were used to cover the oral cavity defect and line the left lateral nasal wall. **K,** Thirteen months after initial surgery and adjuvant radiation, three implant fixtures were placed along the superolateral orbital rim. Note the significant shrinkage of the latissimus dorsi muscle within the orbital cavity. **L** and **M,** Orbital prosthesis with magnetic attachment. **N** and **O,** Postoperative clinical photos with orbital prosthesis in place.



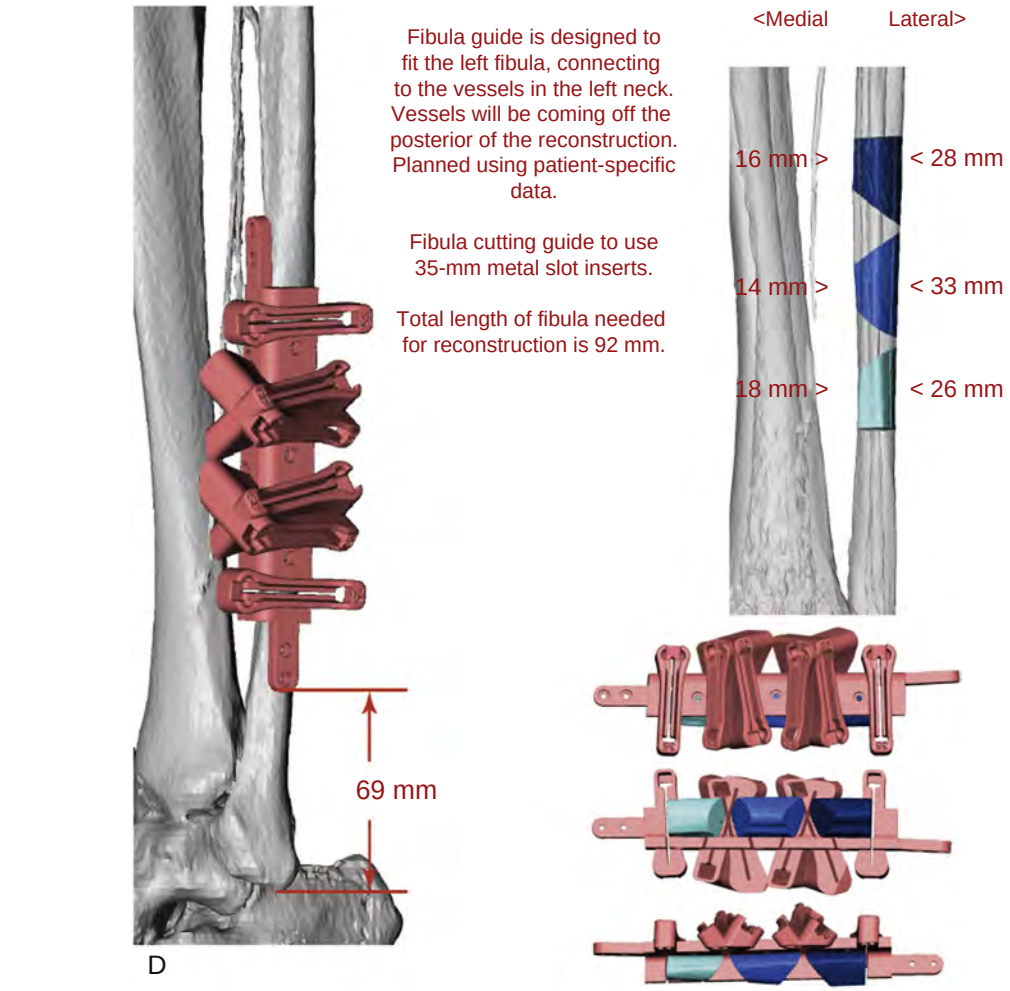
Preoperative anatomy

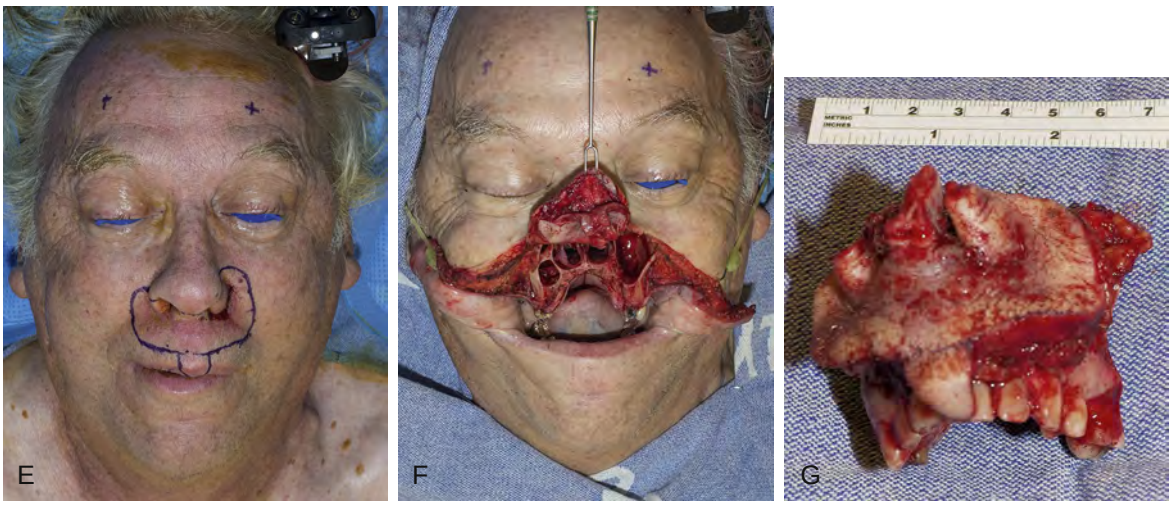


Simulated postoperative anatomy



• **Fig. 12.18** Reconstruction of an Okay class III anterior maxillary and nasal defect with a three-segment fibula osteocutaneous free flap and delayed implant rehabilitation. **A** and **B,** Squamous cell carcinoma (SCC) of the anterior maxillary alveolus with invasion toward the philtrum and floor of nose. **C** and **D,** Virtual surgical planning showing before and after virtual resection and fibula cutting guide with the three segments used to reconstruct the anterior alveolar segment.

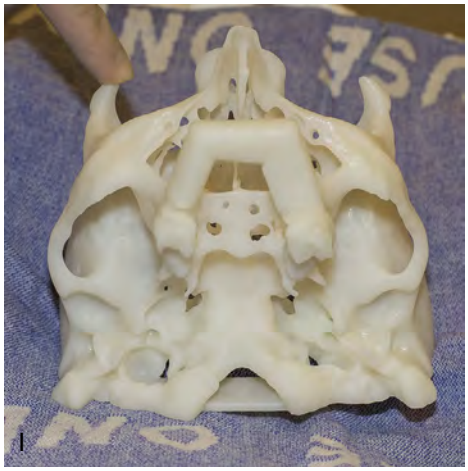




• **Fig. 12.18, cont'd** **E** to **G,** Intraoperative photographs showing the extent of soft and hard tissue defect and the use of navigation with the skull-mounted sensors for resection.

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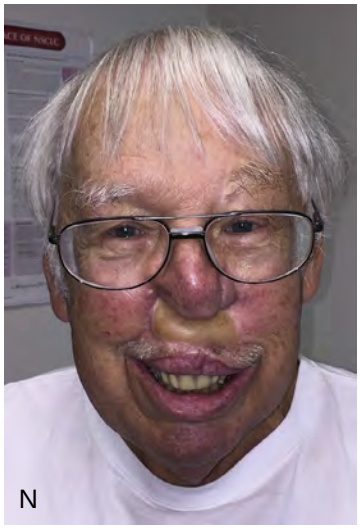












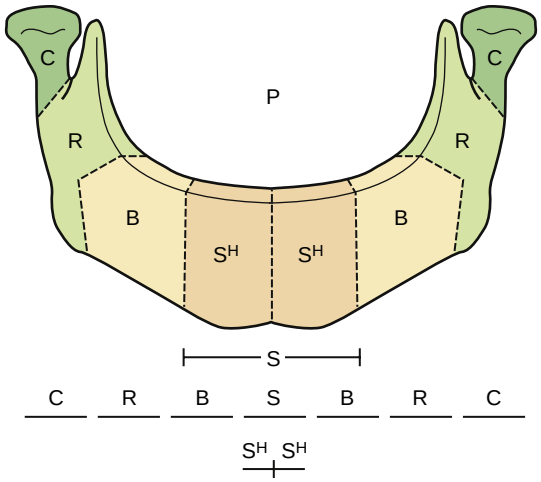
• **Fig. 12.18, cont'd** **H** and **I,** The use of a cutting guide for the fibula osteotomies. Once the fibula has been osteotomized and the closing wedges have been removed, the segments are brought together and inset into the maxillary defect with the aid of navigation and biomodel. **J,** Fibula osteocutaneous free flap inset completed with the skin paddle used to reconstruct the lower perinasal skin, alar region of the nose, and intraoral mucosa. A portion of the skin paddle was de-epithelialized to fold deep to the upper lip. Note the discontinuity defect of the left alar fold and columella. **K,** Staged reconstruction of the columella and left alar fold with a cartilage graft and a combination of forehead flap and superiorly based nasolabial flap. **L,** Four fixtures placed into the fibula after soft tissue revision, vestibuloplasty, and debulking of flap. **M** and **N,** Postoperative result after dental prosthetic rehabilitation with maintenance of upper lip length.

1. In bilateral maxillectomy defects, when planning for zygoma implants, ensure that there is a minimum of one zygoma implant on each side.
2. Zygoma implants are best inserted at the same time as resection owing to the wide access already available for the maxillectomy. If secondary insertion of implants is considered, then the severity of trismus and buccal mucosa scarring must be assessed, because these factors will significantly influence the ability to insert these long implants in the ideal position.
3. Ipsilateral coronoidectomy on the side of the tumor resection at the time of implant insertion is recommended to minimize trismus and prevent displacement of the prosthesis from the antero-inferior movement of the coronoid process during mouth opening.
4. In the immediate insertion setting after maxillectomy, when a Weber-Ferguson approach is used, access to the body of the zygoma is seldom an issue. A slot is made in the zygomaticomaxillary buttress and extended all the way to the body of the zygoma for visualization of the path of insertion of the fixture. Proper angulation can be aided by the use of a prefabricated provisional denture prosthesis or surgical guide, which helps avoid the tendency of placing the fixture heads too far buccally or lingually.
5. If two zygoma implants are to be used, the orientation of these two fixtures should allow a minimum of 3 mm of bone between them.
6. When the resection margin has traversed across the midline of the palate and the entire nasal floor has been removed with the resection, zygoma implants can be placed transnasally through the contralateral maxillary sinus to engage the contralateral body of the zygoma.
7. Maxillectomy patients require daily cleansing of their maxillectomy defects, which are open to the oral cavity. Hygiene considerations of the exposed implant fixture within the maxillectomy defect may be addressed with either a smoothly machined, threaded, but nontextured implant (Nobel Biocare, Kloten, Switzerland) or an implant with a smooth, nonthreaded shaft extending through the maxillectomy defect with threads only on its apical aspect (Southern Implants, Pretoria, South Africa).

Preoperative Assessment: Mandibular Defects

Vascularized free flaps have revolutionized reconstruction of continuity defects of the mandible in which bone and soft tissue can be obtained from a single donor site and used to reconstruct the defect following ablative surgery. There is no ideal replacement for the mandible and intraoral soft tissue, and each flap has its own advantages and disadvantages, with institutional preference and experience being among the main factors influencing which flap is used for mandibular reconstruction.

There is also no universally accepted classification of mandibular defects after oncologic resection; however, in our opinion, the classification proposed by Urken is the simplest



• **Fig. 12.19** Urken classification of mandibular defects. *B,* body; *C,* condyle; *R,* ramus; *S,* symphysis; S^H, hemisymphysis. (From Urken ML: *Multidisciplinary Head and Neck Reconstruction.* 2009, Lippincott Williams and Wilkins.)

(Fig. 12.19). Many of the existing classifications provide description of defects without any consideration of the different complexities of the defects and how best to reconstruct them. A recent review by Brown and colleagues[21] discusses current practice and proposes a new classification system for mandibular defects based on current trends and practices worldwide. Although this classification describes bony defects, there is no incorporation of soft tissue defects and dentate status, which has implications for future implant planning and dental rehabilitation.

Vascularized free flaps used for mandibular reconstruction include the deep circumflex iliac artery (DCIA), fibula, scapula, and osteocutaneous radial forearm flap. The fibula and DCIA are the two more commonly used flaps, each having advantages and disadvantages.

The fibula is a long, thin, non–weight-bearing bone of the lower extremity. It has a tubular shape and is a thick cortical bone, which provides it with good foundation for osseointegrated implants. Approximately 22–25 cm of bone may be harvested while preserving 6–7 cm of bone proximally and distally to maintain integrity and functional stability of both the knee and ankle joints, respectively. The major disadvantage of the fibula is the fact that it is thin and straight compared with a native mandible, and the challenge has been to overcome the limitations in size and position relative to the dentate mandible and maxilla.

Our approach has been to customize the inset of the fibula by optimizing the position of the neo-mandible with respect to the occlusal plane, the inferior mandibular border, the chin and the opposite dental arch. VSP and the use of cutting guides and guide stents have facilitated a high degree of predictability, and in most patients provide a foundation for dental implant supported prosthetic rehabilitation.

The DCIA flap is particularly useful for young, dentate patients with lateral mandibular defects. It can be harvested as a bone-only, an osteocutaneous, or a myo-osteocutaneous (internal oblique) flap. One of the main advantages of this flap is the bone volume available, which is more conducive for

implant placement. However, despite better bone volume, the length of the bone available is somewhat limited, and the volume of soft tissue that must be included with this flap can be bulky. Its shorter pedicle length (4–5 cm) also limits its routine use because of the occasional requirement for vein grafts.

Special Considerations for Implants in the Reconstructed Mandible

After ablative surgery, mandibular defects can be either segmental defects or marginal defects. Segmental defects are reconstructed with vascularized bony free flaps (e.g., fibula free flap, deep circumflex iliac artery) in the vast majority of patients. Implants in the mandible are usually used to help retain a fixed dental prosthesis owing to the associated soft tissue defects that are usually associated with postcancer ablation. (Figs. 12.20 and 12.21) These types of prostheses are preferably retained by screws so that they may be removed by the restoring prosthodontist or dentist for maintenance. Composite free flaps that include muscle and skin may atrophy over time, necessitating relining procedures to prevent plaque and debris accumulating underneath the prosthesis. Alteration in function resulting from segmental mandibulectomy is unique; there is a reduction in bite force, and, because of the shorter height of the fibula, the usual crown-to-root ratio for prosthetic design does not apply. An additional challenge is that the reconstructed jaws often lack a vestibule secondary to soft tissue resection or limited vertical height of microvascular flaps.

It is becoming standard practice at our institution that most mandibular reconstructions are now done with VSP and cutting guides to improve the accuracy of the osteotomy. The accuracy and ease of placing dental implant-supported prosthetic rehabilitation has also improved.[22]

Acknowledging the drawbacks of a fibula flap (1.2–15 cm thick) for mandibular reconstruction with its lack of height when compared with native dentate mandible (up to 4 cm thick), several methods have been introduced.[23] One is to use a double-barrel technique in which the fibula is osteotomized and the fibula segments placed on top of each other (Fig. 12.22). To avoid kinking of the pedicle, a 3-cm segment of bone is removed to allow folding of the fibula segments without twisting of the periosteal blood supply. Double-barreling does carry the disadvantage of reducing the pedicle length, which may not be ideal in large segment defects or vessel depleted neck surgeries. A second method that has been described is vertical distraction of the fibula (Fig. 12.23). Distraction can only be done once the neo-mandible is consolidated and can be osteotomized horizontally at its midpoint without injuring the periosteal blood supply. The main challenge with this technique is controlling the distraction vector, which is influenced by the anterior surface of neo-mandible to which the distractors are applied. Distraction is not recommended in previously irradiated tissue.

A much simpler technique to overcome this is to position the fibula to abut the native mandible with a slightly more superior than inferior border, thereby reducing the fixture-prosthesis distance. The step along the lower border does not seem to produce any clinically significant contour deformity as long as there is adequate soft tissue integrity (see Fig. 12.21L). However, in some patients, insetting the fibula superiorly along the occlusal plane can result in asymmetry of the inferior border. For this reason, we are increasingly using double-barrel designs.

Preoperative Assessment: Extraoral Defects

Orbital Defects

When the contents of the orbit have been removed, autogenous reconstruction can provide coverage of the orbit only with a poor esthetic result. Although there is not yet a truly functional replacement for a missing globe, orbital prostheses retained with osseointegrated implants have become the primary method of reconstruction for these types of orbital defects.

Key factors in the planning of an orbital prosthesis are to ensure minimal soft tissue bulk of the surgical site. Commonly, reconstruction is done as a staged process whereby any vascularized free flap placed to cover the defect is allowed to atrophy. Debulking of the flap is virtually always required, and this can be done at the same time as implant insertion (see Fig. 12.17 J and K).

It is very important that the margins of the exenteration have no mobility that would dislodge the orbital prosthesis from its implant retention. This needs to be carefully planned at the surgical stage of treatment to ensure a stable base for the orbital prosthesis. The smaller the defect that is left after surgery, the easier is the prosthetic rehabilitation. Circular defects from the exenteration lend themselves to more esthetic orbital prostheses than do irregular margins.

Thin overlying soft tissue maximizes the contact between the orbital prosthesis and the underlying skin and allows for a smooth imperceptible transition point between prosthesis and native skin. In general, three or four implants placed along the superior and lateral orbital rim are sufficient to retain an orbital prosthesis. The implants need to be placed approximately 1 cm inside the eventual margin of the orbital prosthesis owing to the necessity for space for the magnet within the orbital prosthesis to have enough silicone to cover it and to allow it to have no show-through in the prosthesis (see Fig. 12.7M). This requires excellent coordination between the head and neck surgeon and the maxillofacial prosthodontist preoperatively. Three or four implants placed in the superior and lateral rim are needed to retain a prosthesis. Magnetic attachment is preferred over framework attachment for ease of removal, oral hygiene cleaning, and minimizing the load applied to the fixtures during insertion and removal of the prosthesis.

Nasal Defects

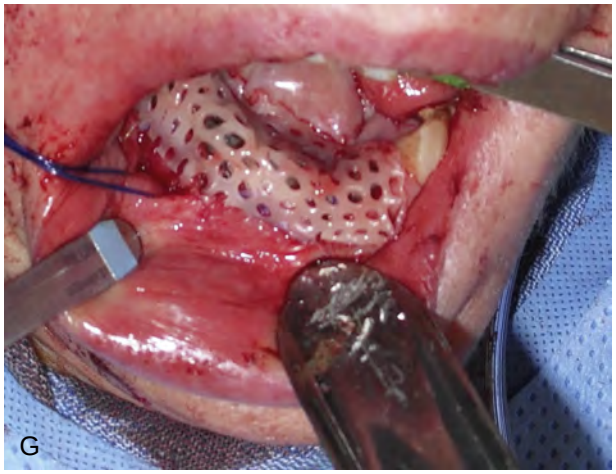
Nasal prostheses for total rhinectomy defects have been shown to produce a more esthetic outcome with better patient acceptance compared with autologous reconstruction, which often requires multiple staged surgeries[24] (Fig. 12.24). Implant placement around the nasal region can be challenging owing

Text continued on p. 263



• **Fig. 12.20** Reconstruction of a right mandibular body, symphysis, floor of mouth, and lateral tongue defect with a two-segment fibula osteocutaneous free flap and delayed implant rehabilitation. **A** and **B,** cT4aN1M0 squamous cell carcinoma (SCC) of right floor of mouth with invasion toward lateral tongue. **C,** Fourteen-month postoperative appearance of skin paddle just before implant placement. **D** to **H,** Four fixtures along the fibula bone with simultaneous vestibuloplasty, and palatal mucosal graft overlying the fixtures.

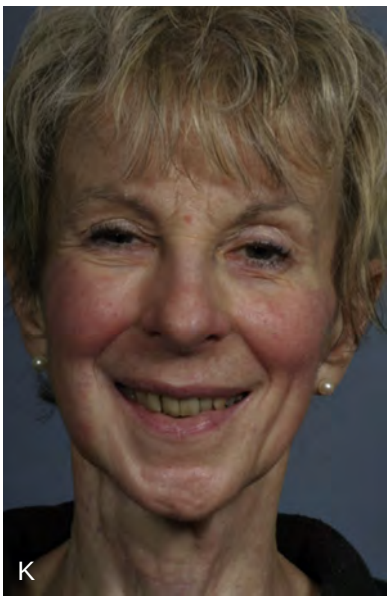
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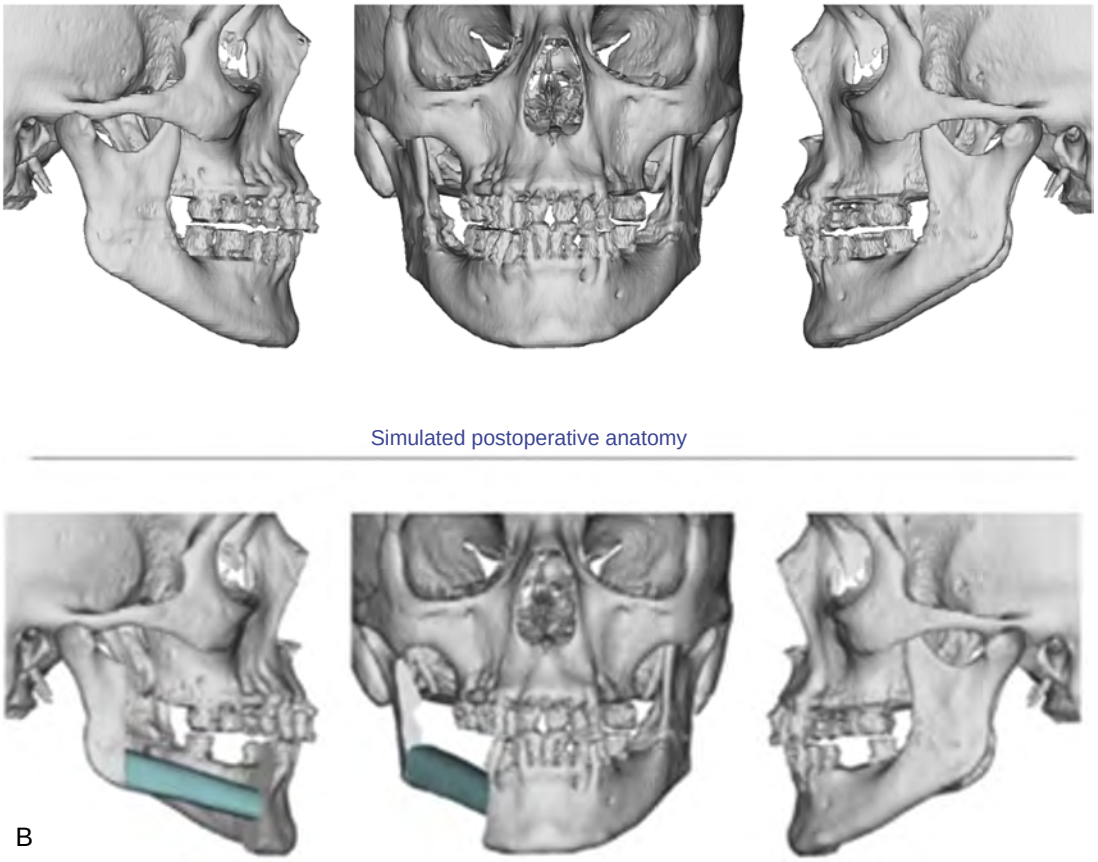






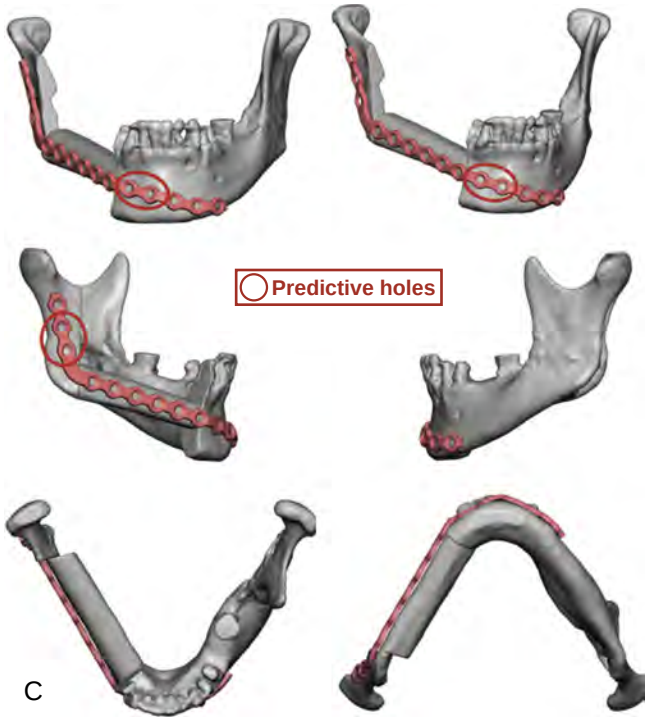
• **Fig. 12.20, cont'd I,** After second-stage surgery, good thin keratinized mucosa appears around the implant with some residual fibula skin paddle along the right floor of the mouth and lateral tongue. **J** and **K,** After insertion of fixed dental prosthesis.



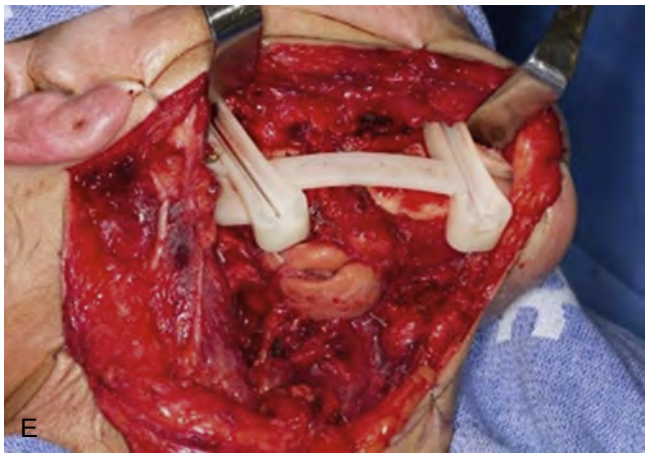


• **Fig. 12.21** Reconstruction of a right mandibular body defect with a single-segment fibula osteocutaneous free flap and delayed implant rehabilitation. **A** to **C,** cT4N0M0 right retromolar trigone squamous cell carcinoma (SCC) with preoperative virtual surgical planning (VSP) showing resection and reconstruction plan.

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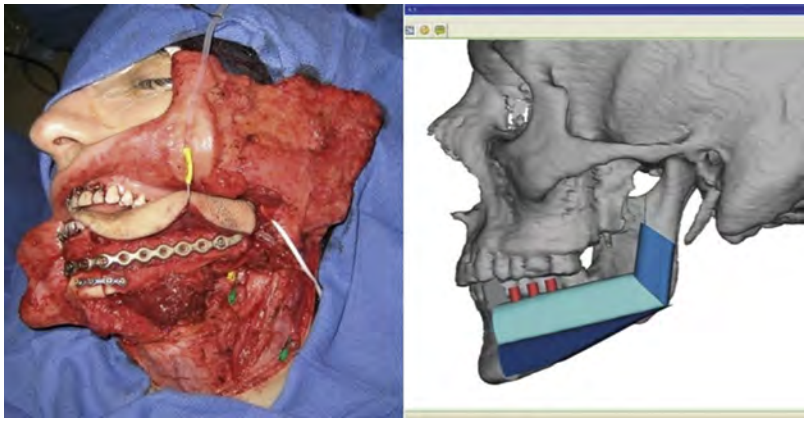


• **Fig. 12.21, cont'd** **D** to **F,** Intraoperative photographs showing the soft and hard tissue defect. **G**, Nine months postoperatively. Image shows extent of soft tissue bulk before implant insertion. **H,** Note that the fibula segment has been placed superior to the lower border to reduce the fixture-prosthesis distance. **I** to **K,** Secondary implant placement along the fibula done 9 months after flap reconstruction. Skin paddle was excised and the underlying periosteum left to granulate. Note that lower anterior teeth were extracted and additional implants placed.

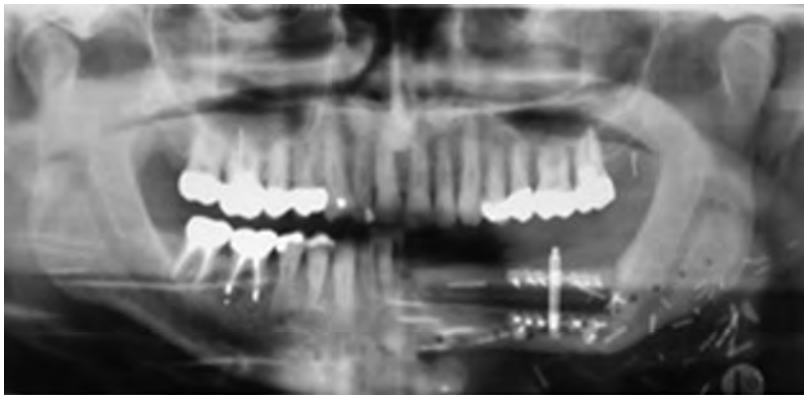


• **Fig. 12.21, cont'd** **L,** Despite the step along the lower border, postoperative photograph does not show any clinically significant cosmetic deformity or asymmetry of the neo-mandible.

to the lack of good cortical bone and the thin nasal mucosal tissue that often lines the areas where implants are placed. Various strategies to overcome these problems have been suggested to provide a secretion-free, immobile base for the prosthesis—most commonly the use of split-thickness skin grafting around the implants.[25] As part of the preparation, all bone margins are trimmed and smoothed to allow a sufficient base for implant placement. In the past, implants were placed in a triangular arrangement with one fixture at the radius and two placed along the piriform buttresses of the maxilla. However, the glabella implant has been shown to have very poor success rates in integration and is therefore not used to reconstruct nasal prostheses at the present time.[26,27] This is related to the lower implant survival rates in the frontal bone as reported in several studies.[27–30] However, in most circumstances the minimum fixtures required are two placed along the piriform buttress. The implants must be placed slightly within the nasal cavity to engage adequate bone, and as is the case of the orbital reconstruction, provide for adequate prosthetic thickness. The implants need to be placed so that they are vertically oriented to allow for the abutments and magnetic retention to be placed within the outline of the nasal prosthesis. Nasal prostheses are fabricated "hollow" to maintain the airway.



• **Fig. 12.22** Double-barrel fibula for reconstruction of mandibular body.



• **Fig. 12.23** Distraction osteogenesis of fibula segment.



• **Fig. 12.24** **A,** Nasal prosthesis with magnetic attachments corresponding to three fixtures placed along the piriform buttress bilaterally and hard palate in the midline. **B,** Nasal prosthesis in situ.

Auricular Defects

Prosthetic reconstructions of acquired ear defects are considered when the soft tissue overlying the mastoid region is of poor quality or absent. In the majority of cases, ablative procedures requiring total auriculectomy would often require adjuvant radiotherapy. The relative roles of autogenous and osseointegrated reconstruction remain controversial. Autogenous reconstruction of the lower half of the ear is most challenging owing to the complex anatomy and multiple staged procedures, and therefore an implant-retained prosthesis may be the preferred approach.[31]

Prosthetic reconstruction of the auricle yields a much better esthetic result and is superior to a surgical reconstruction. Two or three implants are needed to support and retain an auricular prosthesis. Based on a preclinical study done by de Sousa and Mattos, a magnetic retention system for the prosthesis showed very little loss of retention than the bar-clip systems, suggesting higher durability under clinical simulation despite the lower retention initially provided.[32]

Rapid prototype modeling and three-dimensional scanning technology have also been applied to the planning of implant placement and construction of ear prostheses. A laser scanner was used to digitize the normal ear. Using specialized software, the digitized normal ear was then mirrored to form the contralateral side, and three-dimensional printing allowed a very accurate reproduction of the missing soft tissue. The use of this technology can guide optimum planning for implant placement and construction of the definitive silicone prosthesis.[33]



• **Fig. 12.25** **A,** Ear implants placed overlying the mastoid process inferiorly, and along the anticipated position of the conchal bowl of the prosthesis. **B** and **C,** Auricular prosthesis with magnetic attachments. **D,** Auricular prosthesis in situ with good color match and imperceptible prosthesis-skin margin.

Special Considerations for Extraoral Implants

Prosthetic requirements for extraoral implants are quite different from those for intraoral implants. Special considerations for extraoral implants include the following:

1. Retention and support of the facial prosthesis should be located around the periphery of the prosthesis. The implants need to be carefully located so that they are within the confines of the eventual prosthesis. This may require the creation of a diagnostic wax-up by the maxillofacial prosthodontist to allow visualization of the eventual implant placement areas. For an orbital prosthesis, the implants should be located at least 10 mm from the eventual border of the prosthesis. For a nasal prosthesis, the implants need to be at least 5 mm from the front border of the prosthesis. For an auricular prosthesis, the best location is to place the implants posterior to where the external auditory meatus would be located. This is in the concha region from the cymba superiorly to the cavity inferiorly (Fig. 12.25).
2. Implants should be angulated so that they point internally, because external placement will cause difficulties in masking the abutments. Placement of the implants internally allows sufficient thickness of prosthetic material to camouflage the anchorage device.
3. Mechanical or magnetic attachments or a combination of both can be used to retain prosthesis. The support system should be designed to allow uniform distribution of forces among the fixtures.
4. As with intraoral implants, periimplant soft tissue of extraoral implants should be thin and immobile against the abutment. For this to be achieved, the periimplant skin can be thinned in the area where the implant is inserted at the time of placement.
5. If periimplantitis still occurs with ingrowth of soft tissue in the abutment-bone-skin interface, all the hyperplastic tissue and periimplant skin should be excised and a split-thickness skin graft placed overlying the fixtures.
6. In the mastoid region, where the success rate of osseointegrated implants is high, implants can be placed as a single-stage or two-stage procedure, with the second-stage procedure done within 3–4 months. In other craniofacial regions or in previously irradiated bone, a healing period of 6 months for osseointegration is recommended.
7. The soft tissues lining the orbital defects need to have no mobility to allow excellent retention of the prosthesis as well as to camouflage the margin. Any mobility results in the potential for dislodgement of the prosthesis during daily activity.
8. It is recommended that all implants used for facial prostheses be of the intraoral type that has been used for dental reconstruction for many years. With the advent of CT scans and stereolithic model fabrication, we now have the ability to plan very precisely to use much longer intraoral implants

in facial areas where the amount of bone may be sparse. Through use of longer intraoral implants, a distinct advantage for successful osseointegration is possible.

Effect of Radiation Therapy and Hyperbaric Oxygen on Implant Treatment

A systematic review showed that implant failures were rarely seen in sites where cumulative doses were less than 45 Gy[34,35] and were more commonly seen at doses greater than 65 Gy. Based on this, there is agreement that implant survival in patients treated with a cumulative radiation dose of lower than 50 Gy is comparable to that in non-irradiated patients.

Timing of implant placement after radiotherapy was also systematically reviewed by Claudy and colleagues. In their review of 236 publications, 10 of which were included in the final analysis, the pooled relative risk (RR) of implant failure was higher in individuals who had dental implants placed 6–12 months after radiotherapy.[36] This supports our institution's practice of delaying implant placement until after 12 months, not only to allow for improved implant success, but also to allow a period of cancer-free surveillance and soft tissue contraction.

In keeping with outcomes in standard dental implant literature, because of the better bone quality and primary stability, implants in the mandible have shown to have higher survival rates than those in the maxilla.[11] In the mandible, the region between the mental foramina is usually exposed to lower radiation and has a better blood supply from the muscle attachments of the mentalis and genial muscles. This area is clinically relevant in implant rehabilitation, where despite reduced bone availability after resection, a combination of two angled fixtures and two conventional straight fixtures can be used to retain full-arch dental rehabilitation.[37] Concurrent adjuvant chemotherapy is often incorporated in postoperative radiation treatment for high-risk disease, and to date there is little evidence to suggest that chemotherapy influences implant survival.[38]

The survival rates of extraoral implants are 73.2–78.8% in irradiated bone and 95.2% in non-irradiated bone.[29] The sites with the highest failure rates are the frontal bone, zygoma, mandible, and perinasal region.[39]

Despite a relatively high degree of predictability in osseointegration associated with implant placement in an irradiated field, caution should be exercised when contemplating surgery because the consequences of osteoradionecrosis can be disastrous. When placing implants into an irradiated fibula, for example, care should be taken to avoid stripping the periosteum because the usual endosteal blood supply is compromised.

We use a hyperbaric oxygen (HBO) protocol as described by Marx before stage I placement in irradiated tissue in an effort to prevent osteoradionecrosis (ORN). This usually includes 20–30 sessions before and 10 sessions after tooth extraction or implant placement, at a compression of 2.4 atm absolute pressure with 100% oxygen. It is important to note that at present there still have been no randomized, controlled, double-blind studies conducted to prove that HBO really has a significant osseointegration-stimulating effect in irradiated patients. Despite this, there have been several case series showing better wound healing around mandibular implants in irradiated patients who received HBO during a 3- to 7-year follow-up period.[40] In the craniofacial region, there were also lower rates of implant failure in HBO-treated patients than in those who did not receive HBO treatment (8.1% vs. 53.7%, respectively).[41,42]

Summary

Computer-aided surgical simulation and intraoperative navigation for head and neck oncologic surgery is a recent advancement toward refining surgical technique and improving functional outcomes. It aids the surgeon in the planning and execution of tumor ablation, subsequent reconstruction, and rehabilitation with osseointegrated implants. Dental rehabilitation with osseointegrated implants after head and neck cancer reconstruction has become an integral stage of the reconstructive plan. With the currently available technology in VSP and rapid prototype modelling and refinements in prosthesis engineering, extremely functional and cosmetic outcomes can be achieved. Dental rehabilitation in patients with cancer has been shown to positively affect patients' quality of life with improved function and cosmesis. Unfortunately, in the majority of cases worldwide, patients' or institutional financial barriers continue to be the main factors affecting the use of dental rehabilitation.

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13

Radiation Therapy

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Radiotherapy is the mainstay of organ-preserving treatment of locally advanced head and neck carcinoma, either alone or combined with chemotherapy, targeted molecular agents, or surgical resection. Radiation oncologists compile biologic and clinical information to create a personalized radiation treatment plan with the best evidence-based approaches in mind. The general principles of radiobiologic, physical, and clinical factors important in head and neck radiotherapy are presented in this chapter. The role of radiotherapy for specific head and neck subsites is then described.

Radiobiology in Head and Neck Cancer

Ionizing radiation can lethally and sublethally damage cancer cells. Although the primary target of the lethal effect of radiation is thought to be nuclear DNA, ionizing radiation can damage many components of the cell, including the cell membrane and the mitochondria. Radiation can damage nuclear DNA by either direct or indirect effects. Direct effects include ionization of atoms within the DNA molecule, thereby "directly" altering the molecular integrity. The driving mediator of lethal damage to DNA, however, is via indirect effects, whereby ionizing radiation interacts with intracellular water molecules to create free radicals that in turn "indirectly" damage the DNA (Fig. 13.1).

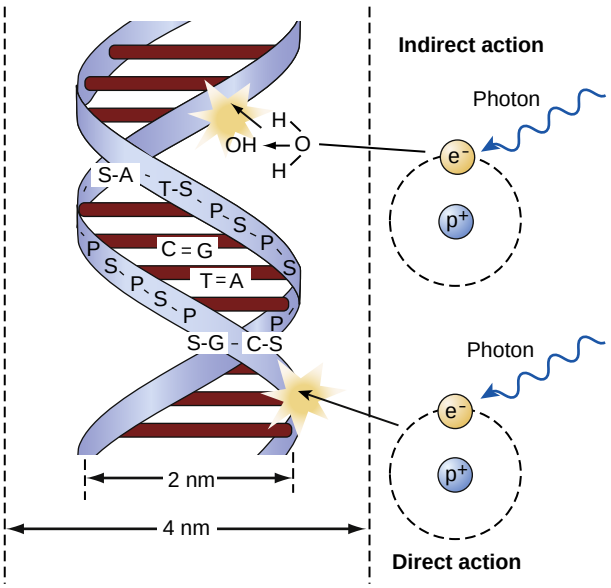
DNA damage can lead to cell death by various mechanisms. Radiation can lead to reproductive or clonogenic death, where a cell may still be able to perform various cellular functions such as protein synthesis. However, these damaged cells are not able to undergo mitosis. Radiation damage can lead directly to apoptosis.

Ionizing radiation can damage any cell, normal or malignant. The key to successful cancer radiotherapy is to kill cancer cells while limiting damage to normal surrounding tissues, the concept referred to as the therapeutic ratio. Certainly, one way to improve the therapeutic ratio is by improving the precision of radiotherapy, using techniques such as intensity-modulated radiotherapy (IMRT) with daily cone beam computed tomographic (CT) image guidance. In so doing, tumor targets may be treated more accurately with tighter margins so that there is decreased dose to adjacent normal tissues.

Additionally, to improve the therapeutic ratio we take advantage of four basic principles of radiation biology, the 4 *R*s: *r*epair, *r*eassortment, *r*epopulation, and *r*eoxygenation. Both normal and cancer cells can repair radiation damage, but malignant cells generally have impaired repair mechanisms that promoted their malignant transformation the first place. Splitting radiotherapy into multiple lower-dose treatments ("fractionation") limits normal tissue damage because, before the next delivered radiation treatment fraction, normal tissues are able to repair radiation damage better than malignant cells. In general, all curative radiotherapy is delivered via fractionated therapy.

In certain circumstances, radiotherapy fractionation may be altered to exploit the differences in repair capacities between normal tissues and tumors. It has been hypothesized that hyperfractionation, using two or more small doses of radiation per day, could also lead to redistribution or reassortment of dividing cancer cells into more radiation-sensitive stages of the cell cycle (late G2/M).[1] With hyperfractionation, total dose is increased, but dose per fraction is reduced, and usually two treatments are delivered per day at least 6 hours apart, with overall treatment duration in the number of days relatively unchanged. With accelerated fractionation, the overall number of treatment days is reduced to decrease the opportunity for tumor cell regeneration during treatment. Both strategies may be combined with hybrid accelerated hyperfractionation. Altered fractionation radiotherapy has been shown to provide superior locoregional control compared with standard once-daily radiotherapy treatments for advanced head and neck cancer in the seminal RTOG 90-03 phase III randomized trial and in subsequent meta-analyses of randomized trials.[2,3]

The presence (or lack) of intracellular oxygen is extremely important for ionizing radiation to lethally damage dividing cells per indirect effects as described above. Experimental studies have shown that with conventional radiotherapy up to twice the radiation dose is generally needed to achieve the same degree of cancer cell death in hypoxic tumors versus well-oxygenated tumors. It is believed that oxygen plays an important role in the creation of the lethal double-strand breaks in DNA.[4] Radiation dose fractionation may lead to reoxygenation between treatments, thus improving the effectiveness of radiation to induce lethal DNA damage. Still hypoxia remains a clinical challenge limiting the ability to cure some head and neck cancers. Pretreatment anemia (hemoglobin <13 g/dL) has been correlated with poorer outcomes when treating locally advanced head and neck cancer with chemoradiation. Prosnitz



• **Fig. 13.1** Direct and indirect actions of radiation. The structure of DNA is shown schematically. In direct action a secondary electron resulting from absorption of an x-ray photon interacts with the DNA to produce an effect. In indirect action the secondary electron interacts with, for example, a water molecule to produce a hydroxyl radical (OH), which in turn produces damage to the DNA. Indirect action is dominant for sparsely ionizing radiation, such as x-rays. (From Hall EJ, Giaccia AJ: *Radiobiology for the radiologist*, ed 7, Philadelphia, 2011, Lippincott Williams & Wilkins, with permission.)

showed improved 5-year failure-free survival rate from 50% in patients with pretreatment hemoglobin <13 g/dL to 75% if the hemoglobin was 13 g/dL or higher.[5] However, paradoxically, adding erythropoietin for anemic patients (hemoglobin 9 g/dL to 13.5 g/dL) failed to improve outcomes for locally advanced head and neck cancers.[6] Similarly, blood transfusions were actually found to be associated with poorer outcomes of anemic patients receiving chemoradiation for head and neck cancer.[7] Unfortunately, attempts over decades to try to target hypoxic tumor cells with oxygen-mimicking hypoxic cell sensitizers like etanidazole[8,9] and more recently with tirapazamine, a compound designed to selectively kill hypoxic cells,[10] have been unsuccessful. Prolongation of the radiation treatment course may allow for reoxygenation of hypoxic tumors and may also lead to reassortment of cancer cells into more radiosensitive phases of the cell cycle; but these potential benefits are greatly outweighed by the fourth R—repopulation.

Cancer cells surviving radiation can divide and repopulate tumors during a course of therapy. In fact, in head and neck malignancies, surviving cells can actually increase their rate of division, leading to accelerated repopulation. Withers and colleagues hypothesized that surviving tumor cell repopulation accelerates at approximately 28 days after the start of radiation with a corresponding increase of about 0.6 Gy per day necessary to compensate for this regrowth.[11] There are various ways to accelerate the course of radiotherapy to try to correct for repopulation. All techniques share the principle of shortening the overall length in number of days of the radiation course. Most tend to shorten the treatment length from 7 to 6 weeks. MD Anderson popularized the technique of concomitant boost radiotherapy where 72 Gy is delivered over 6 weeks by adding a second "boost" fraction per day for the final 12 treatment days. This technique, as well as twice-a-day hyperfractionation, has been shown to improve locoregional control in phase III trials.[2,3,12]

Intensifying treatment with altered fractionation radiotherapy is but one strategy to improve oncologic outcomes. Concurrent systemic therapy is another. Two randomized trials, however, have not shown further added benefit of combined accelerated radiotherapy with concomitant chemotherapy versus standard fractionated concurrent chemoradiotherapy.[13,14]

Interaction of Radiotherapy and Chemotherapy and Targeted Agents

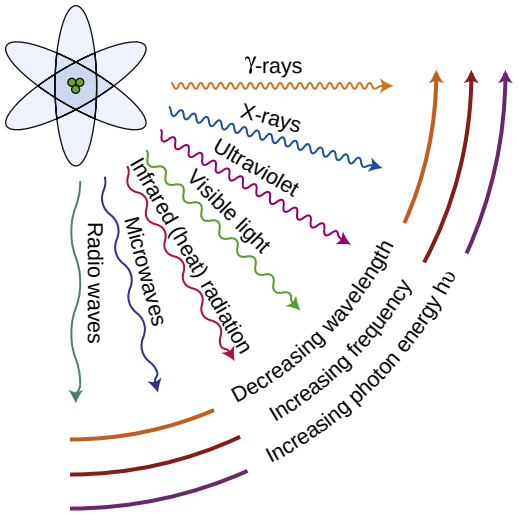
At least 87 randomized trials have investigated the role of sequential or concurrent chemotherapy with radiotherapy for head and neck cancer. A meta-analysis of individual data of 16,192 patients with median follow-up 5.6 years showed that adding chemotherapy improved 5-year overall survival rate by 9%, 8%, 5%, and 4% for oral cavity, oropharynx, larynx, and hypopharynx tumors, respectively.[15] The greatest benefit was with concurrent chemotherapy and radiotherapy. Two recent trials have shown no benefit, but increased toxicity, with induction chemotherapy before standard concurrent chemoradiotherapy.[16,17] Concurrent cetuximab, a monoclonal antibody against the epidermal growth factor receptor, was shown in a randomized trial to improve locoregional control and overall survival rate for locoregionally advanced head and neck cancer treated with standard-fractionated radiotherapy.[18] Radiotherapy and cetuximab is now a standard option for patients with locally advanced head and neck squamous cell carcinoma not considered medically fit for standard chemoradiotherapy regimens. So far, there are limited data directly comparing the efficacy and toxicity of cisplatin radiotherapy and cetuximab radiotherapy regimens.

Radiation Physics and Treatment Technique

Electromagnetic Radiation

Electromagnetic radiation is a form of energy that propagates as both electrical and magnetic waves traveling in packets of energy called photons. There is a spectrum of electromagnetic radiation with variable wavelengths and frequency, which in turn imparts different characteristics. Examples of energy within the electromagnetic spectrum include x-rays (most widely clinically used to treat malignant lesions), visible light, infrared light, and radio waves (Fig. 13.2).

The energy of electromagnetic radiation is quantified by an electron volt (eV), where 1 eV describes the energy gained by an electron as it is accelerated through a potential difference of 1 volt. Electromagnetic radiation deposits energy in two forms as it passes through biologic material: excitation and ionization. Excitation describes the deposition of enough energy to raise an electron to a higher electron shell without ejection of the electron. However, ionizing electromagnetic radiation has



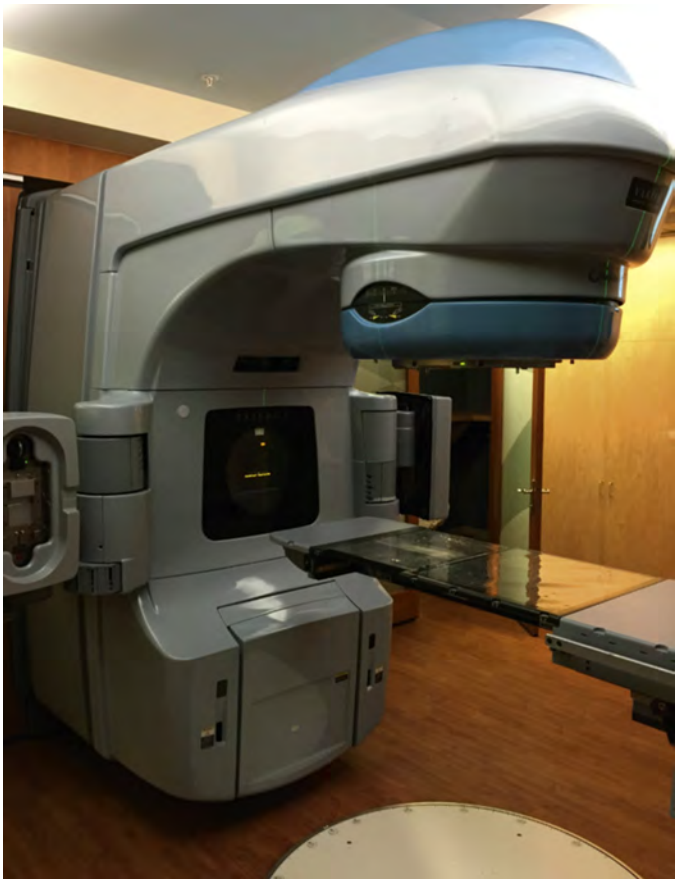
• **Fig. 13.2** Illustration of the electromagnetic spectrum. X-rays and gamma rays have the same nature as visible light, radiant heat, and radio waves; however, they have shorter wavelengths and consequently a larger photon energy. As a result, x-rays and gamma rays can break chemical bonds and produce biologic effects. (From Hall EJ, Giaccia AJ: *Radiobiology for the radiologist*, ed 7, Philadelphia, 2011, Lippincott Williams & Wilkins, with permission.)

enough energy to eject one or more electrons from the atom. X-rays and gamma rays, whose properties are equivalent, are clinically the most important form of ionizing electromagnetic radiation in the treatment of cancer.

Intranuclear production of ionizing radiation occurs when unstable atoms decay to more stable nuclides via beta minus decay, beta plus decay, or electron capture. These "gamma rays" are often produced from elemental sources that are used clinically for head and neck brachytherapy. Brachytherapy describes any procedure in which an elemental source of radiation is implanted or placed in close proximity to achieve therapeutic radiation delivery to a target. Teletherapy is the use of ionizing radiation delivered with no direct contact with the patient. Historically, teletherapy machines housed a source of cobalt-60; however, due to higher skin dose and the necessity to replace the source as it decayed, teletherapy machines have transitioned to extranuclear production of ionizing radiation (i.e., x-rays) using *lin*ear *ac*celerators (linacs) (Fig. 13.3). A linac is a high-voltage electrical device that accelerates electrons to very high energies and aims them into a target in the linac gantry head, usually containing tungsten or gold. During the collision process, the kinetic energy of the electrons is converted to high-energy photons. Therapeutic external beam radiation x-ray energies generally range between kilo- and mega-electron volts (keV or MeV). The x-ray beams are narrowed and shaped with a collimator in the treatment machine head before delivery to the patient.

Particle Radiation (Electrons, Protons, Carbon Ions, and Neutrons)

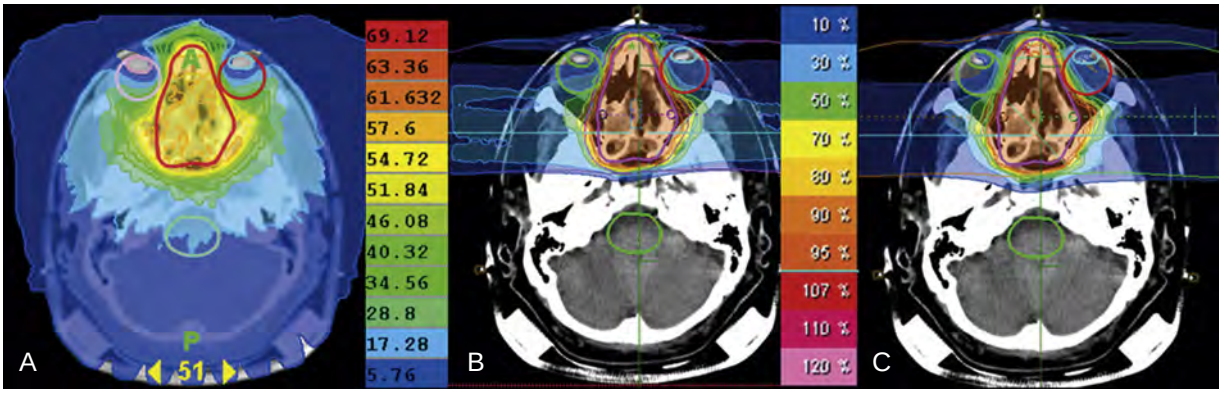
Electrons are small negatively charged particles that can be accelerated close to the speed of light by a standard linac and can be used therapeutically to treat superficial lesions (e.g., skin cancers and superficial neck nodes) since they have relatively shallow penetration. On the other hand, protons are positively charged particles almost 2,000 times the size of an electron, and because of their size, special equipment (a cyclotron) is needed to accelerate them to high enough energy to use therapeutically. Protons deposit the maximum amount of energy near the end of the track, termed a Bragg peak, which can be taken advantage of to create very sharp and steep radiation dose gradients, in turn sparing critical normal tissue toxicity (e.g., for treatment of skull base tumors in close proximity to the optic apparatus or brainstem) (Fig. 13.4). Heavy ions, such as carbon ions, can be accelerated in similar fashion with similar dose deposition. Neutrons, which are slightly larger than protons, hold no charge and cannot be accelerated in a linac or cyclotron. They have a radiobiologic advantage in hypoxic environments given the reduced oxygen enhancement ratio. Although they have limited clinical use, neutrons may play a role in treatment of localized salivary gland cancers.[19]



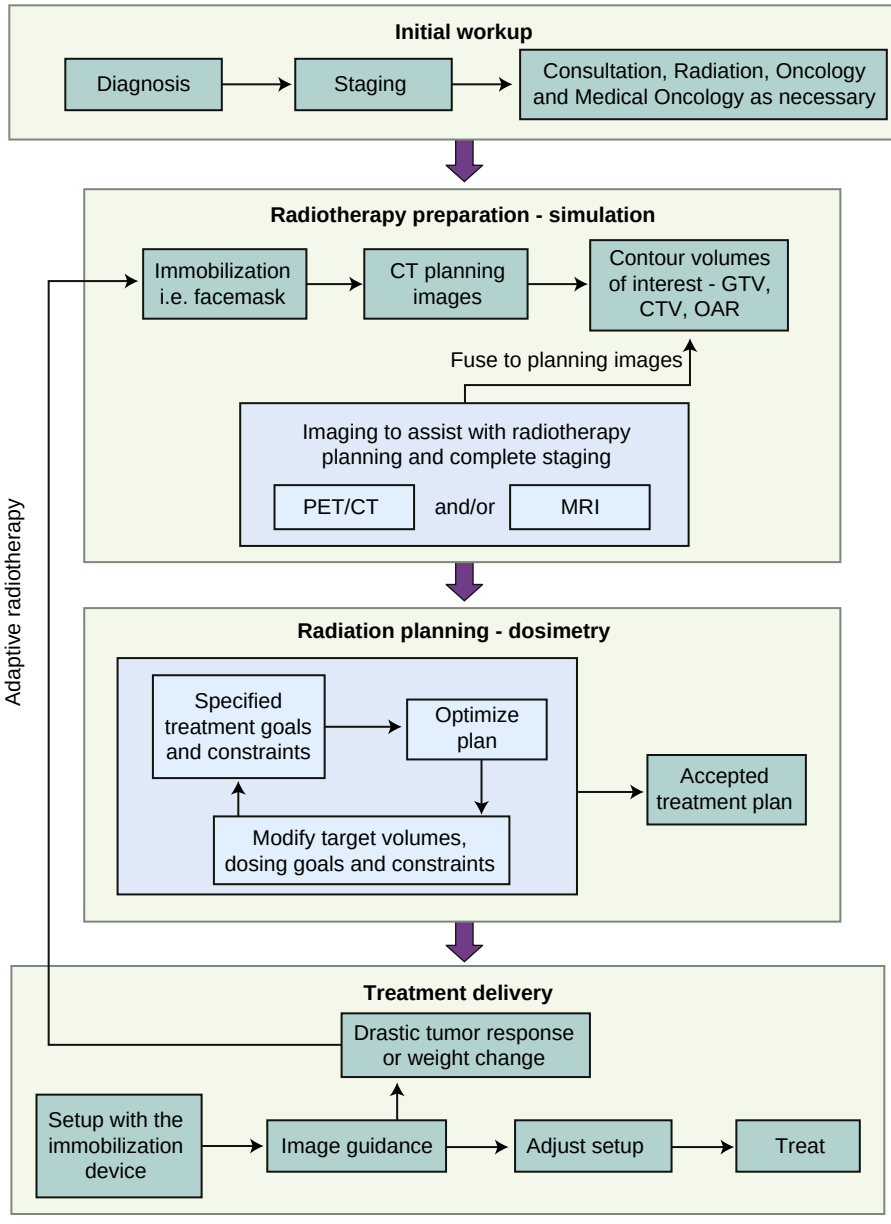
• **Fig. 13.3** Photograph of a modern clinical linear accelerator, or linac, where external-beam radiation treatments are administered.

Radiation Treatment Process

The logistics of radiotherapy planning and treatment are quite detailed and complicated. Fig. 13.5 describes the typical flow of a patient through a course of radiotherapy. Radiation oncologists work closely with trained physicists, medical dosimetrists, nurses, radiation therapists, dietitians, and social workers to get



• **Fig. 13.4** Dose distribution in transverse plane for **(A)** photon IMRT, **(B)** carbon ion, and **(C)** proton treatment planning techniques for a patient with a skull-base meningioma. The same beam arrangements were used for carbon ion and proton plans. These plans consisted of two lateral beams and one cranial beam. One can see that will particle radiotherapy **(B** and **C),** the brainstem and cochlea are spared of low-dose radiation (*light* and *dark blue* volumes). (From Kosaki K, Ecker S, Habermehl D: Comparison of intensity modulated radiotherapy [IMRT] with intensity modulated particle therapy (IMPT) using fixed beams or an ion gantry for the treatment of patients with skull base meningiomas. *Radiat Oncol* 7:44, 2012, with permission)



• **Fig. 13.5** Generalized flowchart of the radiotherapy process.



• **Fig. 13.6** A rigid thermoplastic facemask used for immobilization during radiotherapy, custom-fit to the contours of a patient's face.

patients through treatment. Robust quality assurance testing is performed daily, weekly, monthly, and annually on treatment machines, and individual patients' plans are tested and monitored to ensure safe and accurate treatment delivery.

Simulation

As part of the radiotherapy planning session, patients initially undergo simulation, consisting of head/neck immobilization and usually CT imaging. A common head and neck radiotherapy immobilization device is a thermoplastic facemask (Fig. 13.6). A thermoplastic mask when warmed in a water bath becomes a soft malleable material. The mask is stretched over the patient in the treatment position and hardens rather quickly while it cools. This minimizes patient motion to ensure precise, reproducible radiotherapy treatments. One can breathe and see through the mask, and with a reasonable force, a patient can release the mask from the tabletop. After the facemask is constructed, a CT scan is obtained with contrast enhancement if necessary. The simulation CT images may be fused with other imaging modalities, such as magnetic resonance imaging (MRI) or positron emission tomography (PET), to better aid in target and/or organ-at-risk delineation. A PET scan can be beneficial when delineating targets for radiotherapy, as increased or decreased metabolic uptake may alter treatment fields.[20] MRI can also be useful, as it improves soft tissue contrast to better delineate target volumes and normal tissue structures, especially in nasopharyngeal cancer or patients with perineural spread at the base of the skull. Supplemental imaging to be used for treatment planning is best done in the treatment position with a thermoplastic facemask in place; however, logistic reasons sometimes do not allow for this, and planning software with manual adjustment can minimize translational and rotational differences between scans. Following CT simulation, permanent tattoo dots approximately 2 mm in size are placed as reference points to define the patient in space and help with correct positioning prior to subsequent treatments. The CT imaging dataset and all supplemental imaging are uploaded to radiation oncology–specific software for contouring of target structures and normal organs-at-risk and subsequent radiation planning.

Radiation Treatment Planning

Medical dosimetrists work side-by-side with physicians and medical physicists to develop a personalized radiation treatment plan. Organs-at-risk are contoured in their entirety (e.g., salivary glands, mandible, or spinal cord), and tumor target volumes are contoured on the CT images taking into account pre- and postoperative imaging, pathology reports, physical exam, and any supplemental imaging fused with the simulation CT. Target volumes have specific definitions recognized by all radiation departments: the gross tumor volume (GTV) defines the area(s) of known measurable tumor either on imaging or examination, and it receives the highest dose of radiation. The clinical tumor volume (CTV) is an expansion of the GTV to cover subclinical spread of disease surrounding the GTV and also includes at-risk lymph node volumes in proximity to the primary tumor. CTVs are expanded after they are finalized to create a planning treatment volume (PTV). The PTV expansion accounts for daily variations of patient setup and anatomy and varies between treatment centers based on institutional certainty as to the accuracy of the setup procedure, which may be affected by image guidance, immobilization devices, and so on.

Intensity-Modulated Radiation Therapy (IMRT)

Over the past three decades, radiotherapy technology has evolved from strictly two-dimensional techniques based primarily on x-ray plain film imaging, surface anatomic landmarks, and manual dose calculations, to three-dimensional conformal radiation therapy (3D-CRT), to IMRT. 3D-CRT and IMRT incorporate volumetric imaging and complicated computer algorithms to create personalized radiation plans improving the coverage of tumor targets and minimizing dose to surrounding normal tissues. 3D-CRT consists of an iterative methodology termed "forward planning" in which multiple beam arrangements are created, doses are calculated, and then either approved or rejected if the plan does or does not meet the radiation dose constraints set by the treating radiation oncologist for the target volume and normal tissues. When radiotherapy planning goals and constraints cannot be met with 3D-CRT planning, IMRT may be used to further improve dose conformality. IMRT is capable of conforming to concave target volumes by using nonuniform radiation beam intensities, to minimize the irradiation of normal tissues outside the targets while simultaneously treating irregularly shaped target volumes. IMRT uses a planning process termed "inverse planning," in which predetermined radiation dose constraints for targets and normal organs are entered into the treatment planning system and a best-fit radiation treatment plan is subsequently calculated by complex computer algorithms. IMRT has swiftly become the preferred technique for head and neck radiotherapy because of the complexity of head and neck anatomy. However, this technique takes considerably more time for planning, quality assurance testing, and treatment delivery.

Dose inhomogeneity is increased with IMRT, and hot spots may be identified in planning. These need to be thoroughly reviewed by the physician and dosimetry team to verify that they are within acceptable limits and are preferably located within the GTV.[21,22]

By better sparing normal tissues, patients treated with IMRT for head and neck cancer may have reduced treatment-related toxicity, resulting in improved quality of life.[23] A recent meta-analysis of five prospective phase III randomized control trials comparing IMRT with two-dimensional radiotherapy or 3D-CRT showed that IMRT reduced the incidence of grade 2 to 4 xerostomia without compromising local-regional control and overall survival rate.[24]

Image-Guided Radiation Therapy

Image-guided radiation therapy (IGRT) is the process of near real-time imaging during a course of highly conformal radiotherapy, with the ultimate intent of improving target accuracy and precision by correcting for geometric and anatomic deviations. IGRT techniques consisting of planar or volumetric imaging with or without implanted fiducial markers allow for the possibility of tighter treatment margins. A common and very useful pretreatment imaging modality used in head and neck radiotherapy is cone-beam computed tomography (CBCT). CBCT is a type of volumetric imaging that has been integrated into treatment linear accelerators. It allows reconstructed 3D volumes to be created of patient anatomy while the patient is in the treatment room in the treatment position. A CBCT is taken prior to treatment, and the reconstructed 3D images are directly compared to the planning CT with millimeter adjustments made as needed to ensure accurate and precise radiation targeting. Historically, planning target volumes have needed large margins to compensate for variability in daily treatment setup and localization; however, with the increasing use of daily image guidance, treatment volumes have decreased in size given the greater confidence in targeting.[25] The pretreatment CBCT also allows providers to visualize anatomic changes, such as tumor shrinkage, that may necessitate replanning of radiotherapy during the course of therapy. This process is termed adaptive radiotherapy.

Stereoscopic x-ray image guidance uses orthogonal kV x-rays and occasionally an infrared or optical camera system. A great benefit of this technique is the very quick image acquisition time to allow for intrafraction evaluation of patient position. The kV x-rays identify bones very well, making this a good modality for image guidance for targets near fixed bony anatomy, such as the nasopharynx and sinonasal cavity. Infrared and optical cameras can also be used for surface-based localization, where cameras are used to generate three-dimensional models of the patient surface to verify position compared to the planning scans.[26]

Adaptive Radiotherapy

Adaptive radiotherapy (ART) for head and neck cancer is an emerging tool to counter morphologic changes in patient and tumor anatomy during a course of radiotherapy by creating new radiation plans during the course of treatment. The most common form of anatomic change rendering the necessity of ART is excessive weight loss secondary to disease and treatment-related side effects.[27,28] These anatomic changes have been shown to reduce doses to target volumes while increasing the dose to critical structures.[29] The provider initiates ART when significant weight loss or tumor shrinkage is seen on image guidance done prior to treatment delivery. ART can be technically challenging and also requires a significant amount of time and resources to perform; however, it has been shown to improve normal tissue sparing, such as reduced parotid mean dose. Given the heavy technical and staffing requirements to facilitate ART, departments have used deformable registration as a way to automate adaptive planning.[30,31]

Morbidity of Head and Neck Radiation

Modern radiotherapy treatment techniques, such as IMRT, IGRT, and ART, have the same goal: to tightly treat tumor volumes and spare adjacent normal head and neck tissues in order to maximize chance of cure and minimize risk of acute and long-term morbidity—that is, to improve the therapeutic ratio. Head and neck radiotherapy can cause temporary and/or permanent damage to the parotids, submandibular glands, mandible, and teeth, among other tissues. IMRT, in particular, is useful to reduce dose to these tissues. Studies have shown that parotid gland function is preserved if mean dose to the gland is kept lower than 24 to 26 Gy.[32] In a review of radiation effects on parotid gland function, recommendations to limit severe xerostomia (defined as long-term function that is <25% baseline) was felt best achieved when at least one parotid received a mean dose of 20 Gy or less and if both glands received mean dose less than 25 Gy.[33]

Even with effective parotid sparing, many patients still complain of xerostomia after IMRT. The submandibular glands are important in producing saliva in the non-stimulated state. Further, submandibular gland saliva is higher in content of lubricating mucins than the saliva from the parotid glands[34] and both stimulated and non-stimulated salivary flow rates recover if the mean dose to the submandibular gland can be kept less than 39 Gy.[35]

Radiotherapy for head and neck cancer, and particularly for cancers of the oral cavity, has long been associated with significant morbidity to the teeth and mandible. Of course, the first step in the management of oral complications of head and neck radiotherapy is prevention, which begins with proper multidisciplinary consultation with dental and oral surgery.[36] Careful examination and imaging are necessary prior to radiotherapy, with proper identification of teeth that need to be removed before treatment. Ideally, extractions should be completed prior to the imaging used for treatment planning at simulation. Furthermore, dental consultation before radiotherapy can initiate therapeutic care for periodontal disease and begin preventative fluoride therapy, including fabrication of fluoride delivery trays. In general, the alveolar bone should be allowed 14 to 21 days to heal after extractions before beginning radiotherapy.

Radiation and chemotherapy can alter the environment of the oral cavity leading to infections by opportunistic organisms. *Candida albicans,* or thrush, produces painful white spots that cover the tongue and mucosal surfaces. Nystatin suspension may be useful in therapy for thrush, but greater efficacy is found with oral agents such as fluconazole. Care must be taken when using these oral agents, however, as there are frequent drug-drug interactions with other common medications including statins. Herpes infections can also flare during head and neck radiotherapy and can sometimes be challenging to diagnose because of dermatitis and/or mucositis from treatment.

Ultimately, xerostomia can lead to dental caries. Saliva has antimicrobial properties, and the partial or permanent loss or alteration of saliva increases caries-causing bacteria. This often presents with periodontal disease seen as erythema and plaques. The gums then retract away from the dental neck, and further decay erodes the now-exposed neck of the tooth with teeth ultimately breaking off or "decapitating" at the gum line. Sometimes fluoride and regular preventive dental care are just not enough. We may see this more and more in the human papillomavirus (HPV)-positive era where young patients are cured with a higher frequency and therefore live longer with chronic xerostomia for many years.

Osteoradionecrosis (ORN) can occur after head and neck radiotherapy. This can include the development of a small amount of mandibular exposure on the posterior, often lingual surface a few months after radiation. This process is usually self-limited with healing aided by removal of protruding bone sequestrum or curettage. Most of these patients present with pain a few months after radiation and are best treated with good oral hygiene, improving nutritional status, appropriate use of pain medication, and time. More serious ORN is considered as "a non-healing exposure of bone of at least 6 months' duration."[37] The most significant risk factor for the development of ORN is trauma, usually caused by post-radiation extractions. Smoking is also a risk factor. ORN can also occur spontaneously. The risk of developing ORN is associated with the dose of radiation delivered, with most cases developing after doses greater than 60 Gy and few developing below doses of 50 Gy to the mandible.[38] As the blood supply to the maxilla is greater than that to the mandible, the incidence of ORN is significantly greater in the mandible, especially after extractions of mandibular molars. The role of hyperbaric oxygen in the management of ORN is controversial. Data are conflicting, with one prospective, randomized double-blind placebo-controlled study showing no benefit from the use of hyperbaric oxygen to treat ORN.[39]

The French have reported phase II data suggesting a benefit from the use of daily pentoxifylline 800 mg, vitamin E 1000 IU, and 1600 mg clodronate 5 days per week alternating with prednisone 20 mg and ciprofloxacin 1000 mg 2 days per week in the management of refractory ORN.[40] This treatment appears to be well tolerated and, when combined with serial sequestrectomies, has resulted in improvement in ORN.

Overall, it appears the incidence of ORN is decreasing. Clayman reviewed the incidence of ORN using pooled studies and reported a rate of 11.8% before 1968 decreasing to 5.4% from 1968 to 1992.[41] IMRT may result in radiation dose gradients across the mandible that may further decrease the incidence of ORN. Eisbruch found no episodes of ORN after initiating a policy of uniform dental examination and extractions of high-risk "nonrestorable" mandibular teeth combined with the use of IMRT plans with maximal mandibular dose constraints and parotid sparing.[42] Among 176 patients, most (75%) had received at least 65 Gy to at least 1% of the mandible. Fifty percent had received 70 Gy or higher to at least 1% of the mandible. With median follow-up 34 months, no cases of grade 2 or higher ORN were seen. With proper dental evaluation before radiotherapy, improving radiation techniques, and good dental care after radiotherapy, it is hoped the incidence and severity of ORN will continue to decline.

Radiotherapy for Specific Disease Sites

Oropharyngeal Cancer

Radiotherapy has a long history in the management of squamous cell carcinoma of the oropharynx. Traditional surgical techniques required median mandibulotomy to gain exposure. Postoperative radiation was still required in the majority of cases. Hansen described the use of postoperative radiotherapy in 43 patients with advanced-stage (88% stage IV) oropharynx cancer.[43] Five-year local control of the resected primary bed was 96% with actuarial locoregional control of 80%. In this series of patients treated before 2000, the 5-year overall survival rate was only 34%, with 46% developing distant metastases.

The benefit of adding concurrent chemotherapy to radiation for locoregionally advanced oropharynx cancer was established by the French GORTEC 9401 study,[44] where 226 patients with stage III/IV disease were randomized to either radiation alone (70 Gy) or radiation combined with three cycles of carboplatin and fluorouracil chemotherapy. Overall survival rate and locoregional control were both significantly improved with the addition of concurrent chemotherapy. Five-year survival rate was increased by 6% and locoregional control by 23%.[45] The improvement in survival rate and locoregional control came at the cost of increased grade 3 to 4 complications (30% vs. 56%, $P = .12$).

As seen in other head and neck cancer sites, IMRT also has had an impact on outcomes in oropharynx cancer. Multiple published series have reported consistently high local/regional control rates and low risks of severe acute and late toxicity. Memorial Sloan Kettering reported their experience of 442 patients treated between 1998 and 2009.[46] Almost all patients had stage III/IV disease (94%). Three-year local control was seen in 94.6% with regional control of 94.4%. Three-year overall survival rate was 84.9% with only 12.5% developing distant metastases. IMRT lessened late effects, with grade 2 or higher dysphagia seen in only 11% and xerostomia reported in 29%. MD Anderson reported their experience for 776 patients with oropharynx cancer treated with IMRT and achieved 5-year overall survival rate 84% and local regional control 90%, with only 7% of patients recurring at the primary site

and neck recurrence in only 3% of patients with controlled primary site.[47] Clearly, using IMRT and "dose painting" allows for more conformal radiotherapy and less long-term toxicity for local/regionally advanced patients.

Reducing the irradiated volume for selected patients also can reduce toxicity. Well-lateralized tonsil cancers have a low incidence of spread to the contralateral neck. Data from Princess Margaret and MD Anderson have shown that appropriately selected patients with early-stage tonsil cancer can be safely treated with only ipsilateral tonsil and neck radiotherapy.[48,49] In a study of 102 patients treated with ipsilateral technique for well-lateralized tumors with disease restricted to the tonsillar fossa or anterior pillar with <1 cm involvement of the soft palate and median follow-up 38 months, only two patients failed in the contralateral neck for 5-year freedom from contralateral nodal recurrence rate of 96%. Of note, this series included node-positive patients (65%) including 43% with N2 necks. Neither of the two contralateral neck failures occurred in node-positive patients. Clearly, careful selection of the appropriate patient is critical, however, when considering unilateral treatment. Patients with extension into the tongue base are generally excluded from this technique because of concern about bilateral lymphatic drainage.

When patients receive radiation to the primary and only the ipsilateral neck, Langendijk and colleagues noted that the risk of late swallowing complications is significantly reduced, even when T-stage was introduced into the multivariate analysis.[50] Similar observations were reported by Frowen and co-workers, who demonstrated that irradiation of only the ipsilateral neck significantly reduced the risk of late dysphagia with liquids.[51] They also noted that the length of the radiotherapy fields directly correlated with the risk of swallowing dysfunction at 3 months with a trend at 6 months.[51] The ability to spare the contralateral neck and parotid and submandibular glands also results in lower risk of permanent xerostomia.

In the past 20 years, not only has the treatment for oropharyngeal cancer changed with the addition of systemic therapy and the development of IMRT, but also the disease itself has changed. In the late 1990s, HPV, particularly HPV-16, was found to be associated with squamous cell carcinoma of the oropharynx.[52,53] These HPV-associated tumors tend to have poorly differentiated histologies and a basaloid appearance under the microscope. Clinically, they often present with small primaries in the tonsil or tongue base and are frequently associated with large cystic lymph nodes.

The incidence of this disease has increased dramatically over the past 15 years, making cancers of the oropharynx the most common head and neck cancer in the United States in 2015. HPV-associated oropharyngeal cancer generally has a better prognosis in comparison to HPV-negative oropharyngeal cancer. Ang and colleagues performed a post hoc analysis of the effect of tumor HPV status on survival in stage III/IV oropharynx cancer treated on the RTOG 0129 trial.[54] This negative study sought to evaluate whether accelerated chemoradiotherapy was better than standard chemoradiotherapy and included 721 evaluable patients with oral cavity, oropharynx, hypopharynx, and larynx primaries. Most patients (60%) had oropharyngeal primaries, and HPV status was determined in 75%. HPV-positive tumors were more frequently seen in patients who had never smoked and those patients with a lower cumulative pack-year history of smoking. Overall, patients with HPV-positive cancers had better survival rate than the HPV-negative patients: 82.4% versus 57.1% at 3 years ($P < .001$). Patients with HPV-positive cancers had a 58% reduction in the risk of death compared with HPV-negative patients and a 51% reduction in the risk of death or recurrence. An additional important finding of this study was the negative effect of tobacco use. The risk of death and cancer recurrence increased by 1% for each additional pack-year of smoking. This deleterious tobacco effect was similar for both HPV-positive and HPV-negative tumors.

The Princess Margaret group has confirmed and expanded these findings.[55,56] They identified high- and low-risk HPV-positive and HPV-negative groups with significantly different 3-year locoregional control (LRC) and distant control (DC): HPV-negative high-risk (T3/T4N0-N2c; N3) LRC 62%, DC 72%; HPV-negative low-risk (T1/T2N0-N2c) LRC 76%, DC 93%; HPV-positive high-risk (T4N0-N2c; N3) LRC 82%, DC 76%; HPV-positive low risk (T1/T3N0-N2c) LRC 95%, DC 93%.

One possible reason for the improved outcome in HPV-positive tumors is that the administration of radiation might enhance immune surveillance to viral antigens. One study supporting this notion suggested improved prognosis from high HPV-16 viral loads.[57] Increased numbers of $CD3^+$ tumor infiltrating lymphocytes (TILs) have also been associated with a lower incidence of nodal metastases in HPV-positive tumors and improved survival that approach statistical significance.[58]

In the modern era of chemoradiation with IMRT for oropharyngeal cancer, local or regional failure is unusual (<15%).[59,60] In recent series, the most common pattern of failure is distant recurrence, which occurs in approximately 20% of patients.[59] Another virus-related malignancy, nasopharyngeal cancer, appears to have a similar natural history when treated with chemoradiation.[61] Epstein-Barr virus–related nasopharynx cancer (WHO types II and III) is considered more radiosensitive than their non–virally induced counterparts (WHO type I), and the combination of IMRT and chemotherapy achieves LRC over 90% with predominant distant failures. LRC with primary chemoradiation is 50% or less for non–virally induced tumors originating in the brain, paranasal sinus, esophagus, lung, pancreas, and rectum. For most of the common solid tumors, surgery is considered a mainstay of curative therapy due to the relative ineffectiveness of non-surgical therapy. In contrast, HPV-related cervical and anal cancers were among the first solid tumors successfully treated with organ-conserving non-surgical therapy.[62,63] With modern radiation and chemotherapy techniques, nasopharyngeal and oropharyngeal cancers are controlled with IMRT and concurrent chemotherapy at very high rates. These data are consistent with the notion that virus-associated malignancies tend to respond especially well to radiation.

With the improved outlook for HPV-associated oropharyngeal cancers, investigators have sought to reduce long-term morbidity by de-intensifying therapy. One approach is to use cetuximab with radiotherapy instead of cisplatin. RTOG 1016 randomized patients with locoregionally advanced HPV-positive oropharynx cancer to receive accelerated radiotherapy plus cisplatin or cetuximab. This study finished accrual of more than 940 patients in 2014, and final results are pending.

Another way to de-intensify therapy is to reduce the prescribed radiation dose. Eastern Cooperative Oncology Group (ECOG) 1308 is a recently completed randomized phase II trial that used the response to induction chemotherapy (cisplatin, paclitaxel, and cetuximab) to select patients to receive either low-dose IMRT (54 Gy) with weekly cetuximab if they achieved a complete response to induction chemotherapy or full-dose IMRT (69.3 Gy) plus cetuximab if they achieved a partial response or disease stabilization.[64] In this small study, the 2-year overall survival rate was 93% and 2-year progression-free survival rate was 80% for the patients receiving 54 Gy. Repeating a theme in HPV-positive tumors, the best predictor for outcome was smoking history. In fact, in select "best patients" (<10 pack-year smoking history, non-T4, non-N2c disease), the 2-year progression-free and overall survival rate was 96% in the 54 Gy arm. This early data raises possibilities regarding dose reduction in HPV-positive oropharyngeal cancer.

New surgical techniques to resect tumors of the tonsil and base of tongue have been developed over the past 10 years. Transoral robotic surgery (TORS) and transoral laser microsurgery (TLM) represent endoscopic surgical techniques not requiring the routine use of mandibulotomy to gain access to these tumors. Although these techniques are discussed thoroughly in other sections of this text, their use presents questions in terms of postoperative radiotherapy. The ongoing ORATOR randomized phase II study assigns patients with ≤3 cm T1/T2N0-N2 tumors with likely negative margins at surgery and without imaging evidence of extranodal extension to either definitive radiotherapy (± chemotherapy) or to TORS (± pathology-directed adjuvant radiotherapy ± chemotherapy).[65] This study and others will help assess the pros and cons of these two treatment approaches.

Established indications for consideration of postoperative radiotherapy are close or positive surgical margins, extracapsular nodal extension, angiolymphatic invasion, spread to cortical bone, perineural invasion, N2/N3 disease, and nodal disease in levels IV or V.[66,67] For patients with positive margin(s) and/or extracapsular extension, concurrent postoperative chemoradiotherapy with cisplatin should be considered to improve local/regional control and survival rate.[67]

ECOG 3311 is attempting to refine postoperative radiation dose after transoral resection of "intermediate risk" patients with HPV-positive tumors: those with close (<3 mm) margins, <1 mm extracapsular nodal spread and two to four metastatic nodes. Patients are stratified by smoking status (<10 vs. >10 pack-years). They are then randomized to receive 50 Gy versus 60 Gy using IMRT planning and delivery. The hope is to determine if radiation dose reduction is feasible in the postoperative setting for HPV-positive oropharynx cancer.

While postoperative radiation dose de-escalation is the primary question of ECOG 3311, RTOG 1221 seeks to evaluate whether "intensifying" therapy by adding transoral endoscopic surgery will improve outcomes in HPV-negative tumors over chemoradiation alone. Select HPV-negative oropharynx tumors (T1/T2, tumors not approaching within 1 cm of midline) that are felt amenable to transoral surgery are randomized to receive either standard IMRT (70 Gy) with concurrent weekly cisplatin or treatment first with transoral surgery (TORS or TLM) with neck dissection followed by 60 to 66 Gy postoperative radiotherapy with weekly cisplatin.

In summary, oropharynx cancer is now the most common head and neck cancer diagnosed in the United States. HPV-positive tumors have a much more favorable prognosis than HPV-negative tumors. As results have improved, techniques to decrease long-term morbidities of therapy via transoral surgery and reduction of radiation dose are evolving.

Table 13.1 describes typical radiotherapy dose prescriptions for oropharynx cancer.

TABLE 13.1 Typical Radiotherapy Prescriptions for Oropharynx Cancers

Target	Dose
Gross disease at primary site and involved LN with coverage of possible local and/or LN subclinical extension	66–70 Gy (2–2.2 Gy/fx daily), 72 Gy (1.8 Gy/fx with 1.5 Gy/fx boost last 12 treatments) or 81.6 Gy (1.2 Gy twice daily)
High-risk areas of suspected subclinical spread	59.4–63 Gy (1.8 Gy/fx)
Low- to intermediate-risk areas of suspected subclinical spread	50–56 Gy (1.6–2 Gy/fx)
Postoperative high-risk areas (e.g., positive margin, extranodal extension)	66 Gy (2 Gy/fx)
Postoperative primary site with negative margins and involved LN levels	60 Gy (2 Gy/fx)
Postoperative low-risk areas of suspected subclinical spread	50–54 Gy (1.8–2 Gy/fx)

fx, Fraction; *LN,* lymph nodes.

Nasopharyngeal Cancer

Nasopharyngeal carcinoma is challenging to treat because of its potential patterns of spread. The proximity to the skull base gives potential access for direct extension through foramen rotundum (cranial nerve V2), foramen ovale (cranial nerve V3), and foramen lacerum to the cavernous sinus (cranial nerves III, IV, V1, V2, VI). The parapharyngeal and masticator spaces are potential avenues of spread. It also has high proclivity to spread both regionally and distantly. It is a disease best treated by radiation, usually combined with chemotherapy. Staging should include MRI to assess local tumor infiltration and PET/CT to evaluate for regional spread and rule out distant metastases. Using these imaging modalities is critical for meticulous radiotherapy planning to ensure all visible and suspected disease is treated appropriately.

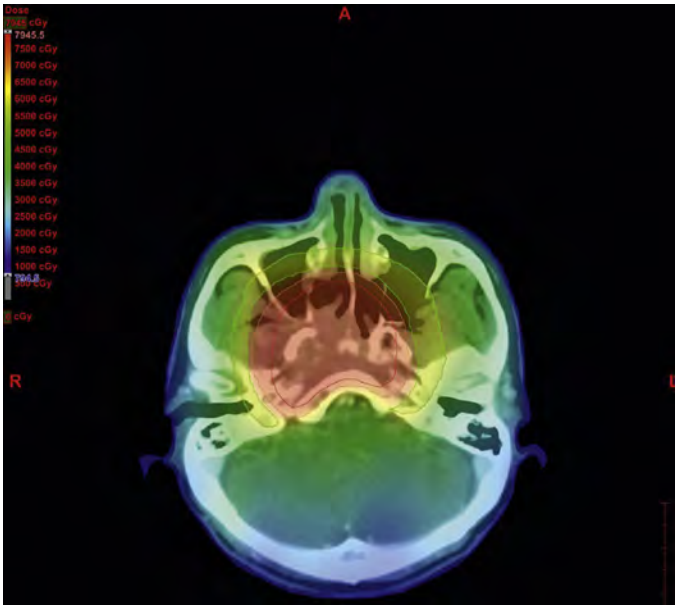
Nasopharyngeal carcinoma is associated with Epstein-Barr virus (EBV) infection. Lin has shown that measuring plasma EBV DNA is prognostic for outcome.[68] Overall survival and recurrence-free survival rates were shown to be significantly improved in patients with plasma EBV DNA concentrations less than 1500 copies per milliliter. Further, if EBV DNA remains detectable 1 week after completion of radiotherapy, patients had significantly worse overall survival and relapse-free survival rates.

As most patients with nasopharyngeal carcinoma present with locoregionally advanced disease, concurrent chemoradiation has become the standard of care. Intergroup study 0099 compared radiotherapy alone versus chemoradiation in 193 patients with stage III/IV disease.[69] Patients were randomized to receive 70 Gy alone or with concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 of radiotherapy. Chemoradiotherapy patients also received chemotherapy after the completion of radiation: cisplatin 80 mg/m^2 on day 1 and fluorouracil 1000 mg/m^2 per day on days 1–4, delivered every 4 weeks for three cycles. Combining chemotherapy with radiotherapy increased 3-year survival rate from 47% to 78% (P = .005). This study and subsequent meta-analyses including other randomized trials established chemoradiation as standard of care for the majority of nasopharyngeal cancer patients.[70]

Improvements in radiation planning and delivery, such as IMRT, have also improved locoregional control rates and reduced acute and long-term toxicity. IMRT is ideal for nasopharyngeal cancer to spare multiple adjacent normal tissues in close proximity to the tumor target volumes (Fig. 13.7). Lee and colleagues reported the UCSF experience treating 67 patients from 1995 through 2000.[61] Exceptional locoregional control was achieved using IMRT. With median follow-up of 31 months, only one patient suffered local recurrence and one patient failed in the neck for 4-year locoregional progression-free survival rate 98%. Most patients (75%) received chemotherapy as per the Intergroup 0099 guidelines. Importantly, late toxicity, including xerostomia, was reduced with IMRT compared to historical reports. The ability of IMRT planning to improve the therapeutic ratio for nasopharynx cancers has been confirmed in multiple subsequent retrospective and prospective studies.

Although a majority of patients receive concurrent cisplatin with IMRT, many patients do not receive the post-radiation adjuvant chemotherapy used in Intergroup 0099. Often, the acute toxicities of 7 weeks of concurrent chemoradiation limit the ability to deliver adjuvant chemotherapy. Using post-radiation EBV DNA titer information may help to guide therapy. The NRG-HN001 phase II/III trial is investigating this possibility. For patients with detectable plasma EBV DNA following chemoradiation, adjuvant chemotherapy using gemcitabine/paclitaxel is compared to cisplatin/fluorouracil as used in Intergroup 0099. In contrast, patients having undetectable plasma EBV DNA are randomized to observation or adjuvant cisplatin/fluorouracil.

While outcomes for patients with nasopharyngeal cancer have improved with the addition of chemotherapy and IMRT, locoregional failures still occur. Various approaches have been used to attempt salvage for local recurrence, including re-irradiation with IMRT, stereotactic radiotherapy or radiosurgery, brachytherapy, or proton radiotherapy.[71] Encouraging local control and survival rates have been reported for carefully selected patients, but toxicity can be significant. Stereotactic techniques deliver radiation to small, well-defined targets. Queen Mary Hospital in Hong Kong has used fractionated stereotactic radiotherapy to treat persistent or locally recurrent nasopharynx cancer. Three-year local control is 75%, but late complications were seen in 19%, including two patients dying of hemorrhage.[72] Reviewing their experience with locally recurrent nasopharyngeal cancer, Memorial Sloan Kettering found improved results when combining external beam radiation



• **Fig. 13.7** IMRT dose distribution for nasopharyngeal cancer showing optimal sparing of the brainstem.

TABLE 13.2 Typical Radiotherapy Prescriptions for Nasopharynx Cancers

Target	Dose
Primary site and involved LN with coverage of possible local and/or LN subclinical extension	70 Gy (2–2.12 Gy/fx)
High-risk areas of suspected subclinical spread. Often this includes entire nasopharynx, sphenoid sinus, cavernous sinus, base of skull, posterior ½ of nasal cavity, posterior 1/3 of maxillary sinuses, posterior ethmoid sinus, pterygoid fossae, lateral and posterior pharyngeal walls to level of mid-tonsillar fossa, bilateral retropharyngeal and cervical nodes.	59.4–63 Gy (1.8 Gy/fx)
Low- to intermediate-risk areas of suspected subclinical LN spread (e.g., in selected patients low neck or supraclavicular nodes)	54–56 Gy (1.6–1.64 Gy/fx)

fx, Fraction; *LN,* lymph nodes.

with intracavitary brachytherapy.[73] With this technique, an applicator connected to rubber catheters is positioned into the nasopharynx adjacent to the recurrent disease. Radiation is then delivered via temporary iodine-125 or iridium-192 radioactive sources. Five-year local control was 52% with 60% survival rate in this series. Importantly, the incidence of late grade 3 or higher complications was lower in those patients treated with combined external beam and brachytherapy (8%) compared with those patients treated entirely with external beam radiotherapy (73%) ($P = .005$). Re-irradiation techniques and results for recurrent head and neck cancers have been summarized nicely in a number of recent reviews.[74-76]

Table 13.2 describes typical radiotherapy dose prescriptions for nasopharynx cancer.

Nasal Cavity and Paranasal Sinus

Primary tumors of the nasal cavity and paranasal sinuses are uncommon, making it difficult to complete randomized clinical trials to formalize treatment recommendations. In the United States, their incidence is 0.556/100,000 per year, with a predilection towards males of 1.8:1.[77] Common histologies in the nasal cavity and paranasal sinuses, from most common to least, include squamous cell carcinoma, adenocarcinoma, olfactory neuroblastoma/esthesioblastoma, adenoid cystic carcinoma, melanoma, and undifferentiated carcinoma.[78]

Surgery is the mainstay of treatment; however, a multidisciplinary approach is recommended to optimize local control, especially for advanced-stage disease.[79] Early-stage disease can be treated with surgical resection alone.[80] However, postoperative radiotherapy should be used in the setting of positive or close margins that are unable to be re-resected. Postoperative radiotherapy should be used after resection of resectable T3/T4 and node-positive disease as well. The addition of concomitant chemotherapy to postoperative radiotherapy should be considered for high-risk features (e.g., extracapsular extension and positive margins).[67] Definitive radiotherapy or chemoradiotherapy is the treatment of choice when the patient is not a surgical candidate of if the tumor is unresectable or recurrent.

Radiotherapy to these locations is very challenging given the close proximity to multiple critical normal tissues, including the eyes, optic nerves and chiasm, other cranial nerves, brain, brainstem, spinal cord, pituitary, lacrimal glands, parotid glands, and others. These critical structures make it challenging to deliver sufficient radiation dose to the target volumes while keeping normal structures at doses that minimize risk of severe acute or late toxicity. As such, advanced radiotherapy techniques, such as IMRT, are generally recommended.[81,82] When available, proton therapy or other charged-particle therapy may be considered in certain circumstances to improve normal tissue sparing.[78,83] Finally, radiosurgery has been shown to be feasible for the paranasal sinus and nasal cavity primary and recurrent tumors.[84]

Table 13.3 describes typical radiotherapy dose prescriptions for sinonasal cancers.

Oral Cavity Cancer

Oral cavity cancers are primarily a surgical disease. Although there may be discussion regarding equal efficacy when using either surgery or radiotherapy to treat small primary lesions of the oral cavity, surgery is generally preferred. It is quicker and results in less long-term morbidity than definitive radiotherapy. Brachytherapy may be considered for small tumors of the oral tongue,[85] floor of mouth, or lip,[86] but for the most part, surgical techniques have improved with partial glossectomies leaving reasonable tongue function and partial or rim-mandibulectomies sparing the mandible. Definitive radiotherapy to the oral cavity is challenged by the normal tissue constraints of the lips, teeth, and mandible.

Although primarily evaluating tumors of the supraglottic larynx and hypopharynx, RTOG 73-03 established postoperative radiotherapy to be superior to preoperative radiation with improved locoregional control while having similar rates of severe surgical and radiation complications.[87] These results have generally been extrapolated for use in other head and neck

TABLE 13.3 Typical Radiotherapy Prescriptions for Sinonasal Cancers

Target	Dose
Gross disease at primary site and involved LN with coverage of possible local and/or LN subclinical extension	66–70 Gy (2–2.2 Gy/fx daily), 72 Gy (1.8 Gy/fx with 1.5 Gy/fx boost last 12 treatments) or 81.6 Gy (1.2 Gy twice daily)
High-risk areas of suspected subclinical spread	59.4–63 Gy (1.8 Gy/fx)
Low- to intermediate-risk areas of suspected subclinical spread	50–56 Gy (1.6–2 Gy/fx)
Postoperative high-risk areas (e.g., positive margin, extranodal extension)	66 Gy (2 Gy/fx)
Postoperative primary site with negative margins and involved LN levels	60 Gy (2 Gy/fx)
Postoperative low-risk areas of suspected subclinical spread	50–54 Gy (1.8–2 Gy/fx)

fx, Fraction; *LN,* lymph nodes.

sites including the oral cavity, although occasionally surgeons will request preoperative radiation in an attempt to improve resectability.

Indications for postoperative radiation after resection of oral cavity primaries are similar to other head and neck sites and include close or positive surgical margins, perineural spread, angiolymphatic invasion, spread to multiple lymph nodes, and extracapsular nodal spread. Oral cavity tumors may invade into the mandibular cortex. This bone invasion is generally felt to be an indication for postoperative radiation reflecting the challenge of interpreting surgical margins when bone is invaded and as a sign of the tumor's aggressive biology. There is occasionally the scenario where a small primary oral tongue lesion is resected with hope for sparing the patient the morbidity of ipsilateral neck dissection. Depth of invasion or tumor thickness can be predictive for risk of spread to regional nodes.[88] Neck dissection is generally recommended unless there are other indications for postoperative radiation based on the primary pathology, in which case elective neck radiotherapy may be used in lieu of neck dissection with high regional control rates.

MD Anderson performed a prospective trial involving 240 resected head and neck patients seeking to define optimal postoperative radiotherapy dose.[89] This study found that doses of 54 Gy or less were associated with a significantly higher rate of recurrence. Today, the postoperative tumor bed is generally treated to 60 Gy in 2-Gy fractions with consideration of boost to 63 to 66 Gy to sites of increased risk, such as close or positive margins or areas of extracapsular nodal extension.

Both European Organization for Research and Treatment of Cancer (EORTC) 2293 and RTOG 9501 have demonstrated the benefit of adding cisplatin chemotherapy to postoperative radiotherapy to improve outcomes for high-risk patients.[90,91] Bernier and Cooper and their colleagues performed an analysis of data from the two studies using cisplatin on days 1, 22, and 43 of the radiotherapy and found that extracapsular extension and/or positive surgical margins were the two pathologic risk factors where the addition of cisplatin showed a particular benefit.[67] RTOG 1215 is an ongoing randomized phase II/III trial of cisplatin versus docetaxel versus combined docetaxel/cetuximab with postoperative radiotherapy for high-risk resected head and neck cancer to identify the optimal chemotherapy regimen in the high-risk postoperative setting. RTOG 0920 is a phase III trial evaluating the addition of cetuximab to postoperative radiation for "intermediate risk" postoperative head and neck cancers with pathologic risk factors that do not include positive surgical margins or extracapsular nodal spread.

Most practitioners have adopted IMRT planning and delivery for postoperative radiotherapy in oral cavity cancers. Multiple published series have reported good locoregional control rates with acceptable toxicity using IMRT.[92-95] In the largest published series of 180 consecutive patients, 2-year local control was 87% and regional control 83%.[96] Careful and comprehensive target volume delineation is critical to minimize risk of marginal or out-of-field recurrences.

Brachytherapy for head and neck squamous cell carcinomas requires specialized techniques, training, and experience. Guidelines have been published regarding patient selection, techniques, dose selection, planning, reporting, and post-treatment care [97] High local control rates have been reported for lip (90–95%), buccal mucosa (80–90%), mobile tongue (>90%), floor of mouth (>90%), and base of tongue T1/T2 (80–90%), T3/T4 (65–80%). Brachytherapy can be sole treatment or combined with surgery or as a boost after initial external beam radiotherapy. Brachytherapy sources are implanted in an operating room, generally always with a head and neck surgeon present in the unlikely but possible event of arterial bleeding or other complication. Low-dose-rate (LDR) brachytherapy usually delivers dose at 0.3–0.6 Gy/hour to 20–35 Gy when combined with 50 Gy external beam radiotherapy, or 60–70 Gy over several days when used alone. High-dose-rate (HDR) brachytherapy delivers 21 Gy at 3 Gy/fraction over minutes if combined with 40–50 Gy

TABLE 13.4 Typical Radiotherapy Prescriptions for Oral Cavity Cancers

Target	Dose
Gross disease at primary site and involved LN with coverage of possible local and/or LN subclinical extension	66–70 Gy (2–2.2 Gy/fx daily), 72 Gy (1.8 Gy/fx with 1.5 Gy/fx boost last 12 treatments) or 81.6 Gy (1.2 Gy twice daily)
High-risk areas of suspected subclinical spread	59.4–63 Gy (1.8 Gy/fx)
Low- to intermediate-risk areas of suspected subclinical spread	50–56 Gy (1.6–2 Gy/fx)
Postoperative high-risk areas (e.g., positive margin, extranodal extension)	66 Gy (2 Gy/fx)
Postoperative primary site with negative margins and involved LN levels	60 Gy (2 Gy/fx)
Postoperative low-risk areas of suspected subclinical spread	50–54 Gy (1.8–2 Gy/fx)
LDR brachytherapy at 0.4–0.5 Gy/hour	20–35 Gy when combined with 50 Gy external beam radiotherapy. 60–70 Gy over several days when used alone
HDR brachytherapy	21 Gy at 3 Gy/fraction if combined with 40–50 Gy external beam radiotherapy. 45–60 Gy at 3–6 Gy/fraction if used alone.

fx, Fraction; *HDR,* high-dose-rate; *LDR,* low-dose-rate; *LN,* lymph nodes.

external beam radiotherapy, or 45–60 Gy at 3–6 Gy/fraction if used alone.

Table 13.4 describes typical radiotherapy dose prescriptions for oral cavity cancers.

Laryngeal Cancer

Radiation remains a primary treatment option for larynx cancer for organ preservation. Fortunately, most of the 13,560 patients diagnosed with laryngeal cancer in 2015 will present with early-stage glottic disease.[98] About 60% of laryngeal cancers originate in the true vocal cords or glottic larynx, and most of these present with early-stage disease because hoarseness manifests as an early symptom. These early glottic cancers rarely present with spread to lymph nodes with <5% incidence seen with T1 and T2 tumors. Surgical excision and laser resection are viable therapeutic options. Radiotherapy also provides excellent results with local control rates about 90% for T1 lesions and about 80% for T2 disease while preserving good voice quality. Since regional spread is unlikely, small opposed fields can be used with treatment volume centered on the vocal cords (Fig. 13.8).

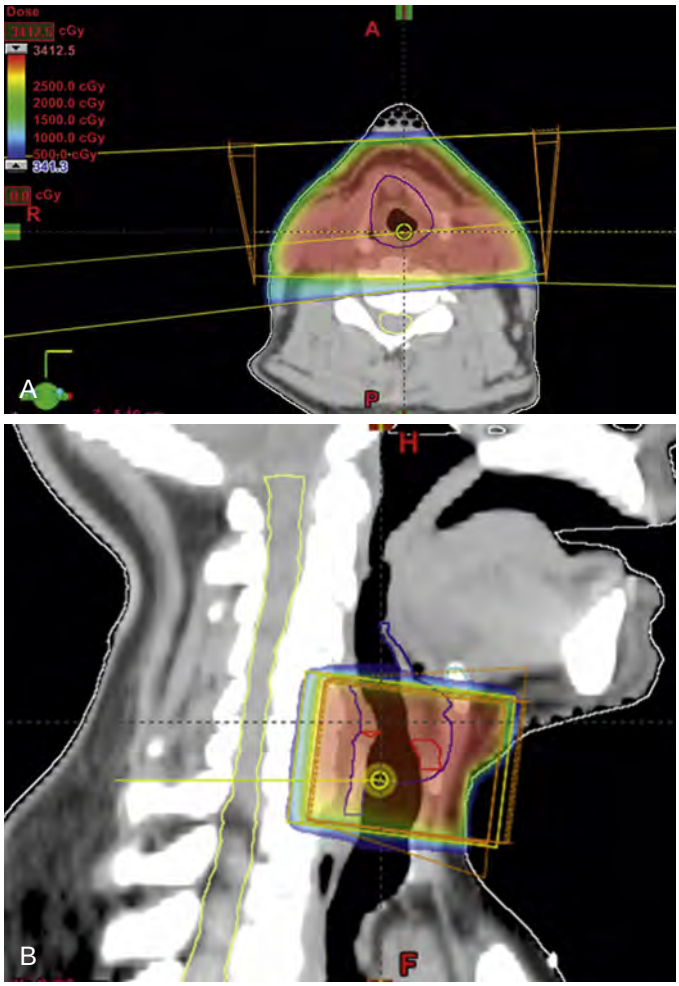
Accelerated radiotherapy to decrease the negative effect of tumor repopulation is a proven technique for early-stage glottic carcinomas. In a randomized trial comparing 60–66 Gy in 2-Gy fractions versus 56.25–63 Gy in 2.25-Gy fractions for T1 glottic tumors, using larger fraction size and shortening overall treatment time by 1 week improved 5-year local control (92% versus 72%, $P = 0.004$) with no significant differences in acute skin or mucosal reactions or late effects.[12]

Although most patients with early glottic cancers are cured, it is important to remember that most of these patients are former or current smokers. As such, follow-up should include surveillance for second cancers, including lung cancer. In one series, more patients eventually died of a secondary cancer unrelated to the original early laryngeal cancer.[99] Low-dose screening chest CT scan might be considered as part of routine workup and surveillance in patients with >30 pack-year smoking history.[100,101]

Supraglottic tumors have higher risk of regional spread and usually present with more advanced disease. Early-stage T1/T2N0 supraglottic carcinomas may be cured with larynx-preserving surgery or with definitive radiotherapy. For T1N0 supraglottic carcinomas, the primary site and level II/III nodes are treated. For T2 and more advanced tumors, the lower neck nodes are treated also.

Historically, laryngectomy followed by postoperative radiotherapy was standard care for patients with T3 or node-positive larynx cancer. The Veterans Affairs Laryngeal Cancer Study Group first evaluated induction chemotherapy as a means to select patients with advanced laryngeal cancer who could be treated successfully with larynx-preserving radiation.[102] In this study, 332 patients with stage III/IV laryngeal cancer were stratified by response to two cycles of induction cisplatin/fluorouracil chemotherapy, with at least partial responders receiving one more cycle of chemotherapy followed by definitive radiation. Non-responders following two cycles of induction chemotherapy received laryngectomy followed by adjuvant radiation. Overall, 85% of the patients in this study had a response to chemotherapy (31% complete, 54% partial) and received the third cycle of chemotherapy followed by radiation. Using this approach, the larynx was preserved in 64% of the patients. Two-year survival rate was not impacted by this organ-preservation approach: 68% for both study arms.

The relative value of induction and concurrent chemotherapy with radiation was subsequently addressed in the RTOG 91-11 randomized trial. Patients with advanced larynx cancer were randomized to one of three arms: induction cisplatin/



• **Fig. 13.8** Radiation alone to treat early glottic cancer. Small opposed lateral fields. Axial **(A)** and sagittal views **(B).**

fluorouracil as per the VA Larynx Trial, concurrent radiation and cisplatin 100 mg/m^2 on days 1, 22, and 43, or radiation alone.[103] Patients with T4 stage (penetrating through the cartilage or with more than 1 cm base of tongue invasion) were excluded. With median follow-up of 3.8 years, laryngeal preservation was significantly higher in those patients receiving concurrent cisplatin and radiation (84%) than in those treated with induction chemotherapy followed by radiotherapy (72%) or radiation alone (67%). Overall survival rate was not better in any of the arms, with 5-year overall survival rate 54–56%. Ten-year results confirm that concomitant cisplatin and radiation continues to provide the highest locoregional control and laryngeal preservation rates.[104] However, although there were no statistically significant differences in late toxicity or long-term swallowing function, there was concern that concurrent cisplatin and radiation produced a level of fibrosis that may have contributed to late deaths unrelated to laryngeal cancer.

The European TREMPLIN study employed an induction strategy for organ preservation with three cycles of docetaxel (75 mg/m^2) and fluorouracil (750 mg/m^2). Patients not achieving at least a partial response underwent laryngectomy. Responders were then randomized to radiation with concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 or concurrent cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2 per week during radiotherapy.[105] This study showed no significant difference in laryngeal preservation or overall survival rate. There were fewer overall local failures in the cisplatin arm, but salvage surgery was only possible in the cetuximab arm because of the increased cervical fibrosis seen with concurrent radiation and cisplatin.

There remains some controversy regarding the extent of disease that qualifies for attempted organ preservation. RTOG 91-11 initially excluded tumors with any cartilage invasion because of the high need for salvage laryngectomy needed for T4 tumors in the VA Larynx Trial (44%). Patients with "minimal" cartilage invasion were ultimately allowed to accrue. Ultimately, the decision needs to be made by experienced practitioners. There is an extent of cartilage destruction and loss beyond meaningful preservation. This relates to pragmatic long-term issues of speech, airway and aspiration risk, and swallowing. The EORTC describes laryngoesophageal dysfunction–free survival as a way to describe patients who have no evidence of cancer but also do not need a tracheostomy or feeding tube long-term.

For patients with large bulky tumors with significant cartilage destruction, laryngectomy remains the standard up-front therapy. Indications for postoperative radiotherapy are the same as described earlier in this chapter, pT4, pN2-N3, close or positive margins, and perineural invasion. Concurrent cisplatin chemotherapy should be considered with postoperative radiotherapy for patients with positive surgical margins and/or extracapsular nodal extension.

Radiation technique after laryngectomy must include special attention to the peristomal tissues. Salvage of stomal recurrence is challenging due to the adjacent vessels and airway. The key to therapy is to prevent recurrence by adequate coverage of the peristomal tissues.[106] The tracheostoma may be boosted to 60–66 Gy or higher for patients requiring emergent tracheostomy, tumors with greater than 5 mm subglottic extension, and tumors with significant invasion of soft tissues of the neck, extranodal extension in level VI, or close or positive margins.

Table 13.5 describes typical radiotherapy dose prescriptions for larynx cancers.

Hypopharyngeal Cancer

Hypopharynx cancers tend to present with locally and regionally advanced disease. The hypopharynx can be a difficult area to examine, with early subtle changes in the pyriform sinus often going undetected on fiber-optic examination. The postcricoid area can be difficult to examine in the best of circumstances using an office fiber-optic scope. Unlike oropharynx cancer, these tumors are usually not associated with HPV infection, so we have not seen similar improvements in outcomes.

Given the rarity of these tumors, they are often combined with laryngeal malignancies in trials. Standard surgical approach usually includes partial pharyngectomy combined with total laryngectomy. Most providers, therefore, attempt chemoradiation as a means to spare the larynx unless the tumor

TABLE 13.5 Typical Radiotherapy Prescriptions for Larynx Cancers

Target	Dose
Glottic TisN0	56.25–60.75 Gy (2.25 Gy/fx)
Glottic T1N0	63 Gy (2.25 Gy/fx)
Glottic T2N0	65.25 Gy (2.25 Gy/fx)
For supraglottic, subglottic, and T3/T4 glottic gross disease at primary site and involved LN with coverage of possible local and/or LN subclinical extension	66–70 Gy (2–2.2 Gy/fx daily), 72 Gy (1.8 Gy/fx with 1.5 Gy/fx boost last 12 treatments) or 81.6 Gy (1.2 Gy twice daily)
High-risk areas of suspected subclinical spread	59.4–63 Gy (1.8 Gy/fx)
Low- to intermediate-risk areas of suspected subclinical spread	50–56 Gy (1.6–2 Gy/fx)
Postoperative high-risk areas (e.g., positive margin, extranodal extension)	66 Gy (2 Gy/fx)
Postoperative primary site with negative margins and involved LN levels	60 Gy (2 Gy/fx)
Postoperative low-risk areas of suspected subclinical spread	50–54 Gy (1.8–2 Gy/fx)

fx, Fraction; *LN,* lymph nodes.

TABLE 13.6 Typical Radiotherapy Prescriptions for Hypopharynx Cancers

Target	Dose
Gross disease at primary site and involved LN with coverage of possible local and/or LN subclinical extension	66–70 Gy (2–2.2 Gy/fx daily), 72 Gy (1.8 Gy/fx with 1.5 Gy/fx boost last 12 treatments) or 81.6 Gy (1.2 Gy BID)
High-risk areas of suspected subclinical spread	59.4–63 Gy (1.8 Gy/fx)
Low to intermediate-risk areas of suspected subclinical spread	50–56 Gy (1.6–2 Gy/fx)
Postoperative high-risk areas (e.g., positive margin, extranodal extension)	66 Gy (2 Gy/fx)
Postoperative primary site with negative margins and involved LN levels	60 Gy (2 Gy/fx)
Postoperative low-risk areas of suspected subclinical spread	50–54 Gy (1.8–2 Gy/fx)

fx, Fraction; *LN,* lymph nodes.

is associated with extensive cartilage destruction, making this approach futile.

Accordingly, organ preservation has been explored in the management of hypopharynx cancer. EORTC 24891 evaluated the use of three cycles of induction chemotherapy with cisplatin and fluorouracil to select patients for definitive radiotherapy.[105] Those patients achieving a complete clinical and radiographic response went on to radiotherapy, and patients with less than a complete response underwent surgery followed by radiotherapy. This strategy of induction chemotherapy to select patients for organ preservation did not compromise disease control or overall survival rate. More than half of the long-term survivors were able to retain their larynx. Unfortunately, 10-year survival rate was only 13.8% after surgery and 13.1% after induction chemotherapy followed by radiotherapy.

In the United States, most locally advanced hypopharynx patients are treated with concurrent chemoradiation approaches similar to that used for locoregionally advanced larynx cancer as in RTOG 9111.[103,104] The French included hypopharynx primaries in their recent TREMPLIN study of induction docetaxel, cisplatin, and fluorouracil followed by radiation combined with either concurrent cisplatin or cetuximab.[107] Induction chemotherapy remains a reasonable approach for selected patients.

From a radiation treatment planning perspective, it is important to recognize the frequent spread of hypopharynx cancer to regional lymph nodes. It is critical to cover the retropharyngeal nodes when treating hypopharynx carcinomas. Finally, surgical salvage can be particularly challenging for hypopharynx cancers with high rates of fistula formation.

Table 13.6 describes typical radiotherapy dose prescriptions for hypopharynx cancers.

Managing the Neck after Radiation to Regional Disease

Planned postoperative neck dissection was once considered standard of care for patients with bulky adenopathy treated with radiation or chemoradiation. Intergroup studies

would incorporate neck dissection into the treatment plan for patients presenting with lymph nodes 3 cm or greater in size. This approach was often used even in patients who had achieved a complete clinical or radiographic response. The problem was that most patients (70–85%) were found to have no viable tumor in their neck dissection specimens. The Trans Tasman Radiation Oncology Group prospectively omitted planned neck dissection in their N2-N3 patients achieving complete clinical response after chemoradiation (as determined by physical examination or imaging) and found no isolated regional failure.[108] With this and other data, planned neck dissection for patients achieving a complete regional response to chemoradiation is no longer recommended.[109]

However, many patients with initial bulky adenopathy do not achieve a clinical complete response at the completion of chemoradiation and continue to have nodes that are palpable or easily visualized on CT. Some have recommended routine neck dissection for these patients to provide the best chance for regional control. Still, most of these patients will not have viable residual disease found in these persistently enlarged nodes. Yao and colleagues recommend fluorodeoxyglucose (FDG)-PET as a means to determine the need for post-radiation neck dissection.[110] Khodayari and co-workers reported that patients with post-chemoradiotherapy PET scans having a standard uptake value (SUV) less than 3.0 may be spared neck dissection and followed regardless of the size of the residual node on exam or CT.[111] In their series, only 4% of patients with residual adenopathy but negative PET scan had viable residual cancer following neck dissection. The timing of the post-chemoradiotherapy PET scan is critical. If the scan is performed too early, the results may be difficult to interpret, as radiation-induced inflammation may provide false positives. The best time to perform post-chemoradiotherapy PET scan is approximately 10 to 16 weeks after therapy.[112]

Cervical Squamous Cell Carcinoma of Unknown Primary

Even with remarkable improvements in panendoscopy, fiber-optic examination, and imaging, patients still present with squamous cell carcinoma in cervical lymph nodes with no clearly identifiable primary site of origin. Historically, 3–5% of head and neck cancers presented as cervical squamous cell carcinomas of unknown primary (CUP). This number may be increasing in the era of HPV-associated cancers.[113] Most patients undergo CT scan with IV contrast as well as fiber-optic in-office examination. PET/CT scan appears to be more sensitive than CT with contrast or MRI in detecting primary sites.[114] Nodal location can also lead to closer examination of a likely primary site. Upper posterior cervical nodes should focus attention on the nasopharynx. Upper anterior nodes (level IIA) should lead to suspicion of the oropharynx. Submental or submandibular nodes should lead to closer examination of the oral cavity. Nodal appearance on CT scan can also be useful, as large cystic nodes are more commonly seen with HPV-associated tumors of the oropharynx. Molecular evaluation of biopsy material can prove helpful. Staining for EBV points to the nasopharynx. Detection of HPV correlates with an oropharyngeal location.

Tonsillectomy has become part of the initial work-up for these tumors, especially for nodes in the upper and mid-jugular group.[115] Recently, transoral approaches including TORS and TLM have been used to find primaries in CUP. In fact, in one series using TLM for select cases, the overall rate of primary tumor detection was 75%.[116] When lingual tonsillectomy was used, the detection rate increased to 86%. Tumors were most commonly found in the lingual tonsils (65%) and the palatine tonsils (27.5%).

The University of Florida has recently questioned the value of randomly directed biopsies of the nasopharynx and pyriform sinuses as part of the work-up for CUP.[117] In their review of 156 patients treated between 1985 and 2014 using modern imaging, they had no patient with positive biopsies of the nasopharynx or hypopharynx.

Although work-up for CUP is directed at finding the primary site of disease, management should be based on the extent of neck disease. Surgery is preferred for N1 disease. For pathologic N1 disease without extranodal extension, postoperative radiotherapy may be considered or observation, depending on extent of neck dissection or other risk factors. Ipsilateral neck dissection alone may be adequate therapy for the patient presenting with a solitary, small node. In a series of patients treated with ipsilateral neck dissection with ipsilateral radiation reserved for patients with N2/N3 disease, Patel and colleagues found 84% control in the ipsilateral neck.[118] In this series the primary tumor site ultimately developed in 11% of patients.

For patients with pathologic N2-N3 disease or extranodal extension, or for clinical N2-3 disease, radiotherapy is routinely administered either postoperatively or definitively. Radiation techniques focus on covering likely mucosal primary sites as well as the at-risk neck nodes. Traditionally, radiotherapy targets extended from the nasopharynx down to the pyriform sinus.

Reducing mucosal radiation target size can decrease morbidity, however. The University of Florida reported that omitting radiotherapy to the larynx and hypopharynx in patients with CUP did not compromise outcomes and likely reduced toxicity.[119] Mucosal control in their series was 100% at 5 years in patients where mucosal radiotherapy (median dose 5670 cGy) was limited to the nasopharynx and oropharynx.

There remains controversy about further decreasing radiotherapy coverage for CUP. An EORTC randomized trial of ipsilateral versus bilateral neck radiotherapy unfortunately failed to adequately accrue patients. Some retrospective studies, however, have suggested that unilateral neck radiotherapy may be considered for carefully selected patients.[120,121]

IMRT technique is often preferred today for CUP, especially with bilateral neck and mucosal radiotherapy, to spare adjacent normal tissues. Studies have reported high

locoregional control rates using IMRT. At MD Anderson, a 5-year actuarial primary mucosal control rate of 98% and regional control of 94% was achieved using IMRT.[122] Two patients experienced grade 3 dysphagia/stricture. At Memorial Sloan Kettering using IMRT, 2-year regional control was 90% and only one patient required gastrostomy tube support at last follow-up.[123]

The role of concurrent chemotherapy with radiotherapy for CUP is primarily extrapolated from results described earlier for other primary site head and neck cancers. Concurrent cisplatin is usually considered for patients with extranodal extension or for multiple positive nodes. However, adding chemotherapy significantly increases toxicity and might not be necessary for certain patients.[124]

Radiotherapy doses for CUP are similar to those for other head and neck sites (see Table 13.1).

Salivary Gland Cancers

Salivary gland tumors are relatively rare, accounting for approximately 3–5% of all head and neck cancers. In addition to their rarity, phenotypic, biologic, and clinical heterogeneity exists, rendering any randomized investigation on optimal treatment very difficult. Pleomorphic adenomas are the most common benign histology of the parotid, mucoepidermoid carcinoma are the most common malignant histology of the parotid, and adenoid cystic carcinomas are the most common malignant histology of the submandibular and minor salivary glands. Primary squamous cell carcinoma (also known as primary epidermoid carcinoma) of the salivary glands is rare, and diagnosis requires exclusion of another primary head and neck site.

Surgical resection is the primary treatment of choice. Neck dissection is recommended for clinically positive lymph node involvement or high-grade morphology. Adjuvant radiotherapy is recommended if the postoperative pathologic specimen exhibits evidence of perineural invasion, close or positive margins, high-grade morphology, T3/T4 disease, or lymph node involvement. For medically or surgically inoperable tumors, radiotherapy alone may be considered with mixed results.

A recent large review of 538 patients treated for major salivary gland tumors reported that postoperative radiotherapy improved 10-year local control compared to surgery alone for patients with T3/T4 tumors (18 vs. 84%), close margins (55 vs. 95%), incomplete resection (44 vs. 82%), bone invasion (54 vs. 86%), and perineural invasion (60 vs. 88%).[125]

Unfortunately, over a third of patients with initially localized disease will develop distant metastases despite adjuvant treatment. Given this, the role of postoperative chemoradiotherapy with weekly cisplatin versus radiotherapy alone for patients with multiple high-risk factors is an area of active investigation (RTOG 1008).[126-129]

Unresectable or locally recurrent disease remains a challenge. Mendenhall and colleagues retrospectively analyzed 101 patients treated with radiotherapy for adenoid cystic carcinoma and found 10-year local control of 43% for radiotherapy alone compared to 91% for surgery and postoperative radiotherapy.[130] A clear dose-response relationship is seen for patients treated with primary radiotherapy.[125] Fast neutron radiotherapy, which has relative radiation damage that is four times that of x-rays, may be considered for unresectable disease, including adenoid cystic carcinoma. Densely ionizing radiation, including neutron particle therapy, has a high propensity for creating a large amount of lethal double-strand DNA breaks independent of the presence of oxygen as a radiosensitizer. Currently only offered in the United States at the University of Washington or Wayne State University, fast neutron therapy has been evaluated and compared to conventional radiotherapy in a randomized phase III trial showing improved local-regional control but no significant improvement in overall survival rate, with distant metastases accounting for most failures.[19] The improved local-regional control must be weighed against increased early and late adverse effects (dermatitis, mucositis, xerostomia, and fibrosis) seen with fast neutron therapy.

Radiotherapy doses for salivary gland tumors are generally similar to those for other head and neck sites (see Table 13.1).

Skin Cancer of the Head and Neck

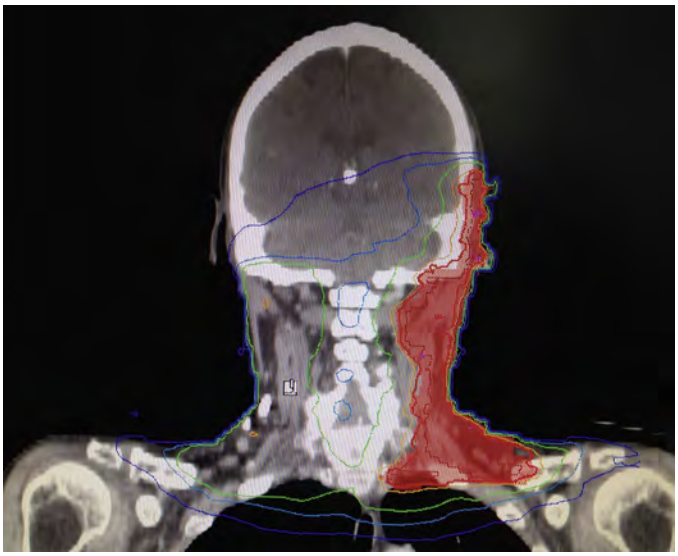
Skin cancers are the most common malignancies in the United States. Most of these are basal cell cancers. Small lesions are effectively treated with simple in-office techniques. Mohs micrographic surgery, with tumor margins microscopically delineated using serial radial resections, achieves negative margins with real-time frozen section analysis.[131] Radiotherapy may be considered for inoperable patients or for cosmetically challenging locations, such the eyelid, pinna or nose.

Much of the older literature describing the use of radiation for skin cancer describes the use of superficial or orthovoltage radiotherapy. Most radiation centers today do not have this equipment and use more readily available electrons from the linear accelerator to treat skin cancer. When extrapolating older data to current use, radiation oncologists should account for the difference in relative biologic effect (RBE) between electrons and orthovoltage radiation. Most consider the RBE of electrons to be approximately 80–90% that of orthovoltage radiation.[132] Various fractionation schemes exist for treating small skin cancers[133] (Table 13.7). In general, small lesions can be treated with short courses of radiotherapy using large fractions of radiation. Larger tumors or tumors associated with cartilage or bone invasion should be treated using smaller fractions over a more protracted course to improve cosmetic outcome while still providing excellent local control. Recently, high-dose-rate electronic brachytherapy has been reported to be effective in treating small skin cancers.[134] This electronic brachytherapy system uses a small, high-dose-rate, low-energy x-ray tube with a flexible multi-lumen catheter. The x-ray tube produces photons of 50 keV maximum energy. Using the appropriate surface applicator, most patients receive 40 Gy over eight fractions of 5 Gy each with two treatments delivered per week at least 48 hours between fractions. Follow-up is short with this new

TABLE 13.7 Typical Radiotherapy Prescriptions for Skin Carcinomas

Target	Dose
Tumor <2 cm	60–64 Gy (2 Gy/fx) 50–55 Gy (2.5–2.75 Gy/fx) 45–50 Gy (3–3.33 Gy/fx) 40 Gy (4 Gy/fx) 30–35 Gy (6–7 Gy/fx)
Tumor >2 cm	66 Gy (2 Gy/fx) 55 Gy (2.5–2.75 Gy/fx)
Postoperative adjuvant	50 Gy (2.5 Gy/fx) 60 Gy (2 Gy/fx)
Regional disease (all 1.8–2 Gy/fx)	66 Gy for extranodal extension 50–56 Gy without extranodal extension 66–70 Gy for unresected clinically involved nodes

Note: Rapid fractionation schemes have similarly high cure rates but generally poorer cosmetic results.



• **Fig. 13.9** Radiation dose distribution using IMRT to treat the parotid bed and ipsilateral neck after resection of skin cancer metastatic to the parotid.

technology, but it is well tolerated with good to excellent cosmesis. Long-term efficacy of this approach is awaited.

Brigham and Women's Hospital (BWH) has published a proposed updated staging system for high-risk cutaneous carcinomas.[135] In their series of 1818 patients, risk factors were tumor diameter ≥2 cm, poor differentiation, perineural invasion ≥0.1 mm, bone invasion, or tumor beyond fat. Stage T1 is 0 risk factors, T2a is 1 risk factor, T2b is 2-3 risk factors, and T3 is >3 risk factors or bone invasion. The 10-year local and regional recurrence risk by stage is T1 <2%, T2a <5%, T2b 21%, T3 67%. With high local and regional recurrence rates, BWH stage T2b/T3 carcinomas should be strongly considered for adjuvant radiotherapy.

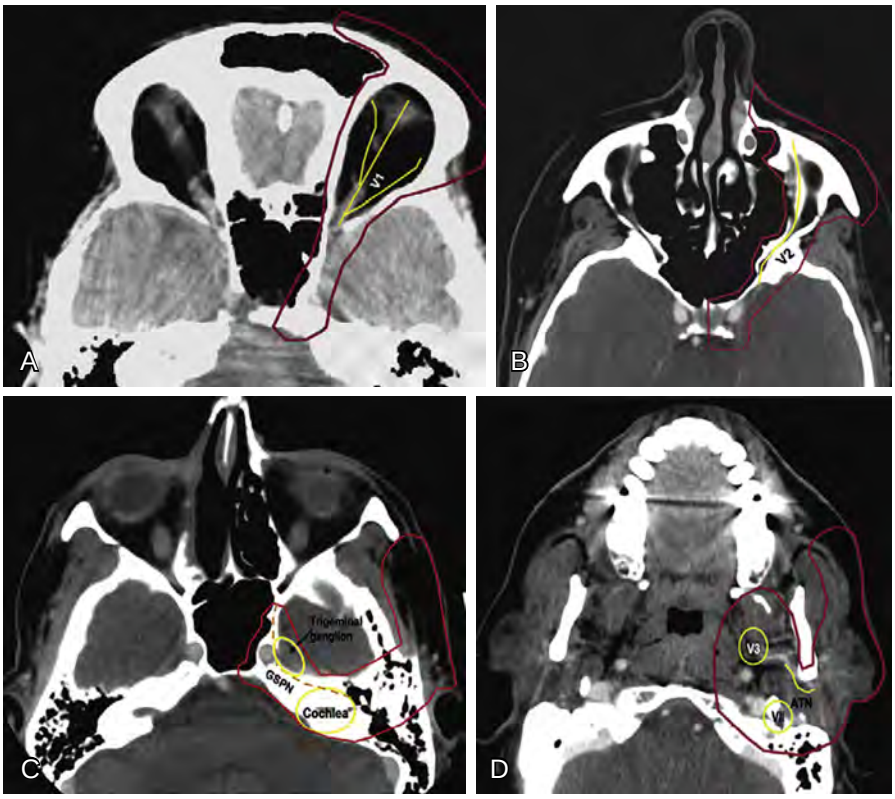
Aggressive tumors often require a combination of surgery followed by postoperative radiotherapy. Nodal spread from basal cell cancers is fairly uncommon, but large squamous cell carcinomas of the scalp or face often present with malignant adenopathy to the parotid gland. Surgery often includes superficial facial nerve–sparing parotidectomy and ipsilateral neck dissection. Postoperative radiation is often best delivered using an IMRT plan to treat the primary site as well as the remaining parotid and ipsilateral neck (Fig. 13.9). Whereas postoperative radiotherapy for high-risk pathologic features is considered standard of care, the role of adjuvant chemotherapy is less defined. Many providers extrapolate from other head and neck sites and consider adding cisplatin or even cetuximab to postoperative radiotherapy for patients with positive surgical margins or extracapsular nodal extension.

Perineural involvement is found in aggressive squamous cell and basal cell carcinomas. Clinically asymptomatic perineural involvement seen on microscopic review of the pathologic specimen can be an indication for postoperative radiation to decrease the risk of local and/or regional recurrence. Patients presenting with clinical signs or symptoms of perineural spread, pathologic evidence of disease, or radiographic documentation of perineural extension have a much poorer prognosis with 5-year local control about 25–50%.[136] Once such clinical nerve involvement occurs, the chance of salvage is poor, so prevention is critical for high-risk patients as discussed earlier.

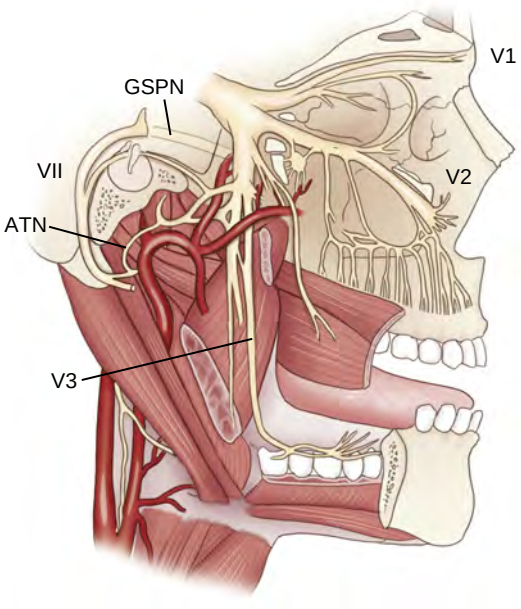
Patients with gross or extensive perineural spread generally benefit from IMRT planning and image guidance to adequately treat the at-risk nerves at the base of the skull. Gluck has provided a good reference discussing radiation target volumes for patients with skin cancer associated with perineural invasion.[137] Recurrence along the paths of cranial nerves is most common for cranial nerves V and VII (Fig. 13.10). The authors review tumor spread through potential communications between these two cranial nerves as well: (1) the auriculotemporal nerve connects V3 with cranial nerve VII as it exits the stylomastoid foramen and (2) the greater superficial petrosal nerve connects the geniculate ganglion of VII with the pterygopalatine ganglion of V2 (Fig. 13.11).

Palliative Radiotherapy

For incurable patients or patients not fit for definitive treatment, palliative radiotherapy can offer effective treatment to improve and preserve quality of life. Palliative radiotherapy should be considered for relief or prevention of locoregional symptoms, such as pain, airway compromise, neurologic deterioration, or bleeding. Up to 80–85% of patients have at least temporary treatment response with improvement in their symptoms or reduced need for analgesics.[138] The prognosis of incurable head and neck cancer is poor with best supportive care only, with median survival time about 3–4 months versus up to 4–17 months when treated. Palliative radiotherapy regimens are tailored individually (Table 13.8).



• **Fig. 13.10** Clinical target delineation to cover cranial nerve V and VII branches in skin cancers with perineural invasion (nerves at risk shown in *yellow,* CTV shown in *red.*) **A**, CTV covering V1 branch of the trigeminal nerve. **B**, CTV covering V2 branch of the trigeminal nerve. **C**, CTV coverage including the greater superficial petrosal nerve (GSPN), trigeminal and geniculate ganglia. D, CTV coverage including the auriculotemporal nerve (ATN), V3 branch of the trigeminal nerve, and the facial nerve as it leaves the styloid foramen. (From Gluck I, Ibrahim M, Popovtzer A, et al: Skin cancer of the head and neck with perineural invasion: defining the clinical target volumes based on the pattern of failure. *Int J Radiat Oncol Biol Phys* 74:38-46, 2009, with permission.)



• **Fig. 13.11** Cranial nerve innervation of the scalp, face, and neck. Communication via the greater superficial petrosal nerve *(GSPN)* and auriculotemporal nerve *(ATN),* allowing tumor spread between these cranial nerves V and VII. (From Gluck I, Ibrahim M, Popovtzer A, et al: Skin cancer of the head and neck with perineural invasion: defining the clinical target volumes based on the pattern of failure. *Int J Radiat Oncol Biol Phys* 74:38-46, 2009, with permission.)

TABLE 13.8 Typical Palliative Radiotherapy Prescriptions for Head and Neck Cancers

Dose
50 Gy in 20 fractions
37.5 Gy in 15 fractions followed by 5 fraction boost after 1- to 3-week break if well tolerated
30 Gy in 10 fractions
30 Gy in 5 fractions (only 2 fractions per week at least 3 days apart)
3.7 Gy twice daily for 2 days, repeated up to 2 more times every 2–3 weeks depending on tolerance and response, up to total dose 44.4 Gy

Conclusion

Radiotherapy plays a critical role in contemporary management of head and neck squamous cell carcinomas. Modern techniques have improved outcomes and reduced toxicity rates. Postoperative and primary radiotherapy is also used to treat other malignancies of the head and neck, including cutaneous and mucosal melanomas, salivary gland tumors, and Merkel cell carcinoma, among others. Palliative radiotherapy can improve patients' quality of life when cure is not an option. A multidisciplinary team approach is critical for management of patients with head and neck cancer, and early input from radiation oncology is strongly encouraged.

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Chemotherapy

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Squamous cell carcinoma of the head and neck (SCCHN) encompasses a diverse group of diseases affecting multiple anatomic sites (oral cavity, pharynx, larynx, nasal passages, and salivary glands) and affects 600,000 patients worldwide annually. In the United States, it accounts for 3–7% of all cancers and affects 50,000 patients, of whom 11,000 succumb to their disease annually.[1,2] Historically, tobacco and alcohol abuse used to be the major risk factors and still account for a majority of cases in certain geographic locales. More recently, infection with certain subtypes of high-risk human papillomavirus (HPV), particularly HPV subtype 16, has emerged as a significant risk factor for oropharyngeal cancer (OPC).[3] These tumors tend to segregate within a younger patient population with less exposure to tobacco who have prominent nodal disease and primary tumor in the oropharynx on presentation.

Early Chemotherapy Trials in Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

The term *squamous cell carcinoma of the head and neck* encompasses a heterogeneous group of malignancies that share a common cell of origin, the squamous lining of distinct anatomic subsites within the head and neck and upper aerodigestive tract, namely the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx. Recent realization that the underlying pathogenesis of these diverse diseases could be subdivided into two major etiologies—exposure to carcinogenic agents (tobacco and alcohol) or oncogenic viruses (high-risk HPV serotype 16 and Epstein-Barr virus (EBV)—led to renewed interest in identifying novel disease-specific biomarkers that could guide the development of appropriate treatments for each of these specific subsets.

Chemotherapy has been successfully integrated into multiple treatment algorithms designated for different aspects of head and neck cancer. These include newly diagnosed locally advanced (LA) disease as well as management of recurrent/metastatic (R/M) cancer. For newly diagnosed patients, chemotherapy has been studied as induction or as a radiosensitizing component of concurrent chemoradiation therapy (chemoradiotherapy [CRT]) that could be applied as a definitive treatment or as adjuvant therapy in the postoperative setting.

In general, chemotherapy is used in the management of head and neck cancer within three distinct contexts: (1) adjuvant postoperative concurrent chemoradiotherapy (CCRT); (2) management of LA or unresectable disease through definitive CCRT where it is occasionally preceded by induction chemotherapy (ICT), referred to as sequential therapy (ST); and (3) R/M disease. The choice of applying chemotherapy either in the adjuvant postoperative setting versus definitive CRT or ST (ICT followed by CCRT) is often guided by a number of factors including the anatomic subsite of the primary tumor dictating a need for organ preservation, the stage of disease at presentation, and the consensus opinion of a multidisciplinary team regarding pursuit of primary surgical resection versus organ preservation.

Definitive Concurrent Chemoradiotherapy

CCRT has emerged as the generally accepted treatment for advanced stage oropharyngeal, hypopharyngeal, and laryngeal cancer in North America. There have been numerous randomized trials examining the role of CCRT in advanced stage head and neck cancer. These were well summarized in a meta-analysis of chemotherapy in head and neck cancer (MACH-NC) evaluating over 17,000 individual patients enrolled on 93 randomized trials conducted from 1965 to 2000.[4–7] For concomitant trials, the absolute benefit of adding chemotherapy to radiation was 6.5% at 5 years with a hazard ratio (HR) of death of 0.81% ($P < .0001$). The observed benefit of concomitant chemotherapy (HR, 0.81 [0.78–0.86]) was significantly greater than in the induction group, in which chemotherapy was administered first followed by radiation (HR, 0.96 [0.90–1.02]). In general, CCRT was associated with 8–11% improvement in overall survival (OS). This benefit varied by tumor site, with the 5-year absolute benefit associated with concomitant chemotherapy ranging from 8% for oral cavity and oropharynx cancer to 5% for hypopharynx and larynx cancer. Pattern of failure also varied between CCRT and ICT; the latter significantly decreased the rate of distant metastases (HR, 0.73; 95% confidence interval [CI], 0.61–0.88; $P = .001$) but had little effect on locoregional failure. CCRT, on the other hand, improved locoregional control (LRC) (HR, 0.74; 95% CI, 0.70–0.79; $P < .001$).

Induction Chemotherapy vs. Concurrent Chemoradiation for Larynx Preservation

Concerns over functional loss and psychosocial stigma associated with total laryngectomy gave rise to multiple therapeutic avenues to pursue larynx preservation (LP). Success of such efforts, although not entirely without limitations, has been one of the most salient achievements of modern chemotherapy and radiotherapy (RT). The origins of LP trace back to the early 1980s, when a series of phase II trials showed the effectiveness of cisplatin and infusional fluorouracil (5-FU) against LA-SCCHN.[8,9] This early success gave rise to the concept of ICT using cisplatin/5-FU followed by radiation for good responders, whereas nonresponders were referred for laryngectomy followed by adjuvant radiation. Availability of an effective chemotherapy regimen in the form of cisplatin/5-FU[9–13] allowed for testing of the hypothesis that tumors with favorable response to chemotherapy could be eradicated through radiation therapy, ensuring LP. On the other hand, surgical intervention with total laryngectomy for poor responders to ICT and those with residual tumor after adjuvant RT was essential to ensure acceptable OS. In 1985 the Cooperative Studies Program of the Department of Veterans Administration (VA) launched a large randomized study to test the hypothesis that ICT with cisplatin/5-FU followed by definitive radiation, with salvage laryngectomy reserved for patients with less than partial response, was an appropriate first option for patients with stage III/IV laryngeal cancer. The results of this study, known as the Department of Veterans Affairs Laryngeal Cancer Study Group (VALCSG) trial, were published in 1991.[14] The study randomized 332 patients with stage III/IV squamous cell cancer of the larynx (patients with T1, N1 disease, unresectable cancer, or distant metastases were excluded) to the standard of care of laryngectomy and postoperative radiation or three cycles of cisplatin/5-FU (PF) ICT followed by radiation (66–76 Gy) for responding patients. Patients who did not respond to ICT or still had residual tumor after radiation were recommended to undergo salvage laryngectomy. Thirty-one percent achieved complete response and 54% had partial response on the chemotherapy arm. Both treatment arms had a similar 2-year OS rate of 68% (95% CI, 60–76%), whereas the ICT arm achieved an LP rate of 64%. The study left open two unanswered questions that formed the basis for the follow-up Radiation Therapy Oncology Group (RTOG) 91-11 trial, namely (1) Could similar results (OS and laryngeal preservation) be achieved using RT alone, without the need for ICT, and (2) Could CCRT improve on the sequential delivery ICT followed by radiation as used in the VA trial?

The VALCSG trial was pivotal in proving that LP was achievable in a majority of patients through ICT followed by radiation without compromising OS. Success of such concepts gave rise to two competing approaches to be tested in the following two decades: (1) ICT with cisplatin and 5-FU, and later including taxanes and cetuximab followed by radiation therapy, as pioneered by the VALCSG trial and subsequently popularized through a series of European trials[15–20]; and (2) definitive concurrent chemotherapy (cisplatin) and radiation, an approach that was pioneered by RTOG and favored in North America, as illustrated by RTOG 91-11 and RTOG 0129.[21–23]

RTOG 91-11 was designed to compare three treatment strategies: ICT with cisplatin plus 5-FU followed by radiation as used in the VALCSG[14] trial; definitive CCRT using high-dose cisplatin (100 mg/m^2 on days 1, 22, and 43), previously studied by the Intergroup trial[23]; and conventional fractionation RT alone. The study excluded T4 cancers that penetrated laryngeal cartilage or extended more than 1 cm into the base of the tongue and used a composite primary end-point of laryngectomy-free survival (laryngectomy or death as events). The study, the findings of which were initially published in 2003[21] and updated in 2013,[24] showed that LP and LRC rates were significantly higher for the CCRT arm, with 42% relative risk reduction (HR, 0.58; 95% CI, 0.37–0.89; $P = .005$) for undergoing laryngectomy compared with the ICT arm and 54% relative risk reduction (HR, 0.46; 95% CI, 0.30–0.71; $P < .005$) compared with RT alone. There was no significant difference in OS. One of the provocative findings from RTOG 91-11 was the OS data from the CRT arm, which had the lowest rate of death from larynx cancer and the highest non–cancer-related death rate. Potential explanations include an unrecognized late toxicity affecting swallowing function and consequent silent aspiration that contributed to the non–cancer-related deaths observed in the long-term follow-up. This raises the question as to whether modern radiation technology could reduce normal tissue damage by sparing pharyngeal wall muscles.[25,26]

The concept of ICT using the three-drug regimen docetaxel, cisplatin, and 5-FU (TPF) has steadily gained momentum starting in the late 1990s with a series of phase I and II trials showing improved response rate[27–32] and culminating with the publication of the findings of two large phase III trials in 2007 showing improved OS and progression-free survival (PFS) with the addition of docetaxel to cisplatin/5-FU combination (TPF) compared with cisplatin/5-FU (PF) alone.[33,34] Collectively, these were mixed-site trials that did not focus on laryngeal cancer. This prompted the French Groupe d'Oncologie Radiothérapie Tête et Cou (GORTEC) in 2000 to launch the GORTEC 2000-01 study, a prospective randomized trial to test the hypothesis that TPF ICT followed by RT would improve 3-year LP, OS, overall response rate (ORR) to ICT, disease-free interval, and acute and late toxicity rates over PF induction regimen. The trial enrolled 220 patients with stage III/IV larynx and hypopharynx cancer. TPF induction was associated with a better response rate of 80.0% (41.8% complete response and 38.2% partial response) versus 59.2% (30.1% complete response and 29.1% partial response) in the PF group (difference = 20.8%; $P = .002$), leading to more patients being eligible for definitive RT (76.4% of patients in the TPF group and 61.2% in the PF group) and significantly better LP with a 3-year actuarial LP rate of 70.3% following TPF ICT and 57.5% after the PF regimen (difference = 12.8%; $P = .03$). All other outcomes including OS, distant metastases, and local recurrence requiring late salvage surgery were similar for both treatment groups.[19,20]

The high rate of LP after TPF ICT as shown by GORTEC 2000-01, coupled with similar success of the CCRT arm in

RTOG 91-11, prompted the question as to whether ST using a modern induction regimen such as TPF followed by CRT or bioradiotherapy could further improve on LP results from GORTEC 2000-01. The TREMPLIN trial (Radiotherapy With Cisplatin Versus Radiotherapy With Cetuximab After Induction Chemotherapy for Larynx Preservation) was designed to evaluate the feasibility of a sequential approach (ICT followed by concurrent chemotherapy or biotherapy with RT) for LP and to assess whether the therapeutic index could vary between BRT and CRT after ICT in terms of LP and OS.[17] The study enrolled 153 operable patients with larynx or hypopharynx cancer (T2–3 and N0–3) to receive three cycles of TPF ICT. Responders were randomly assigned to either cetuximab or cisplatin concurrent with RT. The primary endpoint was LP 3 months after treatment, with an expected rate of 80%. Random assignment occurred after TPF treatment and was limited to patients with responsive disease. The study accrued a total of 153 patients who received initial TPF induction with a response rate of 82% (126 of 153 patients). Only 116 patients were randomly assigned to the subsequent investigational CRT or bioradiotherapy treatment phase. Randomly assigned patients achieved a high larynx-preservation rate at 3 months of 95% and 93% and an 18-month survival of 92% and 89%, respectively. Although OS and larynx-preservation rates in the two study arms were high, only responding patients who were randomly assigned were included in these statistics, and survival for the entire study cohort of 153 patients was not reported.

Induction Chemotherapy Beyond Cisplatin/5-Fu

ICT using cisplatin plus 5-FU (PF) followed by radiation first gained wide acceptance as a standard of care on the basis of its ability to achieve LP by sparing responding patients the need for laryngectomy.[35] This was premised on two large phase III trials for larynx and hypopharynx cancers.[14,16] However, the tide has shifted with the subsequent publication of the findings of RTOG 91-11[21] and a large meta-analysis, MACH-NC,[6] which confirmed concurrent platinum-based CRT as an effective standard of care for LA-SCCHN. The MACH-NC analysis revealed a 6.5% absolute 5-year OS benefit (HR, 0.78; 95% CI, 0.73–0.84) and 8.6% absolute increase in *cancer-specific* survival at 5 years with CCRT (HR, 0.81; 95% CI, 0.78–0.86), in comparison with local locoregional treatment without chemotherapy. Survival benefit attributed to CCRT is mostly due to improved LRC (HR, 0.88; 95% CI; 0.77–1.0). This compared favorably with ICT trials' absolute benefit of 2.4% at 5-year OS (HR, 0.96; 95% CI, 0.90–1.02). However, ICT had a clear advantage at reducing the risk of distant metastases (HR, 0.73; 95% CI, 0.61–0.88), but this did not translate into survival advantage.

In an effort to integrate the theoretical benefit of ICT—namely, improved control of distant metastases along with better LRC seen with CCRT—the concept of ST was developed to integrate the best of two modalities. In the meantime, efforts to improve on the historic cisplatin/5-FU (PF) induction regimen proceeded with the addition of docetaxel to create the TPF regimen. This regimen was tested in a series of phase II trials and proved to be more effective than PF.[36] Efficacy of TPF in the first-line setting of SCCHN revitalized interest in the concept of ICT, thus setting the stage for a direct comparison against PF in a series of large phase III trials. Successful publication of the findings of two of these trials, namely TAX 323 and TAX 324, in which the TPF regimen was shown to be superior to the parent regimen of PF,[37,38] led to the U.S. Food and Drug Administration (FDA) approval of TPF as an induction regimen in SCCHN. Currently there are five randomized trials comparing a three-drug induction regimen (taxane/cisplatin/5-FU) with cisplatin/5-FU (PF).[19,20,33,34,39–41]

The question of whether ST (three-drug ICT followed by concurrent chemoradiation) is more effective than CCRT alone remains unanswered. The findings of four trials comparing ST and CCRT have been reported[14,42–44]; three were negative and one positive.

In the PARADIGM study,[42] patients were randomly assigned (in a 1:1 ratio) to receive either ICT (three cycles of TPF) followed by CCRT, known as ST (group A), or definitive CCRT (group B). For ICT, TPF was given as docetaxel 75 mg/m^2 intravenously on day 1; cisplatin 100 mg/m^2 intravenously on day 1, and 5-FU 1000 mg/m^2 on days 1–4 as continuous infusion for three cycles. Following ICT, patients were stratified by response to a more (A1) or less (A2) intensive CRT. Patients who responded poorly to ICT (any progressive disease; patient did not complete all three cycles of ICT; clinical partial response in neck adenopathy and greater than 2 cm neck adenopathy on computed tomography [CT] or magnetic resonance imaging [MRI]; grossly positive primary site tumor; and clinical partial response or stable disease in the primary site and positive biopsy) were assigned to receive CCRT with weekly docetaxel at 20 mg/m^2 for 4 weeks (group A1). All other patients were assigned to group A2, in which CRT was given with weekly carboplatin area under the curve (AUC) 1.5 for 7 weeks. The CRT group (group B) received two doses of cisplatin at 100 mg/m^2 given on days 1 and 22 of radiation therapy. Elective neck dissections were done if necessary after the completion of CRT. Radiation schedule differed between the treatment arms. For groups A1 (ICT followed by CRT with weekly docetaxel) and B (CRT with cisplatin only), RT was given as accelerated concomitant boost over 6 weeks. The total dose was 72 Gy, in 1.8/1.5 Gy fractions. For group A2 (ICT followed by CRT with weekly carboplatin), RT was given once daily over 7 weeks. Total dose was 70 Gy, in 2.0 Gy fractions.

The trial was designed to enroll 300 patients with stage III/IVB SCCHN; however, it closed early owing to slow accrual after enrolling only 145 patients. The primary endpoint was 3-year survival. There was no difference in PFS (HR, 1.07; CI, 0.59–1.92; P = .82) or OS (HR, 1.09; CI, 0.59–2.03; P = .77).

The Docetaxel Based Chemotherapy Plus or Minus Induction Chemotherapy to Decrease Events in Head and Neck Cancer trial (DeCIDE) was a multicenter phase III study of ST vs. CRT for N2/N3 LA-SCCHN patients.[43] ICT was delivered

through two cycles of TPF; CRT was identical between the two study arms and consisted of docetaxel, 5-FU, and hydroxyurea concurrent with hyperfractionated radiotherapy (DFHX-RT). The study was planned for 400 patients but closed early owing to slow accrual after 280 patients were enrolled. The primary end-point was OS at 3 years. There was no significant difference in OS (HR, 0.92; CI, 0.59–1.42; $P = .70$); however, there was a trend for improved OS in patients with N2c or N3 disease ($P = .19$). Use of ICT was associated with a reduction in the incidence of distant metastases—10% for the TPF arm vs. 19% for the CRT arm ($P = .025$). This did not translate into improvement in the 3-year OS, distant failure–free survival, or recurrence-free survival.

The Spanish Head and Neck Cancer Cooperative Group (TTCC) conducted a randomized phase III trial of 439 patients with unresectable stage III/IV SCCHN.[40] Patients were randomized into three treatment arms: three cycles of ICT with TPF followed by CRT, or three cycles of PF followed by CRT or CRT alone. The CRT regimen was identical for the three treatment arms and consisted of cisplatin 100 mg/m^2 on days 1, 22, and 43, concurrent with conventionally fractionated RT up to 70 Gy. The study took the unusual step of including of two separate ICT regimens (TPF vs. PF) because it was conceived before the establishment of TPF as a standard induction protocol.[39] The primary endpoints were PFS and time to treatment failure (TTF). In the intent-to-treat (ITT) population, median PFS was 14.6 months (95% CI, 11.6–20.4) for the TPF arm, 14.3 months (95% CI, 11.8–19.3) for the PF arm, and 13.8 months (95% CI, 11.0–17.5) for the CRT-alone arm (log-rank $P = .56$). Median TTFs were 7.9 (95% CI, 5.9–11.8), 7.9 (95% CI, 6.5–11.8), and 8.2 months (95% CI, 6.7–12.6), respectively (log-rank $P = .9$). There were no statistically significant differences for OS. Compliance was rather poor, with only 68%, 73%, and 92% of patients treated on the TPF, PF, or CRT arms receiving any CRT, respectively. This steep drop in the number of patients assigned to ICT being able to proceed to CRT, let alone complete such treatment, highlights one of the main criticisms of ST—namely, the inability to deliver adequate doses of CRT. The latter observation raises a number of questions about patient selection for such treatment and the proper CRT regimen to be used after ICT.

The Gruppo di Studio Tumori della Testa e del Collo (GSTTC) conducted a randomized 2 × 2 factorial design trial to evaluate ST versus CRT.[44] A total of 421 patients with stage III/IVB disease were randomized to ICT with three cycles of TPF followed by CRT versus CRT alone as follows:

- Arm A1: CRT with cisplatin/5-FU (PF) × 2 cycles concomitant with standard fractionation RT up to 70 Gy
- Arm A2: Cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly dose concomitant with standard fractionation RT
- Arm B1: ICT with three cycles of TPF followed by CRT with PF + RT
- Arm B2: Three cycles of TPF followed by cetuximab + RT

For the ICT group, the 3-year OS was 57.6% versus 45.7% for the chemotherapy/bioradiotherapy-alone group. The median OS was 53.7 months versus 30.3 months (HR, 0.72; 95% CI, 0.55–0.96; $P = .025$, respectively). PFS favored the ICT group—29.7 versus 18.5 months (HR, 0.73; 95% CI, 0.57–0.94; $P = .0155$). In an unplanned subgroup analysis, patients with the nonoropharyngeal carcinoma sites and those who received cetuximab bioradiotherapy seemed to benefit the most from ICT. To date, the GSTTC study remains the only well-powered randomized trial to show OS benefit for ST (ICT followed by CRT) over CRT alone. However, the study was criticized for a number of features including the lack of a standard cisplatin-alone CRT arm, unfavorable treatment outcome for both treatment groups (ST and CRT) when compared with other large randomized ICT trials for LA-SCCHN (TAX 324, PARADIGM and DeCIDE), and lack of data on HPV status.

Epidermal Growth Factor Receptor in Squamous Cell Carcinoma of the Head and Neck

Epidermal growth factor receptor (EGFR) is a member of the ERBB/HER family of transmembrane receptor tyrosine kinases (RTKs) that includes HER2 (ERBB2), HER3 (ERBB3), HER4 (ERBB4). Binding of the extracellular domain of EGFR, HER3, and HER4 to their cognate ligands induces receptor dimerization and activation of the intracellular kinase domain to initiate downstream signaling.[45] EGFR was originally identified as an oncogene owing to its homology to the viral oncogene *v-ERBB,* which enables the avian erythroblastosis virus to transform chicken cells.[46] Both EGFR and its ligand, transforming growth factor–alpha (TGF-α), are overexpressed in up to 90% of head and neck cancers,[47–50] with an increase in *EGFR* gene copy number reported in 10–58% of patients.[51,52] However, these estimates of gene copy number amplification ought to be readjusted in view of the recent The Cancer Genome Atlas (TCGA) data detecting only 15% *EGFR* alterations in HPV-negative SCCHN and 6% in HPV-positive SCCHN.[53] Such an overexpression was found to correlate with poor prognosis and resistance to treatment[54–59] but did not necessarily point to a favorable response with EGFR-targeted therapies.[60] In current practice, EGFR expression is no longer viewed as a biomarker for treatment selection in SCCHN. This is partly because of wide expression of EGFR on SCCHN and the lack of correlation between the levels of protein expression and response to anti-EGFR–targeted therapy and quick emergence of resistance to anti-EGFR therapies.[61–64] EGFR is targeted through either monoclonal antibodies (mAbs) against the extracellular domain of the protein (cetuximab, panitumumab, and zalutumumab) or small-molecule tyrosine kinase inhibitor (TKI), which can reversibly or irreversibly inhibit the binding of adenosine triphophate (ATP) to the tyrosine kinase domain of the EGFR. In SCCHN, mAbs, particularly cetuximab, have demonstrated more significant clinical success than TKIs, possibly because of the prominent role played by ligand-dependent receptor activation that renders the receptor more susceptible to antibodies targeting the extracellular domain.

Cetuximab is a chimeric human/murine immunoglobulin G1 (IgG1), whereas panitumumab (IgG2) and zalutumumab (IgG1) are fully human mAbs. In addition to direct inhibition

of ligand binding to the receptor extracellular domain and inhibition of downstream signaling, IgG1 mAb can activate antibody-dependent cellular cytotoxicity (ADCC) when Fcg receptor on natural killer (NK) cells, monocytes, and dendritic cells (DCs) recognizes the Fc tail of IgG1 mAbs.[65,66] In addition, EGFR has been reported to interact with nuclear DNA-dependent protein kinase, catalytic subunit (DNA-PKcs) to facilitate repair of radiation-induced DNA double-strand breaks.[67–69] Cetuximab-mediated inhibition of EGFR nuclear transport could augment radiation-induced tumor cell killing,[70] supporting the use of cetuximab as a radiosensitizer.

Currently, cetuximab is the only FDA-sanctioned targeted therapy in SCCHN. This approval was first granted in March 2006 in combination with radiation therapy for LA-SCCHN[71] or as a single agent for treatment of R/M SCCHN in patients in whom platinum-based therapy has failed.[72] Subsequently, in November 2011, cetuximab was approved in combination platinum-based chemotherapy plus 5-FU for the first-line treatment of patients with R/M SCCHN.[73]

The approval in LA-SCCHN was based on the IMC-9815 trial by Bonner and colleagues,[71] a phase III randomized trial of 424 patients with stage III/IV SCC of the oropharynx, hypopharynx, or larynx who had had no prior therapy. Patients were randomized to receive either cetuximab plus RT (211 patients) or RT alone (213 patients). Cetuximab was administered as a 400-mg/m^2 initial dose, followed by 250 mg/m^2 weekly for the duration of RT (6–7 weeks), starting 1 week before RT. RT consisted of one of the following three regimens: once-daily RT delivered at 2 Gy/day to a total dose of 70 Gy to gross disease; twice-daily RT delivered as 1.2 Gy in two separate fractions each day (separated by ≥ 6 hours) to a total dose of 72.0–76.8 Gy; and concomitant boost RT delivered as 1.8 Gy/day for 30 fractions, with a second fraction of 1.5 Gy delivered more than 6 hours after the first fraction during the last 12 days of treatment for a total dose of 72 Gy. At least 50–54 Gy was to be delivered to the uninvolved nodal areas of the neck.

The median survival time was 49 months in patients receiving cetuximab plus RT versus 29.3 months in patients receiving RT alone (P = .03, stratified log-rank test; HR, 0.74; 95% CI, 90.56, 0.97). The median duration of LRC was 24.4 months in patients receiving cetuximab plus RT versus 14.9 months for those receiving RT alone (P = .005, stratified log-rank test; HR, 0.68; 95% CI, 0.52, 0.89). The observed effect was primarily confined to patients enrolled in sites in the United States. The most common adverse events reported for both treatment arms were mucositis and radiation dermatitis. Serious adverse reactions, some with fatal outcome, were observed in the cetuximab plus RT arm and included infusion reactions, cardiopulmonary arrest and/or sudden death, and acneiform rash. The incidence of grade 3 or 4 late toxicities (severe mucositis and in-field dermatitis) were initially reported to be similar between the two treatment groups, but this was later questioned in subsequent reports of enhanced toxicity with the addition of cetuximab to radiation.[74] Severity of cetuximab-related dermatitis is a predictor of anti-EGFR treatment response; however, this could not be predicted before the start of treatment. This trial was criticized for lack of radiosensitizing chemotherapy in the control arm, because RT alone—as used here—was no longer a standard of care and raised two additional questions of whether cetuximab plus RT was equivalent to CRT and whether synergy existed between the two radiosensitizing treatments. The answer to the first question will await publication of the U.S.-based RTOG 1016, the U.K. trial De-ESCALaTE (Determination of Epidermal Growth Factor Receptor Inhibitor [cetuximab] Versus Standard Chemotherapy [cisplatin] Early and Late Toxicity Events in Human Papillomavirus–Positive Oropharyngeal Squamous Cell Carcinoma), and the Australian trial TROG 12.01. Both the De-ESCALaTE and TROG 12.01 trials randomly assigned patients with HPV-positive oropharyngeal carcinoma to standard cisplatin-RT versus cetuximab-RT, with end-points including morbidity and quality of life. The second question of synergy between cisplatin and anti-EGFR mAb in the definitive CRT setting has been answered through the RTOG 0522 and CONCERT-1 (CONcomitant Chemotherapy and/or EGFR inhibition with radiation therapy) trials.

RTOG 0522 was a phase III trial (940 patients with LA disease) comparing concomitant CRT as a standard of care arm and the same CRT plus cetuximab.[75] A total of 895 evaluable patients with stage III or IV nonmetastatic SCCHN were randomized to receive either CRT (72 Gy in 42 fractions over 6 weeks plus cisplatin 100 mg/m^2 on days 1 and 22) or the same regimen plus weekly cetuximab. Over 90% of the patients received the planned two doses of cisplatin in both arms. The 2-year PFS (primary end-point) was 64.3% with CRT and 63.4% with CRT plus cetuximab (HR, 1.05; 95% CI, 0.84–1.29; P = .67). The 2-year OS rates were 79.7% and 82.6%, respectively (HR, 0.87; 95% CI, 0.66–1.15; P = .17). The estimated 2-year locoregional relapse rates were 19.8% and 24.5%, respectively (P = .92). The 2-year distant metastasis rates were 12.0% and 7.6%, respectively (P = .07). Overall, there was no difference regarding acute grade 3 or 4 toxicities between both arms. However, grade 3 or 4 mucositis (33% in CRT vs. 43% in CRT plus cetuximab) and in-field dermatitis (15% in CRT vs. 25% in CRT plus cetuximab) was more common in the cetuximab-containing arm. Grade 3 or 4 dermatitis outside the radiation field occurred in 19% of the patients treated with cetuximab. Based on these data, the addition of cetuximab to standard CRT cannot be recommended.

Cetuximab was studied as part of ICT regimens in a series of phase II trials and found to be both safe and effective. Argiris and colleagues[76] added weekly cetuximab to docetaxel 75 mg/m^2 on day 1, cisplatin 75 mg/m^2 on day 1 (TPE), repeated every 21 days for three cycles, followed by RT with concurrent cisplatin 30 mg/m^2 and cetuximab weekly (XPE), and maintenance cetuximab for 6 months. Thirty-nine patients were enrolled, of whom 36 had stage IV disease and 23 had an oropharyngeal primary. With a median follow-up of 36 months, 3-year PFS and OS rates were 70% and 74%, respectively.

Haddad and colleagues[77] conducted a phase I study of a docetaxel/cisplatin/5-FU (TPF) regimen (docetaxel 75 mg/m^2 on day 1, cisplatin 100 mg/m^2 on day 1, and 5-FU at three dose levels (DLs) of either 700, 850, or 1000 mg/m^2 per day administered as a continuous infusion on days 1–4) combined

with cetuximab (C) for induction treatment of LA-SCCHN. At DL 3 of 5-FU at 1000 mg/m^2, one dose-limiting toxicity (DLT) was encountered; three more patients were enrolled with no DLTs. In the expansion cohort at the maximum tolerated dose (MTD), three DLTs were encountered. The decision was made to decrease the 5-FU from 1000 mg/m^2 to DL 2 of 850 mg/m^2. A total of 13 patients were enrolled at the MTD of 850 mg/m^2. All patients received CRT after C-TPF. The main toxicity was gastrointestinal (mucositis, diarrhea, and enteritis). A total of 30 patients were enrolled, and 28 were assessable. ORRs at the end of IC and before the start of CCRT were six partial responses and 22 complete responses for an ORR of 100%.

Jordan and colleagues[78] treated 152 SCCHN patients with T3 or T4 tumors with three 3-week cycles of TPF (docetaxel 75 mg/m^2 on day 1, cisplatin 35 mg/m^2 on days 1 and 2, and 5-FU 750 mg/m^2 per day, as a continuous infusion on days 1–5, with pegfilgrastim support) followed by CRT (63 Gy in 35 fractions of 1.8 Gy over 7 weeks and weekly cisplatin, 40 mg/m^2) plus weekly cetuximab. The complete response rate in the 142 patients who were evaluated after the completion of therapy was 57%. Grade 3 or 4 toxicities occurred in 34 of the 142 patients (24%). In 15 patients, CRT had to be interrupted because of dermatitis.

Keil and colleagues[79] treated 49 LA-SCCHN patients with three 3-weekly cycles of TPF (docetaxel 75 mg/m^2 day and cisplatin 75 mg/m^2 day 1, and infusional 5-FU 750 mg/m^2 per day on days 1–5) followed by RT plus cetuximab at the recommended dose. After completion of ICT, 44 of 49 patients received RT plus cetuximab. Three months after therapy completion, tumor response was observed in 33 patients and after 2 years, 25 patients still had a complete response. The most common grade 4 toxicity during the whole treatment period was dermatitis (30%), followed by mucositis (27%), and neutropenia (17%) without fever. One toxicity-related death was observed during ICT. The 2-year PFS rate was 59% and the 2-year OS rate was 63%.

Kies and colleagues[80] added cetuximab to ICT with six weekly doses of paclitaxel 135 mg/m^2 and carboplatin (AUC 2). The most common grade 3 or 4 toxicity was skin rash (45%), followed by neutropenia (21%) without fever. After ICT, 19% of the patients achieved a complete response and 77% achieved a partial response. After ICT, patients underwent risk-based local therapy, which consisted of RT, CRT, or surgery, based on tumor stage and site at diagnosis. At a median follow-up time of 33 months, locoregional or systemic disease progression was observed in six patients. The 3-year PFS and OS rates were 87% (95% CI, 78–97%) and 91% (95% CI, 84–99%), respectively. HPV-16 was found in 12 (46%) of 26 biopsies and was associated with improved PFS (P = .012) and OS (P = .046).

The Eastern Cooperative Oncology Group (ECOG) E2303[81] evaluated 63 patients with resectable stage III or IV SCCHN who were treated with 6-weekly doses of paclitaxel, carboplatin (AUC 2), and cetuximab, followed by CRT (weekly paclitaxel 30 mg/m^2, carboplatin AUC 1, and cetuximab). If at week 14, after a radiation dose of 50 Gy, tumor was still present on biopsy, salvage surgery was performed. In case of a negative biopsy (9% of the patients), CRT was continued to a total dose of 68–72 Gy. Two-year PFS and OS rates were 82% and 66%, respectively. A local recurrence occurred in 17.5% of the patients.

Adkins and colleagues[82] treated 30 patients with stage III or IV SCCHN with ICT consisting of nab-paclitaxel 100 mg/m^2 weekly on days 1, 8, and 15; weekly cetuximab; cisplatin 75 mg/m^2 on day 1; and 5-FU 750 mg/m^2 per day as a continuous infusion on days 1–3 (ACPF). Patients received three 3-week cycles before CRT consisting of intensity-modulated radiotherapy (IMRT) 70 Gy in 35 fractions of 2 Gy over 7 weeks and cisplatin 100 mg/m^2 on days 1, 22, and 43. One patient died during ICT owing to a neutropenia-related pneumonia. Three patients could not be treated with cisplatin according to protocol because of toxicity. The complete response rate at the primary tumor site after two cycles of ACPF was 53% and the ORR was 100%. Twenty-nine (96%) patients completed three cycles of ACPF, 26 (90%) completed definitive RT per protocol, and 22 of the 27 evaluable patients (81%) received at least two of the three planned doses of cisplatin with RT. The estimated 2-year OS and PFS rates were 84% and 65%, respectively.

Panitumumab was studied in a phase I dose-finding study that investigated escalating doses of paclitaxel (Taxol) given concurrently with panitumumab, carboplatin, and IMRT for stage III/IVB SCCHN.[83] The study enrolled patients with oral cavity, oropharynx, larynx, hypopharynx, or unknown primaries. Patients received weekly fixed doses of panitumumab and carboplatin plus escalating doses of paclitaxel with IMRT. Nineteen patients were enrolled onto two DLs: weekly paclitaxel 15 mg/m^2 (n = 3) and 30 mg/m^2 (n = 16). One dose-limiting toxicity occurred in DL 2, which was declared the maximum tolerated dose. All patients experienced mucositis, primarily grade 3 or more. Oral pain, xerostomia, dysphagia, weight loss, dermatitis, nausea, and acneiform rash were frequent. The overall complete clinical response rate was 95%. At median follow-up of 21 months, 18 of 19 patients (95%) remained disease free.

Subsequently, panitumumab was tested in a series of randomized phase II trials in combination with RT or CRT. The phase II CONCERT-1 study showed that the addition of panitumumab to cisplatin-based chemoradiation resulted in increased toxicity with no improvement in response rate or survival. There was also no difference in efficacy when patients were stratified according to the tumor p16 status.[84] In the CONCERT-2 trial, the investigators compared the safety and efficacy of radiation therapy combined with panitumumab without chemotherapy versus concurrent chemoradiation.[85] The investigators reported a trend in favor of CCRT for LRC at 2 years (the primary end-point); 51% (40–62%) with irradiation plus panitumumab compared with 61% (47–72%) with concurrent chemoradiation. Both PFS (HR, 1.73; P = .03) and OS (HR, 1.59; P = .10) outcomes favored the CCRT arm.

A randomized (1:1) phase II study investigated docetaxel and cisplatin with or without panitumumab as first-line palliative treatment.[86] Median PFS, median OS, and ORR were 6.9 months, 12.9 months, and 44% in the panitumumab arm versus 5.5 months, 13.8 months, and 37% in the arm without panitumumab. Crossover to panitumumab monotherapy was allowed in the docetaxel/cisplatin arm and occurred in 57% of the patients and may have impaired the OS analysis. Panitumumab is currently being studied as second-line monotherapy

(PARTNER: Panitumumab Added to Regimen for Treatment of Head and Neck Cancer Evaluation of Response).

The National Cancer Institute of Canada (NCIC) Clinical Trials Group randomized 320 stage III/IV SCCHN patients between standard fractionated RT (70 Gy over 7 weeks) plus cisplatin (100 mg/m^2, three cycles) versus accelerated RT (70 Gy over 6 weeks) plus panitumumab (9 mg/kg for three doses). The 2-year PFS rates were 73% and 76%, respectively. In addition, noninferiority of bioradiotherapy was not proven in this study.[87]

So far, in LA-SCCHN, the combination of radiation therapy and anti-EGFR mAb has not been proven to be equivalent to platinum-based chemoradiation. The results of the RTOG 1016 study that randomized p16-positive OPC patients between accelerated chemoradiation (high-dose cisplatin) and accelerated RT plus cetuximab are pending. Outside of clinical trials, platinum-based chemoradiation remains the standard of care for fit patients. Cetuximab plus RT should be considered only for patients with stage III/IV SCCHN and when contraindications to cisplatin such as kidney dysfunction, hearing loss, or cardiovascular insufficiency are present.

Small-molecule TKIs have been highly successful against several malignancies possessing kinase domain driver mutations or chromosomal translocations leading to constitutive activation of such kinases.[88] Given the lack of such driver mutations or chromosomal translocations in SCCHN, it should be no surprise that this class of agents has underperformed in SCCHN. Data from single-arm and randomized phase II/III trials testing first-generation EGFR-TKIs such as gefitinib[89–94] and erlotinib[95–97]—either as single agents or in combination with chemotherapy,[93,98–102] RT,[103,104] or CRT[105–111]—have been mostly underwhelming. Therefore neither of these two drugs is routinely used in the management of SCCHN.

More recently, afatinib, an irreversible pan-ERBB inhibitor (EGFR, HER2, and HER4), proved to be effective against *EGFR*-mutated adenocarcinoma with improvement in OS[112] and to lesser degree against non–small cell lung carcinoma (NSCLC) with squamous histology.[113] These data prompted an interest in comparing afatinib versus cetuximab in patients with R/M SCCHN.[114] This open-label randomized phase II trial included 124 patients with platinum-refractory R/M SCCHN. In stage I, 121 patients were randomly assigned to daily afatinib (61 patients, 50 mg/day) or weekly cetuximab (60 patients, loading dose of 400 mg/m^2 followed by weekly doses of 250 mg/m^2 per week), until disease progression or unacceptable toxicity occurred, at which time crossover was permitted (68 patients crossed over at stage II). Results from stage I demonstrated comparable tumor shrinkage, response, and disease control rates as well as similar median PFS (13.0 weeks with afatinib vs. 15.0 weeks with cetuximab; HR, 0.93; 95% CI, 0.62–1.38; P = .71). Fifty-six percent of patients crossed over to stage II, with disease progression as the primary reason. Disease control rate by independent central review was 33% for afatinib (19% with cetuximab), and median PFS was 9.3 weeks (vs. 5.7 weeks) during stage II. Median OS was 35.9 weeks for afatinib-treated patients and 47.1 weeks for cetuximab-treated patients during stages I and II (HR, 1.06; 95% CI, 0.70–1.62; P = .78). Grade 3 or greater toxicities were more frequent in patients treated with afatinib versus cetuximab (47% vs. 16%, respectively). It is noteworthy that the dose of afatinib used in this trial, 50 mg/day, is significantly higher than the dose used in NSCLC at 40 mg/day, and this might have contributed to the substantially higher grade (3 or higher) of adverse events observed in the afatinib arm. These data suggest that patients may benefit from ST, especially treatment with afatinib after cetuximab failure.

Afatinib has also been compared with chemotherapy (methotrexate) in a phase III trial for R/M SCCHN.[115] In the LUX-Head and Neck 1 trial, 483 patients who experienced disease progression after platinum-based therapy were randomly assigned in a 2:1 fashion to receive afatinib (322 patients who received 40 mg/day) versus methotrexate (161 patients who received 40 mg/m^2 per week). Afatinib, compared with methotrexate, was associated with a significantly higher disease control rate (49.1% vs. 38.5%, respectively; P = .035) and PFS benefit (2.6 vs. 1.7 months, respectively; HR, 0.80; 95% CI, 0.65–0.98; P = .03). The PFS benefit was also associated with positive patient-reported outcomes, including less pain and delay in time to worsening symptomatology. Despite a modest PFS benefit (primary endpoint), there was no improvement in OS (6.8 months with afatinib and 6.0 months with methotrexate; HR, 0.96; 95% CI, 0.77–1.19; P = .70). In preplanned analyses of PFS, it was noted that afatinib tended to exert more therapeutic activity in patients who had not previously been treated with an EGFR-targeted therapy and in HPV-negative patients. This observation was similar to subgroup analysis data from SPECTRUM (Study of Panitumumab Efficacy in Patients With Recurrent and/or Metastatic Head and Neck Cancer), in which patients with p16-negative tumors experienced a 3-month improvement in OS.[116]

Dacomitinib, another irreversible pan-ERBB inhibitor (EGFR, HER2, and HER4), demonstrated a modest response rate of 12.7% and median PFS and OS times of 12.1 and 34.6 weeks, respectively, in a phase II study of dacomitinib monotherapy in 69 patients with R/M SCCHN.[117] In a subsequent study to evaluate predictive biomarkers of dacomitinib in 48 patients with heavily pretreated R/M SCCHN, mutations in the phosphatidylinositol 3–kinase (PI3K) pathway (PIK3CA and PTEN) and high inflammatory cytokine expression (interleukin [IL]-6, IL-8, IL-1α, IL-1β, IL-4, tumor necrosis factor) were significantly associated with both reduced PFS (2.9 months with PI3K mutations vs. 4.9 months without PI3K mutations, P = .013; 2.8 months with high inflammatory cytokine expression vs. 9.9 months with low inflammatory cytokine expression, P = .004) and shorter median OS (6.1 months with PI3K mutation and high inflammatory cytokine expression vs. 12.5 months without PI3K mutation and low inflammatory cytokine expression; P = .005).[118]

Human Papillomavirus–Positive Cancer of the Oropharynx

High-risk HPV serotype 16 (HPV-16) has recently emerged as a causative agent for a subset of SCCHN arising from the

oropharynx (tonsil, base of tongue, soft palate, and oropharynx).[119–121] Morphologically, HPV-positive OPC is characterized by poor differentiation, basal cell histology, and lack of keratinization. At presentation the disease often appears as a locoregionally advanced primary tumor with advanced nodal involvement. Diagnosis is established by detecting viral nucleic acid through in situ hybridization for high-risk HPV DNA, by quantitative polymerase chain reaction (qPCR) for viral E6 and E7 messenger RNA (mRNA) and HPV DNA, or by immunohistochemistry for p16 protein, a product of *CDKN2A,* as a surrogate marker for HPV infection.[122–126] Unfortunately, owing to technical difficulties with some of the nucleic acid–based tests, these assays are not always in agreement, and a discrepancy of 25% in favor of p16 immunohistochemistry has been reported.[127] Given the common incidence of HPV infection followed by long latency until cancer develops in a fraction of infected patients, there has been significant interest in identifying a premalignant lesion or a predictive biomarker that could potentially differentiate bystander infections from oncogenic ones. Such a test or biomarker is yet to be identified.

In 2008, Fakhry and colleagues published a landmark study documenting the favorable prognosis of HPV-positive OPC. ECOG 2399 enrolled 96 patients with stage III/IV SCCHN of the oropharynx or larynx who received two cycles of ICT with paclitaxel and carboplatin followed by concomitant weekly paclitaxel and standard fractionation RT.[127a] HPV infection was documented using multiplex polymerase chain reaction (PCR) and in situ hybridization. HPV-positive patients had higher response rates after both ICT (82% vs. 55%, difference = 27%; 95% CI, 9.3–44.7%; P = .01) and chemoradiation treatment (84% vs. 57%, difference = 27%; 95% CI, 9.7–44.3%; P = .007). The HPV-positive population had an improved 2-year OS of 95% (95% CI, 87–100%) versus 62% (95% CI, 49–74%) (difference = 33%; 95% CI, 18.6–47.4%; P = .005, log-rank test). This observation was subsequently confirmed in multiple phase III trials.[128–131]

Rationale for De-escalation

Multiple lines of evidence support the notion that favorable prognosis associated with HPV-positive OPC is a platform-independent phenomenon,[132] observed in patients treated with CCRT,[128] radiation alone,[133] sequential CRT (neoadjuvant chemotherapy or ICT followed by CRT).[129] Given the well-recognized functional sequelae associated with definitive chemoradiation (xerostomia, dysphagia, hypothyroidism, dental complications) in the setting of favorable prognosis associated with HPV-positive OPC affecting a younger demographic population, there have been questions about appropriateness of such dose intensity. Lifelong complications from standard-dose curative CRT (generally accepted as 70 Gy concurrent with radiosensitizing chemotherapy, most commonly in the form of cisplatin delivered either weekly or every 3 weeks) have prompted new research into dose deintensification as a strategy to overcome post-treatment effects. Current approaches take aim at the three main treatment modalities—namely, radiation, chemotherapy, and surgery. The following section outlines a number of significant completed and ongoing dose deintensification trials and highlights some of the salient findings from completed trials.

Radiation

ECOG 1308 was a randomized phase II trial that enrolled 90 patients (80 analyzed) with locally advanced stage III/IV HPV-positive OPC.[134] The primary question asked was whether sensitivity to chemotherapy (delivered as part of a neoadjuvant or induction regimen) could predict for radiation sensitivity and hence be used to select patients who could be safely treated with reduced-dose radiation concurrent with cetuximab instead of full-dose chemoradiation.

All patients were treated with three 21-day cycles of ICT with cisplatin 75 mg/m^2 on day 1; paclitaxel 90 mg/m^2 on days 1, 8, and 15; and a cetuximab 400-mg/m^2 loading dose on day 1 of cycle 1, then 250 mg/m^2 on subsequent weeks. Seventy-one percent of patients achieved complete remission (CR) at the primary site and went on to receive reduced-dose radiation (54 Gy at 2-Gy fractions over 5½ weeks concurrent with cetuximab). Patients with incomplete response received 69 Gy concurrent with cetuximab. Early results from this trial were released at the American Society of Clinical Oncology (ASCO) meeting in 2014. The 2-year PFS and OS for the 54-Gy group were 80% and 93% versus 65% and 87% for the 69-Gy group, respectively. According to E1308, a best-prognosis group could be defined as light smokers (10 or fewer pack-years) and clinical stage below T4 and N2c; for this group, both the 2-year PFS and OS were 96%. The study demonstrated that for a select group of HPV-positive OPC patients, the radiation dose could be safely reduced to 54 Gy and concurrently delivered with cetuximab instead of cisplatin. On the other hand, such selection was dependent on administration of three cycles of ICT, a practice that is not commonly followed in North America.

Surgery

Adjuvant De-escalation, Extracapsular Spread, P16+, Transoral (ADEPT) trial for oropharynx malignancy (NCT01687413) is a phase III trial from the University of Washington with a planned randomization of 496 p16-positive oropharyngeal squamous cell carcinoma (OPSCC) patients to study the intensity of adjuvant therapy in p16-positive oropharyngeal cancer patients who have had all known disease removed surgically by a minimally invasive approach and who have extracapsular spread in their lymph nodes. After the surgery, patients are randomized to receive either radiation alone (60 Gy in 30 fractions), or radiation and cisplatin (40 mg/m^2 intravenously weekly during RT).

ECOG 3311 (NCT01898494—Transoral Surgery Followed By Low-Dose or Standard-Dose Radiation Therapy With or Without Chemotherapy in Treating Patients With HPV-Positive Stage III-IVA Oropharyngeal Cancer) is a randomized phase II trial to evaluate transoral robotic surgery in the management of patients with III/IVA OPC. A total of 377 patients with p16-positive OPSCC will undergo transoral robotic surgery and neck dissection followed by histopathologic risk stratification into three groups—low, intermediate,

or high risk—according to findings on surgical pathology. Low-risk patients will not have adjuvant therapy. Patients with intermediate histopathologic risk factors will be randomized to either low-dose (50 Gy) or standard-dose IMRT (60 Gy). High-risk patients will receive IMRT (66 Gy) with weekly cisplatin (40 mg/m^2). The primary end-point of the trial is PFS and grade III/IV bleeding rate at 2 years. Secondary outcomes will include acute and ate toxicities.

Chemotherapy

RTOG 1016 was conceived at the 2008 NCI conference on the role of HPV in head and neck cancer. RTOG 1016 is a noninferiority design phase III trial that enrolled 987 untreated patients with LA HPV or p16-positive OPC. Patients were randomized into two treatment arms of accelerated IMRT to a dose of 70 Gy concurrent with either cisplatin 100 mg/m^2 for two cycles versus weekly cetuximab at a 400-mg/m^2 loading dose followed by a weekly dose of 250 mg/m^2. Accrual was completed by September 2014.

The purpose of the study was to examine whether substitution of cetuximab in place of cisplatin would achieve similar 5-year OS with less toxicity. The cetuximab regimen was selected based on data from the study by Bonner and colleagues (IMCL-9815), first published in 2006 and updated in 2010, that compared RT with RT plus cetuximab in stage III/IV SCCHN. Although the study showed improved OS with the combination therapy, maximum benefit was achieved in patients who fit the profile of HPV-positive OPC (oropharyngeal primary, low tumor stage, and high nodal stage). Although the trial did not evaluate p16 status a priori, a retrospective subset analysis of the impact of p16 status on treatment outcome was presented at the ASCO 2014 meeting. According to this analysis, p16 status was evaluable in 74% of the ITT population, and univariate analyses showed a more pronounced treatment effect of radiation plus cetuximab versus radiation alone in p16-positive patients across all end-points (LRC, OS, and PFS) in both the ITT and the OPC populations. The results of RTOG 1016 are awaited.

The Quarterback trial (NCT01706939–Reduced Dose Radiotherapy for HPV-Positive Oropharynx Cancer) is a randomized phase II/III noninferiority trial with a planned accrual of 365 patients with LA HPV-positive OPC, who will be treated with ICT with three cycles of TPF. Patients who respond to ICT will be randomized to low-dose IMRT (56 Gy) with weekly carboplatin or standard dose IMRT (70 Gy) with weekly carboplatin. The primary end-point of the trial is equivalent LRC and PFS at 3 years.

NRG-HN002 is an ongoing randomized phase II trial involving good-prognosis HPV-positive OPC patients. The study is expected to enroll 296 nonsmokers or light smokers (10 or fewer pack-years) with T1–2, N1–2b or T3, N0–2b tumors into one of two treatment arms: (1) reduced-dose accelerated fractionation radiation (60 Gy over 5 weeks) or (2) chemoradiation with reduced-dose standard fractionation (60 Gy over 6 weeks concurrent with weekly cisplatin at 40 mg/m^2). Primary objective is 2-year PFS rate of 85% or more without unacceptable swallowing toxicity at 1 year.

Adjuvant Concurrent Chemoradiotherapy

Surgical resection of LA head and neck cancers followed by adjuvant radiation is often associated with suboptimal outcome in the form of locoregional recurrence, distant metastases, and 4-year disease-free survival (DFS) and OS rates of 29%, 23%, 38%, and 44%, respectively.[135] Risk factors for such poor prognosis, extrapolated from RTOG 85-03 and RTOG 88-24, included positive margins of resection, extracapsular extension (ECE) of disease from cervical nodes, levels IV and V lymph node involvement from oral cavity and oropharynx carcinoma, perineural invasion, vascular embolism, and involvement of two or more lymph nodes.[136–138] More recently, these high-risk pathologic features were narrowed to positive margins of resection and ECE of disease from cervical nodes as the most significant high-risk features for recurrence.[139] In addition, delayed start of radiation or treatment interruption, prolonging overall treatment time, measured from time of surgery to completion of radiation, beyond 11 weeks is often associated with worse 5-year LRC rates.[137,140,141] Efforts to remedy the shortcomings of single-modality adjuvant postoperative radiation were guided by a series of clinical trials and meta-analyses published during the 1990s that examined the effect of systemic chemotherapy following surgical resection and highlighted the activity of CCRT as a therapeutic strategy in head and neck cancer with emphasis on the role of platinum plus 5-FU regimens.[4,142–149] These data formed the basis for the European Organisation for Research and Treatment of Cancer (EORTC) and RTOG to launch two similar but independent trials: EORTC 22931[150] and RTOG 9501.[151] Both studies compared concomitant high-dose cisplatin 100 mg/m^2 on days 1, 22, and 43 plus radiation versus radiation alone, in patients with resected SCCHN with poor risk for recurrence. Radiation dose was similar for both trials—66 Gy for 6.5 weeks for EORTC 22931, and 60–66 Gy for 6.0–6.5 weeks for RTOG 9501. Definition of high-risk for both trials included positive margins of resection and ECE.[152] In addition, RTOG 9501 included two or more positive lymph nodes, and EORTC 22931 included oral cavity or oropharynx cancer with positive nodes at levels IV or V, perineural invasion, or vascular embolism. The results of both studies were first published in 2004, followed by a pooled analysis in 2005[139] and a 10-year long-term follow-up on RTOG 9501 in 2012.[153]

The initial report on RTOG 9501 after a median follow-up of 45.9 months came out in favor of the combined modality approach, with significant improvement of the primary end-point of LRC (HR, 0.61; 95% CI, 0.41–0.91; P = .01). Similarly, DFS was significantly prolonged in the chemoradiation arm (HR, 0.78; 95% CI, 0.61–0.99; P = .04), with a trend toward improved OS that was not statistically significant (P = .19).[151]

A 10-year follow-up of the study was published in 2012, and most of the initial advantages seen in the chemoradiation arm were no longer statistically significant. LRC rates were 28.8% versus 22.3% (P = .10), DFS was 19.1% versus 20.1% (P = .25), and OS was 27.0% versus 29.1% (P = .31) for patients receiving radiation alone versus chemoradiation, respectively. An unplanned subset analysis suggested significant benefit for patients with positive margin of resection and/or ECE. For

these patients, locoregional failure occurred in 33.1% versus 21.0% ($P = .02$), DFS was 12.3% versus 18.4% ($P = .05$), and OS was 19.6% versus 27.1% ($P = .07$) for patients receiving radiation alone versus chemoradiation, respectively. This subset analysis suggested that patients included on the basis of two or more positive lymph nodes did not benefit from the addition of chemotherapy to radiation.

The findings of the EORTC 22931 trial were reported in 2004 with 60 months of follow-up, showing significant improvement of PFS, the primary end-point, in favor of CRT[150] of 47% versus 36% (HR, 0.75; 95% CI, 0.56–0.99; $P = .04$). Five-year OS rate was 53% versus 40% (HR, 0.70; 95% CI, 0.52–0.95; $P = .02$) and locoregional failure was 31% versus 18% ($P = .007$) in favor of combined-modality therapy.

In a follow-up joint analysis that pooled data from the EORTC and RTOG trials,[139] ECE and positive surgical margins were the only risk factors for which the addition of chemotherapy to radiation was considered significant. The analysis also noted a trend in favor of chemoradiation for patients with stage III or IV disease, perineural invasion, vascular embolism, and/or disease involvement of level IV or V lymph nodes that drain oral cavity and oropharynx cancers. On the other hand, patients whose evidence of high-risk disease was limited to two or more involved lymph nodes without evidence of ECE or positive margins of resection did not appear to benefit from addition of chemotherapy, a finding that was subsequently confirmed on the long-term subset analysis of RTOG 9501 published in 2012. This would also explain the discrepancy noted in outcome data (LRC, DFS, and OS) favoring the similarly designed EORTC 22931 over RTOG 9501. Such discrepancy could be attributed to the fact that although both trials came to a consensus that the presence of ECE and/or positive margins of resection was a key "high-risk" feature for study inclusion, the EORTC trial did not include the pathologic finding of two or more histologically involved lymph nodes within the "high-risk" definition for trial inclusion.

Subsequent studies evaluated non–cisplatin-based radiosensitizing chemotherapy regimens against the standard of cisplatin-radiation. These studies were prompted by the fact that a substantial proportion of SCCHN patients who are at high risk for recurrence after surgical resection harbor comorbidities and exhibit poor performance status that would preclude the safe administration of three cycles of high-dose cisplatin as previously described. Data from phase III trials demonstrated cetuximab to have activity as a bona fide radiosensitizer in SCCHN,[71,154] as well as displaying synergistic activity in combination with systemic chemotherapy in the R/M setting.[73] In the meantime, docetaxel has been shown to be a potent radiosensitizer for SCCHN that could be effectively paired with cetuximab.[155–157] RTOG 0234 is a randomized phase II trial that enrolled 238 patients with resected stage III/IV SCCHN and the same high-risk features used to select patients for RTOG 9501 (positive margins of resection, extracapsular nodal extension, two or more nodal metastases). All eligible patients were randomized to receive 60 Gy radiation plus weekly cetuximab and either concurrent cisplatin 30 mg/m^2 or docetaxel 15 mg/m^2 weekly.[158] With a median follow-up of 4.4 years, the study reported 2-year OS of 69% for the cisplatin arm and 79% for the docetaxel arm, and 2-year DFS of 57% and 66%, respectively. DFS was compared with the CRT arm from RTOG 9501[151] and both arms showed significant improvement, with HR of 0.76 ($P = .05$) for the cisplatin arm and 0.69 ($P = .01$) for the docetaxel arm. For OS comparison, there was 28% reduction in the death rate for the cisplatin arm (HR, 0.72; 95% CI, 0.5–1.03; $P = .04$), and a 44% reduction in the death rate for the docetaxel arm (HR, 0.56; 95% CI, 0.39– 0.82; $P = .01$). In this trial, the main advantage of the docetaxel treatment appears to have been its ability to lower the incidence of distant metastases, with a 2-year distant metastasis rate of 13% in the docetaxel arm versus 25% in the cisplatin arm, reflecting a 45% reduction in distant metastases ($P = .03$). Based on these results, RTOG will further test the docetaxel/cetuximab combination in a phase II/III trial (RTOG 1216) that will compare 60 Gy radiation plus cisplatin versus 60 Gy plus docetaxel versus 60 Gy plus the combination of docetaxel and cetuximab for high-risk resected SCCHN.

Systemic Chemotherapy for Recurrent/Metastatic Head and Neck Squamous Cell Cancer

At presentation an estimated 60% of patients with SCCHN have LA disease, for which aggressive multimodality therapy with curative intent is indicated.[159] Given the propensity of high-risk disease to reemerge as locoregional failure, distant metastases, or both, salvage therapy in the form of surgical resection, reirradiation, systemic chemotherapy, or a combination of all three modalities is often indicated to manage symptoms, improve quality of life, or extend survival.[160,161] For a select group of patients with locally recurrent disease, reirradiation with systemic therapy with or without salvage surgery remains an option,[162,163] and durable disease control could be achieved in approximately 10% of patients without surgery and 20% in those with resected tumor[164,165]; however, impact on OS was modest, and preexisting comorbidities and organ dysfunction could compromise such treatment outcome.[166] Pattern of recurrence depends on the primary site of tumor, stage, and initial treatment and is often projected to range from 25% to 50%.[150,151,167–169] For the majority of patients with R/M SCCHN, the purpose of treatment remains palliation.

The systemic chemotherapy landscape is dominated by a limited number of chemotherapeutic agents, including platinum compounds (cisplatin, carboplatin), antimetabolites (methotrexate, 5-FU), and taxanes (paclitaxel, docetaxel).[170–172] Initial trials identified bleomycin, methotrexate, vincristine, and, later, cisplatin as potentially active agents in head and neck cancer.[173–179] In 1985, Morton and colleagues published the findings of a randomized phase III trial with a 2 × 2 factorial design in which patients were randomized to one of four arms: cisplatin, bleomycin, cisplatin plus bleomycin, and no treatment.[180] A comparison of the cisplatin arm (31 patients) versus no-treatment arm (26 patients) revealed a 10-week improvement in median OS in favor of cisplatin treatment. This study remains the only randomized trial showing improved median OS with chemotherapy versus no treatment in patients with

R/M SCCHN. Cisplatin was compared with methotrexate in the R/M setting and proved to be comparable.[181,182] Similarly, carboplatin was found to be effective as a single agent in a series of small phase II trials, with the advantage of being less emetogenic, nephrotoxic, and neurotoxic than cisplatin. Single-agent activity of carboplatin in the R/M SCCHN setting ranged from 24% to 26%.[183,184]

Cisplatin and 5-FU (administered through continuous infusion over 4–5 days), developed at Wayne State University,[9,10,13] comprised one of the most actively studied regimens in the 1980s and 1990s; it was compared with its individual components (cisplatin, 5-FU), methotrexate, carboplatin plus 5-FU, and CABO regimen (cisplatin, methotrexate, bleomycin, and vincristine). A common theme that emerged from these trials is that combination regimens achieved a higher response rate than single-agent chemotherapy but at the expense of higher toxicity and no improvement in OS over single agents.[12,177,179,185–187] Current practice has moved toward a platinum doublet (with either 5-FU or taxane) with an objective response rate ranging from 12% to 36%, median PFS of 3–4 months, and median OS of 6–8 months, depending on patient population, prior therapy, and performance status.[171,188–190] The shift from monotherapy to a platinum doublet resulted in a consistent improvement in response rate but not OS.

Following their introduction into clinical practice in the 1990s, taxanes proved to be highly effective against R/M SCCHN, with an ORR of 40–42% in a series of small nonrandomized trials.[191–193] ECOG (E1395) compared cisplatin plus 5-FU versus cisplatin plus paclitaxel in patients with incurable SCCHN. There were no significant difference in ORR (27% vs. 26%, respectively) or OS (8.7 vs. 8.1 months, respectively).[190]

Argiris and colleagues performed a combined analysis of two phase III ECOG trials (E1393 and E1395) that randomized 399 patients to four cisplatin-based regimens for R/M SCCHN (201 patients in E1393, which evaluated cisplatin 75 mg/m^2 plus+ paclitaxel at two different DLs of 200 vs. 135 mg/m^2; 198 patients in E1395, which evaluated cisplatin plus 5-FU vs. cisplatin plus paclitaxel).[194] The median OS was 7.8 months for all patients, 1-year OS was 32.4%, and overall objective response rate was 32%. On multivariate analysis, five factors emerged as unfavorable independent prognostic predictors of shorter OS: (1) weight loss greater than 5%, (2) ECOG performance status of 1 versus 0, (3) good to moderate tumor cell differentiation, (4) hypopharyngeal or oral cavity primary site versus other sites, and (5) prior radiation therapy. A prognostic model for OS was constructed based on these five prognostic factors: Patients with no, one, or two adverse prognostic factors had a median OS of 0.98 years (95% CI, 0.79–1.14 years), whereas patients with three or more poor prognostic factors had a median OS of 0.52 years (95% CI, 0.47–0.62 years). Response to chemotherapy was found to be a favorable predictor of outcome.

Targeted Therapy for Recurrent/Metastatic Head and Neck Squamous Cell Cancer

Therapeutic strategies that target EGFR are of particular interest in the management of R/M SCCHN, given the abundant expression of both EGFR and its main ligand, TGF-α, in SCCHN and their correlation with poor prognosis. EGFR signaling is targeted through mAbs against the extracellular domain to block its interaction with its cognate ligand and small-molecule TKIs that compete with ATP for kinase domain binding. In addition to blocking downstream receptor signal, mAbs, particularly IgG1 subtype, possess the potential to trigger ADCC. In SCCHN, the anti-EGFR mAb cetuximab has been incorporated into management of R/M SCCHN, where it has proved therapeutic activity both as monotherapy[72] and in combination with systemic chemotherapy[73,195–197]; such activity led to the FDA approval of cetuximab in R/M SCCHN in combination with platinum/5-FU as a first-line treatment and as a monotherapy for platinum-refractory disease.

Cetuximab in the Management of Recurrent/Metastatic Head and Neck Cancer

Cetuximab is a chimeric (human-murine) IgG1 mAb with high affinity to EGFR and has been studied in the first- and second-line settings of R/M SCCHN.[198] Three phase II trials studied cetuximab in the second-line treatment of platinum-refractory R/M SCCHN; it was either added to a platinum compound in an effort to restore sensitivity to platinum compounds[195,196] or used alone.[72] The three studies achieved similar outcome with ORR seen in 10–13% of patients, disease control in 46–55%, and median OS of 5.2–6.1 months, regardless of whether cetuximab was delivered as a single agent[72] or in combination with a platinum compound.[195,196] Two salient conclusions could be drawn from these three trials: The first was that the reported 5- to 6-month median OS achieved with cetuximab in platinum-refractory patients was close to that achieved with first-line therapy in R/M SCCHN[194] and represented a 2.5-month increase in OS when compared with platinum-refractory historical controls.[199] Second, this degree of concordance in outcome suggested that the therapeutic benefit was attributable solely to the antitumor activity of cetuximab rather than the much-hoped-for reversal of platinum resistance by cetuximab.

ECOG trial E5397 was the first to evaluate cetuximab in first-line therapy for R/M SCCHN.[197] The study randomized 117 patients to either cisplatin (100 mg/m^2 every 4 weeks) plus cetuximab or cisplatin plus placebo. The primary end-point was a 2-month improvement in PFS, from 2 to 4 months. Cetuximab treatment was associated with a significantly higher response rate (26% vs. 10%, respectively; P = .03); however, a better-than-expected PFS in the control arm (2.7 months) led to a nonsignificant trend toward better median PFS (4.2 months vs. 2.7 months; P = .09). Improvement in median OS was also not significant (9.2 months vs. 8.0 months; P = .21). Even though the study did not meet its primary end-point, it laid the groundwork for a follow-up landmark trial, Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer (EXTREME), which confirmed the therapeutic advantage of adding cetuximab to chemotherapy for patients with R/M SCCHN.[73] This study randomized 442 patients to cisplatin 100 mg/m^2 or carboplatin AUC of 5 mg/mL per minute on

day 1, followed by 5-FU 1000 mg/m^2 per day by continuous infusion for 4 days, every 3 weeks, with or without cetuximab at a 400-mg/m^2 loading dose then 250 mg/m^2 weekly. Chemotherapy was administered for a maximum of six cycles; patients randomized to the cetuximab arm continued to receive single-agent cetuximab maintenance until disease progression or unacceptable toxicity occurred. The primary end-point was OS, and no crossover was allowed. Prior chemotherapy was allowed only if this was part of the primary treatment and was completed at least 6 months before enrollment in the study. Addition of cetuximab to platinum/5-FU significantly improved median OS from 7.4 months in the chemotherapy-alone arm to 10.1 months in the chemotherapy plus cetuximab arm (HR, 0.80; 95% CI, 0.64–0.99; P = .001); median PFS improved from 3.3 months to 5.6 months, respectively (HR, 0.54; 95% CI, 0.43–0.67; P < .001); and ORR improved from 20% to 36% (P < .001). Patients receiving cetuximab had a significantly higher incidence of grade 3 skin toxicity (9% had grade 3 skin toxicity), hypomagnesemia (11 patients in the cetuximab group vs. 3 in the chemotherapy alone group; P = .05), and sepsis (9 patients in the cetuximab group vs. 1 in the chemotherapy alone group; P = .02); there were no cetuximab-related deaths. The EXTREME trial was the first to show superiority in terms of OS of a new regimen over standard platinum-based combination chemotherapy in the R/M SCCHN setting since the introduction of cisplatin over three decades earlier.

Cetuximab has also been studied in combination with weekly paclitaxel (80 mg/m^2) in a single-arm phase II trial.[200] The study enrolled 46 patients with R/M SCCHN who achieved an ORR of 54% (95% CI, 39–69%), complete response rate of 22%, and a disease control rate of 80%. Median PFS was 4.2 months (95% CI, 2.9–5.5 months), and median OS was 8.1 months (95% CI, 6.6–9.6 months).

Panitumumab is a fully human IgG2 mAb. Panitumumab was evaluated in the R/M SCCHN in three studies: SPECTRUM, PRISM, and PARTNER.

SPECTRUM[116] is a phase III trial that was modeled after the EXTREME trial, randomizing 657 patients to the cisplatin plus 5-FU chemotherapy backbone, with or without panitumumab (9 mg/kg on day 1). Chemotherapy was administered for a maximum of six cycles; patients randomized to the panitumumab arm continued to receive single-agent panitumumab maintenance until disease progression or unacceptable toxicity occurred. The primary end-point was OS, and crossover was not permitted. Panitumumab prolonged median PFS by 1.2 months (5.8 months for the panitumumab arm vs. 4.6 months for the chemotherapy alone arm; P = .004); there was no difference in median OS (11.1 months for the panitumumab arm vs. 9.0 months for the chemotherapy alone arm; P = .14). In addition, several grade 3 or higher toxicities were more frequent with panitumumab, and there were more treatment-related deaths with panitumumab versus chemotherapy (4% vs. 2%, respectively). An analysis of the results stratified by tumor p16 status suggested that panitumumab improved OS and PFS in patients with p16-negative tumors but not in those with p16-positive disease. These results should be interpreted with caution because of the low number of patients with p16-positive tumors as well as the definition of p16 positivity (>10% of the tumor cells expressing p16 in contrast with the more commonly accepted criterion of >70%). A similar analysis in the EXTREME study, using the 70% cutoff point, did not show the same results. Therefore further evaluation is needed to better understand the impact of HPV and/or p16 status on the activity of anti-EGFR mAbs.

The PRISM trial (Panitumumab Regimen In Second-line Monotherapy of head and neck cancer) evaluated the safety and efficacy of panitumumab as a single agent in the second line of R/M SCCHN.[201] PRISM was an open-label, single-arm, multicenter trial of panitumumab 9 mg/kg every 3 weeks. The primary end-point was ORR; secondary end-points included disease control rate, OS, PFS, and safety. The ORR (primary end-point) was 4% (2 of 51 patients); the disease control rate was 39%; and median PFS was 1.4 months (95% CI, 1.3–2.4 months). Median OS was 5.1 months (95% CI, 4.3–8.3 months). The most common adverse events were rash/dermatitis acneiform (69%), fatigue (33%), dry skin (21%), and hypomagnesemia (21%). There was one treatment-related death (angioedema). The authors concluded that panitumumab monotherapy was of limited usefulness in previously treated patients with R/M SCCHN.

The randomized phase II Panitumumab Added to Regimen for Treatment of Head and Neck Cancer Evaluation of Response (PARTNER) trial preliminarily demonstrated improved PFS and response rate with the addition of panitumumab to docetaxel/cisplatin versus docetaxel/cisplatin alone as first-line treatment for R/M SCCHN but with an increased frequency of grade 3 or 4 toxicity and no survival advantage.[86] Median PFS, median OS, and ORR were 6.9 months, 12.9 months, and 44% in the panitumumab arm versus 5.5 months, 13.8 months, and 37% in the arm without panitumumab, respectively. Crossover to panitumumab monotherapy was allowed in the docetaxel/cisplatin arm and occurred in 57% of the patients, which may have impaired the OS analysis.

Zalutumumab, a humanized anti-EGFR IgG1 mAb was evaluated in the R/M SCCHN setting with disappointing results (1.5-week prolongation of PFS compared with best supportive care [BSC] alone), which led to the suspension of further clinical development.[202]

Immunotherapy for Head and Neck Cancer

The vast repertoire of somatic mutations associated with defects in DNA repair or exposure to carcinogens (tobacco use in the case of SCCHN) seen in cancer yields a panoply of neoantigens for the adaptive immune system to exploit in its fight against cancer.[203–206] Unfortunately, such an immune attack rarely succeeds on its own, owing to a combination of T-cell extrinsic suppressive mechanisms (TGF-β, FoxP3+ regulatory T cells [T-reg], and tryptophan metabolites [indoleamine-2,3-dioxygenase or IDO]) and T-cell intrinsic immune checkpoints (e.g., cytotoxic T-lymphocyte–associated protein 4 [CTLA4], programmed cell death protein [PD-1]) designed to thwart autoimmunity and hamper development of anti-tumor immunity.[207] The discovery that blocking CTLA-4 was associated with antitumor immunity

in murine models[208] was a seminal finding that led to the development of ipilimumab, a humanized anti-CTLA4 mAb, as the first checkpoint inhibitor with activity against solid tumors.[209,210] Ipilimumab gained initial approval against melanoma in 2011,[211,212] and success of anti-CTLA4–mediated immunotherapy generated interest in exploring another immune checkpoint pathway, namely the PD-1/programmed death-ligand 1 (PD-L1) pathway against other solid tumors.[213,214] Blockade of the PD-1/PD-L1 pathway has been of particular interest in the management of SCCHN, given the observation that upregulation of PD-L1 has been reported in 66–77% of head and neck cancers.[215–218] This prompted a series of phase II/III trials investigating the anti–PD-1 pembrolizumab (NCT01848834, NCT02255097, NCT02289209, NCT02252042), nivolumab (NCT02105636), and anti–PD-L1 MEDI4736 (durvalumab) (NCT02369874, NCT02551159, NCT02262741) in R/M SCCHN, with some early data being presented in abstract form. At the ASCO 2015 meeting, two such trials were presented. Seiwert and colleagues presented data from the SCCHN expansion cohort of KEYNOTE-012 (NCT01848834).[219] The study enrolled 132 patients with R/M SCCHN, 99 of whom had evaluable disease. The primary end-point was ORR (Response Evaluation Criteria in Solid Tumors or RECIST 1.1). Patients were treated with pembrolizumab at a fixed dose of 200 mg every 3 weeks. ORR was 18.2% (95% CI, 11.1–27.2) with 18 partial responses and 31.3% with stable disease. Grade 3 or greater adverse events occurred in 7.6%. The most common drug-related adverse events (≥5%) of any grade were fatigue (12.1%), decreased appetite (6.8%), pyrexia (6.1%), and rash (5.3%). Pembrolizumab is being further evaluated in KEYNOTE-040 (NCT02252042), an open-label randomized phase III trial, with a planned enrollment of 466 patients with R/M SCCHN. Segal and colleagues presented data from the phase I/II, multicenter, open-label study (NCT01693562) evaluating the safety and efficacy of MEDI4736 (durvalumab), a human IgG1 mAb that blocks PD-L1 binding to PD-1 and CD80.[220] The trial enrolled 62 patients, of whom 51 were evaluable for response with 24 or more weeks of follow-up; ORR was 12% (25% in patients whose tumors expressed PD-L1), and DCR at 24 weeks was 16% (25% in PD-L1–positive patients). These results are being further evaluated in an ongoing open-label randomized phase III trial—Phase II Open Label Study of MEDI4736 With/Without Tremelimumab Versus Standard of Care in Recurrent/Metastatic Head and Neck Cancer (KESTREL)—with a planned enrollment of 628 patients (NCT02551159).

In addition to developing immune checkpoint blockade as a means to mount a therapeutic antitumor immune response, there has been a concerted effort to augment the proimmunogenic function of cetuximab.[221,222] It is well established that the antitumor effect of cetuximab is derived from two activities: (1) inhibition of EGFR signaling[45] and (2) immune cell activation through recognition of the IgG1 Fc portion of cetuximab[65] by the Fc receptor CD16/Fc γ RIII on NK cells.[223–225]

In an effort to augment the immunogenic potential of cetuximab, it has been combined with two NK-activating immunotherapeutic agents. The first of these, anti-CD137 (4-1BB), is based on the observation that 4-1BB is upregulated on NK cells after exposure to cetuximab.[226,227] Targeting the 4-1BB on NK cells augments their cetuximab-dependent ADCC activity, crosstalk with both CD8 and DC.[225] A phase Ib open-label, multicenter trial of cetuximab and anti-CD137 mAb (urelumab) has been designed for patients with advanced/metastatic colorectal and head and neck cancer (NCT02110082).

The second strategy to enhance cetuximab-induced NK-mediated ADCC is through integration of TLR agonists within the treatment regimen. Toll-like receptors (TLRs) are an integral part of the innate immune system and play a critical role in detecting pathogen-associated molecular patterns and activating the adaptive immune system.[228,229] TLR ligands have gained wide popularity in the field of vaccine adjuvants and as a means to enhance antitumor immunity.[230,231] Motolimod (VTX-2337) is a small-molecule TLR8 agonist capable of activating monocytes, myeloid DC and NK cells[232] that has shown antitumor activity in a phase I trial for patients with advanced cancer.[233,234] Preclinical models have demonstrated synergy between cetuximab and Motolimod (VTX-2337),[235] and a phase Ib dose-escalation study of motolimod in conjunction with cetuximab in patients with R/M SCCHN achieved a response rate of 17% and disease control rate of 50%.[236] Initial success of motolimod in the phase Ib trial led to two follow-up trials. The first is Active8, a randomized phase II trial comparing the EXTREME regimen (platinum, 5-FU, cetuximab) with or without motolimod (NCT01836029), which has completed accrual. The second is a phase I neoadjuvant protocol for patients with stage II–IVA disease with a planned surgical resection who will receive 3–4 weeks of therapy on one of two cohorts (cohort 1, cetuximab and motolimod; cohort 2, cetuximab, motolimod, and nivolumab) (NCT02124850).

Chemotherapy for Nasopharyngeal Carcinoma

Nasopharyngeal carcinoma of the undifferentiated subtype is predominantly a disease of Southeast Asian ethnicity with an annual incidence of 84,400 cases and with 51,600 deaths in 2008.[237] The modern era of chemotherapy treatment of nasopharyngeal cancer could be traced to the publication of the Intergroup trial 0099 in 1998 by Al-Sarraf and colleagues.[238] This trial randomized 193 patients to CCRT with high-dose cisplatin 100 mg/m^2 every 3 weeks for three cycles plus 70-Gy RT in standard fractionation followed by three cycles of adjuvant chemotherapy with cisplatin 80 mg/m^2 and 5-FU 4000 mg/m^2 over 96 hours every 4 weeks for three cycles versus radiation alone. At the time of study publication, the CRT group had not reached its median OS although the RT-alone group had a median OS of 34 months. This translates into a 3-year survival rate of 78% for the CRT and 47% for the RT-alone group, respectively. This cisplatin-based CCRT followed by three cycles of adjuvant chemotherapy became the next standard of care for LA nasopharyngeal carcinoma (NPC) and was confirmed by four individual trials.[239–245] Subsequent trials substituted weekly cisplatin (40 mg/m^2) instead of the 3-weekly regimen and showed improved PFS and OS for patients with advanced T stage over the radiation-alone arm.[246,247] These results were further confirmed by the Meta-Analysis of Chemotherapy

in Nasopharyngeal Carcinoma (MAC-NPC), which examined data from 1753 individual patients from eight trials and showed that addition of chemotherapy to radiation achieved a 6% improvement in OS at 5 years. It is interesting to note that this benefit accrued only in trials employing concurrent with or without adjuvant chemotherapy, but not in trials using adjuvant chemotherapy alone,[248,249] which in turn raised questions about the value of adding adjuvant chemotherapy after completion of the initial CCRT phase. The current National Comprehensive Cancer Network (NCCN) standard of care for management of NPC calls for RT alone for stage I and for CCRT for stages II–IVB (concurrent plus adjuvant as the first choice, followed by concurrent alone [category 2B] and induction-concurrent [category 3]).[250] Although there is little doubt that CCRT is needed for proper management of LA stage III/IVB, a number of controversies remain regarding the role of chemotherapy in the management of stage II disease, the therapeutic value of adding either induction or adjuvant chemotherapy to CRT, and the role of predictive biomarkers in patient selection.[251–253] The following section briefly examines each of these questions.

Role of Chemotherapy in Management of Stage II Disease

Chen and colleagues examined the role of chemotherapy (weekly cisplatin 30 mg/m^2) when added to RT in patients with stage II nasopharyngeal carcinoma (staged according to the 1992 Chinese staging system).[254] A total of 230 patients were randomized to RT versus CRT. Because of a major change in staging criteria with the introduction of the fifth edition of the AJCC Cancer Staging Manual, only 87% had stage II disease, and the remaining 13% were upstaged to clinical stage III NPC according to AJCC/Union for International Cancer Control (UICC) seventh edition criteria.

The authors reported significant improvement in 5-year OS with CRT over RT alone—95% versus 86% (HR, 0.30; 95% CI, 0.12–0.76; P =.007). The study was criticized for using two-dimensional RT instead of the now widely used standard of IMRT. This point is well illustrated by two retrospective studies showing that patients with stage II NPC treated with three-dimensional conformal RT or IMRT technique could achieve 5-year disease-specific survival of 95% with RT alone.[255,256] In view of recent data from the recent individual patient meta-analysis (MAC-NPC2)[249] showing a very modest benefit to chemotherapy above RT alone (HR, 0.95; 95% CI, 0.65–1.44) the current thinking is to use a more personalized approach that would limit chemotherapy to high-risk stage II NPC—for example, patients with large-volume disease[257] or high pretreatment EBV plasma DNA level.[258]

Induction Chemotherapy

ICT significantly improved distant metastatic disease failure-free rate (D-FFR) (HR, 0.62 [0.48–0.79]), but did not translate into significant reduction of cancer deaths (HR, 0.89 [0.73–1.09]).[249] Hui and colleagues[259] in 2009 were the first to report an OS benefit with this approach. This study was not powered to detect a survival difference, but a significant finding of 26.5% absolute improvement in 3-year OS with cisplatin and docetaxel induction before CRT generated sufficient interest to launch a series of phase III trials to test this approach. Most of these trials had a small sample size (range, 65–172), and others closed early owing to slow accrual. Two recent trials using the triplet combination of docetaxel-cisplatin-fluorouracil (TPF) reported encouraging results. The French Head and Neck Oncology and Radiotherapy Group (GORTEC) 2006-01 trial (NCT00828386),[260] initially designed to enroll 260 stage II–IVB NPC patients, was prematurely terminated owing to slow accrual. Eighty-three patients had been randomized, and early results showed significant improvement in OS, PFS, and locoregional failure-free rate (LR-FFR). A trial from China (NCT01245959), which accrued 480 stage III/IVB patients, demonstrated significant improvement in 2-year failure-free survival and D-FFR. The median follow-up, however, was only 21 months; longer follow-up is needed to evaluate efficacy and late toxicity.

The NPC-0501 trial by the Hong Kong Nasopharyngeal Cancer Study Group used the Intergroup 0099 regimen as the standard arm to evaluate the therapeutic benefit by changing the timing of chemotherapy from concurrent-adjuvant to induction-concurrent, replacing 5-FU with oral capecitabine, and changing RT from conventional to accelerated fractionation.[261] A total of 803 patients were randomized. The study showed that ICT was much better tolerated than adjuvant chemotherapy: a significantly higher proportion of patients in the induction group completed three nonconcurrent cycles compared with the adjuvant group (88% vs. 64%; P < .001); however, a lower proportion had two or more concurrent doses in the induction arm (90% vs. 95%; P = .009). Preliminary results (median follow-up 3.3 years) showed that changing the timing alone did not achieve significant improvement in PFS, but more encouraging results were achieved by changing both the sequence and the induction regimen. Unadjusted comparison of induction cisplatin-capecitabine versus adjuvant cisplatin-fluorouracil showed a favorable trend when given with conventionally fractionated RT (81% vs. 75% at 3 years; P = .045). Reduction in hazard of progression (HR, 0.54 [0.36–0.80]) and death (HR, 0.42 [0.25–0.70]) reached significance when adjusted for other significant factors and fractionation. For comparison of induction using cisplatin-capecitabine versus cisplatin-fluorouracil, unadjusted comparisons did not show significant difference, but adjusted analyses showed lower hazard of death (HR, 0.57 [0.34–0.97]); in addition, induction cisplatin-capecitabine incurred less toxicity (neutropenia and electrolyte disturbance). Longer follow-up will be needed to confirm the current findings, but in view of convenience, favorable toxicity profile, and at least equivalent (if not better) efficacy, this regimen of induction cisplatin-capecitabine and concurrent cisplatin warrants further validation. In addition, this study confirmed that accelerated fractionation is not recommended for patients treated with CRT.

Adjuvant Chemotherapy

The role of adjuvant chemotherapy in the management of LA NPC is often confounded by the fact that most patients assigned to such treatment are either unable to initiate adjuvant chemotherapy on time or do not complete the treatment as planned because of toxicity from prior CRT. This is well

illustrated in the trial by Chen and colleagues,[244] in which 508 patients with stage III/IVB NPC were randomized to CRT versus CRT followed by adjuvant chemotherapy. The study did not achieve a statistically significant difference in the primary end-point of failure-free survival at 2 years. However, after a 38-month follow-up, there has been a trend toward favorable findings for the concurrent-adjuvant arm compared with the concurrent chemotherapy alone arm: LR-FFR with HR of 0.5 (95% CI, 0.21–1.16; P = .10), D-FFR with HR of 0.71 (95% CI, 0.46–1.10; P = .12), and failure-free survival HR of 0.74 (95% CI, 0.49–1.10; P = .13). Compliance with adjuvant chemotherapy was poor; only 18% of the patients assigned to adjuvant chemotherapy received the treatment, another 20% discontinued treatment after the start of adjuvant chemotherapy, 49% required dose reduction, and 69% had delays in treatment. Indirect evidence from the MAC-NPC[249] meta-analysis supports the use of adjuvant chemotherapy; the magnitude of the OS benefit observed in patients receiving CRT plus adjuvant chemotherapy (n = 1267 patients; HR, 0.65; 95% CI, 0.56–0.76) was larger than that in the CRT-alone subgroup (n = 1834 patients; HR, 0.80; 95% CI, 0.70–0.93). Therefore no definitive recommendation could be made regarding the use of adjuvant chemotherapy after CRT in locoregionally advanced NPC. Similar to the guidelines regarding role of chemotherapy in management of stage II disease, efforts are being made to personalize treatment to identify patients at high risk of recurrence. Elevated level of plasma EBV DNA at 6 to 8 weeks after RT could be a biomarker for high-risk disease, and two trials are currently evaluating this approach—namely the Hong Kong Nasopharyngeal Cancer Study Group trial (NCT00370890) and the NRG Oncology trial (NCT02135042). Both trials are investigating the usefulness of post-treatment plasma EBV DNA in individualizing adjuvant chemotherapy.[258,262,263] NRG Oncology trial (NCT02135042) is a randomized phase II/III study for patients with NPC stage II–IVB disease treated with IMRT and concurrent cisplatin. Patients without detectable plasma EBV DNA 1-week after RT, thought to be the low-risk patients, are randomized to either adjuvant chemotherapy using standard cisplatin-5-FU or observation, whereas those with detectable plasma EBV DNA after radiation, thought to be the high-risk patients, will be randomized to adjuvant chemotherapy with either standard cisplatin/5-FU or gemcitabine-paclitaxel.

Summary Practice Guidelines

Concurrent Definitive Chemotherapy and Radiation Therapy for Stage III/IV Squamous Cell Carcinoma of the Oral Cavity, Oropharynx, Hypopharynx, and Larynx and Choice of Agents

The current standard of care for patients with LA SCCHN of the hypopharynx and larynx is CCRT using cisplatin as a radiosensitizing chemotherapy. There is no consensus regarding whether 100 mg/m^2 every 3 weeks is superior to weekly cisplatin (30–40 mg/m^2). For patients who cannot tolerate cisplatin, cetuximab is an acceptable alternative. For patients with OPC, a number of ongoing trials are evaluating various de-escalation protocols, and the results of these trials are awaited.

Adjuvant Chemotherapy and Radiation Therapy for Patients With Extracapsular Extension and Positive Margins With Choice of Agents

The current standard of care for patients with high risk of recurrence after surgical resection (positive margin of resection or ECE, based on the pooled analysis of EORTC 22931 and RTOG 9501), adjuvant CCRT with three cycles of cisplatin 100 mg/m^2 remains the standard, although a significant proportion of these patients might not easily tolerate such a regimen. For these patients, data from the randomized phase II trial RTOG-0234 using weekly cetuximab plus docetaxel offers an attractive alternative.

Quick Description of Role of Induction Chemotherapy

ICT has been a contentious subject in the management of locally advanced SCCHN. The main appeal of such treatment is its ability to induce rapid tumor shrinkage, eradication of metastatic disease, and organ preservation in patients with OPC and laryngeal cancer. However, data from recent phase III trials did not show survival advantage for ICT over CCRT. Ongoing trials might establish a role for ICT in the management of OPC for organ preservation and to reduce the long-term toxicities from full-dose radiation.

Options for Recurrent/Metastatic Disease and How to Decide

The EXTREME trial established the role of cetuximab when combined with chemotherapy in first-line treatment of R/M SCCHN. Platinum doublets with either platinum plus 5-FU or a taxane are considered therapeutically equivalent, and either doublet could be paired with cetuximab in first-line therapy.

Definitive Chemotherapy and Radiation Therapy for Stage III/IV Nasopharyngeal Carcinoma

The NCCN guidelines recommend RT alone for stage I and chemotherapy in combination with RT for all other stages of nondisseminated NPC. CCRT followed by adjuvant chemotherapy and concurrent-alone are listed as category 2B, whereas ICT followed by concurrent chemotherapy, listed as category 3, is the recommendation for stages II–IVB.

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15 Immunotherapy

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Recent advances in immunotherapy are poised to transform the practice of oncology. In particular, adoptive cell transfer with tumor-infiltrating lymphocytes (TILs)[1,2] or receptor-engineered T cells,[3–8] as well as checkpoint inhibitors, such as anti–cytotoxic T-lymphocyte–associated protein 4 (anti–CTLA-4) and anti–programmed cell death protein 1 (anti–PD-1), are resulting in durable responses and improved survival in patients with numerous types of cancer.[9–16] These advances led the journal *Science* to declare immunotherapy the "breakthrough of the year" in 2013.

Patients with head and neck squamous cell carcinoma (HNSCC) have a relatively poor prognosis, which has not significantly improved even after five decades of advancements in surgery, radiation therapy, and chemotherapy. Recurrent/metastatic (R/M) HNSCC is especially challenging, regardless of human papillomavirus (HPV) status, and has few effective treatment options. HPV-negative HNSCC is associated with a locoregional relapse rate of 19–35% and a distant metastatic rate of 14–22% following standard of care, compared with rates of 9–18% and 5–12%, respectively, for HPV-positive HNSCC.[17–19] The median overall survival for patients with R/M disease is 10–13 months in the setting of first-line chemotherapy and 6 months in the second-line setting. The current standard of care is platinum-based doublet chemotherapy with or without cetuximab. Second-line standard of care options include cetuximab, methotrexate, and taxanes. All of these chemotherapeutic agents are associated with significant side effects, and only 10–13% of patients respond to treatment. HNSCC regressions from existing systemic therapies are transient and do not add significantly increased longevity, and virtually all patients succumb to their malignancy.

The promise of immunotherapy lies in improving overall survival so that responses to therapy are durable—generating the so-called "tail on the [Kaplan-Meier] curve" (Fig. 15.1). Two anti–PD-1 antibodies, nivolumab and pembrolizumab, have shown efficacy in clinical trials for R/M HNSCC and were approved by the U.S. Food and Drug Administration (FDA) for use in the second-line setting in 2016.[20,21] These findings have ushered in a new era in the treatment of HNSCC and give cause to reassess therapeutic approaches as anti–PD-1 and other immunotherapies are integrated into the standard of care. This chapter focuses on immunotherapy for head and neck cancer and provides a historical context from which to predict future therapeutic advances. The current new age of immunotherapy is full of hope, but in fact, immunotherapy for cancer has been investigated for more than a century and as a treatment modality is older than either radiation therapy or cytotoxic chemotherapy. Before this is discussed, the major historical discoveries that led to the current state of the art will be explored.

Immunology

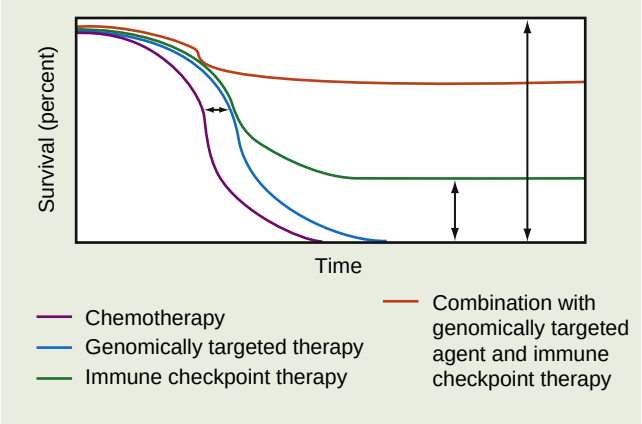
The Germ Theory of Disease

The first recorded evidence that individuals could be immune to disease dates to the 5th century BC in the writings of Thucydides, who recorded that some individuals who recovered from the plague subsequently became "immune". The first recorded attempt to induce immunity, however, occurred in 10th century China during a smallpox epidemic. A process called *variolation* was described, which involved treating healthy people by either subcutaneous injection or intranasal application of material obtained from the smallpox lesions of infected patients. Variolation was practiced widely in the Ottoman Empire and in England by the 18th century, but it was not until 1796 that Edward Jenner developed the cowpox vaccine as a safe method to prevent smallpox.

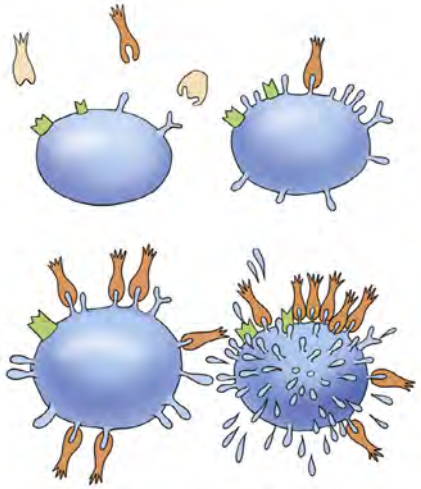
More than 100 years after Jenner's pioneering work, Robert Koch demonstrated in an animal model (rabbit) that disease (anthrax) passed from one animal to another via bacterial transmission. He subsequently discovered techniques to cultivate these microorganisms, in part through the development of agar growth medium. At the same time, Louis Pasteur serendipitously discovered a method of attenuating bacteria (chicken cholera bacillus) and went on to develop the first safe vaccine for anthrax and rabies. The science of immunology was thus born.[22,23]

Humoralists and Cellularists

Although Koch and Pasteur firmly established the germ theory of disease, little was known at the dawn of the 20th century about the mechanisms by which immunity to disease



• **Fig. 15.1** The promise of immunotherapy: the Kaplan-Meier curve tail. Previously, cancer therapies, such as genomically targeted therapies or chemotherapy, would extend progression-free intervals for the majority of patients with metastatic cancer, but overall survival was not improved—virtually all patients still died, as indicated by the horizontal change in the survival curve. With immune checkpoint therapy, not as many patients respond to treatment, but a percentage of those who do respond receive lasting benefits, as evidenced by the vertical change in the overall survival curves (i.e., the "tail on the curve"). It is postulated that the combination of checkpoint inhibitors with other immunotherapies and genomically targeted agents will further improve overall survival in the future. (Adapted from Sharma P, Allison JP. Immune checkpoint targeting in cancer therapy: toward combination strategies with curative potential. *Cell* 161(2):205–214, 2015.)



• **Fig. 15.2** Ehrlich's side-chain theory. This theory suggested that the chemical structure of cells was responsible for the action of immune recognition. Ehrlich postulated that living cells had side-chains that could link with a particular toxin "like a key in a lock," from which grew additional side-chains to bind the toxin, and that these additional side-chains broke off to become the antibodies that circulate through the body. (From Penso G: La conquête du monde invisible : parasites et microbes à travers les siècles. 1981. Les Éditions Roger Dacosta.)

was conferred. Two schools of thought prevailed at the time: the humoralists and the cellularists. Cellularists were lead by Metchnikoff, who was the first to describe the existence of phagocytes, which engulfed infectious agents and were an important line of defense in the development of immunity. The humoralists, on the other hand, were lead by Paul Ehrlich, who described, with remarkable accuracy given the technology of the day, the existence of antibodies and their cognate receptors through his "side-chain" theory, and that these antibodies functioned in a specific capacity independent of erythrocytes (Fig. 15.2). Ehrlich was heavily influenced by the work of von Behring,[24] who described a soluble "anti-toxin" that transferred immunity against diphtheria, and Ehrlich later postulated that immunity was regulated by antibodies, which differentiated between "self" and "nonself".[25] Thus by the end of the 19th century, it was generally recognized that the immune system consisted of two components that offered protection from pathogens: humoral immunity to infection, which was transferred by antibodies released from specialized immune cells; and cellular immunity, which involved the recruitment of phagocytes to recognize and destroy microbes. For his work on "serum therapy," von Behring[26] was awarded the first Nobel Prize in Physiology or Medicine, and Metchnikoff and Ehrlich[27] shared the award in 1908 for their work on "immunity".

The humoralists dominated the immunologic landscape for most of the first half of the 20th century. This led to a greater understanding of how the immune system actually functions, an understanding that was radically advanced in the late 1950s by the work of Nobel Laureates Gerald Edelman[28] and Rodney Porter,[29] who described the structure of antibody molecules.

However, observations of delayed hypersensitivity reactions, such as those seen with tuberculin, as well as the allograft rejection described by Medawar in 1944, were unexplained by antibody responses alone. Landmark studies by Landsteiner and Chase[30] in 1942 demonstrated a cell-mediated memory response and distinguished between an immediate (antibody-mediated) immune response and a delayed (cell-mediated) hypersensitivity reaction. Eventually, in 1962, Gowans identified lymphocytes as the cell type responsible for the cell-mediated responses.[31] This led to the discovery of the importance of the thymus in the immune system and to the distinction of T cells, which include cytotoxic cells (CD8) and helper T cells (CD4), and B cells, which produce antibodies. Just how these lymphocytes and antibodies respond to the seemingly infinite number of antigens, however, remained the most important unanswered question of that day.

The Clonal Selection Theory

Despite important discoveries of the first half of the 20th century, an explanation of antibody diversity remained elusive. In 1955, Jerne published his "natural selection theory". This theory proposed that antigens "selected" for a specific "globulin" to which they would bind; they would then be transported to antibody-producing cells, which would make identical copies, or clones, of the specific globulin presented to them, and would proliferate.[32] This work, along with that of Burnet,[33] would form the basis of the clonal selection theory as an explanation of the diversity of the antibody repertoire. Burnet also published his theory of acquired immunologic tolerance, which proposed that lymphocytes are able to achieve recognition of self versus nonself.[34] This model was later validated by Peter Medawar, and the two shared the Nobel prize in medicine in 1960.[35]

The field of tumor immunology was significantly advanced in 1957, when Richmond Prehn and Joan Main demonstrated the unique specificity of tumors by showing that tumors induced by chemical carcinogens in mice could stimulate tumor-specific responses that were able to reject those same tumors on subsequent inoculation (challenge)—but spontaneously arising tumors were not rejected.[36] Such experiments implied that there must be antigens associated with tumor cells that can be recognized by the immune system, later known as *tumor-associated antigens* (TAAs), and that immune cells had memory capacity.

By the 1960s Burnet had begun to champion the view that a major function of the immune system was to eliminate malignant cells.[37] In a process he termed "immunosurveillance", he suggested that lymphocytes are continually patrolling tissues and eliminating transformed cells, presumably via recognition of TAAs, thus supporting Erlich's more rudimentary suggestion from decades earlier.

Major Histocompatibility Complex

Although immunoglobulin was a key functional element to immune surveillance, little was known about the regulation of immune cells until the work of Baruj Benacerraf, Jean Dausset, and George Snell,[38] who from the late 1950s through the 1960s contributed to the description of the major histocompatibility complex (MHC) found on cell membranes, and elucidated genetic factors that regulate immunity. Rolf M. Zinkernagel and Peter Doherty further described the adaptive immune response to antigen presentation and defined the specificity of cell-mediated immunity through their discoveries related to MHC-restricted T-cell recognition of both self and viral antigens.[39–41] In other words, T cells recognize antigen only in the context of MHC molecules. This self/nonself hypothesis was elaborated in 1968 by Bretscher and Cohn,[42] who proposed the first two-signal model of lymphocyte activation, a critical step required for immune-mediated killing of pathogens. The original hypothesis has evolved over the years, but it essentially states that in addition to the delivery of antigen-MHC–mediated signals to the lymphocyte ("signal 1"), a second signal must also be present to activate the cell. "Signal 2" was later shown to be the interaction of CD28 on the T cell and B7 (CD80/CD86) on the antigen-presenting cell (APC). This would have profound implications in the field of immunotherapy decades later.[43,44]

During the 1970s and 1980s, different immune cell subsets were phenotyped and generally classified into two types: type 1, which results in cell-mediated immunity, and type 2, which are related to B cell–mediated humoral immunity. T helper cells assume one of these two distinct phenotypes when naïve $CD4^+$ helper T cells (Th) are exposed to certain antigens and cytokines. T_H1 cells produce immune-stimulating cytokines, such as interferon-γ (IFNγ) and interleukin-2 (IL-2), whereas T_H2 cells secrete predominantly immunosuppressive factors, such as IL-4, IL-6, and IL-10. A clearer understanding of the innate and adaptive immune responses came during the 1990s, when Bruce Beutler and Jules Hoffmann discovered the receptor proteins Toll and Toll-like receptors (TLRs), which can recognize microorganisms and cancer cells and activate innate immunity—the first step in the body's immune response. Ralph Steinman discovered dendritic cells (DCs) at about the same time and described their unique capacity to activate and regulate adaptive immunity, the later stage of the immune response, during which microorganisms (or tumors) are cleared from the body.

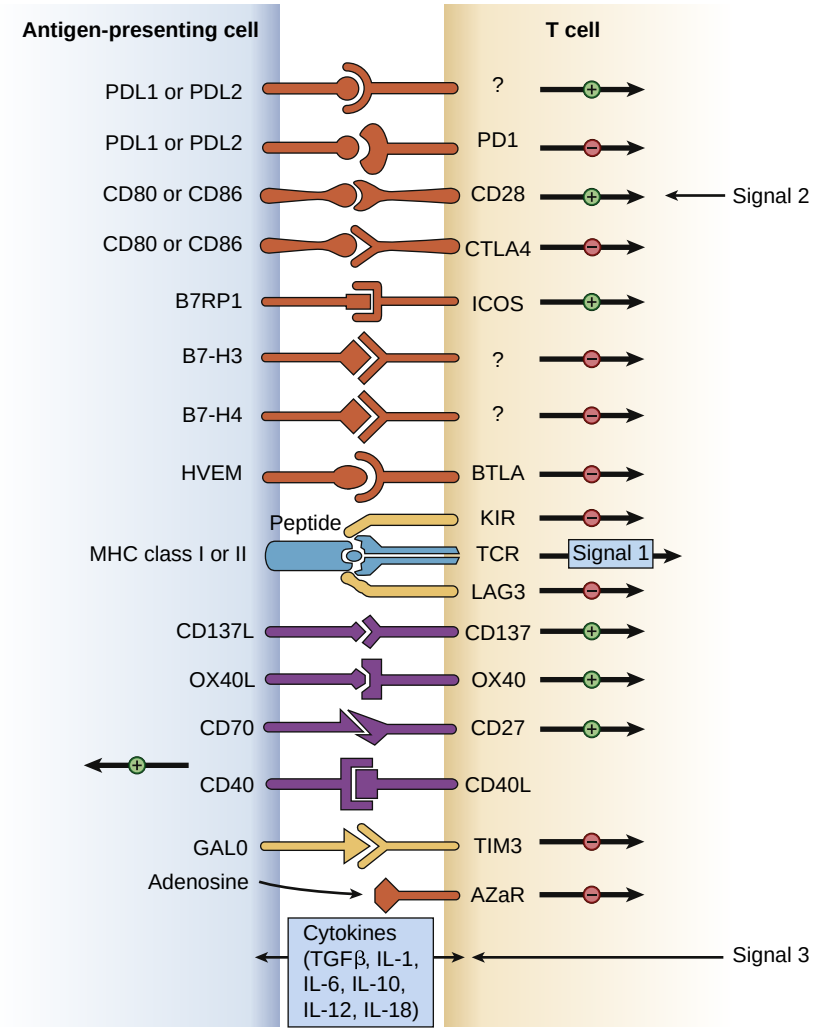
Thus evolved a general understanding that the innate immune system provides the body's initial response to cancer by directing specialized pre-programmed leukocytes such as natural killer (NK) cells and macrophages toward tumor cells. The adaptive immune system, on the other hand, takes a longer time to initiate and is focused on specific antigenic targets in tumor cells. Adaptive immunity relies on lymphocytes, such as T cells and B cells. T cells recognize antigens associated with the tumor, secrete cytokines, and directly lyse or kill tumor cells in a granzyme- and perforin-dependent manner. B cells produce antibodies, which can bind to antigen on the surface of tumor cells and mediate cell lysis via NK cells and macrophages in a process termed *antibody-dependent cellular cytotoxicity* (ADCC). These antibodies typically target proteins that are expressed on the surface of the tumor.

By the mid 1970s the capacity of the immune system to recognize self and foreign antigens was realized and the structure of antibodies and their regulation was known, but an explanation as to how the immune system can recognize the seemingly endless number of antigens and make antibodies to these remarkably diverse substances (T- or B-cell "repertoire") was unknown. In a pioneering study published in 1976, Susumu Tonegawa conducted a series of experiments that explained how DNA is rearranged or deleted to form a remarkably diverse "variable region" on antibodies.[45] As scientists began to understand the scope of genomic instability, it became clear that thousands of novel TAAs are generated in any one individual that are not recognized by the host's immune system. Tonegawa's discovery of the genetic principle of generation of antibody diversity earned him the Nobel Prize in 1987.

Tumors express many proteins that are not usually expressed in healthy cells. Sometimes, because of overexpression, gene mutation, or viral origin, these proteins—referred to as *tumor-associated antigens*—can be immunogenic and initiate an immune response to cancer cells. Cancer testis antigens, such as B melanoma antigen (BAGE) and melanoma-associated antigen (MAGE), are examples of aberrantly expressed proteins. Another example is proteins that result from genetic mutation, such as the tumor suppressor gene *TP53.* In addition, oncoviruses, such as HPV and Epstein-Barr virus (EBV), can be important antigen sources via E6 and E7 oncoproteins, and latent membrane protein (LMP) and EBV nuclear antigens, respectively. The oncoproteins (E6 and E7), in particular, being viral proteins that are necessary for cancer development after HPV infection, are considered optimal targets of immunotherapy for HPV-related malignancy.

For cytotoxic (CD8) T cells to be effective against specific tumor targets, they must first recognize tumor cells as being foreign—a process termed *activation*—which occurs through

a complex series of events involving TAAs. TAAs are released by tumor and captured by APCs, such as DCs. In the presence of a "maturation signal", such as TLR ligands, DCs can migrate to the regional lymph nodes and process the TAAs. Once in the draining lymph node, tumor antigens presented via MHC molecules on APCs initiate activation and differentiation of tumor-specific T cells (Fig. 15.3). Activation requires a second signal, termed *co-stimulation,* via the (B7) CD80/86:CD28 receptor complex. In addition to antigen presentation and co-stimulation, a third signal consisting of



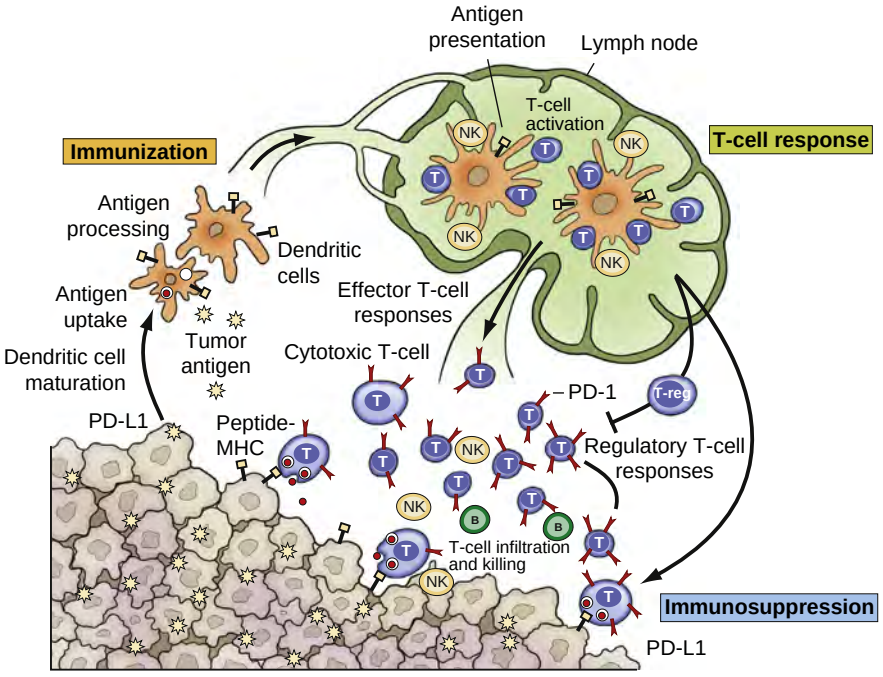
• **Fig. 15.3** Regulation of T-cell response. T-cell activation is mediated by peptide–major histocompatibility complex (MHC) molecule complexes that are recognized by the T-cell receptor (TCR) and modulated through various ligand-receptor interactions between T cells and antigen-presenting cells (APCs). In the presence of a "maturation signal" such as Toll-like receptor (TLR) ligands, APCs can migrate to the regional lymph nodes and process the tumor-associated antigens (TAAs). Once in the draining lymph node, tumor antigens presented via MHC molecules on APCs initiate activation and differentiation of tumor-specific T-cells. Activation requires a second signal, termed *co-stimulation,* via the (B7) CD80/86:CD28 receptor complex. Signal 2 generally consists of pairs of co-stimulatory and co-inhibitory receptors that bind the same ligand or ligands, such as CD28 and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4), and display distinct kinetics of expression, with the co-stimulatory receptor expressed on naïve and resting T cells. However, the inhibitory receptor is commonly upregulated after T-cell activation. The B7 family of membrane-bound ligands is particularly important in that bind they bind to both co-stimulatory and inhibitory receptors. Tumor necrosis factor (TNF) family members, on the other hand, bind to cognate TNF receptor family molecules and deliver primarily co-stimulatory signals. In addition to antigen presentation and co-stimulation, a third signal consisting of a variety of cytokines, such as interleukin-12 (IL-12) or type I interferon (IFN), is required to avoid T-cell tolerance or death. Antigen presentation via MHC is insufficient without all three signals and will result in T-cell tolerance (anergy). Communication between T cells and APCs is bidirectional. In some cases, this occurs when ligands themselves signal to the APC. In other cases, activated T cells upregulate ligands, such as CD40L, that engage cognate receptors on APCs. *A2aR,* adenosine A2a receptor; *B7RP1,* B7-related protein 1; *BTLA,* B and T lymphocyte attenuator; *GAL9,* galectin 9; *HVEM,* herpesvirus entry mediator; *ICOS,* inducible T-cell co-stimulator; *IL,* interleukin; *KIR,* killer cell immunoglobulin-like receptor; *LAG3,* lymphocyte activation gene 3; *PD1,* programmed cell death protein 1; *PDL,* PD-1 ligand; *TGFβ,* transforming growth factor–beta; *TIM3,* T-cell membrane protein 3. (Adapted from Pardoll D. The blockade of immune checkpoints in cancer immunotherapy. *Nature Rev Cancer* 12:252, 2012.)

a variety of cytokines, such as IL-12 or type I IFN, is required to avoid T-cell tolerance or death.[46] Antigen presentation via MHC is insufficient without all three signals and will result in T-cell tolerance (anergy). Once activated, effector T cells can be modulated by positive co-stimulatory signals, via receptors such as OX40 or 4-1BB, or negative co-inhibitory signals, such as cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1), which bind to their cognate ligand and can traffic back to the tumor, where they can cause the destruction of antigen-bearing tumor cells (Fig. 15.4).

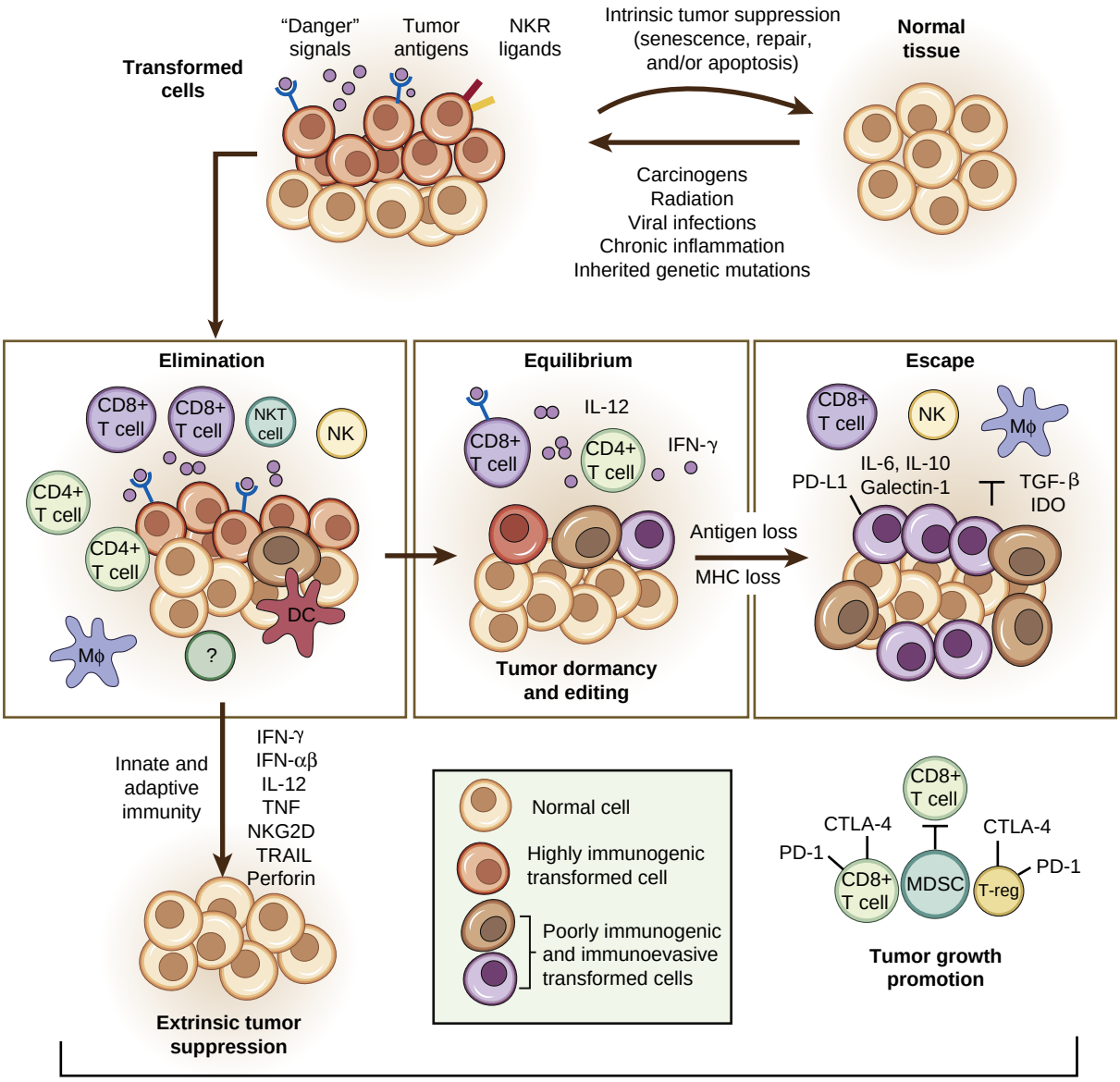
Additional factors may prime the immune response. Janeway predicted the existence of microbial pathogens that bear repetitive structures different from the host, which he termed "pattern recognition receptors".[43] Matzinger[46] later suggested the presence of "danger signals" (danger-associated molecular patterns [DAMPs]), which can be released from dying cells, possibly resulting from T-mediated cytotoxicity or even from therapeutic intervention, such as chemotherapy or radiation. A number of proteins released from necrotic cells, including heat-shock proteins, have been shown to prime APCs, such as macrophages.

Immunoediting

Building on Burnet's immunosurveillance theory, Schreiber suggested an "immunoediting" theory to describe how the immune system works to prevent cancer growth and development in the human body[47] (Fig. 15.5). There are three phases of immunoediting, which have been described as the "3 Es": elimination, equilibrium, and escape. Elimination involves the initiation of an immune response to tumor growth and the release of cytokines, such as IFNγ, and chemokines, which contribute to T cell–mediated tumor destruction, followed by the adaptive, antigen-specific immune response. As described earlier, once activated by the DC–MHC–antigen complex, effector T cells are trafficked to the tumor and cause the destruction of antigen-bearing tumor cells anywhere in the body. It should be noted that presentation of antigens by DCs in the absence of a maturation signal promotes tolerance and the development of regulatory T cells (T-reg). T-reg upregulates immunosuppressive molecules in HNSCC and other tumors, which inhibit an anti-tumor response. Tumor cells that survive the elimination phase enter the equilibrium phase, which is characterized by a lymphocyte-mediated response to rapidly



• **Fig. 15.4** Anti-tumor immunity. Anti-tumor immune responses are initiated via the capture of antigens by antigen-presenting cells, such as dendritic cells (DCs). The DCs process the captured antigen for presentation or cross-presentation on major histocompatibility complex (MHC) class II and class I molecules, respectively, and migrate to draining lymph nodes. DCs will ignite an anti-cancer effector T-cell response within the lymph node if capture and presentation occurred in the presence of signals 2 and 3; however, in the absence of a maturation stimulus, DCs will instead induce tolerance leading to T-cell anergy or the production of regulatory T cells (T-reg). Antigen presentation to T cells in the lymph node will elicit a response depending on the type of co-stimulatory or co-inhibitory signal generated. Thus the interaction of CD28 or OX40 with CD80/86 or OX40L will promote potentially protective T-cell responses, whereas interaction of cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) with CD80/86 or programmed cell death protein 1 (PD-1) with PD-L1/PD-L2 will suppress T-cell responses, and possibly promote T-reg formation. Antigen-educated T cells (along with B cells and natural killer [NK] cells) will exit the lymph node and enter the tumor bed, where immunosuppressive mechanisms can be produced by tumors (or infiltrating myeloid cells) that oppose effector T-cell function and contribute to immune escape. These include the upregulation of PD-L1/L2 on the cancer cell surface and other factors that limit T-cell infiltration into the tumor bed. (Adapted from Mellman I, Coukos G, Dranoff G. Cancer immunotherapy comes of age. *Nature.* 480:480–488, 2011.)



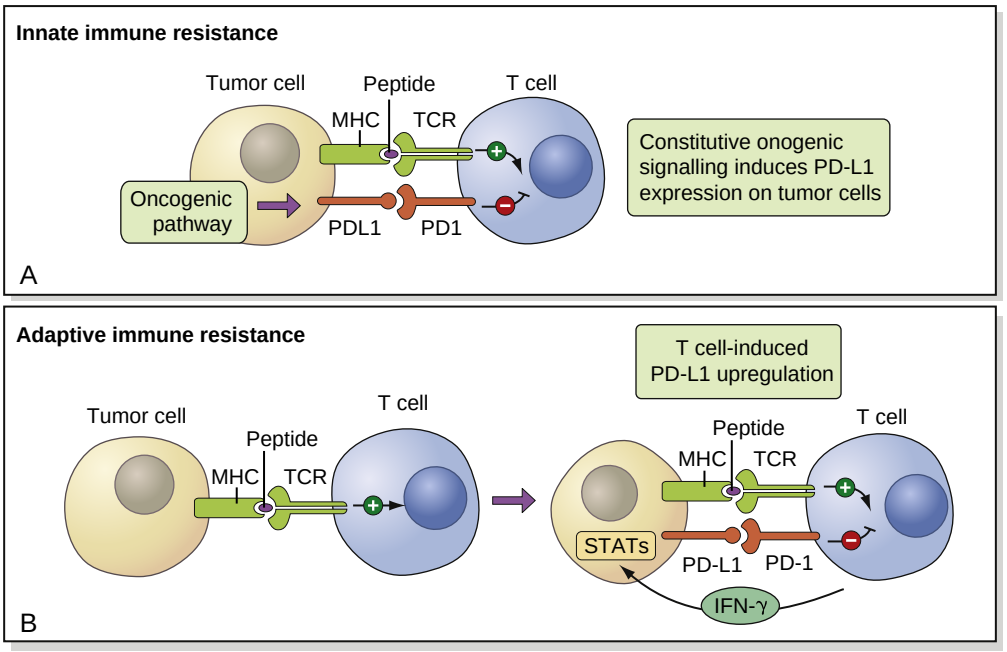
• **Fig. 15.5** The cancer immunoediting concept. Cancer immunoediting consists of three potential phases: elimination, equilibrium, and escape. In the elimination phase, the innate and adaptive immune systems destroy developing malignancies before they become clinically apparent. Ideally, all tumor cells are eliminated in this phase and the host remains free of cancer, in which case the process is complete. However, if tumor cells are allowed to remain, the host then enters the equilibrium phase, in which tumor progression is kept in check by immunologic mechanisms, and subclinical disease remains stable. Equilibrium is a function of adaptive immunity only. It is possible that the cancer immunoediting process may prevent clinical progression for the lifetime of the host and is the terminal process. Over time, however, some tumors develop "escape mechanisms," such that cancer cells are no longer recognized by the adaptive immune system owing to antigen loss or defects in antigen processing machinery, insensitivity to immune effector mechanisms, or the induction of immunosuppressive mechanisms within the tumor microenvironment, such as PD-L1. These cancer cells then proliferate, causing clinically significant disease, with the ability to metastasize and kill the host. *CTLA-4,* cytotoxic T-lymphocyte–associated antigen 4; *DC,* dendritic cell; *IDO,* indoleamine 2,3-dioxygenase; *IFN,* interferon; *IL,* interleukin; *MHC,* major histocompatibility complex; *NK,* natural killer; *NKT,* natural killer T cell; *PD-1,* programmed cell death 1; *PD-L1,* programmed cell death ligand 1; *TGF,* transforming growth factor–beta; *T-reg,* T-regulatory cells. (From Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science* 331:1565–1570, 2011.)

mutating cells. Tumor cells that resist elimination then enter the escape phase, which is characterized by tumor cell proliferation and metastasis.

Immunosuppression in Head and Neck Squamous Cell Carcinoma

Why does a patient with large numbers of T cells in his or her tumor and a high proportion of T cells recognizing the tumor appear in the clinic with symptomatic advanced malignancy? One of the ways cancer cells escape immune surveillance and facilitate tumor growth is through complex immunosuppressive mechanisms that usually play a role in control of normal antibacterial and antiviral immune responses and prevent overly exuberant immune responses and associated immunopathologies. For example, strongly or chronically activated T cells upregulate PD-1, and most cells will express its ligand PD-L1 following exposure to T cell–derived IFNγ. Thus, in a process known as "adaptive immune resistance", an anti-tumor T-cell response will result in PD-L1/PD-1–mediated suppression of activated $CD8^+$ T cells[48] (Fig. 15.6). Like other tumors, HNSCCs also can release suppressive factors that impair DC and T-cell function, thus limiting effective anti-tumor immunity.[49]

One of the major cellular components within the tumor microenvironment (TME) is T-reg, which are defined by co-expression of CD4, FoxP3, and CD25. High numbers of T-reg in TILs have correlated with poor survival in a number of reports.[50–52] HNSCC-derived suppressive factors can condition T cells and myeloid cells to adopt suppressive features, converting them to T-reg and myeloid-derived suppressor cells (MDSCs), respectively.[53] T-reg in the TME express immune checkpoint receptors, such as CTLA-4, T-cell membrane protein–3 TIM-3, and PD-1, as well as immunosuppressive molecules, such as CD39 and transforming growth factor–beta 1 (TGF-β1), which contribute to an IL-10– and TGF-β–induced functionally anergic state within T-cells.[54] Furthermore, MDSCs in TME produce inflammatory mediators such as IL-1, IL-6, inducible nitric oxide synthase (iNOS) and reactive oxygen species (ROS), which impair APC maturation and contribute to the suppression of activated immune effector cells.[53] Chikamatsu and colleagues[55] reported elevated numbers of $CD14^+$ HLA-DR-MDSCs in the blood of HNSCC patients and showed that they suppress T-cell effects through PD-L1 and the release of TGF-β. In a recent publication, MDSCs isolated from blood, lymph nodes, and tumors from patients with HNSCC were shown to suppress T-cell responses through arginase-1 activity.[56] Signal transducer and activator of transcription 3 (STAT3) inhibition decreased this arginase-dependent suppression, and STAT3 activation has also been implicated in functional inhibition of DCs and thus antigen presentation. Collectively, these and other suppressive events exerted by HNSCC can ultimately inhibit the development of an effective anti-tumor T-cell response.



• **Fig. 15.6** Immunosuppression in the tumor microenvironment. **A,** Innate immune resistance. In some tumors, constitutive oncogenic signaling can upregulate PD-L1 expression on all tumor cells, independently of inflammatory signals in the tumor microenvironment. Activation of the AKT and signal transducer and activator of transcription 3 (STAT3) pathways has been reported to drive PD-L1 expression. **B,** Adaptive immune resistance. In some tumors, PD-L1 is not constitutively expressed, but rather it is induced in response to inflammatory signals that are produced by an active anti-tumor immune response. The non-uniform expression of PD-L1 which is commonly restricted to regions of the tumor that have tumor-infiltrating lymphocytes, suggests that PD-L1 is adaptively induced as a consequence of immune responses within the tumor microenvironment. Adaptive induction may be a common mechanism for the expression of multiple immune-checkpoint molecules in tumors. *IFNγ,* interferon-γ; *MHC,* major histocompatibility complex; *PD-1,* programmed cell death 1; *PD-L1,* programmed cell death ligand 1; *TCR,* T cell receptor. From Pardoll D. The blockade of immune checkpoints in cancer immunotherapy. *Nature Rev Cancer* 12:252, 2012.

The Prognostic Significance of Tumor-Infiltrating Lymphocytes

It has long been observed that some HNSCCs generate a robust inflammatory cell infiltrate within the tumor, and others do not. Recently, a method of characterizing the type, number, and location of TILs using standard immunohistochemistry (IHC), digital imaging, and computer algorithms—termed the "immunoscore"—has been shown to be significantly ($P < .001$) more prognostic than American Joint Committee on Cancer (AJCC) TNM staging in patients with colon cancer.[57,58] Furthermore, these studies demonstrate that patients with a high immunoscore have increased disease-free and overall survival compared with patients with low immunoscore. This potential new prognostic biomarker is based primarily on the density of cytotoxic (CD8) and memory (CD45R0) T cells (CD3/CD45R0, CD3/CD8, or CD8/CD45R0) located at the tumor's center and at its invasive margin. Although the immunoscore has not yet been prospectively evaluated in HNSCC, evidence that TILs may be prognostic has been shown by several investigators who demonstrated that high frequencies of activated ($CD8^+$) effector T cells correlate with improved survival independent of stage.[50–52] In fact, Ward and colleagues[52] were able to stratify HPV-positive patients into high-risk and low-risk groups based on TILs and developed a prognostic model for HPV-related tumors that incorporated TIL scoring, heavy smoking, and T stage. It has been hypothesized that increased numbers of TILs and the improved prognosis of patients with HPV-related HNSCC may be related to E6/E7-specific T-cell responses against viral epitopes.[49]

In addition to absolute numbers of $CD8^+$ T cells, some investigators have shown that expression of chemokine receptors (CCR7) might protect cells from apoptosis.[54] Elevated levels of apoptosis-sensitive $CD8^+CCR7^-$ effector T cells in the blood and TILs and decreased levels of $CD8^+CCR7^+$ central memory T cells have been shown to be negative prognostic factors in patients with HNSCC.[54] In addition, it has been suggested that the frequency of $CD8^+CCR7^+$ T cells in the circulation[55] and TILs[56] may serve as a surrogate marker for disease recurrence and appears to affect survival favorably in patients with cancer.

More recently, investigators at our institute have demonstrated that it is not just the number of $CD8^+$ effector T cells that is important, but that the ratio of T-cell subsets and their relationship to other cells in the TME may be even more discriminating than the frequency of $CD8^+$ cells alone.[59] Furthermore, a transcriptional signature in HNSCC consistent with a T-cell response has also been correlated with prolonged survival.[60] Gene expression profiles performed at our institution on a cohort of HNSCC tumors showed that a lower number of immune response–related transcripts was associated with recurrence, and analysis of this discovery cohort by hierarchical clustering indicated that the immune infiltrates in HNSCC may prove prognostic.[61] Although these findings await validation in a larger cohort of patients, these data support the hypothesis that HNSCC lacking a T-cell infiltrate or a transcriptional signature driving a T-cell response may benefit from immune interventions that augment adaptive immunity and increase the number of TILs within the TME.

Immunotherapy

History

William Coley (1862–1936), a New York surgeon, is credited with being the father of immunotherapy and was the first to seriously investigate and write about the association between infection and cancer remissions (Fig. 15.7). Coley became interested in the connection between immunity and oncology after one of his patients was apparently cured of cancer after two attacks of erysipelas, caused by an acute infection with the bacteria *Streptococcus pyogenes.* After this, Coley began injecting bacterial cultures obtained from Robert Koch into cancer patients in his surgical practice, observing tumor regression in some cases and publishing his initial findings in 1893.[62]

Coley subsequently embarked on a lifetime of exploration, during which he treated almost 900 cancer patients with a bacterial preparation that became known as *Coley's toxin.* Even though the majority of patients treated had inoperable sarcomas, the bacterial toxin reportedly achieved a cure rate of over 10%.[63]

In 1909 the Nobel laureate, Paul Ehrlich, offered his considerable weight to the field when he suggested that cancers may occur at an "overwhelming frequency" if it were not for the immune system.[64] Unfortunately (for immunologists), Coley's successes could not be reliably reproduced and one of his early patrons, John D. Rockefeller, Jr., began to support the burgeoning field of radiotherapy instead. Despite the occasional successes of "Coley's toxin," and possibly in part because of the enthusiasm surrounding radiation therapy, immunotherapy was not widely accepted by the scientific and clinical communities and few, if any, advancements were made in the field until the middle of the 20th century. Patients would have to wait for the science of immunology to catch up.



• **Fig. 15.7** **A,** William Coley (1862–1936), a New York surgeon, is credited with being the father of immunotherapy. **B,** Signor Zola, Coley's first clinical trial subject. On May 3, 1891, Coley initiated the American era of cancer immunotherapy by treating Zola's head and neck sarcoma. Zola was treated with cultures of erysipelas as an outpatient and achieved remission for more than 2 years. (Source: Cancer Research Institute.)

As reviewed earlier, the field of immunotherapy was relatively silent in the 50 years after Coley's pioneering observations. However, in 1976 a successful trial was conducted to assess the use of the attenuated tuberculosis vaccine bacillus Calmette-Guérin (BCG) as a means of preventing the recurrence of non–muscle-invasive bladder cancer.[65] BCG remains in clinical use today and was the first of the modern cancer immunotherapies.

Also in 1976, the T-cell growth factor IL-2 was identified.[66] High-dose IL-2 enhanced T-cell production and was shown to be effective when administered to patients with metastatic cancers.[67] The use of IL-2 as a cancer immunotherapy gained FDA approval for use in metastatic kidney cancer in 1991 and for treatment of metastatic melanoma in 1998.

A watershed for the field of immunotherapy occurred at around the same time, with the work of Cesar Milstein and George Köhler, who pioneered the production of monoclonal antibodies.[68] They used antibody-secreting cell lines formed by the fusion of lymphocytes with myeloma cell lines called *hybridomas.*[6] This research on antibody-based therapies eventually led to the development of rituximab, which binds to CD20 on the surface of immature B cells and targets them for elimination by NK cells.[69] In 1997, rituximab became the first monoclonal antibody to be approved by the FDA for the treatment of a cancer (non-Hodgkin lymphoma).

Throughout the 1990s, numerous investigators attempted to capitalize on the demonstration of an antigen-specific T-cell response to a melanoma-associated antigen in a human by investigating the use of therapeutic vaccines.[70] However, it was not until 2010 that the FDA approved the first cancer vaccine, sipuleucel-T, a DC vaccine, for castration-resistant prostate cancer. Although the vaccine had no effect on the time to disease progression, it was able to extend overall survival.[71]

During this time, the American surgeon Steven A. Rosenberg, chief of the Surgery Branch of the National Cancer Institute (NCI-SB), pioneered the use of IL-2 combined with autogenous TILs for the treatment of patients with melanoma and other cancers in a procedure termed *adoptive cell therapy* (ACT).[72] ACT with TILs that are selectively expanded in IL-2 in vitro and re-infused following a lymphodepleting regimen has demonstrated response rates (RRs) of 50% in melanoma, including durable complete responses in 12–20% of patients, and is a promising modality for several other cancers.[73]

Recently, ex vivo antibodies targeting proteins expressed on tumor cells and the immune cells of the tumor have been developed for the treatment of cancer and are part of an exciting new class of agents poised to have a profound effect on treatment outcome for patients with solid cancers, including HNSCC. Therapeutic antibodies activate or block specific signaling pathways to modify the behavior of cancer cells (e.g., epidermal growth factor receptor [EGFR]) or T cells (e.g., PD-1, CTLA-4). James Allison and colleagues in 1996 first described that CTLA-4 blockade in mice enhanced anti-tumor immunity.[74] The following year, Leiping Chen's group showed that an immune-stimulating agonist to the TNF receptor, 4-1BB, had potent therapeutic responses in tumor-bearing mice.[75] In 2000, a scientist at our institute, Andrew Weinberg, and his group showed that enhancing T-cell function in tumor-bearing hosts led to therapeutic efficacy through OX40 agonist injections.[76] Checkpoint inhibitors, such as anti–CTLA-4 and anti–PD-1, are resulting in objective clinical responses or durable stable disease in patients with a wide spectrum of cancers.[9–17,77] Co-stimulatory agents, such as anti-OX40 and 41-BB, are in early-phase clinical trials. Collectively, the success of immunotherapy has lead to multiple FDA approvals for numerous indications and has catapulted the status of this modality into standard of care for patients with metastatic melanoma, non–small cell lung cancer (NSCLC), renal cell carcinoma, and most recently HNSCC, truly making it the "fourth modality" of cancer treatment.[78]

Immunotherapy for Head and Neck Cancer

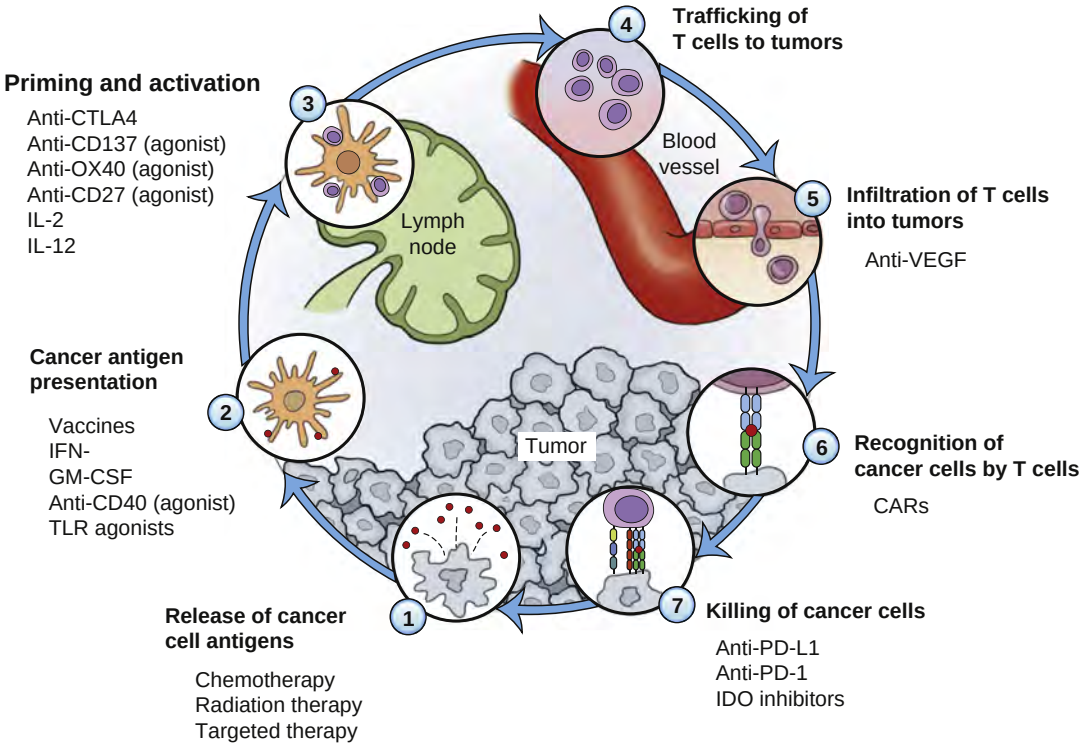
Improved understanding of the tumor microenvironment suggests that there are at least six therapeutic approaches to enhanced anti-tumor immunity: (1) release of cancer cell antigens through conventional cancer therapy; (2) enhancement of cancer antigen presentation with vaccines, IFNα, granulocyte-macrophage colony-stimulating factor (GM-CSF), anti-CD40 agonists, or TLR agonists; (3) priming of T-cell activation in the lymph nodes with anti–CTLA-4, co-stimulatory agonists, or ILs such as IL-2 or IL-12; (4) enhancement of T-cell trafficking to tumors with chemokines; (5) enhancement of T-cell infiltration into tumors with anti–vascular endothelial growth factor (VEGF); (6) enhancement of recognition of cancer cells with adoptive T-cell transfer; and (7) enhancement of cytotoxicity by overcoming immunosuppression within the tumor microenvironment with checkpoint inhibitors such as anti–PD-1[79] (Fig. 15.8).

To achieve these goals, two types of immunotherapy approaches have been described, termed *passive* and *active.* Passive immunotherapy involves the administration of therapeutic antibodies or patient-specific T cells (adoptive cell transfer) in an effort to boost immune-related tumor cell killing. Active immunotherapy is characterized by vaccine strategies, the administration of cytokines, or other immune therapies that activate the patient's existing immune cells to destroy cancer cells.

Passive Immunotherapy

Checkpoint Inhibitors

T-cell Receptors. As noted earlier, the activation of $CD8^+$ cytotoxic T cells is a multistep process. The first step (signal 1) is the engagement of the antigen to T-cell receptors (TCRs) via major histocompatibility complex I (MHCI).[80] T-cell activation is dependent on signal 2, or the binding of CD80/CD86 from APCs to the co-stimulatory receptor CD28.[80] After receiving both signal 1 and signal 2, the proliferation of T cells requires signal 3, or the local cytokine milieu.[81] Cytokines such as IL-12 and IL-2 can strongly support T-cell polarization and proliferation, leading to rapid expansion of these antigen-specific T cells, which are the basis for an anti-tumor immune response.[81,82]



• **Fig. 15.8** Therapeutic approaches to enhance immunity. *CARs,* chimeric antigen receptor; *CTLA4,* cytotoxic T-lymphocyte–associated antigen 4; *GM-CSF,* granulocyte-macrophage colony-stimulating factor; *IDO,* indoleamine 2,3-dioxygenase; *IFN α,* interferon-α; *IL,* interleukin; *PD-1,* programmed cell death 1; *PD-L1,* programmed cell death ligand 1; *TLR,* Toll-like receptor; *VEGF,* vascular endothelial growth factor. (Adapted from Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. *Immunity* 39[1]:1–10, 2013.)

The immune response is tightly regulated. There are multiple immune checkpoints, or receptors, that serve to dampen an overactive immune response to restore homeostasis.[44] These checkpoints are critical in the prevention of autoimmune diseases; however, in the case of tumor immunotherapy, they are used by tumor cells to resist immune-mediated killing.[44]

Checkpoint blockade antibodies are at the forefront of immunotherapy; blocking these immune checkpoints with antibodies results in restoration of T-cell function and a heightened anti-tumor response. The efficacy of these antibodies, especially in combination, across a variety of cancer types is unprecedented. Although most of the excitement has been focused on anti–CTLA-4, anti–PD-1, and anti–PD-L1, other novel checkpoint blockade inhibitors and co-stimulatory agonists are also being tested in both preclinical and clinical settings for HNSCC[119] (Table 15.1).

Anti–Cytotoxic T-lymphocyte–Associated Protein 4 (Anti–CTLA-4). CTLA-4 is a CD28 homologue expressed on the surface of T lymphocytes.[80] CTLA-4 is expressed transiently on the surface of early activated CD8 T cells; however, its expression is constitutive on T-reg.[83] The inhibition of CD8 T cells by CTLA-4 is twofold: engagement of co-stimulatory molecules (1) CD80 and (2) CD86 to CTLA-4 on CD8 T cells, which results in the dephosphorylation of TCR signaling proteins such as CD3, leading to T-cell inhibition.[84] In addition, CTLA-4 has higher affinity for CD80/CD86 than CD28.[85] This effectively reduces the availability of signal 2 required for the activation of CD8 T cells, a process that eventually leads to T-cell anergy.[85] Blocking antibodies to CTLA-4 results in significant improvement in preclinical models.[75,86] Ipilimumab (anti–CTLA-4) was approved for the treatment of metastatic melanoma in 2011 based on a randomized phase III study demonstrating superior efficacy when compared with vaccine alone (gp100 peptide vaccine).[9] The mechanism of action of anti–CTLA-4 is currently under investigation (Fig. 15.9). Several groups have indicated that anti–CTLA-4 can induce priming of new T-cell responses and deplete T-reg in a macrophage-dependent mechanism.[87] The efficacy of anti–CTLA-4 in head and neck cancer is currently being tested in combination with radiation (NCT01935921).

Anti–Programmed Cell Death Protein 1 (Anti–PD-1). PD-1 is another inhibitory receptor expressed on T-cell activation (Fig. 15.10).[88] Similar to CTLA-4, binding of PD-1 to its ligand PD-L1 induces dephosphorylation of CD3 resulting in T-cell anergy and exhaustion.[89,90] The blocking antibody to PD-1 has demonstrated restoration of CD8 T-cell function and has augmented anti-tumor activity in numerous preclinical models[91–95] and significantly improved survival in patients with melanoma, RCC, and NSCLC.[96–100] For some patients, the RR can be further increased when blocking antibodies to PD-1 are used in combination with an anti–CTLA-4 agent.[101]

TABLE 15.1 Current Immunotherapy Trials Open for Head and Neck Cancer

Agent	Tumor Site	Status/Setting	Combination Agent	Current Trial
Pembrolizumab	Solid tumors	Phase III/recurrent/metastatic	None	NCT02358031
Pembrolizumab	Solid tumors	Phase III/recurrent/metastatic	None	NCT02252042
Pembrolizumab	Solid tumors	Phase II/advanced	ACP-196	NCT02454179
Pembrolizumab	HNSCC	Phase II/recurrent/unresectable	Reirradiation	NCT02289209
Pembrolizumab	Solid tumors	Phase I/II advanced	None	NCT02318901
Pembrolizumab	Solid tumors	Phase I/II recurrent/metastatic	Vorinostat	NCT02538510
Pembrolizumab	Solid tumors	Phase I/II advanced	PLX3397	NCT02452424
Pembrolizumab	HNSCC	Phase I/stage III, IVA or IVB	Cisplatin + radiation	NCT02586207
Pembrolizumab	Solid tumors	Phase I/advanced	INCB039110/050465	NCT02646748
Pembrolizumab	Epithelial cancer	Phase I/advanced/metastatic	Enadenotucirev	NCT02636036
Pembrolizumab	Solid tumors	Phase I/refractory	MGA217	NCT02475213
Pembrolizumab	Solid tumors	Phase I/recurrent/metastatic	Radiation therapy	NCT02318771
Pembrolizumab	HNSCC	Phase I/II/recurrent/metastatic	Docetaxel	NCT02718820
Durvalumab	HNSCC	Phase III/recurrent/metastatic	± Tremelimumab	NCT02551159
Durvalumab	HNSCC	Phase III/recurrent/metastatic	± Tremelimumab	NCT02369874
Durvalumab	HNSCC	Phase II/recurrent/metastatic	Tremelimumab	NCT02319044
Durvalumab	Solid tumors	Phase I/II/advanced	Epacadostat	NCT02318277
Durvalumab	HNSCC	Phase I/II/relapsed/metastatic	AZD9150/ AZD5069	NCT02499328
Durvalumab	Solid tumors	Phase I/advanced	Selumetinib	NCT02586987
Durvalumab	HNSCC	Phase I/recurrent/metastatic	Tremelimumab	NCT02262741
Nivolumab	HNSCC	Phase II/metastatic	SBRT	NCT02684253
Nivolumab	Solid tumors	Phase I/II/advanced	Varlilumab	NCT02335918
Nivolumab	Solid tumors	Phase I/II/advanced	Epacadostat	NCT02327078
Nivolumab	Solid tumors	Phase I/advanced	FPA008	NCT02526017
Nivolumab*	HNSCC	Phase I/locally advanced	Chemotherapy	NCT02764593
Monalizumab	HNSCC	Phase I/II/head and neck	None	NCT02643550
Atezolizumab	Solid tumors	Phase I/II/advanced	Varlilumab	NCT02543645
PF-06801591	HNSCC	Phase I/advanced	None	NCT02573259
PF-04518600	Solid tumors	Phase I/advanced/metastatic	± PF-05082566	NCT02315066
Avelumab	Solid tumors	Phase I/advanced/metastatic	PF-05082566	NCT02554812
Ipilimumab	HNSCC	Phase I/advanced	None	NCT01860430
Ipilimumab	HNSCC	Phase I/locally advanced	Cetuximab/radiation	NCT01935921
Ipilimumab	Solid tumors	Phase I/refractory	MGA217	NCT02381314
MGA217	Solid tumors	Phase I/refractory	None	NCT01391143
MGD009	Solid tumors	Phase I/unresectable/metastatic	None	NCT02628535
AMG 228 GITR Ab	Solid tumors	Phase I/advanced	None	NCT02437916
CPI-444	Solid tumors	Phase I/advanced	± Atezolizumab	NCT02655822
Interleukin-15	Solid tumors	Phase I/metastatic	None	NCT02452268
Poly-ICLC	Solid tumors	Phase II/advanced	None	NCT02423863
TIL HPV-16	HPV (+) tumors	Phase II/recurrent	T cells recognize	NCT02280811

TABLE 15.1 Current Immunotherapy Trials Open for Head and Neck Cancer—cont'd

Agent	Tumor Site	Status/Setting	Combination Agent	Current Trial
TIL	HPV (+) tumors	Phase II/metastatic	Fludarabine	NCT01585428
CAR T cell	HNSCC	Phase I/recurrent,+/-metastases	None	NCT01818323
T cell, TBI-1301	Solid tumors	Phase I/unresectable	None	NCT02366546
T cells HPV-16, 18	HPV (+) tumors	Phase I/recurrent	None	NCT02379520
TAA-specific CTLs	Solid tumors	Phase I/refractory	None	NCT02239861
MM-151, EGFR Ab	Heregulin (+) Ca	Phase I/advanced	MM-121	NCT02538627
Ficlatuzumab	HNSCC	Phase I/recurrent/metastatic	None	NCT02277197
CPI-444	Solid tumors	Phase I/advanced	± Atezolizumab	NCT02655822
AlloVax*	HNSCC	Phase II/recurrent/metastatic	None	NCT02624999
PDE5 inhibitor	HNSCC	Phase II/advanced, not metastatic	None	NCT01697800
TBI-1201	Solid tumors	Phase I/unresectable	None	NCT02096614
EBV CD8 T cells	NPC EBV (+)	Phase III/recurrent/metastatic	Gemcitabine Carboplatin	NCT02578641
EBV T cells	NPC	Phase I/unresectable/metastatic	None	NCT00431210
RM-1929	HNSCC	Phase I/recurrent/unresectable	Photoimmunotherapy	NCT02422979
ALT-803	Solid tumors	Phase I/advanced	None	NCT01946789
Autologous TIL IL-2	Solid tumors	Phase I/advanced/metastatic	None	NCT01462903
TIL	NPC EBV (+)	Phase II/advanced	Chemoradiation	NCT02421640
VicOryx-2 Vaccine	HPV (+) tumors	Phase I/advanced	Cisplatin	NCT02526316

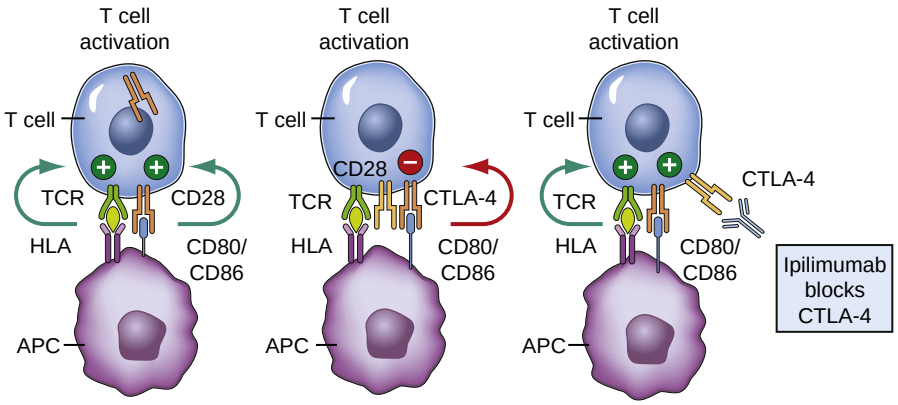
HNSCC, head and neck squamous cell carcinoma; *HPV (+),* human papillomavirus positive; *HPV (–),* human papillomavirus negative; *NPC EBV (+),* nasopharyngeal carcinoma Epstein-Barr virus positive; TIL, tumor-infiltrating lymphocyte.
*Active, not yet recruiting.

Two checkpoint inhibitors that target PD-1 have recently been tested in HNSCC, and the results are creating a new standard of care. A phase III trial (CheckMate 141) comparing the anti–PD-1 antibody nivolumab versus standard of care for metastatic HNSCC was halted early because the survival end-points were met.[77] The interim results demonstrated improved survival in patients with HNSCC who progressed within 6 months of platinum therapy as part of first-line treatment for R/M disease. Nivolumab reduced the risk of death by 30% compared with investigator's choice standard chemotherapy and doubled the 1-year overall survival, which was 36% in the nivolumab arm versus 16.6% in the control arm. Median survival was 7.5 months for nivolumab and 5.1 months for patients assigned to investigator's choice of chemotherapy. In a related study, Seiwert and colleagues[113] published the results from the phase I KEYNOTE-012 trial of the anti–PD-1 antibody pembrolizumab in patients with R/M HNSCC, which demonstrated an overall response rate (ORR) of 18% (25% in HPV-positive patients; 14% in HPV-negative patients). These encouraging results led to FDA approval in 2016 for pembrolizumab and nivolumab in second-line treatment of metastatic HNSCC.

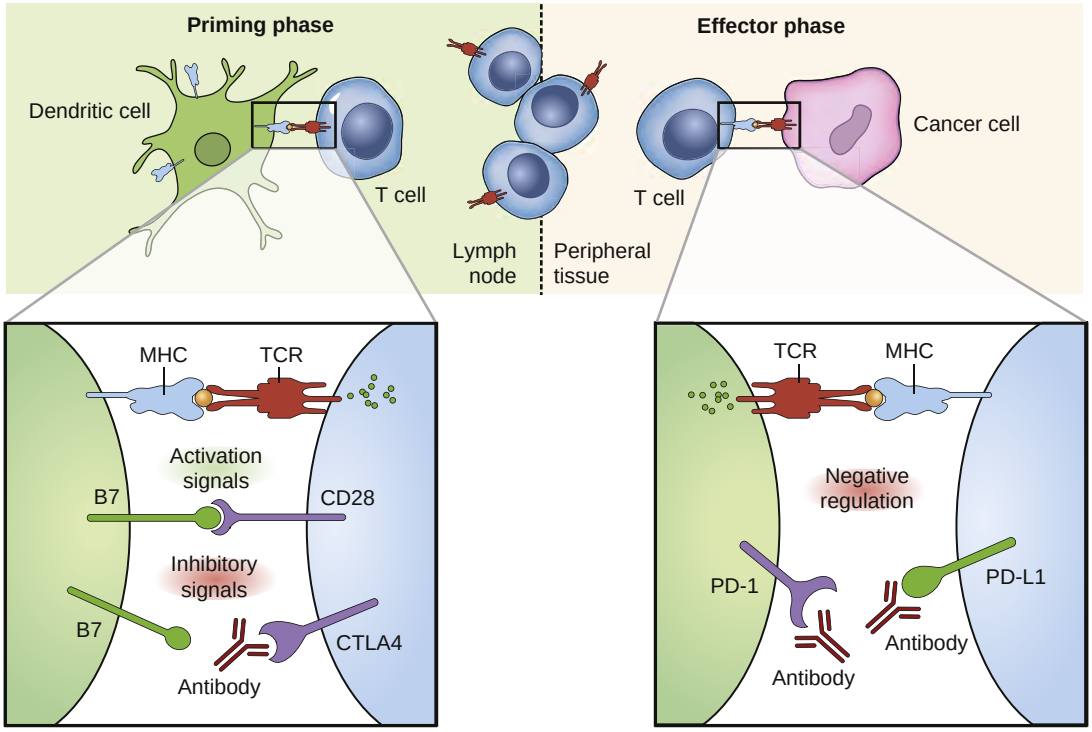
Recently, two studies were opened for accrual to investigate the safety and efficacy of nivolumab (NCT02488759) or pembrolizumab (NCT02296684) in the preoperative setting to treat patients with HNSCC. These trials are recruiting both HPV-positive and HPV-negative individuals and not only will help determine the effects of PD-1 blockade in the TME of HNSCC, but also will inform the future of adjuvant therapy for patients with locoregionally advanced disease.

The adverse effects of anti–PD-1 are distinct from those of anti–CTLA-4, emphasizing the different mechanisms of influence of these agents on the immune system. Anti–PD-1 is expressed on activated T lymphocytes and is thought to play less of a role in priming of new T-cell responses.[102] Consequently, it is currently hypothesized that the efficacy of anti–PD-1 is limited to patients with a preexisting tumor-specific immune response.[103] At the moment, there are multiple trials testing the efficacy of anti–PD-1 in head and neck cancer as a single agent or in combination with radiation and other immunotherapies such as anti-killer-cell immunoglobulin–like receptor (KIR), an inhibitory receptor present on surface of NK cells.

Anti–Programmed Cell Death Receptor Ligand 1 (Anti–PD-L1). PD-L1 is the ligand for PD-1, and ligation of PD-L1 to PD-1 leads to T-cell inhibition.[102] PD-L1 is expressed in



• **Fig. 15.9** Anti–cytotoxic T-lymphocyte–associated protein 4 (anti–CTLA-4) (ipilimumab). Cytotoxic T-lymphocyte–associated protein 4 (CTLA-4) is a CD28 homologue expressed on the surface of T lymphocytes. CTLA-4 is expressed transiently on the surface of activated CD8 T cells. The inhibition of CD8 T cells by CTLA-4 occurs by engagement of co-stimulatory molecules CD80/CD86 to CTLA-4 on CD8 T cells, which results in the dephosphorylation of T-cell receptor (TCR) signaling proteins, leading to T-cell inhibition. Ipilimumab is an antibody that binds to CTLA-4 on the surface of CD8 T cells and blocks the inhibitory signal, thereby releasing the effector function of the T cell. *APC,* antigen-presenting cell; *HLA,* human leukocyte antigen.



• **Fig. 15.10** Programmed cell death receptor 1 (PD-1) is an inhibitory receptor expressed on T-cell activation. Similar to CTLA-4, binding of PD-1 to its ligand PD-L1 induces dephosphorylation of CD3, resulting in T-cell anergy and exhaustion. PD-L1 is expressed in a multitude of tissues including tumor cells, tumor-associated macrophages (TAMs), and T cells. The blocking antibody to PD-1 causes restoration of CD8 T-cell function and tumor cell killing. It is currently hypothesized that the efficacy of anti–PD-1 is limited to patients with a preexisting tumor-specific immune response (effector function), whereas anti-CTLA may help prime immunity. *MHC,* major histocompatibility complex; *TCR,* T-cell receptor. (Adapted from Ribas A. Tumor immunotherapy directed at PD-1. *N Engl J Med* 366:2517–2519, 2012.)

a multitude of tissues including muscles and nerves. Of relevance for cancer immunotherapy, PD-L1 can be expressed on the surface of tumor cells, tumor-associated macrophages (TAMs), and T lymphocytes and can subsequently inhibit PD-1–positive T cells.[103,104] The expression of PD-L1 can be induced by cytokines such as IFNs, or alternatively PD-L1 can be expressed autonomously through aberrations in the EGFR signaling pathway.[105–108]

In clinical studies, antibodies blocking the PD-L1 and PD-1 interactions have demonstrated 6–21% ORR in nonselected tumors,[109–110] 19% in triple-negative breast cancer,[111] and 38% in NSCLC demonstrating high PD-L1 expression.[112] Zandberg and colleagues[114] showed slightly less efficacy than the PD-1 inhibitors, with a preliminary ORR of 11%, 71% of which were durable at 55 weeks and somewhat dependent on PD-L1 expression. The toxicity profile for anti–PD-L1, like that of anti–PD-1, is thought to be distinct and generally milder compared with the adverse events observed with anti–CTLA-4.[110]

The mechanism of action of anti–PD-L1 is currently under investigation. However, several studies have shown that clinical benefit is directly correlated with high expression of PD-L1.[112]

Other Checkpoint Blockade Agents. A large number of immune checkpoint inhibitors have been discovered, and a significant portion of them are currently being tested in either a preclinical setting or directly in clinical trials for the treatment of cancer. Two examples that have moved into the clinical setting are anti–lymphocyte activation gene 3 (anti–LAG-3), targeting an inhibitory receptor on the surface of T cells, and anti-KIR, to reverse the inhibited NK cells. Trials involving anti–LAG-3 and anti-KIR are ongoing in the treatment of hematologic and advanced solid malignancies, including HNSCC.

Immune System Agonists (Co-stimulatory Molecules)

Co-stimulatory molecules, such as anti-OX40 and anti–4-1BB, cause T-cell proliferation, memory, cytotoxic effector function, and cytokine production. An agonist antibody that targets the TNF-receptor family member, 4-1BB, was shown by Melero and colleagues in preclinical mouse models to result in therapeutic responses.[75] A similar agonist antibody to OX40 was described in 2000 by Weinberg and colleagues,[76] who demonstrated therapeutic effects and enhanced T-cell function in numerous mouse models.

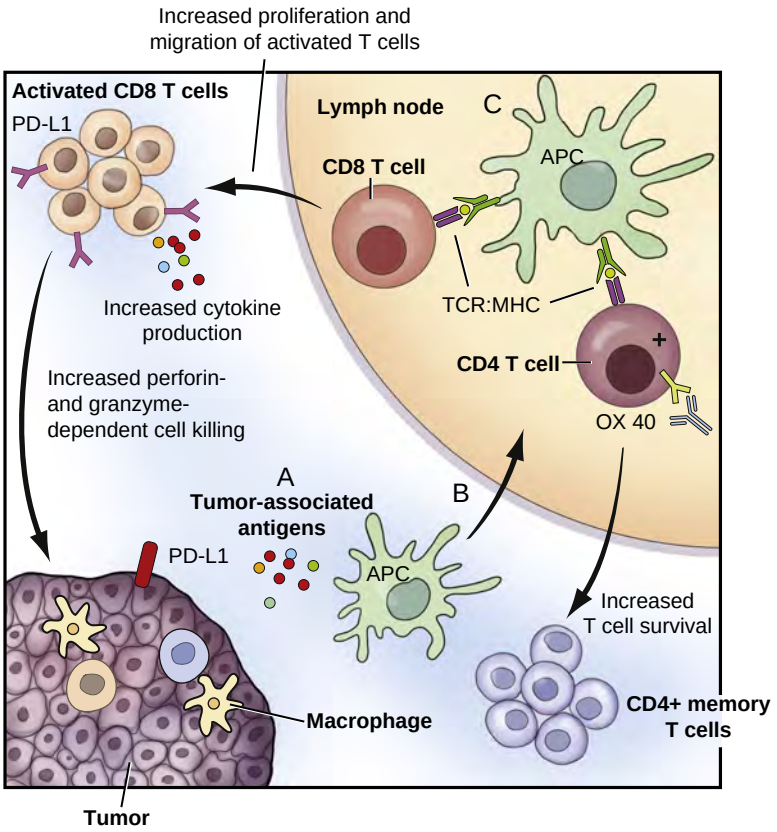
Anti-OX40. OX40 is a member of the tumor necrosis factor receptor (TNFR) superfamily and is present on the surface of T cells, in particular CD4 T cells and T-reg.[119,120] Activation of OX40 through an agonist antibody, either directly or indirectly, increases CD4 and CD8 T-cell priming, proliferation, and function (Fig. 15.11).[115] Interestingly, although OX40 activation in T-reg does not seem to affect their proliferation, their ability to inhibit the function of CD8 T cells appears to be hindered partly through the disruption of FoxP3 expression and inhibitory cytokine release.[116] This tips the effector-to-inhibitor balance in the tumor microenvironment and results in significant anti-tumor efficacy in many immunogenic preclinical models.[117] In poorly immunogenic models, combination with a vaccine appears to substantially improve therapeutic efficacy (unpublished data). Clinically, OX86, an agonist antibody to OX40, has demonstrated great safety in a phase I trial,[118] and the antibody is currently being tested as a single agent in the neoadjuvant setting for the treatment of patients with HNSCC (NCT02274155).

4-1BB. 4-1BB is another member of the TNFR superfamily expressed stably on activated T cells and NK cells.[121] Its activation by 4-1BB ligand (L) or by an agonist antibody on CD8 T cells results in increased proliferation, cytokine production, and survival.[122] 4-1BB activation also has a profound impact on the humoral immune system and CD4 T cells.[123] Studies in preclinical models of lupus demonstrated suppressed B-cell response and induction of CD4 T-cell anergy on 4-1BB stimulation.[124] In preclinical tumor models, in vivo administration of 4-1BB agonist antibody demonstrated enhanced anti-tumor activity in a CD8 T-cell–dependent manner,[125,126] and currently these agents are being tested in clinical trials for the treatment of solid and hematologic malignancies. 4-1BB agonists, either as a single agent or in combination with checkpoint blockade, are currently being proposed for the treatment of HNSCC, and new trials could open in the near future.

CD40. CD40 is another member of the TNFR superfamily that is mainly expressed on the surface of APCs. CD40 plays an important role in the licensing of APCs by T cells. Ligation of CD40 to CD40 ligand (L) or an agonist antibody leads to expression of MHCs and co-stimulatory molecules, secretion of proinflammatory cytokines (e.g., IL-12), and increased antigen-presenting capacity. This in turn facilitates the priming of CD4 and CD8 T cells, leading to the activation of NK cells and to enhanced anti-tumor immune response. CD40 agonist antibodies such as CP-870,893 (Pfizer) and dacetuzumab (Seattle Genetics, discontinued) demonstrated preclinical therapeutic efficacy in both solid and hematologic malignancies. Among solid tumors, CD40 agonist antibodies had been tested in the treatment of pancreatic cancer with an objective RR of approximately 20%. A preliminary study with combination CP-870,893 and tremelimumab (anti–CTLA-4; Pfizer) was performed, with an ORR at 27.3% and complete response (CR) at 9.1%.[127] The use of anti-CD40 in HNSCC has not yet been extensively explored.

Adoptive T-cell Therapy

Adoptive T-cell therapy (ACT) involves harvesting T cells from autologous tumor resection or biopsy, expanding them ex vivo with IL-2, testing for tumor specificity, and then rapidly expanding them for re-infusion into a non-myeloablative lymphodepleted patient (Fig. 15.12). The NCI-SB has pioneered novel T cell–based cancer therapies for chemotherapy-refractory cancers in multiple tumor types, including HNSCC. This work has its foundation in the successful treatment of metastatic melanoma with adoptive transfer of TILs. High-dose IL-2 is also administered to support the in vivo expansion of transferred T cells.[128,129] CD8 T cells often constitute the majority of the tumor-specific T cells in culture; other cells such as CD4 T cells, NK cells, and gamma delta T cells are also present in culture and have been shown to possess significant



• **Fig. 15.11** Anti-OX40 enhances anti-tumor immunity. Agonist antibodies or an OX40-ligand–immunoglobulin fusion protein *(not shown)* targeting OX40 can enhance CD4+ and CD8+ T-cell responses in both preclinical mouse models and in patients with solid tumors. The OX40-mediated response is attributed to enhanced effector T-cell function through increased cytokine production and increased survival of memory T cells. **A,** Tumor-associated antigens are released and captured by dendritic cells and are processed for presentation or cross-presentation on major histocompatibility complex *(MHC)* class II or I molecules, respectively. **B,** Dendritic cells migrate to the draining lymph nodes. **C,** In the presence of the required CD28:B7 signal and a co-stimulatory signal, such as OX40, dendritic cells will activate the T cells in the lymph nodes. **D,** Activated CD8+ cytotoxic T cells exit the lymph node and traffic to tumor, where they may exert their effector function, depending on the immunosuppressive defense mechanisms produced by the tumor, such as PD-L1. OX40 ligation also enhances the proliferation of CD4+ memory T cells. *APC,* antigen-presenting cell; *PD-1,* programmed cell death 1; *PD-L1,* programmed cell death ligand 1; *TCR,* T-cell receptor.

anti-tumor activity.[129] T-reg are also present in the culture, and depletion of them before re-infusion positively correlated with increased response to ACT.[130–132]

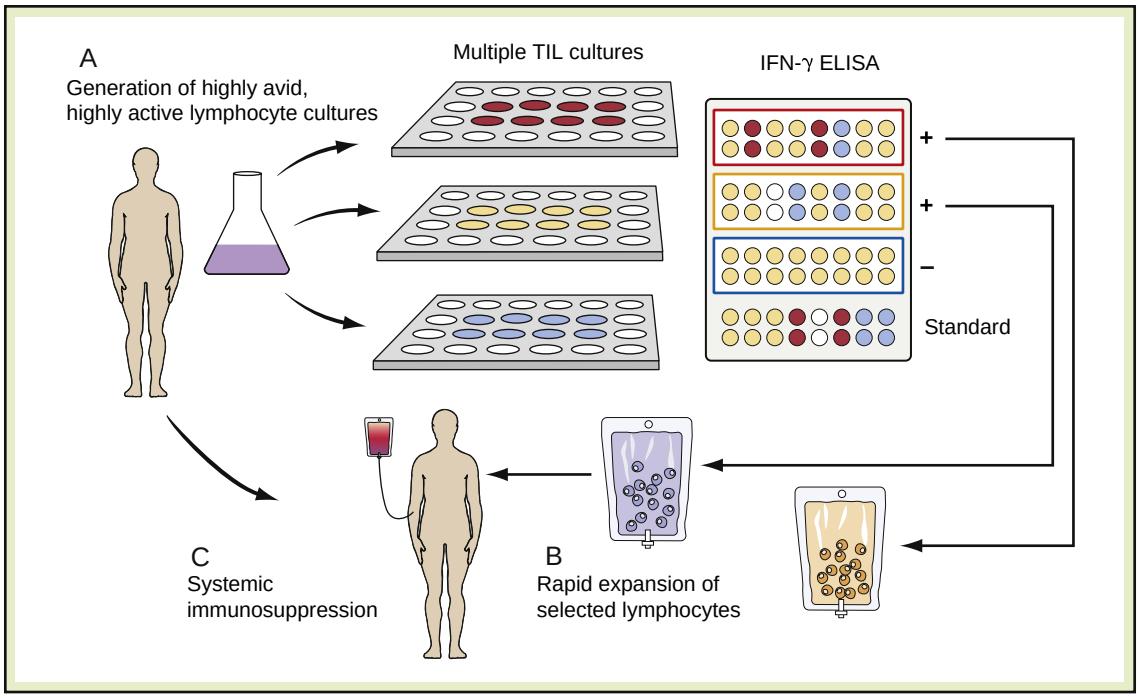
In a seminal publication in 2008, investigators at the NCI-SB reported the results of adoptive transfer therapy in 93 patients with metastatic melanoma who received TILs after a lymphodepleting regimen plus IL-2 administration, with or without total body irradiation.[133] The ORR using Response Evaluation Criteria in Solid Tumors (RECIST) in these 93 patients was 56%. Of the 52 responding patients in this trial, 42 had disease that was refractory to aldesleukin therapy and 22 had disease that was refractory to prior aldesleukin plus chemotherapy. Thus, TIL therapy shows promise as an effective treatment for chemotherapy-refractory metastatic melanoma and warrants investigation in other malignancies.

In metastatic melanoma, tumor-specific T cells can be recovered from 35–70% of patients, and the response in these patients is 50–75%.[134–136]

Notably, 95% of the complete responders demonstrated a durable response for at least 5 years.[16] The use of ACT for patients with HNSCC has been pioneered at a few centers, with one reporting a remarkable RR of 43% in the seven patients studied.[137] Of note, a significant hurdle to ACT is the ability to culture and expand tumor-specific T cells from the patients' autologous tumors. In renal, breast, and colon cancer, the recovery rate is extremely low (0–20%).[138] Interestingly, in HNSCC the success in obtaining tumor-specific T cells from autologous tumors is around 60%, a number similar to that in melanoma.[139,140] In our center, we have successfully cultured tumor-specific T cells from a similar percentage of patients and have treated a single patient with HNSCC.[141]

Strategies to increase the success of recovering tumor-specific T cells from tumor specimens are currently being studied. Data from our group generated using multispectral fluorescent IHC suggest that the ratio of CD8 effector T cells to FoxP3-positive T-reg is an important biomarker that predicts the success of culturing tumor-specific T cells in melanoma (Feng et al, manuscript in revision). Our group is applying the same multispectral imaging strategy to characterize the tumor environment in HNSCC (Fig. 15.13).

Modulation of the tumor environment either during culture or before surgery can potentially enhance this ratio, leading to greater recovery of tumor-specific T cells. Administration of 4-1BB agonist antibody during culture has been shown in



• **Fig. 15.12** Adoptive cell therapy (ACT). ACT involves harvesting T cells from autologous tumor resection or biopsy, expanding them ex vivo with IL-2, testing for tumor specificity, and then rapidly expanding them for re-infusion into a non-myeloablative lymphodepleted patient, usually with concurrently high-dose IL-2. *ELISA,* enzyme-linked immunosorbent assay; *IFN γ,* interferon-γ; *TIL,* tumor-infiltrating lymphocyte. (Adapted from Dudley ME, Rosenberg SA. Adoptive cell transfer therapy for the treatment of patients with cancer. *Nat Rev Cancer* 2003;3(9):666–675; Gattinoni et al. Adoptive immunotherapy for cancer: building on success. *Nat Rev Immunol* 2006;6(5):383–393.)

patients with melanoma to increase the tumor- specific T-cell function,[142] and a study evaluating the effect of neoadjuvant anti–PD-1 therapy on success of culturing tumor-specific T cells is underway.

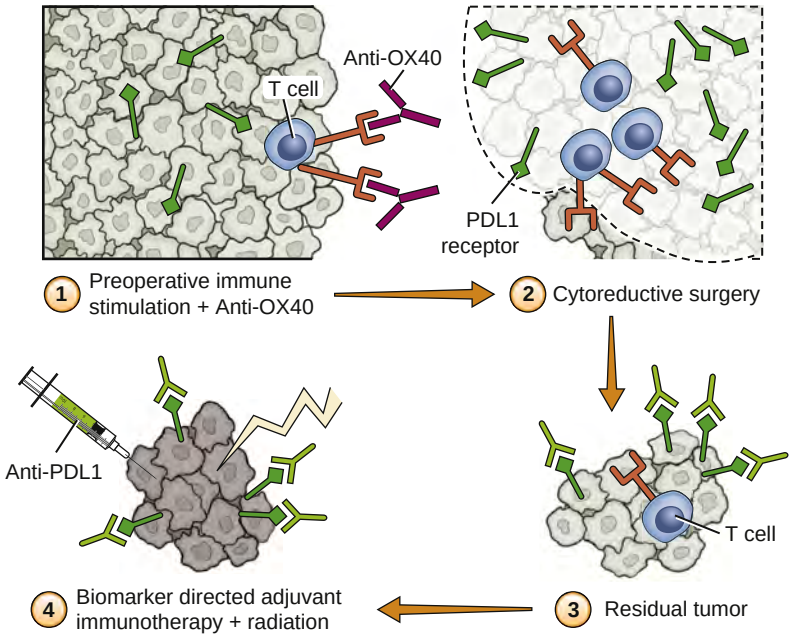
Virus-associated cancers, such as EBV-related nasopharyngeal carcinoma or HPV-related oropharyngeal carcinoma, are rational targets for adoptive immunotherapy with TILs because they express oncoproteins, which are nonself antigens and therefore good immunologic targets. These proteins are particularly attractive therapeutic targets because they continue to be expressed after transformation and their expression is required for survival of the transformed cells. The clinical importance of immune responses against E6 and E7, for example, is suggested by studies linking immune responses against E6 and E7 to improved clinical outcomes,[143–147] and a number of studies have indicated that E6 and E7 could be targeted with TIL therapy.[148,149] Several clinical trials are currently enrolling patients with virus-induced HNSCC (NCT01585428, NCT01462903, NCT02421640, NCT00431210), and this therapeutic approach will undoubtedly have an important role to play in the future.

Active Immunotherapy

Vaccines

A coordinated anti-tumor immune response that induces both CD4 and CD8 T cells is critical to mediating therapeutic effect. To activate tumor-specific CD4 and CD8 T cells, TAAs are processed and cross-presented by APCs. When the immune system is functioning optimally and in the presence of adequate co-stimulatory signals and cytokines, T cells are activated and expanded in numbers that can recognize and eliminate tumor cells. It is currently hypothesized that a preexisting anti-tumor T-cell response is critical for the therapeutic effects of checkpoint blockade, especially anti–PD-1. For patients lacking this preexisting tumor-specific immune response, priming a new anti-tumor response through vaccines is expected to provide substantial benefit to therapy involving checkpoint blockade or immune system agonists. The many forms of vaccines are briefly discussed here.

Peptide and Whole-Protein Vaccine. The use of peptide vaccine for the treatment of cancer has expanded since one of the first studies used a MAGE-1 peptide for the treatment of melanoma.[150] Delivery of peptide-based vaccine with an immune adjuvant or pulsed onto DCs has been shown to elicit peptide-specific CD8 T-cell responses. Peptide cocktails have been used with various degrees of success in certain solid tumors, with one study using IDM-2101, a 10-peptide vaccine cocktail, for the treatment of patients with stage IIIB and IV NSCLCs. The study reported no significant adverse effects with 17.3-month median overall survival.[151] For vaccines containing single whole proteins, progression-free survival and median overall survival benefit



• **Fig. 15.13** Synergizing conventional therapy with immunotherapy (hypothetical model). The tumor microenvironment consists of tumor cells, infiltrating lymphocytes, macrophages, and other factors that either promote or suppress tumor growth. Tumors express a variety of proteins that are not usually expressed in healthy cells. Sometimes, because of overexpression, gene mutation, or viral infection, T cells can recognize antigenic proteins (tumor-associated antigens [TAAs]) in tumors. TAAs are released by the tumor and are captured by dendritic cells (DCs). *1,* Priming new immune responses by promoting the antigen presentation functions of DCs via low-dose hypofractionated radiation therapy might be given to prime immunity. DCs process the TAAs and, in the presence of a maturation signal, migrate to the regional lymph nodes and initiate the differentiation of specialized tumor-specific T cells by presentation of antigen to naïve T cells via major histocompatibility complex (MHC) class I and class II molecules. Once activated by the dendritic cell–MHC–antigen complex, effector T cells are trafficked to the tumor and cause the destruction of antigen-bearing tumor cells anywhere in the body. *2,* T-cell proliferation and effector function within the tumor microenvironment is enhanced via co-stimulation with anti-OX40. This results in increased immune-mediated cell killing and an increase in the number and quality of effector T cells before extirpative surgery. *3,* Surgical extirpation is performed, followed by development of a NextGen immunoprofile that classifies the effector and suppressive elements of the tumor microenvironment as well as molecular profiling, with the hope that the information can be used as a biomarker to guide immunotherapy as well as conventional treatment. *4,* Immunohistochemistry (IHC) or multiplex immunofluorescence analysis is used to define immunosuppressive mechanisms (potential targets for current or future immunotherapies), which will be correlated with cancer signaling pathways (targeted with small molecule and chemotherapies) and patient outcome. Clustering of suppression mechanisms and signaling pathways in subsets of patients may help discriminate between patients with a good prognosis and those with poor outcomes. We hypothesize that ultimately these prospective biomarkers will not only be prognostic, but will also identify different types of cancer-immunity interactions that will allow an evidence-based approach to tailor combination therapies and overcome the suppressive immune landscape present in that patient's tumor and eradicate disease. Based on the immunoprofile (e.g., upregulation of PD-L1), microscopic deposits of tumor could be treated with a combination of radiation therapy and anti–PD-1 with or without anti-OX40 or other co-stimulatory molecules to enhance immunity and improve outcome. (Adapted from Bell RB, Gough MJ, Seung SK, et al: Cytoreductive surgery for head and neck squamous cell carcinoma in the new age of immunotherapy. *Oral Oncol* 61:166–176, 2016.)

have also been observed.[152] These results led to the first FDA-approved cancer vaccine, sipuleucel-T, for the treatment of castration-resistant prostate cancer.[71] However, no durable responses were observed with single-peptide vaccines, potentially owing to immune evasion as a result of protein downregulation by tumor cells.[153]

Whole-Cell Vaccines. Whole-cell vaccines are prepared using irradiated whole tumor cells and are frequently delivered with an adjuvant, such as GM-CSF. One advantage of whole-cell vaccines compared with peptide vaccines is that whole-cell vaccines contain a richer antigenic source. Through use of the autologous tumor, multiple relevant antigens can potentially be targeted in a single vaccine, aimed to induce anti-tumor immune response when combined with a stimulatory adjuvant. Genetic modification of the tumor has also been accomplished, particularly with GM-CSF, which stimulates recruitment of

DCs to the vaccine site and results in augmented antigen processing and presentation to both T and B cells.[154] Owing to the cost and difficulty of coordinating autologous vaccine preparation, allogeneic vaccine strategies now represent the bulk of whole-tumor vaccine trials.[155] The assumption with allogeneic vaccines is that many antigens are shared among tumors, so vaccination with an allogeneic tumor can effectively prime an immune response toward antigens commonly overexpressed by a patient's autologous tumor. This approach demonstrated promise with one phase II study that found a median survival of 24.8 months in patients with pancreatic adenocarcinoma vaccinated with a GM-CSF–secreting allogeneic tumor.[156]

Autophagosome-based Vaccines. Generation of an effective tumor-specific T-cell response largely depends on cross-presentation of tumor-derived proteins by professional antigen-presenting cells (pAPCs).[157,158] Vaccine strategies using whole irradiated tumors have shown some clinical promise[159,160]; however, these vaccines are not optimal because they contain the same antigenic repertoire of long-lived proteins as previously cross-presented by the tumor, resulting in an inefficient (tolerized) immune response. Likewise, tumor-associated peptide vaccines are not optimal because of the limited scope of antigen.[161]

Autophagy, the process by which cells recycle cellular components through autophagolysosomal fusion, is essential in the immune recognition of cancer.[162–164] Tumor autophagy is necessary for tumor-specific T-cell priming through the induction of cross-presentation of tumor antigens by DCs.[165,166] In addition, tumor-derived autophagosomes contain short-lived proteins and defective ribosomal products, which represent the major source of proteins for MHC class I–restricted self-peptides.[167,168] These two types of proteins degrade rapidly and are not enriched in whole-cell vaccines but are captured and enriched in the autophagosome-based vaccines.

To overcome these problems, investigators at our institute developed a tumor-derived autophagosome vaccine containing short-lived proteins (SLiPs) and defective ribosomal products (DRiPs) (termed DRibble), which was shown to be more effective than the laboratory's gold standard GM-CSF gene-modified (GVAX) tumor cell vaccine.[165,166] Further studies by Twitty and colleagues[169] evaluated whether the wide spectrum of antigens postulated to be present in autophagosomes from tumors undergoing proteasome blockade could provide cross-protection against other histologically similar tumors. Using the classic paradigm of the unique specificity of chemically induced 3-methylcholanthrene (MCA) sarcomas, established by Prehn and Main,[36] it was documented that autophagosome vaccines protect against multiple independently derived sarcomas.[169]

Anti-tumor efficacy has been shown in several different preclinical models,[170] and DRibble (UbiVac), an autophagosome-based vaccine, is currently being tested in an ongoing multicenter phase II clinical trial in patients with NSCLC (NCT01909752). A trial for the treatment of patients with HNSCC is currently in the planning stages.

Human Papillomavirus Vaccine. HPV-related HNSCC has been steadily on the rise for the last three decades in the United States with a concurrent decrease in smoking-related HNSCC.[171] It is estimated that by 2020, HPV-related HNSCC cases will be more frequent than HPV-negative cases.[172] HPV is a DNA virus that can inhibit the function of p53 and Rb through the E6 and E7 oncoproteins, respectively. A direct causal relationship has been established between high-risk HPV and HNSCC, and the E6 and E7 oncoproteins can be readily detected in many HPV-positive tumors.

The therapeutic use of HPV vaccine is still being explored in HNSCC; studies in patients with cervical intraepithelial neoplasia grade 2/3 demonstrated that intramuscular vaccination with HPV E6/E7 vaccine-induced CD8 T-cell response that localized to the dysplastic mucosa. Currently, there are multiple trials opened for the treatment of HNSCC using HPV vaccines delivered using different platforms. These include ADXS 11-011 (Advaxis), using *Listeria* as a vector for vaccine delivery; NCT 02002182, using peripheral blood mononuclear cells pulsed with E6 and E7 peptide; and NCT00019110, employing intramuscular vaccination with VGX3100 and INO-9012 (Inovio Pharmaceuticals) followed by electroporation (NCT02163057). In addition, a vaccine against high-risk HPV subtypes has successfully reduced the incidence of cervical intraepithelial neoplasia (CIN) by 90–96%[173,174] and is currently being implemented in the prevention of HPV-induced HNSCC (NCT02382900).

Oncolytic Virus Vaccine. Oncolytic viruses are currently under investigation for use as vaccines. One of the most interesting approaches involves the use of a modified herpes simplex virus, talimogene laherparepvec (T-VEC). T-VEC contains the cytokine GM-CSF and holds promise as an adjuvant to boost immunity either alone or in combination with checkpoint inhibitors.

Cytokines

Cytokines are molecular signaling molecules that allow intercellular communication over a long distance to generate rapid and robust immune responses in a controlled manner. The immune-mediated anti-tumor activities of a few cytokines have been well characterized in preclinical settings and led to many clinical trials testing the efficacy of ILs including IL-2, IL-7, IL-12, IL-15, and IL-21; IFNs; and GM-CSF. Of these, high-dose IL-2 was approved for the treatment of metastatic melanoma and renal cell carcinoma,[156] and IFNα was approved for adjuvant therapy for stage III melanoma.[174]

Interleukin-2. IL-2 is a member of the IL-2–related family that functions to stimulate T-cell growth through the IL-2 receptor. IL-2 exhibits myriad effects on the immune system in addition to promoting CD4 and CD8 T-cell proliferation and differentiation into effector T cells and memory T cells. IL-2 also expands T-reg, which express high-affinity IL-2 receptors.[175,176] This acts as a negative feedback mechanism to decrease CD8 T-cell activity through both depletion of IL-2 and inhibition by T-reg. Systemic high-dose IL-2 plays a key role in the treatment of metastatic melanoma and renal cell carcinoma. Although limited to patients in otherwise good health owing to acute toxicities, high-dose IL-2 induces objective clinical response in 15–25% of patients with metastatic melanoma and renal cell carcinoma, with complete response

in approximately 7–12%.[177–180] Importantly, of the patients achieving complete response, 70–90% remain disease free in an ongoing 20-year follow-up.[178,181]

The use of IL-2 in HNSCC has been limited to locoregional or intralesional injection with mixed results. High-dose IL-2 injected locoregionally demonstrated induction of tumor-specific T cells in the draining lymph nodes of patients with HNSCC.[182] However, perilymphatic injection of low-dose, but not high-dose, IL-2 demonstrated temporary regression of HNSCC and two complete responders in lip cancer.[183–187]

The results of a randomized, multicenter, phase III trial using perilymphatic low-dose IL-2 in patients with oral squamous cell carcinoma were reported in 2002. Five thousand units of recombinant (r)IL-2 were injected around the ipsilateral cervical lymph node chain daily for 10 days before surgery. After surgery, contralateral 5-day rIL-2 courses were administered monthly for 1 year. Multivariate analysis demonstrated improved disease-free survival ($P < .01$) and overall survival compared with the control group ($P < .03$).[187]

The mechanism for resistance to IL-2 therapy in HNSCC is unclear. It has been suggested in melanoma that patients who did not demonstrate significant T-reg induction experienced an increased response to therapy.[188] One explanation for this observation is that the presence of abundant T-reg unique to HNSCC could be rapidly expanded with IL-2 and limit the anti-tumor CD8 response. Combination therapy with systemic high-dose IL-2 and T-reg depleting agents, such as cyclophosphamide, may be an avenue to overcome this pathway for the treatment of HNSCC.[189] To test this hypothesis, a phase III trial of IRX-2, a human cell–derived biologic with multiple active cytokine components, including low-dose IL-2 plus a single dose of cyclophosphamide, followed by 21 days of indomethacin, zinc-containing multivitamins, and omeprazole opened for accrual to patients with oral squamous cell carcinoma (NCT02609386). Other trials using, for example, high-dose, pegylated IL-2 in patients with HNSCC are being planned.

Interferon-α. IFNα is a type I IFN that is involved in the immune response to viral infections. In cancer immunotherapy, administration of IFNα can activate CD8 T cells as well as the innate immune system, specifically NK cells, DCs, and macrophages.[190,191] This has led to a heightened anti-tumor immune response in preclinical models, especially when used in combination therapy with checkpoint blockades.[194] The use of IFNα clinically has so far been limited to the adjuvant setting in high-risk melanoma, where it significantly improves disease-free survival; however, the overall survival benefit seems to be limited to a very small subset of patients.[174] Currently IFNα is being tested in solid tumors in combination with various targeted and immunotherapy agents.

Other Cytokines. Administration of cytokines such as IL-7, IL-10, IL-12, IL-15, IL-21, and GM-CSF and inhibition of suppressive cytokines such as TGF-β are still being explored in the treatment of a variety of solid malignancies, including HNSCC. IL-12 has been reported to increase B-cell distribution and activation when injected intratumorally in an adjuvant setting for the treatment of HNSCC; however, the clinical benefit is currently unclear.[192,193] More recently, a trial of injectable IL-10 with a TLR agonist opened for patients with multiple tumor types, including HNSCC (NCT02731742). It is possible that we may see an increasing number of these agents used in combination therapies for HNSCC, because preclinical evidence points to increased efficacy of these agents when used in combination with checkpoint blockade or T-cell agonists.

Radiation and Immunotherapy

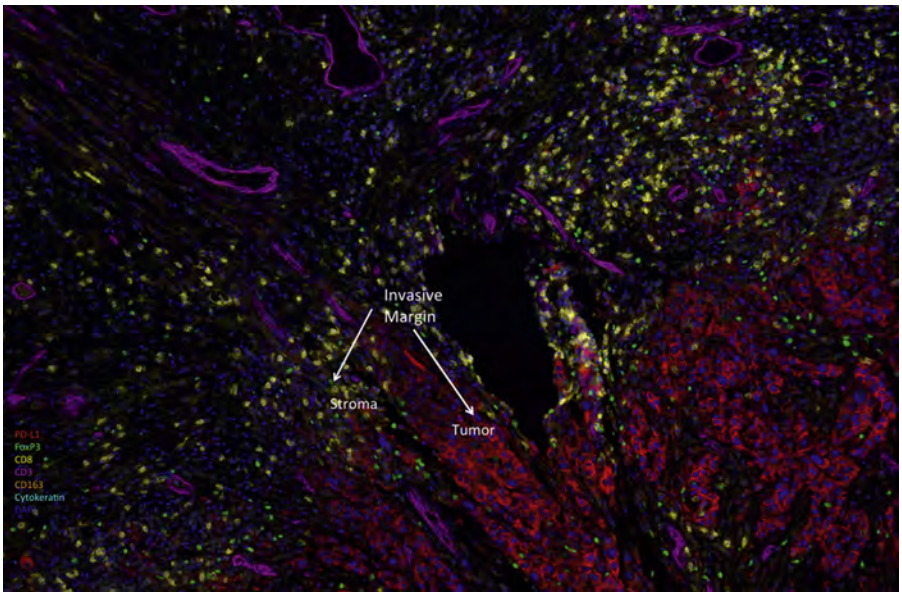
There is preclinical evidence to suggest that hypofractionated radiation can prime immunity in tumors owing to the release TAAs from tumor cells and the surrounding stroma after radiation-induced cell death.[195,196] For most of the last 100 years, radiation has been delivered in standard fractions of 1.5–3 Gy, with the understanding that a higher dose per fraction produces unacceptable toxicity. On the other hand, preclinical experiments have shown that radiation doses per fraction of 5–20 Gy may be more optimal in terms of generating a potentially effective anti-tumor immune response. Advances in radiation delivery have recently facilitated the safe administration of higher doses per fraction (10–20 Gy) without causing a significant increase in toxicity. Stereotactic body radiotherapy (SBRT) incorporates computer planning and body immobilization protocols to allow safe delivery of radiation to the tumor site, while sparing adjacent tissues.

Recently our group performed a pilot study of SBRT followed by high-dose IL-2, a potent pro-inflammatory cytokine, to assess safety and tumor RR and to perform immune monitoring studies in patients with metastatic melanoma or renal cell carcinoma.[196] Immune monitoring demonstrated a significantly higher frequency of proliferating $CD4^+$ T cells and an early activated effector memory phenotype in the peripheral blood of responding patients. Of patients in the trial, 67% responded to hypofractionated radiation followed by IL-2, compared with historical cohorts with IL-2 alone, in which only a 15% RR was observed. These results have encouraged us to explore the potential of co-stimulatory molecules and checkpoint inhibitors as an adjuvant to hypofractionated radiation in the preclinical setting, and work is underway to translate this approach into HNSCC patients.

Surgery and Immunotherapy

Cytoreductive surgery is an approach to cancer treatment that aims to reduce the number of cancer cells via resection of primary tumor or metastatic deposits, in an effort to minimize a potentially immunosuppressive tumor burden, palliate symptoms, and prevent complications[223,224] (Fig. 15.14). Furthermore, it provides a platform for investigation of biomarkers with the goal of optimizing immunotherapy to reverse the immunosuppressive tumor microenvironment and enhance adaptive immune responses.

Our group is focused on integrating immunotherapy into conventional HNSCC treatment.[223] Although T cell–targeted immunotherapy such as with anti-OX40 and anti–CTLA-4 is effective in many models, it is limited by the immune suppressive environment of the tumor and the size of the primary tumor.[197–199]



• **Fig. 15.14** Multiplex immunohistochemistry. Example of staining and tumor-stromal recognition for head and neck squamous cell carcinoma specimens. Tissue sections were stained with seven different markers; 20× images with highest immune infiltrate were taken at the invasive margin, which is further separated into tumor and stromal components (*red,* PD-L1; *green,* FoxP3 T-reg; *yellow,* CD8; *magenta,* CD3; *blue,* DAPI).

Larger tumors are associated with significant numbers of T-reg, as well as inhibitory macrophages, which express arginase and TGF-β (in mice).[199] Treatment of these larger, well-established tumors with anti-OX40, for example, may result in delay in tumor progression and enhanced infiltration of CD8 T cells, but tumor cure occurs infrequently owing to the immunosuppressive microenvironment that limits adaptive immune responses.[200]

Gough and colleagues developed a sarcoma mouse model in which surgical resection of 10- to 14-day established tumors resulted in 50% local tumor recurrence.[201] When CD8 T cells were depleted in a matched group of mice, tumor recurred in 100% of the animals. This suggests that the adaptive immune response is necessary for elimination of residual disease. In the same sarcoma model, the investigators treated the mice with an agonistic antibody to OX40, stimulating CD4 and CD8 activation. Adjuvant anti-OX40 delivered at the time of surgical resection resulted in cures for 100% of the mice after the operation.[201] These data confirm that the adaptive immune response plays a critical role in and may be deployed to control local tumor recurrence from minimal residual disease. A phase Ib clinical trial using anti-OX40 (MEDI6469) at various dose intervals before definitive surgical resection of HNSCC patients is currently underway (NCT02274155). A number of other immunotherapies are also being tested in the surgical setting (Table 15.2).

In addition to T cell–targeted therapies, our group has been investigating therapies that target the suppressive macrophages in the tumor environment. STING (STimulator of INterferon Genes) is a cytosolic sensor of microbial infection.[202] Hyperactivity of STING to host DNA can result in autoimmunity,[203] and activating mutations in STING can result in immunopathology.[204] Investigators at our institute showed that ligands of the STING sensor, cyclic dinucleotides (CDNs) potently overcome tumor immune suppression and enhance adaptive immunity to TAAs.[205] However, CDNs must be applied directly to the tumor and CDNs are ineffective if delivered systemically. In a setting of cytoreductive surgery, this may not be a limitation. This approach has been tested using gene therapies, in which adenoviral vectors have been "painted" into a resection cavity, resulting in local gene delivery and therapeutic consequences in cardiovascular models.[206] Thus, cytoreductive surgery may represent an opportunity to deliver an obligate local therapy.

Biomarkers

The final part of this chapter briefly covers biomarkers, a rapidly advancing area for immunotherapy. With increasing numbers of immunotherapy strategies available for the treatment of solid malignancies, including HNSCC, identification of prognostic and predictive biomarkers is paramount to stratify patients and direct therapy. Understanding these biomarkers is an active area of research, with a majority of the attention focusing on the checkpoint blockades such as anti–PD-1.

Programmed Cell Death Ligand 1 (PD-L1)

Recent studies have demonstrated that response to anti–PD-1 is heavily dependent on the expression of PD-L1 in the tumor microenvironment as well as the mutational burden of the tumor itself.[28,29,103] These findings suggest that the response to anti–PD-1 is hinged on a preexisting anti-tumor immune response and that anti–PD-1 acts to free the CD8 T cells from inhibition to exert their anti-tumor activities. A biomarker for anti–CTLA-4 is also being researched; preliminary studies suggest that the response is dependent on FcgRIIIA (CD16)-expressing monocyte-mediated elimination of T-reg.[87]

IHC is the most frequently used technique in the identification of these biomarkers. Studies using quantitative IHC have

TABLE 15.2 Current Immunotherapy Surgical Trials Open for Head and Neck Cancer

Agent	Tumor Site	Status/Setting	Combination Agent	Current Trial
Nivolumab	Solid tumor virus (+)	Phase I/II/resectable/neoadjuvant	Ipilimumab	NCT02488759
Pembrolizumab	HNSCC	Phase II/high-risk resectable	None	NCT02296684
Pembrolizumab	HNSCC	Phase II/ resected/neo + adjuvant	Cisplatin + radiation	NCT02641093
Pembrolizumab*	HNSCC	Phase II/locally recurrent/adjuvant	Salvage surgery	NCT02769520
Anti-OX40	HNSCC	Phase I/resectable/advanced	None	NCT02274155
VGX-3100	HNSCC HPV (+)	Phase I/IIa/resectable/neoadjuvant	INO-9012	NCT02163057
KTN3379	HNSCC	Phase I/resectable	None	NCT02473731
IRX-2	HNSCC	Phase II/resectable/neo + adjuvant	None	NCT02609386
ADXS11-001	HNSCC HPV (+)	Phase II/resectable/neoadjuvant	None	NCT02002182
Multikine	HNSCC	Phase III/resectable/neoadjuvant	Surgery + radiation	NCT01265849
AMG 319	HNSCC HPV (–)	Phase II/resectable/neoadjuvant	None	NCT02540928
VTX-2337	HNSCC	Phase I/resectable/neoadjuvant	Nivolumab	NCT02124850

(+), Positive; *(–),* negative; *HNSCC,* head and neck squamous cell carcinoma; *HPV,* human papillomavirus.
*Active, not yet recruiting.

identified CD8 T-cell infiltration as an important prognostic factor in predicting outcome for patients with HNSCC.[207,208] More recently, multiplex IHC has emerged as a more advanced tool for the analysis of the tumor microenvironment, offering a more efficient and comprehensive analysis of the tumor microenvironment for both diagnostic and mechanistic studies.[209–211] This also allows us to explore the relationship among cell types in the peritumoral and intratumoral compartments, quantify the expression of specific biomarkers, and examine their impact on patient prognosis and response to therapy. As research on biomarkers advances, we will hopefully be able to better direct patients, based on their tumor microenvironment and mutational status, to the immunotherapy that potentially offers the best RR and ultimately a cure for their disease.

Future Directions

It is becoming increasingly apparent that only a minority of patients will respond to and receive benefit from anti–PD-1 and other immunotherapies when given as monotherapy. Evolving evidence suggests that in general, only those tumors with a high mutational load[212] or mismatch repair deficiency[213] will respond to immunotherapy, and many of these clinical responses are mediated by T cells that target unique somatic mutations expressed by the patients' tumors.[214–218]

As discussed earlier, analysis of gene expression profiles of tumors has identified a subgroup of patients with a particular gene expression pattern associated with immune responses. This has been termed an inflammatory TME, and in melanoma is characterized by a type I IFN signature and various chemokines and T-cell markers.[219] Tumor with an inflammatory TME demonstrates $CD8^+$ T cell–driven upregulation of suppressive elements, such as T-reg and PD-L1, making treatment with checkpoint blockers such as anti–PD-1 or anti–PD-L1 compelling. Therefore, if checkpoint inhibition is effective primarily in the inflamed TME, a critical, if not the most important, area of immuno-oncology research is discovering how to generate an anti-cancer response in patients without preexisting immunity.

Studies have shown that as tumors grow, they develop mutational neoantigens that may drive immunotherapy responses and can be potentially exploited to provide a patient-specific therapy. McGranahan and colleagues[220] showed that in patients who underwent treatment with anti–PD-1 or anti–CTLA-4, there was a direct relationship between clonal neoantigen burden and overall survival in lung cancer. The microbiome may contribute to immunotherapy response as well.[221] To improve the effectiveness of these therapies in patients who lack a preexisting inflammatory response, Tran and colleagues[218] used next-generation sequencing combined with high-throughput immunologic profiling to show a neoantigen specific anti-mutation T-cell response against a gastrointestinal cancer with a low mutational burden. Thus neo-epitopes derived from the tumor's somatic mutations might be engineered in vitro and adoptively transferred to elicit a response, even in tumors with relatively few mutations or without shared epitopes.[222]

The year 2016 marked a new era in the treatment of HNSCC with the FDA approval of anti–PD-1, and more novel therapies are on the way. To advance the field, immunotherapy must be vigorously integrated into conventional therapies such as surgery, radiation, and chemotherapy, by sequencing rational combinations of immunotherapies for patients with preexisting immunity and by developing novel, personalized therapeutic approaches for patients lacking an effective immune response. For this to be accomplished, predictive biomarkers must be developed and validated to inform treatment decisions by correlating immunosuppressive mechanisms (potential targets

for current or future immunotherapies) with cancer signaling pathways (targeted with small molecule therapies and chemotherapies), the microbiome, and patient outcomes. It will take years to achieve these goals, but the new era of immunotherapy harbors increasing optimism for improved outcomes in the near future.

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16

Oral/Dental Oncology

AMBER L. WATTERS, HEIDI J. HANSEN

The Role of the Oral/Dental Oncologist

An oral health provider who is familiar with treatment protocols and the potential short- and long-term oral complications and sequelae of cancer treatment should evaluate patients with a diagnosis of head and neck cancer (HNC). A multidisciplinary approach for the treatment of head and neck cancer patients is essential for the betterment of patient outcomes and for preserving optimal function, form, and esthetics and is linked to patient care quality improvement.[1] The expanding field of oral/dental oncology is comprised of a diverse group of oral health providers including oral medicine specialists, dental oncologists, maxillofacial prosthodontists, orofacial pain specialists, special care dentists, hospital dentists, and dental hygienists. Providers who are actively engaged in promoting evidence-based guidelines and protocols such as speech language pathologists, nutritionists, nurse navigators, social workers/psycho-oncologists, and dental oncologists are recognized members of the head and neck cancer team and are essential to supporting patient-centered care. As survival in head and neck cancer treatment improves, oral adverse effects and postsurgical functional defects can profoundly impact post-treatment quality of life.

Host-driven chronic inflammation has been suggested as part of the pathway to carcinogenesis, and investigations have therefore attempted to discover links between dental caries and periodontitis and the development of cancer.[2,3] Although these studies do not represent causation, they do call attention to the fact that the same individuals who are at risk for developing cancer may also be at risk for developing dental disease. Whether or not cancer and the dental diseases, periodontitis and caries, share genetic or environmental risk factors, a patient at risk for developing head and neck cancer is also at risk for dental disease. Additionally, health-related behaviors such as daily smoking are independently related to the development of dental caries and periodontitis. Investigations have shown that many patients who present with a new cancer diagnosis also report with poor dental status[4] (Figs. 16.1 through 16.3).

While planning for presurgical and adjuvant treatment depends on the location and extent of disease, all patients with any site or stage of diagnosis of oral or head and neck cancer may potentially be treated with surgical resection, radiotherapy, and/or chemotherapy. Patients with nasopharynx and occult oropharynx primary cancer are at particularly high risk for developing short and long-term oral cavity sequelae and are likely to be treated with definitive chemotherapy and radiotherapy. For nasopharyngeal tumors, radiotherapy involves the maxilla in early-stage disease and the mandible if neck metastases are present.[5] Patients with oral cavity primary tumor sites including lip, buccal mucosa, floor of mouth, anterior tongue, alveolar ridge, retromolar trigone, and hard palate require assessment to determine the functional impacts of surgical resection on oral function. This is essential, even when microvascular free flap reconstruction is indicated at the time of ablative surgery, as flap failure or defect is possible and some patients may require a combination of surgical and prosthetic reconstruction (Figs. 16.4 through 16.8). Patients with oropharynx tumors including tonsil, posterior pharyngeal wall, and the soft palate are also at risk for surgical defects requiring prosthetic intervention or of deficits in function due to mucosal fibrosis or neuropathy from surgical resection and/or chemoradiation. Immediate surgical defects require palatal augmentation devices while long-term consequences such as fibrosis and neuropathy leading to functional impairments and progressive paralysis may require palatal lift appliances. Hypopharynx cancers including pyriform sinus, postcricoid region, and posterior pharyngeal wall may or may not be treated with the mandible in the direct field of radiation, but these patients should also have their oral health optimized prior to cancer treatment.

Dental examination and necessary treatment prior to head and neck cancer treatment is recommended by multiple professional organizations including the National Comprehensive Cancer Network (NCCN), National Cancer Institute (NCI) and the Multinational Association of Supportive Cancer Care/International Society of Oral Oncology (MASCC/ISOO).[6-8] Patients should be informed of the potential oral and dental side effects of anticipated treatment, including dry mouth (xerostomia), increased risk for dental disease, functional deficits, orofacial pain or dysfunction, osteoradionecrosis, and secondary bacterial, viral, or fungal infections[9] (Boxes 16.1 and 16.2). Patients who are evaluated by an oral health professional early in their diagnostic work-up have been reported to experience a lower occurrence of dental disease.[10] The demographics of head and neck cancer patients for both human papillomavirus (HPV)-related and non-HPV-related cancers, namely



• **Fig. 16.1** Calculus bridge on remaining mandibular teeth. Patient presenting for dental evaluation prior to HNRT.



• **Fig. 16.2** Patient presenting with dental decay prior to treatment for oral cancer. (Photo courtesy Head and Neck Surgical Associates.)

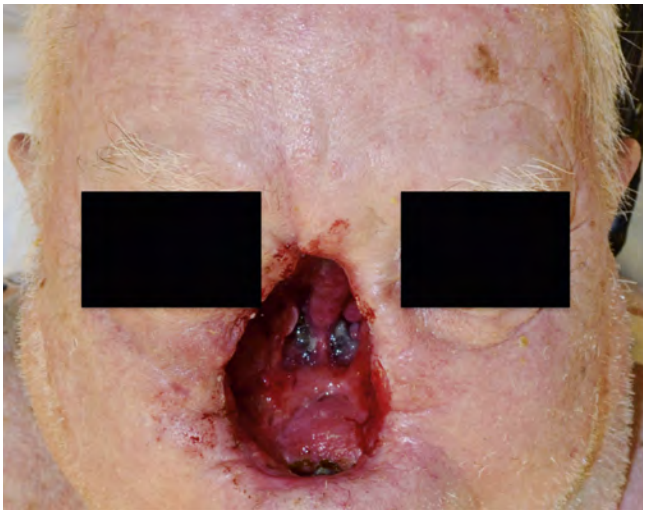


• **Fig. 16.3** Squamous cell carcinoma of the right tongue arising in area affected by oral ulcerative lichen planus. Note dental caries on adjacent teeth. (Photo courtesy Head and Neck Surgical Associates.)

male gender, age older than age 50, and a history of smoking and alcohol use, make it more likely for these patients to have poor dental status at the time of diagnosis.[11,12] As this population ages and approaches Medicare eligibility, long-term dental follow-up may be impacted by a lack of dental insurance coverage. Currently, Medicare explicitly excludes dental treatment coverage, with the exception of an examination prior to head and neck radiation therapy (HNRT) and pretreatment dental



• **Fig. 16.4** Total rhinectomy. (Photo courtesy Head and Neck Surgical Associates.)



• **Fig. 16.5** Second stage surgery, post total rhinectomy and reconstruction. (Photo courtesy Head and Neck Surgical Associates.)



• **Fig. 16.6** Interim maxillary obturator for combined surgical and prosthetic reconstruction.

extractions. Post-treatment dental reconstruction, such as conventional removable dentures, is also excluded. Although there is some coverage for removable prosthetics for surgical defects, implant restorations for implant-retained reconstructions are excluded. Additionally, HNC is a financially debilitating



• **Fig. 16.7** Combined prosthetic and surgical reconstruction using interim removable obturator.

BOX 16.1 Acute Oral Complications of Head and Neck Cancer Treatment

- Oral pain
- Mucositis
- Oral fungal/bacterial/viral infections
- Dysgeusia/ageusia
- Salivary gland dysfunction
- Surgical defects requiring interim prosthetic intervention

Brennan MT, Elting LS, Spijkervet FKL: Systematic reviews of oral complications from cancer therapies, Oral Care Study Group, MASCC/ISOO: Methodology and quality of the literature. Support Care Cancer 2010; 18:979-984.



• **Fig. 16.8** Residual intraoral, hard palate defect.

BOX 16.2 Chronic Oral Complications of Head and Neck Cancer Treatment

- Dental disease (caries, periodontitis)
- Dysgeusia/ageusia
- Mucosal fibrosis/trismus
- Neuropathy
- Oral fungal/bacterial infections
- Oral pain
- Osteoradionecrosis (ORN)
- Salivary gland dysfunction
- Surgical defects requiring definitive prosthetic reconstruction

Brennan MT, Elting LS, Spijkervet FKL: Systematic reviews of oral complications from cancer therapies, Oral Care Study Group, MASCC/ISOO: Methodology and quality of the literature. *Support Care Cancer* 2010; 18:979-984.

disease which may be one of the most costly forms of cancer to treat, even without considering the pre- and post-treatment dental needs.[13]

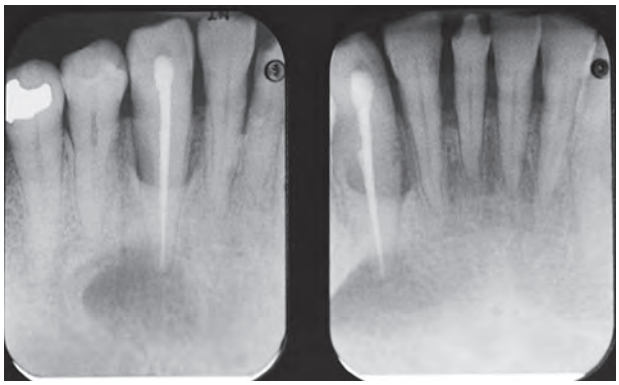
As HPV-related oropharyngeal cancers are more frequently diagnosed and survival is improved compared to HPV-negative cancers, the long-term management and prevention of oral sequelae is increasingly important to reduce impacts on post-treatment quality of life.[14,15] With the advent of intensity-modulated radiotherapy (IMRT), short- and long-term dental adverse effects have been reduced in comparison to conventional radiotherapy.[16] Although these results are promising, the long-term effects to the oral cavity are not eliminated, and additional studies are needed to investigate the magnitude by which IMRT decreases oral toxicities.

Unfortunately, the majority of both NCI-designated and community cancer centers do not have an oral/dental oncologist as part of their multidisciplinary head and neck cancer team.[17] This may lead to reliance on community dentists, who are often unaware of and untrained in management of the short- and long-term sequelae of head and neck cancer treatment, which may lead to either undertreatment or overly aggressive treatment prior to HNRT.[18] Additionally, without an embedded oral/dental oncologist, referrals may occur at a later time in the pretreatment process, leading to inadequate time for removal of all potential dental foci of disease. Oral/dental oncologists as part of the multidisciplinary cancer center are more likely than community dentists to be in-network medical insurance providers, which reduces financial barriers to pretreatment dental consultations. If the patient has an established relationship with a general dentist, dental treatment can be preformed with the patient's community dentist in consultation with the dental oncology service.[19] Patients who receive a cancer diagnosis may become overwhelmed by the discussion regarding dental disease in addition to planning for a cancer treatment. Despite this, early, evidence-based preventive care plans can help to reduce the burden of oral disease in both the short and long term.

Pretreatment Dental Evaluation

The involvement of the oral/dental oncologist should begin early in the diagnostic process. If surgical resection is indicated for oral cavity tumors, the comprehensive oral examination should provide baseline records, including pretreatment photographs, diagnostic models, occlusal registration, range of motion measurements, charting diagrams, digital imaging, and rapid prototyping. This information provides invaluable knowledge for prosthetic and surgical reconstruction to maintain presurgical or preradiation conditions.

Along with thorough patient education, the pretreatment evaluation should include the identification of existing dental disease along with an evaluation of teeth with questionable



• **Fig. 16.9** Intraoral radiograph of tooth #27. Patient presenting prior to initiation of definitive chemoradiotherapy with no complaint of dental symptoms.



• **Fig. 16.10** Example of acute gingivitis on the anterior buccal gingiva due to poor oral hygiene.

or fair long-term prognosis. While numerous protocols for pretreatment dental considerations exist, no standard protocol is currently accepted, and decisions are often made based on individual providers' experience rather than rigorous evidence-based guidelines. Because much of the pretreatment dental planning relies on expert opinion, a provider with knowledge and experience with cancer treatment must be consulted. During the pretreatment consultation, all necessary intra- and extraoral radiographs should be taken according to ALARA (as low as reasonably achievable) radiation safety guidelines[20] (Fig. 16.9). Documentation and evaluation of both hard and soft tissue disease, including periodontal screening or full-mouth periodontal charting, should be completed. If patients will undergo HNRT and have a significant number of metallic dental restorations, radiation guards of at least 1 mm thickness may be indicated and should be fabricated and inserted prior to radiation simulation.[6] Teeth with a poor or guarded prognosis, acute infection, or severe chronic periodontal compromise that will be included in the direct field of radiation should be considered for extraction. Overzealous extraction of healthy teeth is contraindicated, even with the commonly suggested 2-week healing period between extraction and HNRT, as this can put the patient at higher risk of osteoradionecrosis.[21,22] Teeth that can be restored and have an excellent or good prognosis should be conservatively treated prior to cancer treatment.

Oral Care

During the pretreatment oral evaluation, oral care and preventive guidelines should be discussed (Fig. 16.10). Neutral sodium fluoride 1.1% with twice daily application regardless of the method of application is recommended. Avoidance of acidulated and stannous fluoride is suggested due to the potential for mucosal sensitivity post HNRT. Historically, fluoride carriers are suggested as the best method for fluoride application; however, recent reviews suggest that the method of application is irrelevant and that compliance with fluoride carriers is extremely low, even within the first year of treatment.[23] Avoidance of mints, spearmints, and cinnamons in topical dentifrice, which may cause mucosal irritation after HNRT, may help with patient compliance with dentifrice use. The addition of casein phosphopeptides–amorphous calcium phosphate (CPP-ACP), tricalcium phosphate, and calcium phosphosilicate to the oral care regimen, either as a separate product or combined with a high-dose fluoride dentifrice or through varnish applications, has been suggested to improve remineralization, particularly at the root surface where radiation caries are likely to start.[24-26] Xylitol-containing products that stimulate hard tissue remineralization should be encouraged after treatment is complete and mucosal healing takes place. Patients should avoid acidic rinses aimed at increasing salivary flow due to increased risk of dental erosion; also, the low pH of the rinse can cause tissue irritation or erythema to irradiated oral tissues. Unfortunately, many of the products, which are at a neutral pH, also contain glycerin as a major ingredient that may increase mucosal dryness and should be avoided if mucositis is present. Natural products including sugar-free formulations of marshmallow root,[27] green tea, olive oil , coconut oil, aloe vera, or honey[28,29] have been advocated. Additional oral care recommendations[30,31]are presented in Table 16.1.

Dental Prostheses

Ill-fitting dentures can be relined with soft silicone reline material or chair-side acrylic (polymethylmethacrylate [PMMA]) hard reline material, whereas soft acrylic reline material is more likely to harbor *Candida* species adherent to the liner.[32] A stable, soft silicone liner may be used to allow patients to wear their prostheses through treatment. Many authors suggest discontinuation of prosthesis wear during HNRT, but this can negatively affect patient nutritional intake during a critical time. Patients may willingly discontinue denture wear if they develop severe oral mucositis, but those who experience minimal tissue irritation during treatment can continue to wear well-fitting prostheses to improve nutritional intake. Patients should be encouraged to contact the dental oncology service if they develop sore spots or irritations under the denture border (Fig. 16.11).

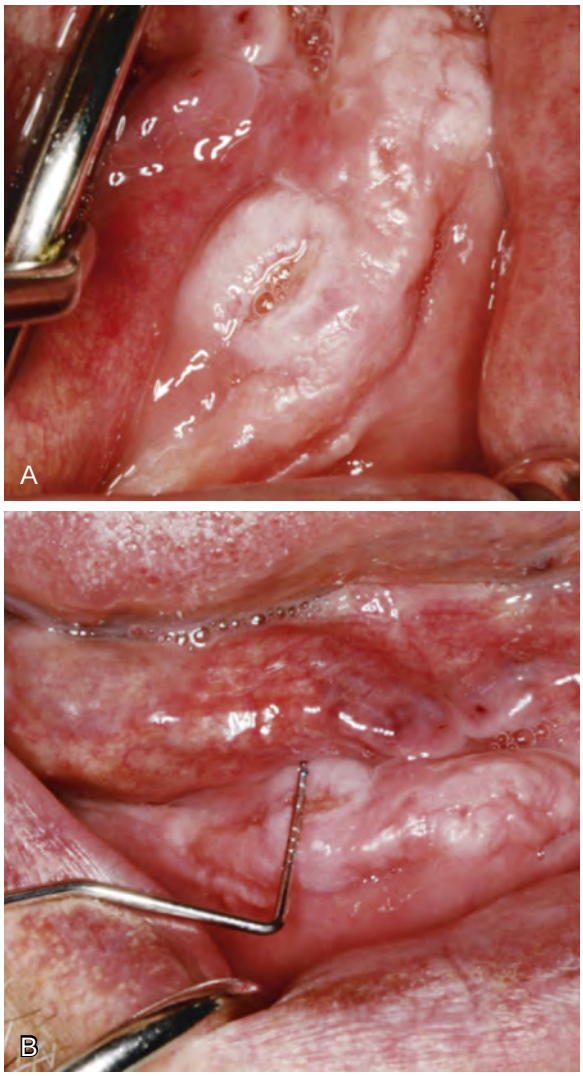
If a patient's dental condition necessitates extraction of all remaining teeth prior to HNRT, prosthesis fabrication can begin as soon as any mucositis, tissue erythema or discomfort, and hyperactive gag reflex has resolved. Historically, patients have been told to delay fabrication for up to 1 year

TABLE 16.1 Oral Care During Cancer Therapy

Rinsing	*Use:* 1. Bland rinse, prepared daily (1 teaspoon salt: 1 teaspoon baking soda: 4 cups water) temperature as tolerated by patient 2. Alcohol-free 0.12% chlorhexidine gluconate, OTC CloSYS *Avoid:* 1. Alcohol-based rinses 2. Glycerin/glycerol based rinses (includes most OTC formulated dry mouth products) 3. Hydrogen peroxide 4. Rinses below pH 6
Brushing	*Use:* 1. Extra-soft brush (postsurgical brush, Dr. Collins Perio Brush, tapered/ultra-fine bristles) 2. New brush at start, changing frequently *Avoid:* a. Glycerin mouth swabs b. Whitening products c. Mint, cinnamon, spearmint as tolerated
Flossing	*Use:* Unflavored, waxed, continue as tolerated *Avoid:* Mint, whitening, unwaxed
Dentifrice	*Use:* 1.1% neutral sodium fluoride, fruit or child-friendly flavors *Avoid:* Whitening products, citrus, mint, spearmints, cinnamon
Dentures	*Use:* 1. Remove every night 2. Soft, manual brushing 3. Antibacterial liquid soap 4. For prevention/treatment of oral candidiasis soak 15 minutes per day in 1 part bleach: 9 parts water solution *Avoid:* OTC cleaners[31]
Diet	*Use:* Extra gravy and sauces *Avoid:* 1. Spicy food 2. Vinegar 3. Highly processed, high-sugar foods
Lip care	*Use:* Lanolin, coconut oil, shea butter, beeswax, cocoa butter, olive oil, calendula oil, vitamin E, hemp oil, castor seed oil, sunflower seed oil *Avoid:* Petroleum, flavors (including natural additives)

Adapted from Collaborative OCSM: *Cancer Care Ontario's symptom management guide-to-practice: oral care 2012.*

after treatment, but this can lead to delayed nutritional recovery and dependence on feeding tubes, IV nutrition, or total parenteral nutrition. There is no evidence to support this delay in fabrication beyond healing from the immediate effects of chemotherapy or HNRT. [33] Last, many state-funded safety net programs place timelines on denture fabrication, and delaying fabrication may result in a patient losing coverage for this service.



• **Fig. 16.11** **A** and **B,** Long-standing ulceration due to ill-fitting denture in patient with a history of head and neck cancer.

Oral and Mucosal Complications

Oral Mucositis

Mucositis is a common toxicity of the gastrointestinal tract associated with antineoplastic therapies. In head and neck cancer patients, mucositis of the oral cavity and oropharynx is often severe and can be dose limiting and negatively impact quality of life and nutritional status. Mucositis often requires an increased use of analgesics and placement of G-tubes to maintain nutrition.[34] Oral mucositis can affect patients' ability to maintain oral care, and the oral mucosa can have increased susceptibility to injury and local infection, increasing the risk for systemic infection.[35] The frequency and severity of mucositis varies with tumor type, radiation field and type, and dose and type of chemotherapy (Fig. 16.12). Patients receiving HNRT with or without concomitant chemotherapy are at high risk of developing mucositis with a reported prevalence of nearly 100%.[36]



• **Fig. 16.12** **A** to **D,** Generalized lichenoid mucositis associated with targeted therapy, distributed on all four quadrants of attached gingiva and the buccal mucosa, compounded by localized poor oral hygiene.

Clinical Features

Mucositis secondary to chemotherapy presents within a week of infusion and begins with soreness that progresses to atrophy, erythema, and later ulceration and pain. Any movable mucosal surface can be affected. Radiation mucositis becomes apparent after doses exceed 10 Gy and frank ulceration is noticeable around 30 Gy. Both keratinized and non-keratinized mucosal surfaces can be affected. The ulcerations of oral mucositis tend to be irregular, shallow and can coalesce.

Pathobiology

It is known that radiation and chemotherapy cause initiation of mucositis through direct tissue damage, but evidence suggests a more complex pathogenesis. Sonis[35] has developed a five-stage biological model for the stages of oral mucositis development:

1. *Initiation* occurs through chemo- and radiation-induced DNA damage causing direct cellular injury in the basal epithelium and submucosa and generation of reactive oxygen species.
2. The *primary damage response* describes an activation of transduction pathways that activate transcription factors such as nuclear factor-κB (NF-κB) leading to upregulation of genes that modulate the damage response. This results in the production of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, which cause damage to both epithelium and connective tissue.
3. *Signal amplification* occurs as a consequence of gene upregulation and cytokine production. The pro-inflammatory cytokines, in addition to causing direct tissue damage, activate a positive feedback loop amplifying the primary damage caused by chemotherapy and radiation. An example of this is further activation of NF-κB and sphingomyelinase by TNF-α, causing more cell death and thereby mucosal thinning and initiation of the symptoms of mucositis.
4. Loss of mucosal integrity and ulceration occur after approximately 10 days of chemotherapy or at a cumulative radiation dose of 30 Gy. The mucosa breaks down and the

ulceration is prone to colonization by oral bacteria, which penetrate the submucosa, causing production of additional pro-inflammatory cytokines potentiating the tissue lesion.

5. Mucositis is an acute and self-limiting process in which *healing* occurs by migration of epithelium at the wound margins usually starting 2 to 3 weeks following completion of radiation therapy or after 2 to 3 weeks of peak chemotherapy-induced mucositis.[35,37]

Treatment of Oral Mucositis

Based on an improved understanding of the pathobiology of mucositis, there are many emerging therapies. Systematic reviews resulting in clinical practice guidelines for the management of oral mucositis have been conducted in detail by the Oral Care Study Group of the International Society of Oral Oncology, and these were updated in 2014. They include suggestions and recommendations based on levels of evidence of the reviewed studies.[38]

Basic oral care: The use of oral care protocols that include flossing, brushing, and the use of mouth rinses other than chlorhexidine is suggested for the prevention of oral mucositis across all cancer treatment modalities.[38,39]

Growth factors and cytokines: The use of recombinant human keratinocyte growth factor-1 (KGF-1/palifermin) is recommended for the prevention of oral mucositis in patients receiving high-dose chemotherapy or total body irradiation for autologous stem cell transplant.[38,40]

Anti-inflammatory agents: Benzydamine mouthwash is recommended for the prevention of oral mucositis in head and neck cancer patients receiving doses up to 50 Gy.[38,41]

Antimicrobials, coating agents, anesthetics, and analgesics: To treat pain due to oral mucositis, patient-controlled analgesia with morphine is recommended and transdermal fentanyl is suggested. Also suggested are mouthwashes containing 2% morphine and 0.5% doxepin.[38,42]

Laser and other light therapy: Low-level laser therapy is recommended to prevent oral mucositis in patients receiving high-dose chemotherapy for hematopoietic stem cell transplantation and suggested for patients receiving head and neck radiation.[38,43]

Cryotherapy: This is recommended for prevention of oral mucositis in patients receiving 5-fluorouracil and suggested for prevention in patients receiving high-dose melphalan.[38,44]

Natural and miscellaneous agents: Zinc supplementation is suggested for prevention of oral mucositis in patients receiving radiation therapy or chemoradiation.[38,45]

Candidiasis and oral herpetic infection can be present in oral mucositis or misdiagnosed as oral mucositis, and their accurate detection and treatment is essential.[46]

Several scoring systems have been developed to aid in consistent grading of oral mucositis, for both clinical reporting and research purposes. Of these the three most commonly used are the National Cancer Institute Common Toxicity Criteria for oral mucositis (NCI-CTC) and the World Health Organization scoring criteria for oral mucositis (WHO) scales[46] (Table 16.2).

In addition to mucositis from cytotoxic chemotherapies, oral adverse effects can occur with targeted therapies and can include mucositis, aphthous-like stomatitis, and lichenoid reactions[46a] (see Fig. 16.12).

TABLE 16.2 Mucositis Grading Scales: WHO, NCI-CTC, and Radiation Therapy Oncology Group (RTOG)

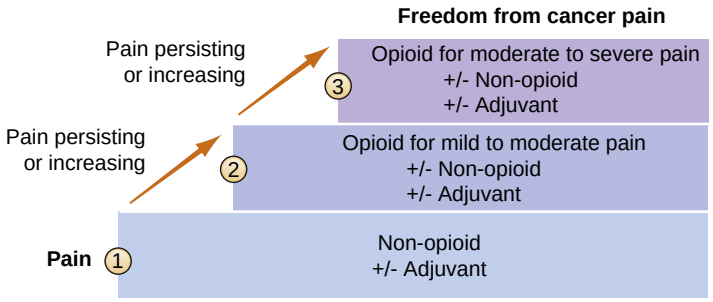
Grade	Description
WHO	
0 (None)	None
I (Mild)	Oral soreness, erythema
II (Moderate)	Oral erythema, ulcers, solid diet tolerated
III (Severe)	Oral ulcers, liquid diet only
RTOG	
0 (None)	No change over baseline
I (Mild)	Irritation, may experience slight pain, not requiring analgesic
II (Moderate)	Patchy mucositis that may produce inflammatory serosanguineous discharge; may experience moderate pain requiring analgesia
III (Severe)	Confluent, fibrinous mucositis, may include severe pain requiring narcotic
IV (Life-threatening)	Ulceration, hemorrhage, or necrosis
NCI-CTC	
0 (None)	
I (Mild)	Painless ulcers, erythema, or mild soreness in the absence of lesions
II (Moderate)	Painful erythema, edema, or ulcers but eating or swallowing possible
III (Severe)	Painful erythema, edema, or ulcers requiring IV hydration
IV (Life-threatening)	Severe ulceration or requiring parenteral or enteral nutritional support or prophylactic intubation
V (Death)	Death related to toxicity

From Scully C, Sonis S, Diz PD: Oral mucositis. *Oral Dis* 2006; 12:229-241.

Orofacial Pain

Orofacial pain (OFP) is a common complaint of patients with HNC and can be reported prior to, during, and after cancer treatment. OFP in head and neck cancer patients is often multifactorial and can be caused by local or metastatic tumors, or by cancer surgery and chemotherapy and/or radiotherapy. The underlying pathophysiology of OFP in HNC can be nociceptive, inflammatory, infectious, or neuropathic.[47] Recognizing the underlying cause is essential to the management of OFP in the cancer patient.

Pain reported at the time of diagnosis is often inflammatory or neuropathic as a direct result of tumor-mediated damage and may present as the inciting symptom prompting patient-directed clinical evaluation for initial diagnosis as well as recurrence.[48] Initial symptoms of nasopharynx and oral cavity tumors may be confused with temporomandibular joint dysfunction, sinus problems, and pain of dental origin. The exact



• **Fig. 16.13** World Health Organization Pain Relief Ladder. (Adapted from Forbes K. Pain in patients with cancer: the World Health Organization Analgesic Ladder and beyond. *Clin Oncol* 23:379-380, 2011.)

cause of pain in cancer patients may result from direct bone or tissue destruction and nerve injury, but may also be influenced by cytokines secreted by cancer cells themselves and immunological factors.[49] In addition, surgical procedures result in acute pain, which can lead to chronic pain through inflammatory and neuropathic mechanisms. In a systematic review, OFP was reported in 49.5% at the time of diagnosis, 80.8% during treatment, 69.7% at end of treatment, and 36.2% at 6 months after treatment for patients with HNC. Patients who underwent multimodality treatment reported higher pain intensity, which often remained elevated for up to 1 year.[50]

Orofacial pain has been reported to have a significant negative impact on functional quality of life and social interactions in patients with advanced cancer.[51] Patients who have advanced-stage cancer, older age, and difficulty with eating or speech are more likely to experience oral pain, which can increase anxiety and depression. Patients with advanced cancer are more likely to have experienced surgery, including neck dissection, chemotherapy, and radiation, and to report a higher amount of oral pain and oral functional decrease.[52]

Neuropathic orofacial pain is a pathophysiologic pain that is complex in both its etiology and treatment. Neuropathic pain can occur through peripheral or central nervous system sensitization secondary to direct nerve injury (deafferentation pain) or through neuroplastic changes following prolonged nociception. This results in nerve fibers that have altered function, or signaling, which can lead to progressive and debilitating pain long after tissue healing has taken place. Post surgical neuropathic pain is frequently reported after ablative surgery and neck dissection and may be compounded by adjuvant radiotherapy.[53] Additionally, chemotherapy and paraneoplastic syndromes have been reported to produce pain in the head and neck region due to neurotoxicity and peripheral neuropathies, even for primary tumors located outside of the head and neck.[54] Certain cytotoxic agents such as vincristine, vinblastine, platinum agents, taxanes, and thalidomide may directly cause jaw pain and neuropathy.[47]

Patients who are immunosuppressed are at a higher risk of developing oral viral infections, as discussed in subsequent sections, and therefore are also at risk of developing post-herpetic neuralgias that contribute to the overall prevalence of orofacial pain in people with cancer. Mucositis is a significant source of OFP in patients undergoing radiation and chemotherapy, and the pain associated with mucositis can be compounded by secondary mucosal infection and hyposalivation.

Management

Successful management of OFP in cancer patients requires accurate assessment and diagnosis of the underlying pathophysiology. The management of orofacial pain during cancer treatment is typically aimed at controlling and reducing the inflammation that results from oral mucositis. Unfortunately, even with current guidelines to prevent and treat oral mucositis, treatment-related pain is rarely adequately controlled. One study reported up to 29% of patients had inadequate pain control.[55] Recommendations for management of mucositis pain include basic oral care approaches to maintain oral hygiene and minimize tissue irritation as well as the application of topical therapies and the use of systemic medications (see the earlier section on oral mucositis).

Post-treatment pain management presents a complex challenge to patients and providers. As mentioned earlier, decreased oral function and difficulties with eating or speech contribute to oral pain, and oral pain contributes to decreased function. Therefore, interventions aimed at improving maxillomandibular range of motion, postsurgical functional limitations, and oral mucosal adverse effects may improve non-neuropathic oral pain. Physical therapy is suggested for pain related to shoulder or neck dysfunction after neck dissection surgery and after flap harvesting from the cervical or facial region.[56]

As with many forms of chronic pain, cognitive behavioral therapy (CBT) has been shown to improve outcomes as an adjunct to other treatment modalities for chronic orofacial pain, although this has not been documented in chronic orofacial pain arising from cancer treatment.[57] Neuropathic pain unfortunately may not respond to over-the-counter treatment with nonsteroidal anti-inflammatory medications (NSAIDs) and frequently requires high doses of narcotics and opioids. This type of pain may respond to antidepressants and anticonvulsants or to local topical treatment.[56] Alternative therapies have also been suggested and include acupuncture, hypnosis, biofeedback, cannabinoids, and massage therapy.[54]

The World Health Organization (WHO) has developed a three-step "ladder" for cancer pain relief in adults, and this has been recommended for the use of managing pain in cancer patients[58] (Fig. 16.13). A stepwise approach to pain control starting with administration of non-opioids such as aspirin, acetaminophen, and NSAIDs, followed by mild to strong opioids is described (WHO, *Cancer Pain Relief,* 2nd edition, 1996). Multiple opioid preparations exist that can be administered by oral, parenteral, transdermal, or transmucosal routes.

TABLE 16.3 Descriptive, Qualitative, and Evaluative Patient Reports of Orofacial Pain

Neuropathic and Nociceptive Common Words	% Reporting	Qualitative and Evaluative Descriptors	% Reporting	Pattern	% Reporting
Burning	21.0	Tiring	22.6	Constant	65.5
Tender	26.6	Nagging	17.7	Intermittent	57.3
Soreness	25.0	Nauseating	7.3	Transient	33.1
Throbbing	20.2	Exhausting	7.3		
		Annoying	35.5		
		Troublesome	8.9		
		Miserable	8.9		

From Epstein JB, Wilkie DJ, Fischer DJ, et al: Neuropathic and nociceptive pain in head and neck cancer patients receiving radiation therapy. *Head Neck Oncol* 2009; 1:26.

Daily pain assessments are needed, with medications given for breakthrough pain. Adjuvant medications—for example, centrally acting pain medications such as antidepressants and anticonvulsants—are indicated for neuropathic pain in addition to opioids, and anxiolytics are indicated for sleep and to calm anxiety[59] (Table 16.3).

Hyposalivation/Salivary Changes

Changes in salivary quantity and quality have a profound impact on the oral cavity beyond the development of demineralization of enamel, cementum, and dentin. Saliva maintains proper oral pH, which provides antimicrobial (viral, fungal, and bacterial) properties, coating of the mucosal membranes, and protection from dehydration and injury. Additionally, saliva is essential for dental prosthesis retention, mucosal healing, taste perception, and oral function such as chewing, speaking, and swallowing.[60] The perception of lack of saliva, or xerostomia, occurs early in treatment and has been reported as a contributor to significant psychological stress and a reduction of quality of life after treatment concludes.[61] Xerostomia is the most common and at times permanent complaint of conventional radiotherapy.[5] The extent of this effect is dependent on cumulative dose and volume and type of salivary glands included in the therapeutic treatment field. With the use of parotid-sparing IMRT, there is potential for decreased rates of salivary hypofunction, and many patients report improvement in salivary-related symptoms during recovery over 1 to 2 years, as the submandibular and sublingual glands are unlikely to be spared if in the field of therapy. However, although there may be a decrease in the reported prevalence of xerostomia when compared to conventional radiotherapy, it remains unclear to what degree. 68.% of patients continue to report xerostomia after IMRT after more than 2 years of recovery.[5]

Hyposalivation is often quantified as a resting saliva rate of less than 0.1 mL/min. Damage occurs to salivary glands at doses between 26 and 40 Gy, and the extent of this damage depends on the dose and the volume of the salivary glands which are included in the treatment area.[5] Attempts to spare the parotid gland, which provides serous saliva and makes up 50% of whole, stimulated saliva is often considered during IMRT treatment planning. The submandibular gland, which provides serous and mucous saliva and makes up over 60% of resting saliva, and the mucous producing sublingual gland and minor salivary glands distributed throughout the oral cavity are more difficult to spare and some glands may have been surgically removed during primary tumor resection. Recent reports have investigated the role that mucins play in preventing dental disease and maintaining the integrity of the oral mucosa, and they highlight the importance of protecting and maintaining the submandibular, sublingual, and minor salivary glands during cancer treatment planning to minimize long-term oral sequelae[62] (Fig. 16.14).



• **Fig. 16.14** Well-healed right mandibular fibular free flap reconstruction for mandibular SCC. Note dental decay on remaining dentition.

Management

Novel methods to prevent irreversible damage of salivary gland tissues are currently being investigated. At present the use of parotid-sparing IMRT, the use of oral pilocarpine following HNRT, and the short-term use of mucosal lubricants or saliva substitutes have been recommended, while submandibular gland transfer and the use of acupuncture for salivary stimulation have been suggested to have clinical significance.[5] Pilocarpine hydrochloride has been reported to be effective in 42–51% of patients after 12 weeks, and around one third report medication-related side effects.[63,64]

The most common recommendation for palliation of xerostomia discomfort is frequent oral hydration. Artificial saliva in the forms of gels, rinses, and sprays is widely available in

retail stores and online. Mouth rinses and sprays should be at a pH close to neutral and above 6 to prevent dental erosion.[65] Patients should be educated to read product labels carefully to ensure that rinses do not contain alcohol or other products such as citric acid, which may cause mucosal irritation and dehydration. Many products have not been studied specifically in patients who have received HNRT and there has been a lack of analysis of product impact on oral mucosa. Products which may prove helpful to patients with xerostomia include Xerostom[66] and Mighteaflow. Mighteaflow contains green tea and xylitol and has been shown to increase both stimulated and unstimulated saliva; however, the sample excluded participants treated with head and neck radiation.[67] Small studies have shown green tea mouth rinses to reduce cariogenic bacterial colony counts and reduce pain and trismus associated with pericoronitis compared to 0.12% chlorhexidine.[68-70] Mouth rinses containing thyme and tea tree oil have been suggested to inhibit *Candida* species colonization.[71]

Additional products include lozenges, "mints," gums, or chews with various ingredients. Gums including calcium phosphate (in various formulations) and xylitol may be helpful to stimulate saliva and aid in dental remineralization. The Xeros dry mouth pump is a type of mechanical water device that is available commercially and provides water through a sponge/pump mechanism. Other companies produce "dental sprays," which are aerosolized water sprays. All of these commercially available products should be used with caution during active treatment, as they have not been studied for use in the presence of mucositis. While many patients continue to complain of xerostomia for years after treatment is complete, factors such as cost and treatment fatigue often prevent patients from using various over-the-counter and prescription methods, opting instead for frequent oral liquid intake for palliation.

Dysgeusia/Ageusia

Dysgeusia is the impaired sense or perception of taste and is common during chemotherapy (56.3%) and radiotherapy (66.5%). It is most pronounced with chemoradiotherapy (76%).[72] Taste perception is a complex sensation, which can be affected by primary tumor location, nerve damage from radiotherapy, salivary hypofunction, and secondary oral mucosal infections, particularly oral candidiasis. Direct damage by cancer treatment, through either surgical resection or radiotherapy, to the oral structures such as the palate and tongue also has an impact on taste perception. Dysgeusia can impact nutritional intake during cancer therapies and lead to malnutrition, weight loss, and anorexia. Taste changes related to radiotherapy tend to develop 3 to 4 weeks after the start of treatment and can occur when the dose is as low as 30 Gy.[73] Tumor invasion or surgical resection can lead to taste abnormalities through damage to various cranial nerves at multiple points of the nerve distribution and include cranial nerves V (trigeminal), VII (facial), IX (glossopharyngeal), and X (vagus). These changes are often underreported and may resolve as soon as 8 weeks after treatment or become a persistent problem.[74] Treatment or tumors that impair the sense of smell also have an impact on taste perception and lead to increased taste alterations. Unfortunately, many studies investigating dysgeusia include heterogeneous cancer diagnoses and treatments and do not uniformly define or test for taste disturbances.

Management

After treatment, changes in taste perceptions can lead to a reliance on overly sweetened or highly processed foods, which increases the risk for dental caries. Although numerous methods for prevention and management have been suggested, evidence supports nutritional counseling and education while recommending against the use of zinc gluconate and amifostine.[72] Management includes dietary counseling regarding increasing seasoning and rotating food choices, as taste alterations have been associated with changes in food preference.[75] Additionally, addressing salivary hypofunction, although the degree of this effect is unknown, along with decreasing use of alcohol or tobacco may be helpful. Treating dental disease, such as rampant caries and periodontitis, may help improve taste perception if the disease is severe and advanced.

Nutrition

Dietary and nutritional counseling should be included as part of the pretreatment dental and oral evaluation as well as reinforced at post-treatment follow-ups. Loss of more than 15% of body weight has been associated with reduced survival, and poor nutritional intake can lead to increased morbidity during cancer therapy and psychological stress.[76] Malnutrition has been widely reported in head and neck cancer patients, with a range from 30% to 90%.[77] The dental oncologist is uniquely prepared to discuss dietary needs for patients undergoing cancer treatment with a focus on maintaining weight and nutritional status while minimizing exposure to and reliance on high-sugar and overly processed foods that may lead to dental decay. The importance of maintaining a low-cariogenic diet throughout treatment and during recovery should be discussed with other members of the head and neck cancer team. Recommendations for maintaining weight and for palliation of oral adverse effects are often at odds with the need to reduce the risk for the development of dental disease. Nutritionists, nursing staff, medical and radiation oncologists, and surgeons should be educated on the negative effects of many recommended strategies that aim to help patients gain weight without improving nutritional intake. As BMI (body mass index) is not a reliable tool for establishing nutritional status, one study found that 96% of patients were malnourished when using NRI (Buzby nutritional risk index) versus only 36% identified through BMI analysis.[77] This points to the importance of nutritional analysis with recommendations aimed at improving nutritional intake rather than focusing on weight gain alone. As an example, a person with an obese or overweight BMI can certainly be malnourished.

Management

Although nutritionists are essential members of head and neck cancer teams, most cancer care is not delivered with nutritional support embedded in the team. Models for care delivery are typically available through referral-based services, and therefore

TABLE 16.4 Dietary Recommendations in Oncology With Consideration of Oral Disease

Recommendation	Problem	Dental Disease	Alternative
Lemon drops, hard candies, peppermints	High sugar, acid	Dental decay Enamel erosion	Sugar-free, xylitol-containing hard candies
Lemon in water/sports drinks	Acidic/ high in sugar	Mucosal irritation, enamel erosion	Sugar-free electrolytes
Flavored ice pops	Added sugar	Dental decay	Frozen fruit (grapes, blueberries, mango) Ice chips

are less likely to rely on evidence-based protocols.[78] Reduced nutritional intake is best supported by dietary counseling along with management of treatment-related side effects that further impair oral intake, such as xerostomia, dysgeusia, oral pain, dysphagia, and trismus, as well as promoting optimal dental health and prosthesis function. Suggestions for improved oral intake include additional butter, gravies, and sauces along with eating soft foods in small pieces. Blending or processing foods may be necessary for patients with severe oral pain. Patients report difficulty in eating a variety of nutritious foods due to changes in texture, degree of hydration, and consistency. Many report foods with a creamy consistency meant to improve swallowing ability, such as pudding, Jell-O, and mashed potatoes, as feeling like "glue." Patients also report distress and social isolation due to the amount of time they need to complete a meal post-treatment.[79]

At times patients may be required to depend on gastrostomy tube (G-tube) or nasogastric tube feeding if oral intake is impossible or inadequate. When reviewed, these strategies, along with oral nutritional supplements, show inconsistent findings in relation to nutritional status.[80] Additionally, as the impact of a high-sugar diet is being elucidated, concerns regarding a diet with a high glycemic index for weight gain are emerging, and this is especially concerning in the oncologic setting[81] (Table 16.4).

Oral Infections

Oral Fungal Infection

Candida species are natural inhabitants of the oral cavity that, with any local or systemic change in host factors, can cause opportunistic infection. In cancer patients, multiple factors predispose to fungal infection, including systemic immunosuppression and local changes to the oral environment such as tissue injury from mucositis and hyposalivation. Oral candidiasis is by far the most common superficial fungal infection and is most commonly caused by *Candida albicans*, but other species, including *C. glabrata* and *C. tropicalis*, have been shown to cause infection.[82] Prevalence of oral candidiasis has been reported to be 37.4% during HNRT and 38% during chemotherapy[83] (Fig. 16.15).

Candidiasis occurs in the oral cavity in four recognized clinical patterns:

- *Pseudomembranous candidiasis:* White, removable plaques that leave an erythematous base when wiped off
- *Atrophic or erythematous candidiasis:* Friable, erythematous mucosa that bleeds easily



• **Fig. 16.15** Chronic hyperplastic candidiasis in an immunosuppressed patient.

- *Angular cheilitis:* Fissured, crusted commissures of the lips
- *Chronic hyperplastic candidiasis:* White plaques that cannot be wiped off, occurring in immunocompromised patients

Diagnosis. The diagnosis of candidiasis can often be made on clinical exam because of its characteristic clinical manifestations. In some cases, however, adjunctive diagnostic techniques can be useful. Cytopathology from a clinical smear can demonstrate *Candida* quickly and accurately. Culture and sensitivity testing may be useful, especially if first-line treatments fail and resistance is suspected. *Candida* can also be demonstrated by tissue biopsy, although this is rarely necessary except in cases of hyperplastic candidiasis.

Prevention and Treatment. Topical agents tend to be preferred for the management of mild oral candidiasis because of their lack of systemic side effects. Examples include clotrimazole troches and nystatin rinse and pastilles. Troches and pastilles may be limited in their effectiveness in the presence of hyposalivation. Also, most topical formulations contain sugar, which is of concern in a patient population at significant risk for the development of caries.[83]

Fluconazole is an effective systemic agent for the prevention and treatment of oral candidiasis in patients receiving cancer treatment. For candidiasis that is not responsive to fluconazole, agents such as itraconazole, posaconazole, voriconazole, and



• **Fig. 16.16** Mucormycosis involving the mandible.

amphotericin B are recommended. The echinocandins (micafungin, for example) are additional agents that can be useful in refractory candidiasis.[83] Short duration of systemic therapy is recommended because of the emergence of resistant species of oral *Candida*.[83]

Invasive Fungal Infections

In the oral cavity, deep fungal infections can present as ulcerative, invasive infections with associated granulomas and necrosis. These infections are usually indicative of disseminated infection and severely immunocompromised status. Aspergillosis, cryptococcosis, histoplasmosis, geotrichosis, blastomycosis, and mucormycosis are examples of such infections, but rarely involve the oral cavity. Diagnosis is by tissue sample using special stains to detect fungal pathogens.[83a]

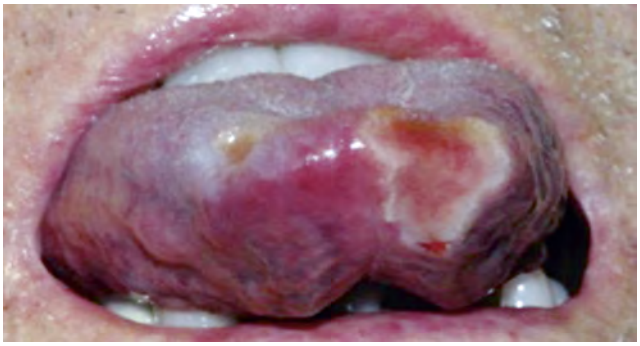
Mucormycosis is an acute opportunistic fungal organism of the class Zygomycetes. It is a saprophytic fungus that is present naturally in soil, bread mold, and fruits and vegetables. In the immunocompromised host it can be a highly virulent pathogen, causing a rapidly progressive infection that results in widespread ischemic tissue necrosis.[84]

Clinically, oral mucormycosis can present with palatal ulceration and necrosis often originating from infection in the nasal cavity and paranasal sinuses (Fig. 16.16). Patients typically have associated facial cellulitis, nasal ulceration, necrosis and discharge, anesthesia or pain, headache, and fever. Without treatment the infection is rapidly progressive and can lead to death.[84,85]

The infection is diagnosed by the presence of typical fungal hyphae in tissue sections. Treatment involves control of the underlying immunodeficiency, surgical excision/radical debridement of necrotic tissue, and administration of amphotericin B or the newer antifungal agent isavuconazonium sulfate. Close follow-up with computed tomography (CT) scans and nasoendoscopy to detect recurrence is recommended.[85]

Oral Viral Infection

Oral viral infections are commonly caused by Herpesviridae, notably herpes simplex (HSV), varicella zoster (VZV), Epstein-Barr (EBV), and cytomegalovirus (CMV). Human papillomavirus is another common virus in the oral cavity but will not be discussed here.



• **Fig. 16.17** Herpes simplex virus (HSV) infection of immunosuppressed patient.

Herpetic viral infections are a common occurrence during cancer therapy. Oral infections can be debilitating and cause severe pain that can reduce oral intake. Even in the immunocompromised host, viral infections have distinct clinical features, and it is important to recognize these early and treat accordingly. The prevalence of oral HSV infection in patients undergoing radiation therapy with concurrent chemotherapy has been determined to be 43.2%[86] (Fig. 16.17).

Clinical Presentation and Diagnosis. Oral and perioral HSV infection in the immunocompromised patient occurs as a reactivation of latent HSV. Ulcerations typically present on the keratinized mucosa of the gingiva, palate, and tongue, but in immunocompromised individuals, ulcerations can occur on any mucosal surface.[87] Lesions begin with vesicle formation and progress to ulceration where multiple ulcers can coalesce to form large ulcers with a typical yellow/red base and yellowish border.

Diagnosis can often be made on clinical presentation; however, this can vary greatly in immunocompromised patients, and adjunctive diagnostic techniques can therefore be helpful. Cytology is an easy and expedient way to confirm or rule out viral infection. A smear can confirm the presence of virus by identifying cytopathic effects on cells infected with virus, but cannot differentiate between infections with different herpes viruses. Culture is the gold standard and can differentiate between herpes species with sensitivity testing that can determine presence of resistance to antiviral medications. Direct fluorescent assay can also be performed on tissue culture for rapid diagnosis. Serology is useful especially in immunocompromised patients to determine susceptibility to recurrent HSV.[88]

Prevention and Treatment. Most studies have focused on the treatment of HSV infections in the oral cavity. Acyclovir and valacyclovir are indicated prophylactically in the prevention of HSV infection in seropositive patients. Both are also effective for treatment of HSV infection. Famciclovir and foscarnet are alternative agents for refractory disease.[86]

Oral Lesions of Immunological Origin: Aphthous Stomatitis

Aphthous stomatitis is a common condition in the general population, and multiple etiological theories considering local and systemic factors have been proposed with several studies pointing towards an immunological role in the pathogenesis



• **Fig. 16.18** Major aphthous ulceration in a child on high-dose chemotherapy.

of this condition. Immunocompromised patients may have an increased incidence of aphthous stomatitis, and major aphthae may be seen in immunosuppression.[89,90]

Diagnosis is primarily based on exclusion, as histopathology shows non-specific ulceration and cytology and culture are negative. Aphthous ulcerations characteristically occur on movable mucosa, are round, and have an erythematous halo and a base covered with a whitish-gray pseudomembrane. Three clinical types are recognized: minor aphthous with ulcerations usually less than 5 mm in diameter, herpetiform aphthous characterized by crops of multiple pinpoint ulcerations; and major aphthous where ulcerations are typically greater than 10 mm in diameter, are slow to heal, and can heal with scarring[90,91] (Fig. 16.18).

Treatment of aphthous stomatitis in the cancer population starts with proper diagnosis to rule out infectious etiology or ulcerations secondary to the cytotoxic effects of cancer therapy. Once diagnosed, aphthous ulcerations typically respond to a potent topical steroid such as clobetasol; however, major aphthous ulcerations can require intralesional steroid injection or systemic steroid treatment for resolution.[92,93]

Chronic Oral/Dental Complications

Oral Mucosal Fibrosis and Trismus

Fibrosis of the oral tissues can occur as a late effect of radiation therapy. This can affect mouth opening and tongue and lip movement, thereby influencing mastication, speech, and delivery of oral care.[94] Trismus is defined as a reduced mandibular range of motion due to contraction of the muscles of mastication (MOM). This can occur from postsurgical damage to nerves, proliferation of scar tissue, or radiation-induced fibrosis of the MOM (Fig. 16.19). Patients who receive over 60 Gy to the temporomandibular joint, pterygoid, or masseter muscles are most at risk for developing trismus; these include patients with nasopharynx, oral cavity, and oropharynx tumors.[95] Prevalence of trismus in cancer populations has been found to be 25.4% for conventional RT, 5% for IMRT, and 30.7% for combined RT and chemotherapy. Reports vary greatly, however, with some citing up to a 42% prevalence



• **Fig. 16.19** Trismus developed after surgical resection for maxillary osteosarcoma.

rate.[95] Radiation-induced trismus can begin during treatment and progress during the healing phase, and in some cases, it can be both progressive and irreversible. This pathologic contracture of the MOM can impair nutritional intake, precipitate social isolation, and reduce quality of life.[96]

Systematic reviews have found little evidence supporting preventive therapy and have produced one suggested intervention, the use of a passive motion device, the Therabite Jaw Motion Rehabilitation System.[95] This intervention has been found to be cost-effective as a preventive measure when compared to the cost of treating aspiration pneumonia, orofacial pain, and feeding substitutes along with usual care and management from physicians, dentists, and speech and language pathologists.[97] The study did not account for or estimate the expense of loss of oral function on dental health or the potential social impact for patients with trismus. Interventions aimed at preventive mobility exercises have not been shown to be effective.[98] Injection of botulinum toxin to the masseter muscles has not been shown to improve opening but may reduce pain and improve oromandibular dystonia.[99] There is sparse evidence in the area of interventions for trismus and radiation-induced fibrosis of the muscles of mastication so that no generalizable protocols are available. More research is needed in this area.[100]

Oral Pre-cancer and Secondary Malignancies

Patients who have undergone cancer therapies are at an increased risk for development of secondary malignancies.[101] The incidence of secondary malignancies in patients treated for head and neck cancer has been reported as 3–7% per year.[102] Risk factors include a history of smoking, alcohol use, very young or old age, immunosuppression, previous radiation therapy, and the presence of HPV serotypes 16 and 18.[102] A history of index tumors in the hypopharynx, larynx, oropharynx, or oral cavity is associated with the highest risk of second primary malignancy, more so than tumors of the nasopharynx.[103] Tsou and colleagues reported an incidence of 30.6% of second primary malignancies occurring in the oral cavity[103] while Vaamonde and co-workers reported 6.2% in the oral cavity.[104]

The concept of premalignant lesions as the precursors to squamous cell carcinoma of the oral cavity is well accepted. Oral leukoplakia and erythroplakia are lesions that are associated

clinically with premalignancy because they have a higher incidence of dysplasia histopathologically than that of normal tissue. Between 1% and 30% of oral leukoplakias exhibit dysplasia, and follow-up studies have shown that between less than 1% and 18% of oral leukoplakias will develop into oral cancer. In contrast, erythroplakias almost always reveal dysplasia. Also, 16% to 62% of squamous cell carcinomas arise from a premalignant lesion.[105]

Although the preceding findings reported by Reibel and associates are not from studies exclusively on cancer patients, it is only logical that patients who have received radiation and/or chemotherapy for head and neck cancer be kept under close surveillance and that any oral changes in this population that cannot otherwise be diagnosed should be biopsied to rule out secondary malignancy.

Osteoradionecrosis

Although osteoradionecrosis (ORN) of the jaw has been a recognized entity since the early 20th century, Marx first described a model for its definition and pathogenesis in 1983.[106] He described ORN with the "3 H" hypothesis of hypoxia, hypocellularity, and hypovascularity and proposed a treatment protocol based on hyperbaric oxygen (HBO) therapy.[107] Since that time, ORN has come to be recognized as one of the most significant long-term complications of HNRT with a considerable negative impact on quality of life. The majority of patients with head and neck cancer are at risk of ORN, as radiation therapy (RT) is used with or without concurrent chemotherapy both for primary treatment and as an adjuvant to surgical management. The mandible is at higher risk for development of ORN than the maxilla, and this is thought to be because of the lesser vascularity present in mandibular bone.[108] Since Marx's theory of pathogenesis, other theories have been proposed, including a mechanism of radiation-induced fibro-atrophy of endothelium by direct and indirect (free radical) damage and a radiation-induced osteoclast dysfunction.[109-111]

The reported prevalence of ORN varies greatly in the literature. In a recent review, Peterson and co-workers reported a weighted prevalence of ORN in patients treated with conventional RT of 7.4%, with IMRT 5.2%, with chemo-RT 6.8%, and with brachytherapy 5.3%.[112] With advances in radiation therapy and the use of IMRT, recent studies have reported lower incidence rates. Gomez and colleagues reported retrospectively on a group of 168 patients in which 2 patients with floor-of-mouth cancer developed ORN (1.2%).[113] Sulaiman and associates reported a 2.14% incidence of ORN in 1,194 patients seen between 1988 and 2001,[114] and Ben-David and colleagues reported 0 cases of ORN in 176 patients treated with IMRT between 1996 and 2005, both studies attributing their low rate of ORN to meticulous prophylactic dental care.[115]

Disease-related risk factors for ORN are related to tumor size and location, with larger tumors resulting in higher radiation doses to the entire mandibular bone.[116] Tumors located in the oral cavity, specifically the tongue, floor of mouth, and retromolar trigone, are associated with a higher risk of ORN, likely due to the position of the mandible directly in or adjacent to the radiation field and because surgical management of these tumors often involves resection of mandibular bone.[117] Similarly, radiation features related to risk of ORN include the type of radiation (external beam vs. brachytherapy), the field of radiation and its proximity to the jaws, and the dose and fractionation schedule of radiation delivered to the bone. Risk of developing ORN is reported in areas of the bone receiving more than 50 to 60 Gy.[118]

Patients with increased risk of ORN include those with a complex medical history, poor nutritional status, history of trauma to the jaws, history of tobacco and alcohol use, and, most importantly, poor oral health or advanced dental disease.[110,112] It has been shown that dental extractions after radiotherapy are less likely to cause ORN if outside the field of high-dose radiation, but it is also of importance that preradiation extractions can contribute to the risk of ORN.[114] Comprehensive evaluation prior to radiation therapy and appropriate preradiation dental treatment and education have been shown to significantly reduce the risk of ORN.[114,115] An atraumatic surgical technique and adequate healing time prior to radiation has also been associated with a reduced risk of ORN.[114]

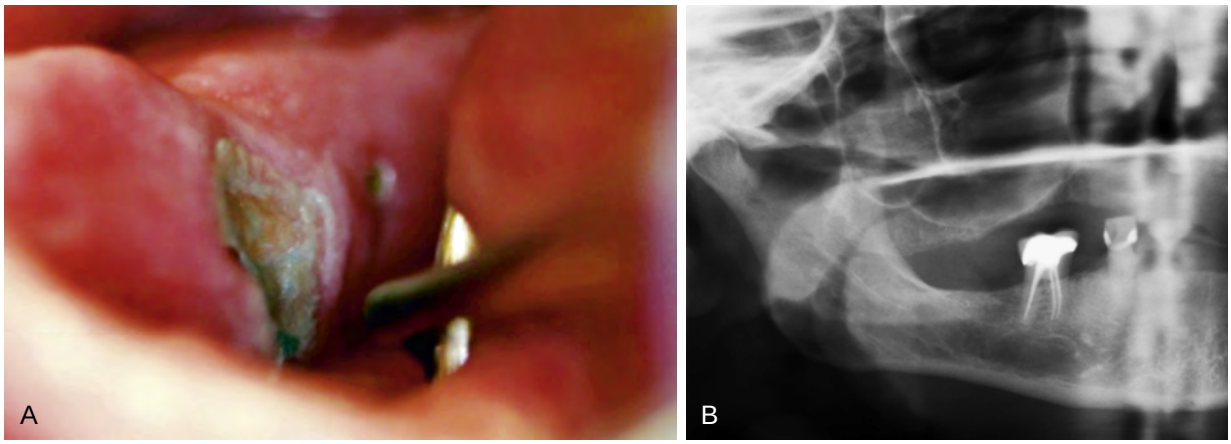
Clinical Presentation

The hallmark of ORN is the clinical presence of non-healing exposed devitalized bone in a site previously irradiated and free of tumor.[110] Infection, if present, is considered secondary.[108] ORN is more common in the mandible than the maxilla and can present asymptomatically or with pain or paresthesia. It can progress to cause mobility of involved teeth, pathologic fracture, and orocutaneous fistula. Radiographic signs of ORN include rarefaction of bone trabeculation, loss or irregularity of crestal bone, and widened periodontal ligaments. Sequestration of bone may be seen in lytic areas[119] (Figs. 16.20 through 16.22).

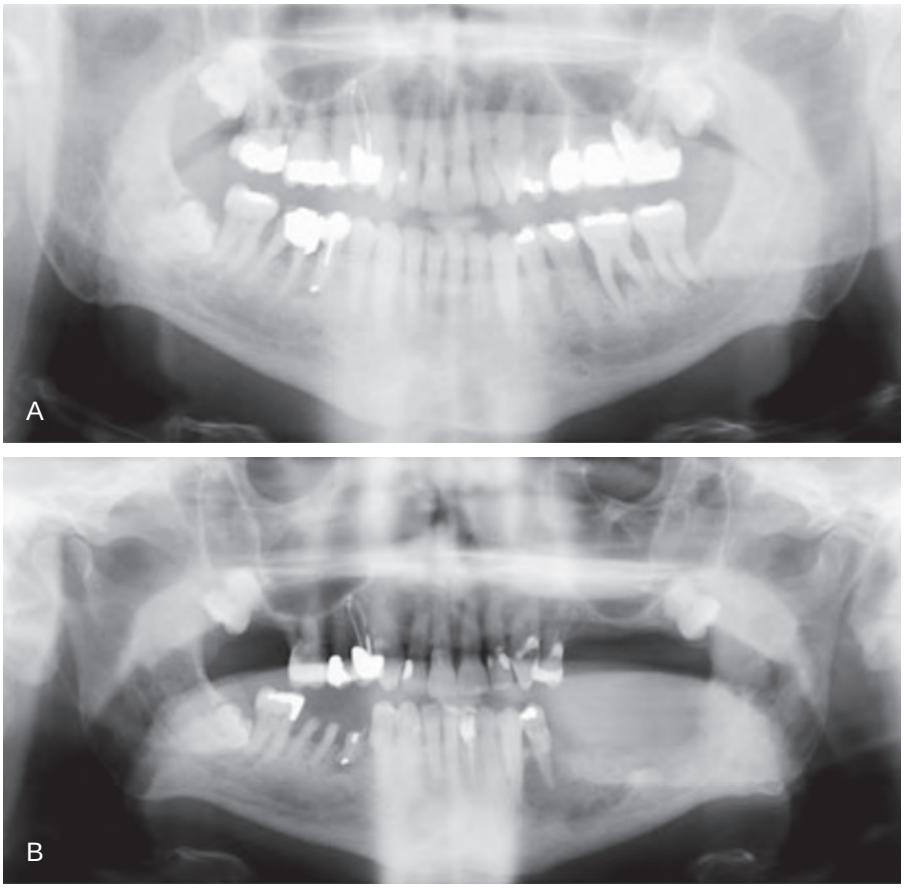
Prevention and Treatment of ORN

Prevention of dental disease necessitating post-RT extractions, as mentioned earlier, is key in the prevention of ORN. Meticulous preradiation dental treatment planning that takes the long-term prognosis of the dentition into consideration is imperative. Dental factors such as extent, type, and state of repair of existing restorations, caries status, and periodontal status must be considered. Also important in preradiation dental treatment planning is the anticipation of future prosthetic rehabilitation. Supra-erupted teeth without opposing dentition and exostoses/tori should be considered for removal. All of these factors should be evaluated with the details of the patients' oncologic disease and treatment in mind. Knowledge of anticipated radiation dose to dentate areas will help in proper treatment planning.[116] Factors such as extent of surgical morbidity and trismus will play a role in patients' ability to maintain their dentition after their oncological treatment is complete.

Treatment of ORN has historically been based on staging. Marx initially proposed three stages related to HBO therapy response,[106] and in 1987 Epstein and associates proposed three stages with subdivisions considering the presence of pathologic fracture.[120] Later classifications proposed by Schwartz and Kagan[121] and Notani and colleagues[122] were based more on imaging and clinical findings.[123]



• **Fig. 16.20 A** and **B,** Right lingual mandibular alveolar ridge osteoradionecrosis. Patient was treated with chemotherapy and radiation for squamous-cell carcinoma of the base of the tongue. Dental extractions took place 6 weeks prior to intensity-modulated radiotherapy (IMRT). Comorbid conditions include smoking, type 2 diabetes, and alcohol abuse.



• **Fig. 16.21 A** and **B,** Progression of osteoradionecrosis over a period of 2 years in a patient treated with intensity-modulated radiotherapy (IMRT) for squamous cell carcinoma of the base of tongue.

In early lesions of ORN, conservative management, consisting of analgesics, antibiotics for superficial infection, basic wound care including an antiseptic mouth rinse such as chlorhexidine, and removal of loose sequestra, is recommended. Many early cases will resolve with conservative treatment.[123,124]

The use of hyperbaric oxygen therapy in the management of ORN is controversial, and there is a lack of conclusive evidence on the subject. HBO can be used prophylactically, therapeutically, or as an adjunct to the surgical treatment of ORN. Although Marx's original study showed a positive response to HBO,[107] more recent studies have shown less positive effects. Annane and colleagues conducted a large randomized controlled trial that was stopped because of potentially poor outcomes in the HBO arm.[125] Based on the new understanding of the pathophysiology of ORN,[111] HBO therapy is not recommended as primary therapy for ORN, but only as adjunctive therapy for cases where mandibular resection and/or reconstruction is needed. This is due to the fact that HBO exerts an effect on viable, not necrotic, tissue.[112,123,126,127]

New pharmacological treatments are in use with the changes in the understanding of the pathophysiology of ORN. Pentoxifylline is known to promote vascular dilation and increased erythrocyte flexibility as well having an anti TNF-α effect. Tocopherol is an antioxidant and capable of scavenging reactive oxygen species. Clodronate is a non-nitrogenous bisphosphonate that has been shown to promote osteoblast activity.[128] These agents have been used in combination in trials showing encouraging results. Delanian and associates prescribed pentoxifylline 400 mg twice daily and tocopherol 1000 IU daily to 18 patients for 6 to 24 months. Patients with severe ORN also received 1600 mg clodronate 5 days a week.[129] In a later trial, 54 patients were given doses of 800 mg pentoxifylline, and prednisone and ciprofloxacin were added with all patients experiencing complete resolution. It was concluded that the treatment was well tolerated and effective.[130] McLeod and co-workers reported a more moderate response in 12 patients.[131]



• **Fig. 16.22** Osteoradionecrosis of the mandible. (Photo courtesy Dr. Joel Friedman.)

In advanced cases of ORN with pathologic fracture or orocutaneous fistula involvement, surgical resection and reconstruction with a vascularized flap is recommended. These modalities are discussed elsewhere.

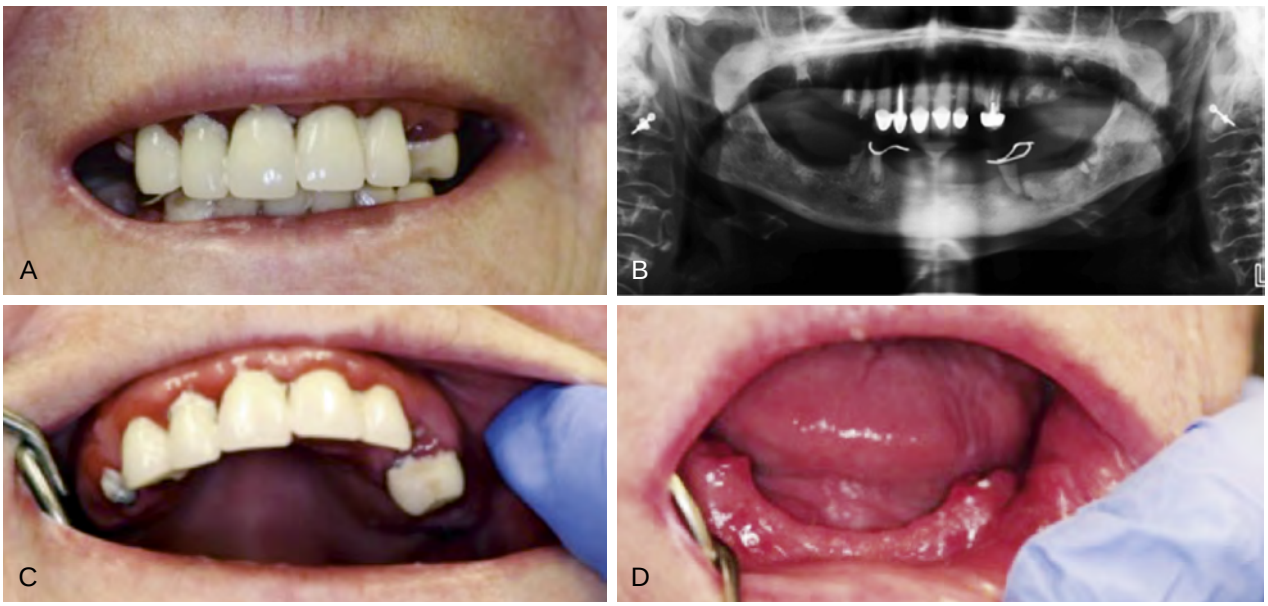
Periodontal Disease

Periodontitis is an inflammatory response to subgingival pathogenic bacteria which results in progressive destruction of the gingiva, periodontal ligament, and supporting alveolar bone. Increased sensitivity of oral tissues can lead to impaired oral hygiene, which may lead to increased supra- and subgingival plaque and calculus accumulation, which triggers the host-regulated response that leads to periodontitis.

In addition to the impairment in optimal oral hygiene after ablative and reconstructive surgery, postoperative adjuvant radiation may increase the risk for altered healing, exacerbation of the inflammatory response, and impaired or exaggerated local host response.[132] Salivary dysfunction may lead to changes in the subgingival bacterial biome causing a shift to more pathologic species.

Periodontal disease by definition involves the destruction of alveolar bone and therefore presents a risk factor for the development of osteoradionecrosis if the disease is left untreated in the irradiated field.[21]

Tobacco use is a co–risk factor for oral, head and neck squamous cell carcinoma and for periodontitis. Patients who experience head and neck cancers with tobacco use as a contributor to disease onset are at particularly high risk of presenting with existing periodontal disease or a history of periodontal disease with reduced periodontium. Tobacco use and smoking have been estimated to be responsible for nearly half of the cases of periodontitis in the United States and are a major risk factor for periodontitis[133] (Fig. 16.23).



• **Fig. 16.23** **A** to **D,** Patient treated 10 years prior for stage IVA squamous cell carcinoma of the tonsil. Trismus, periodontal disease, poor oral hygiene, dental decay, and oral erythematous candidiasis.

Dental Decay/Radiation Caries

Patients who receive HNRT are at a higher risk of developing severe dental caries due to hyposalivation, which can cause a shift in bacterial oral flora in favor of more acidic and cariogenic species. Controversy exists regarding which direct effects radiation has on the hard structures of the teeth. Studies have found conflicting results, and consensus is difficult due to the heterogeneity of previous investigations.[134] Proposed mechanisms of degradation include reduced tensile strength and decreased microhardness of enamel and dentin.

There remains conflicting evidence regarding the effects of radiation on dental pulp, including its vasculature, innervation, and extracellular matrix.[135] The primary site of tumor and radiation dose is frequently cited as correlated with an increased risk of dental decay.[26] The typical pattern of damage occurs at or near the cervical region of the tooth with brown discoloration and/or enamel hypoplasia and may progress at a rapid pace. Restorations placed at the gingival third of the clinical crown and those placed in cervical cementum may have less restorative success than other direct alloy, composite, or glass ionomer restorations placed in occlusal or interproximal enamel. Additionally, cervical tooth destruction can occur on both buccal and lingual surfaces, leading to the "apple-core" effect, which significantly weakens the remaining non-carious tooth structure. Potential for increased microleakage of existing restorations has also been proposed as a potential mechanism for rampant decay.[136] Prevalence of dental caries in patients treated with cancer therapies has been reported as 37.3% for chemotherapy alone, 24% post radiotherapy, and 21.4% post chemotherapy and radiotherapy[137] (Fig. 16.24).

Management

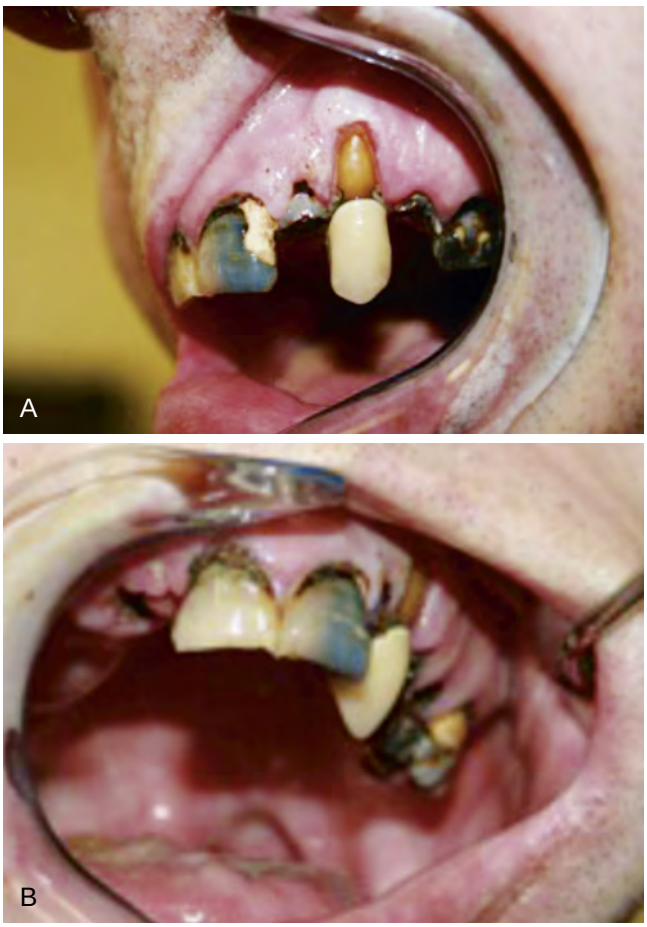
Prevention and management of periodontitis and dental caries for people undergoing cancer treatment remains similar to the general population and includes daily oral hygiene and routine preventive visits with oral health care professionals. However, physical discomfort following surgical resection and reconstruction, chemotherapy, and radiation may interfere with preventive home care. Limitations on physical access to areas of the oral cavity after surgery may lead to poor oral hygiene and increased risk of dental disease. Additionally, patients with dysgeusia and hyposalivation may tend to gravitate toward a diet of softer, higher-carbohydrate foods.

To prevent dental decay, 1.1% neutral sodium fluoride, regardless of the administration, continues to be recommended by many guidelines.[137] Recent investigations have found products containing tricalcium phosphate (Clinpro 5000) to improve availability of surface fluoride ion in the setting of xerostomia.[138] Incorporation of products aimed at remineralization, such as xylitol-containing gums, candies, and lozenges may be helpful for patients at high risk for dental disease. Investigations into the use of fluoride varnishes, chlorhexidine varnishes, use of honey or cheese, and various toothpaste formulations have been suggested, but no guidelines can be suggested due to lack of available evidence.[137]

Patients who receive head and neck radiation should be followed closely and carefully by the patient's general dentist in conjunction with the dental/oral oncologist. "Radiation caries" or cervical carious lesions that occur after treatment with head and neck radiation can be difficult to control and restore. Resin-modified glass ionomer, composite resin, and/or amalgam restorations are recommended over conventional glass ionomer restorations for use in patients treated with head and neck radiation. As patients who have been treated with HNRT are more likely to develop dental decay, the response of the apical periodontium to bacterial insult from the dental pulp may be altered, and more likely to develop apical periodontitis when compared to non-irradiated teeth and bone.[139]

Removable Prosthetic Rehabilitation

The head and neck team provides a continuum of care for cancer patients to manage xerostomia, trismus, prosthetic care and comfort, oral hygiene, and psychosocial issues, as well as to monitor the disease process. Maxillofacial prosthodontics encompasses both a restorative component and a supportive component in treating cancer patients, traumatically injured



• **Fig. 16.24** **A** and **B,** Patient who had been treated 15 years earlier with surgical resection and chemoradiation for multiple squamous cell carcinoma of oral cavity sites presented with severe dental caries, failed restorations, and periodontitis.

patients, and patients who have congenital defects of the head and neck. Optimal treatment requires an understanding of the engineering, architecture, physics, and psychotherapy that is needed to provide treatment to improve speech, deglutition, and social acceptance.[140]

Obturators

When immediate microvascular free-flap reconstruction is not indicated, a surgical obturator is fabricated with the methodology of fabricating an immediate prosthesis by taking initial impressions and altering the cast under direction of the head and neck surgeon as to the planned resection for cancers of the maxilla, hard, and at times soft palate. Depending on the extent of the resection, the retention mechanism can be by wiring the surgical obturator to remaining teeth or by wrought-wire clasping systems. A second interim obturator will also be fabricated on the initial cast. After the surgical obturator is removed in 7 to 10 days, the interim obturator will be delivered and adapted to the surgical site with chairside reline material. The chairside reline material is a tissue conditioner that is kind and forgiving to the healing tissue, yet is resilient enough to provide retention, stability, and comfort when adapted to undercut areas.

Interim obturators are worn during the initial healing period. Factors that affect interim obturators and length of healing time are radiation therapy, chemotherapy, and individual healing ability. The interim obturator will be continually modified during the healing phase to adjust for changes in the tissues. After 6 months to 1 year, when healing has stabilized, evaluation is made for fabrication of a definitive prosthesis (Figs. 16.25 and 16.26).

Definitive maxillary obturators are fabricated using conventional removable prosthodontic methods. Initial impressions for diagnostic casts are made. If remaining dentition is adequate for supporting a removable partial denture obturator prosthesis, a framework design is planned on the diagnostic cast using remaining teeth for retention and stability of the prosthesis. Consideration should be made for a retention clasp designed to incorporate as much retention and as many teeth as possible. Retainer bars and plates will also be designed to encompass as much surface area as possible.

The complete denture obturator prosthesis is fabricated with the same methodology as conventional complete denture prostheses, except that the design of the obturator bulb must be impressed differently. Initial impressions are made by blocking out the resection area with gauze and then making an alginate impression. A custom tray is fabricated on the initial cast. The custom tray should be border molded, and a definitive impression is made using a resilient material that will capture the resection area but is viscous enough not to flow into unwanted areas. This impression will be used to pour the master cast in Type IV dental stone. The occlusal rims will then be fabricated on the master cast. The occlusal rim will be used during the records appointment to record the occlusal line parallel to the ala tragus line, the anterior teeth line parallel to the interpupillary line, the midline, and the vertical dimension of occlusion. These records will then be used to complete a wax setup of denture teeth. The wax try-in will follow to confirm jaw relation records. Patients should be included to verify esthetics and phonetics. The obturator bulb can be redefined during this appointment, if needed, with an impression material or denture reline material with a moderate viscosity. The wax-up is then ready for processing in heat-cured acrylic resin, is polished, and finished for delivery.

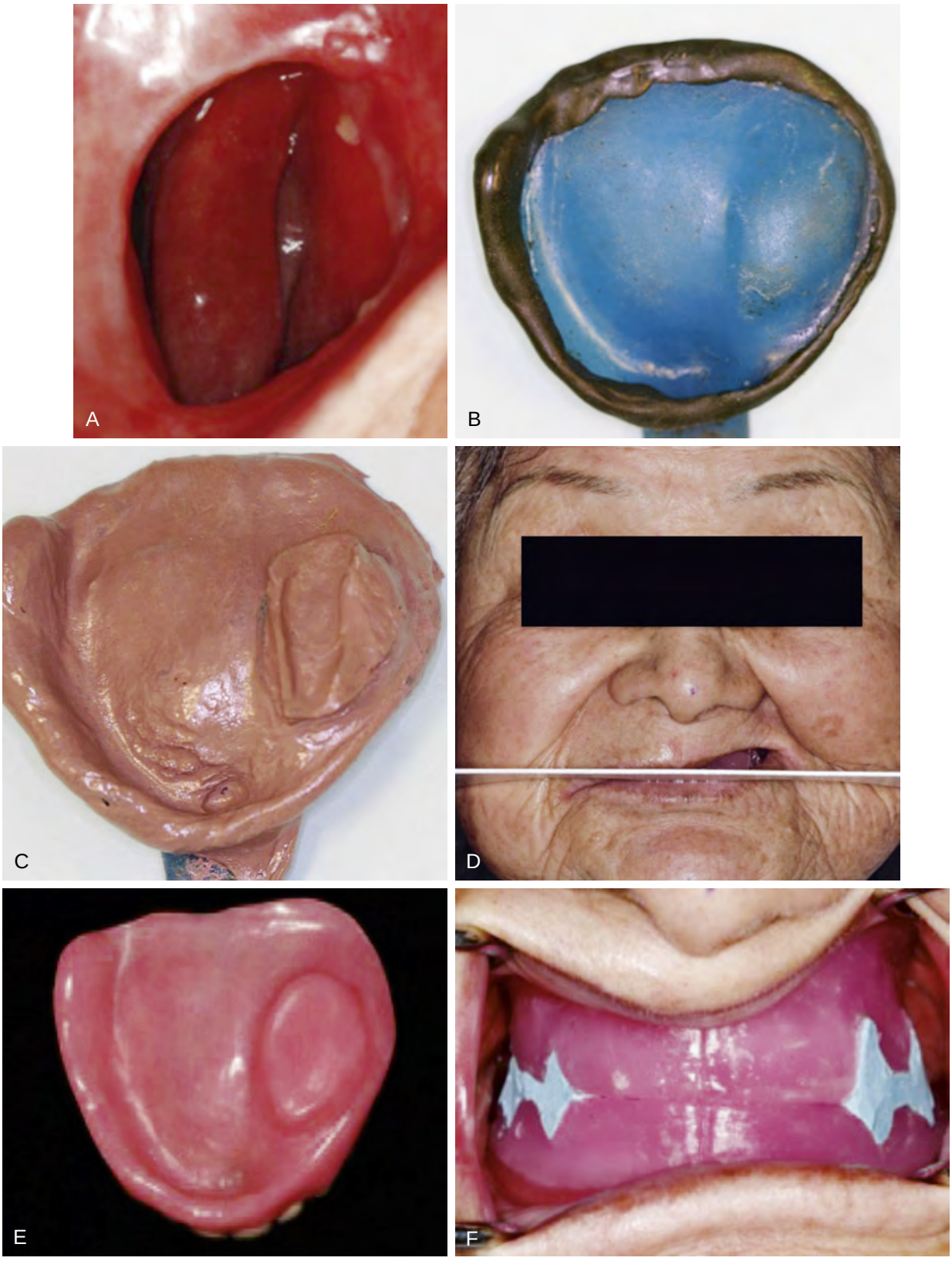
Mandibular Resection Appliances

Mandibular resections are often primarily reconstructed with vascularized bone and soft tissue free flaps to replace missing anatomy by the micro-vascular reconstructive surgeon. For prosthodontic reconstruction, these resections are often better served with the use of dental implants for retention and stability. Tissue-borne removable prostheses may be challenging, as soft-tissue reconstruction is achieved through cutaneous grafting, which poses a challenge for prostheses designed to rest on mucosal soft tissue. Additionally, many patients undergo adjuvant radiotherapy, which may lead to xerostomia that impairs prosthesis function. Surgeons who pay attention to the importance of creating a residual ridge with adequate bone height and width along with lingual and buccal vestibules are more likely to achieve a functional result through removable prosthetic rehabilitation. Dental implants can be placed at the time of grafting or postoperatively. Prosthetic designs for mandibular resections are dependent on the anatomy that remains after the resection and type of reconstruction. Often innovative prosthetic designs are needed because of missing anatomy and lack of keratinized tissue (Figs. 16.27 through 16.30). Unfortunately, reported rates of success of complete implant-supported dental reconstruction after mandibular microvascular free-flap reconstruction have been as low as 25% of patients.[141]

Extraoral prostheses for replacement of missing eyes, nose, ears, and facial components are fabricated by impressing the resected area and fabricating prosthetics with silicone material or combinations of acrylic and silicone materials. Proper anatomy can aid in retention of prostheses, but often craniomaxillofacial osseointegrated implants are used with special attachments or magnets for retention of prostheses. Silicone prostheses can be retained by the aid of prosthetic adhesives, which have a limited time of effectiveness and require daily maintenance of removing the prosthesis, removing the residual adhesive, and reapplication. This process results in wear and tear on the prosthesis, requiring the fabrication of numerous replacement prostheses (Fig. 16.31).

Quality of Life: Removable Prostheses

Although immediate surgical reconstruction has become the standard of care for many patients undergoing oral cavity ablative surgery, the acceptability of implant-supported or removable prostheses continues to be well documented.[142] Obturator reconstruction has been found to be acceptable



• **Fig. 16.25** **A** to **F,** Maxillary obturator fabrication steps.



• **Fig. 16.26** Maxillary obturator removable prosthesis.





• **Fig. 16.27** **A** and **B,** Preoperative view of squamous cell carcinoma of the right mandible. Retained tooth #31 improved restorative outcome.

and equivalent to surgical reconstruction in many situations including extended maxillectomy.[143] Although it is becoming more common for patients to receive microvascular free flaps for reconstruction after surgical defects, some patients are not appropriate candidates for surgical reconstruction



• **Fig. 16.28** Mandibular resection appliance in place.





• **Fig. 16.29** **A** and **B,** Lip support without and with mandibular resection appliance.

and may require prosthetic reconstruction. Additionally, healing may be incomplete at times, leaving a much smaller defect, but one that still requires obturation or prosthetic rehabilitation. Unfortunately, medical insurance coverage for implant-supported prostheses that replace the teeth and alveolar structures is limited, even in the case of surgical resection and reconstruction for the treatment of malignant tumors. Cost may be prohibitive for many patients whose surgical needs require implant support for final dental reconstruction.

Closure of palatal defects with prosthetics has been described since 1500 and can be an acceptable option for closure of acquired or congenital defects.[144] The most commonly referenced classification systems were proposed by Aramany and Brown; however, many other classification systems exist. The Aramany system is based on the



• **Fig. 16.30** **A** to **C,** Mandibular resection appliance. Squamous cell carcinoma of the right mandible. Full-mouth extraction prior to adjuvant HNRT at time of surgery.

defects' relationship to the remaining dentition in the horizontal plane only. The Brown classification system takes into account the vertical component of surgical oncologic resection.[145]

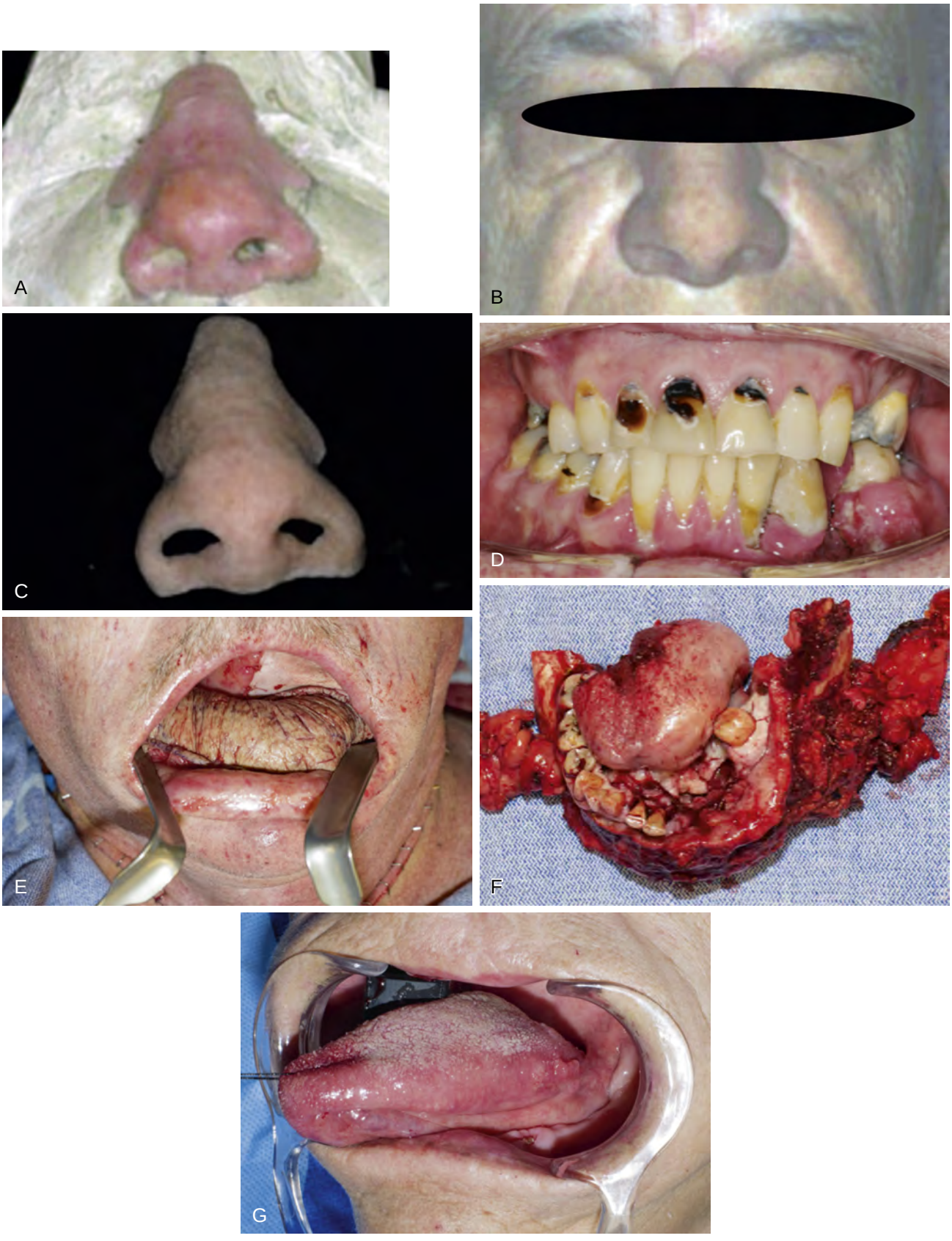
Quality of life with the use of removable prosthetics has been reported to be acceptable in many areas including swallowing,[146] reducing hyper-nasality in speech,[147] intelligibility of speech, ability to masticate, and reducing changes in quality of voice.[148,149] Masticatory performance of obturators after maxillary resection has been reported to be equal to equivalent dental prostheses.[146] The success of the prosthetic outcome is favorable when the defect is a smaller size, one third or less resection of the soft palate, or one fourth or less of resection of the hard palate, and also depends on the number of retained adjacent teeth.[149] Many studies focused on quality of life do not provide adequate representation of gender or ethnic backgrounds, and future investigations aimed at elucidating these demographic differences or similarities are warranted.

Conclusion

Few studies have looked at the cost of providing medically necessary dental care prior to oncologic treatment. One study has looked at the estimation of cost prior to stem cell transplantation, but none have investigated the cost prior to treatment for head and neck cancer. Patients who received dental care prior to stem cell transplantation cost $522 on average for private insurance and $384 for state-subsidized coverage.[150] Although it is unknown whether the dental status of people treated for all cancer is generalizable, the cost associated with dental treatment before cancer therapy gives an indication of the potential cost for the head and neck cancer patient. The cost of treating metastatic head and neck cancer was estimated to be $60,414 for a 6-month period in one study,[151] whereas the annual costs are estimated to be $4.2 billion. Future studies should be aimed at the potential cost savings by optimizing oral health prior to cancer treatment, as minimizing treatment interruptions and preventing short- and long-term sequelae are likely to lead to a reduction in treatment costs. It is important to note that the least expensive treatment option available, which is typically extraction of the remaining dentition, may not produce the highest cost reduction across the treatment timeline. Patients who are edentulous may require artificial feeding assistance through a feeding tube and rely on meal supplements, which may impair their ability to maintain weight and adequate nutrition. This may lead to more costly problems that are difficult to manage, such as long-term reliance on artificial feeds, reduced ability to swallow, increased risk of trismus, and chronic diseases of impaired nutrition.

Additionally, lack of pretreatment dental consultation and optimization of oral health prior to cancer treatment may lead to increased direct costs, which in the most severe form may require systemic medication, surgical intervention, and extensive dental and prosthetic rehabilitation. The indirect costs of the side effects of head and neck cancer and treatment are difficult to assess. These include time away from work and loss of productivity, psychosocial impacts such as impaired quality of life due to social isolation, pain, discomfort, and decreased oral function.

Detection and treatment of dental decay and periodontal infection should commence in the early stage to prevent complications that may place the patient at risk for infection, tooth loss, and healing and wound complications such as osteoradionecrosis. Early detection and treatment of dental disease can only occur when patients are closely followed by dental health professionals. Many patients experience treatment fatigue during the course of head and neck cancer treatment, and oral health professional visits may be viewed as optional, particularly when other concerns such as financial barriers are present. Head and neck surgeons, medical oncologists, and radiation oncologists should be familiar with the risk, prevalence, and preventive protocols for oral complications and oral disease so they can educate and inform patients as to the importance of oral health. The oral health care provider with experience and expertise in oncologic care is an essential member of the multidisciplinary head and neck cancer team. As this dynamic and growing field continues to investigate treatment protocols and intervention, disease prevention, and prevalence, evidence-based protocols will continue to evolve.



• **Fig. 16.31** **A** to **C**, Extraoral prosthesis. **D** to **F,** Surgical resection and free flap reconstruction. **G,** Clinical T1 lateral border of the tongue squamous cell carcinoma, identified on routine dental appointment using comprehensive oral, head and neck cancer screening.

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17

Speech Pathology and Rehabilitation

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The Role of the Speech Pathologist

A crisis intervention approach to the rehabilitation of the individual with head and neck cancer (HNC) was described by in a classic article by Sanchez-Salazar and Stark.[1] They described the process of dealing with HNC as a series of crises that challenge the coping mechanisms of the individual and his or her family. This model was based on the authors' combined approach as a social worker and a speech pathologist and has been used effectively in the rehabilitation of individuals after laryngectomy.[2] We have found that this model is very useful in understanding the experience of HNC patients in general. The first crisis occurs when the individual is given the initial diagnosis of cancer. At this time the catastrophic implications of the diagnosis itself and the threat of mortality eclipse all other considerations. The second crisis occurs during and after treatment as the individual tries to deal with the immediate side effects of treatment. This may include postoperative changes or, for the individual undergoing radiation or chemoradiation, the gradual worsening of symptoms over time. If the individual has been hospitalized, the next hazardous event is discharge. The patient is faced with leaving the protective environment of the hospital to cope and adjust at home. Finally, once the patient has convalesced and completed rehabilitation, the HNC survivor may have to come to terms with the reality of their status and the fact that this is "as good as it gets" and that that they must continue to deal with their remaining deficits long-term and learn to accept a "new normal." The speech-language pathologist (SLP) has a role in all of these phases, and that role will vary according to the individual patient's treatment and how far along the patient is in that treatment.

An understanding of the anatomy and physiology of the upper aerodigestive tract and its role in the processes of voice, speech, and swallowing makes SLPs uniquely qualified to treat HNC patients. In addition to the training that they take in order to receive their master's degree, certification, and licensure, most SLPs who work with the HNC population also pursue significant specialty education to further enhance their expertise in this area. The SLP who works in this field must understand the different therapeutic modalities for HNC and their impact, the current literature regarding optimal rehabilitation methodology and techniques, and the role of the various professionals involved in treatment and rehabilitation. They must also understand how the rehabilitation course should be individualized to meet the specific needs, goals, and wishes of the individual. The SLP may become involved with the HNC patient and his or her family at any point in the continuum of care, from prediagnostic work-up to long-term rehabilitation. The needs of the patient will vary substantially over that time and, consequently, it is essential that the SLP understand how intervention should best be targeted in order to optimize patient outcomes. One of the greatest challenges for HNC patients is the number of health care professionals involved in their care. It has been estimated that as many as 20 different medical specialties may be involved in the treatment of the HNC patient and that the communication and coordination between these individuals is often chaotic.[3] Difficulties with communication and poor coordination of care can be a major source of frustration for clinicians as well as for patients and their families.[4] Consequently, the SLP may sometimes function in the role of intermediary, advocate, and educator, facilitating communication between the separate parties. In addition, sometimes patients and family members are more comfortable sharing information with a therapist, and so the SLP may become aware of important information that can, in turn, be communicated with the rest of the care team. The SLP may also be uniquely qualified to educate other specialties about the nature of treatment-related functional deficits, their implications, and the timeline and prognosis for recovery.

Evaluation of the HNC Patient

Pretreatment Assessment and Counseling

The pretreatment assessment can be a critical time for the patient, family, and other members of the social support system to understand the anticipated functional impact of HNC treatment as well as the course of recovery and treatment timeline. Therefore it is optimal for all patients whose treatment is likely to involve a significant impact on speech and swallowing to have a pretreatment visit with a qualified SLP. Providing accurate information to the patient depends on getting detailed information from the medical team regarding the nature and aggressiveness of treatment, short-term implications such as

the likelihood of short-term tracheostomy or feeding-tube dependency, and the prognosis for long-term function and recovery. For the SLP it is also a critical time to evaluate the patient's understanding of treatment as well as their baseline voice, speech, communication, and swallowing function. The SLP and other members of the HNC team need to be aware of factors that might affect the course of treatment such as cognitive status, literacy, vision, hearing, manual dexterity, respiratory status, depression/anxiety level, and the presence of other comorbidities. Other factors that may affect treatment include the patient's level of education, vocational status, hobbies, interests, and personality. The presence of significant baseline dysphagia may inform decisions about the need for short-term versus long-term enteral nutrition. This information is valuable for consideration of treatment options and planning for rehabilitation. Other important factors include the availability of caregiver support during treatment and recovery. The SLP can then, in turn, share with the medical team relevant information that may affect the decision-making and planning process.

Voice and Speech Evaluation

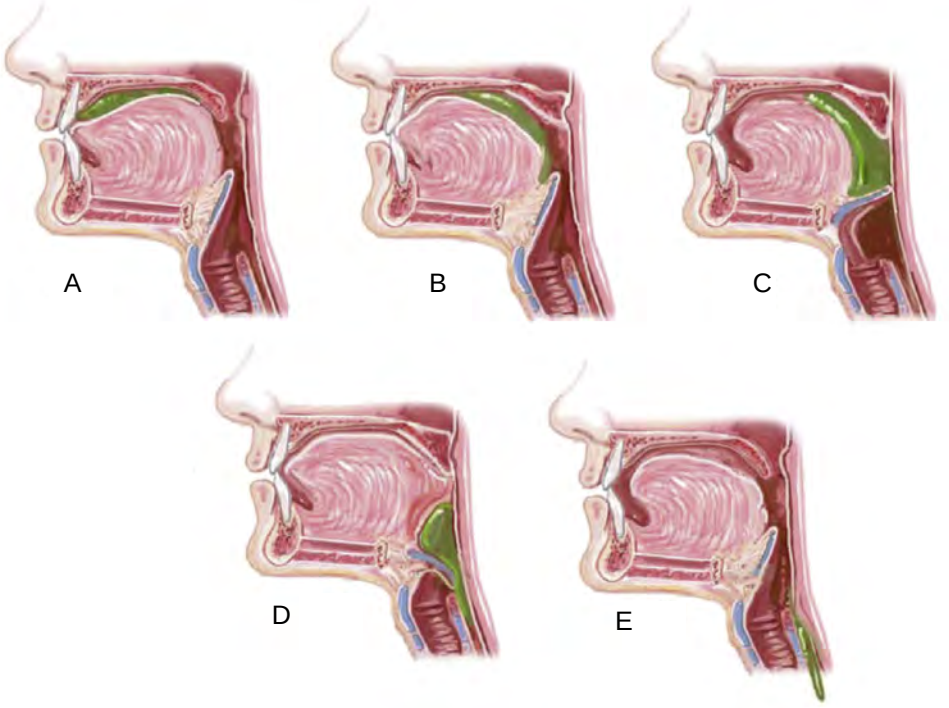
There are a number of protocols for the assessment of the voice, speech, and communication of the individual with head and neck cancer that may be used before, during, and after treatment. For the individual with a voice disorder or *dysphonia,* a comprehensive voice evaluation will typically comprise endoscopic evaluation of the larynx, acoustic and perceptual assessment of the voice, and subjective self-assessment of vocal impairment. The laryngeal examination frequently incorporates videostroboscopy, a means of studying the phases of motion of the vocal folds by means of light source that is periodically pulsed. Videostroboscopy provides a detailed assessment of the vibratory properties of the vocal folds as well as the presence of hyperfunction during phonation. Typically acoustic vocal measurements are also collected as part of a comprehensive voice evaluation. The individual is audio-recorded while completing a number of vocal tasks, reading standardized passages, and during normal conversation, and these recordings are then analyzed using acoustic software. Aerodynamic tests can also be performed that include measurement of the average airflow rate during phonation and laryngeal efficiency. The individual's audio-recorded speech sample can also be rated using one of a number of standardized protocols for documenting how the voice is perceived by others. Examples of perceptual assessment batteries include the GRBAS scale,[5] which assesses the voice in terms of its overall dysphonia grade, roughness, breathiness, asthenia, and strain, and the Consensus Auditory-Perceptual Evaluation of Voice (CAPE-V).[6] In addition, there are a number of validated instruments for measurement of the impact of voice impairment on daily function and voice-related quality of life, such as the Voice Handicap Index.[7]

The term *dysarthria* refers to a speech impairment secondary to weakness or reduced coordination of the muscles of speech production. Speech evaluation can be accomplished by one of a number of methods. There are a number of published instruments that assess the production of each of the sounds in American English, such as the Goldman-Fristoe Test of Articulation[8] and the Fisher-Logemann Test of Articulatory Competence.[9] Other measures include scoring the intelligibility of audio-recorded speech samples of conversation or standardized batteries of words and sentences of varying lengths, such as the Assessment of Intelligibility of Dysarthric Speech.[10] Ratings of speech intelligibility using the Performance Status Scale for Head & Neck Cancer Patients[11] can be used in addition to a self-assessment instrument of functional daily communication such as the Communication Effectiveness Survey.[12]

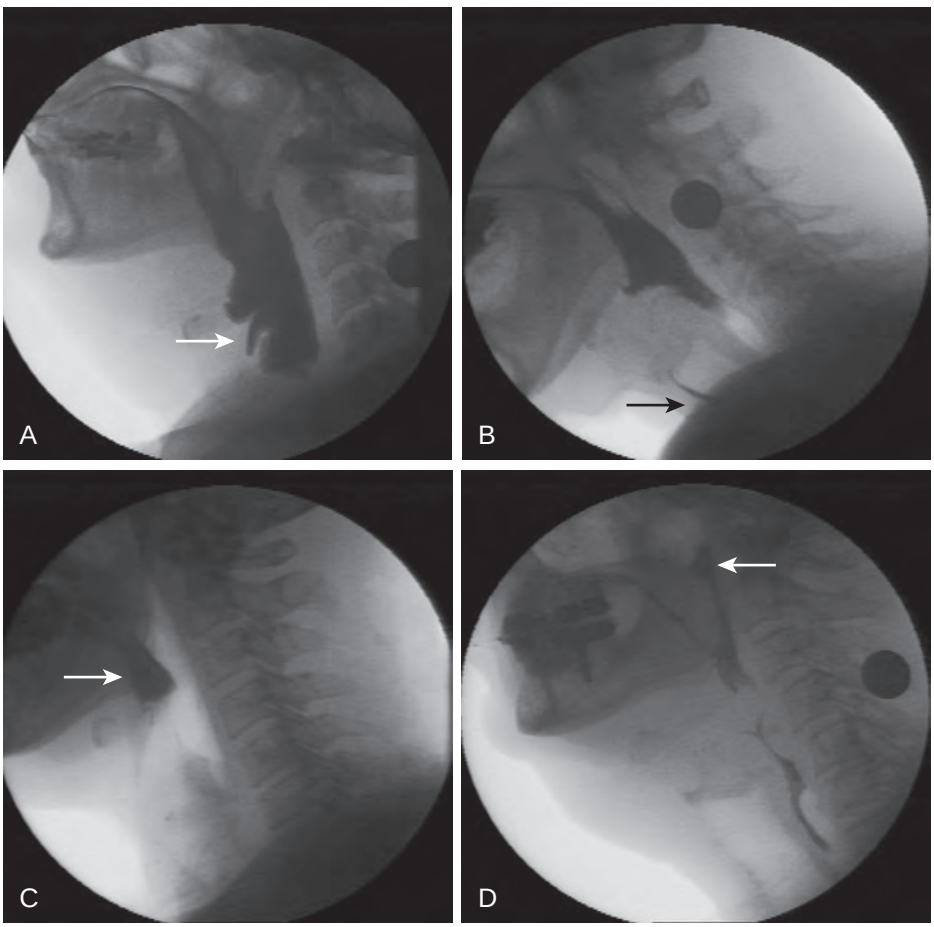
Swallowing Evaluation

The term *dysphagia* refers to any difficulty swallowing, from the initial placement of food or liquid in the mouth, through the oral, pharyngeal, and esophageal stages of the swallow, until the material passes the lower esophageal sphincter to enter the stomach. Oropharyngeal dysphagia following treatment for tumors of the upper aerodigestive tract is common.[13] Aspiration, or the entry of food and liquids into the trachea below the level of the vocal folds, may be caused by any one of a variety of swallowing pathophysiologies, such as delayed triggering of the swallow, incomplete laryngeal closure, reduced laryngeal elevation, or the presence of residue subsequent to the swallow due to pharyngeal weakness. Alternative nutrition may be required in the form of a feeding tube for patients who are unable to sustain themselves by taking adequate oral nutrition. There are a number of methods of evaluating an individual's swallowing function, each of which may be appropriate based on the context, nature of the complaint, and availability of imaging resources. The clinical swallow evaluation (CSE) or "bedside swallow evaluation" is the most widely used form of swallowing assessment.[14] The advantages of this test are that it is inexpensive, is noninvasive, can be performed in any setting, and does not require access to imaging equipment. Typically a history is obtained; the individual's behavioral, cognitive, and language abilities are assessed; the sensory and motor function of the oral, pharyngeal, and laryngeal structures is evaluated; and trial feeding of various food and liquid consistencies is attempted, if appropriate. A disadvantage of the test is that it cannot identify the physiologic cause of dysphagia, and so the test may be used to screen individuals in order to identify those who require an objective evaluation.

The videofluorographic swallowing study (VFSS) or modified barium swallow (MBS) is a well-standardized assessment technique for dysphagia.[15] The MBS is perhaps the ideal method of swallowing assessment for the individual who has undergone HNC treatment because it allows visualization of all of the structures that may have been affected by any of the three treatment modalities of surgery, radiation, and chemotherapy. The test is performed in a radiology suite where the individual is presented with a variety of barium consistencies to assess the ability to swallow foods and liquids. While swallowing, the effectiveness of the various stages of swallowing can be observed, including the oral preparatory, oral transit, pharyngeal, and esophageal phases (Fig. 17.1). A variety of abnormalities can be observed, including disorders in the oral phase, laryngeal penetration, aspiration, post-swallow residue, and nasal regurgitation (Fig. 17.2). During the test a variety of compensatory strategies can



• **Fig. 17.1** Stages of a normal swallow of a liquid bolus as visualized on videofluoroscopy: **(A)** oral preparatory phase with containment of the bolus; **(B)** oral transit phase with elevation of the tongue tip to assist with oral transit; **(C)** initiation of the pharyngeal phase with laryngeal elevation for airway closure; **(D)** completion of the pharyngeal phase with base of tongue to pharyngeal wall approximation; and, **(E)** esophageal phase with post-swallow relaxation of the pharyngeal musculature.

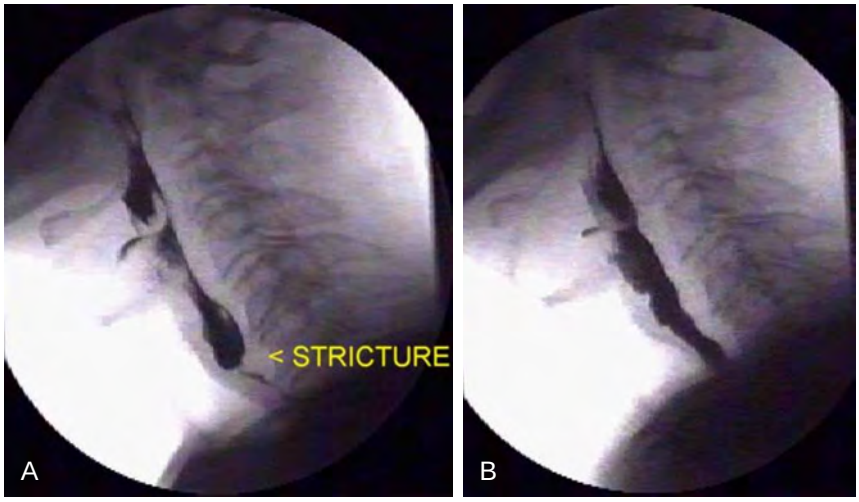


• **Fig. 17.2** Abnormal findings on modified barium swallow study including **(A)** laryngeal penetration; **(B)** aspiration; **(C)** post-swallow pharyngeal residue; and **(D)** nasal regurgitation.

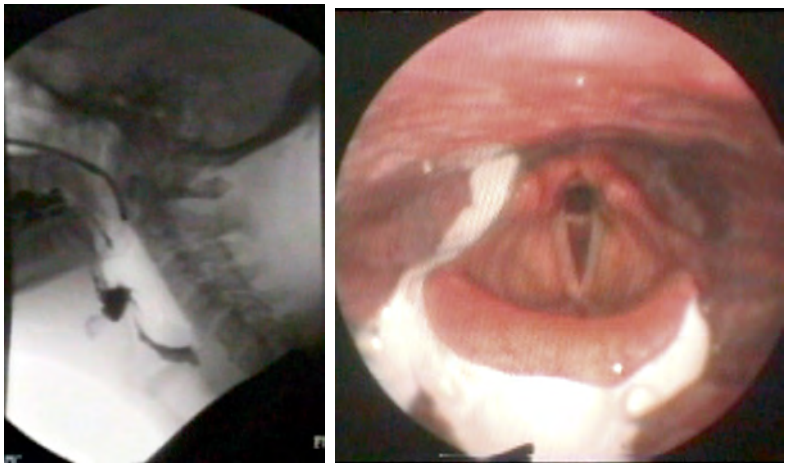
be trialed to determine their effectiveness. Beyond these bolus-related characteristics, however, the clinician is able to identify the physiologic abnormalities underlying the deficit and design a treatment program targeting these deficits. Following the test, the study can be reviewed with the patient, family members, and caregivers for education about the nature of the disorder, and findings can be shared with other medical professionals in order to determine the need for additional medical or surgical interventions or work-up. Based on the study, the SLP will usually make recommendations regarding appropriate diet texture, the appropriate compensatory techniques to use when eating and drinking, whether therapy is indicated, and the targets for remediation. A common finding in individuals who have previously had radiation or chemoradiation is a stricture of the hypopharynx or cervical esophagus that can be effectively improved by dilation (Fig. 17.3).

Fiber-optic endoscopic evaluation of swallowing (FEES) in another objective method of swallowing assessment that has been shown to be beneficial in individuals with HNC.[16,17] The test can be performed in a variety of settings because of the relative portability of the equipment. During the test, the individual is observed eating and drinking normal foods and liquids after light topical anesthesia of one nostril. During the test, the individual can often see the evaluation in real time on a monitor, and various compensatory maneuvers can be trialed. Advantages of the test are that there is no radiation exposure, real foods and liquids can be trialed, and there is the potential for use as biofeedback during therapy. One study found that HNC patients with a history of aspiration progressed more quickly to an oral diet when FEES was used for biofeedback to help them achieve therapeutic goals.[18] The endoscopic image provides excellent visualization of the laryngeal and pharyngeal structures but does not provide as detailed imaging of other structures, particularly the esophagus, which limits the ability of this test to identify other causes of dysphagia (Fig. 17.4).

The rehabilitation of the head and neck cancer patient has been shown to be qualitatively different from that of patients treated for cancer of other sites.[19] General health measures do



• **Fig. 17.3** Post-chemoradiation cervical esophageal stricture **(A)** before dilation; and **(B)** after dilation.



• **Fig. 17.4** Simultaneous comparison of fluoroscopic image with the endoscopic image during swallowing demonstrating the differences between the two views. On the left the arrow points to the flexible endoscope. On the right the white material is oral barium contrast. (From Leder SB, Murray JT: Fiberoptic endoscopic evaluation of swallowing. *Phys Medicine Rehabil Clin N Am* 2008; 19:789.)

not adequately address the specific needs of this patient population, which consist of alterations in eating, swallowing, speech, communication, and appearance.[20] Although individuals may be able to sustain themselves orally, dietary restrictions and substantially increased eating times may have an impact on quality of life. There are a number of dysphagia-specific patient-rated tools that have been shown to be valid in the HNC population, including the Eating Assessment Tool (EAT-10)[21] and MD Anderson Dysphagia Instrument (MDADI).[22] In addition, there are a number of HNC-specific quality-of-life instruments that allow scoring of several domains including voice, speech, and swallowing.[23]

Rehabilitation After HNC Treatment

The Impact of Cancer Stage and Treatment Type

Treatment of HNC, as with most other cancers, is based on the three modalities of surgery, radiation, and chemotherapy. Because in many cases early-stage disease can be treated adequately with either surgery or radiation therapy alone, the choice of treatment is often based on which treatment is associated with better functional outcomes. Higher cancer stages (stage III or IV) are typically treated with multimodality treatment with a correspondingly greater impact on functional outcomes. Treatment variables such as tumor location and size and the extent of surgical resection will predict the impact on speech and swallowing, the amount of rehabilitation that an individual will need, and the amount of time that this will take.[24,25] Earlier onset of therapy and use of biofeedback may be associated with quicker attainment of therapy goals, and in some cases, aggressive rehabilitation during the inpatient stay may avoid the need for a long-term feeding tube.[18,25,26] In addition, there is some evidence that demographic and health variables also play a part. Post-treatment recovery, for example, is often slower in the older individual.[27]

Principles of Rehabilitation

Rehabilitation of voice, speech, and swallowing deficits is typically structure-dependent and the choice of intervention is guided by the nature of the underlying deficit. Treatment usually involves a combination of techniques that are *compensatory* (i.e., to minimize deficits without changing the underlying physiology) together with those that are *rehabilitative* (i.e., those that change the strength, flexibility, and range of motion of structures over time).[28] During the course of HNC treatment, efforts may be primarily devoted to exploiting the patient's ability to compensate for treatment-related deficits and maintenance of function. At this time the patient may be dealing with a "storm of symptoms" that affect their ability to participate in treatment, such as pain, nausea, fatigue, anxiety, and depression.[29] As the patient's health and medical status improve, the focus of treatment may turn increasingly from compensatory to rehabilitative techniques. Rehabilitative exercises should be targeted to the areas affected by HNC treatment and performed several times per day for optimal outcomes. Additionally, therapy exercises designed to strengthen affected musculature should follow the principles of exercise physiology in that the exercise must be appropriate for the targeted task/behavior *(specificity);* and that tasks must be initiated at a moderately challenging level *(intensity)* over time *(duration),* which must then be progressively increased to continue making ongoing gains *(progressive resistance).* For a description of a complete rehabilitative program, there are a number of published case studies that detail the complete treatment course of individuals after HNC.[30,31]

Compensatory strategies involve postural changes when eating, such as a head tilt or head turn, placement of foods and liquids on the unaffected side of the mouth, diet and texture modification, and the use of facilitative maneuvers during swallowing behavior, such as the supraglottic safety swallow, controlled swallow, effortful swallow, double swallow, or alternation of liquids and solids. Rehabilitative exercises include oral-motor exercises for the lips, tongue, jaw, or soft palate, as well as strengthening techniques such as the Mendelsohn and Masako maneuvers and the Shaker head-lifting exercise for the laryngeal and pharyngeal musculature.

Radiation and Chemoradiation

There have been numerous studies of the impact of radiation treatment (RT) on speech and swallowing. Generally, the impact of RT varies depending on the size and location of the tumor. Characteristic swallowing changes include: (a) slower oral transit and increased oral dysphagia due to xerostomia, reduced oral sensation, lingual weakness, and impaired dentition; (b) slower pharyngeal transit, greater risk of aspiration, and increased residue due to reduced sensitivity, delayed swallow initiation, and reduced laryngeal and pharyngeal strength; (c) increased nasal regurgitation due to impaired soft palate closure; and (d) reduced upper esophageal opening due to reduced laryngeal elevation and/or stricture formation.[32-34] Further, dysphagia can occur long after RT has been completed secondary to muscle fibrosis and placing the individual at risk for aspiration, impaired nutrition and hydration, and feeding-tube dependency. Voice changes after RT to the larynx include reduced vocal loudness, reduced pitch, hoarseness, breathiness, and vocal fatigue secondary to edema, muscle atrophy, mucosal dryness, and fibrosis of the affected tissues, and all of these symptoms may be improved by voice therapy.[33] Trismus is another well-known complication of HNC treatment and is the result of fibrosis of or tonic contractions of the muscles of mastication that lead to reduced mouth opening. Trismus is associated with a number of complications, including reduced oral intake, difficulty speaking, and poor oral hygiene. The use of a TheraBite device (Fig. 17.5) and tongue blades have both been found to be effective in increasing mouth opening.[35,36]

The impact of concurrent CRT on swallowing is similar to that described for RT alone but may be complicated and exacerbated by the combination of the two modalities resulting in more severe side effects. Acute mucositis of the oropharynx during treatment is associated with prolonged tube-feeding dependency and worse swallowing outcomes. In general, voice, speech, and



• **Fig. 17.5** Individual using a TheraBite Jaw Motion Rehabilitation System to prevent trismus. (Courtesy Atos Medical.)

swallowing function deteriorate during and after CRT treatment and then gradually improve over time, although long-term function often remains abnormal.[37] Studies have shown that rates of feeding-tube dependency are higher for those who receive CRT than for RT alone.[32] Some of the most common late effects of CRT include dry mouth, thick saliva, dysphagia, altered taste, and pain. Because of the high rates of eating/swallowing impairments after CRT, there has been significant interest in strategies to reduce the impact of treatment on swallowing function. Techniques to reduce the incidence and severity of xerostomia include the use of intensity modulated radiation treatment (IMRT) to reduce damage to the salivary glands, cytoprotective medications to reduce the risk of mucosal injury and mucositis, and the use of sialogogues to stimulate salivary flow.[38] There has also been an interest in designing protocols to be implemented during CRT in order to reduce the short- and long-term functional impact of treatment.[34] The performance of pharyngeal exercises during CRT results in improved swallowing function and reduced tube-feeding rates after treatment.[39-42] A typical treatment protocol consists of exercises targeting the oral, pharyngeal, and laryngeal musculature performed several times per day, as well as the use of a TheraBite device to prevent trismus. Even with the side effects of CRT, therapy during treatment is feasible, compliance rates are often high, and it is also cost effective.[42,43]

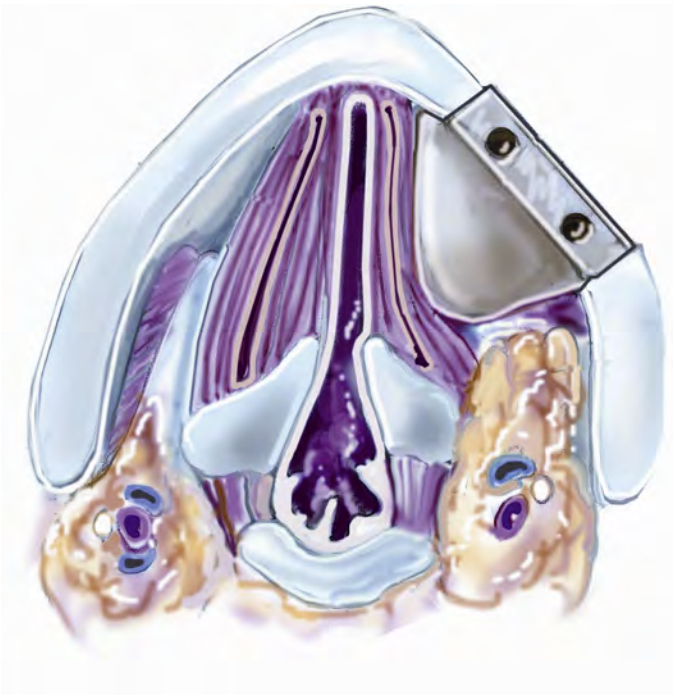
Oropharyngeal Surgery

For small tumors, surgical intervention can take the form of primary resection in which there is sufficient viable soft tissue to simply suture the defect closed. As with postoperative outcomes generally, the smaller the resection, the less impact surgery will have on speech and swallowing outcomes.[44,45] Surgical resection frequently causes functional impairments in swallowing due to physiologic defects, such as reduced strength, limited mobility, and reduced or absent sensation.[13,46,47] Typical swallowing deficits include reductions in oral control, palatal closure, base-of-tongue propulsion, pharyngeal wall motion, laryngeal elevation, glottic closure, and cricopharyngeal opening. Mastication may also be affected by reduced tongue control, loss of dentition, and trismus. In anterior oral cavity resections involving the lip, anterior tongue, floor of mouth, or cheek, the patient may experience decreases in strength, sensation, and range or speed of motion resulting in oral dysphagia and dysarthria. Symptoms may include reduced sensation, decreased oral transit, and poor oral control. Measures of conversational understandability and articulatory precision have been shown to be significantly associated with the volume of tissue surgically resected.[44] Speech outcomes are generally worse in those who have undergone free flap reconstruction of the oral cavity rather than primary closure.[48] For more posterior resections, which may involve the base of tongue, tonsil, or soft palate, the patient may experience velopharyngeal incompetence, delayed swallow initiation, and decreased tongue-base range of motion. These may result in difficulties with nasal regurgitation, pre-swallow spillage of the bolus, aspiration, and post-swallow residue.

The types of deficits that HNC patients experience are often site-specific. Rehabilitation exercises should be tailored to the deficit, target the function that needs rehabilitation, and combine range of motion and strengthening exercises for the affected musculature. Therapy has been shown to benefit speech function even for those who undergo significant surgical resection of the tongue[49] and swallowing rehabilitation has been shown to correlate with a reduction in dysphagia.[25] When surgery involves the soft or hard palate or tonsil, rehabilitation may involve exercises designed to reduce nasal regurgitation and improve velopharyngeal function for speech. If the velopharyngeal incompetence is too great for the remaining anatomy to be able to compensate, a palatal prosthetic may be required. A *palatal lift* prosthesis can support the soft palate when there is adequate tissue but reduced mobility of the musculature. Alternatively, a *palatal obturator* can be used to fill in a surgical defect when there is inadequate soft palate or tonsillar tissue. For those with significant oral dysphagia or dysarthria secondary to reduced tongue range of motion, a *palatal augmentation* or *palatal drop* prosthesis can be used to enable the tongue to make contact with the roof of the mouth for bolus transit and for speech. Prosthetic fabrication requires an evaluation by an SLP and prosthodontist and can begin once all HNC treatments have been completed and post-treatment edema has completely subsided.

Laryngeal Surgery

The primary functions of the larynx are to separate the pathways of respiration and deglutition and allow the generation of increased thoracic pressure for physical exertion, cough, and bearing down. The secondary function of the larynx is phonation, which in turn creates voice for speech. Surgical intervention for laryngeal cancer may affect voice, breathing, and swallowing, and the postoperative patient may require significant rehabilitation. Studies have shown that vocal function can be severely impaired after surgical as well as non-surgical interventions for even small glottic tumors.[50] In addition to dysphonia, reduced airway protection during swallowing may result in an increased risk of aspiration. Post-swallow residue secondary to reduced laryngeal elevation may also occur. Vocal fold paralysis or paresis may occur either from surgery or from radiation. In addition to rehabilitative exercise, improvements in both voice and cough can be accomplished using augmentation with vocal fold



• **Fig. 17.6** Medialization thyroplasty.

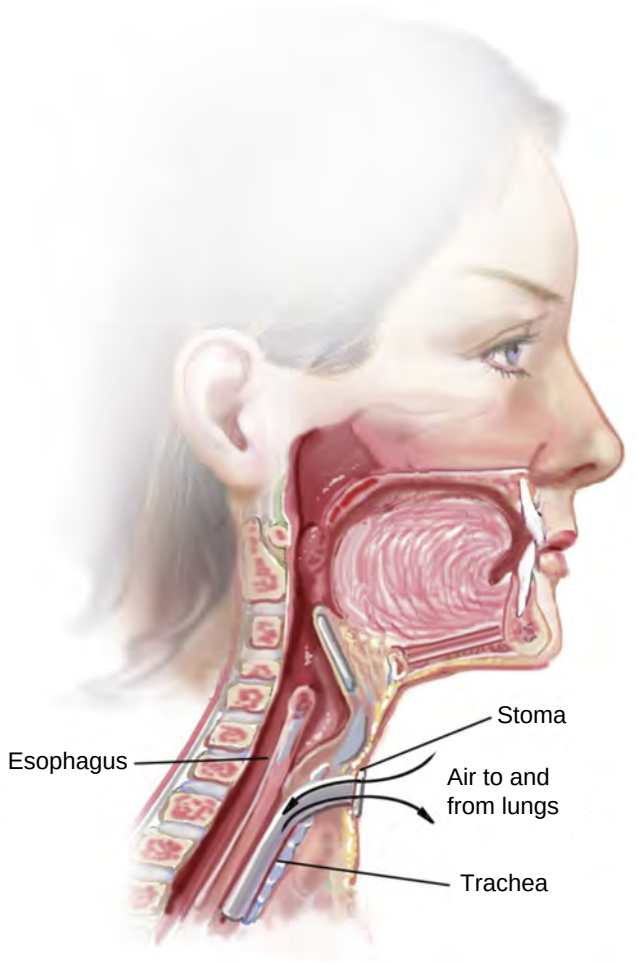
injection for short-term deficits or medialization where recovery of function is not expected (Fig. 17.6).

Partial Laryngectomy

A number of surgical procedures have been described in the literature, including vertical hemilaryngectomy, supraglottic laryngectomy, supracricoid partial laryngectomy, and other variations of these procedures. Although the specific nature of each of these surgeries varies quite substantially, there are a number of commonalities to treatment. A tracheostomy tube and feeding tube are typically required postoperatively. Dysphagia symptoms include delayed and reduced airway closure, decreased sensitivity to the presence of a bolus, and aspiration. If there is resection of the tongue base, then swallowing strength and efficiency may also be affected, resulting in post-swallow residue. Rehabilitation initially involves work on communication and secretion management in the tracheotomized patient with the goal of decannulation. Dysphagia treatment involves compensation with super-supraglottic safety swallow, effortful swallow, and Mendelsohn maneuver, in addition to short-term dietary modification. Postural changes may also be beneficial. An exercise program including adduction exercises to increase glottic closure and base of tongue to arytenoid closure is performed intensively, supplemented by base of tongue exercises as needed.[26] Voice therapy should focus on techniques to maximize vocal efficiency and improve loudness while reducing strain.

Total Laryngectomy

Total laryngectomy (TL) involves the removal of the hyoid bone, thyroid cartilage, strap muscles, epiglottis, cricoid cartilage, and upper two or three tracheal rings, which results in the complete diversion of the airway to the neck and creation of a tracheostoma (Fig. 17.7). Ideally, the process



• **Fig. 17.7** Anatomy after total laryngectomy.

of alaryngeal rehabilitation begins at the preoperative visit with an SLP. As discussed previously, the patient is assessed, and the three methods of alaryngeal speech are reviewed, namely, the artificial larynx, esophageal speech, and the tracheoesophageal voice prosthesis. There are many factors that must be considered when deciding which option is likely to be the most appropriate for a particular individual. Factors such as the extent of the planned surgery as well as the patient's medical status, motivation, preferences, proximity to rehabilitation resources, and medical insurance coverage must be taken into account when discussing communication options. Each method of voice restoration has advantages and disadvantages, but the primary goal of each method is functional communication. Most individuals who undergo TL will require tube feedings temporarily but will ultimately resume an oral diet once healing is complete and postoperative edema has subsided. Because of the presence of the tracheostoma, another focus of treatment is pulmonary rehabilitation. There are a wide variety of cloth and foam stoma covers available commercially for the purpose of improving hygiene and cosmetic appearance. Improving pulmonary function, however, is done most effectively by use of a heat-and-moisture exchanger (HME) system, which consists of a disposable filter cassette placed in a housing that is attached



• **Fig. 17.8** An HME cassette worn in place with a peristomal adhesive housing. (Courtesy InHealth Technologies.)

peristomally or intraluminally within the stoma (Fig. 17.8). Long-term use of the HME has been shown to significantly decrease cough and sputum production and improve pulmonary function.[51]

Surgical Salvage

In patients previously treated with radiation therapy or chemoradiation who are found to have recurrence or persistent disease, surgery is the most common treatment option. For individuals with advanced laryngeal cancer, concurrent CRT is often delivered as the first curative approach with salvage total laryngectomy being kept in reserve.[52] Some studies have shown that a partial laryngectomy can be successful even in the post-irradiated patient, but for many individuals, salvage total laryngectomy is the only option.[53] Rehabilitation for these individuals may follow the same course as that of those who undergo primary surgical resection, but the prognosis is more guarded. Individuals may have baseline deficits in their voice, speech, and swallowing secondary to previous treatment. They may have other sequelae such as weight loss, pain, and fatigue. If the tissues of the head and neck previously have been irradiated and have changes consistent with substantial radiation effect, then the use of a reconstructive flap may reduce postoperative wound healing problems. As a result of the cumulative impact of the three modalities, there is an increased risk of complications including delayed healing, wound breakdown, and fistula formation. This can affect the timeline and intensity of rehabilitation, and many individuals require prolonged intervention to achieve functional gains.

Nonverbal Communication Options

In the literature on health care communication, it is now widely recognized that effective communication is an essential component of patient safety and quality care.[54] Individuals who experience communication difficulties during their hospitalization experience feelings of anger, fear, frustration, and loss of control.[55] Those who are unable to resume speech after HNC treatment tend to have the lowest levels of satisfaction with their communication and overall quality of life.[56-58] Consequently the SLP must work to facilitate communication across a variety of settings and respond to changes in communication needs over time. For HNC patients who experience speechlessness in the acute postoperative period, many patients prefer to use writing, mouthing, and gestures, as these strategies are familiar and require the least effort and new learning.[59,60] Providing guidance to medical staff and communication partners regarding how to promote effective communication in a yes/no format is often beneficial. The risk of being unable to communicate wants, needs, and wishes or summon help in an emergency is greater in this context for those who have cognitive impairments, low levels of literacy, impaired vision, or poor strength or coordination of the upper extremity. For those with longer-term speech/communication disabilities, and for those in whom functional speech is not an achievable goal, other communication options should be explored. Long periods of non-vocal communication typically require the use of text-to-speech applications or software, dedicated speech-generating devices, and the use of telephone communication devices such as a teletypewriter (TTY). Fox and Rau[61] described a collaborative approach between SLPs and a psychiatric nurse to successfully rehabilitate an individual who had undergone total laryngectomy and total glossectomy, allowing him ultimately to return to work. With the advent of widespread, affordable technology for text-to-speech applications, instant messaging, and videoconferencing, nonverbal communication options are more readily accessible than ever before. Recent evidence suggests that HNC patients are increasingly turning to these technologies to meet their communication needs.[62]

Summary

The SLP is uniquely positioned to address the needs of the HNC patient and his or her family. Although many of the techniques and strategies that SLPs use are the same as those used for other populations, the rehabilitation of the HNC patient is qualitatively different. Early intervention is associated with better long-term outcomes, and knowledge about the impact of HNC and its treatment is essential in designing an effective treatment program. In order to be successful, therapy goals should shift over time, from compensation/management and maintenance during the acute phase of treatment, to more aggressive rehabilitation once side effects have subsided, and should follow the principles of exercise physiology. Treatment is usually multidisciplinary, involving a large number of medical specialties, and must be coordinated for optimal outcomes. Effective communication between providers and also with the patient/family is essential, and all members of the medical team must take into account the wishes and needs of the individual for the rehabilitation of the whole individual.

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18

Early Tongue Cancer

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Overview and Epidemiology

Of the 300,000 oral squamous cell carcinoma (SCC) cases to be diagnosed worldwide per year, a large majority will involve the oral tongue. Tobacco and significant alcohol consumption are reported as the major lifestyle-related risk; nevertheless, the rate of oral tongue SCC is increasing in the younger population and in never smokers, never drinkers, and white females, according to recent meta-analyses and Surveillance, Epidemiology, and End Results (SEER) program data review.[1-3] In persons younger than 45 years, rates of 11% in women and 16% in men have been reported.[1-3] Whether there is an association between human papillomavirus (HPV) and oral cavity carcinoma is unknown, with rates of concurrent HPV infection reported in 2–20% of cases. This is very different from oropharyngeal squamous carcinoma, in which HPV-associated carcinomas and rates are reported in as many as 80% of cases.[4] Regardless of etiology, the incidence of oral tongue SCC is increasing, but with early detection and aggressive management, good prognosis of early stage oral tongue SCC can be obtained.[5]

Staging/Imaging/Management

This section discusses the clinical staging of early stage oral cancer, defined as stages I and II disease (T1N0M0, T2N0M0) (Figs. 18.1 and 18.2). Clinical staging (cTNM) includes clinical examination, imaging, and pretreatment pathology according to the TNM staging manual guidelines.[6,7] At the University of Maryland, the majority of our patients have already had initial biopsy by a community oral and maxillofacial surgeon before referral. It is policy at the University of Maryland to review all "outside" pathology slides by the university oral and head/neck pathologists. Although the histologic diagnosis of SCC is usually straightforward, pseudoepitheliomatous hyperplasia associated with candida, granular cell tumors, and sialometaplasia may lead to a false-positive diagnosis. Similarly, the spindle cell carcinoma variant may be difficult to differentiate from sarcoma without special histochemical stains. In one retrospective study at Johns Hopkins University of 814 cases, a major diagnostic change was found in 7% of cases between initial outside diagnosis and final diagnosis after review by university pathologists.[8] Twenty-four percent involved a change from a benign to a malignant diagnosis, 15% involved a change from a malignant to a benign diagnosis, and 61% involved a change in tumor classification. A review in 2005 of head and neck histopathologic diagnoses found diagnostic discrepancy rates of 1–53% for surgical pathology and 17–60% for cytology.[9]

A particular problem with biopsies may occur with small T1 tumors or sometimes even larger primary lesions when the referring surgeon has undertaken "excisional" biopsy. In these cases, the diagnosis was often not made clinically before excisional biopsy and the "excision" is frequently inadequate to obtain an oncologically sound margin (5 mm). At best the surgeon now only has a line of sutures to guide subsequent definitive treatment and at worse the area will have healed completely, leaving the oncologic surgeon little clue as to where the original tumor margins were situated. Although the tumor is now classified TX (cannot be evaluated), it is usually possible to determine the tumor's initial size from the size of the biopsy specimen. A 1- to 1.5-cm biopsy specimen that completely excised the SCC indicates that the tumor was initially less than 2 cm, or T1. Our policy when the "excisional biopsy" margins are "close" or positive is to re-excise these cases with a 1-cm margin around the scar. Often the final specimen shows no residual tumor. This is an unrewarding surgery; however, even though the original margins are not visualized and more tissue is probably removed in such a specimen, no adverse effect on recurrence or survival in a study from our unit has been demonstrated.[10]

The authors prefer and advocate incisional biopsy to ensure the entire depth at the thickest portion of the lesion is reached. Although superficial biopsy may yield a diagnosis, for decisions regarding the neck, it is important to know whether SCC infiltrates more than 3 mm. Because of the cytologically benign nature of the cells in verrucous carcinoma, diagnosis may not be possible unless the deep invasive front of the tumor is seen.



• **Fig. 18.1** **A,** Exophytic T1 lateral tongue squamous cell carcinoma. **B,** Ulcerated T1 lateral tongue squamous cell carcinoma.



• **Fig. 18.2** T2 squamous cell carcinoma of the anterior ventral tongue. Note the ulceration and indurated rolled tumor edges.

Clinical examination of the histologically positive SCC is the foundation for staging. Although neck palpation is only reported as 70% accurate in the diagnosis of positive lymph nodes, it is the initial mandatory examination. In early stage disease, the neck is clinically negative (cN0) by definition. We do not routinely use fine-needle aspiration biopsy (FNAB) or ultrasound-guided FNAB to obtain nodal tissue in the cN0 neck. The size of the intraoral primary tumor, whether less than 2 cm or 2 to 4 cm, is initially by inspection, but more importantly, by palpation. Tumors with extensive submucosal spread can be underdiagnosed by visual inspection alone, and palpation is essential to assess both size and depth of invasion.

At this point following clinical examination and tissue biopsy, a full and frank discussion is undertaken with the patient. In early stage oral SCC, our choice for primary therapy is surgery for all cases unless the patient refuses or is too medically compromised to undergo general anesthesia. The patient is sent for imaging (discussed later) and medical work-up, which consists of a full history and physical examination by the primary care physician, electrocardiogram, chest radiograph, full blood count, and serum electrolytes. Other tests, such as a stress test, echocardiogram, pulmonary function testing, and liver function tests, are ordered as indicated by the history and physical examination.

The authors routinely image early SCC with either computed tomography (CT) or magnetic resonance imaging (MRI). We do not use isotope bone scans or ultrasound for early oral cavity SCC. Positron emission tomography (PET) scanning or fused PET/CT has not been shown to improve diagnostic accuracy in the N0 neck,[11-13] so we do not use this modality in stages I and II disease. When deciding to use CT or MRI, a number of factors are considered, including the surgeon's personal choice. Patient factors, such as pacemakers—a contraindication to MRI—or renal disease—a contraindication to CT with contrast—may be a deciding factor. We prefer CT for detecting abnormal nodes in the neck. CT is also our imaging choice for floor of mouth, gingival/alveolar, or retromolar fossa cancer that abuts the bone, because it is more accurate for early cortical bony invasion. Conversely, where deep soft tissue invasion is suspected in the tongue, MRI gives better diagnostic information regarding the extent of muscle involvement.

After reviewing the imaging, a final decision is made regarding treatment. We advise surgery as the preferred modality in stages I and II disease, including tracheotomy and endoscopy. The neck, the primary tumor, and the need for reconstruction are all also considered.

In general terms, tracheotomy is rarely used for wide local excision of T1 tongue tumors with or without neck dissection. Consideration is given to keeping the endotracheal tube in place overnight for these cases and in cases of small T2 primary tumors. In larger T2 tongue primaries, more posterior lesions, or areas where formal regional or free flap reconstruction is planned, we believe elective tracheotomy is the safest option. Tracheostomy technique varies, with one surgeon (RAO) using a vertical tracheal incision with traction "safety sutures" through either side of the trachea whereas other surgeons in our unit (JEL, DD) prefer a Björk flap. We do not routinely undertake esophagoscopy because of the low incidence of second simultaneous primary cancer at this site. Laryngoscopy and bronchoscopy are reserved for smokers and patients with significant alcohol intake.

With regard to the management of the N0 neck, the senior author (RAO) has published his own evidence-based approach.[14] In summary, all T2N0 tumors of the oral cavity should receive a supraomohyoid neck dissection (SOHND). We do not routinely include level IV for any site including tongue and do not



• **Fig. 18.3** **A** and **B**, Planned surgical resection of a stage I lateral tongue squamous carcinoma with the appropriate 1-cm margin. **C,** Postoperative surgical wound bed following resection of an early stage squamous cell carcinoma of the lateral tongue. The tongue defect was reconstructed via primary closure.

routinely dissect level IIb (the submuscular triangle). We regard this SOHND dissection as a diagnostic/staging procedure. In floor of mouth tumors that cross the mid-line, we undertake bilateral supraomohyoid neck dissections. In stage I disease, any patient with a T1 primary lesion with a depth greater than 3 mm will be advised to undergo SOHND.

If a suspicious node is encountered during SOHND, it is removed intact and sent for frozen section. If this node is reported as positive, level IIb will be dissected and consideration given to removing level IV nodes. Intraoperative palpation of suspicious nodes without frozen section is not accurate enough to make this decision.[15,16]

All primary tumors are palpated to assess their edges, and a 1-cm margin of normal tissue is marked around the tumor (Fig. 18.3). Dissection is carried out with a needle tip Bovie cautery. Once the mucosa is incised in all thin T1 and T2 tumors, frozen sections of the mucosal margins are sent for pathology evaluation immediately before starting the excision. In deeper tumors, especially T2 tongue, deep margins are also sent after the resection is completed, but this is not routine for all tumors. If a major nerve (e.g., lingual) must be excised due to tumor involvement, then frozen sections are obtained from the sectioned nerve.

In primary tumors with diffuse margins or surrounding leukoplakia, the authors have found the use of Lugol's iodine dye helpful[17] (Fig. 18.4). When leukoplakia is extensive and total excision of all leukoplakia will involve gross tissue loss despite a small primary tumor, we use frozen sections. The usual 1-cm margin is marked and frozen sections are obtained of any leukoplakia crossing the margin. If the frozen section shows severe dysplasia or carcinoma in situ, a further 1-cm strip of mucosa



• **Fig. 18.4** Lugol's iodine stain to highlight a squamous carcinoma of the lateral tongue. Areas of carcinoma and dysplasia do not pick up the stain.

is removed again, guided by frozen sections. If a diagnosis of mild-moderate dysplasia is obtained on frozen section, no more tissue is resected and the patient undergoes laser ablation in the office after recovering from ablative surgery. This treatment plan is discussed with the patient before surgery. In tumors that abut the bone, we usually undertake a marginal bone resection, although for smaller T1 tumors with no penetration of the periosteum, periosteal stripping is a safe procedure in the mandible. In anterior floor of mouth lesions, the Wharton's ducts that we identify as crossing the tumor margins are sectioned and transposed posteriorly. All cases and their final postoperative pathology are discussed with the University of Maryland Tumor Board to assess the need for adjuvant therapy.

Radiation and Chemotherapy

As stated previously, at the authors' institution, surgery is the preferred method of treatment for early stage oral tongue squamous carcinoma. Definitive radiation is selected for only those patients who are unable to tolerate surgery or refuse surgery as primary treatment. With early stage SCC, the hope is to avoid the need for adjuvant therapy and radiation side effects. Surgery also allows for complete pathologic evaluation and the identification of those patients who may require adjuvant therapy.

Following surgical resection and pathologic evaluation, patients identified as having high-risk features, such as perineural invasion, lymphovascular invasion, nodal involvement, extracapsular extension, and positive margins, are recommended for adjuvant radiotherapy or concurrent chemoradiotherapy. Cases are presented to a multidisciplinary head and neck tumor board with recommendations for adjuvant radiation therapy or combined chemo-radiotherapy using American Joint Commission on Cancer (AJCC) or National Comprehensive Cancer Network guidelines.[6,7] Data for adjuvant therapy are based on two large randomized trials and subsequent follow-up data from both U.S. (RTOG9501) and European (EORTC22931) oncology groups identifying high-risk patients who could benefit from postsurgical therapy.[18,19]

Chemotherapy as a sole method of therapy has no role for the management of early stage I/II oral tongue squamous carcinoma. If adverse pathologic features are present, the decision for the addition of chemotherapy would depend on patient functional status and performance tolerance. Toxicities to therapy increase with the combination of chemoradiotherapy. At the authors' institution, postoperative chemotherapy includes cisplatin every 2 to 3 weeks in conjunction with adjuvant radiotherapy. Patients with perineural invasion as the only adverse pathologic feature may receive cetuximab in the adjuvant setting combined with radiotherapy (intermediate risk for recurrence).

Radiation Treatment Planning

The role of radiotherapy in the management of patients with early stage oral cavity malignancies is most typically reserved for the postoperative setting. While definitive radiotherapy is certainly a viable therapeutic option for these patients, decades of institutional data have documented improved outcomes for patients managed with primary surgical resection and appropriate adjuvant therapy. Taken together, these data support a 10–15% improved local control of surgery compared to definitive external beam radiotherapy. The most significant challenge of delivering radiation to this patient population is related to the close proximity of critical anatomic structures to the radiation planning target volumes. In the oral cavity, these structures include the oral mucosa, mandible, salivary glands, and spinal cord.

The advent of powerful computing capabilities has revolutionized the radiation oncology treatment planning process. Computer-based inverse planning algorithms now allow radiation oncologists to use diagnostic quality imaging modalities such as CT and MRI to define 3D target volumes while simultaneously defining critical normal structures that must be avoided. A 3D model is created by outlining tumor-bearing regions and avoidance structures (critical normal tissues) on a series of 2D diagnostic images. A team of physicians, physicists, and dosimetrists work collaboratively to create radiation delivery plans that will achieve the stated goals. The ability to combine intensity modulated radiation therapy with diagnostic quality image guidance has dramatically improved the ability to deliver tumoricidal doses of radiation while also decreasing the radiation delivered to healthy normal tissue.

In the postoperative setting, radiotherapy doses of 60 to 65 Gy are typically delivered to tumor-bearing regions, while normal tissue dose constraints range from 26 Gy for salivary gland tissue, to 45 to 50 Gy for the spinal cord. The development of sophisticated treatment planning and delivery systems now allows for the differential dose delivery to anatomic locations that sit in close proximity to each other. This has resulted in improved clinical outcomes as well as decreased acute and late toxicities.

In the setting of early stage oral cavity disease, the initial treatment planning process often involves the identification of appropriate target volumes. Based on the primary tumor location and risk of nodal involvement, the targets often include the primary tumor bed and levels I to III cervical nodal chains. If a lesion is well lateralized, then there is often an attempt to limit the target volume to the ipsilateral nodal chains. In the setting of a centralized tumor or pathologic evidence of nodal involvement, bilateral nodal chains are most typically targeted. Typical pathologic features that help determine the radiotherapy treatment field design include tumor size, margin status, nodal involvement, perineural invasion, perivascular invasion, depth of penetration of the primary tumor, and evidence of extracapsular extension. Based on the results of multiple phase III randomized trials, patients with either positive margins of resection or extracapsular nodal extension are offered adjuvant chemoradiation in order to improve their disease-free and overall survival. The treatment planning process for these patients is the same; however, a greater value is assigned to sparing of normal tissues in recognition of the increased toxicity risk associated with the delivery of concurrent chemotherapy and radiation.

Reconstruction of the Early Stage Oral Squamous Cell Carcinoma—Oral Tongue

The oral tongue is responsible for both speech and the manipulation of food during the initial phase of swallowing. Reconstruction of the oral tongue defect should focus on the restoration of these functions.

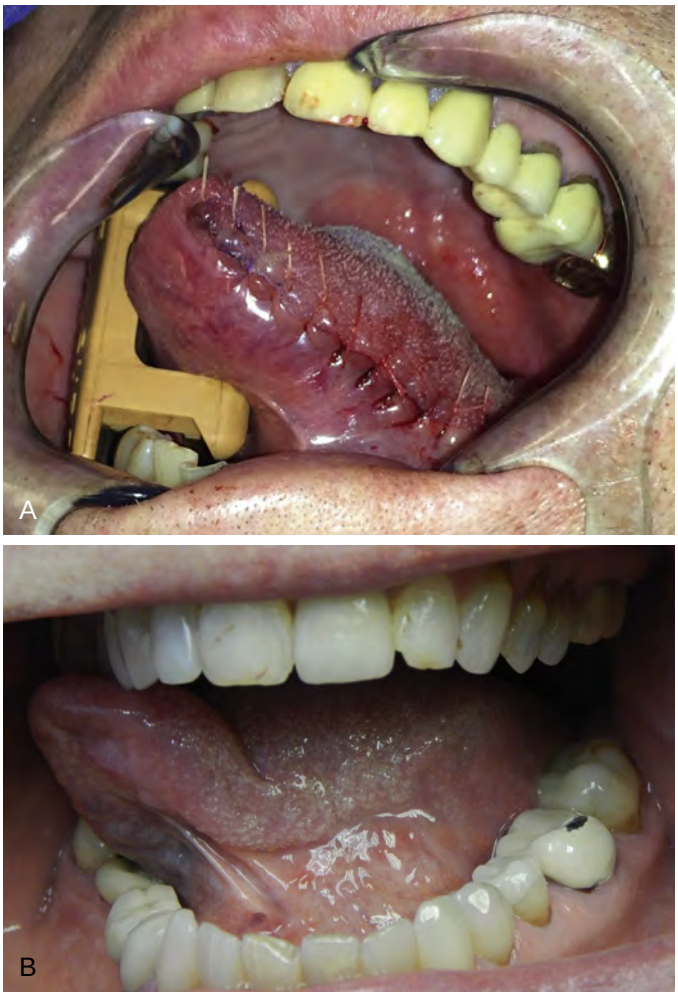
Reconstruction of early tongue squamous carcinoma can be divided into two main categories: those that need formal reconstruction (regional and vascularized free tissue transfer) and those that can be closed primarily or heal by secondary intention or with simple skin grafting. Factors that need to be considered into selection of type of reconstruction should include size and location of the defect and history of previous surgery or radiation. Reconstruction does not replace the highly specialized mucosa and musculature of the tongue (intrinsic/extrinsic muscle) but rather allows for the unrestricted movement of the remaining native tongue tissue.

Controversy remains regarding which patients need formal reconstruction, with a paucity of randomized clinical trials comparing flap reconstruction with non-reconstruction. It is also difficult to assess speech patterns given the variability in languages and dialects among patients. Functional outcomes following surgery are quite good regardless of reconstructive method.[20]

General guidelines that the authors use to select patients for formal reconstruction include defects involving greater than 40% of the tongue, involvement of the floor of mouth that would result in significant tongue tethering, and communication with the neck that could result in salivary leak. Patients who have been previously treated with surgery or radiation should also be considered as candidates for reconstruction because they already have significant scarring or tissue loss. This also holds true for those patients who will likely need adjuvant radiation, because they are also at risk for increased scarring and fibrosis. Reconstruction by primary closure or secondary intention allows for rapid postoperative recovery while avoiding a donor site deformity. It is difficult to assess which method allows for better healing, because many wounds that are primarily closed undergo dehiscence (secondary to powerful tongue musculature) and ultimately heal by secondary intention (Fig. 18.5).

Occasionally it becomes difficult to assess the true size of defect preoperatively. In these situations, the authors will obtain consent for the possibility of formal reconstruction once the primary tumor has been removed. Another general guideline in the selection of whether formal flap reconstruction is necessary is to ask, "If the flap fails, what would I do to reconstruct the defect?" If the answer is primary closure or secondary healing, then one should ask the question: "Is it necessary to do a flap reconstruction in the first place?"

Skin grafting of tongue defects can be performed using patient autogenous tissue or alloplastic materials. The authors most commonly use autogenous split-thickness grafts from the thigh. Full-thickness skin grafts from redundant neck skin (if neck dissection is performed) or the groin are occasionally selected, especially when patients have cosmetic concerns (Fig. 18.6). Alloplastic materials such as AlloDerm are also used depending on surgeon preference. Very often there is partial graft loss of the skin graft, ultimately acting as a barrier/bandage while the wound bed granulates beneath. Bolster dressings can be used to help immobilize the graft for better adherence; however, in view of the difficulty in immobilizing the tongue, the authors find a bolster not necessary. Bolster dressings are cumbersome, annoying for the patient, collect debris, and can become an airway threat even when tightly sutured in place. Significant shrinkage of the graft can occur and even appear as a leukoplakia, which may be mistaken for tumor recurrence.



• **Fig. 18.5** **A,** Primary closure of stage I squamous cell carcinoma of the lateral tongue. **B,** Six months following primary closure of a stage I tongue cancer. The patient did not have any functional deficit with regard to speech or swallowing.

If formal reconstruction is to be considered, tissue that is both thin and pliable should be selected to allow for the most mobility of the remaining native tongue. The most common donor site tissue selected by the authors for formal reconstruction of T1 and T2 size defects is the vascularized radial forearm free flap (RFFF). Advantages of using the RFFF include the ability to use a two-team approach, minimum donor-site morbidity, large caliber vessels, long pedicle length, and thin and pliable tissue ideally suited for tongue reconstruction. Although less commonly used, the ulnar forearm free flap (UFFF) can



• **Fig. 18.6** Full-thickness skin graft to be incorporated into the skin incision during simultaneous neck dissection of an early stage squamous tongue cancer of the lateral tongue.

also be safely harvested for tongue reconstruction. The authors use this flap when forearm tissue is needed but the patient has dominant perfusion of the hand based upon the radial artery. Great care must be taken to protect the ulnar nerve in cases of UFFF harvest; as well, the surgeon must understand that the perforators to the ulnar skin paddle are more visible and can be inadvertently injured if not careful. Other advantages cited with the ulnar forearm flap include a less visible donor site scar and a less hair covered surface. The authors have not found this to be the case especially in the face of adjuvant radiation[21-24] (Fig. 18.7 and 18.8).

The authors do not routinely reinnervate their flap reconstructions; however, this can be performed after vascular reanastomosis (decreased flap ischemia time) to either the remnant lingual nerve or other sensory nerve. Unfortunately, there is lack of level I evidence to suggest the true functional outcomes of sensate flaps with regard to speech and swallowing function compared with non-sensate flaps. In a series of 145 partial or hemiglossectomy defects, Chang and colleagues[25] reported significant speech and swallowing function with innervated flaps compared with non-innervated flap reconstructions. Mah and colleagues[26] found no significant difference between innervated and non-innervated free flaps in terms of speech, swallowing function, or quality of life. Neurosensory recovery has also been described in non-innervated radial forearm flaps.[27]

Larger T2 tongue defects (e.g., hemiglossectomy defects) can be reconstructed with vascularized anterolateral thigh flaps with minimal donor site morbidity (esthetic, functional deficit, wound care requirements) while providing more tissue bulk than is available with the forearm flap[24] (Fig. 18.9). Advantages over the regional pectoralis myocutaneous flap include ease of flap inset with improved geometric variability secondary to the freely mobile vascular pedicle, while providing good tissue bulk.

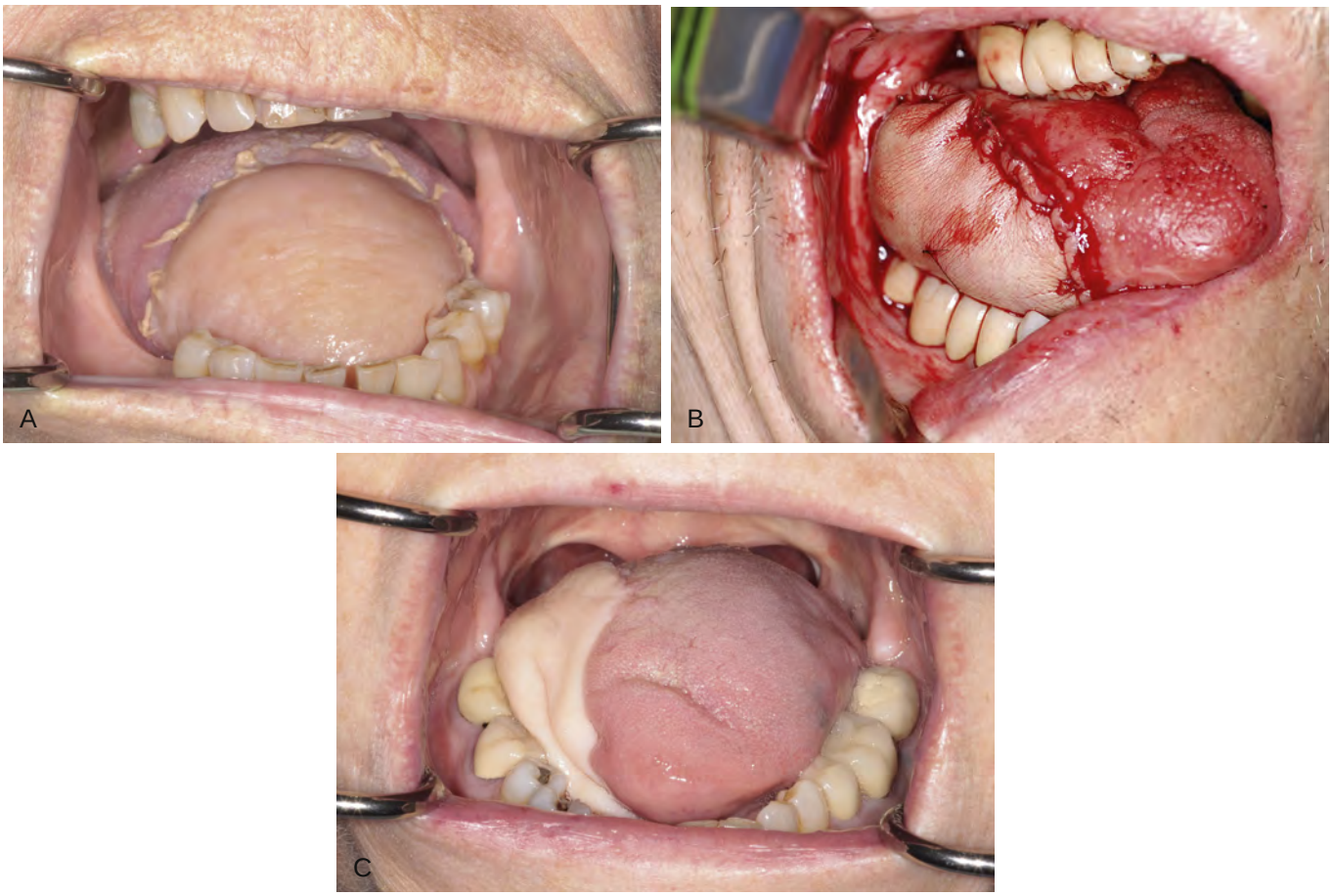
Although there are numerous regional flaps to select from for more extensive tongue reconstruction, the authors most commonly select either the pectoralis major myocutaneous flap or the submental island flap. Reasons cited for regional flap selection include patient co-morbidities requiring decreased operative time, surgeon/patient preference, decreased donor site morbidities (i.e., submental island or platysma flaps), reduced hospitalization time, and the avoidance of free flap monitoring protocols. Although not the case in most major head and neck surgical units, the lack of access to a microvascular surgeon can also be a factor in the decision against free tissue transfer versus a regional flap selection.[28-30] In the case of the submental island flap, the added benefit of improved esthetics (i.e., "neck lift" without a second donor site) is suggested. Arguments against the submental island flap include its questionable oncologic safety, especially with level Ia/Ib lymph nodes, despite the lack of evidence in the literature to suggest this is a problem.[28] To avoid any issue of oncologic safety, the authors do not use the submental island flap when preoperatively the neck is clinically found to be node-positive. When this flap is used and a level I node is identified to be positive intraoperatively, then this flap is abandoned for another method of reconstruction (Fig. 18.10).

The pectoralis rotational flap is a reliable flap that is both easy to harvest and can provide for added bulk as required in larger tongue defects. This bulk can be a disadvantage, making flap inset difficult, especially in cases in which a lip-split mandibulotomy or pull-through approach to a tongue cancer extirpation was not used. To increase the arc of rotation allowing for a more tension free flap inset and to minimize potential tongue tethering from the inferiorly based muscular vector forces, the pedicle can be skeletonized at its origin point at the clavicle or the tendinous insertion at the humerus can be divided (Fig. 18.11).

Rehabilitation of the Early Stage Oral Tongue Reconstruction

Rehabilitation of tongue cancer patients begins almost immediately following surgery. Rehabilitation includes assessment of speech and swallowing, physical therapy, and safety assessment for performance of activities of daily living.

For patients who have undergone resection of small lesions that have been closed primarily or skin grafted, evaluation with bedside swallow examination is initiated once the patient is extubated. Once speech and language pathology service deems it safe for the patient to swallow (i.e., adequate cough reflex



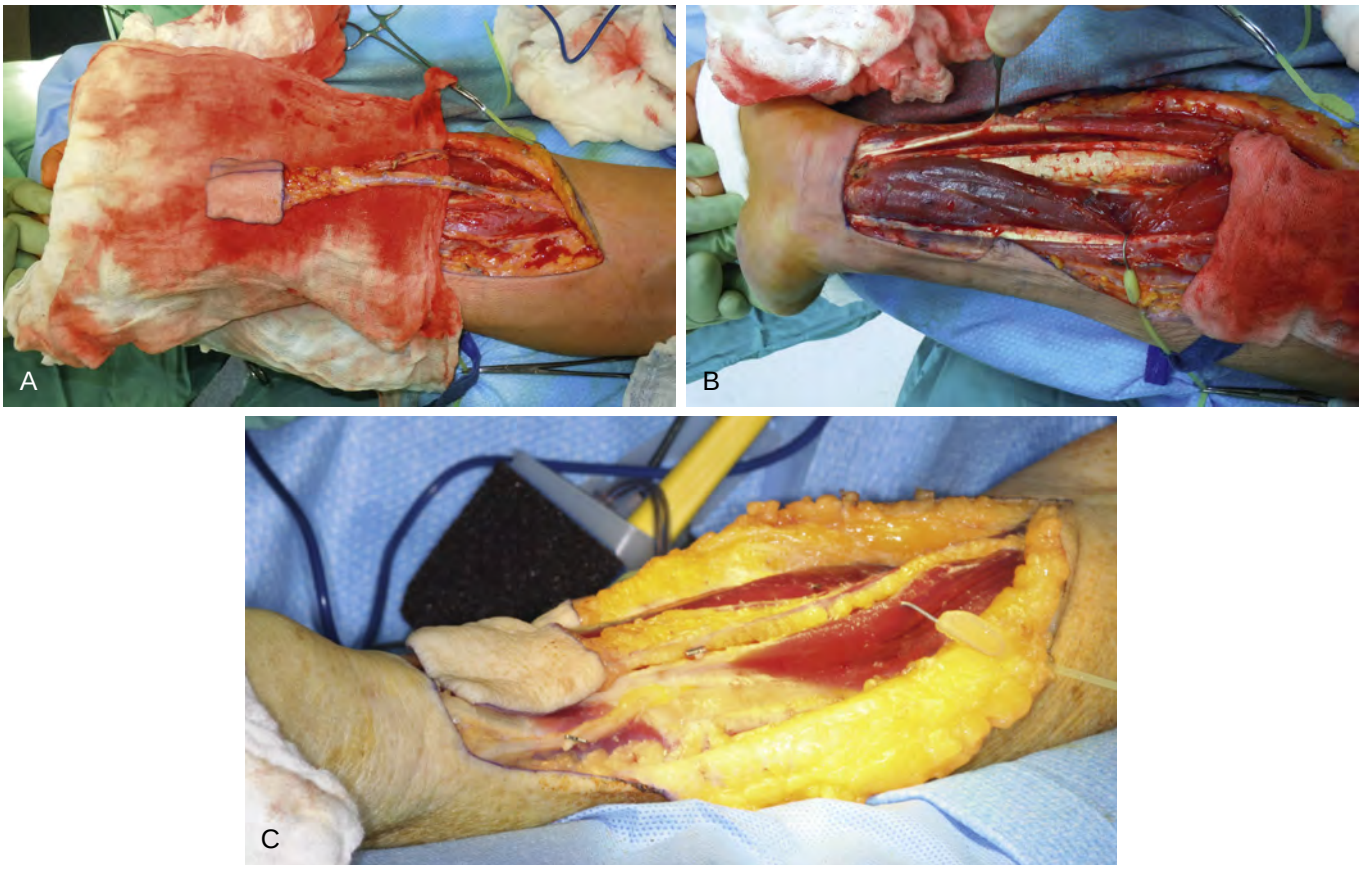
• **Fig. 18.7** **A,** Forearm flap for anterior tongue reconstruction. **B,** Forearm flap for lateral tongue reconstruction. The suture marks the area of Doppler probe placement for postoperative flap monitoring. **C,** Forearm flap for lateral tongue reconstruction at 9 months postoperatively.

and no evidence of aspiration), a liquid diet can be initiated with advancement of food consistencies as tolerated by the patient. Formal flap reconstruction patients are started on a diet either by intraoperatively placed nasogastric feeding tube or with gastrostomy tube (placed either preoperatively or intraoperatively). A swallow examination, either with bedside swallow or modified barium swallow (MBS), is attempted between postoperative days 5 and 8. This gives adequate time for flap/tongue edema to subside, tracheostomy decannulation, and wound healing/flap stabilization. If a salivary leak is suspected (signs of infection, saliva noted from the drains, or wound dehiscence) but cannot be identified on clinical examination, an MBS or esophagram can be performed to rule out a leak.

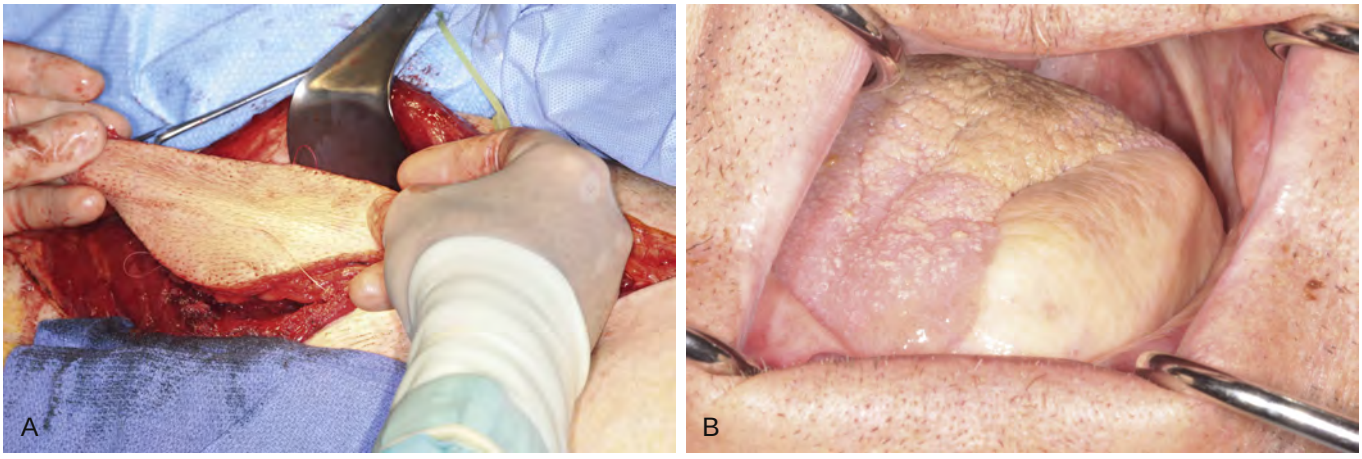
Impairment seen in oral tongue surgery includes reduced control and difficulty with forming/propelling a bolus into the pharynx. In patients whose resection was near or at the base of the tongue, there is further difficulty with clearance of the bolus, with resultant pharyngeal residue and aspiration risk. Nothing by mouth and an alternative feeding method is recommended for patients who fail an MBS due to aspiration. If the speech pathologist thinks that swallowing function will recover within weeks, then nutrition is continued via nasogastric tube. If the dysphagia is anticipated to be for an extended period of time or if the patient will require adjuvant radiotherapy that will result in further swallow dysfunction, then a gastrostomy tube (open or percutaneous endoscopic) is placed for patient comfort. Throughout the rehabilitation, both as an inpatient and outpatient, the patient will receive speech and swallow therapy. This is especially important throughout adjuvant radiotherapy because fibrosis and dysphagia increase during therapy.[31]

Speech will improve throughout the healing course and it is important to provide reassurance to the patient. They often have to be reminded that tongue edema can take months to resolve and this can be further delayed by adjuvant radiotherapy. Manifestations of tongue overuse include "slurred speech," which is worse at the end of a day. Speech exercises and techniques taught to patients during outpatient therapy help improve outcomes. In a study by Riemann and colleagues,[32] speech intelligibility was found to be significantly hampered during the first 2 to 3 weeks postoperatively, but marked improvement was noted at 1 year. Preservation of the tongue tip resulted in a higher level of word recognition after 12 months. There was no difference in radiated versus non-radiated patients.

Almost all patients, regardless of surgical complexity are admitted to the hospital for at least a 23-hour observation to ensure adequate tongue hemostasis, airway safety, adequacy



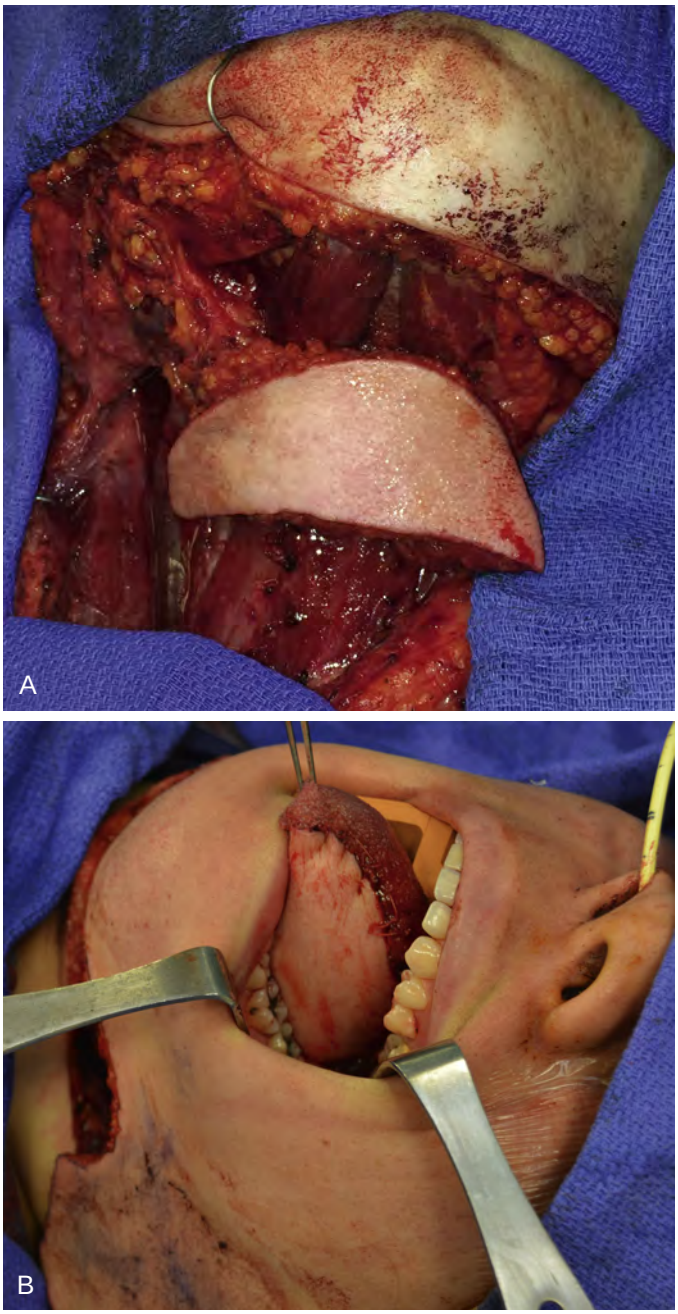
• **Fig. 18.8** **A,** Ulnar forearm flap donor harvest. Note the preservation of the basilica vein for dual venous flap drainage. **B,** Ulnar flap donor site. Note preservation of the ulnar nerve. **C,** Radial forearm flap donor harvest.



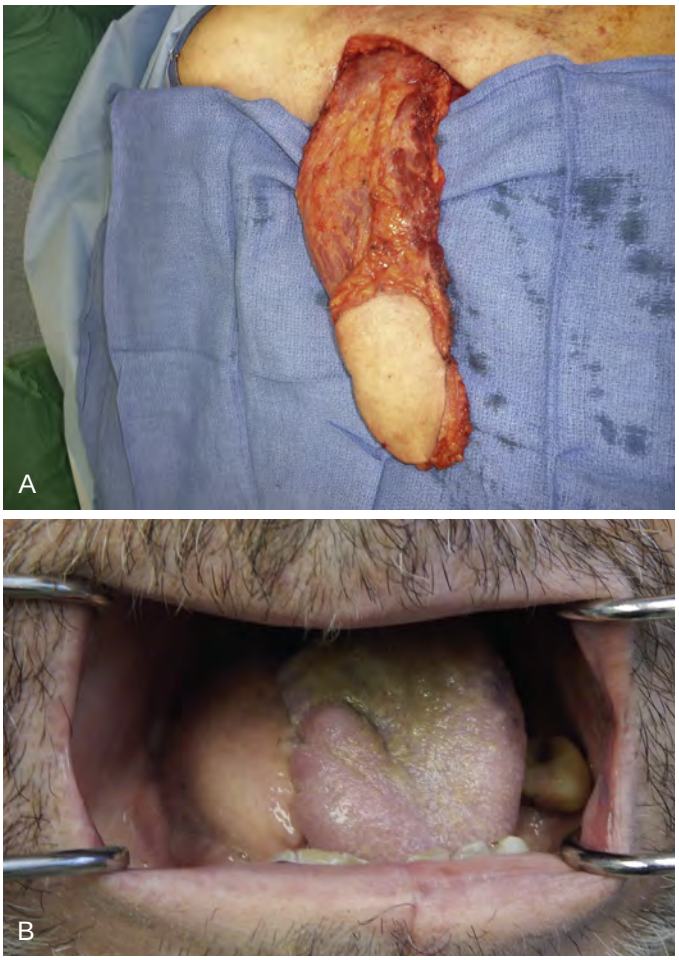
• **Fig. 18.9** **A,** Harvest of anterolateral thigh free flap for hemiglossectomy defect reconstruction. **B,** Anterolateral thigh flap reconstruction for hemiglossectomy defect at 1-year postoperatively.

of oral diet or alternative nutrition, and pain control. Early ambulation is imperative to help minimize the risk of infections, atelectasis, and deep venous thromboembolism.

Not every patient will require assessment by physical therapy and rehabilitation medicine staff as to final hospital disposition. For example, a patient with a small T1 partial glossectomy treated with primary closure may be discharged home without any assessment by rehabilitation medicine staff. Discharge disposition is dependent on ability to perform activities of daily living, adequate pain control, ambulatory status, nutrition requirements, and wound care issues. Patients are discharged to home or to an acute or subacute rehabilitation facility. Arrangements for a visiting nurse can be made to help the patient who is discharged to home.



• **Fig. 18.10** **A,** Submental island flap harvest for planned tongue reconstruction with simultaneous bilateral selective neck dissection. Note the removal of the submental level Ia lymph nodes between the anterior bellies of the digastric muscles. **B,** Submental island flap for T2 tongue reconstruction.



• **Fig. 18.11** **A,** Pectoralis major myocutaneous flap harvest for hemiglossectomy defect. **B,** Post-operative photo of pectoralis flap for right hemiglossectomy defect reconstruction.

Surveillance

Although long-term prognosis of early squamous tongue cancer is good (SEER data from the National Cancer Institute), with rates being quoted anywhere from 75% to 90% for 5-year overall and disease-free survival, especially for favorable pathologic features, the majority of recurrences occur within the first 2 years following treatment.[33] There is also a subset of patients who are at lifelong risk for development of multiple second primary cancers. This risk for metachronous primaries is even higher in those who continue to smoke tobacco.[34] It is for these reasons that oral tongue SCC patients require lifelong surveillance. The authors generally follow the surveillance guidelines of the National Comprehensive Cancer Network and the AJCC (Table 18.1).

A complete head and neck examination is conducted at each office visit. Flexible or rigid fiberoptic examination is performed at the discretion of the surgeon. Use of endoscopes are generally reserved for symptoms necessitating visualization of non-visible structures (e.g., dysphagia) or in cases in which trismus or flap reconstruction has obscured the ability to view the entire oral cavity and superior oropharynx. Restaging/surveillance imaging should be obtained between 3 and 6 months postoperatively. The type of imaging is both controversial and variable but generally includes a contrast-enhanced CT scan for patients with favorable initial pathologic features. MRI can better show soft tissue structures and may help discern postsurgical changes from disease recurrence, especially in flap reconstruction cases. The authors do not routinely use PET scan imaging for early stage oral tongue cancer surveillance unless there is a specific reason to do so. This could include significantly altered anatomy secondary to a flap reconstruction

TABLE 18.1 Timing of Surveillance of Early Stage Oral Tongue Cancer by the University of Maryland Group

- Year 1-2: Patient evaluation every 2 months
- Year 3: Patient evaluation every 4 months
- Years 4-5: Patient returns every 6 months
- >5 years: Yearly patient evaluation
- Initial restaging imaging is obtained between 3 and 6 months; subsequent imaging is based on individual patient assessment

or a suspicious area identified on the CT/MR surveillance images. In a recent study, Müller and colleagues[35] reported a 10% increase in both sensitivity and specificity in the identification of local tumor recurrence in patients having undergone oral cavity reconstruction, such as with the use of PET plus contrast CT scan compared with contrast CT alone. Personal experiences of the authors (JEL, DD, RAO) have also found that health insurance approval has become more difficult to obtain for surveillance PET imaging in patients with stage I/II disease, with the main reason cited being the increased cost-benefit ratio in the detection of disease recurrence.

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19

Advanced Tongue Cancer

RYAN J. SMART, DONGSOO DAVID KIM, G.E. GHALI

Tongue Development and Anatomy

During the fourth week of gestation, two lateral lingual swellings appear along the medial surface of the first pharyngeal or mandibular arch. A midline swelling, tuberculum impar, is also thought to arise from the first pharyngeal arch; however, this does not form an adult structure. As the lateral lingual swellings enlarge, they engulf the tuberculum impar and fuse at the midline, forming the oral tongue. The remnant of that fusion is a relatively avascular fibrofatty plane— the median raphe of the adult tongue. The lingual derivative of the third pharyngeal arch and hypobranchial eminence of the second arch is the tongue base. As the two lateral lingual swellings grow toward the midline, the lingual swelling along the third pharyngeal arch grows forward and fuses with the anterior lateral lingual swellings. This point of fusion constitutes the sulcus terminalis in the adult tongue. During fusion of the posterior one third and anterior two thirds of the tongue, the thyroid gland begins its descent into the neck and at the apex of the sulcus terminalis a depression termed the *foramen cecum* is left as a reminder of the thyroid gland's early embryologic position. Muscular elements of the tongue are derived from occipital myotomes that merge into the deep tongue during the fusion of the lingual eminences.

The oral tongue is the mobile anterior two thirds of the tongue that extends from the circumvallate papillae at the sulcus terminalis posterior to the tip anterior. The ventral surface of the tongue is contiguous with the floor of mouth both anteriorly and bilaterally. The oral tongue can be subdivided for ease of description into the dorsum, tip, and lateral and ventral surfaces. The dorsum of the tongue is covered by specialized stratified squamous epithelial mucosa covered with papillae. Filiform papillae make up the majority of these papillae while fungiform papillae are less numerous. Immediately deep to this layer of specialized mucosa is a layer of connective tissue, the lamina propria, which binds the mucosa to deeper muscular bundles of the tongue. The tip of the tongue is the most freely mobile portion of the tongue, which is important in speech articulation and bolus manipulation during mastication. The lateral surfaces of the tongue are covered by lining mucosa, which consists of nonkeratinized, stratified squamous epithelium. Beneath this lies a lamina propria, which contains fibroelastic connective tissue. Unlike the dorsum of the tongue, the lamina propria of the lining mucosa of the ventral lateral tongue and floor of mouth is not bound tightly to underlying muscle; rather, a loosely organized submucosa is present that allows the lining mucosa a moderate amount of mobility over the underlying structures. Along the posterolateral surfaces of the tongue are the foliate papillae, which lie in vertical furrows within the mucosa. Taste buds are located within the foliate as well as the fungiform and circumvallate papillae. The ventral tongue is contiguous with the floor of mouth. At the midline of the anterior floor of mouth lies the lingual frenulum as well as the paired submandibular duct orifices.

The blood supply to the tongue consists of the paired lingual arteries, a branch off of the external carotid artery. There is a rich, anastomosing, branching network of arteries that renders the tongue relatively resistant to devascularization. After branching from the external carotid artery, the lingual artery passes medial to the greater horn of the hyoid bone as it courses toward the tongue. It passes through Lesser's triangle, which is bordered by the hypoglossal nerve, and anterior and posterior bellies of the digastric muscle. As it curves forward, deep to the hyoglossus muscle, it runs in a mid-sagittal plane, parallel to the long axis of the tongue. The hyoglossus muscle separates the lingual artery from the lingual nerve. It gives off a relatively superficial dorsal lingual branch posteriorly, called the lingual artery profunda, before continuing anteriorly as far as the tip of the tongue.

Venous drainage of the tongue is via the paired superficial and deep lingual veins. Lingual veins can drain directly into the internal jugular vein or more commonly into the common facial trunk of the internal jugular vein. The deep lingual veins frequently anastomose with the comitant vein of the hypoglossal nerve, or ranine vein.

Lymphatic drainage of the tongue is characterized by crossover and an extensive network of interconnected channels draining submandibular as well as upper jugulodigastric cervical lymphatics. First echelon drainage of the tongue depends on the tongue site being drained. The tip commonly drains to the submental, level Ia, lymph nodes while the mid-portion drains to submandibular, level Ib, lymph nodes. Posterolateral and tongue base commonly drain to superior and inferior deep cervical lymph nodes, levels II and III.

Several cranial nerves innervate the tongue, underscoring its importance in communication, feeding, and sensation. The fifth cranial nerve imparts sensation to the anterior two

thirds of the tongue. Along with the lingual nerve, a branch of the mandibular nerve and third division of the fifth cranial nerve, runs the chorda tympani nerve. A branch of the facial nerve, cranial nerve VII, chorda tympani receives taste information from the anterior two thirds of the tongue. Taste and sensory information from the posterior one third of the tongue are received by the glossopharyngeal nerve, cranial nerve IX. Motor innervation is via the cranial nerve XII, or hypoglossal nerve, and cranial nerve X, or the vagus. The hypoglossal nerve passes deep to the posterior belly of the digastric muscle in the neck before entering the tongue lateral to the geniohyoid muscle and parallel to the lingual artery. All of the muscles of the tongue are innervated by the hypoglossal nerve except the palatoglossus muscle, which is innervated by the vagus nerve.

Tongue musculature is categorized as extrinsic or intrinsic. Extrinsic muscles originate from the bone of the mandible, hyoid bone, and styloid process and insert into the tongue, allowing 3D movement of the tongue and stability of the tongue within the oral cavity and oropharynx. The extrinsic muscles are the genioglossus, which arises from the genial tubercle and inserts into the tongue. The genioglossus muscle allows protrusion of the tongue. The styloglossus muscle arises from the styloid process and inserts along the lateral borders of the tongue. The action of this muscle is to elevate and retract the tongue. The hyoglossus muscle originates along the hyoid bone and inserts into the lateral aspects of the tongue. This muscle depresses the tongue. The palatoglossus muscle, the only tongue muscle not innervated by the hypoglossal nerve, does not have a bony origin; rather, it arises from the palatine aponeurosis to insert along the posterolateral borders of the tongue. This muscle, innervated by the vagus nerve, aids in closure of the velopharyngeal aperture during swallowing and aids in speech by elevating the back of the tongue while depressing the soft palate and constricting the palatoglossal fold.

The intrinsic tongue muscles are a collection of paired muscles that originate and insert within the tongue. They act to change the shape of the tongue. These muscles consist of transverse, longitudinal, and vertical fibers.

Epidemiology

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program estimated 42,440 new cancers of the oral cavity and pharynx in 2014, which represented 2.5% of all new cancer cases. The estimated 5-year overall survival rate for those with cancer of the oral cavity and pharynx is 62.7%.[1] The oral tongue and floor of mouth are the most common subsites of oral cavity cancer.[2] Although alcohol and tobacco use are associated with the development of oral squamous cell carcinoma, some studies have demonstrated unique epidemiologic characteristics for oral tongue cancer as well as oral cancer in younger patients without the usual risk factors.[3] Bodner and colleagues[4] retrospectively studied 186 cases of oral cancer in patients younger than 20 years old. The oral tongue was the most common site. The authors cited immune compromise due to systemic disease as an inciting factor, although it was not statistically significant.[4] Other authors examined populations of patients who did not have smoking or alcohol use as risk factors, and found oral tongue involvement to be the most common site among those with oral cavity squamous cell carcinoma. Although it has been postulated that oral cancer tends to be more aggressive in younger patients who do not have the usual risk factors, the findings in the literature are inconclusive.[5-7] The INHANCE consortium pooled data from 25 case control studies to identify risk factors for development of head and neck cancer in people younger than age 45 years, in young adults, and in those older than 45 years. They reported that oral tongue cancer was the most prevalent site of involvement, as well as a positive association with alcohol use, a family history positive for cancer, and a diet low in fruits and vegetables.[8] Human papilloma virus (HPV) is a well-known risk factor for development of oropharyngeal squamous cell carcinoma, but few definitive studies demonstrate the correlation between HPV and oral tongue squamous cell cancer or prognostic significance of HPV-positive oral tongue cancers.[9,10]

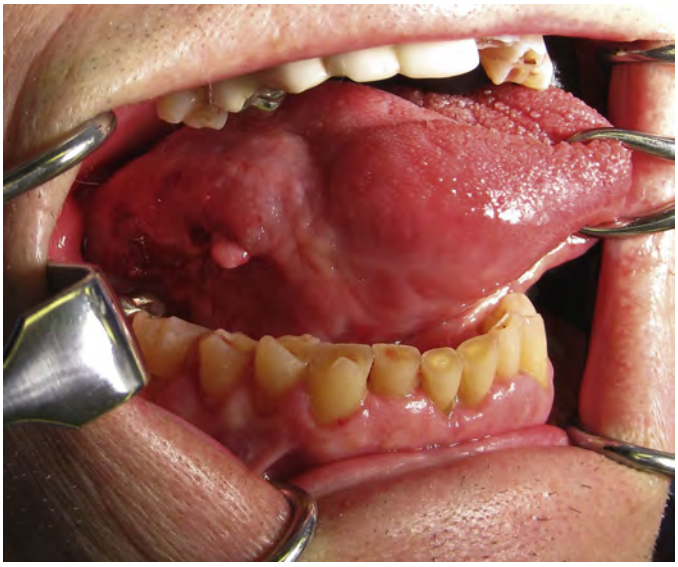
History and Physical Examination

The presenting complaint for most patients is pain. Historically it was thought that pain due to malignancy of the oral cavity was due to superinfection or direct involvement of sensory nerves by tumor invasion. Recently, the molecular and neurobiologic aspects of cancer pain have been explored as causes.[11] Cancer cells have been shown to secrete endothelin 1, which results in nociceptive sensitization both in the tumor microenvironment and at the level of the spinal cord.[12] Patients with advanced oral tongue cancer frequently complain of severe pain at the site of the tumor, as well as referred pain to the ear or the throat due to the rich innervation and cross-innervation of these areas by cranial nerves V, IX, and X and cervical nerves C2 and C3.[13] Other complaints may be tooth pain, unintended weight loss, dysphagia, or odynophagia. Patients often estimate how long a lesion has been present within the oral cavity but this estimate is usually far less time than the actual duration. Occasionally patients are referred for evaluation of asymptomatic lesions that were noticed by other health care providers—frequently dental hygienists—but this is usually not the case for advanced stage tumors.

On physical examination, advanced stage tumors are easy to distinguish as malignancies. The tumors may be exophytic (Fig. 19.1), verrucous (Fig. 19.2), endophytic and ulcerated (Fig. 19.3) or a combination (Fig. 19.4). The tongue may be fixed to the floor of mouth (Fig. 19.5) or demonstrate atrophy and fasciculation with hypoglossal nerve involvement. It is well documented that at the time of presentation, patients with squamous cell carcinoma of the oral tongue are at risk for metastasis to cervical lymph nodes. On presentation, 24% of all patients presenting with cancer of the oral tongue had frank metastasis and 27% had occult metastasis.[14,15] It has long been established that depth of invasion of more than 2 mm in the tongue or floor of mouth is a risk factor for occult neck metastasis.[16]

Staging

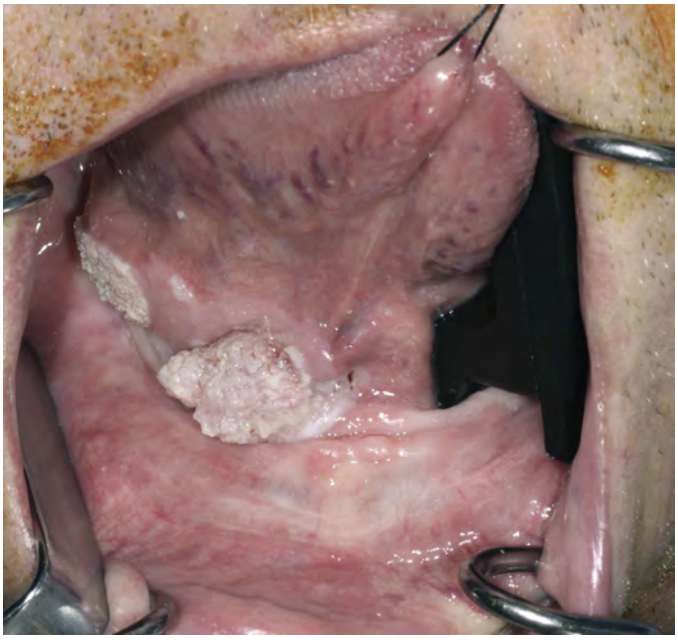
The work-up and clinical staging for patients presenting with advanced stage tongue cancer includes a thorough history and



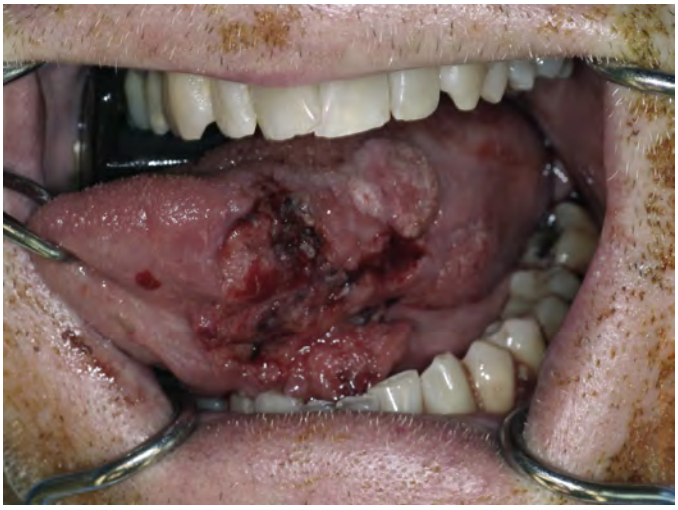
• **Fig. 19.1** Photo of squamous cell carcinoma of the right tongue with exophytic features.



• **Fig. 19.3** Photo of squamous cell carcinoma of the left tongue with endophytic features.



• **Fig. 19.2** Photo of squamous cell carcinoma of the anterior floor of mouth and right ventral and lateral tongue with exophytic as well as verrucous features.



• **Fig. 19.4** Photo of squamous cell carcinoma of the left tongue demonstrating ulceration, an endophytic component, and an exophytic component dorsally.

clinical examination, panoramic radiographic examination of the dental structures, contrast-enhanced computed tomography (CT) of the neck, and chest radiograph. A comprehensive metabolic panel and complete blood count are also routinely drawn. Further medical work-up is dictated by the patient's medical history.

Nasopharyngoscopy and panendoscopy are commonly employed diagnostic modalities in the work-up and staging of head and neck cancer. In a study evaluating the role of an endoscopy in identifying second primary tumors, researchers from Norway conducted a prospective trial of 2,016 head and neck cancer patients, in whom 2.4% had second primary tumors and the majority of those tumors were located in areas covered by panendoscopy. Other second primary tumors were located lower in the aerodigestive tract, such as in the bronchial tree Although the median survival in the study was not different between patients with simultaneous second primary tumors and those with non-simultaneous second synchronous second primary tumors, the researchers concluded that symptom-directed panendoscopy at the initial work-up was successful in finding second primary tumors of the upper aerodigestive tract but not those located in the lower airways.[17]

Based on a recent review of the literature, the role of bronchoscopy in the presence of normal chest CT was found unlikely to improve detection of second primary malignancy; the use of esophagoscopy for patients with hypopharyngeal squamous cell carcinomas improved detection of second primary tumors.[18] The most important aspect of identifying second primary tumors in the upper aerodigestive tract with panendoscopy is proper staging, which may alter the treatment



• **Fig. 19.5** Photo of squamous cell carcinoma of the left tongue with endophytic features and fixation of the tongue to the floor of mouth.

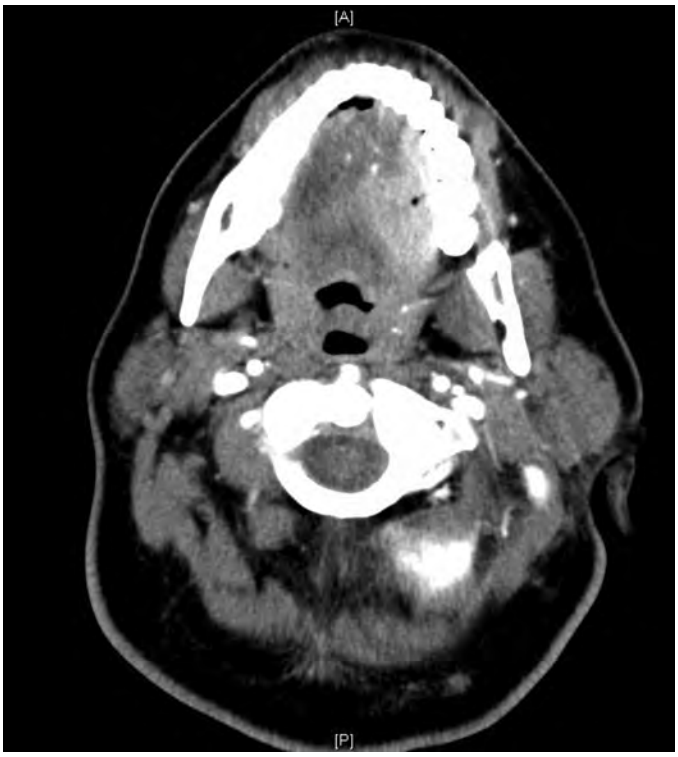


• **Fig. 19.6** Contrast-enhanced CT of the neck showing a large, pathologically involved lymph node that has all the features of malignancy. It is large and round with a necrotic center, and there is loss of definition between it and the adjacent fat planes of normal anatomy.

plan in patients with several tumors or field cancerization. These patients may be better candidates for primary chemotherapy and radiation therapy rather than extensive surgery.

Anatomic as well as functional imaging studies are adjuncts in the head and neck cancer patient work-up. While these modalities can be useful, their limitations must be kept in mind when interpreting the results.

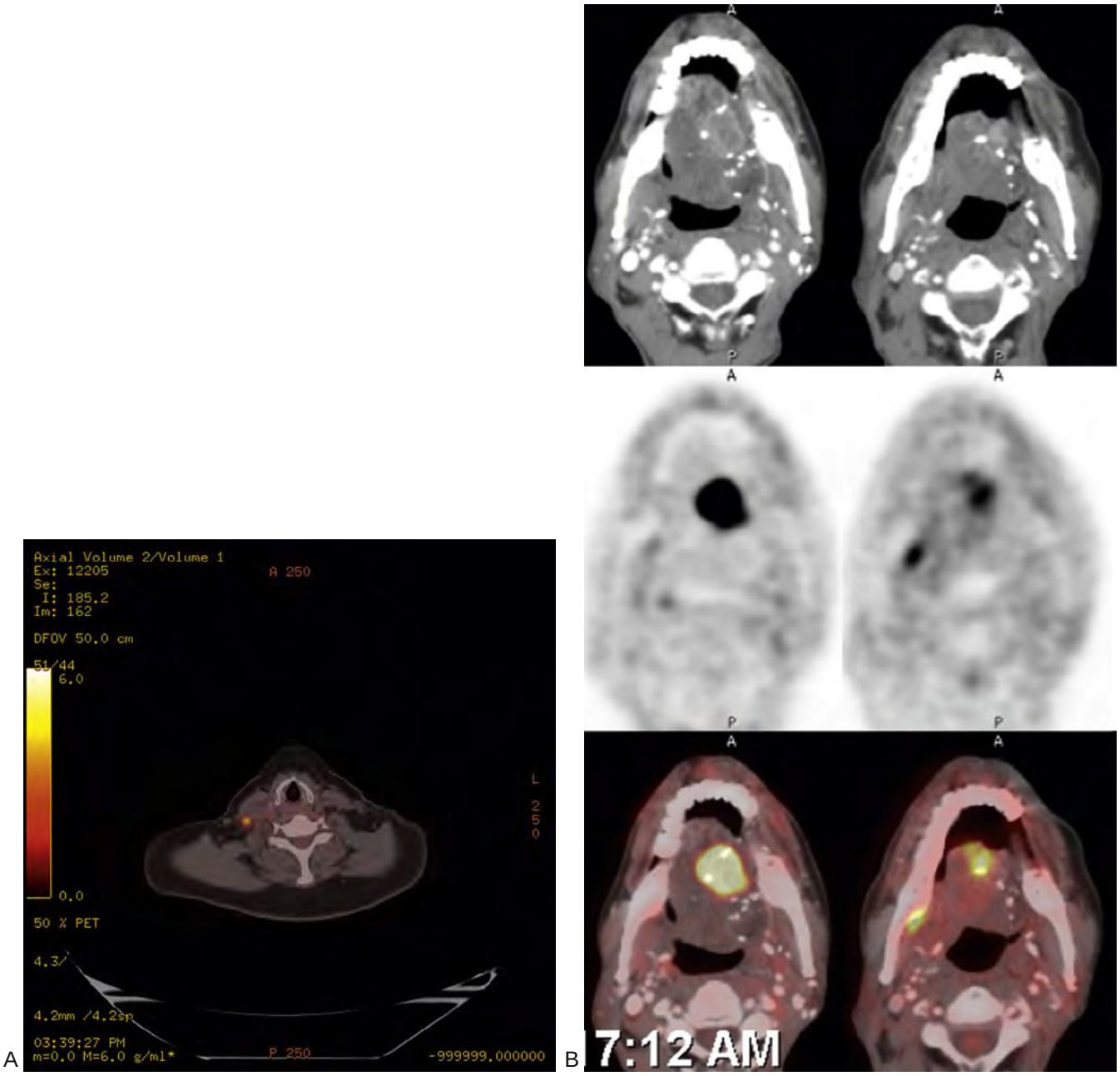
CT imaging demonstrates superior spatial resolution and is best for evaluating bone invasion. Short acquisition times result



• **Fig. 19.7** Contrast-enhanced CT of the tongue showing a hyperemic area along the left tongue corresponding to the tumor. Also note the mass effect of the tumor pushing the median raphe to the contralateral side of the tongue.

in decreased motion artifact and less difficulty for patients. Several radiographic characteristics involving lymph nodes have been described in the literature; however, the sensitivity and specificity remain 83% for evaluating the neck for metastatic adenopathy. Lymph nodes greater than 10 mm in diameter or 15 mm in the submandibular triangle, the presence of central necrosis, rounded shape, loss of a normal fatty hilum, increased or mixed uptake of contrast, and obliteration of adjacent fat planes all suggest carcinomatous involvement of the lymph node (Fig. 19.6). Although tongue imaging on CT is often obscured by the adjacent mandible and dental metallic restorations, lesions within the tongue on a contrast-enhanced CT appear hyperemic with mass effect and infiltration into adjacent soft tissue (Fig. 19.7). Magnetic resonance imaging (MRI) is more effective in evaluating soft tissue, perineural spread, skull base invasion, and intracranial extension of head and neck cancer. With regard to evaluation of the neck, the sensitivity of MRI for detecting pathologic nodal metastases has been shown to be as low as 57%.[19]

Positron emission tomography (PET) with CT fusion (PET/CT) is an important tool in the diagnosis, work-up, staging, and post-treatment surveillance in head and neck cancer. The sensitivity and specificity for PET/CT imaging has been shown to be 98% and 93%, respectively, with a positive predictive value of 63% and a negative predictive value of 99.7% for detecting malignant deposits.[20] A more recent meta-analysis across 13 studies demonstrated the sensitivity and specificity of PET/CT were 0.84 and 0.96, respectively.[21] National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (NCCN Guidelines) do not require PET/CT and the Radiation Therapy Oncology Group (RTOG) does not include PET/CT as



• **Fig. 19.8** **A,** PET/CT of a patient 6 months after resection of a low-grade salivary gland malignancy. Single node uptake with a moderate standard uptake value. A value greater than 3 is suggestive of malignancy. Pathologic specimen demonstrated no evidence of malignancy. **B,** PET/CT of a patient 8 months after resection, reconstruction, and adjuvant chemoradiation therapy for a T4a SCCa of the tongue. Note the areas of uptake in the residual tongue. On surgical exploration and biopsy, no tumor was identified and, at the time of publication, the patient is currently alive with no clinical evidence of recurrence.

a staging tool. Nonetheless, many oncologists routinely employ PET/CT in the work-up for their cancer patients. We do not recommend the routine use of PET/CT imaging in the initial work-up of the head and neck cancer patient even with T3 or T4 tumors unless there is clinical or radiographic evidence of metastasis. For example, in a patient with an advanced tumor of the tongue but no other clinical or radiographic evidence of neck metastasis, a PET/CT would not be sought. However, in a patient with an advanced tumor in which a lung nodule is discovered on initial evaluation or in those patients with extensive neck disease, a PET/CT is considered. Although it is tempting to rely on PET/CT for evaluation of the neck, it lacks the sensitivity to detect lesions less than 5 mm in the smallest dimension. The ECOG-ACRIN study group (ACRIN 6685 trial) is currently evaluating the efficacy of fludeoxyglucose-PET imaging in the staging of head and neck cancer patients.[22] The main limitation of PET/CT is that the modality does not easily differentiate malignancy versus inflammation or tissues with high baseline metabolic activity (Fig. 19.8). Furthermore, many patients present for biopsy of an oral lesion before images are obtained. In the interest of time, many clinicians proceed with biopsy and then obtain the scan. Inflammation due to the biopsy may lead to false-positive results on PET/CT

imaging and overzealous treatment. Routine PET/CT scanning in the work-up of head and neck cancer patients may delay treatment of the primary tumor due to the need for complete work-up of incidental findings on the PET/CT. It is also generally not recommended to obtain surveillance post-treatment PET/CT imaging sooner than 8 weeks post-treatment due to residual inflammation from treatment.[23] At the authors' institution, a minimum of 12 weeks is routinely elapsed before end-treatment PET/CT is obtained. Consensus guidelines based on a review of recent literature regarding use of PET/CT imaging in the work-up of head and neck cancer patients has been developed and include use in patients in which primary imaging modalities are equivocal, when treatment may be altered, in cases of unknown primary tumors, and for restaging.[24]

The American Joint Committee on Cancer (AJCC) has published a staging manual that includes a chapter for staging lip and oral cavity cancer.[25] This includes epithelial tumors; mucosal melanoma, lymphoid tumors, and sarcomas are staged separately. Stage IV has been stratified into three substages:

- Stage IVa, moderately advanced local and regional disease
- Stage IVb, very advanced local and regional disease: tumors that are non-resectable without distant metastasis
- Sage IVc, presence of distant metastatic disease

The AJCC staging manual incorporates the tumor-node-metastasis framework and does not take into consideration histologic risk factors such as depth of invasion, perineural invasion, lymphatic and vascular embolism, or grade. The staging system also does not take into account the patient's performance status or the patient's ability to withstand treatment, whether it be surgery, radiotherapy, or chemotherapy.

T designation stands for the primary tumor and there are several subclassifications:

- Tx is reserved for instances in which the primary tumor cannot be assessed, such as cases in which the primary was ablated or an excisional biopsy done without documenting the T stage.
- T0 indicates there is no evidence of a primary tumor such as in cases of unknown primary malignancy. This is reserved for carcinoma in situ.
- T1 is for tumors 2 cm or less in their greatest dimension.
- T2 tumors are more than 2 cm but not more than 4 cm in the greatest dimension.
- T3 tumors are more than 4 cm in greatest dimension yet have not invaded into adjacent or deeper structures.
- T4a tumors are moderately advanced tumors that invade through cortical bone, inferior alveolar nerve, floor of mouth, skin of the face, or adjacent structures such as the maxillary sinus or extrinsic muscles of the tongue.
- T4b tumors are very advanced and invade into the masticator space causing trismus, invade into the pterygoid plates or the skull base, or encase the internal carotid artery. The importance of this distinction is that tumors that are considered T4b are unresectable.

Regional lymph nodes are staged as Nx through N3:

- Nx staging designation is reserved for cases in which regional lymph nodes cannot be assessed either clinically or pathologically.
- N0 designation is for patients who have been adequately staged and have no evidence of regional lymph node metastasis.
- N1 patients have a single ipsilateral lymph node 3 cm or less in their greatest dimension.
- N2 patients have a metastasis in the single ipsilateral lymph node more than 3 cm but less than 6 cm in greatest dimension or in multiple ipsilateral lymph nodes. N2 staging is subdivided into three subcategories:
  - N2a indicates that there is a single ipsilateral lymph node involved that is more than 3 cm but not more than 6 cm.
  - N2b designates multiple ipsilateral lymph nodes involved, with none being more than 6 cm in greatest dimension.
  - N2c designation indicates there are bilateral or contralateral lymph nodes; again none of the lymph nodes are more than 6 cm in their greatest dimension.
- N3 designation is reserved for any involved lymph node that is greater than 6 cm in greatest dimension.

Staging distant metastasis is straightforward. M0 designates no distant metastasis and M1 designates the presence of distant metastasis. See Table 19.1 for a summary of the anatomic staging and the prognostic groups.

One criticism of the AJCC staging system for oral cavity cancer is that it does not take into consideration histologic

TABLE 19.1 Staging Parameters Based on AJCC 7th ed Staging Handbook

Stage	Tumor	Node	Metastasis
Stage 0	Tis (carcinoma in situ)	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0	M0
	T4a	N0	M0
	T4a	N1	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	N0	M0
	T4b	N1	M0
	T4b	N2	M0
Stage IVC	Any T	Any N	M1

Adapted from Edge SB. *American Joint Committee on Cancer, American Cancer Society. AJCC cancer staging handbook: from the AJCC cancer staging manual.* 7th ed. New York: Springer; 2010.

risk factors that have been shown to have relevant prognostic effects. For example, the international Consortium for Outcome Research in Head and Neck Cancer published a retrospective analysis of 3149 patients with oral squamous cell carcinoma across 11 cancer centers worldwide between 1990 and 2011. The results of that analysis, and those of other studies, suggested that depth of invasion was significantly associated with survival.[26-29]

Another international multicenter study of 3704 patients evaluated the prognosis of patients with lymph node disease in oral squamous cell carcinoma, and demonstrated that the disease-specific survival was determined by the total number of metastatic lymph nodes rather than laterality. Based on those findings, the study authors recommended that the staging system be revised to more accurately reflect the total burden of disease as evidenced by the number of involved lymph nodes.[30] Along the same lines, a large study of 4254 patients diagnosed with oral squamous cell carcinoma was conducted to investigate the lymph node ratio, that is, the number of diseased lymph nodes per total lymph nodes dissected. Statistical analysis demonstrated that the ratio—or lymph node density—was more reliable in stratifying patients according to their risk of failure. On this basis, the authors of that study also recommended modification of the AJCC TNM staging system.[31]

Approach to Treatment Based on NCCN Guidelines

The NCCN is a not-for-profit alliance of several leading cancer centers around the world, many of which are in the United States. NCCN aims to improve resources and provide evidence-based decision-making algorithms and recommendations for clinicians providing cancer care. The most recent version published in 2015 for management of the oral cavity cancers is addressed here.[100]

The NCCN Guidelines recommend a thorough work-up including a thorough history and physical examination with the fiber-optic examination, biopsy, imaging of the chest, and cross-sectional imaging of the primary as well as the neck. For advanced stage disease, stage III/IV, the NCCN Guidelines also recommend considering PET imaging as a diagnostic adjunct. Panendoscopy when indicated, as well as dental and prosthetic evaluation, nutrition, and speech and swallowing evaluation and therapy when indicated are also within the NCCN Guidelines.

The algorithm for the management of T1-3N1-3, T3N0, or T4aN0-3 is the same. The initial treatment of the primary tumor and the neck for these stages includes surgery with resection of the primary tumor and neck dissection. For N2c disease, bilateral neck dissection is recommended.

After surgery, once pathologic analysis has been undertaken, if no adverse features such as extracapsular nodal spread (ECS), positive margins, perineural invasion, or lymphatic and vascular embolism are evident, radiation therapy is considered optional for T1 and T2 lesions. However, for advanced stage primary tumors, T3/T4, the recommendations are for adjuvant radiation therapy despite other histologic risk factors. If ECS or a positive margin exists, the NCCN Guidelines recommend chemotherapy in addition to radiation therapy or re-resection if possible in the case of a positive margin.

Primary modality treatment for advanced stage oral cavity cancer consists of surgery with adjuvant therapy. Patients often receive postoperative radiation therapy (PORT), and if positive margins in which a re-resection are not possible or if surgery does not definitively clear the margin of tumor or lymph node involvement with ECS, the patient will undergo concomitant chemoradiation therapy.

PORT is recommended by the NCCN Guidelines at an interval between resection and postoperative radiation therapy of less than 6 weeks. The rationale is for expeditious treatment of the tumor bed to avoid tumor growth and inadequate treatment of gross tumor. For high-risk sites, such as those with a positive margin, 60 to 66 Gy are recommended in 2 Gy per fraction administered 5 days per week over 6½ weeks. In intermediate- and low-risk sites, 44 to 60 Gy in 1.6 Gy per fraction are administered. Intensity modulated external beam radiation therapy (IMRT) can be employed with a dose of 72 Gy for primary radiation therapy, 66 Gy for high-risk sites such as those with a positive margin, and 50 Gy for low-risk sites such as those with negative margins or the neck in which no lymph nodes with ECS were identified.

The NCCN Guidelines recommend concurrent cisplatin at 100 mg/m^2 every 3 weeks for concomitant postoperative chemoradiation therapy.

The NCCN Guidelines for adjuvant chemotherapy and postoperative radiation therapy are based on several controlled trials evaluating adjuvant radiotherapy alone versus adjuvant radiation therapy plus cisplatin chemotherapy. One study comparing postoperative radiation with or without concomitant chemotherapy for locally advanced head and neck cancer evaluated 167 patients who were randomly assigned either to receive PORT alone or PORT with cisplatin on days 1, 22, and 43 of the radiotherapy regimen. Overall survival rate was significantly higher in the combined therapy group than in the PORT only group.[32] Another trial evaluating 459 patients compared postoperative concurrent radiotherapy with chemotherapy for high-risk squamous cell carcinomas of the head and neck. After surgical resection, 231 patients were assigned to receive radiotherapy alone and 228 patients were assigned to receive identical radiation therapy plus concurrent cisplatin on days 1, 22, and 43 of the radiation therapy regimen. The rate of local and regional control was significantly higher in the combined therapy group than in the group given radiation therapy alone, and disease-free survival was significantly longer in the combined therapy group than in radiation therapy group alone.[33] To identify which patients would benefit most from combined radiation therapy plus chemotherapy in the postoperative period, a comparative analysis using pooled data from EORTC 22931 and RTOG 9501 was done. The investigators identified ECS or microscopically involved surgical margins to be the only statistically significant risk factor for which combined radiation and chemotherapy had local and regional control and

survival benefit.[34] Survival advantage in patients with high-risk tumors have been achieved in other studies as well.[35]

External beam radiation therapy has historically been delivered via a conventional 2D beam using x-ray accelerators that consist of a single beam of radiation delivered to the patient from several directions: posteriorly, anteriorly, or bilaterally. Conventional treatment planning is 2D and the ability to conform the beam to the tumor volume while avoiding adjacent structures such as the mandible or the salivary glands is difficult. IMRT is another form of external beam radiation therapy that uses computer software and complex computer-aided planning and controlled x-ray accelerators to distribute precise radiation doses to the tumor volume while conforming treatment specifically to the tumor and avoiding adjacent structures. The radiation dose is controlled by adjusting beam intensity. Additionally, the beam can be aimed in a full 360-degree radius around the gantry in which the patient is positioned. Chen and colleagues[36] and others have published results comparing IMRT with conventional external beam radiation therapy. These data demonstrate no significant difference in acute toxicity between the two radiation therapy delivery techniques; however, patients receiving IMRT had significantly less late toxicity including severe xerostomia and dysphagia.[36] With the use of IMRT, there is a question of whether local and regional control and overall survival could be improved in patients with primary radiation therapy instead of the adjuvant setting. This would be especially useful in patients unable or unwilling to undergo surgery. In another series of patients treated at Dana-Farber Cancer Institute and Brigham and Women's Hospital Departments of Oncology in Boston, Massachusetts, treatment of oral cavity squamous cell carcinoma with adjuvant or definitive IMRT was evaluated. Adjuvant IMRT was associated with good local and regional control as well as overall survival; lower late toxicity rates and chemotherapy was considered successful for treatment in patients with high-risk disease. Patients who were treated with IMRT or chemotherapy and IMRT alone had an overall 2-year survival of 63% compared with an 85% 2-year survival in patients who underwent surgery first.[37] While IMRT offers better selective irradiation to tumors with less toxicity to adjacent tissues, it is apparent that primary surgery with radiation and chemotherapy as adjuvant therapies remains the most effective treatment of oral cavity squamous cell carcinoma.

Proton therapy has been evaluated for the treatment of head and neck squamous cell carcinoma given the complexity of the regional anatomy as well as limitations of conventional external beam radiation therapy and IMRT. Proton therapy is of interest because of the inherent physical properties of proton energy deposition in which almost no dose of radiation is delivered distal to the target area. From a biologic standpoint, the effects of particle beam radiation therapy are similar at the target site; however, with proton therapy, normal tissues are more easily spared.

A study from the M.D. Anderson Cancer Center that compared multifield optimization intensity-modulated proton therapy for head and neck tumors evaluated 10 patients with squamous cell carcinoma and 5 with adenoid cystic carcinoma, and found that 93.3% had a complete response to treatment.[38] Although this study shows promising results for the potential of proton therapy within the head and neck, studies with more subjects and controls would be necessary to make definitive treatment recommendations. In a systematic review of the literature, the same authors[39] examined clinical experience with proton radiation therapy for head and neck cancer. Although most papers analyzed skull base as well as tumors within the axial skeleton, some investigated proton therapy in paranasal sinus carcinomas, nasal cavity carcinomas, olfactory neuroblastomas, and nasopharyngeal cancers, and two studies evaluated oropharyngeal cancer and mucosal melanomas of the head and neck. Conclusions drawn from the review of these studies suggest that proton therapy may have a tolerable toxicity profile.[39] None of the studies evaluated proton therapy as a primary modality for the treatment of oral cavity squamous cell carcinoma. Simone and colleagues[40] compared IMRT, adaptive radiotherapy, proton therapy, and adaptive proton therapy for the treatment of locally advanced head and neck cancer. Adaptive IMRT reduced dose to adjacent normal structures compared with standard IMRT, and nonadaptive proton therapy had more favorable dosimetric profiles than IMRT or adaptive IMRT, and may obviate the need for adaptive planning. Proton therapy allowed significant sparing of the spinal cord, parotid glands, larynx, and brainstem. Again, this study was small (10 patients), and the primary diseases were located in the oropharynx, nasopharynx, and larynx; none of the patients had a primary tumor within the oral cavity.[40]

Surgical Management

The approach to the patient with the T3 oral tongue lesion depends largely on the position of the lesion. A number of procedures have been described depicting various approaches to the tongue. These include the transoral approach, tongue pull-through, lip split and mandibulotomy, or a procedure involving resection of the tongue, floor of mouth, and a portion of the mandible for tumors invading all three structures. T3 lesions of the tongue have significant risk for nodal metastasis and neck dissection is recommended. In patients with no clinical or radiographic evidence of neck nodal metastasis, a selective neck dissection involving levels I through IV is adequate.[41-44] In patients with evidence of neck disease, however, a modified radical neck dissection or a radical neck dissection should be undertaken to ensure complete removal of tumor and avoidance of tumor spillage within the neck. During neck dissection, care is taken to avoid complete ablation of venous outflow to the head especially in bilateral neck dissections. Preservation of vessels for microvascular anastomosis is attempted because most T3 tongue tumors will require reconstruction with local, regional, or free tissue transfer.

T3 lesions in the anterior and lateral portion of the tongue may be adequately accessed through a transoral approach. When combined with a neck incision for access to the cervical lymphatics, the tongue resection can be maintained in continuity with the neck dissection specimen to remove any tissue



• **Fig. 19.9** A resection specimen showing a partial glossectomy for oral squamous cell carcinoma resected in continuity with the neck specimen to ensure adequate removal of all lymphatic tissue.

intervening with lymphatic channels between the tongue, floor of mouth, and cervical lymphatics (Fig. 19.9). In cases that do not require the floor of mouth resection, the tongue may be resected separate from the neck dissection specimen.

When performing a lip split with mandibulotomy or a pull-through technique for removal of a large tongue tumor, it is best to start with a neck incision and elevation of subplatysmal flaps. Whenever possible, perform a standard utility incision in the neck, avoiding trifurcation incisions that may leave an area over the great vessels prone to wound dehiscence. Once the skin flaps are elevated within the neck, level IA, level IB, and level II dissection are initiated. The marginal mandibular nerve is preserved if possible. By starting this portion of the neck dissection, the floor of mouth can be easily accessed either through the neck or via the mouth, which assists in management of the tumor. Once this is accomplished, the tongue lesion is assessed, and if complete circumferential dissection maintaining 1.5-cm margins can be adequately undertaken, then transoral resection is commenced. If the tumor approaches or crosses the midline of the tongue, or if there is evidence of bilateral nodal metastasis, bilateral neck dissection must be performed.

During tumor resection, care is taken to avoid telescoping or convergence of the surgical margin toward the base of the specimen (Fig. 19.10). Surface landmarks of the tongue with respect to the 1.5-cm margin are relatively clear. However, as dissection is carried into the deeper planes, there is a tendency for the surgeon to reduce that 1.5-cm margin. Furthermore, as the tumor extends into the tongue, it may spread past the surface margin markings. In these cases, it is more likely to develop a positive surgical margin that will be difficult to identify on



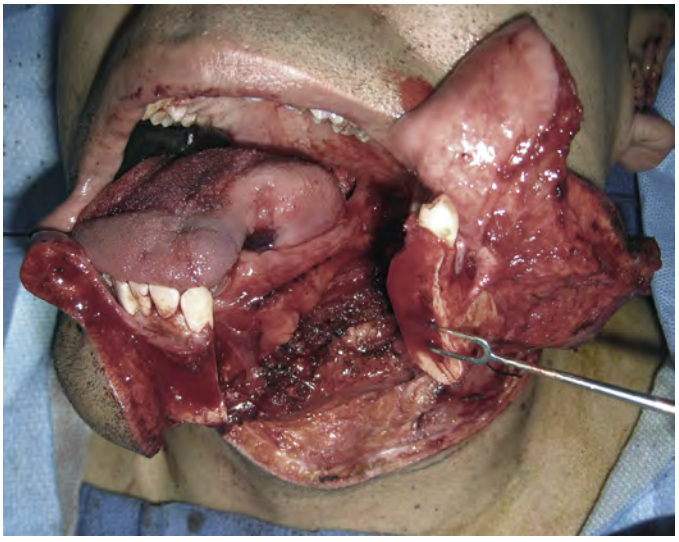
• **Fig. 19.10** **A,** Tumor bed after resection of a T3 tongue lesion. Care was taken to preserve the lingual artery on the contralateral side to avoid necrosis of the remaining tongue. **B,** Another resection bed of a T3 tongue lesion. Note the depth of the resection into the tongue; care was taken to avoid "telescoping" the deep margins toward the tumor.

frozen section analysis. Tumors of the tongue can have a relatively small superficial ulceration but with a much wider area of deep infiltration. Therefore, it is important to palpate along the tongue and specimen during dissection to ensure the 1.5-cm margin is maintained during the entire dissection.

In instances when additional exposure of the tongue is necessary, a lip split and mandibulotomy may be performed. The osteotomy is placed just anterior to the mental foramen on the ipsilateral side of the tumor. This allows optimal retraction of the mandible and lip for greater exposure of the tongue. This aids both the dissection of the tumor as well as the reconstruction. The incision used for the lip split is a midline full-thickness lip incision carried around the mentalis musculature and skin of the anterior chin in a curvilinear fashion into the neck, joining with the incision used for the neck dissection (Fig. 19.11). Reconstruction plates and predrilled holes for the reconstruction of the mandible before any osteotomy are important. It is critical to obtain 3D stability along this osteotomy because this is a common site for fibrous nonunion and hardware failure, particularly in the setting



• **Fig. 19.11** Typical markings for a lip split and mandibulotomy with a neck dissection.



• **Fig. 19.12** A mandibulotomy was made for access to this patient's tumor, which can be seen in the side of the tongue. The osteotomy was made anterior to the mental foramen between the canine and first premolar. The mental nerve can be seen adjacent to the skin hook being used for retraction.

of adjuvant radiation therapy. Once the plates have been adapted to the surface of the mandible and holes drilled, the osteotomy is made. In most cases, this is positioned between the canine and first premolar teeth (Fig. 19.12). Dissection is carried through the oral mucosa and mylohyoid muscle in the mid portion of floor of the oral cavity when possible in light of tumor margins to allow an adequate cuff of tissue for reconstruction (Fig. 19.13).



• **Fig. 19.13** Photograph illustrating the importance of maintaining a cuff of tissue whenever feasible from an oncologic point of view. This facilitates closure and creation of a watertight suture line.

When large tumors or tumors crossing the midline are encountered, a bilateral neck dissection incision can be made with elevation of subplatysmal flaps to the level of the mandible bilaterally. Then the mylohyoid muscle and the anterior bellies of digastric muscles can be separated from the anterior mandible, and the tongue can be brought into the neck as a "pull-through" procedure for excellent exposure. This also allows the tumor to be resected from the tongue in continuity with the neck dissection specimens. The pull-through maneuver avoids a lip split incision and mandibular osteotomy.

Reconstruction of T3 tongue defects is best accomplished with the use of free tissue transfer. It is our experience that well-executed radial forearm free flaps and anterolateral thigh free flaps are well tolerated postoperatively by patients and supply adequate bulk of tissue when needed. The radial forearm free flap is excellent thickness and pliability for adapting to tongue resection defects. Important aspects to consider when reconstructing partial or total oral glossectomy defects are to restore not only the form of the tongue but the functional aspects of the tongue. Most important is to reconstruct a neo-tongue that can aid in speech articulation and propel food bolus from anterior to posterior during the oral phase of swallowing.

In general, free flaps are necessary for glossectomy defects that approach up to one half of the tongue.[45] For T3 tumors, most defects encompass at least one half of the tongue. For those defects of the tongue and floor of mouth, even when less than half of the tongue has been resected, it is still advisable to use free tissue for reconstruction to avoid tethering of the tongue during healing. When one third to one half of the oral tongue is present, thin pliable flaps, such as the radial forearm free flap, are recommended to preserve tongue mobility and provide a small amount of bulk that is needed to fill the oral cavity dead space when the mouth is closed to facilitate the oral phase of swallowing (Fig. 19.14). It is important to keep in mind when fashioning a flap for tongue and floor of mouth reconstruction that the flap is of adequate width to allow folding along the lateral aspect of the tongue to re-create the sulcus

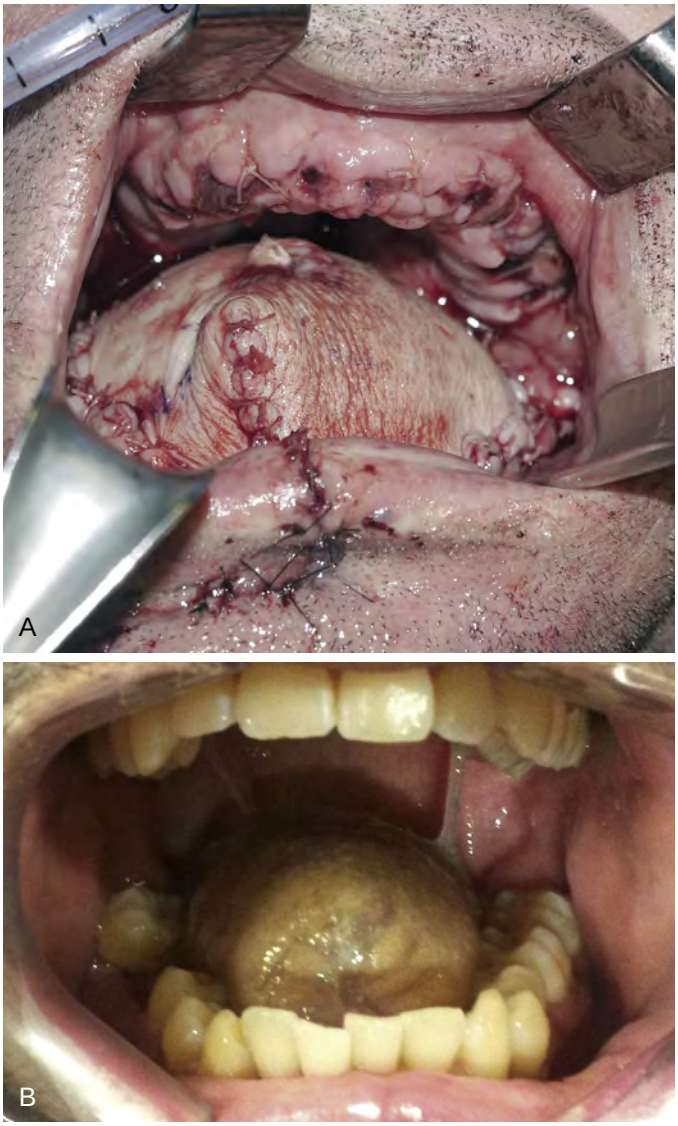


• **Fig. 19.14** Inset radial forearm free flap. It is thin and pliable, and adapts well to use in tongue reconstruction.

between the tongue and floor of mouth and to avoid a concave reconstruction that would result from a flap being too small.[46]

Total oral glossectomy reconstruction requires a bulkier flap, such as an anterolateral thigh flap or a rectus abdominis musculocutaneous flap (Fig. 19.15). Double flap techniques in functional tongue reconstruction or dynamic tongue reconstruction utilizing a gastro-omental free flap along with a free gracilis muscle flap have also been described.[47] The free gracilis muscle flap in this case functions as a motor unit, providing tongue movements and elevation; the gastro-omental flap provides bulk via the omentum and mucosal coverage via the gastric component of the flap. In this case, the obturator nerve would be anastomosed to the hypoglossal nerve stump for motor innervation. In a case series by Vega and colleagues,[48] total glossectomy or subtotal glossectomy defect reconstruction was accomplished with a variety of flaps including deep inferior epigastric perforator flaps and anterolateral thigh flaps. A mushroom-shaped anterolateral thigh perforator flap for subtotal tongue reconstruction is described in which a standard and anterolateral thigh flap is elevated, with the flap being folded upon itself anteriorly to re-create the tongue tip and sulcus of the floor of mouth in order to preserve mobility. In this series of reconstructions, functional outcomes using a Likert scale to assess speech intelligibility, swallowing function, and cosmesis found that of the 13 patients, six recovered a natural or nearly natural ability to chew and swallow, and seven developed normal intelligible speech. Acceptably intelligible speech was achieved in six patients, and eight patients considered their results aesthetic while five considered the cosmesis of their flap was good.[49]

Sensate flaps for tongue reconstruction have been described using the antebrachial cutaneous nerve of the forearm for radial forearm flaps with an anastomosis to the lingual nerve stump. Spontaneous sensory reinnervation with smaller flaps has been documented as well. It is unknown, however, whether sensate flaps in oral tongue reconstruction have any meaningful functional implications.



• **Fig. 19.15** **A,** Larger resections require larger flaps. This reconstruction with an anterolateral thigh flap was sewn together at the end to make a "mound" for the patient to use for speaking and swallowing. **B,** Another flap several weeks after inset to demonstrate healing potential even in the setting of adjuvant therapy.

A systematic review of speech and swallowing following tongue reconstruction addresses the speech outcomes and the swallowing outcomes after resection and reconstruction of the oral tongue and base of tongue. The authors identified six prospective and eight retrospective studies evaluating speech outcomes involving the oral tongue. The majority of reconstructions consisted of radial forearm free flaps while some used lateral arm free flaps and anterolateral thigh or rectus abdominis free flaps. Not surprisingly, there is significant decline in intelligibility in the immediate postoperative period but significant improvement was seen after 6 months. This review also identified seven prospective and five retrospective studies evaluating swallowing in patients who had undergone oral tongue resection and free flap reconstruction. Again, these studies evaluated the radial forearm free flap, anterolateral

thigh free flap, and lateral arm free flap. There were conflicting results among studies regarding early postoperative swallowing and aspiration. Within 6 months postoperatively, swallowing ability improved for the majority of patients to only minimal swallowing complaints. Beyond 6 months, most patients had returned to an unrestricted diet.[50]

Swallow rehabilitation is not only important for the patient to be able to maintain an oral diet, but also important to reduce the risk for recurrent aspiration and pneumonia. The normal swallowing mechanism consists of an oral preparatory phase wherein food is chewed and prepared for swallowing. The tongue plays an important role during the preparatory phase by pushing the food bolus toward the occlusal surface of the teeth and mixing food with saliva. The soft palate and tongue create a seal that prevents spillage of food bolus into the pharynx. Once the food is adequately pulverized and mixed with saliva for lubrication, the tongue contracts from anterior to posterior and pushes the food bolus into the pharynx in a process that takes about 1 second. The next phase is the pharyngeal phase, which is characterized by the soft palate, sealing off the nasopharynx from the oropharynx along with elevation of the larynx. The pharyngeal constrictor muscles contract and the cricopharyngeus muscles relax while the larynx is closed by contraction of the laryngeal musculature. Once food is passed from the pharynx in this pharyngeal phase, which also lasts about 1 second, the food is propelled into the esophagus where peristalsis directs the food along the esophagus into the stomach.

During the early postoperative period, the patient should be seen by a speech and swallow therapist for evaluation. Commonly, patients with tongue resections undergo a swallowing video fluoroscopy to evaluate the transit time of radiopaque materials through the oral cavity, oropharynx, and hypopharynx. Patients with large tongue resections, particularly of the posterior oral tongue or base of tongue, demonstrate pooling of material near the laryngeal inlet at the vallecula. Patients with large anterior oral tongue resections demonstrate delayed oral phase of swallowing, which normally should last only a few seconds. Adaptive maneuvers can be used to compensate for the loss of function and anatomy. The chin tuck and supraglottic swallow techniques are used at our institution. The chin-tuck maneuver aids in widening the vallecula in order to prevent food bolus or liquid from entering the airway. The supraglottic swallow involves the patient concentrating on breath holding during swallow, which increases airway closure.

Researchers in Liverpool conducted a study of 13 patients who had undergone surgical resection of the oropharynx, including the base of tongue, and assessed swallow function by video fluoroscopy postoperatively at 2 weeks, 1 month, 3 months, and 6 months. The subjects were grouped into those who underwent less than one-fourth tongue base resection and those who underwent more than one-fourth tongue base resection. All patients in the series underwent radial forearm free flap reconstruction of the ablative defect. Not surprisingly those with larger resections had greater impairment, and adjuvant radiation therapy exacerbated their problems. Adaptive maneuvers were seen to be effective 50% of the time in patients who had underlying aspiration.[51]

In a study evaluating the effect of swallow training on dysphagia and depression in postoperative tongue cancer resection patients, Zhang and colleagues[52] described training protocols that included the chin-tuck procedure, the supraglottic swallow, and the Mendelsohn maneuver. Using this technique, patients are instructed to hold up the larynx, either using the muscles of the neck or with the hand during the swallow for several seconds after swallowing to elevate the laryngeal inlet above the vallecula and assist in evacuation of material from the vallecula while the larynx is in the elevated position, thereby reducing laryngeal penetration. Dysphagia was more likely both in those patients with larger resections as well as before swallowing training.[52]

Use of a prosthesis in place of the tongue has also been a method of rehabilitation. Prosthetic devices consist of palatal augmentation prosthetics as well as rigid appliances attached to mandibular dentures.[53,54] These devices simulate tongue bulk and reduce the intraoral dead space during deglutition. In these cases, patients are fitted with a prosthesis and given techniques to improve contact between the prosthesis and the opposing arch to facilitate the production of syllables as well as propelling food a bolus from the oral cavity into the oropharynx.

Surveillance

The NCCN Guidelines for follow-up of patients who have completed treatment for oral cavity cancer are based on the risk for relapse and the development of second primaries, as well as monitoring toxicity from treatment. Most recurrences are seen in the first 2 years after definitive treatment and the patient is not considered "cured" until after 5 years following treatment and the patient is alive and disease-free. For the first year, history and physical examination, including a complete head and neck examination and mirror or fiber-optic examination when clinically appropriate, is recommended every 1 to 3 months. For the second year after treatment, the same examination is recommended every 2 to 6 months, and for years 3 to 5 the examination is done every 4 to 8 months. For patients who are more than 5 years from the completion of their treatment, a thorough examination is recommended every 12 months and patients are instructed to return if any new symptoms develop. The protocol at our institution is for clinical evaluation including fiber-optic examination or mirror examination when indicated every 3 months for years 1 and 2, every 6 months for years 3 through 5, and annually in patients who are more than 5 years past treatment.

Imaging recommendations do not include routine PET/CT imaging; however, many patients do undergo a PET/CT scan. In our practice, PET/CT is used only when the patient has new complaints, or there are new findings on clinical examination, new imaging, or other laboratory work-up suggestive of recurrent or metastatic disease. Plain film chest radiography is obtained annually, as are liver function tests, although liver function tests have been questioned as an adequate screening tool for liver metastasis.[55] Thyroid stimulating hormone in patients who have undergone adjuvant or primary radiation therapy is important in that these patients can develop hypothyroidism due to late effects of radiation therapy. We also refer patients for comprehensive dental management. This includes a stringent

recall schedule and frequent cleanings along with fluoride treatments in patients who have undergone radiation therapy given the risk for xerostomia-induced caries. Any patient who continues to use alcohol and tobacco is counseled regarding the risk for recurrence as well as other health effects, and smoking cessation and alcohol treatment programs are made available.

Complications and Outcomes Measures

Complications in head and neck surgery have been well documented. The topic can be viewed in terms of complications of radiation therapy, chemotherapy, or surgical therapy or in terms of treatment failure, such as local recurrence, regional recurrence, or the development of metastatic disease. Complications of treatment consist of long-term side effects of the treatment such as neurologic dysfunction, swallowing disability, speech impediment, and disfigurement. This section focuses primarily on complications of surgical treatment pertaining to the immediate postoperative and early postoperative periods. In depth discussion of complications due to therapeutic radiation or chemotherapy is outside of the scope of this chapter. Treatment failures are addressed in the section regarding outcomes.

Kim and Ord[56] authored a review on the complications in the treatment of head and neck cancer and identified several complications common to patients undergoing head and neck surgery. They identified nutritional status as well as patients' comorbid conditions as measured by the Carlson comorbidity index as predictive of treatment complications. Published complications in the surgical management of head and neck cancer include complications regarding the surgical site, such as the formation of hematomas, wound breakdown and infections, neurologic injury and deficiencies such as facial nerve paresis, spinal accessory nerve weakness, and phrenic nerve injury after neck dissection. Chyle leak, sialocele, and hematoma are also well reported. Other documented complications of head and neck surgery pertain to the functional status of the patient and their medical comorbidities. Most commonly, these are pulmonary complications, which is not surprising in that smoking is a risk factor for pulmonary disease in addition to head and neck carcinoma. Other complications can include cardiovascular complications such as development of dysrhythmias and even cardiac arrest or congestive heart failure. Neurologic complications such as acute delirium and stroke have been documented. These complications can result in irreversible damage to the patient or predispose the patient to prolonged intensive care unit stays, prolonged ventilation, and prolonged hospitalization, which places the patient at risk for nosocomial infection and deconditioning. In a recent study published in the *British Journal of Oral and Maxillofacial Surgery,* authors identified respiratory complications and surgical site complications as the most common complications, with pneumonia being the most common respiratory complication. Wound dehiscence, followed by infection and partial or complete loss of skin graft were the most common wound complications.[57]

In an analysis of the National Veterans Administration Surgical Quality Improvement Program, predictors of prolonged hospital length of stay were analyzed for 3050 patients who underwent surgical treatment for head and neck squamous cell carcinoma. Predictive patient characteristics were age older than 60 years, poor functional status, consumption of more than two drinks of alcohol per day, and history of chronic obstructive pulmonary disease and diabetes requiring insulin therapy. Predictive intraoperative variables were longer operative time and the need for blood transfusion. Postoperative predictors included return to the operating room within 30 days of the initial operation and the occurrence of two or more operative complications.[58] In a retrospective study of 6727 patients matching previously published indices of performance status and medical comorbidities to the American College of Surgeons National Surgical Quality Improvement Program benchmark items, a frailty index was established and tested. The frailty index is based on the patient's functional status as well as medical comorbidity at the time of operation. Similar to other literature on the subject, this study suggests that age alone is not a risk factor for complications after head and neck surgery, rather the patient's comorbidities are more closely associated with complications.[59] These authors found that as the modified frailty index increases from zero (an indicator of no comorbid conditions) to 0.45, which indicates five or more of 11 predictors, the mortality risk increased from 0.2% to 11.9% and major complication rates increased from 1.2% to 26.2%, while the risk of all complications ranging from minor to major including mortality increased from 9.5% to 40.5%.[60] These data are similar to those of another retrospective study of complications of free flap reconstruction and head and neck surgery whereby the authors analyzed 304 cases and found that the overall complication rate was 32.6% with a mortality rate of 0.3% and a flap loss rate of 2%. The only independent predictors of complication on multivariate analysis in this study were tumor stage and reconstruction site. Although the study did analyze smoking, alcohol use, age, diabetes, peripheral vascular disease, history of myocardial infarction, and history of cerebral vascular accident, these were not associated with complications in regard to free flap reconstruction.[61]

In another prospective study of 186 patients with head and neck cancer, predictors of complications after head and neck surgery were tumor location, with laryngeal and hypopharyngeal being most likely to have complications, and advanced tumor stage. These authors also found that a low performance, as measured by Karnofsky scale, was associated with the development of postoperative complications. The statistical analysis also indicated that the presence of a tracheotomy, low Karnofsky performance, low postoperative serum albumin, and operative duration more than 4.3 hours were significant factors in the development of surgical site infections or complications.[62]

Oral cancer surgery is done in a clean/contaminated field. Many patients are malnourished due to the disease process and have impaired immune function. In the setting of salvage surgery, patients may have undergone radiation therapy or recent chemotherapy, further debilitating their ability to fight infection. Consequently, infection in the postoperative period is a significant risk for patients in these settings. The published infection rate has been as high as 10% and poor nutritional status has been implicated as a contributing factor.[63-65]

Postoperative pulmonary and cardiovascular complications are common after head and neck surgery. Pulmonary complications were examined in a retrospective study of 105 patients and almost half developed one or more postoperative pulmonary complications. The most frequent complication was respiratory failure followed by bronchospasm, then pneumonia. Statistical analysis showed advanced age and hypertension were predictive of postoperative pulmonary complications. Interestingly, these authors did not find smoking history to be a statistically significant contributor.[66] In a review of the incidence of cardiovascular complications of head and neck surgery, heart failure was the most common complication followed by acute myocardial infarction and cardiac arrhythmia. Statistical analysis demonstrated that patients with an elevated Lee cardiac risk score had a twofold increased risk for development of postoperative cardiac complication. The Lee Cardiac Risk Index is scored I to IV based on the presence or absence of six items, five of which are related to the patient's medical comorbidities including history of ischemic heart disease, myocardial infarction, congestive heart failure, cerebrovascular disease, chronic kidney disease, or insulin-dependent diabetes. The other variable in this risk analysis is the type of surgery being performed. Aside from high cardiac risk indices, age was the other statistically significant risk factor of cardiac complications and both age and cardiac risk indices were independent variables on multivariate analysis.[67]

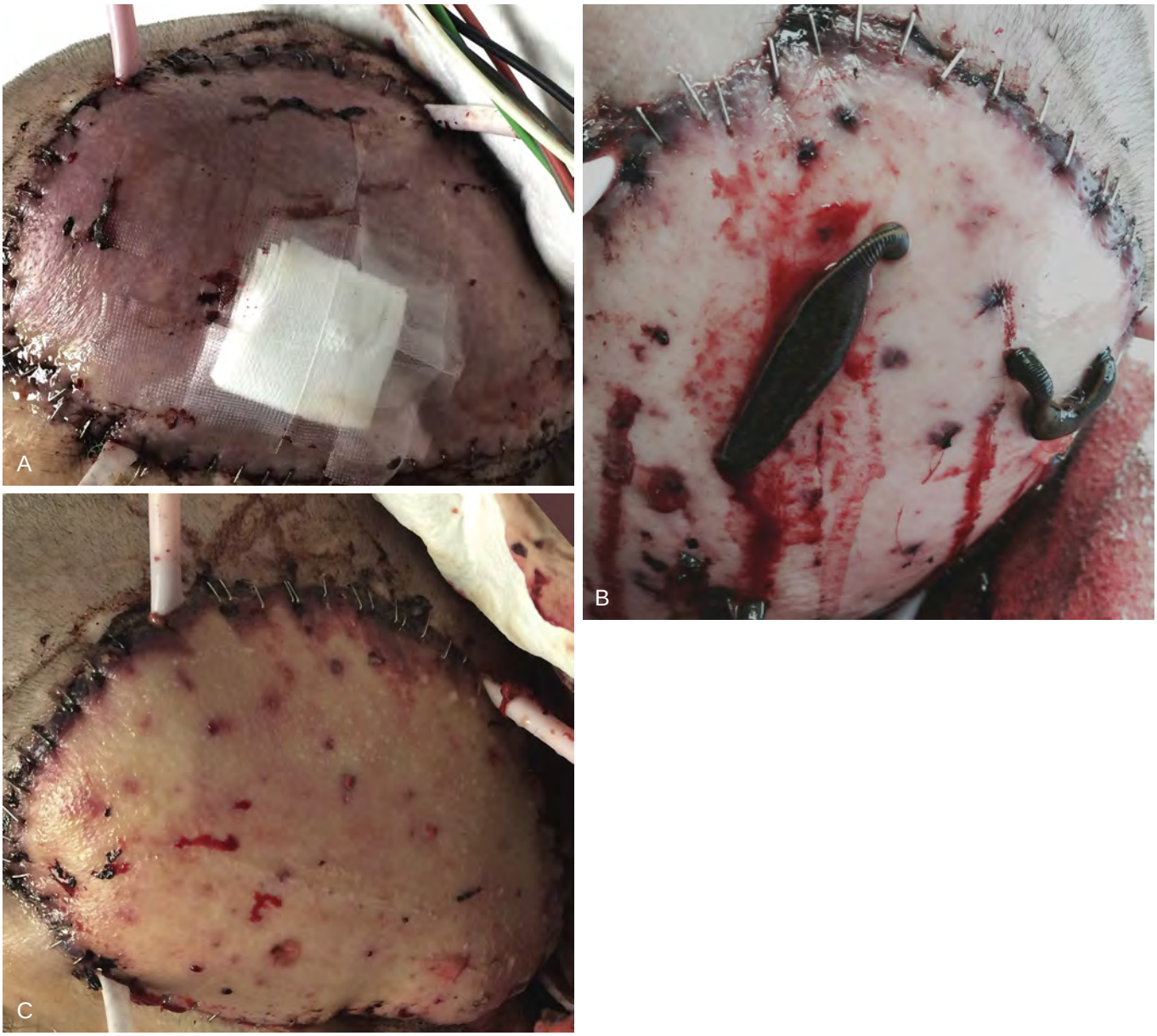
The documented success rate for microvascular free flap reconstruction ranges between 95% and 97%. However, when complications with flaps do occur, they can jeopardize patient outcomes as well patient progress with treatment. Complications of microvascular free tissue transfer can be categorized as those occurring at the recipient or donor site. Complications occurring at the recipient site largely are a result of failed microvascular perfusion and the majority of those are due to venous thrombosis. Frequently, anti-thrombotic therapies, such as aspirin or heparin, are utilized to reduce the risk of vessel thrombosis. While there is a debate within the literature regarding the appropriate use and type of anti-thrombotic therapy, that discussion is outside the scope of this chapter. However, the risk of vessel thrombosis and the use of anticoagulants should be weighed against the risk for the development of postoperative hematoma and bleeding complications. Most thrombotic complications at the anastomosis occur within 48 to 72 hours of surgery.[68]

Donor site complications may range from poor cosmesis to failure of skin graft coverage to more critical issues, such as surgical site infection, hematoma, or distal limb ischemia. Most cases of distal limb ischemia are avoided by thorough preoperative work-up, including a physical examination demonstrating collateral flow such as an Allen test to identify ulnar collateralization in the palmer arterial arcades or a CT angiogram of the bilateral lower extremities to evaluate the lower leg for three-vessel runoff. In patients with known peripheral vascular disease, further vascular surgery consult or noninvasive vascular imaging studies such as ankle-brachial index, Doppler flow studies, and ultrasound may be indicated. Other complications include minor sensory nerve deficits such as injury to the dorsal branch of the radial nerve during radial forearm free flap harvests, injury to the lateral femoral cutaneous nerve during harvests at the hip and proximal lower extremity, or the development of abdominal or inguinal hernias after harvesting of rectus abdominis flaps or motor nerve injuries in lower leg flap harvests due to injury to the peroneal nerve.

In a retrospective study of 1000 flaps, an overall failure rate of 7.6 was identified with the majority of those being total flap losses. The study identified a 12% flap revision rate due to vascular occlusion and half of those revisions were successful at flap salvage. The authors comment that the main reasons for flap failure were use of compression bandages, taping around the neck, or tracheal straps resulting in compression of the vascular pedicle. They also cited tight wound closure and hematoma as contributing factors to microvessel occlusion. Statistical analysis demonstrated radial forearm free flaps to be the most reliable in terms of flap survival. Complications at the donor site consisted of wound dehiscence, tendon exposure, and skin graft loss.[69]

Leech therapy has been suggested for salvage of flaps with venous congestion.[70] Although flaps with venous congestion are best managed surgically as the most common causes of venous congestion is torsion or compression of the vein, in cases wherein this is ineffective, leech therapy may relieve venous congestion. Leeches secrete natural anticoagulants, which may open up microvascular channels within the flap (Fig. 19.16). When using leeches for flap salvage, it is important to keep in mind that a commensal bacteria within the leech gut is *Aeromonas hydrophila,* which necessitates antibiotic prophylaxis. Ciprofloxacin is a demonstrated effective prophylactic agent, although resistance has been documented.[71,72] Antibiotic prophylaxis should persist for 14 days after discontinuation of leech therapy.[73]

Many postoperative complications have modifiable risk factors. Clinical pathways have been developed to standardize patient care and as a means of developing evidence-based and diagnosis-specific treatment algorithms. One prospective study demonstrated a reduction of pulmonary complications and length of stay after implementation of a clinical care pathway following reconstruction of head and neck ablative defects.[74] Another prospective trial with a comparison to a historical cohort evaluated the use of the clinical care pathways and demonstrated that the patients treated via a clinical care pathway were associated with decreased cost and length of stay—14 days rather than 21 days. Although not statistically significant, patients also had a shorter time to tracheotomy decannulation, lower rates of pneumonia, lower rates of readmission to the intensive care unit, and fewer complications requiring return to the operating room for surgical exploration.[75] A Johns Hopkins University study compared responsiveness to postoperative complications among high-volume and low-volume centers by analyzing discharge data for 160,000 patients who underwent a head and neck operation for malignant disease between 2001 and 2010. Failure to rescue was defined as a death after major complication including acute myocardial infarction, acute renal failure, venous thromboembolism, pneumonia, gastrointestinal bleed, pulmonary failure, hemorrhage, or surgical site



• **Fig. 19.16** Patient with a congested scalp flap; one would exercise caution if placing leeches in the mouth as they may enter the airway or esophagus. Note the venous congestion **(A)**. **B,** Various leeches in different stages of engorgement. **C,** Salvaged flap. The margins still appear dark and compromised; however, the majority of the flap improved with leech therapy for 72 hours.

infection. These authors compared the incidence of mortality as well as major complications and failure to rescue rates across various hospitals (low, intermediate, and high volume). They defined low-volume hospitals by the mean number of cases of head and neck cancer treated per year. Low-volume hospitals averaged six while the high-volume hospitals averaged 131 cases annually. While no statistically different rate of complications existed between low- and high-volume hospitals, patients were twice as likely to have their complications go unrecognized or inadequately treated when they were treated at low-volume hospitals rather than high-volume hospitals. Statistically higher mortality was also identified when comparing low- and high-volume hospitals, and the study authors contend that this increased mortality rate was due specifically to the lack of response or inadequate response to complications that they term "failure to rescue."[76]

Since the Institute of Medicine published a document entitled "Crossing the Quality Chasm" in 2001, efforts have been made across surgical specialties as well as clinical oncology to document outcomes and use those outcomes as measures for quality improvement. In light of the Affordable Care Act of 2010 as well as concerns about health care spending in the United States, both governmental and private third-party payers are becoming increasingly interested in mechanisms for controlling cost. In 2007, the American Head and Neck Society adopted several quality measures. These include items pertaining to documentation of disease stage, pathology reporting, documentation of tobacco cessation counseling and

treatment-related quality measures, such as appropriate referral to radiation oncology as well as adherence to the NCCN Guidelines.[77,78]

Surgical quality indicators have been proposed by various national agencies, such as the Agency for Healthcare Research and Quality, and the Advisory Board of the American Society of Clinical Oncology, the NCCN, the Commission on Cancer of the American College of Surgeons, and the National Quality Forum. These quality benchmarks are meant to promote uniformity and identify trends that may be useful in developing process improvement and quality improvement initiatives. Benchmarks include hospital length of stay, readmission within 30 days of an operation, return to the operating room within 7 days of an operation, 30-day mortality, use of blood products, presence or incidence of surgical site infections, and adequacy of pathology reports.[79] As we move forward with the Affordable Care Act and methods to reduce health care spending and improve patient outcomes, these quality indicators and implementation of quality indicators within oncologic practice will be ever more important.

Outcomes

According to the American Cancer Society, the 5-year relative survival rate for local tongue cancers is 78%. Patients with metastasis to regional lymph nodes have a relative survival rate of 63%, and survival rate when distant metastases are involved is 36%.[80] Despite aggressive therapy, patients with squamous cell carcinoma of the oral tongue have lower rates of local tumor control and survival.[81,82]

Several clinical and histologic factors have been identified that contribute to decreased rates of survival and disease control. In a retrospective study of 233 patients, both histologic grade as well as tumor stage were independent factors in predicting survival in patients with oral squamous cell carcinoma.[83] Review of Surveillance, Epidemiology, and End Results (SEER) tumor registries have suggested that older age is more likely associated with poor survival. Continued alcohol use is also associated with decreased survival in patients, especially those with advanced stage tongue squamous cell carcinoma.[84,85] Depth of invasion has been demonstrated to be an independent risk factor for poor outcomes, grading has also been evaluated but is considered to be of little value in prognostication, likely because of its subjective nature between pathologists evaluating histologic samples as well as incomplete sampling from tumors. DNA content, gene expression profiling, the role of other mesenchymal cells such as cancer-associated fibroblasts have been evaluated in other basic science and small translational studies, but there are no large randomized trials evaluating these factors with relationship to survival. Further study is needed to further identify and elucidate the complex nature of molecular biologic and genetic interactions responsible for carcinogenesis and disease progression.[86-88] A study of gene expression profiling and oral tongue cancer identified several novel genetic over-expressions in patients with oral squamous cell carcinoma. These include GLUT3, HSAL2, and PACE4. Statistical analysis suggested that GLUT3 over-expression correlated with depth of invasion as well as tumor size, stage, and recurrence. HSAL2 was positively associated with depth of invasion and advanced stage. However, only GLUT3 showed a prognostic value with disease-free, relapse-free, and overall survival.[89] The virus most commonly associated with head and neck cancer is human papillomavirus (HPV) and subtypes16 and 18, which are oncogenic. While the role in oropharyngeal cancer is clear, HPV infection as an etiologic agent in oral cavity cancer is less clear.[9,10,90,91] Perineural invasion, lymphatic and vascular invasion, as well as muscular invasion, even that which does not constitute T4 tumor, have all been demonstrated in smaller studies to be predictive of local recurrence even in the setting of negative margins.[92-94]

Quality of Life

Quality of life (QOL) is in many ways the most important aspect of head and neck oncologic treatment. Many times the treating team will offer surgery, radiation, and chemotherapy with curative intent; however, this treatment comes at great expense to the patient's ability to carry out activities of daily living and interact with others, to the detriment of the quality of their lives.

Although the therapeutic goal in treating malignancies of the head neck is to achieve cure, there are often serious and life-altering consequences are side effects of treatment. Surgery for head and neck cancer can impact a patient's QOL through impaired physical and functional status as well as psychological and social well-being in terms of deformity and inability to interact with people due to impaired speech or to enjoy regular activities of daily living such as eating. Pain, physical impairment, and neurologic deficit can lead to adjustment disorders that affect social, emotional, and interpersonal areas of the patient's life.

Most studies evaluating QOL use the University of Washington QOL questionnaire which includes eight items: pain, appearance, activity, recreation, swallowing, chewing, speech, and shoulder function. Several studies have shown decreased QOL scores, which can be worse among older patients. Overall QOL scores were relatively preserved in one study but older patients again reported more difficulty in resuming normal life roles due to physical limitations and emotional unavailability.[95,96] It is important to consider that at baseline, older patients have lower physical functioning and surgical interventions including flap harvest from the extremities can result in relatively more significant impediment to their activities of daily life than in their younger counterparts.

Another study identified advanced age as a predictor of poor QOL after major head and neck surgery, and identified gastrostomy tube dependence, presence of complications, and recurrence as indicators of decreased QOL.[97] Those who undergo multimodality treatment are at risk for decreased QOL, especially those who have undergone primary radiation with curative intent.[98]

Other studies demonstrate that adequate reconstruction with local or free flaps after ablation of oral cavity defects due to cancer ablation can result in acceptable QOL scores using the same University of Washington QOL measurement. Improved QOL has been associated with improved survival.[99]

Just as the care of the cancer patient is multidisciplinary, the outcomes sought in the care of the cancer patient are multifaceted and complex. Head and neck cancer care will continue to evolve through more sophisticated molecular research and translational research. Quality assurance and surgeon self-assessment are becoming more important in that performance standards are becoming a method of determining reimbursement for treatment. Most important, though, is the care of the cancer patient. Ultimately, the battle they must fight—the complications and side effects of treatment they must endure— must have meaningful end-points, not just in terms of the number of patients surviving at 5 years, but also in terms of those patients being able to make a meaningful return to pre-cancer life.

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20

Advanced Tongue Cancer (Special Considerations Requiring Total Glossectomy)

PHILLIP PIRGOUSIS, RUI P. FERNANDES, ROI DAGAN

Staging

Advanced T4 tumors of the oral tongue are a particular challenge for the head and neck surgeon from both an ablative and a reconstructive standpoint. The American Joint Committee on Cancer staging system, used universally, differentiates T4 tumors into T4a and T4b subtypes. T4a applies to locally advanced but resectable tumors, while T4b applies to tumors that are not technically resectable but may be suitable for nonsurgical options such as chemoradiotherapy.[1] T4a tumors invade adjacent structures such as cortical bone and/or deep extrinsic muscles of the tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus). T4b tumors invade the masticator space, pterygoid plates, and skull base and/or encase the internal carotid artery.

Survival

The American Cancer Society estimated that approximately 39,500 new cases of oral cavity and oropharyngeal cancers would develop in the United States in 2015. Of these cases, more than 40% were estimated to involve the oral tongue. Furthermore, approximately 7,500 patients were estimated to die of these cancers. Five-year overall survival rates for advanced T4 tumors of the tongue range from 56% in one series[2] to less than 30% in a later analysis.[3]

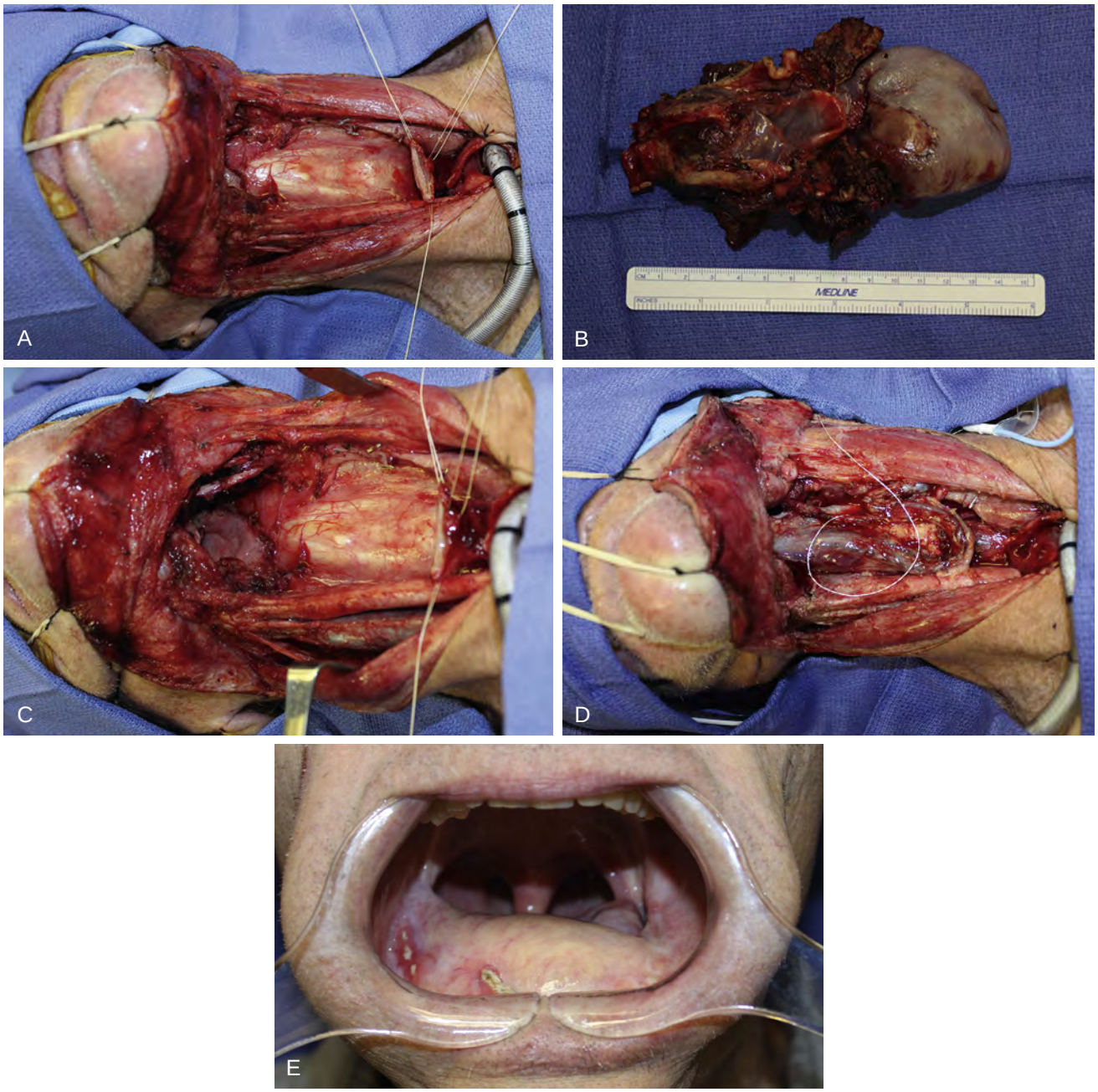
Total Glossectomy Without Laryngectomy

Advanced tumors of the oral tongue or tongue base present a significant impact on survival, function, and quality of life. Treatment options include primary surgical resection with adjuvant radiotherapy or chemoradiation, or primary radiation or chemoradiation therapy followed by salvage surgery.[4] Historically, the ensuing debilitating functional deficits following total glossectomy encouraged reconstructive surgeons to revisit and improve reconstructive principles and techniques in order to optimize functional outcomes, as well as identify those patients at risk for poor outcomes. The tongue is a unique organ playing a vital role in speech and deglutition. Its complete muscular composition together with the dual motor and sensory innervation make surgical reconstruction with free tissue transfer extremely challenging. Functional impairment following glossectomy results from poor articulation and intelligibility of speech and compromised oral and pharyngeal phases of swallowing. In the absence of a mobile tongue, control of the food bolus is lost, leading to increased transit times of the food bolus with subsequent nutritional deficits seen. Critical to the onset of the pharyngeal phase of swallowing, the tongue base together with the palate must act as a piston to propel the food bolus posteriorly. In the normal swallowing reflex, the addition of laryngeal elevation and glottic closure occur to prevent aspiration. In the absence of this latter mechanism, aspiration becomes more likely, and when followed by the associated pulmonary sepsis, often leads surgeons to consider a concurrent laryngectomy for pulmonary protection (Fig. 20.1).

Reconstructive Principles for Optimal Functional Outcomes

Flap Bulk

Optimal speech intelligibility and swallowing after total glossectomy are predicated on adequate flap bulk, allowing for contact of the neotongue with the palate. Numerous published case series have demonstrated this proportionality of flap bulk and better speech and swallowing outcomes. In their series of 30 glossectomy patients, Kimata and colleagues[5] demonstrated statistically significant associations between a protuberant neotongue and higher speech intelligibility, deglutition, and food scores. In addition, they also showed that patients with flat or recessed flap reconstructions suffered greater postoperative weight loss. Thus, they advocated the use of bulky flaps such as



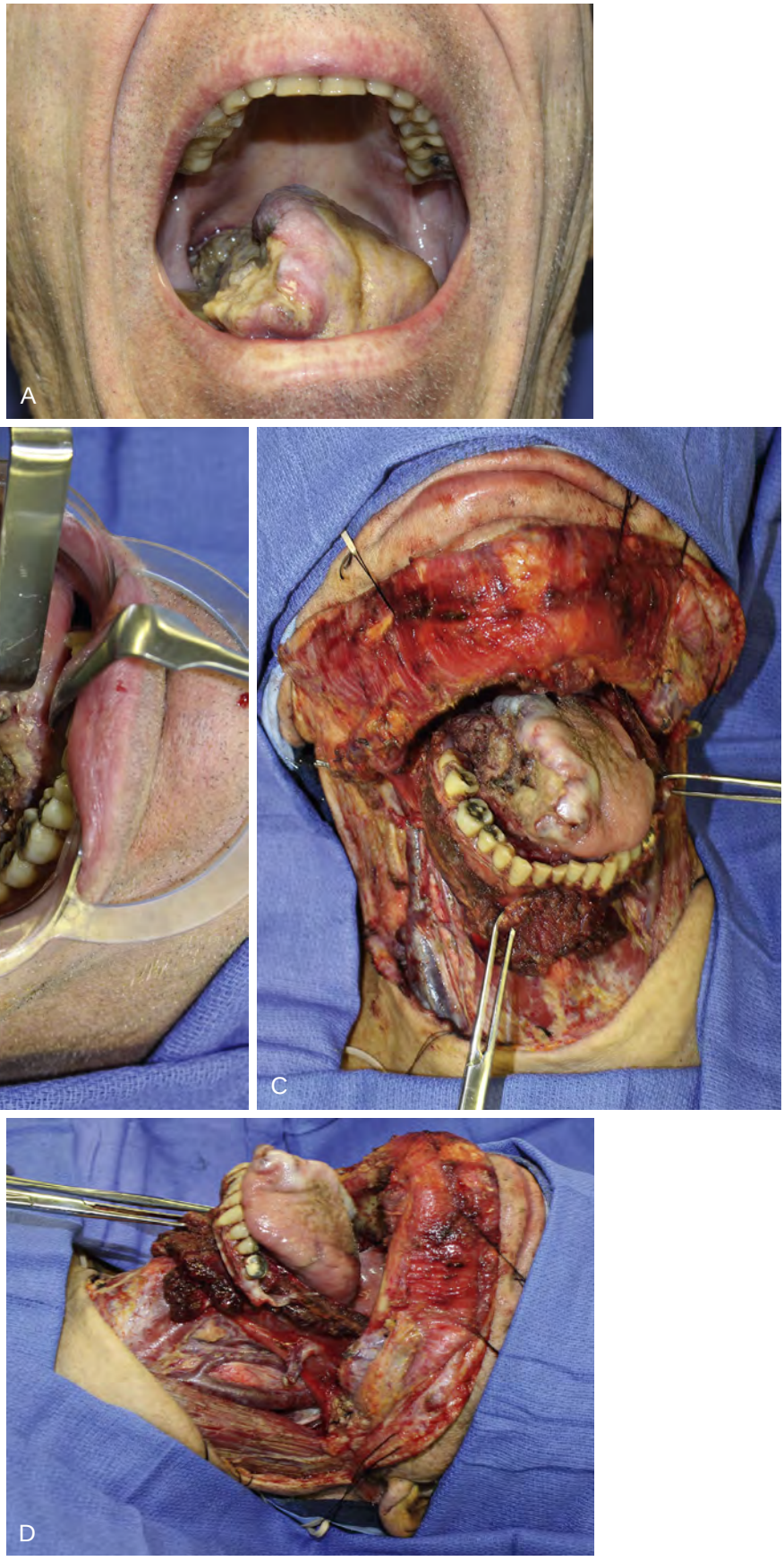
• **Fig. 20.1** **A**, Intraoperative view of total glossectomy with laryngectomy for recurrent base of tongue carcinoma. **B**, View of specimen demonstrating extent of involvement of recurrent base of tongue tumor. **C**, Postablative defect following total glossectomy with laryngopharyngectomy. **D,** Total glossectomy with laryngopharyngectomy defect reconstructed with tubed ALT free flap. **E**, Intraoral view of healed ALT flap replacing total glossectomy and laryngopharyngectomy defect.

the rectus abdominis or anterolateral thigh flap with increased widths up to 30% greater than the requisite defect in order to achieve adequate height of the neotongue (Fig. 20.2).

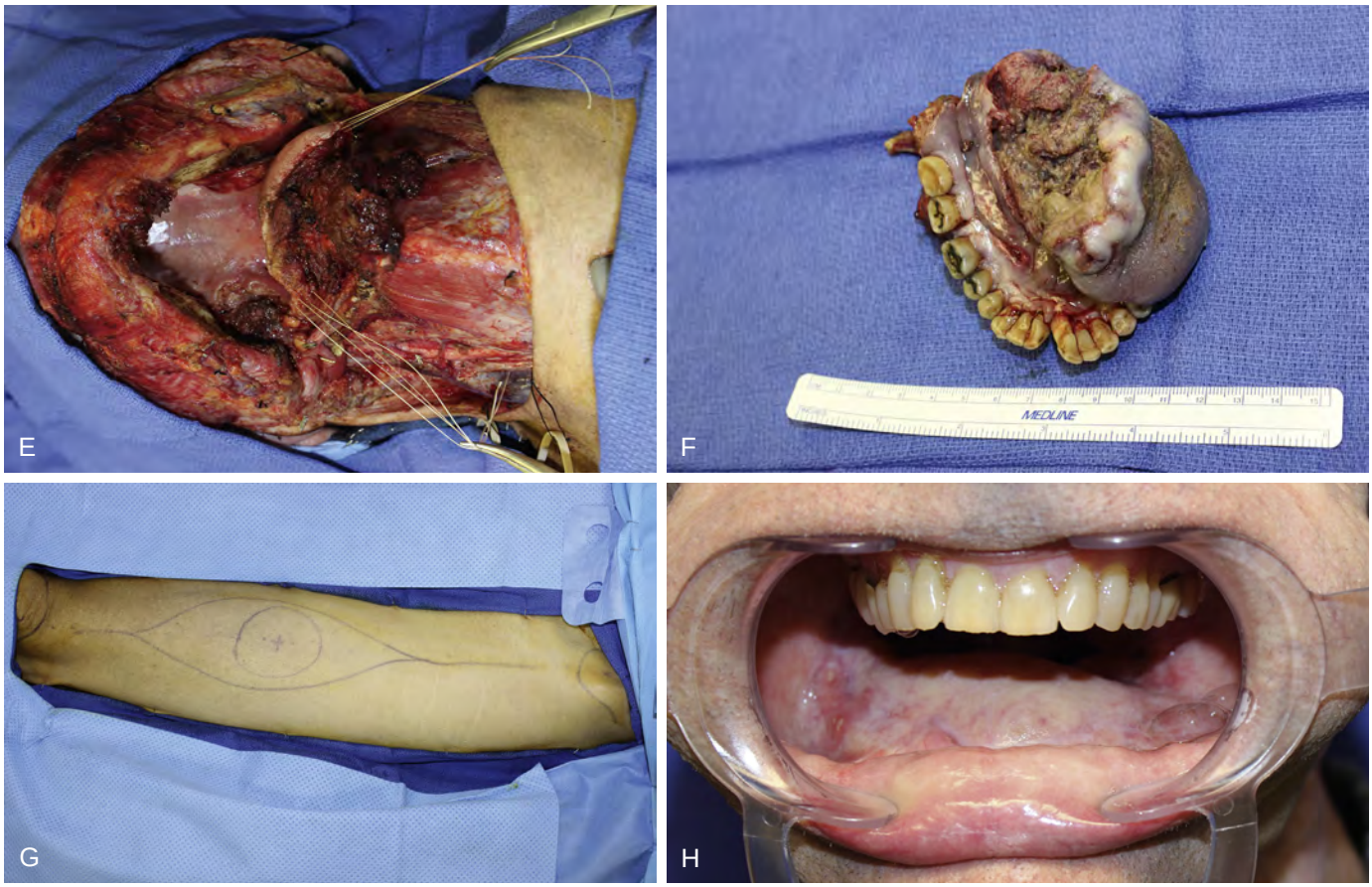
Yun and colleagues[6] in 2010 reported their functional outcomes in 14 patients undergoing total glossectomy and free flap reconstruction. All total glossectomy defects were reconstructed with either the rectus abdominis or anterolateral thigh flaps. Two patients also underwent total laryngectomy and were excluded from the speech results. All remaining patients had laryngeal suspension. Flap bulk indicated by degree of neotongue protuberance correlated significantly with improved speech and swallowing outcomes. In addition, they noticed a tendency for volume shrinkage of the neotongue with time, also advocating the importance of overcorrection of the defect to counter this phenomenon.

Laryngeal Suspension

Imperative to the prevention of aspiration following total glossectomy with laryngeal preservation is laryngeal suspension



• **Fig. 20.2** **A,** Intra-oral view of extensive primary tongue carcinoma. **B**, Intra-operative view of extensive tongue carcinoma. **C**, Intraoperative view of tumor exposure with visor flap and rim resection of mandible delivered into neck. **D**, Lateral view of composite tumor resection demonstrating tumor access and exposure.



• **Fig. 20.2, cont'd** **E**, Residual defect following subtotal glossectomy with rim resection of mandible. **F**, Tumor specimen after enbloc resection of tongue and rim of mandible. **G**, Elliptical design of ALT free flap for reconstruction. **H**, Healed postoperative view of subtotal glossectomy defect with ALT free flap.

(Fig. 20.3). Many published series include this adjunctive procedure during reconstruction and have reported its impact in improved swallowing outcomes.[7-9]

Weber and colleagues[10] describe their technique of laryngeal suspension wherein the remnant larynx is suspended to the menton of the mandible using circumhyoid nonresorbable sutures, which allows for static resuspension of the larynx in a superior and anterior vector re-creating the position of the larynx during swallowing. Furthermore, all 12 patients in the series in whom laryngeal suspension was performed maintained their larynx without evidence of aspiration compared with 3 of 15 patients requiring secondary laryngectomy for persistent aspiration when suspension was not performed.

Supraglottic or Mandibular Involvement

Advanced tumors of the tongue with supraglottic involvement or associated mandibular invasion have high failure rates requiring total laryngectomy[7,11,12] (Fig. 20.4).

Kimata and colleagues[11] reviewed 30 consecutive cases of total laryngectomy with laryngeal preservation; all three cases with supraglottic involvement required subsequent total laryngectomy.

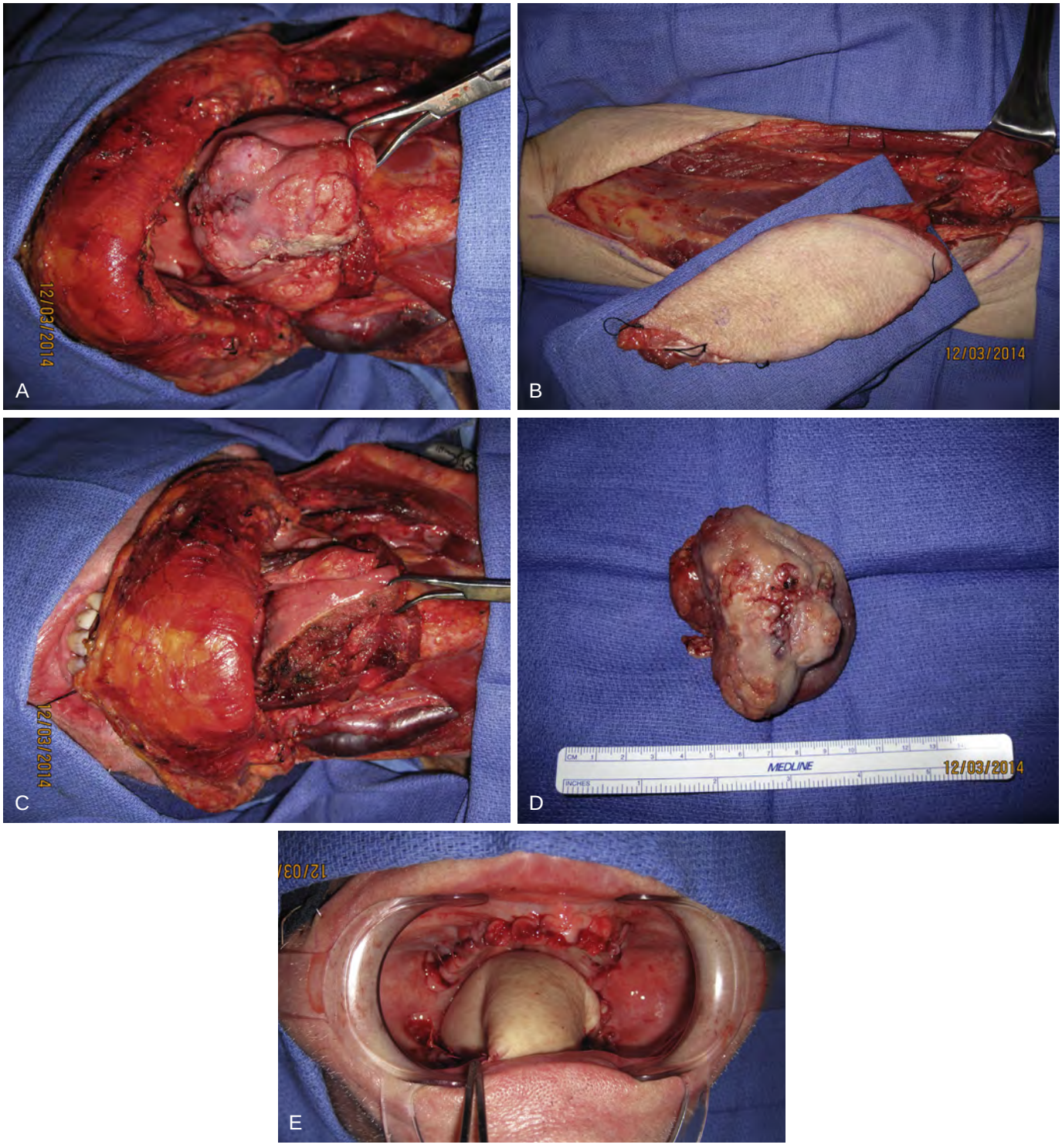
Similarly, mandibular invasion by advanced tongue carcinoma portends poor disease prognosis as well as overt and silent aspiration with subsequent laryngeal sacrifice.[12]

Most series demonstrate worse overall swallowing function with segmental mandibulectomy and total glossectomy than with marginal resections as evidenced by either an inability to successfully decannulate such patients or progression to total laryngectomy due to high aspiration risk.[4,13,14]

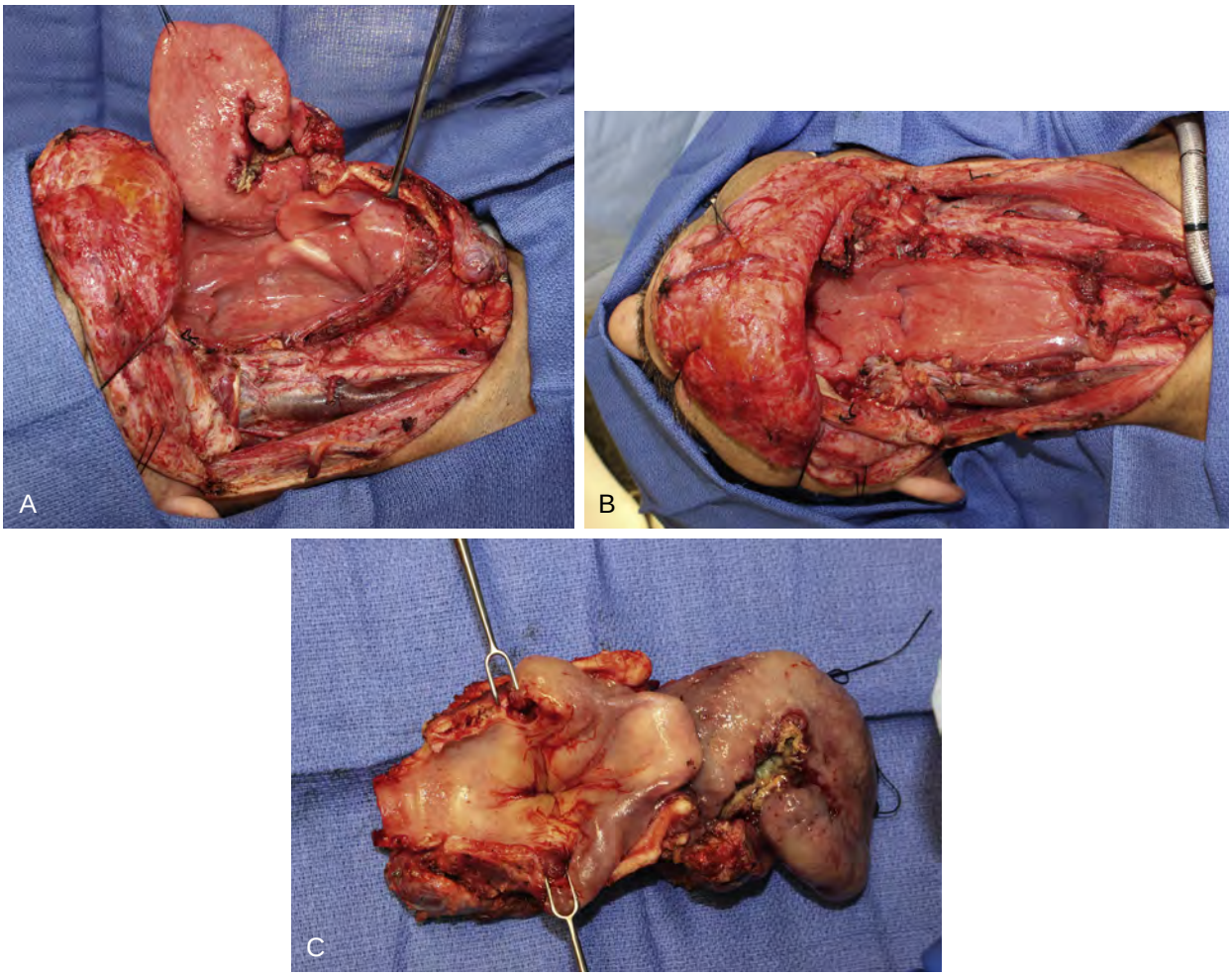
Sensate Flaps

Numerous reports have been published advocating the importance of sensory reinnervation of free flaps and associated swallowing outcomes in total and subtotal glossectomy reconstruction. Even so, the volume of data on this subject remains controversial with regard to degree of sensory recovery achieved and impact on swallowing postoperatively.[8,15]

A systematic review of sensate flaps for tongue reconstruction included 14 articles with a total of 271 tongue reconstructions using a variety of sensate free flaps. When compared with non-sensate flaps, the sensate free flaps improved overall sensory recovery but no demonstrable statistically significant functional benefit was evident.[15] Innervated flaps included radial forearm, anterolateral thigh, rectus abdominis, and tensor



• **Fig. 20.3** **A,** Extensively infiltrative tongue carcinoma delivered into neck through lingual release approach. **B**, Harvested ALT free flap for subtotal glossectomy reconstruction. **C**, Subtotal tongue resection with preservation of left tongue base. **D**, Subtotal glossectomy resection specimen. **E**, Inset of ALT flap to create neotongue mound.



• **Fig. 20.4** **A,** Salvage total glossectomy with laryngectomy for failed primary base of tongue carcinoma treated with primary chemoradiation. **B**, Defect following resection of total tongue with larynx incontinuity. **C**, Tumor specimen demonstrating extent of tongue base involvement including vallecula.

fascia lata flaps with no overall functional differences among these (Fig. 20.5).

Yu[16] published results on his experience with the innervated anterolateral thigh free flap in total and subtotal glossectomy reconstructions in 13 patients, in which the lateral femoral cutaneous nerve was coapted with the lingual nerve. Sensory recovery was confirmed with two-point discrimination, light touch, and temperature at 12 months following surgery compared with preoperatively. Superior sensory recovery in all parameters was seen in the innervated group compared with a similar non-innervated group. Furthermore, comparison between these two groups also showed superior objective speech and swallowing outcomes measured with established grading systems.

Lastly, cineradiographic studies support the importance of superior laryngeal nerve preservation, minimizing the degree of aspiration seen by maintaining supraglottic sensation.[17] This phenomenon is likewise critical in patients after supraglottic and supracricoid partial laryngectomy.

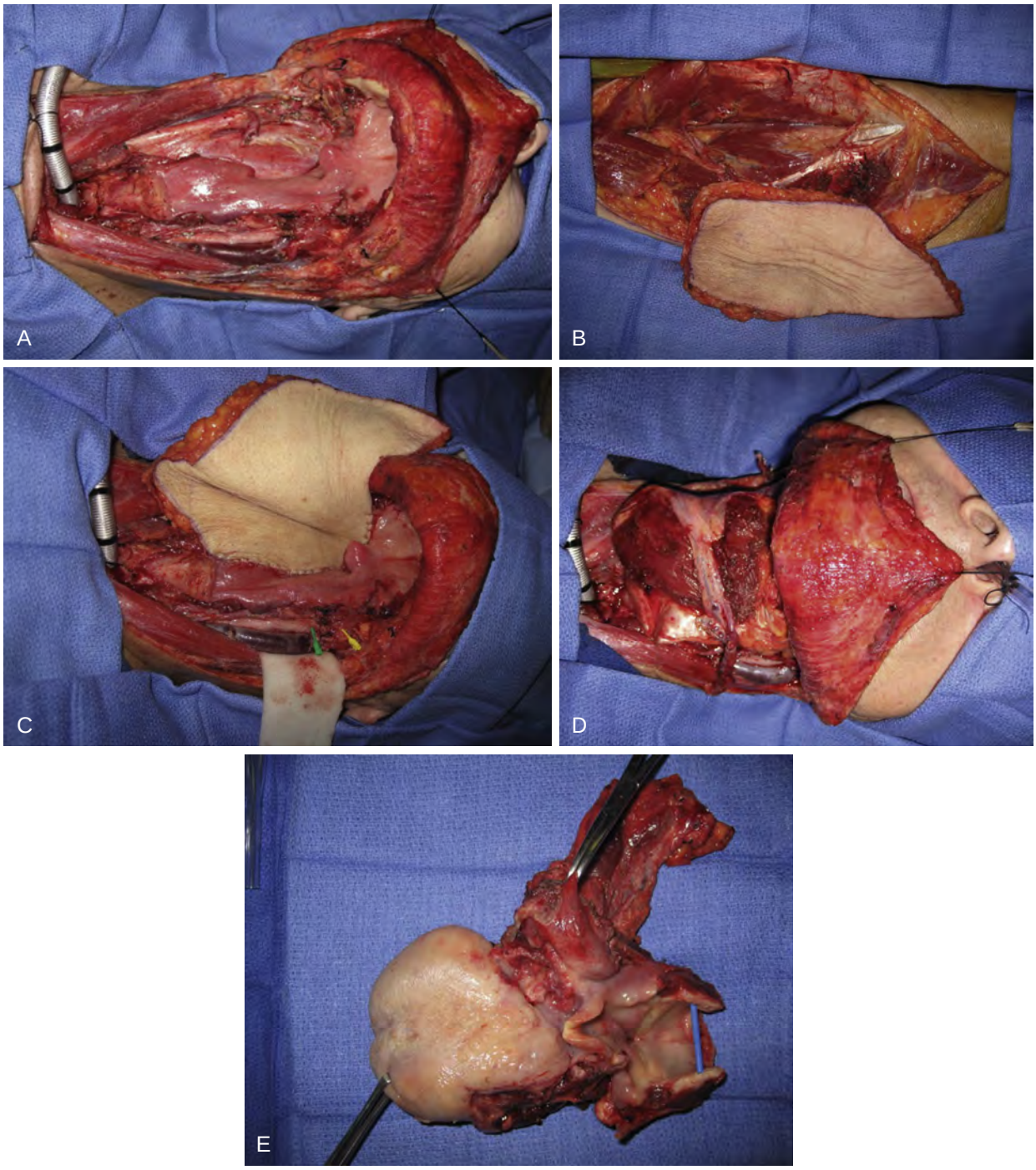
Motor Function

Like sensory reinnervation, motor reinnervation of free flaps has also been described extensively with varied functional results.[18-20] Various free flaps have been tried including rectus abdominis, anterolateral thigh, and gracilis and latissimus dorsi, essentially all resulting in similar speech and swallowing outcomes (Fig. 20.6). However, direct comparison with non-innervated control groups is lacking, thus the true impact of motor function remains poorly established. Regardless, motor reinnervation is likely to play a pivotal role in maintenance of flap volume and palatal contact through prevention of denervation muscle atrophy.

Adjuvant or Prior Chemoradiation

Adjuvant therapy following primary surgery or failed primary chemoradiation with surgical salvage has a major impact on tracheostomy dependence and gastrostomy tube dependence.[7,21]

Rihani and colleagues[7] reported 36 cases of total glossectomy with free flap reconstruction followed by postoperative radiotherapy. Tracheostomy tube dependence rates were 5.5% at 1 year, and gastrostomy dependence was 44% for the same period. In contrast, 58 patients in the surgical salvage group had tracheostomy dependence of 22% and gastrostomy tube dependence of 88% for the same 1-year period. These results were statistically significant.

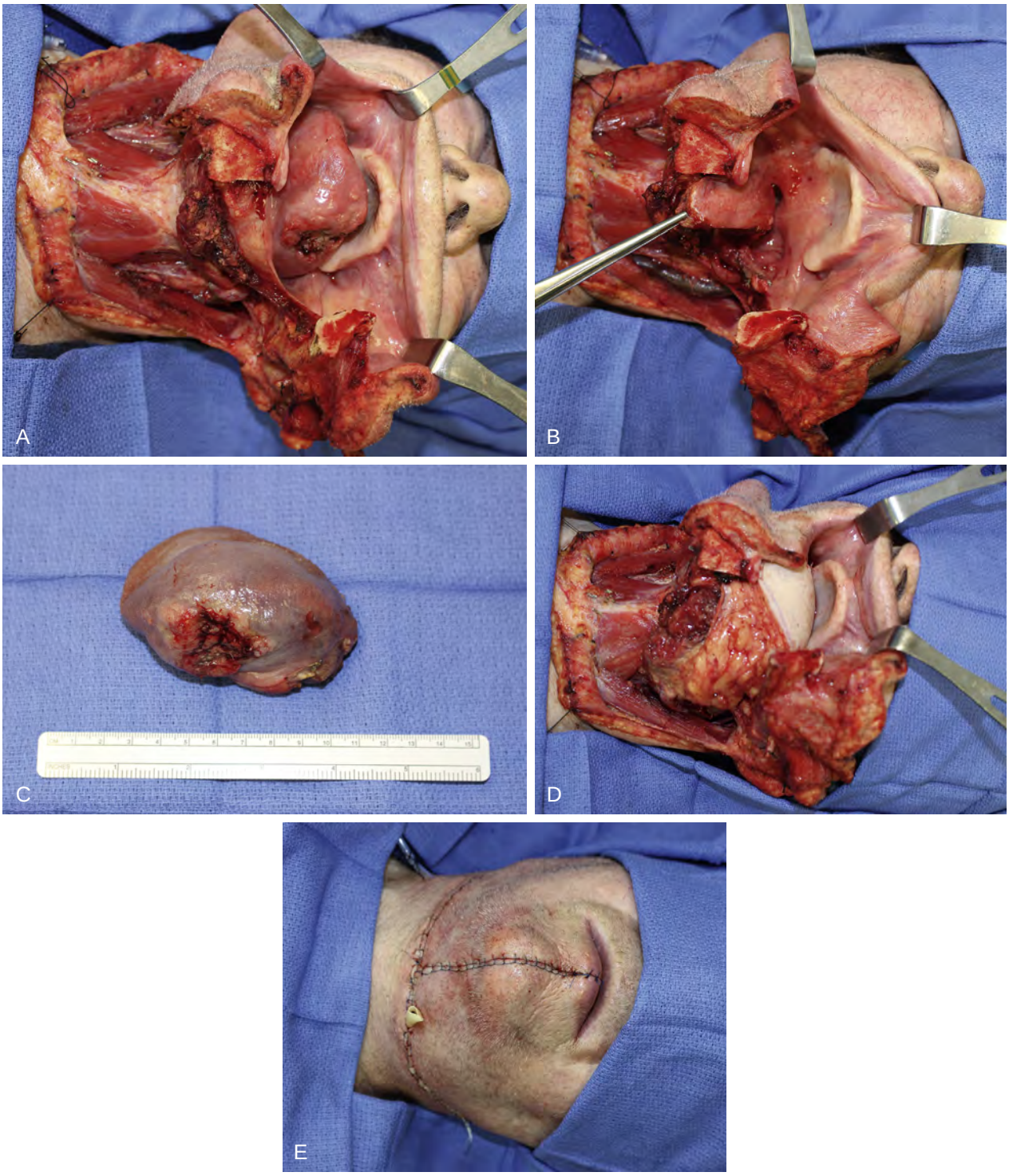


• **Fig. 20.5** **A,** Post resection defect following total glossectomy with laryngectomy with some preserved posterior wall pharyngeal/ hypopharyngeal mucosa. **B**, Harvested ALT free flap with appropriate design. **C**, Insetting of ALT free flap to reconstruct anterior hypopharyngeal wall and total glossectomy defect. **D**, ALT flap insetting and microvascular anastomosis complete. **E**, Resected tumor specimen demonstrating base of tongue, right valleculla and lateral hypopharyngeal wall invasion.

In a larger retrospective study[21] of 109 cases of total glossectomy with laryngeal preservation and primary reconstruction over a 19-year period, no statistical significance was found in gastrostomy dependence. However, 88% of the cases were reconstructed with a pectoralis major myocutaneous pedicled flap and no mention of laryngeal suspension was made. Overall, it remains unclear whether tracheostomy and gastrostomy tube dependence is worse in the adjuvant therapy or salvage surgery groups.

Radiation Therapy

As previously noted, for T4b tumors of the oral tongue, primary radiation therapy is used with either palliative or curative



• **Fig. 20.6** **A,** Midline lip-split with mandibulotomy for access to advanced lateral tongue tumor. **B**, Post-ablative view of tongue defect with residual right base of tongue preserved. **C**, Tumor specimen following subtotal glossectomy. **D**, Inset of ALT free flap into subtotal glossectomy defect. **E**, Final closure following completion of reconstruction.

intent, most commonly for the latter with concurrent chemotherapy. The decision to deliver adjuvant radiation therapy for resected T4a disease often rests on the individual patient's ability to tolerate multimodality therapy independent of other risk factors for recurrence, because T4 alone is an indication for adjuvant therapy to the primary site.[22] Additional indications increase the likelihood of residual disease. Such indications at the primary site include perineural invasion, close margin (<5 mm) or surgeon unease about the margin status, deep invasion (≥5 mm), and lymphovascular space invasion. Indications in the neck include multiple positive nodes and risk for occult lymph node metastasis in an undissected neck.[22,23]

A pre-radiotherapy dental evaluation should be performed with the goal of optimizing dental/oral hygiene and establishing vigilant prophylactic dental care such as fluoride use and frequent cleanings, and most crucially performing prophylactic extractions of teeth that are decayed or in areas at risk for osteoradionecrosis. Ideally this is done before resection to minimize delays to adjuvant therapy.

Radiotherapy should begin within 6 weeks of surgery assuming the surgical wounds are sufficiently healed in order to lower the risk for recurrence from repopulation or residual disease.[24] This requires meticulous postoperative care and coordination between the radiation oncology and surgical teams. Upfront, multidisciplinary evaluations are recommended to facilitate care.

Historically, patients were treated with conventional 2D planned parallel opposed radiation fields using lower energy x-rays (4 to 6 MV) or Co 60. These fields could be weighted unevenly in order to skew the dose distribution for lateralized tumors. The fields are matched through various techniques to anterior-posterior (AP) oriented field that treat the lymphatics of the low neck and supraclavicular fossa. When doses that exceed the spinal cord tolerance are prescribed, the posterior border the lateral fields is reduced anteriorly at 40 to 45 Gy, and posterior electron strips can be matched to supplement dose to cervical nodal regions in the superior aspect of the neck. The same techniques can be planned in modern treatment planning systems using 3D simulation or more sophisticated treatment techniques such as intensity modulated radiation therapy (IMRT) can be used.

During simulation, the patient's head, neck, and shoulders are immobilized in the treatment position using a thermoplastic mask. Shoulders are depressed, leveled, and secured, and reference marks are placed on the patient's skin that are localized by leveling and alignment lasers. The neck should be extended such that the body of the mandible is at an angle of 90 degrees with respect to the treatment table in order to treat the neck with an AP field. Oral stents (obturators) can be used to depress/immobilize the tongue and displace the mucosa of the palate from the radiation field. In cases of extracapsular extension (ECE) or when there is a risk of seeding neck scars, bolus material can be added over scars in order to ensure full dose at the surface.

Computed tomography (CT) images are acquired in the axial plane throughout the treatment volume typically ending at the carina. In modern treatment planning systems, preoperative imaging can be co-registered to the CT-simulation image set to aid in delineating target volumes. The radiation oncologist will then delineate the target volumes and normal tissue structures. Gross residual tumor is called the gross tumor volume (GTV). The clinical target volume (CTV) is defined as the volume at risk for harboring residual microscopic disease. CTVs are often separated into multiple levels of risk (STV standard, intermediate, or high risk or CTV1, 2, 3, and so on) and by primary site and nodal volumes (CTVp or CTVn), so that different dose/fractionations can be prescribed to each volume. The CTVp typically includes the tongue resection bed including the reconstructed flap and an additional 1 cm of tissue at risk for invasion. In the nodal regions, different CTVs can be used to delineate nodal stations with gross residual disease or ECE (CTV1), positive nodes without ECE (CTV2), and those adjacent to positive nodes and undissected lymph node stations (CTV3). Dissected lymph stations that were pathologically negative can be treated in CTV3 or assigned an even lower level of risk, or even omitted from the target volume. Nodal CTV delineation has been standardized in both the primary and postoperative setting in published guidelines.[25,26] The CTVp is typically included in CTV1 for cases with close/positive margins or CTV2, when the margin is widely negative. CTVs are subsequently expanded for planning target volumes (PTVs 1, 2, 3, and so on) by a margin of 3 to 5 mm in order to account for residual uncertainties in planning and delivery. These margins are designed to ensure that the CTVs will receive their prescribed doses with 95% certainty. The margins can be minimized by improving the reproducibility of treatment setup though secure immobilization and on-board image-guided radiotherapy using daily cone-beam CT.[27] The critical normal tissues include the brainstem, spinal cord, salivary glands, larynx, cochlea, brachial plexuses, cervical esophagus, and mandible.

Doses of 66 to 70 Gy, 60 to 64 Gy, 56 to 60 Gy, and 50 to 54 Gy are prescribed to CTV1, 2, 3, and 4, respectively, over 6 to 7 weeks of daily RT, delivered once daily using 2-Gy fractions. Accelerated fractionation using hyperfractionation, concomitant boost techniques, or treating 6 fractions per week has not been demonstrated to be superior to conventional fractionation in the postoperative setting, but may be a means of reducing the risk for local recurrence from accelerated tumor cell repopulation.[28]

Currently, most patients are treated with IMRT. This technique can be used to maximize coverage of target volumes and sparing of critical radiosensitive normal tissue structures. In IMRT, the intensity of each radiation field is modulated through computer optimized sequencing of multileaf collimators, mechanically driven beam shaping devices, to create complex dose clouds in which convexities or concavities are shaped to reduce the dose to critical normal tissues. Specifically, this technique is used commonly with the goal of salivary preservation by sparing the parotid gland on the side of the neck when level II lymph nodes are not involved.[29] Additional IMRT can be used to reduce the dose to the larynx when treating the neck to high doses and the pharyngeal constrictor muscles with the goal of preserving swallowing function.

Concurrent chemotherapy is indicated in cases of positive margins and ECE.[30] For many years the standard regimen has been cisplatin delivered intravenously at 100 mg/m^2 every 3 weeks. Many centers have adopted weekly cisplatin at 30 to 40 mg/m^2 as an alternative because the acute effects of lower dose cisplatin such as myelosuppression and nausea are less intense.[31] Alternatively patients who are not suitable for cisplatin-based chemotherapy can be treated with carboplatin or cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor.

During therapy patients are monitored weekly for management of nutritional status, hydration, mucositis, infection, skin reactions, and other acute effects of therapy. Intense supportive care is required, including the use of feeding tubes in many

patients, and treatment breaks should be minimized because increasing the overall treatment time has been associated with decreased local-regional disease control.

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21

Early Floor of Mouth Cancer

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Head and neck cancers account for about 600,000 patients per year worldwide.[1] In 2015, about 46,000 new cases were estimated to be diagnosed in the United States, and 8650 people were estimated to die of the disease. Cancer of the oral cavity and pharynx represent about 2.8% of all new cancer cases diagnosed in the United States. The male-to-female ratio of oral cavity and pharynx cancers continues to remain at about 2.5:1 despite an increase in human papillomavirus–related cancers. Globally the incidence rate of lip and oral cavity cancers are 2.7 per 100,000, and a mortality rate of 2.1 per 100,000.[1]

Floor of mouth cancers comprise about 5% of total oral cavity and pharynx cases of cancer in the head and neck region. The 5-year survival of all patients with floor of mouth cancers is about 50% for all stages.

Anatomic Considerations

The lingual sulcus is made up of the lingual plate in the mandible and the associated periosteum anteriorly and laterally. Posteriorly, it blends into the ventral surface of the tongue medially while it extends to the lingual sulcus between the mandible and the tongue. The contents below the mucosa of the lingual gutter include the sublingual gland caudally, the submandibular ducts, the genioglossus and geniohyoid muscles with the mylohyoid muscle and the anterior belly of the digastric muscles. Other contents include the investing fascia, the platysma muscle, and loose subcutaneous tissue that lies below the skin.

Lymphatic drainage from the floor of mouth first enters the submental or the sublingual nodes and drains into the upper deep cervical chain of nodes. Tumors may extend into the floor of mouth and associated lymphatic structures by direct invasion, as well as by lymph node metastasis.

The results of one animal model study seem to show that the periosteum in the floor of the mouth is not an intact barrier against infiltration. In fact, the results indicated the lymphatics drained through the periosteum before flowing into the cervical chain.[2,3] This could explain the difficulty with obtaining complete local control despite early detection and therapy.

Floor of mouth carcinomas exhibit three types of invasion routes into the surrounding anatomy, according to the study by Steinhart and Kleinsasser.[4] The most common area of direct tumor extension is infiltration into the sublingual glands. The second most common pattern is infiltration between intrinsic tongue muscles and the genioglossus, while the rarest is direct invasion into the intrinsic tongue muscles themselves. The authors advocate routine resection of the intrinsic tongue muscles, genioglossus, and geniohyoid because of this common involvement. In contrast, the mylohyoid seems to be a somewhat intact anatomic barrier for an indeterminate time and is only involved as a late-stage advanced lesion. Mylohyoid muscle extension is usually spared in early-stage lesions.

According to Steinhart and Kleinsasser, the sublingual glands should be routinely taken within the resection to prevent local recurrences. However, Clark and colleagues[5] advocate that sublingual glands not be removed in early-stage T1/T2 lesions. They argue that removal provides little oncologic benefit while placing other anatomic structures at risk, namely the lingual nerve, the hypoglossal nerve, and the submandibular duct. Removal may also increase the risk for fistula development by weakening the tissue separating the oral cavity from the neck. In their study, 25% of the patients exhibited neck wound complications as a result of sublingual gland excision, whereas such complications were reported in only 14% of patients who did not undergo excision.[5] In regard to oncologic benefit, only 4.2% of patients without gross disease involving the sublingual glands had microscopic evidence of it on histopathologic examination.[5] The authors concluded that routine excision should not be undertaken unless evidence of macroscopic tumor invasion exists.

The submandibular glands are not well studied in relation to floor of mouth carcinoma. In Stienhart and Kleinsasser's study,[4] no cases of involvement of the submandibular glands were found in 14 specimens, despite their proximity to tumor tissue. Submandibular glands are commonly removed as part of a selective neck dissection, although this seems to be more of a holdover from the era of radical neck dissections. Because there are no lymph nodes within the gland itself, there seems to be little oncologic basis for routine excision in early T1/T2 lesions. However, because floor of mouth cancers are so close to the submandibular gland, it should be removed to ensure a complete 3D tumor clearance. The gland should also be excised in the case of direct tumor infiltration, although this was rare in the Steinhart and Kleinsasser series (1/253 glands).[4] What is clear is that preservation of the gland requires careful surgical

technique in clearing all the lymph nodes from level I and skeletonizing the gland itself to ensure all perivascular lymph channels are excised while preserving the vascular anatomy.[6]

Diagnosis and Imaging

A small incisional biopsy remains the standard of care for diagnosis of oral cavity lesions. Fine needle aspiration is also done for small lesions; however, fine needle aspiration is generally reserved for establishing diagnosis in clinical lymphadenopathy.

Imaging for Floor of Mouth Cancers

A good clinical examination forms the backbone of the decision-making process in an area where tumors are easily palpated and visualized. Smee and colleagues[7] demonstrated the superiority of clinical examination in determining the staging and management of patients with floor of mouth cancers. In their series, a computed tomography (CT) scan was performed at presentation in 36 patients, with only one individual receiving treatment different from that determined by clinical examination alone.

Nevertheless, there is a defined role of imaging modalities for the floor of mouth cancers. Imaging can aid in staging, determine the extent of surgical resection, and clarify whether the mandible is to be considered as part of the resection. How to best determine the existence of mandibular invasion is still a debate. According to Steinhart and Kleinsasser,[4] magnetic resonance imaging (MRI) and CT should be included as routine preoperative evaluation of the mandibular bone, and only if the mandible is involved should the patient be subjected to a composite resection with marginal or complete mandibulectomy.[4]

Current imaging techniques include CT with contrast, positron emission tomography (PET), MRI, single photon emission computed tomography (SPECT) imaging, and ultrasound. Other standard imaging techniques include conventional x-rays (mandible series, occlusal radiograph, and an orthopantomogram). Imaging of the neck for lymph node metastasis is also another important consideration for determining treatment and prognosis for patients.

CT scan with contrast remains the gold standard modality of imaging for almost all head and neck cancers. This modality of imaging is recommended by the National Comprehensive Cancer Network (NCCN) guidelines as standard of care. Squamous cell carcinoma is well delineated on a CT scan with contrast. Bone erosion can also typically be appreciated on a CT scan using a bony window. Other methods to determine invasion of mandible include an MRI and or SPECT imaging.

Although not considered standard of care, a PET/CT is now used by a majority of practitioners as the imaging modality for all head and neck cancers.

Staging Floor of Mouth Cancers

Floor of mouth cancers are generally grouped under the staging system for cancers of the oral cavity. These guidelines were set forth by the NCCN. The TNM classification is used for appropriate staging of tumors and in turn determining the optimal treatment for such cancers.

The American Joint Committee on Cancer (AJCC) recently made substative modifications to the TNM staging criteria and staging system for head and neck cancer in general and oral cavity cancer in particular. These changes more accurately represent the unique biologic, clinical, and epidemiologic features of oral squamous cell carcinoma (OSCC) (see Table 24.1 in Chapter 24). In the first modification, the T stage now incorporates depth of invasion (DOI). In the 1980s, Spiro and colleagues identified the importance of tumor thickness as a prognostic indicator in oral cavity cancer. Depth of invasion is a more sophisticated and reproducible method of measuring a tumor. It is measured by first finding the "horizon" of the basement membrane of the adjacent squamous mucosa, and DOI is defined as the deepest point of tumor invasion (in mm) from that line. Extrinsic muscle infiltration has been removed from the staging criteria because DOI is more representative of the clinical problem both clinically and pathologically. DOI assesses the invasiveness of the tumor rather than any exophytic component.

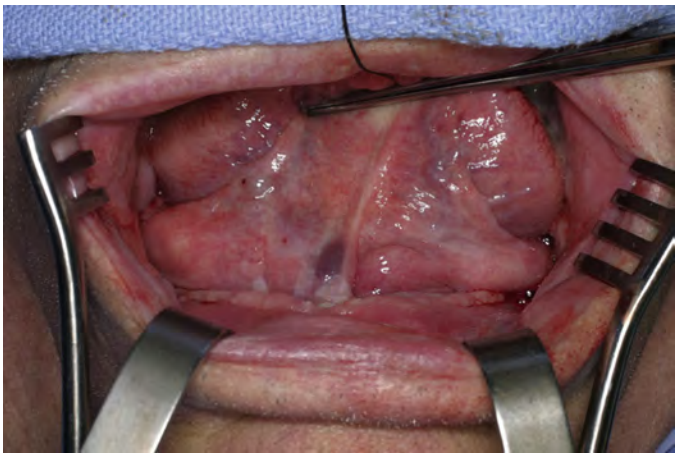
In the second modification, extranodal extension is now recognized when categorizing metastatic cancer to the cervical lymph nodes. Additional updates to this classification scheme include the following:

1. Separate N category approaches are given for patients treated without cervical lymph node dissection (clinical N [cN]) and patients treated with cervical lymph node dissection (pathological N [pN]).
2. Extranodal extension (ENE) is introduced as a descriptor in N categorization for all HPV-negative cancers, and its presence is designated pN2a for a single ipsilateral node <3cm and pN3b for all other node(s).
3. Clinically overt ENE is classified as ENE and is considered ENE(+) for cN.
4. Pathologically detected ENE is classified as either ENEmi (<2 mm) or ENEma(>2 mm) for data collection purposes only, but both are considered ENE(+) for definition of pN.

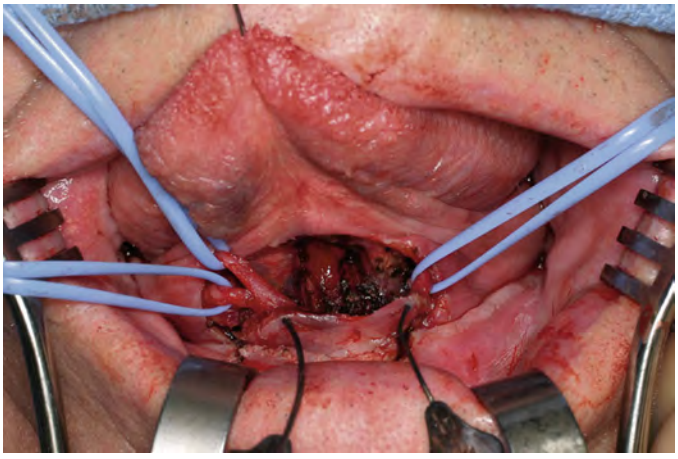
However, pathologic stage does not trump clinical stage, and assignment of ENE should be based primarily on physical examination, rather than on imaging studies.

The primary tumor stage remains essentially the same in the new system, with the exception that DOI will increase the T category by 1 for each 5-mm of tumor depth (up to ≥10 mm). Pathological ENE(+) will increase the nodal category by 1. In addition, the AJCC recommends that other prognostic factors be considered and recorded along with standard staging information, including Eastern Cooperative Oncology Group (ECOG)/Zubrod or Karnofsky performance measures, tobacco and alcohol use, tumor location, number and size of nodes, perineural invasion, and ENE.

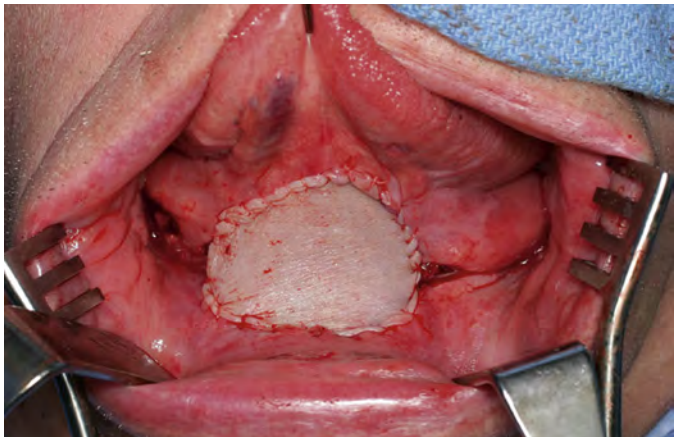
The new AJCC TNM staging highlights the worst pattern of invasion (WPOI) as a validated outcome predictor. It is recommended that WPOI-5, defined as tumor dispersion of ≥1 mm between tumor satellites, be recorded as part of pathologic staging. Even in early-stage oral cancer, a DOI of >4 mm combined with a WPOI-5 increases the probability of



• **Fig. 21.1** T1 squamous cell carcinoma of the floor of mouth.



• **Fig. 21.2** Submandibular duct and the lingual nerve are identified and preserved.



• **Fig. 21.3** Once the skin graft has been placed, the submandibular ducts are repositioned to allow flow of saliva.

recurrence to approximately 42%. Perineural invasion (PNI) or lymphvascular invasion constitute a WPOI-5 classification. When identified, PNI would be subclassified as either intratumoral or extratumoral. Named nerves should be specified and PNI should be subclassified as focal or multifocal.

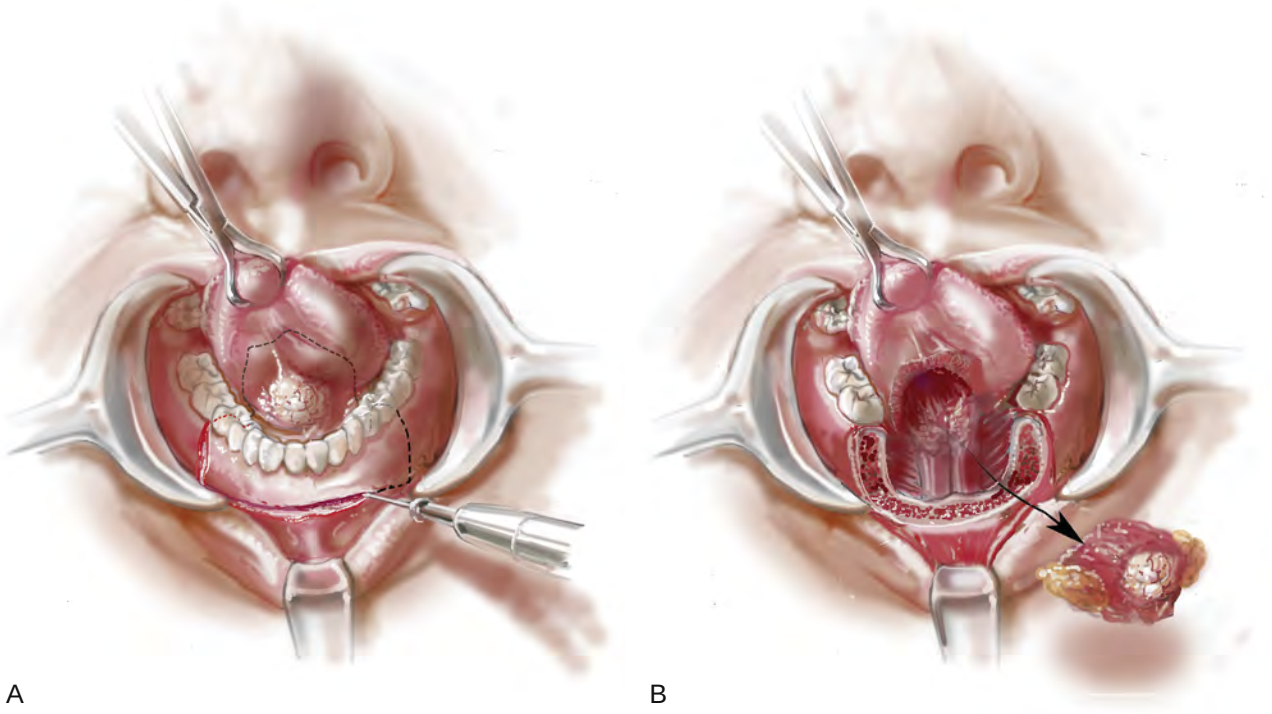
Surgical Management of Floor of Mouth Cancers

Surgery remains the mainstay of treatment for primary T1/T2 squamous cell carcinomas. These smaller stage cancers are typically resected via a transoral approach and rarely involve a lip-split mandibulotomy approach. For T1 lesions that are deeper than 3 mm and for T2 lesions, a neck dissection is recommended per NCCN guidelines. Lesions that are stuck to the mandible also involve removal of part (marginal mandibulectomy) or all of the mandible (composite resection). Conducting a marginal mandibulectomy when the tumor is adjacent to periosteum is now a widely accepted practice, which was earlier advocated by Yco and Cruickshank.[2] The marginal mandibulectomy can be horizontal, vertical, or oblique. A margin or cuff of normal tissue (1.5 to 2 cm) is taken in three dimensions to ensure complete removal of the cancer and to ensure a microscopic clear margin. The concept of a 3D surgical cure, according to Schramm and colleagues[8] and supported by Yco and Cruickshank,[2] includes monobloc resection, 2-cm margins, and resection of the submandibular glands, although that is not without controversy.

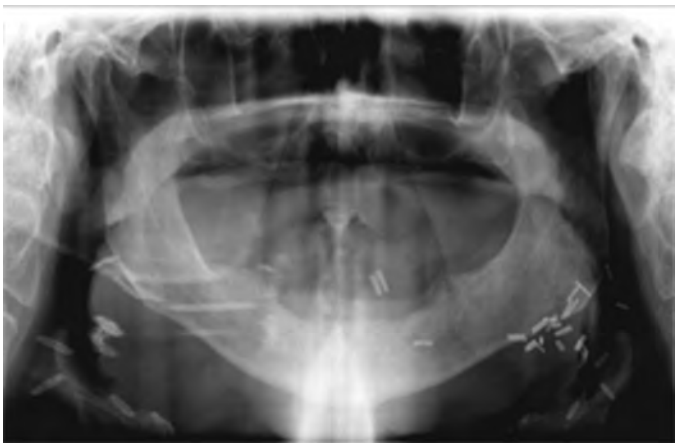
Surgery for a small lesion (T1) that does not involve a marginal mandibulectomy typically begins with the delineation of the tumor with a margin of normal tissue around the cancer (Fig. 21.1). Local anesthesia (1% lidocaine with 1:100,000 epinephrine) is injected around the tumor over the proposed boundary. Once the vasoconstrictor has taken effect, an incision is made with a scalpel blade through the mucosa and into the floor of mouth. The second part involves dissection over the proximal aspect of the tumor over the ventral tongue and the lingual sulcus. The lingual nerve and the submandibular duct are identified (Fig. 21.2). The distal aspect of the duct is usually included as part of the surgical margin and therefore a sialodochoplasty is completed.

Performance of duct repositioning is of benefit to the majority of patients. Wong and colleagues[9] found that 29% of patients who underwent a floor of mouth or lateral tongue excision for carcinoma had symptoms related to their submandibular glands. These ranged from swelling to pain, and generally were self-limited in nature, although they provided significant distress for patients. In those patients who had sialodochoplasty, 13% reported postoperative complications compared with 33% who did not undergo ductal repositioning.[9]

The remainder of the resection is completed to include the ventral tongue and floor of mouth. Once the tumor is resected and margins are noted to be negative, usually the site can be closed primarily or left to granulate. Alternatively, a split thickness skin graft or a full thickness skin graft may be sutured over the defect with a bolster dressing. The ends of the submandibular duct may be closed at the edge of the skin graft using a 6-0 Prolene suture to redirect the ducts (Fig. 21.3). This is especially important when neck dissections are not included as part of the surgery to ensure good patency of the submandibular duct.



• **Fig. 21.4** Marginal mandibulectomy for anterior floor of mouth lesions extending to the mandibular periosteum but without invasion through the cortex. **A,** Incision design for composite resection. **B,** Marginal mandibulectomy defect.



• **Fig. 21.5** Panorex image showing a mandible after completion of a marginal mandibulectomy. Note that the line angles have been smoothed to prevent fracture propagation.



• **Fig. 21.6** Complete healing of the floor of mouth 3 months after surgery.

Surgery that involves a marginal mandibulectomy is started in a similar fashion with delineation of the tumor with a 1.5- to 2-cm cuff of normal tissue (Fig. 21.4). The incision is made over the labial mucosa and taken down through the periosteum and onto bone. Typically the osteotomy, using a reciprocating saw, is made just below the roots and sometimes taken through the tooth roots if a height of 1 cm is to be preserved. Sharp line angles are avoided to prevent propagation of a fracture in the mandible. These angles are usually smoothed off as seen on postoperative Panorex imaging (Fig. 21.5). If the osteotomy is taken through the roots, then it is very important to extract the remaining roots to prevent infection or osteoradionecrosis of the jaw. Again, a sialodochoplasty is performed if a neck dissection is not completed as part of the surgical plan (Fig. 21.6).

For tumors deeper than 3 mm, tumors fixed to bone, or tumors that do have bone involvement a neck dissection is performed as part of the surgery. If the tumor crosses the midline due to the lymphatic drainage being on both sides, a bilateral neck dissection is typically recommended as part of the oncologic surgery. The neck dissection can be included as a continuous resection with the primary specimen or it can be taken in a discontinuous fashion. All sharp edges of the resection bed of mandibular bone are smoothed off. These oncologic defects can be closed using a variety of techniques to include local

tissue arrangement, pedicled flaps, skin grafts, or vascularized free flaps, depending on the dimensions of tissue required.

Primary closure for larger lesions is difficult and usually leads to wound breakdown with de-formation of the lower lip providing a "sunken in" lip defect. To avoid such defects, a small pedicled flap such as a nasolabial flap, facial artery myomucosal flap, or a submental island flap is used for closure. If these are not candidates, then a vascularized free flap (radial free forearm flap, lateral arm flap, or anterolateral thigh flap) could be used to close the defect.

Management of the Neck in Floor of Mouth Carcinoma

It is widely accepted that the most common failures of treatment in floor of mouth carcinoma are within the neck, followed by recurrences at the site of the primary tumor.[10] While examination of tissue margins and frozen sections are well-established standards for treatment of the primary site, the management of the neck continues to be a controversial issue. Given the central location of floor of mouth cancers, both ipsilateral and contralateral nodal sites need to be considered. Several series have identified the most frequent site of failure as an untreated contralateral neck.[11-13] Both sides of the neck are vulnerable with midline lesions and those predominately unilateral lesions that cross over the midline. The risk of nodal disease is also increased by the size of the primary tumor and by the depth of penetration.[14] However, inadequate resection of the primary tumor is the most important factor leading to development of neck failures after surgical treatment.[15,16] Six of seven failures of surgical treatment occurred at the primary site in a study by Yco and Cruickshank.[2]

Proponents of elective neck dissection in T1/T2 floor of mouth lesions cite the high rate of cervical node metastasis, the frequency of occult nodal metastasis in the clinically negative neck, the poor success of salvage surgery in treating subsequent nodal metastases, and the reduction in survival with involvement of the neck. Most clinicians recommend elective treatment of the neck in oral cavity cancers when the risk of occult metastasis is greater than 20%.

The debate over whether a neck dissection is necessary in those patients presenting with a floor of mouth cancer and a N0 neck hinges around the risk of occult nodal disease. Reported incidences range from 4% to 46%, depending on the study, but generally seem to be higher than the 20% threshold for treatment of the neck electively. Dias and colleagues[16] reported the occurrence in 24.5% of patients in their series, which is consistent with other published results, even though the study by Dias and colleagues included floor of mouth and tongue stage I lesions.

Zupi and colleagues[10] recommended a supraomohyoid prophylactic neck dissection for T2/T4 lesions, leaving levels IV and V intact. Their published data indicate an infrequent involvement of levels IV (1.1%) and V (0%) and support previous works establishing the benefit of the removal of levels I-III. Citing a low percentage of occult metastases in their T1 patients (6%), the authors suggested the "watchful waiting" approach to the N0 neck in that patient group.[10]

More recently, a prospective study of 500 patients with T1-T2 tongue, floor of mouth, and buccal squamous cell carcinomas by D'Cruz and colleagues[17] showed that elected neck dissection resulted in higher rates of overall and disease-free survival than therapeutic neck dissection. This study supports more aggressive prophylactic treatment of the neck in early-stage lesions. Other authors have recommended similar rationales for treating the N0 neck, even in early disease, citing the low morbidity of neck dissection and the high rates of occult disease.

When nodal metastasis does occur, the anatomic areas involved are usually levels I-III based on the initial studies by Shah and Byers and colleagues.[18-20] Lower level nodes IV and V are seldomly involved in those studies (0–2%). Zupi and colleagues[10] recorded similar findings, with levels I to III carrying significant risk for occult disease. Levels IV and V mirrored the rates of other studies: 1.1% and 0%, respectively.[10]

The reported extent of lymph node dissection in N0 necks has varied widely in the literature over the past 50 years as knowledge of tumor behavior and anatomic studies of lymph nodes became available. Initial studies included radical neck dissections while more recent results have supported selective neck dissections preserving vital structures. The spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle are no longer routinely sacrificed in N0 necks. The current standard is the functional supraomohyoid neck dissection in N0 necks. Node-positive necks in floor of mouth cancers warrant neck dissections in all cases bilaterally due to the high rate of contralateral metastasis. Based on their findings of high involvement of levels IV and V (16.2% and 2.7%, respectively), Zupi and colleagues[10] recommended a radical neck dissection for all node-positive necks.

Chemotherapy

Systemic therapy for squamous cell cancer of the floor of mouth can be used in various different settings. In the adjuvant setting, it has a limited role in the treatment of lymph node–negative early-stage squamous cell cancers of the floor of mouth. In patients with stage I and II squamous cell cancers, surgical resection remains the primary preferred treatment option.

For higher stage disease, the role of adjuvant chemoradiotherapy after primary resection of patients with high-risk oral cavity, oropharynx, larynx, or hypopharynx squamous cell cancers has been evaluated in two large randomized clinical trials, the results of which may be extrapolated to the patient with floor of mouth cancer. The US Intergroup trial (RTOG 9501) randomized patients with positive margins, two or more positive lymph nodes, or extracapsular spread to receive radiotherapy alone or radiotherapy with concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 of the adjuvant phase of treatment.[21,22] This Intergroup trial did not show improvement in overall survival but there was a statistically significant

improvement in locoregional control and progression-free survival. The European Organization for Research and Treatment of Cancer (EORTC 22931) trial also compared the same treatments in patients with resected high-risk head and neck squamous cell cancers. High risk was defined as T3 or T4 tumors with any nodal stage but also included additional high-risk features such as perineural invasion, vascular invasion, and level IV or V lymph node involvement in patients with oral or oropharyngeal squamous cell cancers. The EORTC 22931 trial reported significant improvement in all survival outcomes (progression-free survival: 47% vs. 36%, $P = .04$; 3-year overall survival: 53% vs. 40%, $P = .02$) in favor of the concurrent cisplatin radiation. Combined analysis of these two trials identified the addition of cisplatin to radiotherapy to result in improved overall survival in patients with extracapsular nodal spread or positive margins.[23]

In patients with stage I or II floor of mouth squamous cell cancer who are not candidates for surgical resection, radiotherapy alone is recommended. The 5-year survival for these patients is greater than 80% and therefore the addition of systemic therapy is not required. For higher stage disease, concurrent chemoradiation offers advantage over radiation alone. The benefit of adding concurrent chemotherapy with radiation was evaluated in the meta-analysis of chemotherapy in head and neck cancer (MACH-NC) analysis. The analysis included 93 randomized studies with more than 16,000 patients with locally advanced head and neck squamous cell cancers; a small but significant improvement in overall survival (absolute benefit of 4.5% at 5 years) for concurrent chemoradiotherapy compared with radiotherapy alone was reported.[24,25] A subsequent updated analysis confirmed that the benefit of adding concurrent chemotherapy to radiation was seen in all tumor sites of head and neck squamous cell cancers, including oral cavity squamous cell cancers.[26] Concurrent high-dose cisplatin with radiation remains the standard treatment option, but other treatment regimens that incorporate carboplatin, 5-fluorouracil, and taxanes may also be considered.[27,28] Targeted therapy concurrent with radiation is also being explored. Epidermal growth factor (EGFR) is highly expressed in head and neck cancers and expression is inversely associated with prognosis. In unresectable disease of the oropharynx, larynx, and hypopharynx, definitive intent anti-EGFR therapy with weekly cetuximab and radiation was compared with radiation alone.[29,30] Regional failure-free survival was 24.4 months versus 14.89 months ($P = .005$), and 3-year overall survival was 57% versus 44% ($P = .02$), with both being more favorable in the cetuximab arm. The data can be extrapolated to patients with floor of mouth cancers in situations precluding the use of cisplatin, such as performance status, age, and comorbid disease.

Surgical resection remains the treatment of choice for patients with T1, T2, or T3 node-negative squamous cell cancers. At present, no data support the use of adjuvant chemoradiotherapy in patients with resected node-negative T1, T2, or T3 cancers. For any T stage with node-positive disease, adverse risk features need to be evaluated carefully upon pathologic examination. Adjuvant chemoradiotherapy is indicated for high-risk characteristics, such as extracapsular nodal spread and positive margins, and may be given consideration for other features such as multiple positive nodes or perineural/perivascular/lymphatic invasion.

When surgical resection is not an option due to patient characteristics or disease features, definitive intent concurrent chemoradiotherapy is a treatment option, even for node-negative disease. However, the decision to proceed with concurrent chemoradiation versus radiation alone must be guided by the treating physicians' clinical judgment in the setting of a multidisciplinary approach. The caveat is that these conclusions are limited by the fact that clinical trials evaluating chemotherapy include floor of mouth squamous cell cancers as a subsite in the general category of oral cavity cancers and outcomes specific to patients with floor of mouth squamous cell cancers are generally unavailable.

Systemic chemotherapy is helpful in patients with locally advanced and distant metastatic disease. Single-agent chemotherapy or targeted therapy, or else immunotherapy, helps palliate symptoms, shrink disease, and prolong life in patients with incurable metastatic disease.

Role of Radiation Therapy in Management of Squamous Cell Carcinoma of the Floor of Mouth

Although the majority of early-stage tumors of the floor of mouth are treated with surgical resection, radiation therapy has been shown to provide comparable control for T1 and early T2 tumors.[31-33] Radiation therapy is associated with significant risk of soft tissue and bone necrosis, making upfront surgery the preferred approach for most patients. Very early superficial tumors, less than 1 cm in size, can be managed with brachytherapy or with an intraoral cone alone. Larger T1 tumors and T2 tumors are associated with a significant risk of occult nodal metastasis.[34,35] Definitive radiation therapy for these patients involves the combination of external beam radiation therapy with a boost using either brachytherapy or an intraoral cone. When brachytherapy is used, the external beam component is delivered first to allow for regression of the primary tumor. When an intraoral cone is used, the boost is delivered first to ensure that the entire primary tumor is well visualized and covered adequately. The specific techniques employed have been well described elsewhere and are beyond the scope of this chapter. Definitive radiation therapy with or without cisplatinum may be considered for patients with unresectable disease or in patients who refuse surgery. In addition, palliative radiation therapy is a reasonable option for patients with medically inoperable symptomatic tumors or in patients with metastatic disease and a symptomatic primary tumor.

Because surgical resection of the primary tumor and neck dissection is the initial treatment for the vast majority of patients with squamous cell carcinoma of the floor of mouth, radiation therapy is generally administered postoperatively. The risk of local recurrence is increased in the presence of T3 or T4 primary tumors, close or positive margins, perineural invasion,

and lymphatic space invasion.[36] Postoperative radiation therapy is generally recommended for patients with these tumor characteristics to reduce the risk of local recurrence. Regional recurrence in the neck is increased in the presence of multiple positive nodes, extracapsular extension of tumor, and with an involved node larger than 3 cm in size. Again, postoperative radiation therapy is generally recommended for these patients. Randomized trials have documented improved outcome with the addition of cisplatinum to postoperative radiation therapy in the setting of positive surgical margins or extracapsular nodal extension.[21-23,37] The combination of postoperative radiation therapy and cisplatinum is recommended for patients with these tumor characteristics who are healthy enough to tolerate the increased toxicity of the combined approach.

Radiation therapy can be delivered using 3D conformal techniques or with intensity-modulated radiation therapy (IMRT). Because of the risk of occult nodal involvement, the primary tumor and regional lymph nodes on both sides of the neck are included in the treatment fields. When radiation therapy alone is used, a number of fraction schemes can be used. Using conventional fractionation, a dose of 70 Gy/35 fractions is delivered to the primary tumor and involved cervical lymph nodes. The areas at risk for harboring subclinical disease in the neck and supraclavicular fossa are treated with a dose of between 44 and 50 Gy using 2-Gy fractions. When IMRT is used, the areas at risk for subclinical involvement concurrently receive a dose of between 54 and 63 Gy at 1.6 to 1.8 Gy/day while the area of gross disease receives the full dose of 70 Gy in 35 fractions. Alternative fractionation schemes include concomitant boost accelerated radiation therapy or hyperfractionated radiation therapy. When primary radiation therapy is delivered with the addition of cisplatinum, a dose of 70 Gy in 35 fractions using conventional fractionation is most commonly used.

When postoperative radiation therapy is indicated, the entire surgical bed is included within the treatment fields. Areas at high risk receive a dose of 60 Gy in 30 fractions. Areas of particularly high risk (i.e., positive margins) are treated with an additional 6 Gy in 3 fractions. The entire surgical bed receives a dose of 56 Gy and the areas at risk for subclinical disease that lie outside of the dissected area receive a dose of 50 Gy. When IMRT is used, dose painting can be used to deliver a dose of 60 Gy in 30 fractions to the high-risk volume while delivering doses of between 54 and 57 Gy to lower risk areas of the surgical bed and undissected neck. Postoperative radiation therapy is ideally initiated within 4 to 5 weeks of surgery, although delayed wound healing may lead to a longer time interval.

Prognosis

In general, patients with early-stage oral cavity cancers do well, which is true of stage I floor of mouth cancers. Guillamondegui and colleagues showed surgical resection was very effective in T1 lesions with acceptable complications and good local control, and an 89% survival rate at 4.5 to 8.5 years of follow-up.[38] Published survival rates vary for 2 years and 5 years, but even with early detection and definitive treatment, these patients can be difficult to cure. Yco and Cruickshank published an 89% survival rate at 2 years and 82% at 5 years.[2] This is similar to other results by Ildstad with 90% at 2 years and 78% at 5 years.[13] With early detection and the appropriate surgical treatment outlined above, T1 and T2 cancers are, for the most part, curative disease.

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22

Advanced Floor of Mouth Cancer

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Squamous cell carcinoma of the floor of mouth is an aggressive and potentially lethal malignancy that warrants special consideration among all oral subsites. The proximity of this disease to the mandible and poor mechanical barrier to spread in part explain the propensity for rapid local progression and challenging locoregional control.[1] Nodal involvement lowers the survival rate considerably. Despite the high incidence of nodal metastasis and poor prognosis, the treatment of the clinically negative neck (cN0) in patients with floor of mouth cancer remains controversial. This chapter addresses our institutional philosophy and approach in the management of stage II floor of mouth cancer in regard to surgical approach, adjuvant radiotherapy, and rehabilitation.

Grading and Staging

Grading and staging of malignancies carry important information regarding the prognosis of cancer. Grading refers to the qualitative assessment of the relative differentiation of the cells at a histologic level and has not been found to be highly correlated with prognosis in patients with oral cancer. Staging, on the other hand, is strongly correlated with 5-year survival and is more anatomically descriptive. The American Joint Committee on Cancer (AJCC) has standardized staging in terms of primary tumor size (T), nodal involvement (N), and metastasis (M).[2] The various TNM categories are then grouped into stages that reflect both the extent and prognosis of the tumor.

T2 floor of mouth squamous cell carcinoma refers to a primary tumor of the floor of the mouth[2] whose greatest diameter is more than 2 cm but not more than 4 cm (Table 22.1). By definition, a T2 cancer automatically qualifies as a stage II, III, IVB, or IVC cancer, depending on lymph node metastasis based on the AJCC cancer staging (Table 22.2). Stage II T2 represents tumor confined to the primary site only. Stage III T2 denotes a primary tumor with single ipsilateral cervical metastasis 3 cm or less in diameter. Stage IV disease represents more extensive regional or distant metastasis.

Epidemiology

Oral and pharyngeal cancer, grouped together, is the sixth most common cancer in the world. It was estimated that in 2014, 42,440 new cases were diagnosed and 8,390 patients died of cancer of the oral cavity and pharynx in the United States.[3] Malignant neoplasms of the oral cavity account for approximately 30% of all head and neck cancers and for 5% of all cancers in the United States.

Incidence

There is a wide geographic variation in the incidence of floor of mouth cancer. Although oral squamous cell carcinoma accounts for 5% of all cancers in the United States, it accounts for 50% of all cancers in southeast Asia. This difference can be explained by cultural preferences for different types of tobacco delivery products. The age-adjusted SEER incidence rate in the United States is 11 per 100,000 for cancer of the oral cavity and pharynx.[3] The age-adjusted SEER incidence rate for floor of mouth cancer is 0.6 per 100,000.[3] There is a higher incidence rate in males compared to females: 0.8 per 100,000 in males, compared with 0.3 per 100,000 in females[3] (Tables 22.3 and 22.4). According to the SEER cancer statistical review, the rate was marginally higher among the White population, at 0.6 per 100,000 compared to 0.5 per 100,000 among the Black population.[3]

Survival and Mortality

The estimated 5-year survival rate for floor of mouth cancer is 51.4%,[3] which is strongly influenced by stage at presentation. The best outcome is for localized floor of mouth cancer, with 74.5% of patients surviving at 5 years. By comparison, the 5-year survival rate is 38.1% and 20.4% for regional and distant disease, respectively[3] (Table 22.5). Survival is highest among White females (57.6) and lowest in Black males (35.4%).[3] SEER data for United States report mortality rates of 3.8 per 100,000 in men and 1.4 per 100,000 in women for oral cavity and pharyngeal cancer overall.

Trends

The incidence of floor of mouth cancer has changed over time. In the United States, rising trends were noticed for incidence

TABLE 22.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor ≥2 cm and ≤4 cm in greatest dimension
T3	Tumor ≥4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease
T4a	Moderately advanced local disease. (lip) Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose); (oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face). Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base or encases carotid artery
Regional Lymph Nodes: Clinical (cN) Oropharynx (p16–) and hypopharynx	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none > 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N3	Lymph node(s) > 6 cm and ENE(–) or metastasis in any node(s) and clinically overt ENE(+)
N3a	Lymph node(s) > 6 cm and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathologic ENE should be recorded as either ENE(–) or ENE(+)
Regional Lymph Nodes: Pathologic (pN) Oropharynx (p16–) and hypopharynx	
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
pN2	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none > 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE(–)
pN2a	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–)
pN2b	Metastases in multiple ipsilateral lymph nodes none > 6 cm in greatest dimension and ENE(–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none > 6 cm in greatest dimension and ENE(–)
pN3	Lymph node(s) larger than 6 cm and ENE(–); or metastasis in a single ipsilateral node > 3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)
pN3a	Lymph node(s) > 6 cm and ENE(–)
pN3b	Metastasis in a single ipsilateral node > 3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)

Continued

TABLE 22.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer—cont'd

Distant Metastasis (M)	Oropharynx (p16–) and hypopharynx
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

From Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In Amin MB, et al, editors: *AJCC cancer staging manual*, ed. 8. 2017, Springer. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

TABLE 22.2 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer

Clinical Stage			Then the Stage
When T is…	And N is…	And M is…	Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0,N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Registry Data Collection Variables

1. Lip location (external or vermilion border)
2. ENE clinical: ENE(+) or (–)
3. ENE pathologic: ENE(+) or ENE(–)
4. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
5. Perineural invasion
6. Lymphovascular invasion
7. p16/HPV status
8. Performance status
9. Tobacco use and pack-years
10. Alcohol use
11. Depression diagnosis
12. Depth of invasion (mm)
13. Margin status (grossly involved, microscopic involvement)
14. Distance of tumor (or moderate/severe dysplasia) from closest margin
15. WPOI-5

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated

From Ridge JA, Lydiatt WM, Patel SG, et al: Lip and oral cavity. In Amin MB et al, editors: *AJCC cancer staging manual*, ed 8. 2017, Springer. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

in both genders and all races from 1975 to 1982 for floor of mouth cancer with an annual percentage change (APC) of 1.1%.[3] However, trends have significantly fallen, with an APC of –2.3% for all races and both sexes from 1982 to 2011.[3] This trend may be the result of changing patterns of cigarette smoking.

Risk Factors

There are multiple risk factors that are known to contribute to the causation of oral cancer. Warnakulasuriya[4] classified these risk factors as established, strongly suggestive, possible, and speculative based on global evidence (Table 22.6). In United States, tobacco and alcohol[5] are the most relevant etiologic factors in floor of mouth cancer. Betel quid usage[6] is also strongly established as causing floor of mouth cancer, but mostly in developing nations because of cultural variability and different oral habits.

Tobacco

All forms of tobacco are carcinogenic. Various studies have shown that 90% of patients with oral cancer use tobacco, and the relative risk of developing oral cancer increases with the amount smoked and the duration of the habit.[7,8] Tobacco use is the strongest risk factor, especially for oral cavity and other head and neck cancers.

Note that there may be a distinct difference between oral cancers that develop in smokers compared with those in nonsmokers. In a study by Perry and colleagues[9] that examined sites of origin of oral cavity cancer in nonsmokers versus smokers, a much higher rate of lateral tongue and floor of mouth cancer was reported in smokers and ex-smokers than in nonsmokers. It is postulated that the absorption of the myriad topical carcinogens in cigarette smoke is higher in the floor of the mouth. This is due to the sump effect of pooling carcinogens in saliva, local rubbing, and much thinner floor of mouth mucosa. In recent years, cigar and also pipe smoking in the form of hookah use has increased in United States. It has been postulated that this type of smoking has four to ten times more mortality from oral cancer compared to nonsmokers.[10]

The risk of developing a second primary tumor increases in patients who continue to smoke after the diagnosis of an index aerodigestive tract tumor. Approximately 40% of patients who continue to smoke after treatment of their oral cancer develop

TABLE 22.3 Age-Adjusted SEER Incidence by Sex, Race and Age* (2007–2011)

Site	Total	Sex		Race			Age		
		Males	Females	White	Black	Other	All	<65 Years	≥65 Years
All oral cavity and pharyngeal cancer	11.0	16.5	6.2	11.4	9.4	8.8	11.0	6.6	40.9
Floor of the mouth only	0.6	0.8	0.3	0.6	0.5	0.3	0.6	0.3	2.2

*SEER 18 areas. Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population (19 age groups—Census P25-1130).

TABLE 22.4 SEER Incidence Stage Distribution by Site* (2007–2011)

Site	Localized	Regional	Distant	Unstaged
All oral cavity and pharyngeal cancer	33%	45%	17%	5%
Floor of the mouth only	44%	46%	7%	4%

*SEER 18 areas. Rates are per 100,000 and are age-adjusted to the 2000 U.S. standard population (19 age groups—Census P25-1130).

TABLE 22.5 Five-Year Relative Survival by Site and Stage (2004–2010)

Site	All Stages	Localized	Regional	Distant	Unstaged
All oral cavity and pharyngeal cancer	62.7%	82.7%	60.5%	37.3%	49.3%
Floor of the mouth only	51.4%	74.5%	38.1%	20.4%	42.0%

*The standard error is between 5 and 10 percentage points.

TABLE 22.6 Risk Factors for Oral Cancer and Precancer

Established	Strongly Suggestive	Possible	Speculative
Smoking	Sunlight	Viruses	Mouthwashes
Chewing tobacco	Radiation	Immune deficiency	Maté drinking
Snuff dipping		Dentition?	Periodontal disease
Alcohol misuse		Ethnicity?	Familial
Betel quid			
Syphilis			

second cancers of the upper aerodigestive tract, compared to 6% of those who completely stop smoking.[11] Exposure to carcinogens via active or passive smoking has substantially declined over the past few decades in many economically developed countries, where the health hazards of smoking are well recognized and tobacco prevention programs have long been established.[12,13] Smoking prevalence in the United States peaked in the 1960s and has since declined.[12]

The evidence for smokeless tobacco causing oral and pharyngeal cancer is also established.[14-16] There are three different types of smokeless tobaccos: chewing tobacco, wet snuff, and dry snuff. Thick areas of leukoplakia appear in areas of smokeless tobacco placement, which eventually may undergo malignant transformation.

More than 60 carcinogens are present in cigarette smoke, and at least 16 in unburned tobacco have been identified. The most important are tobacco-specific nitrosamines, such as 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*-nitrosonornicotine (NNN); polycyclic aromatic hydrocarbons (PAH), such as benzo[*a*]pyrene; and aromatic amines. In particular, NNK, NNN, and PAH have been causally linked to oral cancer. The activity of carcinogens is generally exerted through DNA adducts.[17,18]

Alcohol

Regular alcohol consumption is a dose-dependent risk factor in the pathogenesis of floor of mouth cancer. Among individuals

consuming four to five alcoholic drinks daily, the risk for cancer of the oral cavity is two- to threefold higher than among nondrinkers.[19,20] Overall, 7–19% of oral cancers are attributable to heavy alcohol drinking.[21] The addition of alcohol consumption to tobacco chewing/smoking further increases the risk for oral cancer. A case-control study demonstrated an 11-fold greater risk of developing oral squamous cell carcinoma with concomitant tobacco chewing, cigarette smoking, and heavy alcohol drinking.[22] Tobacco and alcohol are synergistic rather than just additive in their effect of inducing dysplastic or premalignant changes. Acetaldehyde is responsible for the oral carcinogenic effect of ethanol, owing to its multiple mutagenic effects on DNA. Other minor components found in some alcoholic beverages, such as nitrosamines, acrylamide, and oxidized polyphenols, are classified as probable carcinogens in humans, with animal experiments demonstrating mutagenic activity on oral epithelial cells.[23]

Potentially Malignant Disorders

The prognosis and overall survival of oral cancer patients is dependent on the early detection of any lesion that might identify a patient with higher risk for malignant transformation. Given that many oral squamous cell carcinomas of the oral cavity are preceded by a precursor lesion, early detection remains an aspirant outcome metric. Leukoplakia and erythroplakia were traditionally known as two precancerous or premalignant lesions of the oral mucosa. The term *precancerous/premalignant* means that all lesions classified as such have a "precancerous nature," implying that all of them will eventually become malignant. However, it became clear that even clinically normal mucosa may harbor histologic dysplasia and, in some instances, molecular aberrations of early malignant transformation. This is most worrisome in that such changes may be found in patients without any phenotypic or clinically detectable signs or symptoms. The consensus was then to introduce the term *potentially malignant disorders* (PMDs), reflecting the more generalized mucosal involvement in these patients.[24] It remains a challenge to predict the behavior of any of these lesions.

Leukoplakia is defined as a white patch or plaque that cannot be characterized clinically or pathologically as any other disease. Two main clinical types of leukoplakia are recognized: *homogeneous* and *nonhomogeneous* leukoplakia. The distinction between these is purely clinical, based on surface color and morphologic (thickness) characteristics, and does have some bearing on the outcome or prognosis. Homogeneous lesions are uniformly flat, thin, and exhibit shallow cracks of the surface keratin. The risk of malignant transformation is relatively low. Nonhomogeneous lesions carry a much higher risk of malignant transformation.

Erythroplakia when compared to leukoplakia is considered to have a greater potential than leukoplakia for malignant transformation. The World Health Organization defines erythroplakia as a fiery red patch that cannot be characterized clinically or pathologically as any other definable disease. It must be noted that erythroplakia is often flat with a smooth or granular surface. Numerous other red patches/macules that could arise on the oral mucosa should be excluded before considering erythroplakia as the diagnosis. Erythroplakia seem to be relatively uncommon on their own and often present as mixed red-and-white lesions and considered under the term *erythroleukoplakia*.

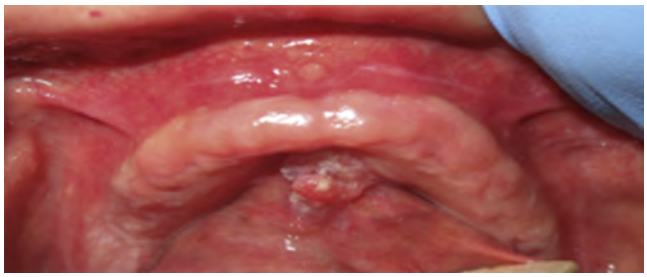
Oral lichen planus (OLP) is a chronic inflammatory disorder and a cell-mediated immune condition of unknown etiology, in which T lymphocytes accumulate beneath the epithelium of the oral mucosa and increase the rate of differentiation of stratified squamous epithelium, resulting in hyperkeratosis and erythema with or without ulceration.[25] Whether oral lichen planus carries an increased risk of developing a squamous cell carcinoma is controversial. Unfortunately, the issue of malignant transformation in OLP is blurred by the frequent lack of clinicopathologic correlation in the diagnosis. Furthermore, there is the somewhat confusing histopathologic term *lichenoid dysplasia* and lesions termed "lichenoid lesions," mainly in cases of a bandlike lymphocytic infiltrate beneath the dysplastic epithelium. The reported annual malignant transformation rate for OLP is usually well below 1%.[26]

Other potentially malignant disorders have been reported in the literature, such as oral submucous fibrosis, but are rarely seen in the United States.

Clinical Presentation and Pertinent Anatomy

The clinical presentation of floor of mouth cancer varies. Many lesions may be exophytic, endophytic, leukoplakic, erythroplakic, or erythroleukoplakic. They are likely to arise from a preexisting leukoplakia or erythroplakia. Early lesions appear as slightly gray or gray-white plaques, which may appear translucent, fissured, or wrinkled. As the lesion progresses, it becomes thicker, and often acquires a distinctly white appearance. Some lesions eventually demonstrate scattered patches of redness. These intermixed red-and-white lesions are called speckled leukoplakia or erythroleukoplakia. They usually have a sharply demarcated border. As these lesions undergo a malignant transformation, they usually become exophytic. An exophytic lesion typically has a surface that is irregular, fungating, papillary, or verruciform, and its color may vary from normal to red to white, depending on the vascularity. As the tumor enlarges, ulceration occurs, and it feels indurated on palpation (Fig. 22.1).

Squamous cell carcinoma of the floor of mouth usually occurs anteriorly near the midline and spreads to contiguous structures radially including the tongue and mandible. They often originate within 2 cm of the anterior midline with extension toward the gingiva and periosteum of the mandible. The path of invasion differs based on the dentate status of the patient. In dentate patients, the spread of the tumor occurs through the alveolar socket of the teeth to the cancellous bone and then to the inferior alveolar canal and the basal bone. However, in an edentulous patient, the tumor invades directly into the porous cancellous bone of the remaining edentulous alveolar process and then to the basal bone and the inferior alveolar canal. Slootweg and Müller studied the tumor-mandible interface in 45 patients.[27] The periosteum proved to



• **Fig. 22.1** An early squamous cell carcinoma of the anterior floor of mouth, with a typical clinical presentation including erythema, ulceration, and leukoplakia.

be an effective barrier to tumor invasion when tumor abutted the bone clinically. Tumor spread through periosteal lymphatics was not observed in the absence of tumor-mandible fixation. McGregor and MacDonald showed the resistance of the lingual periosteum to tumor invasion.[28] Tumor invaded the mandible from above, gaining access into the cancellous bone via the alveolar bone. From the previously cited literature, one could conclude that if the lingual periosteum is resistant to tumor invasion, and there is no clinical or radiologic evidence that invasion has occurred, then the mandible can be spared in most cancers of the floor of the mouth. A partial or marginal mandibulectomy can be performed to gain better exposure to the cancer of the floor of the mouth and still preserve the mandible. A limiting factor would be the preservation of the blood supply to the mandibular remnant and pathologic fracture. The blood supply to the mandible changes over time. In patients older than 50 years, subperiosteal vessels, rather than the inferior alveolar artery, are the predominant blood supplies to the anterior mandible. Bradley[29,30] has shown that the periosteal blood supply is composed of branches of the buccal, lingual, and facial arteries. Hamparian[31] found that the mental arterial plexus vascularized the anteroinferior mandible and was supplied by branches of the facial and lingual arteries. These vessels are carried in muscular branches in the genioglossus, mylohyoid, and digastric muscles.

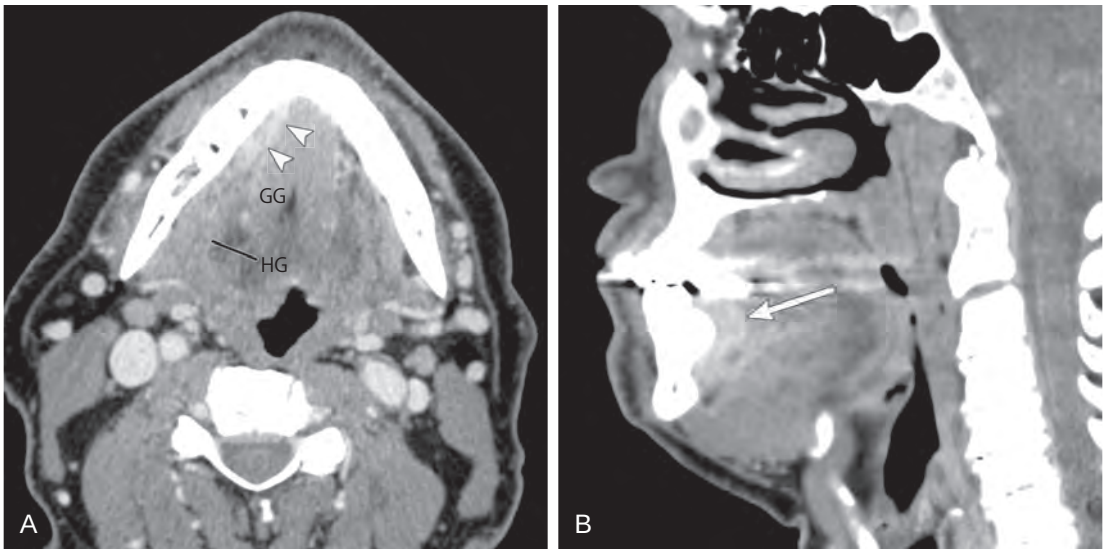
Early T2 floor of mouth cancers are less often seen in the lateral or posterior floor. However, tumors near the orifice of the submandibular duct may track along the duct. Tumors may also demonstrate perineural spread along major nerves including the proximate lingual nerve. As cancer encroaches on the lingual cortex of the mandible, it extends downward through the mylohyoid into the submandibular space to involve the submandibular gland by direct extension. Tumors frequently invade the anterior musculature of the tongue and track inferiorly as far as the hyoid bone and, in rare instances, into the prelaryngeal or pre-epiglottic space.

Imaging of T2 Squamous Cell Carcinoma

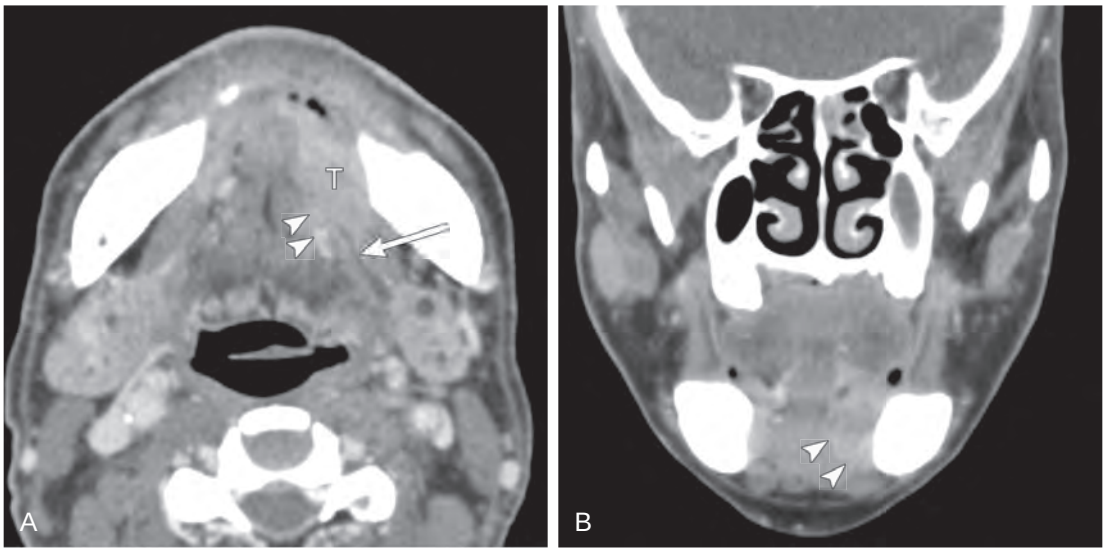
Imaging plays an important role in management of patients with T2 squamous cell carcinoma of floor of mouth, both for evaluation of the primary lesion and regional/distant metastasis. The most-used imaging modalities for diagnosing floor of mouth cancers include computed tomography (CT) and magnetic resonance imaging (MRI). More recently, ^{18}F-fluorodeoxyglucose positron emission tomography combined with CT (^{18}F-FDG PET/CT) was introduced to clinical practice and now plays a crucial role in initial staging, evaluation of treatment response, and surveillance. Floor of mouth tumors have a tendency to spread submucosally; therefore tumor extension into the deeply seated tissue planes can be easily missed by clinical examination alone. Even if the primary tumor has been clinically diagnosed as T1/T2 disease on the basis of inspection, imaging is an important adjunct to exclude a greater extent of the lesion, particularly submucosal extension, and invasion into the adjacent tissue such as mandibular bone, deep extrinsic muscle, and neurovascular bundle. Therefore, cross-sectional imaging is mandatory for completing the staging process and should be included in the diagnostic work-up. CT is often the first cross-sectional imaging modality for floor of mouth tumors because of its wider availability, lower cost, shorter scanning time, and higher success rate compared with MRI, even though the patient is exposed to ionizing radiation. Further, CT is useful to evaluate cortical bone, particularly tumor/bone interface. On the other hand, MRI has higher contrast resolution and can better delineate tumor extension. MRI is superior for evaluation of bone marrow abnormalities, although evaluation of cortical bone is limited. Changes from prior dental treatment such as dental filling/amalgam, dental implants, and braces often cause significant artifact and degrade images on both CT and MRI. However, the degree of artifact or image degradation is usually different between these two modalities, and actually CT and MRI are often complementary.

Most floor of mouth tumors originate near the anterior midline of the floor of mouth and tend to spread horizontally or inferiorly (Fig. 22.2), as the floor of mouth musculature generally forms a relative barrier to tumor spread. Given their location, floor of mouth tumors can obstruct the ostia of the submandibular ducts, resulting in duct dilatation or obstructive inflammatory changes of the submandibular gland (Figs. 22.3 and 22.4). Often MRI provides more useful information regarding local extension of the lesion than CT, which can be significantly degraded by streaking artifact from dental fillings or implants, although MRI is also vulnerable to metallic or susceptibility artifact from metallic substance or air-bone interface (see Fig. 22.4). MRI has superior soft tissue contrast compared to CT and often provides better delineation of the tumor; it is particularly useful in post-treatment evaluation (Fig. 22.5). Involvement of the neurovascular bundles has negative effects on prognosis. It is also important for surgical planning. Vascular invasion also increases the risk of cervical nodal metastases. The presence of aggressive tumor margins (see Fig. 22.2A), invasion of the sublingual space, and tumor extension adjacent to the vessels within the sublingual space (Fig. 22.6) have been shown to increase the likelihood of vascular invasion and perineural spread of tumor.[32]

For T2 floor of mouth squamous cell carcinoma (SCC), mandibular invasion needs to be accurately assessed because it often has a direct impact on therapy and almost certainly influences quality of life. Contrast-enhanced CT offers high spatial and temporal resolution and remains the preferred

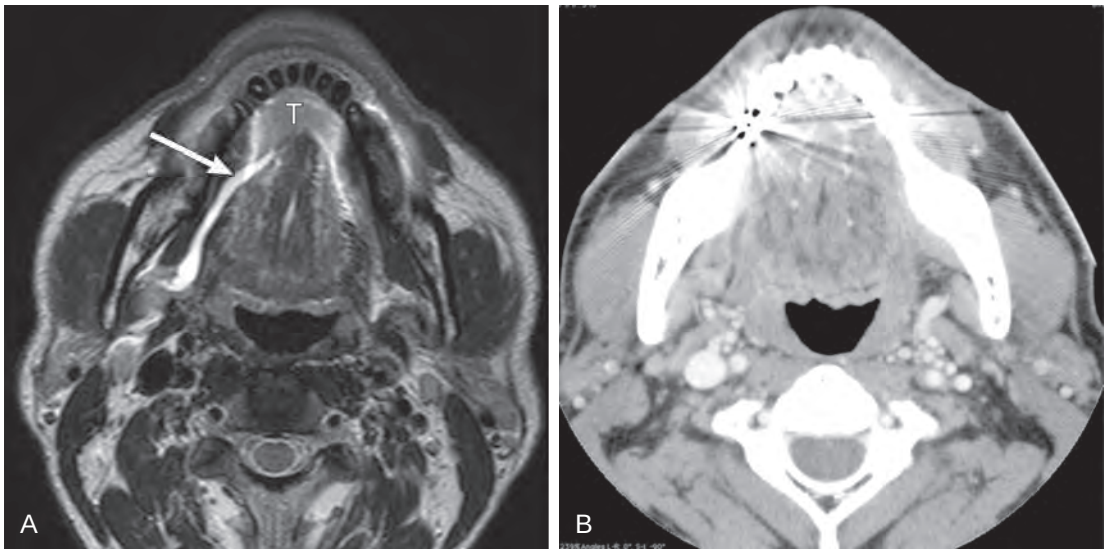


• **Fig. 22.2** **A**, Axial contrast-enhanced CT image demonstrates an ill-defined lesion of the right floor of the mouth *(arrowheads)*. There does not appear to be invasion to the adjacent mandible and extrinsic muscle (*GG,* genioglossus; *HG,* hyoglossus). **B**, Sagittal image demonstrates the limited tumor of the floor of the mouth.

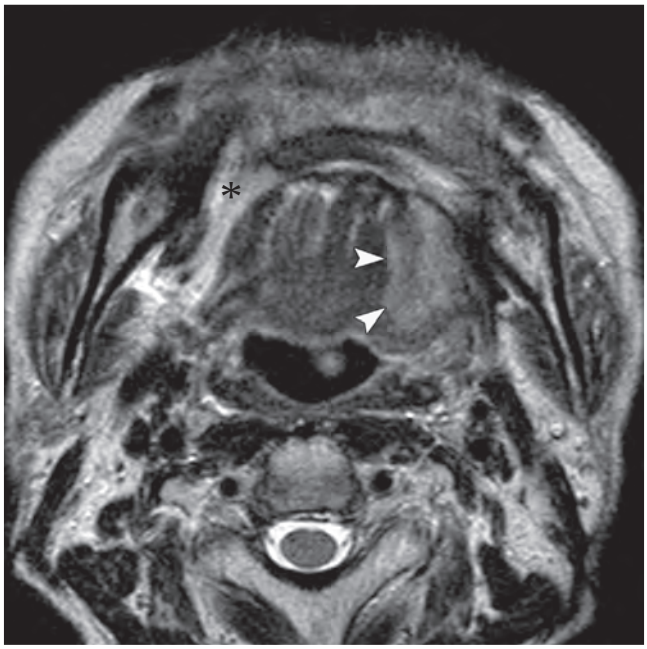


• **Fig. 22.3** Squamous cell carcinoma of the left floor of mouth in a 52-year-old man. **A**, Axial contrast-enhanced CT image demonstrates a mass at the left floor of mouth. The tumor *(T)* appears to remain lateral to the left lingual neurovascular bundle *(arrowheads),* and the obstructed submandibular duct is shown *(arrow)*. **B**, Coronal image demonstrates the tumor extension to the myohyoid muscle *(arrowheads)*.

imaging modality to evaluate for mandibular invasion (Fig. 22.7). Conventional CT with 3-mm sections in bone and soft tissue algorithms had a high specificity of 87% for mandibular invasion by SCC without compromising sensitivity (96%).[33] The advantage of 16-row and greater multidetector CT (MDCT) is that it can provide sections as thin as 0.5 or 0.625 mm. This enables isotropic multiplanar reformations in any plane and, when used with bone algorithms, enables high-resolution views of buccal, lingual, and occlusal cortices, increasing the sensitivity for detecting cortical erosion. MRI, on the other hand, is excellent in terms of tissue resolution and has thus been reported to be a useful diagnostic modality that enables highly sensitive evaluation and provides strong negative predictive values for mandibular invasion.[34,35] However, there are many unresolved problems with MRI, such as difficulty in assessing the extent of tumor invasion masked by tumor-induced secondary changes and post-inflammatory fibrosis. Imaizumi and colleagues,[36] comparing CT with MRI in 51 patients with oral cavity squamous cell carcinomas (OCSCC), found MRI to overestimate cortical erosion and inferior alveolar canal involvement. Correlating findings on clinical examination with combinations of imaging methods and diagnostic algorithms using MRI/CT has the potential to improve specificity.



• **Fig. 22.4** Squamous cell carcinoma of the floor of mouth (FOM) in a 62-year-old man. **A**, Axial T2-weighted MR image demonstrates an ill-defined tumor *(T)* arising from the right anterior FOM with intermediate signal intensity. The obstructed left submandibular duct is shown *(arrow)*. **B**, Axial contrast-enhanced CT obtained at the same level shows the moderate metal artifact, and the tumor cannot be detected in the floor of mouth area.



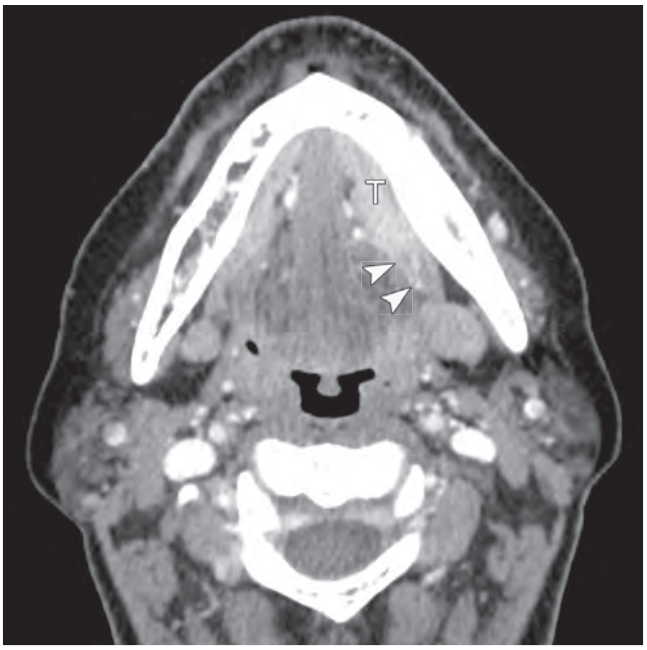
• **Fig. 22.5** Squamous cell carcinoma of the floor of the mouth, same patient as Fig. 22.2, following resection of the floor of mouth tumor and flap reconstruction. Axial T2-weighted MR image shows the hyperintense signal within the left lateral aspect of the tongue, consistent with denervation effect from left hypoglossal nerve injury *(arrowheads)*.

CT and MRI used for staging the primary have comparable accuracy for evaluating neck nodes and extranodal spread.[37] The most important feature indicative of metastasis is necrosis. However, because not all metastatic nodes present with macroscopic necrosis, various size criteria have been used. A minimum axial diameter of more than 11 mm for level II nodes and 10 mm for all other nodes is considered abnormal. For a group of nodes in the lymphatic basin of the primary, the minimum axial diameter criteria decreases to more than 9 mm for level II nodes and 8 mm for other nodes.[38] Despite these criteria using CT and MRI, the false-positive and false-negative rates vary between 15% and 20%.[38] FDG-PET/CT is superior to CT or MRI alone for initial detection of nodal metastasis in head and neck cancers, and PET/CT is superior to anatomic imaging alone for evaluation of recurrent disease and distinction from scar tissue.[39] However, management for patients with a clinically negative (cN0) neck is still controversial. A meta-analysis by Kyzas and colleagues[40] evaluating PET/CT in SCC of the head and neck found that sensitivity of ^{18}F-FDG PET was only 50%, whereas specificity was 87% for cN0 patients. The National Comprehensive Cancer Network (NCCN) guidelines recommend use of PET/CT only in stage III or IV cancers when management may be altered due to detection of distant metastases.[41] Hence, the current role of PET/CT for pretreatment nodal evaluation in T2 floor of mouth cancers lies in detecting the extent of regional nodal metastases in the N-positive neck that could alter radiation therapy fields or extent of neck dissection.

Surgical Management: Resection of T1/T2 Squamous Cell Carcinoma

Approach

The confines of the floor of the mouth do not always allow for easy circumferential access to achieve 1-cm surgical margins. Accessory surgery techniques are often employed, especially in tumors larger than 2 cm. The type of surgical approach depends principally on the size and location of the tumor in the floor of the mouth, as well as the surgeon's comfort and experience with the surgical procedure. Although oncologic



• **Fig. 22.6** Squamous cell carcinoma of the floor of mouth in a 56-year-old woman. Axial contrast-enhanced CT image demonstrates an ill-defined and infiltrative tumor in the left floor of mouth *(T)*. The tumor invades into the left sublingual space and spreads along the mylohyoid and hyoglossus muscle *(arrowheads)*.

control and survival is still the primary end-point, psychological adjustment, degree of functional deficit, and postoperative appearance are important considerations as well. The oral cavity performs multiple complex tasks, making it sometimes difficult to balance the need for adequate margins with the goal of preserving function and minimizing disfigurement. Indeed, because the mouth is central to speech, swallowing, gustation, and cosmesis, it is closely linked to post-treatment quality of life indicators. Surgical approaches that preserve function, minimize complications, and maximize cosmetic outcome should be encouraged in appropriate patients whenever feasible.

Transoral

Most T1/T2 floor of mouth squamous cell carcinomas can be excised transorally (Fig. 22.8). Such an approach leaves minimal esthetic and functional debility and provides a satisfactory surgical resection. However, management may change depending on the extent to which the lesion is adherent to the periosteum or extends into the deep musculature of the tongue or floor of mouth. Tumor spread typically extends along the surface mucosa and the submucosal soft tissues to approach the attached lingual, buccal, or labial gingiva. From this point, the tumor does not typically invade the intact periosteum and cortical bone toward the cancellous part of the mandible, because the periosteum acts as a significant protective barrier.[42] Instead, the tumor advances from the attached gingiva toward the alveolus, extends through the alveolar process into the cancellous bone, and invades the marrow of the mandible and mandibular canal. If the lesion extends to the gingiva without fixation to the periosteum, a mandible-sparing procedure may be employed. As a general rule, early invasion of the mandible can be treated by marginal mandibulectomy, because the cortical component of the mandible inferior to the roots of the teeth remains uninvolved and can be spared safely.[43] In edentulous patients, the feasibility of marginal mandibulectomy depends on the vertical height of the body of the mandible, although it is common practice to attempt to preserve at least 1 cm of bone.[43]

Pull-Through

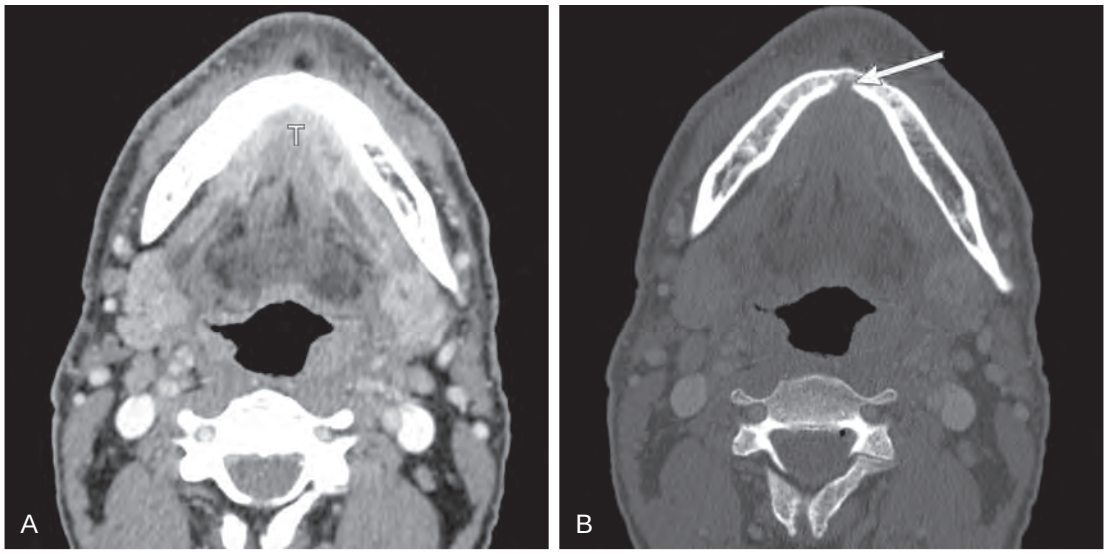
The pull-through approach using mandibular releasing incisions and the visor technique for the resection of floor of mouth cancer is an effective surgical procedure that can facilitate en bloc tumor extirpation. With this technique, an incision is made in a neck crease from mastoid to mastoid and subplatysmal skin flaps are raised initially to the lower border of mandible.[44] At this point the chin and cheek skin flaps are raised, providing excellent visualization of the mandible while preserving the periosteum. On the inner aspect of the mandible, geniohyoid, mylohyoid, and genioglossus muscles are carefully detached. In the mouth, an alveolar crest or lingual gingival sulcus incision is made. The floor of mouth and tongue can then be pulled through into the neck.[45] De-gloving the mandible anteriorly and transecting the mental nerves for later repair can achieve additional access for very posterior tumors (Fig. 22.9).

The advantages of this technique include better cosmetic outcome,[44,46-48] as it avoids facial scarring while maintaining competitive rates of free margins and local recurrence.[47] A utility or apron incision facilitates bilateral neck dissection without the need to modify incisions. The functional outcome with this technique is much debated. It is important to know that accurate reattachment of genioglossus and geniohyoid muscles is essential to restore the oral diaphragm when considering this approach.[48] Failure to achieve this often will lead to poorer speech, swallowing, and chewing abilities.[48]

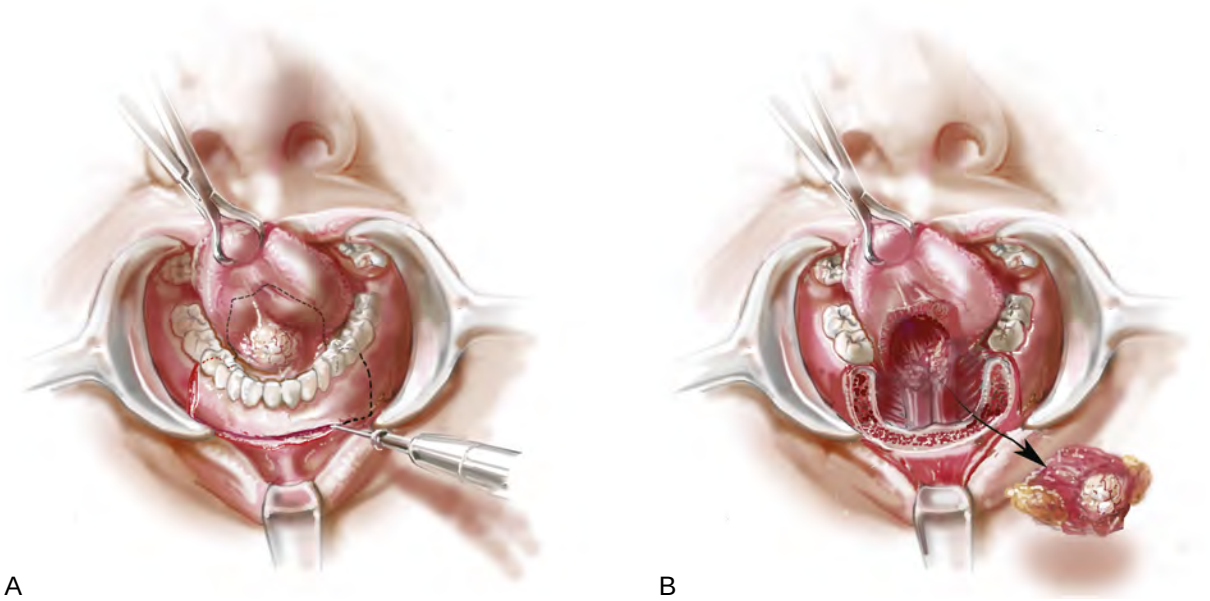
Lip-Split Technique With Mandibulotomy

Lip-split mandibulotomy is a reliable, well-established approach used in the treatment of lateral or posteriorly placed floor of mouth cancer. The vermilion border is incised and the lip divided sagittally. Any one of a number of zigzag or geographic patterns is used as the incision approaches the supramental crease. This jagged incision can be brought down through the mentum or circumferentially around the mentum, preserving the anatomic subunit. The incision is carried down below the mandible and united with the neck dissection in the midline. Bilateral or unilateral cheek flaps are then raised, leaving the periosteum intact. At this point a mandibulotomy is used to access the oral cavity. The lip-split procedure is an alternative to the transcervical approach and has both advantages and disadvantages.

Lip-split mandibulotomy provides excellent surgical access with minimal detrimental esthetic impact. It allows for real-time three-dimensional assessment of tumors compared with other techniques.[48] It is felt that the surgeon has much better control over the anterior margins in this circumstance, which



• **Fig. 22.7** Squamous cell carcinoma of the floor of mouth with mandibular invasion in a 61-year-old man. **A**, Axial contrast-enhanced CT image demonstrates an infiltrative tumor of the bilateral floor of mouth *(T)*. **B**, Axial bone window CT clearly demonstrates the bone erosion *(arrow)*.



• **Fig. 22.8** Transoral anterior floor of mouth resection. **A**, Outline of composite resection of the anterior floor of mouth with marginal mandibulectomy. **B**, Defect following delivery of the specimen.

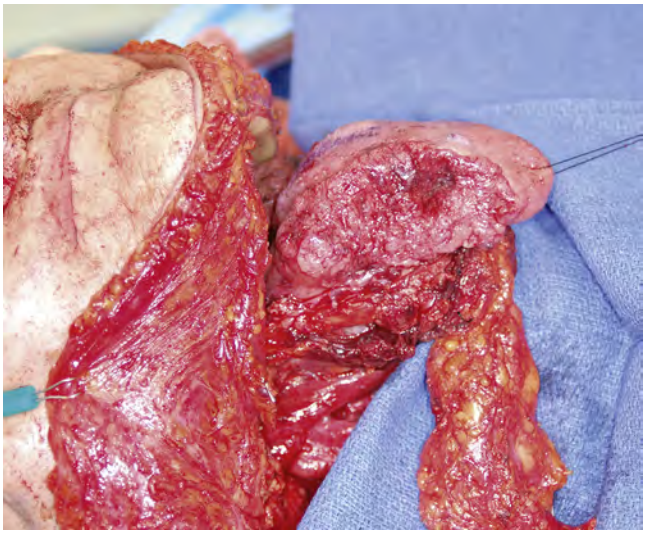
in turn translates into wider tumor margins and better local control. However, some authors have stated that there may be an increased risk of postoperative fistulas, more prominent scarring, notching of the vermilion, and impaired mobility of the lip and chin.[47,49] For some of these reasons, several modifications have been proposed in the literature that improve esthetic results, safety, and functional outcome (Fig. 22.10).

Modifications include a vertical linear incision through the lip and a curved incision through the chin. Mehanna and Devine[50] have proposed a technique where a modified zigzag incision is made and the underlying muscle divided in a linear and vertical fashion. Because the incision and division of muscle are in different planes, a serious breakdown of the wound or formation of a fistula is claimed to be less likely. They have reported that the vertical incision through the muscle (as opposed to zigzag) ensures that the minimum length of muscle is divided, which reduces the inherent amount of muscle trauma and long-term fibrosis.

Management of the Primary

Wide Local Excision

Preoperative planning and evaluation largely dictate the surgical approach. Once the surgeon has adequate access and visibility of the primary, a wide local excision is carried out with the intention of at least a 1-cm margin. The proposed area of excision is first

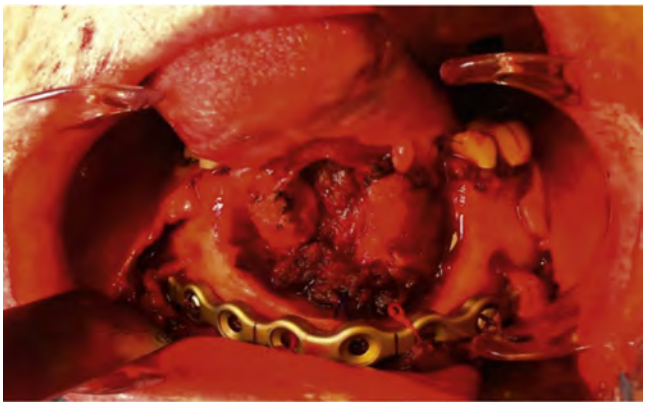


• **Fig. 22.9** This illustrates the access afforded by a pull-through procedure in this advanced-stage squamous cell carcinoma of the tongue and floor of mouth.



• **Fig. 22.10** Intraoperative photograph of the lip-splitting skin incision, which follows an existing skin crease in the submental fold.

outlined with a marking pen or methylene blue ink, though many surgeons choose to mark out using electrocautery. The mucosa is then incised with electrocautery. Before we continue dissecting, a 2-0 silk suture is placed through the anterior margin of resection as an identification marker. The soft tissue is then resected three-dimensionally in an anterior-to-posterior direction using electrocautery. It is very crucial that the surgical specimen not be disrupted during resection; otherwise evaluation of the surgical margins at the frozen section examination may become difficult. Anatomically, as the resection is continued deeper, the margin lies in the sublingual glands and Wharton's duct will become visible. At this point, the duct is obliquely transected. The floor of the mouth is a highly vascular area, and bleeding from the branches of the lingual artery will always be encountered.



• **Fig. 22.11** This illustrates the extent of an anterior marginal mandibular resection, preserving a portion of the native mandible reinforced by a mandibular reconstruction prosthesis.

The inclusion of marginal mandibulectomy modifies the procedure. If a marginal mandibulectomy is planned, then it should be performed before resection of the primary tumor because it improves surgical exposure. However, at the outset of the operation, the margins of resection are outlined. The initial incisions are then made in the ventral surface of the tongue and carried over the alveolar process down to bone and connected anteriorly. At this point, the mucoperiosteum is elevated and osteotomies made. This can be achieved either using osteotomes or a reciprocating saw. For anterior marginal mandibulectomy, the vertical osteotomy cuts are made medial to the canines on either side. The advantage of making the vertical osteotomy medial to the canine is that it allows adequate bone support for the bicuspids. The horizontal osteotomy is made in such a way that the alveolar process is resected without involving the body of the mandible. Even though the alveolar process is not involved with the tumor, it serves as one of the resection margins. Once the mandibulectomy has been completed, the mandibular fragment is freed, the bone is retracted posterosuperiorly with the attached tumor, and the remainder of the resection is carried three-dimensionally in an anterior to posterior direction as described earlier (Fig. 22.11). The sublingual glands are identified and Wharton's duct obliquely transected and included as a deep margin of resection.

Sialodochoplasty

As Wharton's duct is obliquely transected, it is suggested to marsupialize the remaining portion of the duct and create a neo-ostium. The proximal half of the duct, which is not inclusive of the specimen, is sutured with the oral mucosa of the remaining floor of mouth to create a neo-ostium. This is can be achieved using a 5-0 or 4-0 absorbable suture such as Vicryl in an interrupted fashion. This procedure is often superfluous in stage II oral squamous cell carcinoma, in which the majority of patients will be subjected to a bilateral selective cervical lymphadenectomy.

Frozen Sections

The utility of frozen sections continues to be debated; however, the technique is commonly practiced in several ways. Once the

specimen is excised, frozen section examination sites are very carefully selected. The technique is prone to sampling bias and interpretive errors. To improve the ability to locate regions, sutures or Ligaclips may be used to mark the sites of frozen section. Inking resection margins is a crucial step, and it is imperative that this ink be applied accurately. If a margin appears close, it is preferable to excise additional tissue and examine the additional margin. It is highly recommended that the surgeon have direct onsite communication with the pathologist in order to eliminate any error. If required, the surgeon and the pathologist should examine the specimen together. Our institutional approach is to employ frozen sections for oral cavity squamous cell carcinoma.

Management of the Neck

The control of carcinoma of the floor of the mouth is closely related to the extent of the primary tumor and the status of the regional lymph nodes. Involvement of the nodes significantly lowers the survival rate. The treatment of the neck differs in clinically positive and clinically negative necks. The management of the neck, especially when clinically negative, has remained a topic of debate, although there appears to be a survival benefit in early-stage, N0, squamous cell carcinoma. Our institution places high value on elective, selective neck dissection for N0 neck patients. Central to the debate surrounding the value of elective neck dissection in the treatment of floor of mouth cancer is an accurate estimate of the incidence of occult lymph node metastasis and whether treatment at the occult stage confers any survival advantage when compared with treatment of the neck when lymph node metastasis becomes clinically apparent. Further, if there is a survival advantage in treating the neck, what are the prognostic factors that will enable the surgeon to screen patients who must undergo an elective neck dissection? And last, which modality, selective neck dissection (supraomohyoid) or a radical neck, will provide an equally predictable result in terms of better survival, lower failure rate, and less morbidity in clinically negative node status?

Clinically Negative Neck (cN0)

The incidence of occult neck metastasis in early-stage tumors of the tongue and floor of the mouth varies from 20–30%.[51-54] There is abundant literature discussing factors that can influence the rate of cervical metastasis. Pimenta Amaral and colleagues[41] evaluated the demographic, clinical, and pathologic factors associated with the risk of occult metastasis and prognosis in patients with clinical stage I and II squamous cell carcinoma of the tongue and floor of the mouth. In this study it was concluded that tumors with infiltration of the muscular layers had higher occult metastasis rates and decreased disease-free survival. For tumors of the floor of the mouth and for T2 tumors, the histologic grade was the only important risk factor for occult metastasis in lymph nodes. In contrast, Nason and co-workers[55] and Briggs and associates[56] did not find a relationship between tumor grade and occult metastasis in neck lymph nodes.

The correlation between thickness of floor of mouth SCC and the rate of cervical metastasis has been studied by many and is believed to be most crucial in clinical decision making. Mohit-Tabatabai and colleagues[57] examined SCC of the floor of the mouth and suggested that a tumor thickness of more than 1.5 mm posed a clinically significant risk of lymph node metastases. Eighty-four patients with cT1N0 or cT2N0 SCC of the floor of the mouth were examined in this study. The rate of lymph node metastasis with a primary tumor thickness of 1.5 mm was 2%, compared with a rates of 33% with a thickness of 1.6 to 3.5 mm and 60% with a thickness greater than 3.5 mm. In addition the authors reported no correlation between tumor diameter and rates of metastasis. In another study by Wallwork and associates,[58] median tumor thickness of patients with lymph node metastases (14.6 mm) was significantly greater than that of those without lymph node metastases (8.6 mm). The same finding was present when T1 and T2 primary tumors were examined in isolation (11.1 mm with nodal metastases and 4.5 mm without metastases). Similarly, a statistically significant correlation was noted between the incidence of lymph node metastases and the thickness of the primary tumor at intervals of 7.5 and 10 mm. Spiro and coworkers,[59] in a study of 105 patients with either oral tongue or floor of mouth SCC, reported a 12% rate of regional failure with a primary tumor thickness of less than 2 mm compared with a rate of 47% with a thickness of 2 mm or greater. They did not show significant differences in tumors from 3 to 8 mm thickness, but suggested that the increase in thickness was associated with the presence of occult metastasis.

Weiss and colleagues[60] reported that there are three major strategies in the treatment of patients with a stage N0 neck with squamous cell cancer of the head and neck: elective neck dissection, elective neck irradiation, and observation. They constructed a decision tree and performed a sensitivity analysis addressing the question of thresholds for these three treatment options. They conclude that if the probability of occult metastasis is less than 20%, the preferred option is observation. When the probability of occult metastasis is greater than 20%, both elective neck irradiation and elective neck dissection become preferable to observation. According to Jalisi,[61] T1 or T2 SCC with a thickness of more than 1.5 mm in a clinically negative neck has a probability of occult metastasis over 20%, and Jalisi recommends an elective neck dissection.

There has been divided opinion on observation versus elective neck dissection. Those who favor observation argue that there is significant morbidity associated with an elective neck dissection, and since the likelihood of occult metastasis is 20–30%, about 70–80% of patients would be exposed to the morbidity of a neck dissection unnecessarily. In contrast, although T1/T2 cancers of the floor of the mouth can be locally controlled in a high percentage of patients with minimal morbidity, the untreated, clinically negative neck may be the site of recurrent disease in 30–40% of patients. Studies comparing survival rates of patients with clinically negative necks who have undergone elective and therapeutic neck dissection seem to indicate improved survival for those who undergo elective neck dissection. Spiro and colleagues[59]

have indicated that it is beneficial to remove occult cervical lymph node metastases. These authors reported that patients with stage N0 necks who were subsequently discovered to have occult nodal metastasis after elective neck dissection had longer survival than did patients with cervical metastasis at the time of initial examination. Silver and co-workers[62] similarly reported that both control of neck disease and patient survival may be significantly increased if neck dissection is performed before cervical metastases become clinically evident. Dias and associates[63] studied a series of patients with T1 SCC of the tongue and floor of mouth and concluded that patients who underwent elective neck dissection had a 23% higher disease-free survival rate than did those who underwent resection of the tumor only. McGuirt and colleagues[64] performed a retrospective outcome analysis of 129 patients with SCC of the floor of the mouth and clinically negative neck, most consisting of T1/T2 lesions, to evaluate the role of neck dissection. Elective neck dissection was performed in 26 patients. Histologic evaluation revealed occult metastases in 23%. In contrast, of 103 patients managed without elective neck dissection, cervical lymph node metastasis eventually developed in 37%. The determinant survival rate at 3 years was 100% for patients with occult disease who underwent elective neck dissection, whereas the 3-year determinant survival rate in patients receiving no initial treatment of the neck was 85%. The salvage rate for those in whom metastases to the neck did develop was 59%.

In our experience and based on the findings evidenced and supported by the literature, we believe that elective neck dissection in N0 necks is warranted, especially in patients with poor prognostic factors such as tumor thickness greater than 4 mm, where the probability of occult metastasis is higher. There is a significant survival advantage and improved regional control in patients in whom metastasis to the neck eventually develops. Elective neck dissection completes the pathologic staging, and patients with high-risk features identified on neck dissection, such as extracapsular extensions, are stratified for adjuvant chemoradiotherapy. Andersen and colleagues[65] demonstrated that 77% of patients with clinically N0 necks at initial observation had pathologically adverse findings at the time of neck dissection. Furthermore, 49% of these patients had extracapsular spread, a poor prognostic factor. Hence, they argued for elective neck treatment in patients with N0 necks. At our institution, when treating a neck electively, we usually perform a supraomohyoid dissection (selective neck). It has less morbidity when compared to a radical neck dissection and is currently the best modality for detecting cervical metastasis for floor of mouth in the N0 setting. Davidson and co-workers[66] report 98% accuracy, 95% sensitivity, and 100% specificity in detecting cervical metastasis using a selective neck dissection. There is abundant literature supporting the use of prophylactic selective neck dissection for surgical treatment of N0 necks in oral cavity carcinoma. The metastatic rate to level I is 58%, 51% to level II, 26% to level III, and about 9% and 2% to levels IV and V, respectively. The lymph nodes at highest risk of occult metastases from oral cavity cancers are those at levels I, II, and III.[67] Because most T2 floor of mouth SCCs are seen anteriorly and they cross the midline, the dissection should be bilateral, whereas lateral T2N0 lesions not crossing the midline should have a unilateral dissection.

Clinically Positive Neck (cN+)

With clinically positive neck (cN+), a neck dissection should certainly be performed. Over the past few decades, the surgical technique of neck dissection has evolved from radical neck dissection to modified radical neck dissection and then to selective neck dissection. However, the use of selective neck dissection as a therapeutic procedure for SCC in the floor of the mouth, especially when compared with the effectiveness based on oncologic outcomes after radical neck dissection, remains controversial. The concept that was adopted in the management of positive necks was complete neck dissection, and selective neck dissection was not advocated in patients with advanced nodal disease or in a salvage setting.[68] Zupi and colleagues[69] retrospectively reviewed the records of 112 cases of floor of mouth SCC (66.1% were T1 ± 2), where patients with unilateral clinically positive necks were treated with an ipsilateral therapeutic and a contralateral prophylactic neck dissection; those with bilateral clinically positive necks were treated with a bilateral therapeutic neck dissection. They report that in their experience, the global N+ rate was 45.5%, and this usually occurs in regions I, II, III, and IV (45.5%, 34.8%, 34.8%, and 16.1%, respectively). They recommend modified radical dissection. However, if extracapsular spread is present, a radical neck dissection should be performed, sacrificing the structures involved.

In contrast, in a study by Feng and colleagues,[70] a different approach was favored. They retrospectively compared the prognosis and complications between selective neck dissection and comprehensive neck dissection for patients with a pathologically node-positive neck in SCC of the tongue and the floor of the mouth and found no significant difference between the two groups in 3-year neck control (86.2% vs. 85.9%) or disease-specific survival (64.6% vs. 61.9%). Further analyses showed for pN1 without extracapsular spread, 67.7% versus 72.2%; pN2b without extracapsular spread, 64.7% versus 68.8%; and pN+ with extracapsular spread, 57.1% versus 60.0%. They concluded that the modality of neck treatment, pN+ status, and microscopic extracapsular spread did not serve as independent prognostic factors. Selective neck dissection plus adjuvant radiotherapy is a management strategy of high efficiency and minor morbidity for selected oral cancer patients with a pN+ neck with or without microscopic extracapsular spread. Our institutional approach favors a selective neck dissection (I to IV) in N+ patients provided that a single node is confined to level I or II. Patients with positive nodes in level III/IV are treated with a comprehensive neck dissection.

To conclude, in our experience and based on the literature, for a clinically positive neck, a bilateral neck dissection should be performed because of the high incidence of contralateral metastases. This would usually be a modified radical neck dissection bilaterally. However, we recommend a radical neck dissection if there are signs or there is suspicion of macroscopic extracapsular spread. For a clinically negative neck, we suggest a prophylactic selective supraomohyoid neck dissection,

especially for patients with tumor thickness greater than 4 mm; the dissection should be unilateral in the case of lateral lesions and bilateral in the case of anterior median lesions. With the understanding of these key concepts, the decision to treat the neck and the modality used must be discussed with patients along with the risk of a second primary cancer in future. Above all, the patient's preference and the surgeon's experience should be taken into consideration in making treatment decisions.

Reconstruction of the Anterior Oral Cavity After Resection of T2 Squamous Cell Carcinoma

There is currently a paucity of literature that focuses specifically on the reconstruction of the oral floor after resection of T2 SCC, and therefore this section reviews various techniques of reconstruction. When deciding on a method for reconstruction, multiple variables need to be considered, including size and location of the defect; comorbidities such as peripheral vascular disease, atherosclerosis, and smoking; and desired functional and esthetic outcomes. When moving up the "reconstructive ladder," the complexity of the procedure increases; however, the outcomes are often better.[71] This section focuses on reconstruction of the oral floor with pedicled flaps and free tissue transfer flaps. Both pedicle flaps and free flaps have been used for reconstruction of the oral floor, with a majority of cases involving radial forearm free flap (RFFF) and more recently anterolateral thigh (ALT) free flaps, in addition to pectoralis major myocutaneous flaps (PMMF), supraclavicular artery island flaps (SCIF), pedicled flaps, and the submental island flap (SMF). Reconstruction of the oral floor after tumor resection is important to restore form and function—speech and swallow function and esthetics.[72,73]

To provide for the best reconstructive option, it is important for the surgeon to understand the tissue compliance of the floor of the mouth and oral cavity. The anterior oral cavity is composed of the oral tongue, the floor of the mouth, alveolus, lips, buccal mucosa, and mandible. For the purposes of this chapter, we do not focus on mandibular reconstruction. The oral tongue is important in mastication because once the food bolus has been chewed, the tip of the tongue propels the food to the back of the throat. The tongue itself is composed of 100% muscle. Reconstruction of the tongue does not replace muscle with muscle; rather, the concept is to provide a thin lining that will allow mobility of the residual oral tongue. If there is scarring of the tongue to the floor of mouth, mandible, or buccal mucosa, the mobility of the tongue will be compromised and the patient will have difficulty in propelling the food bolus to the back of the throat, resulting in dysphagia.

The floor of the mouth, lip, and buccal mucosal consist of thin sensate mucosa. It is important because it forms the gutters in the mouth in which the food bolus resides while mastication continues. Once mastication is complete, the food passes these lateral gutters on its way to the oropharynx. Hence, floor of mouth and buccal mucosa ideally need to be reconstructed with thin pliable tissue. Unfortunately, all flap choices are insensate, which results in the patient complaining of "food getting stuck in my mouth" or dysphagia because they cannot sense the food in their mouth.

Historically, over the past three decades, the PMMF was used for most oral cavity reconstructions[74]; in recent years, however, with advancements in the field of microsurgery, free flaps have relegated PMMF to a secondary role.[75,76] The soft tissue characteristics of a free flap allow for a large amount of thin pliable tissue, which conforms to the contours of the recipient site, and a long pedicle that allows for anastomoses in the ipsilateral or contralateral neck.[77] The PMMF, in comparison, tends to have a limited arc of rotation, only reaching the zygomatic arch, tends to be bulky, and often causes donor-site cosmetic defects.[77] Furthermore, patients who received PMMF instead of a free flap for tongue reconstruction have an increased rate of flap necrosis and longer hospital stay.[78] It is often difficult to use PMMF in obese patients because of the thickness of the flap.[76] Patients who received free flaps in comparison to PMMF had better speech, swallow, shoulder function, and mood.[72]

Although it may seem that the free flap has made PMMF obsolete, this is not actually the case. The PMMF is still often used for a salvage procedure after free flap failure,[75] in conjunction with a free flap to cover large defects,[76] or in areas where a microvascular surgeon is not available.[79] Additionally, patients with multiple comorbidities who are not able to withstand the increased operative time of free flap procedures are good candidates for PMMF.[80] However, it is possible to decrease the operative time during a free flap procedure if a two-team approach is used rather than a single attending surgeon. Most of the flaps listed earlier, including the radial forearm flap, SCIF, SMF, and PMMF, do not require repositioning of the patient and also save operative time. There have also been arguments that free flap procedures and management are more costly; however, De Bree and Smeele and their respective colleagues proved that the costs for the two techniques are comparable, and the only major difference consistent between the two studies is an increased operative time for free flaps compared to PMMF.[81,82] Historically, it was thought that outcomes of free flap procedures would be worse in the elderly population because of increased operative time, metabolic stressors of surgery, and a more intensive postoperative course; however, Wester and Peters and their respective co-workers demonstrated that age is not directly correlated with surgical outcomes.[83,84] Nevertheless, elderly patients tend to have an increased number of comorbidities that should be well controlled before free flap procedures to optimize outcomes.[83]

Although there are no clear guidelines for management of defects after free flap failure, both PMMF and secondary free flaps have been used to reconstruct the oral cavity defects.[76,85,86] According to Corbitt and colleagues, there was a significant difference in outcomes in subsequent free flaps in comparison to subsequent PMMF after flap failure, with more patients having intelligible speech and independence from tube feeding in the group receiving secondary free flaps.[87] In our institution we favor using a secondary free flap if the patient does not have multiple comorbidities precluding this procedure. The length of the free flap surgery is usually equal to the length of surgery

for PMMF. The decision as to PMMF or secondary free flap is made by the primary surgeons involved in each case, but the use of PMMF in our institution is relegated to less than 5% of cases where the patient has no good donor vessels as determined by a failed Allen test (for RFFF) or injury on the leg (ALT donor site).

The SCIF and the SMF have become more popular in recent years for multiple reasons: they do not require additional specialized microvascular surgery training and result in shorter operative time and hospital length of stay,[88,89] which is why an SCIF or SMF may be preferred in patients with multiple medical comorbidities.[90] Most reported harvest times for the SCIF are less than 1 hour,[91-93] and the overall operative time is also significantly shorter for an SMF compared to free flaps.[89] Furthermore, the skin texture in both SCIF and SMF is more similar to the face than the skin overlying the PMMF, and the flaps are more pliable.[90,94]

The SCIF specifically is also sensate and hairless.[90] The donor site in the SCIF results in decreased deformity in comparison to PMMF,[92] and there have been no reported significant deficits in shoulder function after the SCIF procedure.[95] An additional indication for an SCIF is if the patient has a negative Allen test, which would be a contraindication for the use of an RFFF.[96] Although SCIF can be used for oral floor reconstruction, it has also been used for reconstruction after parotidectomy, release of postburn mentosternal contractures, resurfacing of hemifacial atrophy, and reconstruction of the auricular region, temporal bone region, or skull base.[88] Contraindication to the SCIF is prior neck dissection in which the transverse cervical vessels may have been sacrificed. The SCIF facilitates the goals of oral cavity reconstruction, including management of speech, swallow, and airway control.[97] Some of the concerns, on the other hand, when using an SCIF are large-volume defects that cannot be reconstructed with an SCIF and potential flap necrosis.[90]

The esthetic outcome of an SMF is ideal because the mandible hides the donor scar. Additionally, the incision used for the resection can often be used for dissection of the SMF, preventing multiple incisions.[94] The SMF can also be used for multiple other facial reconstructions, including defects of the lower face, tongue and buccal mucosa defects, palatal defects, nasal reconstruction, lip reconstruction, and repair of pharyngocutaneous fistula.[94] Some of the contraindications for an SMF are medical comorbidities precluding major surgery, metastatic disease involving ipsilateral level 1a and 1b lymph nodes because of possible transfer to the recipient sites,[98] and local trauma to the region.[94] Radiation therapy is not a contraindication to the use of the SMF.[99] Patients who received SMF procedures for reconstruction of the oral floor after tumor resection were found to have excellent chewing, swallowing, and speech functions.[100]

There was also minimal donor site morbidity as a result of the SMF procedure. Patients had normal whistling and smiling function, which is a concern when performing SMF because partial loss of the platysma muscle, damage to the marginal mandibular branch of the facial nerve, and scarring may all interfere with smiling and whistling function. There was a minor decrease in neck extension in patients who previously received chemoradiation, and patients with a skin paddle greater than 32 cm^2 had a poorer subjective esthetic outcome than patients who received a smaller skin paddle.[101] In comparison to patients who received RFFF for oral reconstruction, patients who received SMF for oral reconstruction did not demonstrate an increased risk of tumor recurrence or lymph node metastases.[102] A limitation of the SMF is that the largest skin paddle reported is 16 × 8 cm, and larger defects would require a different type of repair such as a free flap or a PMF.[103]

There are multiple free flaps that can be used for head and neck reconstruction; however, we favor the use of the RFFF and ALT for reconstruction of the oral floor after T2 resection. Lim and colleagues compared outcomes using RFFF and ALT flap in 42 cases and reported no significant difference in failure rate between the two groups.[104] One concern when performing RFFF in comparison to an ALT flap is the possible donor site morbidity with RFFF, which includes decreased sensation because of damage to the superficial radial nerve; hand ischemia if collateral flow is poor because of the need to sacrifice the radial artery; and a large scar on the forearm.[105] Some of the advantages of the RFFF include a flap that is relatively easy to harvest, which makes the procedure easier to learn; constant anatomy of the vessels; a superficial surgical site; and a pedicle vessel size comparable to that of the recipient site. However, the skin paddle is often small and thin, limiting coverage for some larger defects, which is where an ALT flap may be optimal. An ALT flap has multiple perforators, which allows the skin paddle to be divided into multiple islands, and the muscle tissue can be released, forming a composite flap with multiple pedicled islands.[106] There was no statistical difference in functional outcomes including speech, swallow, and donor site complications when comparing RFFF and ALT flap.[107]

The most common arteries used as recipient vessels for the anastomosis are the common facial artery and superior thyroid artery, followed by the transverse cervical artery.[106] The most common recipient veins were the common facial, internal jugular, and external jugular veins.[106,108] Reported free flap success rates are as high as 95–98%,[109] with comparable success rates when training senior residents to perform microvascular anastomoses.[110]

There are multiple possible complications that can occur when reconstructing the oral cavity, which are not specific to any single type of reconstruction. These may include mortality, postoperative coma, nervous system complications, gastrointestinal hemorrhage, cardiorespiratory arrest, metabolic derangement, urinary tract complications, stroke, postoperative hematoma or hemorrhage, postoperative infection, reopening of surgical site, deep vein thrombosis–pulmonary embolism, and pulmonary compromise (specific complications of each type of reconstruction are described next).[111]

Submental Island Flap

The first reported case of an SMF was performed by Martin in 1993 and has become more popular for reconstruction of smaller defects in the oral cavity because of the reasons listed earlier.

Anatomy

The submental artery is a branch of the facial artery; its origin is on average 27.5 mm distal to the division of the facial artery and external carotid artery. It is found 5 mm from the mandibular border and 23.8 mm from the mandibular angle. The diameter of the submental artery is approximately 1.7 mm at the origin. The artery travels superficial to the submandibular gland in 70% of cases and travels between the superior border of the submandibular gland and the body of the mandible in 30% of cases. The total length is 58.9 mm and it anastomoses with the contralateral submental artery 92% of the time.[112] The submental artery is found deep to the anterior belly of the digastric 56–81% of the time, whereas the artery runs superficially to the muscle in all other cases.[113] The facial artery, on the other hand, has a mean diameter of 2.7 mm and crosses the mandibular border 26.6 mm from the mandibular angle.[112]

The diameter of the submental vein is 2.2 mm.[112] There are three sources of venous drainage in the submental region: concomitant submental veins that run in close proximity to the submental artery.[114] The submental vein passes superficial to the submandibular gland and drains into the facial vein, a large superficial vein reaching the lateral border of the anterior belly of the digastric, and the anterior jugular vein that is located near the midline and drains into the external jugular vein.[113]

There are two nerves within the region of the SMF: the marginal mandibular branch of the facial nerve, which travels through the superficial layer of deep cervical fascia that overlies the submandibular gland, and the motor nerve to the mylohyoid, which follows a deep path to the submental artery.[94] The muscles involved in a submental flap include the platysma, the anterior belly of the digastric muscle, and the mylohyoid.

Surgical Technique

The surgical technique described is based on Cheng and colleagues,[94] Vural and Suen,[99] Sebastian and associates,[100] and Rahpeyma and Khajehahmadi.[113] The patient is placed supine with head extended and turned to the opposite side. Ultrasound Doppler is used to identify the facial artery/vein and skin perforators, which will decrease flap failure rate and prevent inadvertent exclusion of the perforator vessels.[94,113] The skin paddle should be sized to match the defect in the oral floor in a crescent-shaped ellipse centered at the midline with anteroposterior axis perpendicular to the patient's midsagittal plane, with the superior incision 1.5 cm inferior to the inferior mandibular border.[94] A skin pinch test should be performed before dissection of the skin paddle to ensure that primary closure will be possible. The flap should include the perforators identified via Doppler, the anterior belly of the ipsilateral digastric, and part of the mylohyoid.[94] Make an incision along the inferior aspect of the skin paddle extending into a planned cervical incision if a neck dissection is planned. Raise the skin paddle in the subplatysmal plane. Dissect and identify the intermediate tendon of the digastric muscle at its attachment to the hyoid bone. If the inferior incision is above the hyoid bone, the initial incision should be down to the superficial layer of deep cervical fascia. The facial vein should be identified and protected as it crosses superficially to the posterior belly of the digastric. Identify the submandibular gland and use blunt dissection to enter the capsule that envelopes the gland. Begin to raise the superior border of the flap deep to the superficial layer of the deep cervical fascia where several branches of the facial artery will be identified along the gland and follow them until the facial artery is identified. Dissect the facial artery until the submental gland is found, branching anteriorly along the superior aspect of the gland, and dissect out the submental artery until it reaches the posterior border of the mylohyoid muscle.

Make a superior incision through the platysma. Identify the anterior belly of the digastric as it attaches to the lingual aspect of the anterior mandible. Extend the dissection laterally and identify the facial artery and vein as they cross the inferior border of the mandible near the antegonial notch. These vessels may be ligated and divided after the submental artery has been identified to extend the length of the pedicle by 1–2 cm. During this part of the dissection, it is necessary to identify the mandibular branch of the facial nerve and protect it. Use of a nerve stimulator can aid in locating the nerve.

Begin elevating the skin pedicle most distal from the pedicle in the plane superficial to the mylohyoid muscle until the anterior belly of the digastric is encountered. Caution should be used to avoid damaging any perforators that run medially to the anterior belly of the digastric.

Divide the anterior belly of the digastric at its attachment to the mandible and at the intermediate tendon. At the medial border of the anterior mylohyoid muscle, dissect through the mylohyoid muscle to the underlying geniohyoid muscle and divide the attachments from the mylohyoid. Inclusion of the anterior belly of the digastric and the mylohyoid muscle increases the blood supply to the flap and creates a more bulky flap in the distal half.[113]

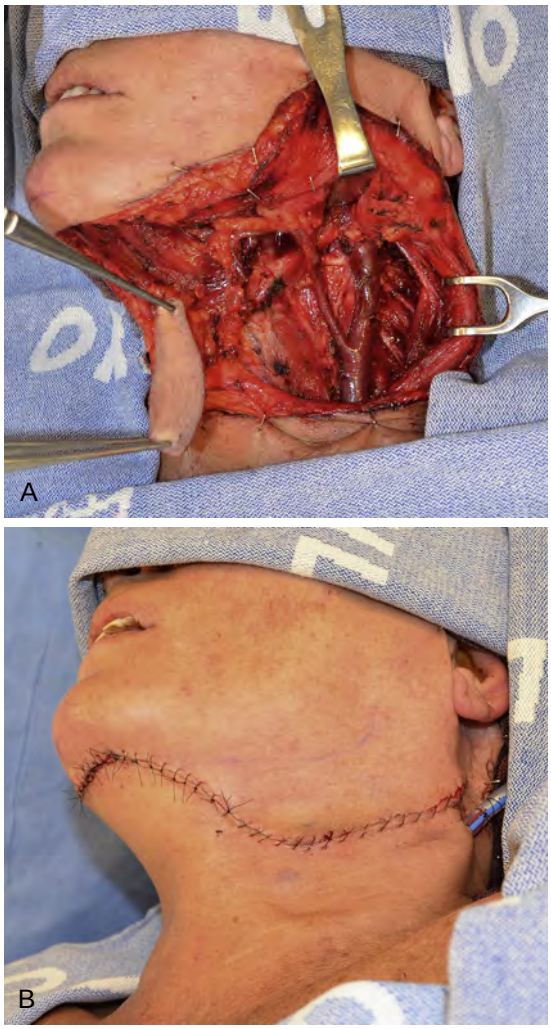
Use blunt dissection to dissect out the rest of the SMF and to create a subcutaneous tunnel 3 fingerbreadths to the oral defect. Suture the flap in place to cover the oral defect, close the donor site using several deep sutures to approximate the cervical skin flaps to the hyoid periosteum, and then suture the wound in layers[94,99,100,113] (Fig. 22.12).

Complications

Some of the complications that are specific to the SMF are damage to the marginal mandibular nerve,[94,98] orocutaneous fistula,[98] intractable hair growth and venous congestion,[100] and total or partial flap necrosis.[99]

Supraclavicular Artery Island Flap (SCIF)

The SCIF was first described by Lamberty in a 1979 paper where he describes the supraclavicular artery as a branch of the transverse cervical artery or the suprascapular artery.[115] Pallua described successful flap harvest and successful use of the SCIF.[116] Chiu and colleagues then described the use of the SCIF in reconstruction of head and neck deformity after resection.[117] Within the flap, the transverse cervical artery gives rise to the supraclavicular artery 93% of the time, and the supraclavicular artery arises from the suprascapular artery 7% of the time. The vessel diameter is 1 to 1.5 mm. The sensory nerve



• **Fig. 22.12** **A**, Completion of neck dissection and elevation of the submental island flap. The ipsilateral anterior belly of the digastric muscle and a portion of the mylohyoid muscle are included with the flap. **B**, With the Burow triangle removed, the wounds are closed into a curvilinear incision. (From Cheng A, Bui T: Submental island flap, *Oral Maxillofac Surg Clin North Am* 26(3):371-379, 2014.)

roots supplying the supraclavicular flap arise from C3 and C4 and course under the sternocleidomastoid with a branch exiting anterior to the flap and a second branch running along the length of the flap, which is usually the major cutaneous nerve.[117] The transverse cervical artery is consistently 7 cm from the sternal notch, 3 cm superior to the clavicle, and 2 cm posterior to the sternocleidomastoid.[88,118] The supraclavicular artery can be found in a triangle formed by the dorsal edge of the sternocleidomastoid muscle, the external jugular vein posteriorly, and the medial part of the clavicle forming the base of the triangle[92,119] (Fig. 22.13).

Surgical Technique

Although Chiu and colleagues[117] performed a preoperative computed tomographic angiogram (CTA), other surgeons have only used handheld Doppler and do not feel a CTA is necessary.[88,91] A handheld Doppler is used to trace the supraclavicular artery from its proximal location starting in the triangle



• **Fig. 22.13** Two titanium miniplates and screws were used to obtain rigid stabilization of the bone. (From Chen WL et al: Mandible reconstructed with mandibular osteomuscular and facial-cervico-pectoral flap, *Asian J Oral Maxillofac Surg* 23(2):69-72, 2011.)

described earlier over the acromion until the end of the deltoid muscle is reached. It is recommended that the flap width not be greater than 10 cm to minimizing the risk of requiring a skin graft to close the donor site, and the length of the flap should not exceed 20 to 26 cm.[91,119] The flap is raised off of the deltoid in the subfascial plane using monopolar cautery until the surgeon approaches the branching point of the supraclavicular artery, at which point the surgeon should switch to dipole cautery.[88] The fascial pedicle should extend from the lateral attachment of the sternocleidomastoid muscle to a point about 3 cm lateral to the identified vascular pedicle at the clavicle.[120] The perforators of the posterior circumflex humeral artery are ligated. Posteriorly the flap is raised to the anterior border of the trapezius, and the spinal accessory artery may be identified.[91] However, there are no reported cases of accessory nerve damage during the harvest of the SCIF. Approximately 2 cm above the clavicle, the platysma muscle is transected to connect the tunnel to the floor of the mouth. Incising the distal tip of the flap assesses the vascularity and checks for bleeding.[91] The flap is then tunneled to the defect in the oral cavity and sutured in place (Fig. 22.14).

Complications

There is no association between previous chemoradiation or radiation and increased failure rate.[91,119] However, there is some debate regarding whether neck dissection in levels IV and V is a contraindication to the SCIF.[93,96] If the thyrocervical trunk is not damaged, it is still possible to perform an SCIF.[1] Some of the reported complications include referred sensation to the shoulder with contact to skin flap island,[118] distal flap necrosis and total flap necrosis,[92] salivary leak,[88] orocutaneous fistula,[96] wound dehiscence and carotid blowout,[122] and donor site dehiscence,[92,119] which usually heals with routine wound care.

Pectoralis Major Myocutaneous Flap

The pectoralis major myocutaneous flap was first described by Ariyan in 1979, when he performed the first series of PMMF for head and neck reconstruction. He describes the blood



• **Fig. 22.14** Distal skin paddle dehiscence: fibula flap skin paddle. (From Ramirez CA, Fernandes RP: The supraclavicular artery island and trapezius myocutaneous flaps in head and neck reconstruction, *Oral Maxillofac Surg Clin North Am* 26(3):411-420, 2014.)

supply to the pectoralis major, including the superior thoracic artery (a branch of the thoracoacromial artery), and the lateral thoracic artery, which both have corresponding veins.[74] Freeman and colleagues then went on to further describe the vascular supply to the pectoralis major, including the pectoral branch of the thoracoacromial artery, which anastomoses with perforators of the internal mammary artery.[123] The innervation to the pectoralis major muscle includes the lateral and medial pectoral branches, which originate from C7, C8, and T1. The lateral pectoral nerve arises more frequently with two branches from the anterior division of the upper and middle trunk or as a single root from the lateral cord. The medial pectoral nerve arises from the medial cord (49.3%) or the anterior division of the lower trunk (43.8%), or lower trunk. The LPN supplies the upper portion of the pectoralis major muscle, and the medial pectoral nerve supplies the lower portion of the muscle.[124] The pectoralis muscle is a large fan-shaped muscle, which is divided into a clavicular portion that is attached to the medial one third of the clavicle, a sternal portion that attaches to the sternum and the first six ribs, and an abdominal portion that arises from the aponeurosis of the external oblique muscle. The muscles form a tendon, which attaches to the greater tubercle. The pectoralis major is closely associated with the medial aspect of the deltoid muscle, forming the deltopectoral groove. The inferior surface is separated from the pectoralis minor by the clavicopectoral fascia.[76] The tendinous insertion on the greater tubercle is sacrificed to increase the arc of rotation for the flap, and the medial aspect of the muscle is most often used because of the anastomoses between the internal mammary arteries and the thoracoacromial artery (Fig. 22.15).

Surgical Technique

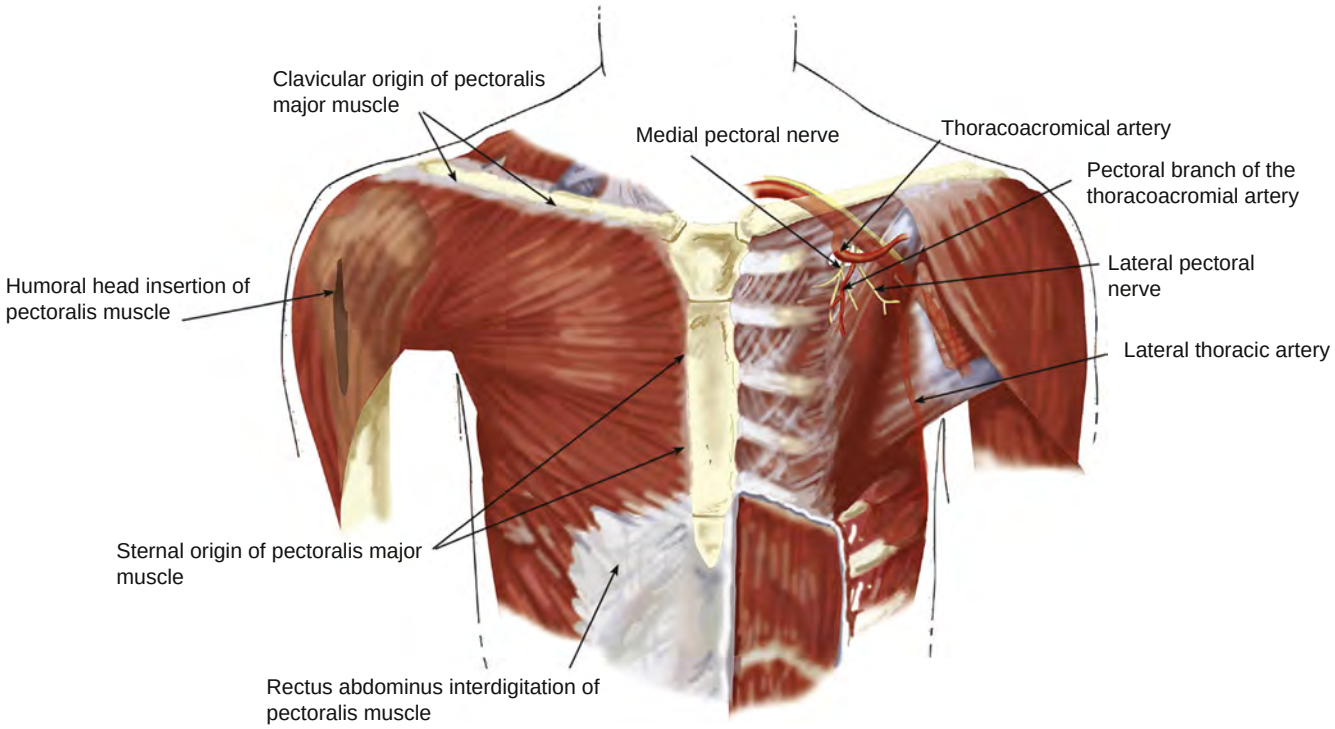
The surgical technique is described according to Patel and colleagues[76] and Gadre and co-workers.[79] A shoulder roll should be placed to allow for optimal neck extension. The incision site and skin paddle in the inferomedial portion of the flap should be delineated with a marker, and the skin paddle length and width should correlate to the size of the defect in the head and neck region. The incision site may be infiltrated with a local anesthetic with a vasoconstrictor, although we do not recommend this because of concern for affecting the cutaneous blood supply to the flap. The clavicle and lateral border of the sternum are outlined. The vascular pedicle runs from the acromion to the xiphoid process.

An incision through the skin and subcutaneous tissue down to the pectoralis fascia encircling the skin paddle is performed, and the plane between the pectoralis major and pectoralis minor is separated with blunt dissection. To prevent shearing of perforators, the skin paddle can be sutured to the pectoralis muscle with 4-0 chromic or Vicryl suture. Dissection is then performed from distal to proximal, starting medially on the lateral aspect of the sternum, maintaining a submuscular plane up until the clavicle. Internal mammary perforators are usually encountered between the second and fourth intercostal spaces and should be clipped to prevent bleeding. The vascular pedicle is located on the upper lateral portion of the flap, and the pectoral branch of the thoracoacromial artery is found on the deep surface of the pectoralis major and medial to the pectoralis minor. The medial and lateral pectoral nerves along the lateral vascular pedicle are sacrificed to allow for a greater arc of rotation and to avoid flap contraction with subsequent arm movement. The lateral pectoral vessels can be left intact or divided, depending on the size of the desired flap.

A broad tunnel (3 to 4 fingerbreadths) is then created in the subcutaneous plane to allow the flap to be passed through the neck, drains are placed into the defect site, and the pedicle is sutured in place with 3-0 Vicryl suture in a layer fashion. Staples or nylon sutures can be used to close the skin. The donor site can be closed primarily if the defect is small enough. In women it is often possible to close the defect by moving the breast, and in men a skin graft is often necessary if the defect is larger than 6 × 6 cm[76,79] (Fig. 22.16).

Complications

Unlike SCIF, there is an association between previous radiation therapy and postoperative complication rate.[86] In a case series of 500 PMMF, Milenovic describes complications including total flap necrosis (2%), total flap skin necrosis (4%), and partial skin necrosis (6.5%), dehiscence intraorally (6%), and an overall complication rate of 33%.[124a] Other surgeons have experienced similar complications, including complete flap failure, partial skin paddle loss, wound infection, or decrease in



• **Fig. 22.15** Arterial supply to the pectoralis major muscle. The blood supply to this muscle includes the pectoral branch of the thoracoacromial artery, lateral thoracic artery, the superior thoracic artery, and the intercostal artery. The latter two are not shown in the diagram. (From Cordova SW, Bailey JS, Terezides AG: Pectoralis major myocutaneous flap reconstruction of the mandible, *Atlas Oral Maxillofac Surg Clin North Am* 14(2):171–178, 2006; with permission.)

function of donor site.[80] Furthermore, orocutaneous fistula is a major concern because it can lead to increased length of hospital stay, infection, wound dehiscence, and vascular rupture.[111,125]

Radial Forearm Free Flap

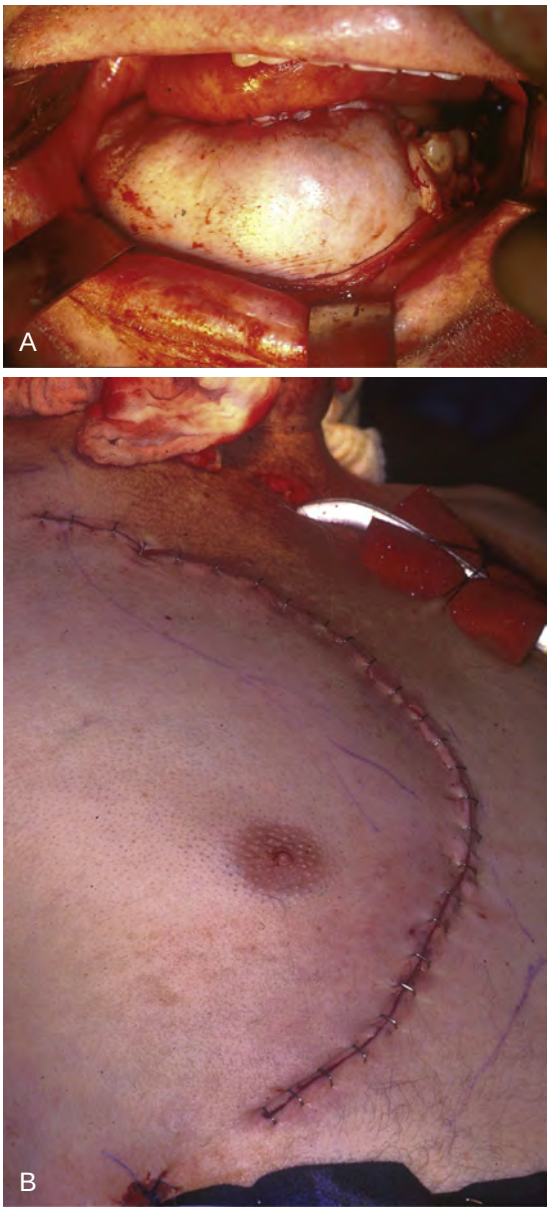
The first reported cases using an RFFF were described by Yang and colleagues in 1981, where they used the flap to resurface contractures in the neck from previous burns.[126] Its use for reconstruction in head and neck cancer patients after resection was first described by Soutar et al.[127]

Anatomy

An anatomic description of the radial forearm flap was given by Urken and colleagues in 2012.[127a] The blood supply to the lower arm originates from the brachial artery, which divides into the ulnar and radial artery. The radial artery leads into the deep palmar arch, and the ulnar artery leads to the superficial palmar arch. The four vascular systems that supply blood to the forearm skin are perforators from radial, ulnar, and anterior and posterior interosseus arteries. The radial artery, in the lateral intermuscular septum, gives off 9 to 17 fascial branches that supply the skin of most of the forearm. There are few fascial branches in the middle third of the forearm, and the inferior cubital artery supplies the proximal fasciocutaneous flaps. The radial artery also supplies the muscles of the flexor compartment, the palmaris longus, and the radial nerve. The length of the pedicle is limited by the radial recurrent artery or the cephalic vein, which would allow for extension of the dissection above the antecubital fossa.

The venous supply to the radial forearm has a superficial venous supply through the cephalic vein and a deep venous supply through the two paired venae comitantes, which run in the intermuscular septum. There are five different types of connections between the deep venae comitantes and the superficial veins. The type 1 pattern (20%) contains wide communication between the superficial and deep system, and the median cubital vein splits into the basilic median vein and the cephalic median vein. The type 2 pattern (43%) is the same as the type 1 pattern, except that the median cubital vein does not bifurcate. The type 3 pattern (18%) contains a confluence of the two venae comitantes to a common trunk, but does not anastomose with the cephalic vein to form a median cubital vein. In the type 4 pattern (5%), the venae comitantes do not converge or join with the cephalic vein. The type 5 pattern (15%) is similar to type 4, except one of the venae comitantes is dominant to the other.[128]

The cutaneous innervation of the forearm is derived from the medial, lateral, and posterior antebrachial cutaneous nerves—the primary sensory nerve to the forearm. The antebrachial nerve branches from the musculocutaneous nerve, runs along the cephalic vein, and continues to the thenar eminence in the hand. The medial antebrachial nerve arises from the medial cord of the brachial plexus, supplies the medial aspect of the



• **Fig. 22.16** **A**, Inset of flap. The flap is subsequently tunneled through the subcutaneous plane created with the skin paddle oriented to prevent torquing of the pedicle. **B**, Donor site closure. The donor site is closed primarily in layers with 3-0 Vicryl sutures; however, if a large skin paddle is used, then a skin graft needs to be placed over the exposed muscle. Staples or nylon sutures can be used to close the skin. (From Patel K, Lyu DJ, Kademani D: Pectoralis major myocutaneous flap, *Oral Maxillofac Surg Clin North Am* 26(3): 421–426, 2014.)

forearm, and runs along the basilic vein. Before performing an RFFF, one should check that the ulnar artery supplies blood to the index finger and thumb because of reported cases of an incomplete superficial arch or noncommunication between the superficial and deep arch.[129]

Surgical Technique

An Allen test should be performed before and during the surgery to test for patency of the radial artery and prevent hand ischemia. The patient should be positioned in the supine position, and a skin paddle should be traced around the radial artery. A scalpel is used to make a lateral incision along the arm down to the flexor carpi ulnaris, and subfascial dissection is performed until the palmaris longus (if present) and flexor carpi radialis are identified. At this point the dissection is performed from the radial aspect of the flap down to the brachioradialis muscle. The radial nerve is identified and preserved, including its branches along the wrist. Subfascial dissection is performed between the brachioradialis and the flexor carpi ulnaris, which is where the vascular pedicle is found. Sharp dissection is performed underneath the brachioradialis to preserve the vascular pedicle. Dissection is performed in the groove between the brachioradialis and the flexor carpi radialis. Hemostasis is obtained with bipolar electrocautery and hemoclips. Dissection is performed distal to proximal into the antecubital fossa. The superficial vein should be identified and followed to the antecubital fossa. After the entire flap is elevated, the radial artery is identified in the region of the wrist, and a clamp is applied to perform an Allen's test. The vessels are ligated, and the flap is brought to the neck region, where 9-0 nylon sutures are used for anastomosis to either the facial or superior thyroid artery, and the vein is anastomosed to the internal jugular, external jugular, or facial vein. Depending on the size of the defect at the donor site, the donor site can be closed primarily, using an ulnar transposition flap, or with a purse-string suture and split-thickness graft.[130]

Complications

Complications that have been reported in cases involving RFFF include total and partial flap loss, venous thrombosis, arterial thrombosis, dehiscence, and fistula formation.[131,132] Venous thrombosis occurs at least twice as often as arterial thrombosis in the case of free flaps.[133] Patient age, smoking history, and presence of comorbid conditions were related to higher rates of complications but were not statistically significant.[131,134] However, arteriovenous thrombosis had significantly worse outcomes than arterial or venous thrombosis alone and multiple takebacks, or takebacks after postoperative day 3, were associated with significantly worse outcomes. Prior radiation therapy is not associated with worse outcomes.[131,135] Venous thrombosis usually occurs from mechanical obstruction, including compression, twisting, kinking, or stretching of the vein.[135] Donor site morbidity includes hand ischemia,[136] tendon exposure,[137] decreased resting temperature in the hand, and subjective impairment in wearing watches or bracelets, numbness, soreness, itching, cold intolerance, and poor cosmetic appearance. There was no significant difference between the RFFF arm and control arm with strength testing and goniometry.[138]

Anterolateral Thigh Free Flap

The first use of the ALT flap was described by Song and colleagues in 1984 and was first described for the use of head and neck reconstruction by Koshima and co-workers in 1993.[139]

Anatomy

The anatomic description of the anterior lateral thigh flap is based on the 2012 publication by Urken and colleagues.[127a] The main blood supply to the anterolateral thigh flap

originates from the perforators of the profunda femoris artery, which is the largest branch of the femoral artery and supplies muscular branches to the adductors in the thigh. The profunda femoris artery originates from the posterolateral aspect of the femoral artery approximately 5 cm below the inguinal ligament within the femoral triangle. The artery runs superficial to the adductor magnus, adductor brevis, and pectineus, while passing deep to the adductor longus. There are four perforating branches (although sometimes there can be two to six branches) from the profunda femoris that pass into the posterolateral compartment through small openings in the adductor brevis and adductor magnus. The first perforator is the primary blood supply to the adductor muscles, the vascular pedicle for the gracilis, and often a cutaneous branch to the upper medial thigh. The second perforator gives off muscular branches to the vastus lateralis, semimembranosus, and the long and short heads of the biceps femoris. The third perforator is most often used in the lateral thigh flap. This perforator passes on or through the short head of the biceps femoris and courses through the lateral intermuscular septum. It supplies the major muscular branches to the biceps femoris and vastus lateralis. The fourth perforator is the terminal branch of the profunda femoris and runs within the lateral intermuscular septum.

The venous drainage in the lateral thigh is through paired venae comitantes. The dominant sensory nerve of anterolateral thigh is the lateral femoral cutaneous nerve, which is a branch of the first three lumbar nerves or femoral cutaneous nerve. The lateral femoral cutaneous nerve runs superficial to the iliacus and iliopsoas, exits the pelvic below the inguinal ligament anterior to the anterosuperior iliac spine, and runs superficial or deep to the deep circumflex femoral artery.[129]

Surgical Technique

The patient should be positioned in the supine position and a skin flap no larger than 8 cm in width or 16% in width of the thigh circumference should be designed to allow for primary closure, which should be confirmed using the pinch test.[140,141] The initial incision is made between the line from the anterior superior iliac spine and the lateral border of the patella using a No. 15 blade to protect the perforating vessels and deepened to the deep fascia to expose the underlying rectus femoris muscle and the vastus lateralis muscle using electrocautery. The main pedicle is identified, and the lateral circumflex femoral artery is identified in the intramuscular groove, between the rectus femoris muscle medially and vastus lateralis muscle laterally. The pedicle is then traced into the profunda junction, where it is ligated and the flap is then freed. The flap is isolated on perforators and descending branch of the lateral circumflex femoral artery. Multiple sutures are used to tether the skin to the subcutaneous tissue and muscle to prevent tearing. The subcutaneous tissue and fat are closed with 3-0 Vicryl, the skin is closed with staples, and a Jackson-Pratt drain is secured with 2-0 silk sutures. At this point, using the microscope, we perform the anastomosis of the artery with the facial artery or superior thyroid artery and the vein with the external jugular or facial vein using a 2.0 coupler system.

Complications

Many of the complications that may occur in the ALT flap at the recipient site are analogous to the complications listed earlier regarding the RFFF. However, some of the complications specific to the ALT flap occur at the donor site and include sensory loss in the distribution of the lateral femoral cutaneous nerve, and also weakness and instability at the initial postoperative visit in 8% of patients, but resolved within 6 months in all patients. There is some concern when dissecting a segment of the vastus lateralis (a crucial muscle in extension of the leg) or the motor nerve innervating the vastus lateralis; however, all patients returned to their preoperative functional level after surgery.[136,142]

Conclusion

At Boston Medical Center we favor the use of a radial forearm free flap or anterolateral thigh flap because of the versatility of the flap and the positive functional and esthetic outcomes received with these techniques. The use of a two-team approach with free flaps shortens the operative time and decreases risks associated with extended anesthesia and longer surgical procedures. SCIF and SMF are rarely used because of the multiple microvascular surgeons at our institution. However, we believe that both of these techniques result in optimal outcomes with reconstruction of the oral floor and are ideal in cases where operative time needs to be shortened because of patient comorbidities or if there is a lack of microvascular surgeons. PMMFs are currently more historical because of the bulky size of the flap and the resulting functional and esthetic deformities at the donor site. However, these flaps can be used for secondary reconstruction after flap failure or for reconstruction of larger defects.

Radiation Therapy Consideration in T2 Floor of Mouth Cancer

Floor of mouth SCC is one of the most aggressive oral cancers.[1,143] Early-stage oral cancer can be effectively treated with surgery or irradiation with equivalent local and regional control.[144] However, because of advancements in reconstructive surgical techniques, surgical excision is preferred to avoid long-term side effects of radiotherapy. Moreover, this will save the radiation option in cases of second primary cancers or recurrences. Definitive radiotherapy is an effective option in patients who refuse surgery or who are not medically fit for it. For locally advanced floor of mouth cancer, combined chemoradiation is considered for patients who are not candidates for surgery. In a series of 115 patients with stage III and IV cancers of the oral cavity, 76.5% partially responded and 20% achieved a complete response. The 3-year overall survival rate was 22%. The 3-year progression-free survival rates are higher in patients with buccal, mouth floor, and gum cancers: 51% compared to patients with retromolar and hard palate primary tumors (18%) and patients with tongue and lip cancers (6%) ($P < .0001$). The 3-year progression-free survival was 41% for N0 patients and 19% for patients with N+ disease ($P = .012$).[145]

The use of preoperative chemotherapy remains investigational. Licitra and colleagues[146] randomized patients with resectable oral cavity SCC into receiving chemotherapy followed by surgery in one arm or surgery alone in the other. Postoperative radiotherapy was given to selected high-risk patients. In the chemotherapy arm, postoperative radiotherapy was used less frequently (33% vs. 46%) and required fewer mandibular resections (31% vs. 52%), but there were three toxic deaths. However, there was no significant difference in overall survival (55% at 5 years).

Indication for Postoperative Radiotherapy

Adjuvant radiotherapy is selected for a subset of patients at significant risk of locoregional recurrence. Risk factors for locoregional recurrence include perineural invasion, lymphovascular invasion, two or more positive lymph nodes, positive margins, and extracapsular extension.[147-150] Based on level I evidence, pooling data from two independent prospective randomized clinical trials examining the addition of chemotherapy concomitantly with postoperative radiotherapy in patients with positive surgical margins or extracapsular extension of a positive lymph node, patients had significant improvement in locoregional control and disease-free and overall survival.[147-150] Patients with intermediate risk factors, including T3 or T4 tumors, perineural spread, vascular invasion, level IV or V pathologic nodes, and/or two or more involved nodes, benefit from adjuvant radiotherapy, but not from the addition of concomitant chemotherapy.[148] Currently, the Radiation Therapy Oncology Group (RTOG) is evaluating in a randomized prospective trial the addition of cetuximab to postoperative radiotherapy in patients with pathologic intermediate risk factors. The use of histologic grading as a prognostic measure of oral SCC is controversial.[151,152] The role of adjuvant radiotherapy for patients with T1/T2 floor of mouth cancers with one positive lymph node is unclear. In Germany, a randomized controlled trial is under way to evaluate the role of adjuvant radiotherapy in patients with early T1/T2 stage lesions with a single positive lymph node. Patients are randomized to postoperative radiotherapy or without adjuvant therapy following curative surgery. The aim is to enroll 560 patients with overall survival as the primary end-point.[153]

Van Es and colleagues studied the importance of surgical margins as a predictor of recurrence at the primary site in early-stage oral cancer.[154] They conducted a retrospective analysis on 82 patients who had complete excision of T1 or T2 N0 SCC of the mobile tongue or floor of the mouth without adjuvant therapy. Only 4% of patients had local recurrence at 4 years despite presence of perineural spread in 16%, angioinvasion in 3%, and a depth of invasion more than 5 mm in 57% of patients. Moreover, 17% of patients had second primary tumors in the head and neck area. Van Es and colleagues recommended saving radiotherapy for second primary tumors in cases of early oral cancers with clear resection margins despite presence of histologic adverse features.

Hicks and co-workers reviewed their experience in the treatment of 458 patients diagnosed with SCC of the floor of mouth over 20 years. They reported a high incidence of occult cervical metastasis in T1 lesions or greater (21%). The local control rate was 92% with negative margins versus 62% with positive or close (<5 mm) ones. Adjuvant radiotherapy increased regional control in stage IV disease.[1]

Shrime and colleagues researched the impact of adjuvant radiotherapy on survival in patients with T1/T2 N1 oral SCC.[155] They reviewed data of 1539 patients from the Surveillance, Epidemiology, and End Results database (SEER). The overall 5-year survival rate was significantly improved (41.4% for surgery alone vs. 54.2% for surgery plus radiotherapy, $P < .001$). The survival benefit was statistically significant for T2 but not for T1 disease. Patients with T2 cancers of the tongue and floor of mouth who received adjuvant radiotherapy showed the greatest survival benefit (52.3% vs. 37.9%, $P = .002$, and 39.9% vs. 17.7%, $P = .003$, respectively). However, the prognostic role of histologic adverse features was not reported in this population-based study.

Oral SCC tumor thickness predicts the aggressiveness of the tumor and its risk of cervical metastasis.[156] However, the optimal cutoff value remains controversial. A meta-analysis of 16 relevant studies of oral SCC concluded that 4-mm thickness is the cutoff for increased risk of cervical metastasis ($P = .007$).[157] Moreover, risk of contralateral metastasis in T1/T2 tongue SCC was significant when tumor thickness was greater than 3.75 mm.[158] In a retrospective review of 343 oral cavity cancers of the tongue and floor of mouth, the patients with FOM tumors 2.1 to 4 mm thick demonstrated a rate of nodal metastasis of 41.7%. In contrast, in oral tongue cancers, a similar thickness demonstrated only an 11.2% risk for nodal metastasis. In this study, the investigators found that FOM cancers reach the critical 20% threshold of probability for nodal metastasis between 1 and 2 mm. Thus, for a floor of mouth cancer with a tumor thickness of 2 mm or more, it is usually recommended to address the neck with a neck dissection or radiation therapy.[159]

Radiation Techniques

The most commonly used techniques in oral cancer radiotherapy are external beam radiotherapy (EBRT) and brachytherapy (BT). Over the past two decades, EBRT techniques have evolved to become more conformal with the increasing use of three-dimensional conformal radiotherapy (3DCRT) techniques and intensity-modulated radiation therapy (IMRT). IMRT ensures a high degree of target coverage while sparing adjacent organs at risk by using computer-generated algorithms for beam optimization and inverse treatment planning. Brachytherapy usually involves placement of a hollow catheter under general anesthesia. Radiation simulation is then performed with placement of "dummy" seeds to determine the optimal dosimetry and placement of the radioactive sources. The radioactive seeds or wires are then usually manually afterloaded when using low dose rate (LDR) brachytherapy at the bedside in a shielded room, and the treatment is delivered over hours to days. More recently, high dose rate (HDR) brachytherapy has evolved to minimize radiation exposure to

personnel. HDR brachytherapy is delivered over minutes in a dedicated HDR room using a remote afterloader.

LDR brachytherapy may also include interstitial permanent seed implants placed intraoperatively under general anesthesia. Brachytherapy allows the delivery of high doses of radiation directly to the tumor with very rapid falloff with minimal radiation to healthy tissues in a shorter treatment time compared to EBRT. Both can be used as a definitive or adjuvant treatment for oral cancer. Despite its effectiveness, BT use for oral cancer has declined, likely because of the technical expertise and specialized training needed, potential hazards to health care personnel, and the increased availability and quality of IMRT.

The French school of radiotherapy, notably at the Gustave-Roussy Institute, advocates definitive primary BT in early-stage floor of mouth cancers. Marsiglia and colleagues[160] presented their experience in 160 patients with T1/T2 SCC of the floor of mouth using afterloaded iridium-192 wires followed by neck dissection (T2 or N1) or observation (T1N0). In addition, they used adjuvant EBRT if pathologic nodes were confirmed histologically. They followed up patients for 9 to 19 years and observed an 89% survival rate at 2 years and 76% at 5 years. Local control rates were 93% in T1 and 88% in T2. A low rate of distant metastasis was noticed (5%), but second primaries developed in 31% of patients. Less than 10% of patients had severe mucosal necrosis; severe bone necrosis was seen in 2.5%. This was mainly observed in patients with poor dental status and those treated without protection during implantation ($P < .001$).

BT has also been used for postsurgical adjuvant radiotherapy. Lapeyre and colleagues[161] evaluated the efficiency of postoperative interstitial iridium-192 BT alone (by manual afterloading) in 36 patients with T1/T2 SCC or oral tongue (19 patients) and floor of mouth (17 patients) with positive or close margins. The overall and cause-specific 5-year survivals were 75% and 85%, respectively. Local control was 88.5% at 2 years. Two patients had new head and neck primaries and underwent curative treatment in nonirradiated tissues. A single patient developed grade III sequelae (bone and soft tissue necrosis). The same group also compared postoperative BT alone to postoperative combined BT and EBRT in 82 patients with close or positive-margin SCC of the mobile tongue or floor of mouth.[162] They concluded that postoperative BT alone for T1/T2 N0 is superior because of comparable overall survival rates and local control at 5 years (75%, 88% vs. 70%, 92%, respectively) with avoidance of post-radiotherapy side effects (e.g., xerostomia) and saving the option of radiotherapy for second primary tumors of the head and neck.

Timing of Adjuvant Radiotherapy

Ideally, radiotherapy should start as soon as the surgical wounds have healed. This usually takes about 3 to 4 weeks after surgery. Rosenthal and colleagues[38] conducted a retrospective review of 208 patients with head and neck SCC who had surgery followed by postoperative RT. They found improved tumor control and survival when the treatment package time (from surgery to completion of RT) was less than 100 days. Moreover, increasing the total radiation treatment time and interruptions of treatment longer than 1 week were predictors of increased locoregional failure.[163] Hosokawa and associates studied the effect of total treatment time in 94 patients with T1/T2 N0 SCC of the oral tongue treated with EBRT and adjuvant BT.[164] Using regression analysis, they found a 2% loss of control per day of treatment extension over 30 days ($r = 0.94$, $P < .01$).

Altered Fractionation Techniques

Altered fractionation schedules have been extensively studied in the treatment of head and neck cancers, which demonstrate a survival benefit compared to standard fractionation when using radiotherapy alone.[165] *Hyperfractionation* uses fraction sizes smaller than the standard 1.8 to 2 Gy daily to exploit the difference in fractionation sensitivity between cancer cells and normal surrounding tissue cells manifesting late morbidity. It is a useful technique in slowly growing tumors. Rationale for hyperfractionation is to spare late-responding normal tissue from radiation injury. A common example of this technique is to deliver 1.15- to 1.2-Gy fractions twice a day, 6 hours apart over 7 weeks for a total of 80.5 to 81.6 Gy.

On the other hand, *accelerated fractionation* regimens are useful in rapidly growing tumors. Standard fraction sizes are used, but the overall treatment time is reduced. It aims to minimize tumor proliferation as a major factor in treatment failure. The many variations in this technique can be classified into those with and without reduction of the conventional total dose. A commonly used regimen is 54 Gy in 30 fractions over 6 weeks in addition to an 18-Gy boost dose given in 1.5-Gy fractions as a second daily dose in the last 2.5 weeks.[166] The use of altered fractionation has been declining despite its proven benefits. This resulted from the introduction of IMRT, which can incorporate principles of both hyperfractionation and accelerated fractionation with the ability to "dose paint" to give higher fractional doses to the tumor, and reduce the dose by smaller fractional doses to the normal tissues/organs at risk.

Most head and neck cancer recurrences usually occur in the high-dose regions of treatment. This indicates that dose escalation alone may improve outcome in a subset of patients. However, escalation of total dose is limited by normal tissue tolerance. Hence efforts have been made to use chemotherapy such as cisplatin and targeted therapies as radiosensitizers to enhance the efficacy of radiation.[167] For example, epidermal growth factor receptor monoclonal antibody (cetuximab) has proven to be an effective biologic agent to improve radiosensitivity without increasing late side effects.[168,169]

Radiotherapy Planning

It is crucial to obtain adequate presurgical imaging that outlines the tumor, especially in early-stage tumors (e.g., PET/CT or MRI) to facilitate mapping the tumor volume for potential adjuvant radiotherapy. Wound healing, reconstruction flaps, and distortion of the original anatomy may complicate postsurgical imaging for radiotherapy planning.

The patient is stabilized in a supine position using a custom-made thermoplastic mask covering head and shoulders. An intraoral device may be used to keep the mouth open and to elevate the tongue tip and dorsum away from the field of radiation in the floor of the mouth and to keep the upper hard palate away from the high-dose radiation field. Thin-slice CT scans are obtained in treatment position, and different target volumes are contoured on the CT. In the postoperative setting, high-risk areas such as the location of positive margins or extracapsular extension may receive 60 to 66 Gy, while low-risk areas receive 54 to 56 Gy in 30 to 33 fractions.

In the definitive radiotherapy setting for a floor of mouth SCC, the gross target volume (GTV) should include the primary tumor and bilateral draining lymphatics, as most cases cross the midline. Neck treatment (with surgery and/or radiotherapy) is recommended when the risk of occult nodal metastasis is greater than 20%.[60] Most commonly involved neck lymph nodes are in levels I through III. The rates of skip metastasis in the clinically N0 neck to levels IV and V are generally low (6.5% and 2%, respectively).[170] Nonetheless, they are commonly covered in the planned target volume (PTV) because, in contrast to surgery, adding levels IV and V in radiotherapy does not significantly increase morbidity.

Treatment radiation dose depends on the primary tumor and node size, fractionation, and clinical findings. The total conventional dose for treatment of oral cancer is 66 to 70 Gy fractionated by delivering 2 Gy over 6 to 7 weeks of treatment. The prescription of the dose requires a balancing act to maximize the *therapeutic ratio* by giving sufficient curative dose of radiation to the tumor while minimizing the dose to normal surrounding tissues within normal tissue tolerance. In cases of adjuvant RT, there is not an actual GTV but a virtual one (vGTV) in the area where the preoperative tumor was seen clinically and radiographically. Generally, two or three clinical tumor volumes (CTVs) are outlined. CTV1 outlines the area that will receive the highest dose (typically 60 to 66 Gy) including the primary and nodal vGTV plus a margin of 0.5 to 1 cm. CTV2 covers the areas of intermediate risk, which includes an additional margin to CTV1 in the area of the primary tumor and dissected neck areas without nodal involvement (60 Gy). Finally, CTV3 covers the area that will receive an elective dose (54 to 56 Gy) for subclinical disease. For example, if perineural invasion is present, treatment should cover the ipsilateral or bilateral (if the tumor crosses the midline) lingual and inferior alveolar nerves up to the mandibular nerve or even to the foramen ovale in larger tumors.

Adaptive radiotherapy in head and neck cancer is of increasing interest because of anatomic and tumor changes in position and shape during radiotherapy, which may be seen with image-guided therapy during treatment using cone-beam CT. Integration of PET/CT using 18-fluorodeoxyglucose (FDG) has been shown to improve defining pretreatment GTV.[171] Moreover, it may potentially improve adaptive radiotherapy planning if there are changing areas of metabolic tumor volume during treatment. If these areas are identified consistently, potential dose escalation to radiation-resistant areas could be considered. In a comparative study of 10 patients using PET/CT at three sequential time points before and twice during radiotherapy, deformable registration was used to co-register the second and third PET/CT scans acquired during treatment.[172] Limitations of FDG-PET in being able to distinguish tumor from inflammation or define the radioresistant areas have led investigators to study alternative radiotracers. These include PET with ^{18}F-fluoromisonidazole (FMISO). FMISO characterizes hypoxic volumes in head and neck cancers, such that potential applications for radiotherapy planning include dose escalation to hypoxic regions using IMRT dose-painting techniques and potentially improving tumor control probabilities by up to 17% without increasing expected complications.[173] Other radiotracers include Cu-diacetyl-bis(N4-methylthiosemicarbazone) (Cu-ATSM), which is a hypoxia-avid positron emitter radiotracer.[174]

Complications

Radiotherapy can produce both acute and late toxicities. Acute side effects usually result from radiation effects on rapidly dividing cells, whereas late complications result from effects on slowly dividing cells. Acute toxicity includes effects on skin, mucous membranes, and salivary glands. This may result in skin erythema, hyperpigmentation, mucositis, and acute xerostomia. Special attention should be paid to areas adjacent to dental implants and metallic fillings, as they cause radiation scatter, intensifying the dose in some areas. Radiotherapy reduces salivary volume and changes salivary composition, making it more viscous. Moreover, patients may develop a bland or metallic taste that may take a long time to disappear.

The exact mechanism for late complications is not fully understood. It may be related to a combination of microvascular endothelial damage, fibrosis, and death of the parenchymal cells. This includes the risk of skin atrophy, fibrosis, contractures, telangiectasias, late xerostomia, hypothyroidism, development of secondary cancers, and osteonecrosis. Floor of mouth cancer treatment will typically include a significant radiation dose to the mandible. Tooth extraction can initiate the osteonecrosis process. Hence, preoperative dental health optimization is critical. Hyperbaric oxygen may help in preventing osteonecrosis prior to dental extractions but has limited benefit if bone necrosis has occurred. Maintaining optimal oral hygiene before, during, and after radiotherapy is of utmost importance to avoid complications.

Speech and Swallow Rehabilitation

Speech After Surgery

The patient with T2 cancer involving the anterior floor of mouth is almost always left with functional deficits involving speech and/or eating and swallowing. The tongue is a major organ used for both talking and eating, and its inferior attachments to the hyoid and thyroid cartilages via various muscles and ligaments are important for swallowing. The severity of the problem depends largely on the extent of resection, the type of reconstruction, and whether there

was additional radiation therapy. Speech, in the most general sense, includes articulation, resonance (nasality), and voice. After surgery, the anterior tongue and floor of mouth cancer patient will usually have more difficulty with articulation, but resonance and voice will not be affected. The extent of the articulation impairment depends on two things: the volume of tongue resected and the type of reconstruction. If less than half of the tongue is resected and is left mobile, there will be minor permanent effects on speech. However, if more than half is resected, articulation will suffer, and this may be difficult to overcome completely. The tissue used for reconstruction may help provide bulk to the tongue, but it may also be detrimental for articulation if it is large, because it will not be native muscular tissue like the rest of the tongue. If tethering of the tongue to the floor of mouth occurs, with or without reconstruction, articulation will almost always be adversely affected. The most vulnerable portion of the tongue is the anterior portion, particularly the tip. This portion of the tongue is characterized by very rapid, fine movements and exact postures to produce many of the sounds in the English language (e.g., t, d, s, z, ch, zh, l, th, r).

At our medical center, the speech-language pathologist (SLP) assesses the altered articulation via a combination of perceptual and acoustic measures as well as more global measures of intelligibility. A physical examination of the oral mechanism is performed to help the examiner understand the severity and nature of the problem. Therapy consists of changing general speech habits, such as teaching the patient to speak more carefully and slowly, and focusing on specific speech sounds that are distorted. The ability of the patient to hear or perceive his or her own speech is a critical factor in clinical progression. Sometimes specific sounds are impossible to produce, and other sounds can be taught to be substituted for the target sounds. The patient's need for acceptable versus "normal" speech in her outside life and the degree to which the postsurgical impairment affects the patient largely determines the aggressiveness of therapy.

Eating/Swallowing After Surgery

The act of deglutition includes an oral stage, a pharyngeal stage, and an esophageal stage. Surgery to the anterior tongue affects the oral stage, whereas surgery to the floor of the mouth affects the pharyngeal stage. The oral stage includes oral preparation of the bolus and lingual propulsion. If some of the tongue is resected, patients will have difficulty manipulating food within the oral cavity and containing it in the mouth. This may require the person to change her diet and restrict consistencies to soft, semi-solid, and puree consistency that do not require extensive chewing and therefore can be swallowed nearly whole. If the patient cannot clear the entire bolus from the mouth with sweeping movements of the tongue, she may learn to compensate with a liquid wash.

The pharyngeal stage encompasses many movements that act to elevate and seal the nasopharynx and airway as well as the movements that cause the pharyngeal walls to constrict against the base of tongue and larynx and squeeze the bolus through the entire pharynx and into the esophagus. The pharyngeal stage begins with movements that form the initiation of the swallow, which can be thought of as a transition from oral to pharyngeal stages. A critical structural movement occurring at the initiation of the swallow is hyoid elevation. Muscles connecting the tongue to the hyoid bone may be affected, weakening tongue propulsion. More importantly, hyoid excursion facilitates laryngeal elevation and airway closure. If some of the suprahyoid muscles that elevate the hyoid are resected, this movement may be reduced, thus compromising airway closure. The patient is then more likely to aspirate at the onset of the swallow.

Immediately after surgery, the patient with a T2 floor of mouth resection is likely to experience dysphagia. However, over time, some of the structural movement will improve as adjacent muscles learn to compensate for the missing ones. This will likely lead to an improved diet and quality of life. Patients receiving adjuvant radiotherapy typically suffer from functional setbacks. Head and neck radiation causes fibrosis in the connective tissue and muscle fibers. It will thicken the connective tissue, and it may cause webs and strictures within the pharynx. The physiologic effect is to reduce the contractile force of the muscles and the range of movement of associated structures. The base of tongue may not retract to the extent of the pharyngeal wall, and the hyoid bone and laryngeal cartilages may not move superiorly and anteriorly to their full extent. From the perspective of the SLP, muscles appear to be "stiff." The result is residue of food and liquid left in the pharynx after the swallow. The patient may be able to clear it with a liquid wash, or he may have to spit it out. Usually this leads to a reduction in diet options.

Evaluation of Dysphagia

At Boston Medical Center we have three evaluation methods to choose from when a patient complains of difficulty swallowing. The clinical evaluation is always done first: The patient is interviewed and an oral motor examination is conducted. This is usually followed by an instrumental examination. We have two types of instrumental examinations: a FEES (fiberoptic endoscopic evaluation of swallowing) or a fluoroscopic study. Our first examination is usually FEES because it is readily available in the clinic or can be brought to the bedside, and is the best tool to visualize the altered anatomy. If there is a question of esophageal or upper esophageal involvement, we will then follow the FEES examination with a fluoroscopy examination of the oral and pharyngeal stages of swallowing, or the modified barium swallow. These examinations help the SLP to understand exactly what is disordered and will help to guide possible interventions that may alleviate the problem. For example, if residue forms in the vallecula, the patient may be taught to chew more, to take wetter foods, or to wash with a liquid bolus. He may also be taught exercises that target the hyoid and larynx such as the Shaker exercise.[175] After training with this exercise for 4 to 6 weeks, the hyoid and larynx may be able to move in a greater range, and this may help to reduce the residue in this region.

Treatment of Dysphagia

There are two modes of treatment for the patient with T2 floor of mouth cancer or tongue cancer: compensatory and rehabilitative. Compensatory techniques may include postural changes, dietary modifications, or behavior changes (e.g., taking a liquid wash after swallowing solid food). Rehabilitative techniques include exercises to strengthen muscles and increase range of movement. Some techniques such as the suprasuper glottic swallow maneuver are mainly compensatory but may be rehabilitative as well, as they require the person to swallow with some effort. This swallow maneuver is ideal for the head and neck cancer patient who cannot contain the bolus in the mouth easily due to limited residual postsurgical tongue volume. The maneuver has four steps that the person needs to implement every time she takes a liquid bolus: (1) Put the liquid in your mouth. (2) Hold it in the mouth for a second or two while you hold your breath tight. (3) Swallow while keeping your breath held tight. (4) Release the swallow with a light cough out. This maneuver will prevent any of the liquid that has spilled out of the mouth before the airway has closed for the swallow from falling below the vocal folds into the trachea. This occurs because the person is purposely holding his breath early, thereby sealing the glottis. When he releases the swallow with a cough out, any residual bolus that is resting in the larynx will be ejected, thus preventing aspiration a second time.

Patients at our institution are evaluated serially during their care, including prior to the primary modality treatment. The goals of therapy, broadly speaking, are to maintain weight, muscle function, and diet. We believe it is important to continue taking some food or liquid orally during radiation so that the swallowing muscles do not stiffen any more than is necessary. A study performed at Boston Medical Center showed that radiated patients who maintained some degree of oral alimentation during radiation therapy attained a more normal diet than patients who stopped taking any food or liquid.[176]

In summary, the speech-language pathologist plays an important role in the rehabilitation of the head and neck cancer patient. Eating and nutrition are major contributors to quality of life. After the cancer is treated, the SLP helps the patient regain a normal life by helping to restore this very important function. Our approach focuses on early and repeated patient assessment and the use of adaptive therapy to meet patient goals.

Conclusion

The management of T2 squamous cell carcinoma of the floor of the mouth fills a unique niche clinically, in which disease has progressed locally, but has not invaded the mandible or metastasized to cervical lymph nodes. The incidence of tumors in this location has decreased over time and is strongly linked to known risk factors. Despite the ease of clinical examination, patients continue to present as stage II and beyond. Although routine screening of the population at large has not been shown to improve outcomes, case findings in higher risk patients have shown that screening improves survival. The assessment of tumors includes a thorough examination and a directed series of imaging studies, both of which provide valuable information for surgical planning and prognosis. Our institutional philosophy closely mirrors that of the NCCN guidelines, including stipulations for surgical margins and treatment of the N0 neck. We recommend surgery as a primary modality, and reserve radiation for the adjuvant setting, with or without chemotherapy based on adverse histologic features. All patients are reviewed at our Head and Neck Interdisciplinary Tumor Board, which serve to address prompt, guideline-driven treatment of the primary and lymphatic basin but function as well. Patients, physicians, and allied health providers are encouraged to comprehensively integrate care with an emphasis on early SLP evaluation, often prior to surgery. Reconstructive modalities take into account patient needs, desires, and willingness to undergo lengthy procedures, and most importantly function and quality of life.

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23

Early Oromandibular Cancer

YAVUZ YILDIRIM, KEVIN ARCE

Clinical Presentation and Pertinent Anatomy

The gingiva is part of the masticatory mucosa that provides an internal defense mechanism against pathogens and mechanical stress. It is composed of a dense, vascular fibrous tissue with a keratinized stratified squamous epithelium. The gingiva extends from the alveolar crest and interdental bony septa to the mucogingival junction.[1] The transition from the gingiva to the alveolar mucosa at the mucogingival junction is marked by a change in color and tissue mobility. The underlying alveolar bone provides support to the existing teeth, and its arbitrary inferior border is the root apices of the teeth. It relies on the presence of teeth for its development and the maintenance of bone mass.

The gingiva has been traditionally subdivided into free, attached, and interdental gingiva. The attached gingiva is firmly bound to the periosteum and to the dentition. The free gingiva is that portion of the unattached gingiva around the cervical region of each tooth; the interdental gingiva (papilla) fills the space between them. The gingiva's densely collagenous lamina propria is composed of the supra-alveolar fiber apparatus, blood supply, lymphatic vessels, and nerves. Lymphocytes, plasma cells, and macrophages can be identified within the lamina propria, where they defend the body against the constant microbial challenge from the oral flora and aid in the healing of the masticatory mucosa from chronic trauma.[1] The supragingival fiber apparatus contains types I and III collagen and provides a dense framework for the attachment of the gingiva to the teeth and bone. It accounts for the gingiva's rigidity and biomechanical resistance.[1]

The arterial blood supply of the mandibular gingiva originates from the perforating branches of the inferior alveolar artery and lingual artery. The venous supply is predominantly from the buccal and lingual veins, which drain into the pterygoid venous plexus. The lymphatic drainage of the labial and buccal mandibular gingiva posteriorly is into the submandibular nodes and anteriorly into the submental lymph nodes. The lymphatic drainage of the lingual gingiva is to the jugulodigastric lymph nodes either directly or indirectly through the submandibular nodes.

Early oromandibular carcinomas can be present in the gingiva. The gingiva is believed to represent an uncommon site for oral cavity malignancies. Gingival carcinomas represent 5.6% of all oral cavity malignancies and 6.4% of oral squamous cell carcinomas.[2] Gingival carcinomas are more common in the mandibular alveolus[3] and are associated with a slightly older patient population with no risk factors when compared with the other oral cavity sites.[4,5] The median age at the time of diagnosis is 69 years,[2] and gingival carcinoma appears to be more common in the edentulous alveolus. This particular characteristic could be secondary to progressive tooth loss from dental disease and not from an increase in the malignant transformation potential of the attached gingiva in the edentulous alveolus.[3] The presence or absence of dentition has been found to not affect the incidence of bony invasion, which, when present, has an impact on survival.[6] Gingival carcinomas have a distinct clinical behavior when compared with other, more common oral cavity sites. The exact mechanism behind this is not completely understood, but the type of oral epithelium from which the oral cavity carcinoma develops appears to influence its clinical behavior and prognosis.[7] Oral cavity carcinomas that originate from keratinized epithelium are more common in women[3,7] with no risk factors. Also, when comparing oral carcinomas that develop in nonkeratinized, keratinized, and tongue epithelium, the nonkeratinized epithelium carcinomas have a lower disease stage and tend to be well differentiated. Therefore patients with nonkeratinized oral epithelium carcinomas have a better survival rate when compared with those originating from the keratinized epithelium.[7]

Gingival carcinomas can represent an insidious disease because their clinical appearance does not typically resemble that of a malignant neoplasm. They are often misdiagnosed as an infectious, traumatic, or inflammatory lesion. Carcinomas typically begin as a red or white patch without ulcerative or mass-like features.[5,7] Because of this, they are typically mistaken for gingivitis, periodontal disease, a tooth abscess, or denture sores. This misdiagnosis leads occasionally to invasive procedures such as a tooth extraction or curettage, which delay definitive treatment of a lesion already present for several months to over a year.[8] Patients may have pain, ulceration, loose teeth, delayed healing of an extraction socket, or ill-fitting dentures. Of these, the most common symptom is pain, followed by loose dentition and an ill-fitting denture.[6] An early review of 606 gingival carcinomas reported that dentists were the first practitioners to see and diagnose over 60% of patients with gingival carcinomas.[9]

Several studies have established the relationship between a tooth extraction and the presence of medullary bone invasion and poor outcomes in patients with gingival carcinomas.[9–13] Suzuki and colleagues found that the incidence of positive lymph nodes was higher in patients undergoing an extraction when compared with the non-extraction group. Not surprisingly, the 5-year survival rate was also worse in the extraction group than in the control group.[11] Two theories have been proposed for the mechanism of bone invasion after a tooth extraction[12] The first is that the tumor originates from the gingival epithelium and the cells spread through the tooth socket and invade the cancellous bone once the tooth has been extracted and the physical barrier is removed. The second theory is that the tumor originates in the gingival epithelium, penetrates through the periodontal ligament space, and leads to subsequent bony destruction. The tooth support is then compromised by this bony destruction, leading to mobility and need for an extraction. The role of the delay in diagnosis in patients undergoing an extraction and overall outcome cannot be ignored. The mean interval between an extraction and diagnosis of a gingival carcinoma has been estimated to be 63 days.[11] Also, one has to consider that patients with medullary bone invasion in need of a tooth extraction might have more aggressive disease, demonstrated by tumor infiltration and bone destruction.

The gingiva is typically 1 to 3 mm in thickness; because of the bone proximity and lack of anatomic barriers, even small gingival carcinomas can demonstrate bone invasion at the time of initial evaluation. There is cortical invasion in approximately one third of patients and cancellous invasion in 12% of patients with a gingival carcinoma.[6,10] Bone invasion may be difficult to assess on clinical examination owing to the firm attachment of the lamina propria to the underlying bone. Perineural invasion may manifest as facial pain or paresthesias of the inferior alveolar nerve and mental nerve distribution. A retrospective study of 155 previously untreated patients with mandibular gingiva carcinoma demonstrated that clinically evident cervical lymphadenopathy can be found in 18.7% at initial presentation. Also, 15% of patients with clinically negative neck examinations had occult nodal metastases, providing a total rate of cervical metastases of 25% in patients with mandibular gingival carcinomas.[14]

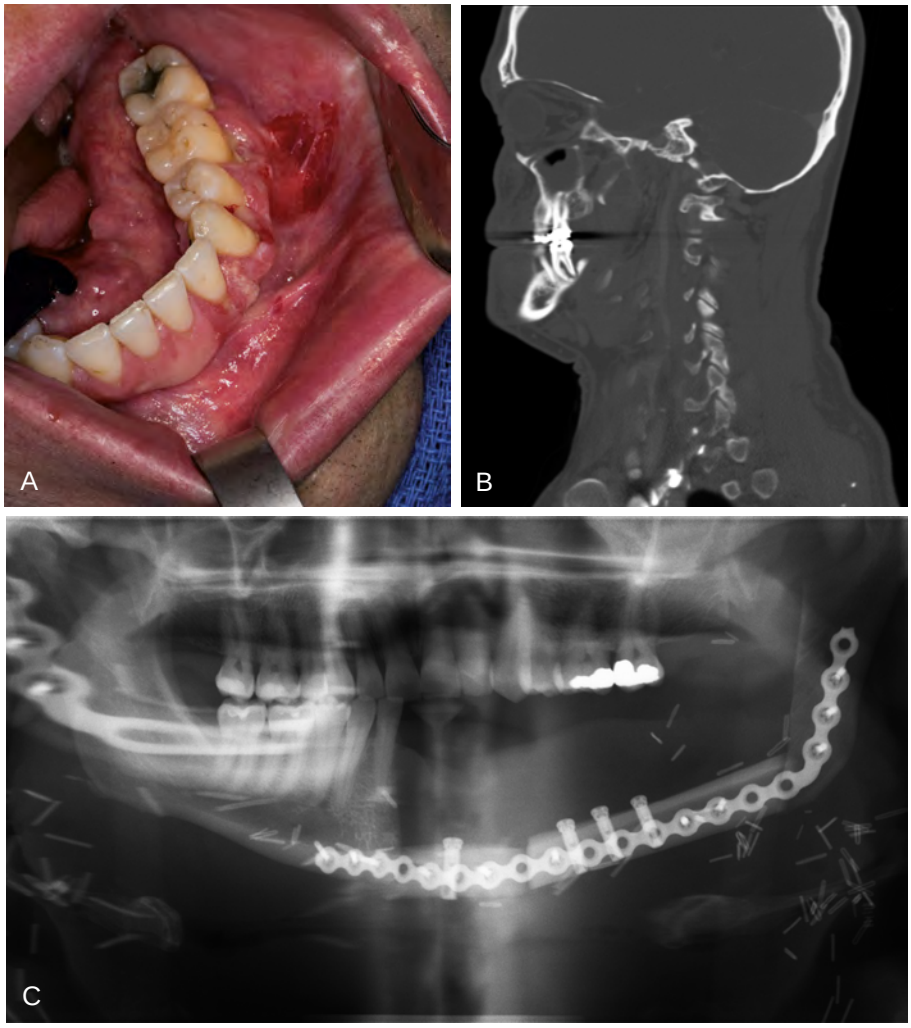
Staging

Tumor staging helps to categorize the anatomic extent of a malignancy. It provides guidance when outlining treatment options, helps to estimate prognosis, and allows for comparison of treatment outcomes of similarly staged patients. The TNM classification devised by the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) is internationally accepted and widely used in head and neck squamous cell carcinomas. The TNM classification does not predict the biologic properties of specific tumors, and as seen on occasion, the clinical behavior of a malignancy does not correlate with its anatomic extent. Clinical stage for alveolar carcinoma is determined by physical examination and radiologic examinations. TNM classification and staging of mandibular gingival squamous cell carcinoma is the same as for the other oral cavity sites. Superficial bony or tooth socket erosion alone by a gingival primary is not sufficient to classify a tumor as T4. Approximately 78% of patients with lower alveolar squamous cell carcinoma exhibit clinical T1/T2 disease.[10]

As part of the medical history, it is important to establish the timeline of initial presentation of the lesion and its progression, presence of risk factors, and previous history of head and neck malignancies. A comprehensive head and neck examination is performed; the tumor dimensions and its thickness are documented, and the remaining oral cavity is assessed for a second primary tumor. Evaluation of the nasopharynx, oropharynx, hypopharynx, and larynx via flexible endoscopy for the presence of a synchronous tumor is also conducted. Mandibular invasion is of clinical importance in oral cavity carcinomas because it influences the clinical staging of tumors and affects the overall prognosis. The presence of bone involvement also affects surgical treatment decisions; underestimating its presence and the tumor extent may lead to incomplete excision, which increases the risk of local, regional recurrence or distant metastasis. Lower gingiva carcinoma is the third most common oral cavity site with bone invasion, after carcinoma of the floor of the mouth and retromolar trigone carcinomas.[15] Although clinical evaluation by an experienced clinician can help predict bone invasion in oral cavity carcinomas,[16] the ability to identify the presence of bone invasion in gingival carcinomas by physical examination alone is challenging, given the natural adherence of the gingiva to the underlying alveolar bone. Clinical assessment can also lead to an overdiagnosis of bone invasion[17,18] (Fig. 23.1). Radiographic imaging, such as orthopantomograms (OPGs), computed tomography (CT) scans, magnetic resonance imaging (MRI), and bone scans, is necessary to determine the presence of bone involvement.[19] No single imaging technique is accurate enough to singlehandedly predict the presence of bone invasion in head and neck carcinomas. The combination of several imaging modalities to increase accuracy is used at times to assess bone invasion.

OPGs provide a complete single view of the mandible and existing dentition. Artifacts from superimposition of the airway, cervical spine, or hardware could limit the effectiveness of this modality in determining bone involvement in certain areas of the mandible such as the symphysis and the angle region. The amount of demineralization that needs to take place before radiographic changes are evident limits its sensitivity and results in failure to capture early cortical involvement.[20] When compared with physical examination alone, OPGs are more specific and have a better positive predictive value.[18] When used for diagnostic evaluation of oral cavity carcinomas, OPGs should be used with a more sensitive test to determine bone invasion in order to increase their reliability.[21]

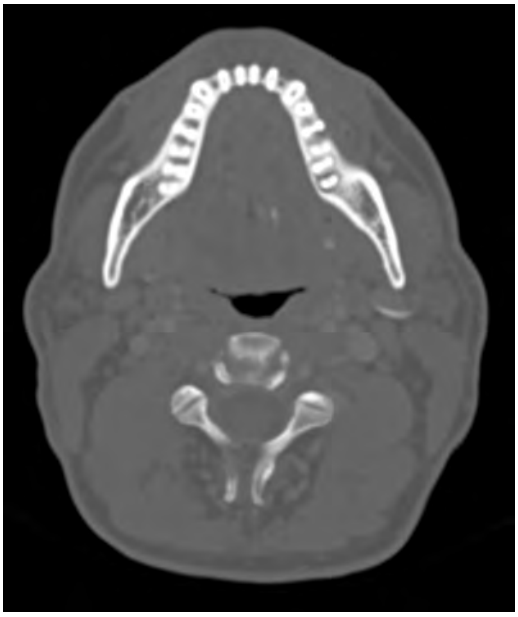
CT scans are readily used in the evaluation of head and neck carcinomas because they provide radiographic assessment of the tumor, surrounding soft tissue, bone, and cervical lymph



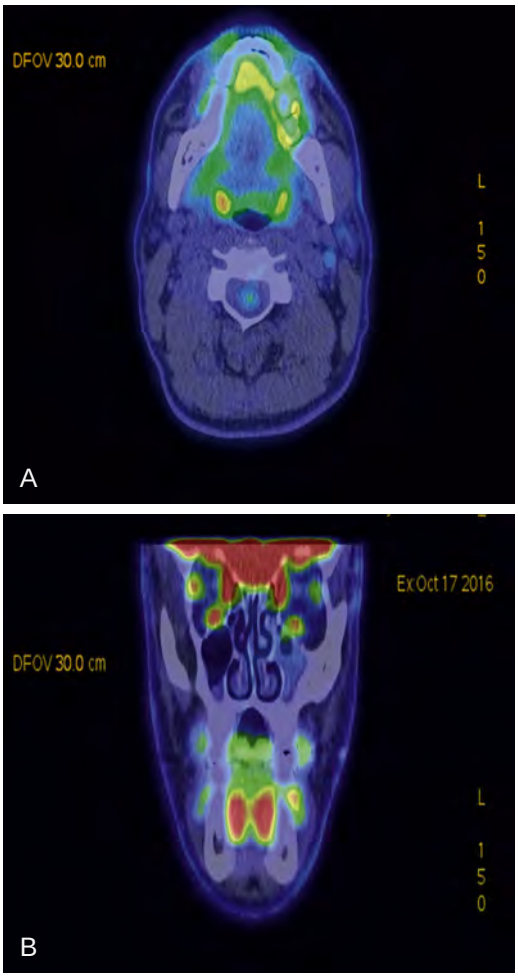
• **Fig. 23.1** **A,** Lower gingiva squamous cell carcinoma in a 45-year-old man. **B,** Bone involvement predicted by computed tomography (CT) scan on patient with a posterior mandibular gingival carcinoma. **C,** Segmental mandibulectomy performed and immediate reconstruction performed with free fibula flap and immediate implant placement. Final pathology revealed T2 tumor.

nodes. CT criteria for bone invasion are cortical or medullary disruption adjacent to the tumor. Artifacts caused by dental restorations can limit the ability of CT to assess the tumor dimensions and the presence of bone invasion. It can also be difficult to distinguish bony changes around the dentition as either being secondary to periodontal disease or indicative of mandibular invasion (Fig. 23.2). Li and colleagues, in a systematic review of the use of CT for diagnosis of mandibular invasion, found that CT had a mean sensitivity of 0.72 and a specificity of 0.90.[22] Cone-beam computed tomography (CBCT) scans are used routinely in dental implant treatment planning and in the assessment of dental pathology and impacted teeth because of their high spatial resolution and low radiation dose. Momin and colleagues examined 50 patients with lower gingiva carcinoma and compared cone-beam CT with OPGs.[23] In evaluating alveolar bone invasion, false-negative results were less frequent with cone-beam CT scans than with OPGs. Cone-beam CT scans had a sensitivity of 92% versus 79% for OPGs in determining bone involvement. The authors found that cone-beam CT scans provide high-resolution images at the alveolus, but their ability to identify early bone invasion can be affected by the presence of dental artifacts along the alveolar crest.

MRI scans are the imaging modality of choice when evaluating soft tissue lesions. MRI can detect early soft tissue changes and the presence of medullary bone involvement in a malignancy. It is not affected by metal artifacts as much as CT scans are but is less reliable in evaluation of cortical bone involvement. MRI scans have a relatively higher sensitivity than CT, but CT scans have a higher specificity.[15,24] Given this, CT scans are a better diagnostic evaluation to exclude mandibular involvement when compared with MRI scans. A systematic review assessing the diagnostic accuracy of different imaging modalities in the assessment of bone invasion in oral carcinomas found sensitivity values of 94% for MRI, 91% for CBCT, 83% for CT, and 55% for panoramic



• **Fig. 23.2** Bone changes along root of tooth #18 adjacent to biopsy-proven gingival carcinoma.



• **Fig. 23.3** **A** and **B,** Positron emission tomography–computed tomography (PET-CT) scans used in staging of left mandibular alveolus carcinoma. Physiologic uptake noted along the lingual aspect of the mandible.

x-ray studies and specificity values of 100% for CT, MRI, and CBCT, 97% for positron emission tomography–computed tomography (PET-CT), and 91.7% for OPGs.[25] With these findings, the authors demonstrated that current diagnostic modalities more precisely rule out mandibular bone invasion than detect it. Their clinical use should be oriented toward diagnostically suspected cases of bone invasion in patients with oral cavity carcinomas rather than as a screening test. A careful clinical examination, plain radiography, and cross-sectional imaging are important to assess the extent of tumor spread and the presence of bony invasion.

The clinical evaluation of cervical lymph nodes is an important parameter in the treatment of oral squamous cell carcinoma. Common modalities include clinical palpation, ultrasound, CT scans, MRI scans, ultrasound, and ultrasound-guided fine-needle aspiration. Clinical palpation is insufficient for detection of cervical lymph node metastasis.[26] The diagnostic accuracy of palpation is estimated to be between 59% and 84%, and a metastatic lymph node has to be at least 1 cm in diameter to be palpated under the sternocleidomastoid muscle.[27,28] Contrast-enhanced CT scans and contrast-enhanced MRI scans are the primary diagnostic tools used when assessing the cervical lymph nodes. CT scans provide a reliable diagnostic tool for the detection of metastatic lymph nodes.[29] The CT criteria for nodal metastases are nodal size and shape, presence of central necrosis, nodal grouping, and radiographic evidence of extracapsular extension.[30] Cervical lymph nodes larger than 1.5 cm in the jugulodigastric chain and larger than 1 cm for all other cervical nodes are suspicious for regional disease. The presence of three or more contiguous lymph nodes in the drainage nodal basin is also suspicious for metastatic involvement. Central necrosis represents radiographic evidence of tumor infiltration and necrosis in the medullary region of the lymph node. Round lymph nodes tend to have tumor deposits, and the loss of tissue planes around a lymph node is suggestive of extracapsular extension.

Ultrasound is a noninvasive and cost-effective diagnostic method for head and neck cancer staging but is limited by the radiologist's experience.[31,32] PET-CT is advised for stage III or IV disease to detect distant metastases and synchronous lesions[33] (Fig. 23.3). Its main limitation in the evaluation of the neck is the inability to detect small positive lymph nodes. Its negative predictive value has been estimated to be 90% because more than 40% of metastatic lymph nodes are less than 7 mm in diameter.[34,35]

Management Principles and Known Outcomes

The overall goals of treatment for oral cavity carcinomas are to eliminate the carcinoma while restoring or preserving form and function and minimizing complications. Treatment of primary carcinomas of the lower gingiva is influenced by tumor-related

factors such as the size and location and the presence of pathologic high-risk factors such as perineural invasion, positive margins, and nodal disease. According to the National Comprehensive Cancer Network (NCCN), T1/T2 tumors may be initially treated via surgical resection of the primary tumor with or without neck dissection or sentinel node biopsy. The principal surgical treatment plan decisions are centered on the need for either partial or segmental mandibulectomy, need for cervical lymphadenectomy, and reconstruction of the ablative defect. Patient-related factors that may influence management strategies include overall health, functional status, social history, and expectations. Definitive radiation therapy may be offered to patients who are medically inoperable or refuse surgery.[36]

The lack of a definitive method for predicting the presence and extent of bone invasion in gingival carcinomas can make the decision of whether to perform a marginal or segmental mandibulectomy a challenging one. T1/T2 mandibular gingival tumors can be treated with a marginal mandibulectomy, which provides appropriate functional and cosmetic results by preserving mandibular continuity without affecting overall outcomes. When considering the type of mandibulectomy and outcomes, marginal bone resection is as effective as segmental resection in the local control of gingival carcinomas, particularly for small lesions.[5,10,15,37–39] Use of the size of the primary lesion to make the determination of whether to perform a segmental or marginal mandibulectomy appears to assign patients into the appropriate treatment category.[6]

For much of the twentieth century, it was believed that the lymphatics in the oral cavity passed through the periosteum of the mandible on their way to the cervical lymph nodes.[40] As a result, segmental resections were advocated for tumors from the floor of mouth or tongue that were in close proximity to or involving the mandible.[41] The first recommendation of mandible preservation in the management of oral cavity carcinomas was by Ward and Robben, who recommended a "pull-through" procedure for tumors located at a distance greater than 1 cm from the lingual aspect of the mandible.[42] The first report of the use of marginal mandibulectomies in patients with floor-of-mouth carcinomas was reported in 1953.[43] The work of Marchetta and colleagues provided the initial evidence disputing the link between periosteal involvement and presence of regional disease. These authors found that tumors invaded the mandible directly through the clefts along the mandible surface and that the periosteum served as a barrier to invasion.[44,45] Several studies thereafter supported the fact that the bony invasion of the mandible was through the occlusal surface of the alveolar ridge, typically through cortical defects or tooth socket in the dentate patient.[46–48] In the previously irradiated mandible, this route of tumor entry changes owing to the loss of the protective barrier from the periosteum. Tumor entry can be through direct invasion and multifocal in nature.[46,47] Patients with a history of radiation therapy for management of head and neck malignancy who have a second primary involving the lower gingiva should undergo segmental resection for oncologic safety.

There are two histologic patterns of bone invasion.[48,49] In the invasive pattern, there are islands and fingers of tumor that invade the cancellous bone with little osteoclastic activity and no connective tissue layer. In the erosive pattern, the tumor advances through a broad front; there is a connective tissue interface, and osteoclastic activity occurs between the tumor and bone. Conventional radiography cannot accurately predict the two types of bone invasion, especially in early cases in which bone defects are localized to the alveolar bone region or on the lingual aspect of the mandible.[50] In patients with radiographic evidence of an erosive pattern, the extent of the bone involvement histologically does not appear to exceed the extent of the radiographically detected bone defect.[50,51] On the contrary, the invasive type is associated with histologic evidence of invasion past the radiographic bone defect.[50] In mandibular gingiva carcinomas, the bone invasion is typically broad and no more than a few millimeters past the tumor front, making a 1-cm bone resection margin appropriate during surgical treatment.[51] Marginal resection is clinically indicated for mandibular gingival carcinomas with an erosive bone pattern that are not beyond the inferior alveolar canal. For patients with an invasive bone pattern, a marginal mandibulectomy can be performed safely only when extent of bone involvement is limited to the alveolus superficially.[52] The type of histologic bone invasion is associated with the biologic behavior of the tumor, with the invasive pattern having a worse prognosis.[53–55] given its higher local recurrence and lower survival rates.

Although the type of bone invasion has an impact on overall outcomes, the soft tissue margin status, nodal status, and tumor size are also important prognostic factors in oral cavity carcinomas with bone involvement.[54] When local recurrence occurs, it is typically at the soft tissue margin.[56] Overholt and colleagues[6] found that the 5-year survival rates for patients with T1 and T2 lower gingival tumors were 85% and 84%, respectively, compared with 66% and 64% for patients with T3 and T4 tumors. Bone involvement did not increase the rate of local recurrence, but survival was negatively affected regardless of the extent of bone invasion. The 5-year survival rate decreased from 85% to 68% in patients with bone invasion. The impact of bone invasion on survival has been reported by other authors.[10,57,58]

In a retrospective analysis of 254 patients with oral cavity carcinomas, primary tumors smaller than 4 cm had similar outcomes regardless of bone invasion. The authors also found that margin status, nodal status, smoking history, and medullary bone invasion adversely affected survival.[57] In a series of 83 patients with gingival carcinomas, the T and N stage and positive margins were significant predictors of survival.[38] Ebrahimi and colleagues, in a retrospective study of 498 patients with oral cavity carcinomas, observed that large tumors (>4 cm) had approximately triple the risk of cancer-related death.[58] These authors also found that cortical bone invasion had no association with recurrence or survival but that there was an increased risk of cancer-specific death in patients with medullary bone invasion. This association was more than likely a result of medullary bone invasion and



• **Fig. 23.4** Mandibular anterior gingival carcinoma.

development of distant metastasis, given that there was no increase in locoregional failure in patients with medullary bone involvement.

There is conflicting evidence regarding the impact of an extraction on local recurrence and survival. Several investigators have suggested that the local trauma associated with an extraction in gingival carcinomas may lead to an increased risk of local recurrence and survival.[10,12] In 181 patients with gingival squamous cell carcinomas, the 5-year survival rate of patients who underwent an extraction within 1 year of treatment was 45%, compared with 67% and 78% in patients who either did not have an extraction or had undergone an extraction more than 1 year before their diagnosis.[12] Other investigators have not found an association between tooth extraction and increased risk of local recurrence and decreased survival.[6,38]

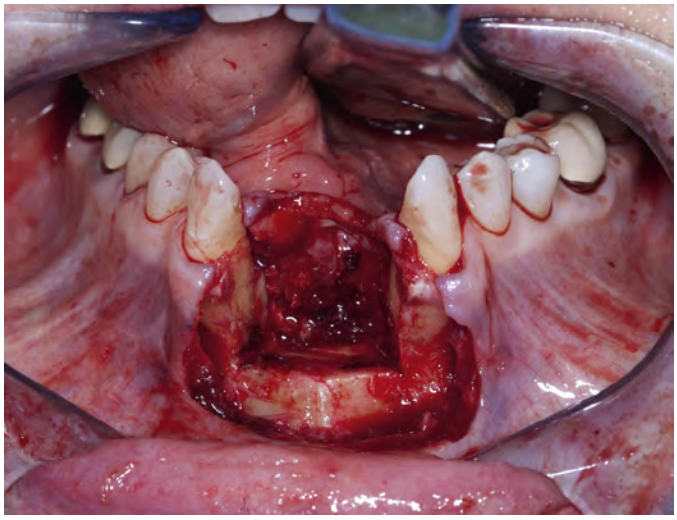
Surgical Management

Early-stage gingival tumors are well controlled with single-modality treatment. The treatment decision is formulated by a multidisciplinary team of providers. Surgical intervention produces minimal esthetic and functional impact in early lower gingival tumors. The goal of surgery is complete tumor resection with negative margins, with the planned extent of resection being determined by the clinical and radiographic examinations. In T1/T2 gingival carcinomas, a transoral approach provides adequate exposure (Fig. 23.4).

Mucosal incisions are carried out with a minimum of 1 cm of clinically tumor-free margins. The use of monopolar electrocautery for the mucosal incisions provides a hemostatic field for better visualization during the resection. Supraperiosteal dissection is performed around the tumor, and the surgical plane is changed to subperiosteal at the alveolus once this is clinically appropriate. Subperiosteal dissection is performed away from the tumor, exposing the alveolus and establishing the bone margins. The piezoelectric bone surgery instrument or the reciprocating saw is used for the marginal mandibulectomy. The advantage of piezoelectric bone surgery is the ability to perform the bony cuts at an appropriate angle transorally without traumatizing the surrounding



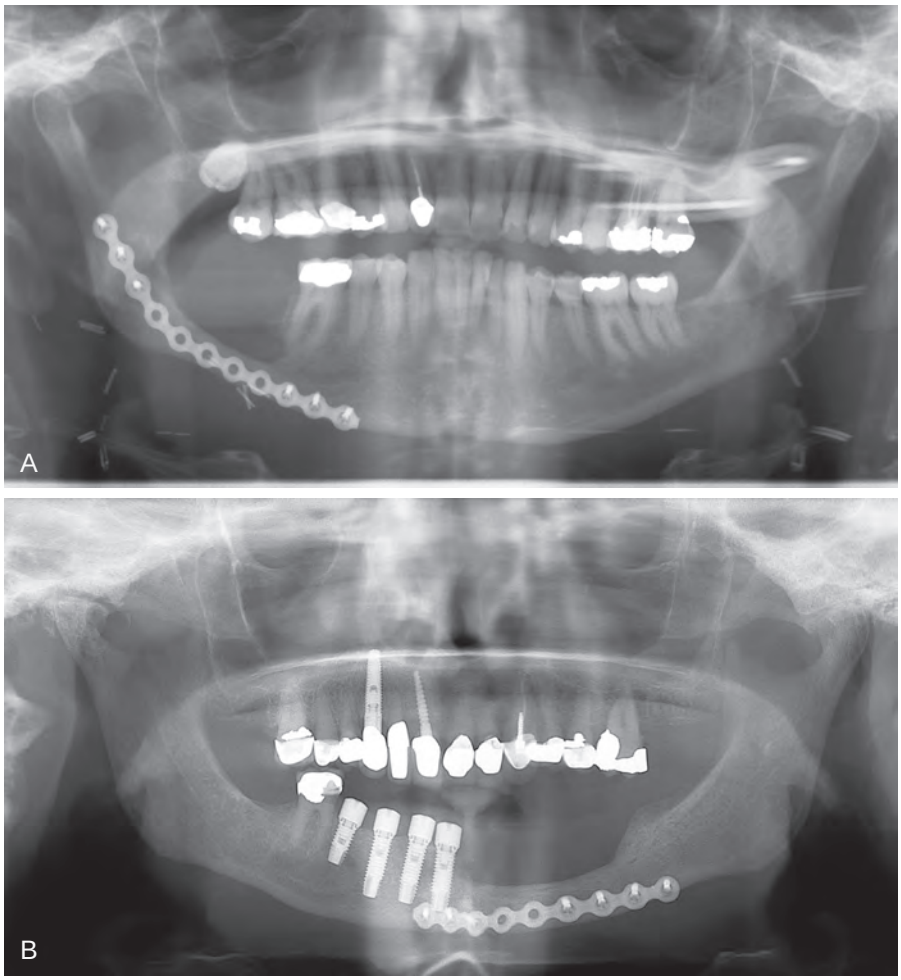
• **Fig. 23.5** Mandibular anterior gingival carcinoma.



• **Fig. 23.6** Bone margins are created and cuts performed 1 cm from midline and alveolar crest.

soft tissue. When planning the bone margins for marginal mandibulectomy, 1 cm of intact bone past the macroscopic tumor margin appears to minimize the possibility of a close or microscopic cut through margin in final histopathologic evaluation[56] (Fig. 23.5). A larger bony margin is advised when an invasive bone pattern is identified radiographically, because of the unpredictable extent of bone invasion and the risk of positive bone margin in permanent histopathologic evaluation.[13]

At least 10 mm of the inferior border of mandible, which accounts for almost 50% of the cross-sectional area of the mandible, needs to be preserved when performing the marginal mandibulectomy[39,50] (Fig. 23.6). If there is less than 10 mm in mandibular height, a reconstruction plate can be placed in order to reinforce the mandible at the surgical site (Fig. 23.7). In an atrophic mandible or partially edentulous site with alveolar bone atrophy, the mandibular height might not be adequate



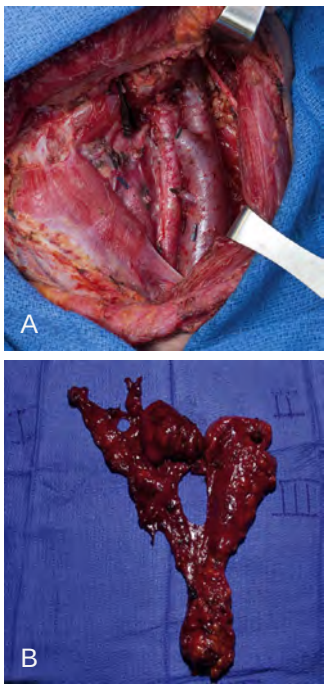
• **Fig. 23.7** **A,** Titanium plate placed at the mandibular inferior border in a marginal mandibulectomy defect with less than 10 mm in height. **B,** Titanium plate at the left inferior border after segmental mandibulectomy was performed in a previously partially dentate mandible.

for safe performance of a marginal mandibulectomy while preserving enough basal bone to prevent a pathologic fracture. In this situation, a segmental mandibulectomy is indicated. It is also important to smooth the edges of the remaining bone to minimize the concentration of mechanical stress in these areas and prevent a pathologic fracture from occurring.

Frozen-section analysis is used to evaluate soft tissue margins during the resection. This allows for the intraoperative assessment of the margins and decreases the risk of local recurrence and need for adjuvant radiation therapy due to the presence of an involved soft tissue margin in permanent histopathologic evaluation. Intraoperative evaluation of the bony margins can also be performed when indicated. Cancellous bone can undergo frozen-section analysis and be as reliable as the standard decalcification when determining the bony margin status.[59,60] Its use intraoperatively helps determine the need for further bone resection or conversion to a segmental mandibulectomy.

The involvement of the regional lymphatics by lower gingiva carcinoma is dependent on the size, grade, location, and presence of mandibular invasion. The spread of metastatic cancer to regional lymph nodes has been established to occur in a predictable and sequential fashion, with typical involvement of levels I–III, and infrequently levels IV and V.[61] When the risk of occult metastasis to clinically negative lymph nodes in the neck exceeds 15–20%, an elective neck dissection is performed to accurately stage the tumor and to help guide the need for adjuvant therapy.[62] The majority of patients with lower gingival carcinoma with subclinical neck disease have involvement limited to levels I and II. Those patients with clinically positive neck disease are more than likely to also have involvement of level III.[14,61] A selective neck dissection in which levels I, II, and III are dissected is indicated in patients with mandibular gingival carcinoma (Fig. 23.8).

Eicher and colleagues, in a retrospective study of 155 lower gingival carcinomas, found that the presence of either cortical or cancellous bone invasion, histologically moderately differentiated or poorly differentiated tumors, and tumors in the symphysis were predictors of cervical metastases.[14] These researchers recommended that patients with T1 and T2 tumors with cortical invasion undergo a selective neck dissection. Lubek and colleagues recommended an elective neck dissection in all cases of mandibular gingival carcinoma. In their study cohort, they found an overall rate of occult nodal



• **Fig. 23.8** **A,** Selective neck dissection performed on a patient with a cT2N0 lower gingival carcinoma. **B,** Neck specimen oriented and sent for histopathologic evaluation.

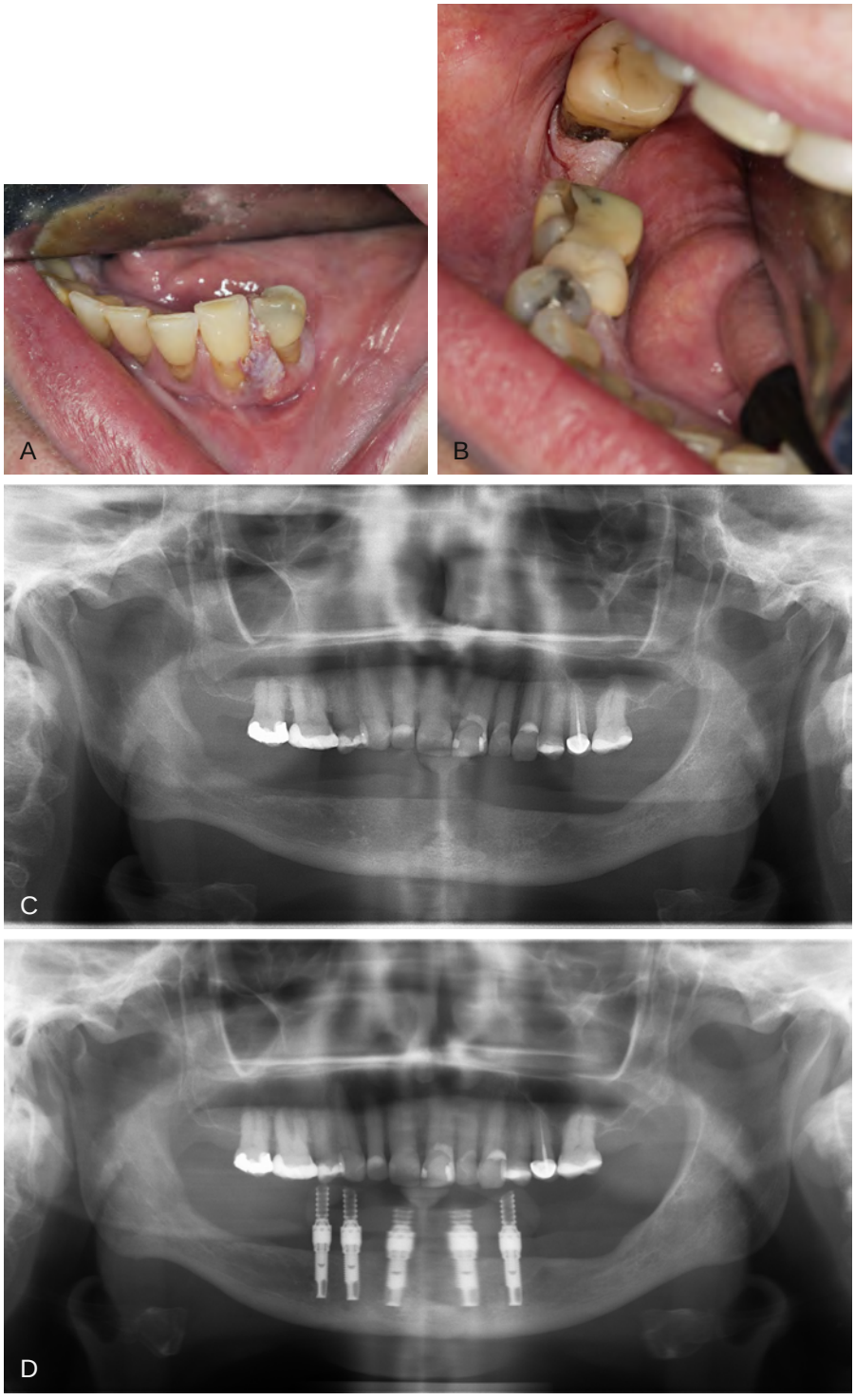
disease of 31% of patients with gingival carcinomas, with a 20% rate in those with T1/T2 tumors. They also found that a higher number of patients with cervical metastasis had bone invasion histologically.[17]

Reconstruction of the surgical defect after resection of a T1/T2 gingival carcinoma is accomplished by primary closure or with the use of a split-thickness skin graft. Primary closure allows for mucosal approximation and a quick recovery. This has to be balanced with the decrease of buccal and lingual vestibule created by the primary closure and the possible impact this would have on future dental rehabilitation. In these instances, endosseous implants provide the necessary retention and stability for a prosthesis (Fig. 23.9). A split-thickness skin graft is appropriate for the reconstruction of oral defects associated with the management of carcinomas.[63] It allows for vestibule maintenance and good adherence over the bony defect (Fig. 23.10). The split-thickness skin graft is secured to the surrounding mucosa with interrupted resorbable sutures (Fig. 23.11). It can be bolstered with an Owens gauze impregnated with Waite's paste, Xeroform dressing with or without the use of a sterile sponge, or an Aquaplast lined with periodontal packing and secured with screws (Fig. 23.12). Each of these bolstering techniques is suitable for stabilization of the split-thickness skin graft during the plastic imbibition and capillary inosculation process. For alveolar defects reconstructed with a split-thickness skin graft, the use of an Aquaplast lined with periodontal packing is convenient because its dimensions can be confined mostly to the required area, minimizing impingement on the tongue and floor of the mouth. The Aquaplast is contoured before placement of the skin graft in order to minimize excessive manipulation and distortion of the graft once it is in place. Once its dimensions and contours are established, the undersurface is then lined with periodontal dressing. It is secured with bone screws and left in place for 5 days. It is easily retrieved in the office without the need for application of local anesthetic.

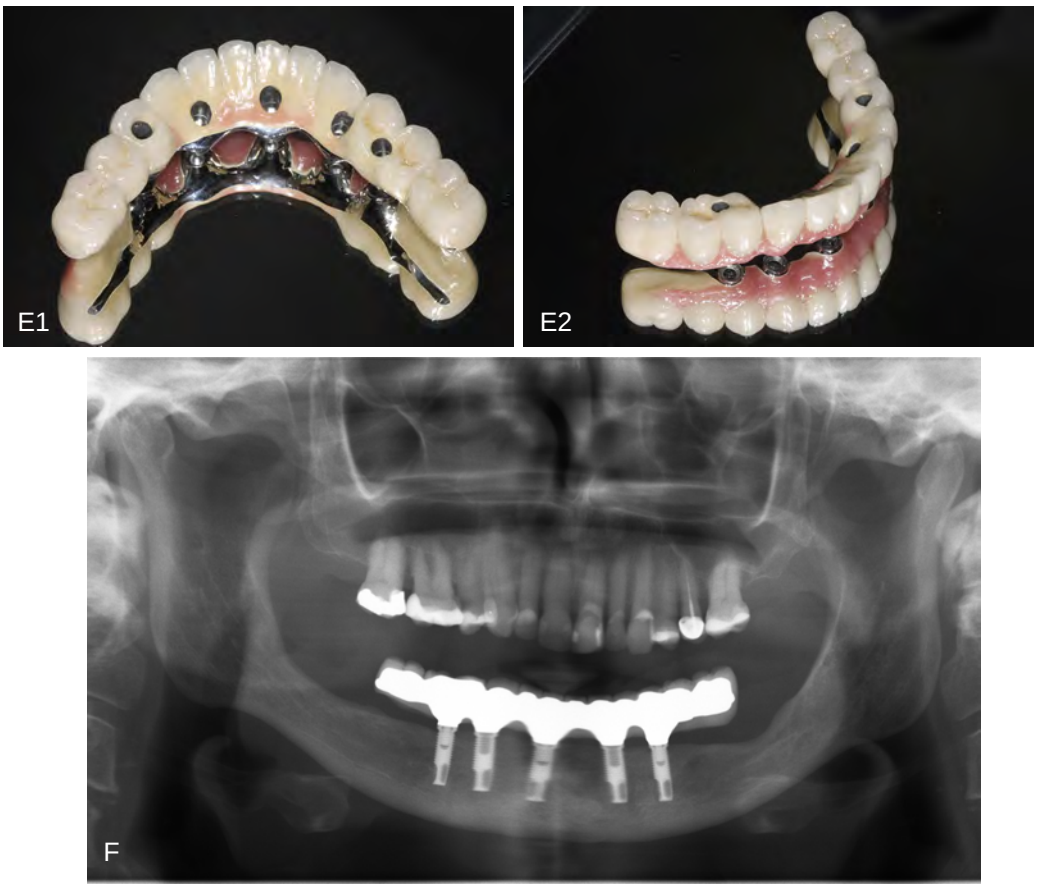
Immediate surgical complications include infection, bleeding, and cardiac or respiratory events. Other, longer-term complications include loss of skin graft, wound breakdown, and bone exposure. A small area of bone exposure can be managed with local wound care, and healing of the site is expected to occur through secondary intention. T1/T2 mandibular gingival tumors will be associated with defects wherein extensive scarring and contracture that limits tongue mobility are not expected. Anterior tumors can be associated with a decrease in lip support secondary to loss of the dentoalveolar complex. Any loss of dentition can affect mastication and management of the food bolus, depending on the location and number of teeth lost. Patients might also experience neurosensory alteration in the inferior alveolar nerve and mental nerve distribution secondary to its involvement during tumor resection (Fig. 23.13). This can lead to a compromise in oral competence and drooling because of the inability to detect fluid and food at the lip margin. The inferior alveolar nerve can be repaired at the time of the ablative surgery if its integrity is compromised during the resection (Fig. 23.14). This can restore sensory innervation, and the nerve could also be lateralized in anticipation of future reconstruction of the composite defect with endosseous implants (Fig. 23.15).

Radiation Therapy

Postoperative management of patients with high-risk mandibular gingival carcinomas may involve adjuvant treatment with external beam radiation or chemoradiotherapy. Positive mucosal margins, presence of perineural invasion, more than one positive lymph node, more than one positive nodal group, a node greater than 3 cm in diameter, and the presence of extracapsular extension have been identified as high-risk pathologic features for locoregional recurrence.[64,65] Ang and colleagues demonstrated a 5-year locoregional control rate of 90% in patients with head and neck carcinomas and no pathologic risk factors who did not undergo adjuvant radiation therapy. In patients with an intermediate risk (defined as one adverse pathologic feature excluding extracapsular extension) who underwent postoperative radiation therapy, the locoregional control rate was similar to that of patients in the low-risk group.[65] Patients with high-risk factors such as the presence of positive surgical margins and the presence of extracapsular extension with good performance status are candidates for postoperative cisplatin and radiotherapy. When one or both of these adverse features are present, there is an improvement in locoregional control and overall survival.[66] This has to be weighed against



• **Fig. 23.9** **A,** Recurrent mandibular left gingival carcinoma in a 63-year-old woman, 1 year after left marginal mandibulectomy and primary mucosal closure. **B,** Synchronous primary posterior gingival carcinoma with contralateral recurrent gingival carcinoma. **C,** Bilateral marginal mandibulectomy bone defect with primary mucosal closure. **D,** Mandibular reconstruction with endosseous implants and immediate load prosthesis 4 months after ablative surgery.



• **Fig. 23.9, cont'd** **E,** Final prosthesis fabricated and inserted 4 months after initial mandible reconstruction with endosseous implants. **F,** Postinsertion radiograph of final prosthesis.

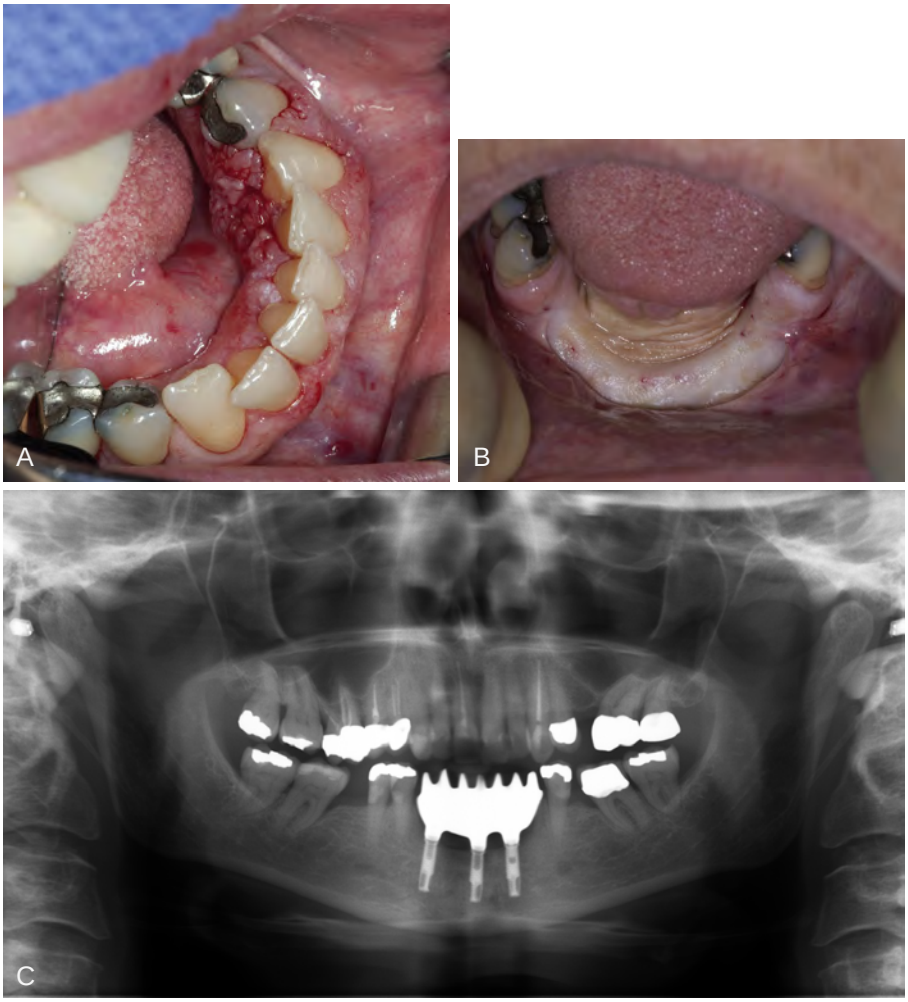
treatment-related toxicity and associated long-term side effects. The addition of chemotherapy to radiation can affect functional status and quality of life. Dysphagia after radiotherapy and chemotherapy is common, with up to two thirds of head and neck cancer patients experiencing some degree of swallowing difficulty and aspiration after chemoradiotherapy.[67] Other radiation therapy side effects include mucositis, xerostomia, dysgeusia, trismus, dermatitis, fatigue, and osteoradionecrosis.

Dental Rehabilitation and Function

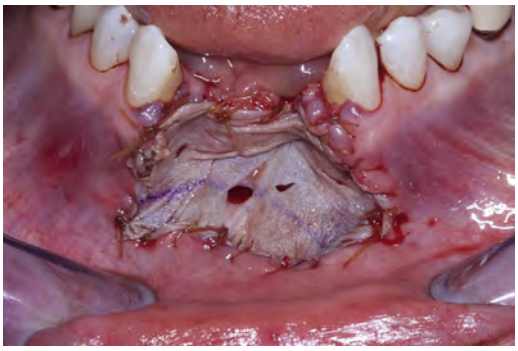
Dental rehabilitation and prosthetic reconstruction are paramount in restoring form and function after tumor ablation. Strides have been made in recent years in this arena, especially thanks to the use of osseointegrated implants and microvascular surgery. Every patient with an oral cavity carcinoma should undergo comprehensive evaluation by a dentist or prosthodontist experienced in managing oral cancer patients. It is essential to have a discussion with the patient before surgical treatment about the risks and benefits of each treatment alternative. This also provides an understanding of the patient's desires and expectations.

Treatment options for patients undergoing a marginal mandibulectomy are several. These are influenced by several factors: (1) the number of teeth present, (2) the amount of bone lost, (3) the patient's radiation history, (4) the status of the remaining dentition, (5) cost, and (6) manual dexterity of the patient. Major classes of prosthetic reconstruction include tooth-borne fixed prosthetics, implant-supported fixed prosthetics, removable prosthetics, or a combination (Fig. 23.16). For patients with a relatively small defect and sound teeth anterior and posterior to the surgical defect, a tooth-borne fixed prosthesis could be considered. The prosthesis should be fabricated to provide soft tissue clearance for hygiene and clinical surveillance.

Removable prosthetics can be a good option for most patients, especially if the prosthodontist is experienced. A definitive prosthesis can be fabricated after complete mucosal healing and bony remodeling, usually at 3 to 6 months. Helping to maintain the depth of labial and lingual vestibules as much as possible during the primary tumor resection is valuable for prosthetic reconstruction. This can be achieved by the use of split-thickness skin grafting initially or with the use of vestibuloplasty techniques such as Kazanjian flap or lip-switch vestibuloplasty during secondary revision. In a survey of prosthodontists, Elzay and colleagues. found that most believed it was



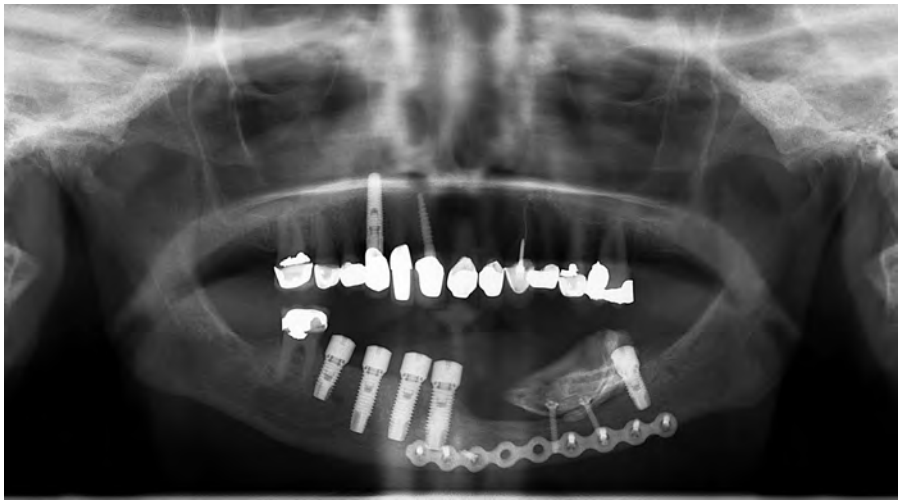
• **Fig. 23.10** **A,** Mandibular lingual gingival squamous cell carcinoma. **B,** Split-thickness skin graft performed for reconstruction of the defect. **C,** Fixed implant retained prosthesis is used for dental rehabilitation.



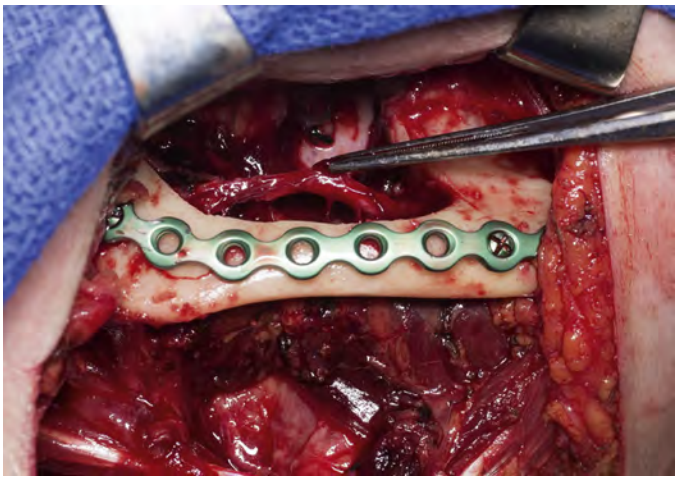
• **Fig. 23.11** Split-thickness skin graft is secured with interrupted chromic gut sutures.

impossible to make a denture that did not produce trauma to the oral mucosa.[68]

Endosseous implants have found a place in the prosthetic rehabilitation of patients with composite alveolar defects by providing improved support, retention, and stability. With the use of frozen-section diagnosis and careful presurgical planning, implants may be placed at the time of primary procedure. This helps avoid an extra procedure and reduces delays in prosthetic rehabilitation.[69] However, immediate placement can be technically challenging owing to absence of a surgical stent. Immediate implant placement decreases the risk of osteoradionecrosis if adjuvant radiation therapy is delivered to the tumor bed, and a significant portion of the osseointegration will have occurred before the start of radiotherapy.[70] Radiotherapy is associated with fibrosis of blood vessels and soft tissues, xerostomia, osteoradionecrosis, and reduction of bone-healing capacity.[71] A recent systematic review with meta-analysis found higher implant failure rates in irradiated patients compared with non-irradiated patients.[72] This information needs to be conveyed to the patient owing to the possible need for adjustment of the prosthetic plan in the future. It also might be of benefit to add an additional implant when appropriate to accommodate for this increased risk and limit the possible need for fabrication of a new prosthesis because of implant loss. The preferred prosthesis for the mechanical rehabilitation of a T1/T2 composite defect is an implant-retained fixed prosthesis (Fig. 23.17). This provides superior esthetic and functional results when compared with other options. Soft tissue clearance is of paramount



• **Fig. 23.12** Aquaplast with periodontal dressing is used as a bolster of split-thickness skin graft and endosseous implant reconstruction of the surgical defect after marginal mandibulectomy.



• **Fig. 23.13** Inferior alveolar nerve at the resection margin.

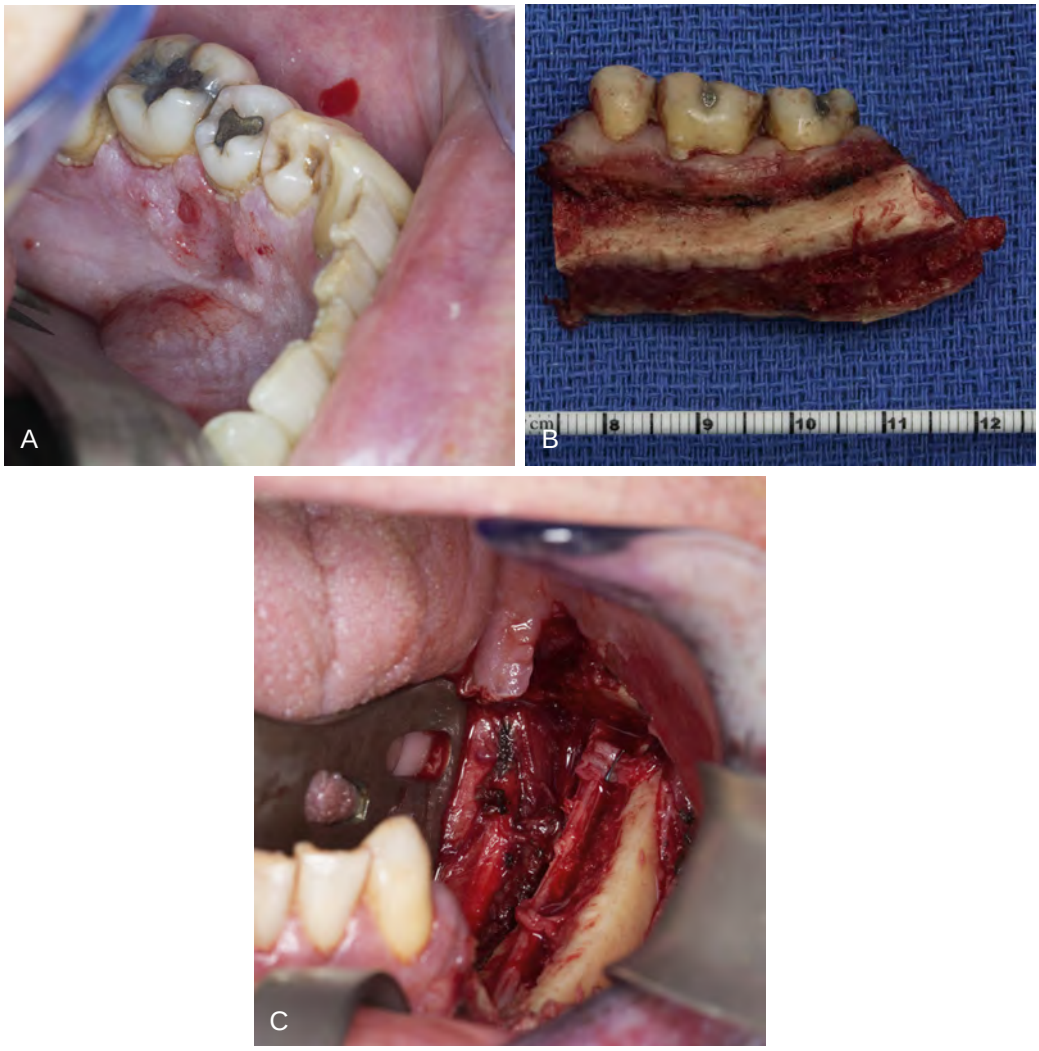
importance for hygiene purposes and allows for visualization of the surgical bed during surveillance visits (Fig. 23.18).

Depending on the extent of disease and treatment, there can be significant structural and functional changes within the oral cavity that can affect speech and swallowing. These are also affected by the loss of dentition, neurosensory alterations, loss of tongue mobility, and radiation associated dysphagia and xerostomia. If the disease or treatment is causing or likely to cause speech and swallowing dysfunction, a formal speech therapy baseline evaluation is recommended. This is important for post-treatment comparison and tailored treatment approaches. The functional impact that treatment of T1/T2 gingival tumors has on speech and swallowing shouldn't be underestimated. Patients might require a speech-language pathologist follow-up once a stable baseline has been achieved after treatment.

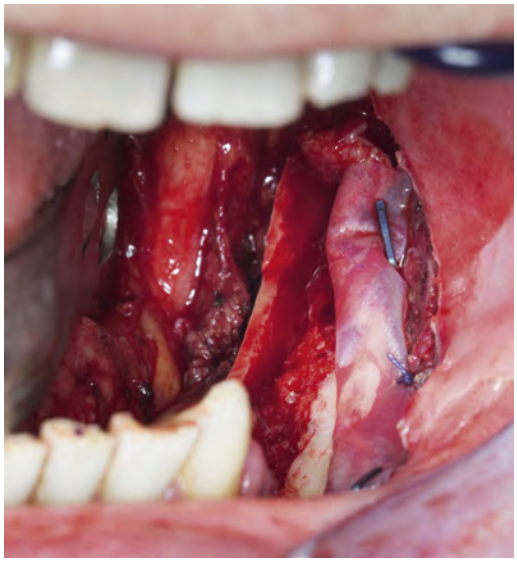
Up to 60% of head and neck cancer patients will be nutritionally compromised at the time of diagnosis. The nutritional status will be furthered compromised by treatment-related side effects such as dysphagia, dysgeusia, appetite loss, and loss of dentition. A registered dietitian should be involved in the multidisciplinary patient care. A comprehensive nutritional evaluation and counseling should be performed before treatment and thereafter as necessary.

Surveillance

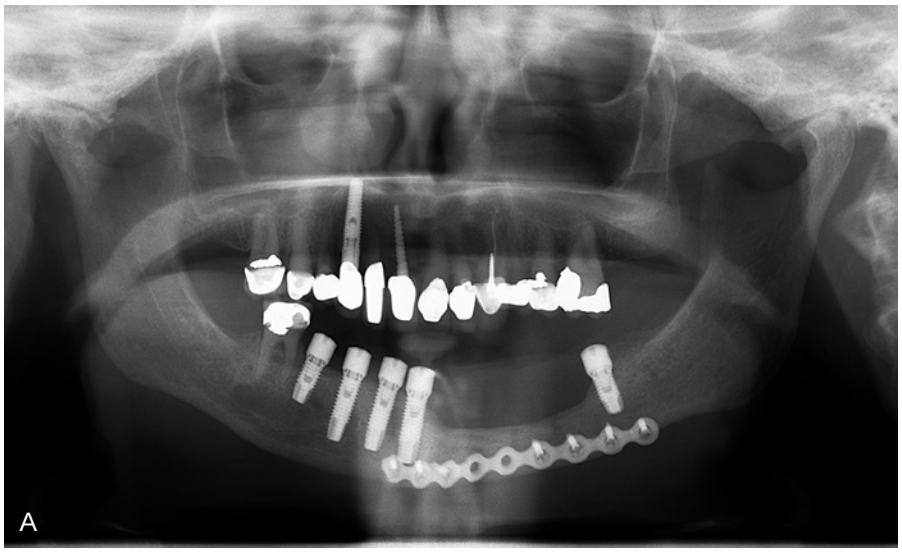
The surveillance protocol for gingival carcinomas is similar to that of other cancers of the oral cavity. It is based on individual risk of recurrence and continued existence of risk factors such as smoking and alcohol use. Patients should be provided with a smoking cessation program and alcohol counseling, given that there is a 30–50% risk of locoregional recurrence and a 10–40% risk of development of a second primary in patients who continue to smoke after treatment of their primary carcinoma. A thorough interval history and complete head and neck examination with a fiber-optic examination as indicated should be performed on a scheduled basis after treatment. In general, this is every 1–3 months for the first year, every 2–6 months for the second year, every 4–8 months for years 3–5, and annually thereafter. Baseline post-treatment imaging can be useful in early disease and it is typically performed within 6 months of treatment.[36]



• **Fig. 23.14** **A,** T2 lower gingival carcinoma involving the lingual mandible. **B,** Composite specimen of left mandibular alveolus. **C,** Integrity of inferior alveolar nerve compromised during the marginal mandibulectomy.



• **Fig. 23.15** Nerve is repaired with an allograft and lateralized in anticipation of endosseous implant reconstruction in the future.





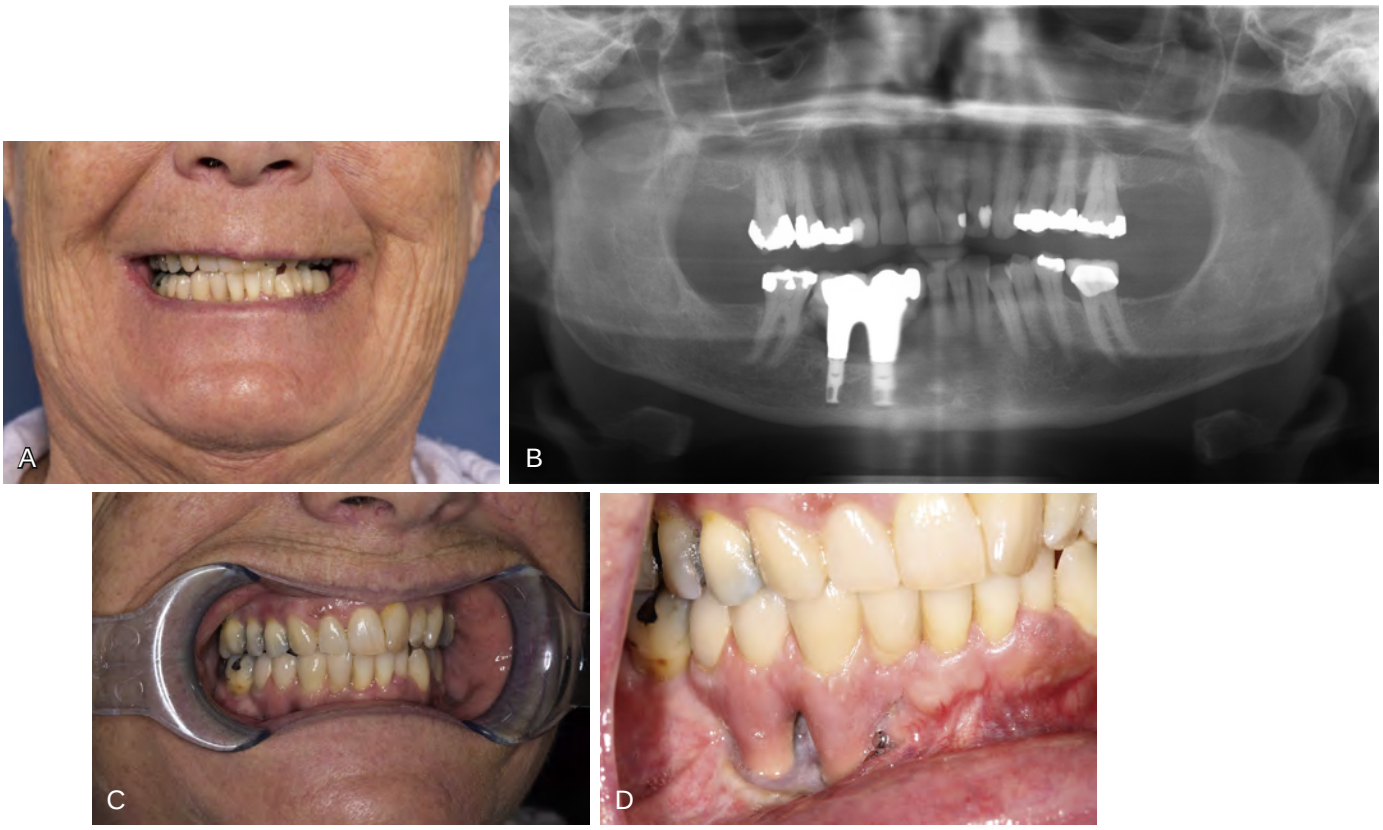




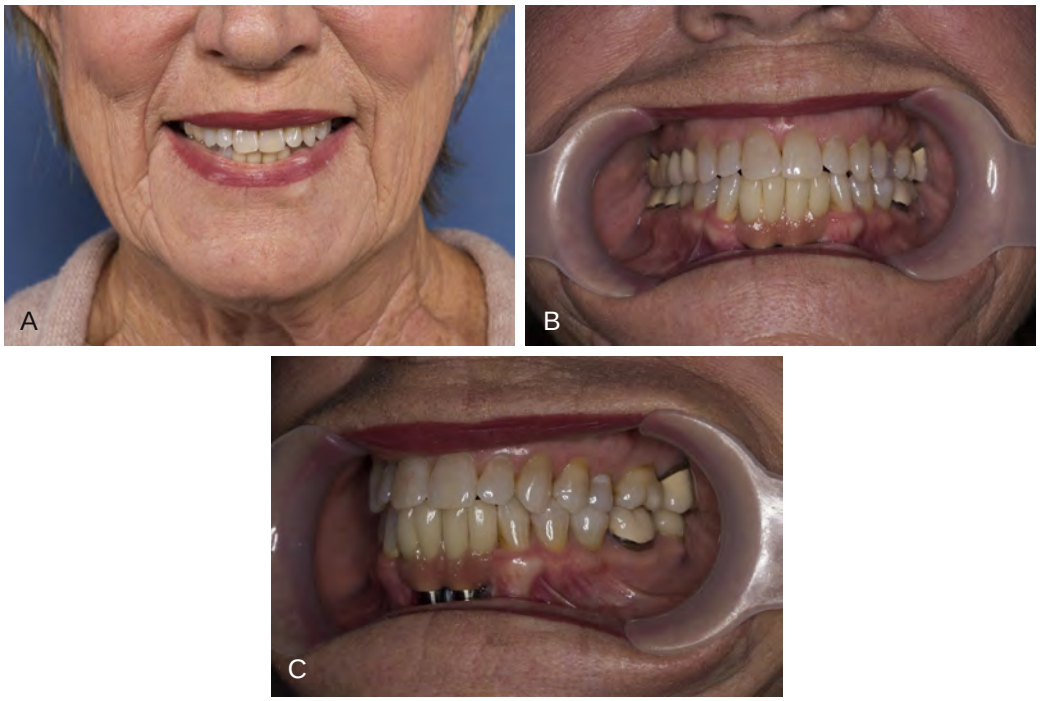




• **Fig. 23.16** **A,** Mandibular left T2 gingival carcinoma in an 84-year-old woman after marginal mandibulectomy, split-thickness skin graft, and endosseous implant reconstruction. **B,** Fixed implant-retained prosthesis for restoration of the right mandible. **C,** Removable implant-supported prosthesis designed for reconstruction of the left mandible. **D,** Implant-supported and retained prosthesis in place. **E,** Cosmetic and functional balance after insertion of prosthesis.



• **Fig. 23.17** **A,** Mandibular right alveolus composite defect restored with an implant-retained prosthesis. **B,** Radiograph of defect and prosthesis in place. **C,** Adequate esthetics and balanced occlusion of the prosthesis. **D,** Split-thickness skin graft reconstruction allows maintenance of vestibule and adequate space under the fixed prosthesis for cleansability.



• **Fig. 23.18** **A,** Good esthetic outcome and lip support are provided by an implant-retained prosthesis. **B,** Function reestablished with reconstruction of the lost dentoalveolar complex with endosseous implant and a fixed prosthesis. **C,** Soft tissue clearance provides adequate exposure for hygiene and surveillance under the fixed prosthesis.

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24

Advanced Oromandibular Cancer

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Cancer of the oral cavity offers considerable challenges. The most common malignancy of the oral cavity, squamous cell carcinoma (SCCA), is a capricious disease that is difficult to tame because of its penchant for local recurrence and regional metastasis. Furthermore, oral cancers affect an area of the body that is at the crossroads of facial appearance, speaking, eating, and breathing, several functions central to a person's identity and how they relate to others.

The oral cavity is divided into the following subsites: oral tongue, floor of mouth, lip, buccal mucosa, retromolar trigone, maxillary gingiva, mandibular gingiva, and hard palate. SCCA of the mandible is at the intersection of a number of these subsites. Medially, the mandible is contiguous with the floor of mouth, which in turn is intimately related to the oral tongue. Laterally, the mandibular gingiva wraps into the buccal mucosa and then lip or facial skin. Posteriorly, the mandible is bounded by the retromolar trigone, which itself borders the anterior portion of the lateral pharyngeal wall, pterygomandibular space, lateral pharyngeal space, and maxilla. Therefore, advanced SCCA of the mandible does not affect this subsite in isolation, but has profound effects on the adjacent areas, which can lead to substantial alterations of orofacial form and function.

Similarly, although mandibular gingiva and mandibular intraosseous sites are less common locations for a primary tumor to originate from, SCCA of the adjacent sites often extends onto the mandibular gingiva and into the mandibular bone.[1] As such, management of the mandible in advanced oral SCCA is often necessary even if the primary starts in an adjacent subsite.

This chapter reviews the authors' multidisciplinary approach to management of locally advanced oral SCCA involving the mandible. The purpose is to provide a rational algorithm for treatment of this complex, but common, clinical scenario.

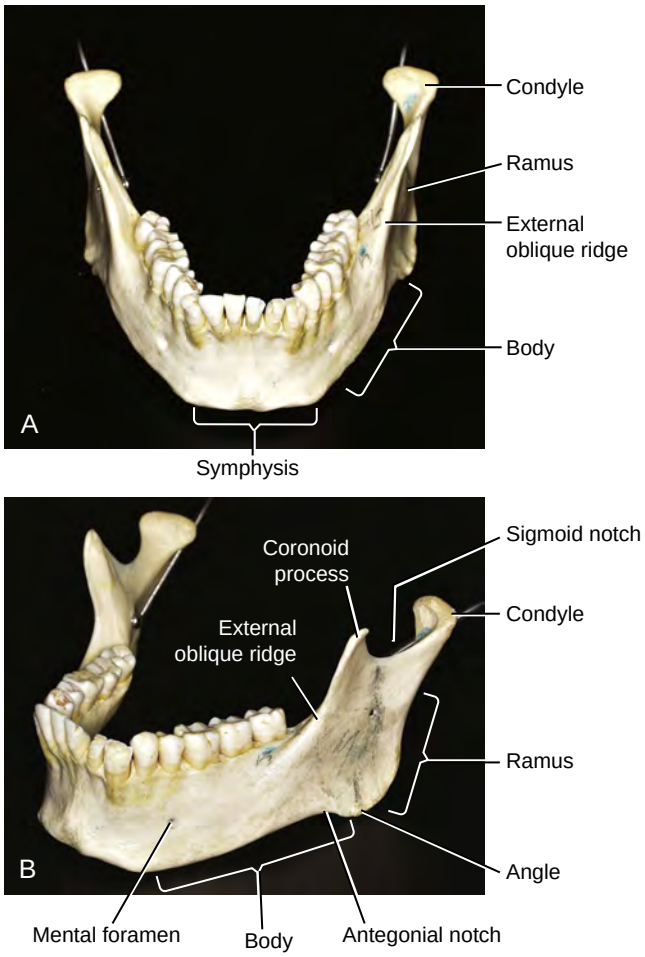
Relevant Clinical Anatomy

Understanding the essential anatomy of the mandible is important for appreciating the nuances of treatment of advanced mandibular cancer as it relates to surgery, radiation therapy, and reconstruction.

Using standard anatomic terminology, "proximal" refers to closer to the temporomandibular joint and "distal" refers to closer to the chin. However, using dental terminology, "distal" refers to further from the midline of the dental arch, and "mesial" refers to closer to the midline of the dental arch. In the body of the mandible "lateral" and "buccal" are synonymous, as are "medial" and "lingual." In the symphysis, "posterior" and "lingual" are synonymous, as are "anterior" and "labial."

The mandible, from a bird's eye view, has an omega shape (Fig. 24.1A). Viewed from the side, it is L shaped (Fig. 24.1B), with its vertical limb comprising the superior-posteriorly directed condylar head and a superior-anteriorly directed process called the coronoid process (which is separated from the condylar head by the sigmoid notch), both of which join inferiorly to form the ascending ramus of the mandible. The vertical limb (ascending ramus) joins the horizontal limb (body) at the mandibular angle. The horizontal portion of the mandible is divided into the body of the mandible posteriorly and the symphysis anteriorly (Fig. 24.1B). The symphysis is the curved region of the mandible, when looking from above, that joins the left and right side. The dividing line between the symphysis and body is the mental foramen, located on the lateral side of the mandible just below the roots of the premolar teeth, where the distal end of the inferior alveolar nerve leaves the mandible to become the mental nerve, which provides sensation to the lip and chin.

Clinically, the authors plan resections based on these subunits (Fig. 24.2). The schema we use for the mandibular subunits is similar to those described by other groups, including the recently published Brown classification of mandibular defects.[2] For example, a resection of a mandibular cancer of the body would involve resection of the entire body, rather than simply a 1- to 2-cm margin around the focus of tumor. If the margin requires encroachment into the symphysis, then the body and symphysis are removed. The rationale for this approach is twofold. First, bony margins are difficult to assess clinically. Tumor can extend beyond what is visibly involved on CT. Classically, bony involvement is thought to be more refractory to radiation therapy. Therefore, it is more oncologically sound to err on the side of removing a greater margin rather than being more surgically conservative. The exception to this is isolated erosion of the alveolar bone, which can sometimes be safely managed with a marginal mandibulectomy.



• **Fig. 24.1** **A,** Mandible from bird's-eye view. **B,** Mandible from three-quarter view.



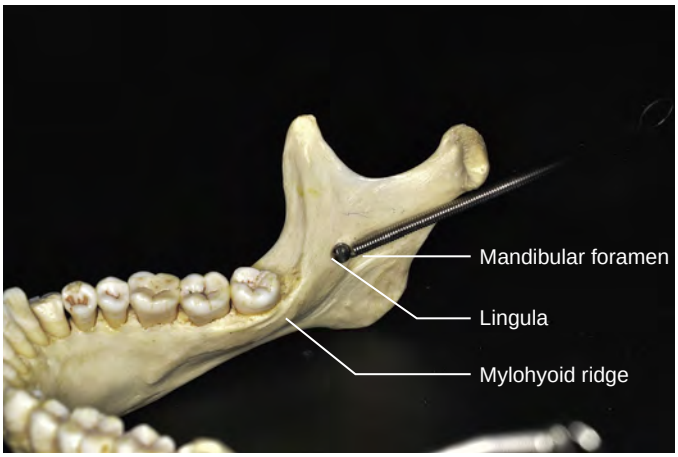
• **Fig. 24.2** Mandibular subunits.

The second reason for this subunit approach is to facilitate the reconstruction. Reconstruction of a portion of the body, a portion of the symphysis, or a portion of the ramus is no easier than reconstruction of the entire subunit. In fact, it is often easier to reconstruct the entire span of the body, symphysis, or ramus. No additional deficit in form or function is avoided by sparing a portion of the subunit. However, sparing a portion of these subunits creates a number of avoidable difficulties. Because patients with advanced mandibular cancer generally receive adjuvant radiotherapy that starts before complete bony healing occurs, the vascularity of the bony junction between native mandible and reconstructed mandible is affected. The mid-body, because of its poor centripetal blood supply from lack of thick muscle attachments, is at higher risk of malunions if the osteotomy is placed there. In the symphysis, symmetry at the chin is difficult to achieve if the osteotomy is placed at the midline. Also, if a free fibula flap is used, the segment of bone required to reconstruct a partial subunit is often so short that the periosteal blood supply to that segment is more tenuous.

The condylar head and neck are tightly bound to the temporal bone by the temporomandibular ligament. It is also supported by the sphenomandibular ligament, which runs from the spine of the sphenoid bone to the lingula of the mandible, a small process located on the medial side of the ramus of the mandible, and the stylomandibular ligament, which runs from the styloid process of the temporal bone to the posterior angle of the mandible.

The coronoid process is covered with the dense tendinous attachments of the temporalis muscle. When planning a posterior osteotomy for a segmental resection including the mandibular body, commonly used landmarks are the sigmoid notch superiorly and the antegonial notch inferiorly (the notch anterior to the gonial angle) (see Fig. 24.1B). This has the benefit of leaving enough good bone for mandibular hardware fixation while also removing the coronoid process, which is helpful in limiting a contributing factor of postoperative limitation in opening. The pull of the temporalis muscle can resist mandibular opening, particularly when stiffened by scar tissue and radiation. However, leaving the coronoid and its attachments can be useful in preserving the vascular supply to the proximal mandible. If this is a concern, as it is in post-radiation patients, the authors may consider either planning an inverted-L shape osteotomy to leave the coronoid, or, if the margins allow, placing the osteotomy at the anterior border of the ascending ramus. When performing an osteotomy through the sigmoid notch, care is necessary to avoid injury to the masseteric artery, which is only a few millimeters from the lowest point of the notch.

The mandibular foramen is located just medial to the lingula and is where the mandibular nerve enters the mandible to become the inferior alveolar nerve (Fig. 24.3). The lingual nerve branches from the mandibular nerve before it enters the foramen. The lingual nerve follows a course within the soft tissue along the lingual aspect of the mandible, generally about 1 cm medial to the lingual cortex until it turns more medially toward the oral tongue around the first molar to premolar region.[3] The inferior alveolar nerve courses in an intraosseous canal of the same name, which generally runs below the roots of the teeth. In edentulous patients with loss of the alveolar bone from atrophy, the nerve may become extraosseous and run along the superior edge. The nerve exits at the mental foramen (as mentioned earlier) to become the mental nerve. The inferior alveolar nerve is commonly divided as part of mandibular



• **Fig. 24.3** View of the mandibular ramus from medial.

resection. The lingual nerve can be preserved, depending on the location and extent of the tumor.

The condylar heads articulate with the glenoid fossae of the temporal bones on either side, with an intervening articular cartilaginous disc, to form the temporomandibular joints (TMJ). It is the only bone with two joints on either end that cannot function independently from one another. The joint opens by a combination of rotation and translation of the condyle. Opening occurs primarily by the function of the lateral pterygoid muscle, which originates at the lateral aspect of the lateral pterygoid plate and attaches to both the articular disc as well as the condylar neck. There is a minor contribution to opening by the digastric muscle. Rotation of the condylar head within the glenoid fossa allows for opening to about 20 to 25 mm. Full opening to around 40 to 50 mm occurs with translation. During mastication, rotation and translation of the condylar heads on the right and left are coordinated, but asymmetric (Posselt's envelope of movement). This complex movement cannot be reconstructed if the condyle is resected as part of the ablative surgery. The loss of the TMJ ligaments, articular disc attachments, temporalis and the lateral pterygoid attachments cannot be reconstructed. As such, a reconstructed condyle opens only by rotation. The loss of the supporting ligaments also can result in recurring dislocation of the reconstructed joint. The authors use a non-resorbing or slowly resorbing stitch, sometimes to a bone anchor, to suspend and secure the condylar portion of the neo-mandible to the skull base to minimize this.

The mandible is a densely cortical bone with a narrow marrow space. The cortical bone is thickest along the posterior border of the ramus and the inferior border of the body and symphysis. Functionally, this provides both the vertical and horizontal buttress of the lower third of the face.

The surfaces of the body and symphysis of the mandible are irregular, with prominent areas related to muscle insertion. On the buccal aspect of the angle and body, there is the external oblique ridge, a flat shelf of cortical bone that is lateral to the mandibular molars that is directed in an oblique direction from superior-posterior to inferior-anterior. It serves as the attachment of the buccinator muscle. Where the ramus joins the body at the mandibular angle is the gonial angle, a thickening at the inferior border where the masseter inserts on the lateral and the medial pterygoid inserts on the medial. Immediately anterior to the gonial angle and the anterior border of the masseter is the antegonial notch. The facial artery and vein cross the mandible in this region. In the symphysis region, the thickened inferior border serves as the attachments for the mentalis muscles, the depressor anguli oris, and the orbicularis oris on the buccal/labial, and the digastric on the lingual.

On the lingual side of the body, there is the internal oblique ridge, or mylohyoid ridge, which marks the insertion of the mylohyoid muscle. It is located below the alveolar bone, when present. Above this muscle is the sublingual space. The lingual nerve, hypoglossal nerve, lingual vessels, and sublingual gland are in this space. Below this line is a lingual concavity that follows the length of the body of the mandible where the submandibular triangle and its contents lie. This includes the submandibular gland and level IB lymph nodes. In the symphysis region, the genial tubercles lie on the lingual side of the anterior mandible. The genioglossus and geniohyoid muscles, which attach here, are critical for holding the position of the tongue anteriorly. Should a segmental resection of the mandible include the symphysis, the hyoid and tongue musculature should be suspended to the reconstructed neo-mandible using a slow-resorbing or non-resorbing stitch. The authors use 2-0 Prolene for this.

The lingual side of the mandible may also include bony exostoses, or tori, in a significant proportion of the population. This is usually of little consequence unless the patient is edentulous and a tissue-borne prosthesis is planned post-treatment. In these cases, tori should be removed prior to radiotherapy, possibly at the time of the initial ablative surgery.

The alveolar portion of the mandible is the portion of the mandible that houses the mandibular teeth. It is located along the superior border of the mandibular body and symphysis. The alveolar bone is less densely cortical, with greater trabeculation. The amount of alveolar bone present is highly dependent on the presence and health of the mandibular teeth. The alveolar bone atrophies down to basal bone, over the course of several years, when teeth have been extracted. In addition, periodontal disease leads to loss of the alveolar bone. Similarly, cancer is believed to erode through the alveolar bone more quickly than it does the basal bone. A theoretical pathway for tumor infiltration is along the periodontal ligament surrounding the teeth.

From a reconstructive standpoint, the anterior teeth and alveolar bone provide much of the lower lip support. Also, the vestibule, or valley between the crest of the alveolar bone and the lip provide a functional gutter for food and liquids to pass back and forth, and provides a dam to prevent saliva from the floor of mouth from flowing out of the mouth resulting in drooling. Ideally, the neo-mandible should recreate the hill-and-valley architecture of the floor of mouth, alveolus, buccal vestibule, and lip.

The actual position of the alveolar bone and teeth is not directly above the inferior border of the mandibular framework, but rather slightly lingual. When viewed from above, the mandible has a double arc configuration, with one arc,



• **Fig. 24.4** Double arc configuration of the mandible.

more lingually situated, representing the alveolus, and a longer and broader arc, more buccally situated, representing the inferior border and mandibular contour (Fig. 24.4). Therefore, during reconstruction of a dentate portion of the mandible, design of the neo-mandible should not mirror the inferior border, but rather an arch slightly lingual and superior to this to allow for later dental prosthetic reconstruction. This is critically important because for dental implants to be usable by a dentist or prosthodontist, they must be appropriately positioned opposing the maxillary teeth. This may be at the expense of some degree of chin projection, but the compromise is not disfiguring.[4]

The fully dentate mandible has 16 teeth. Working from midline to posterior, they are the central incisor, lateral incisor, canine, first premolar, second premolar, first molar, second molar, and third molar. Most people have already had their third molars (wisdom teeth) removed. It is beyond the scope of this chapter to review the complexities of occlusion and dental anatomy. However, it is important to discuss a few clinical pearls. Each tooth is wrapped in keratinized gingiva, referred to as attached gingiva. This is important, as non-keratinized tissue does not withstand the trauma of chewing or dental hygiene well, and is more prone to becoming inflamed. Therefore, reconstruction should include keratinized soft tissue coverage in the area of planned prostheses. Each tooth is held into the alveolar bone by a periodontal ligament. The lining of the gingival sulcus and periodontal ligament is only a few cell layers thick, providing a path of least resistance for invasion into bone. Therefore the oncologic surgeon should have a high degree of suspicion for bony involvement if the tumor wraps around or through the gingiva. Although this alone may not qualify the tumor as a T4 (erosion of the alveolar bone no longer qualifies based on AJCC Staging guidelines), at a minimum, some bony resection should be planned.

The blood supply to the mandible is both intraosseous and external. The inferior alveolar artery, a branch of the maxillary artery, courses within the mandibular canal to provide centrifugal blood flow to the bone and teeth. The mandible is also enveloped in several muscle attachments that provide centripetal blood flow via the periosteum. As a patient ages, develops atherosclerotic disease, or is treated with radiation, the vascular contribution of the inferior alveolar artery diminishes and the contribution from the periosteum increases.

The mandible is at the intersection of several fascial compartments. It is the medial boundary of the submasseteric space and buccal space. It is the lateral boundary of the pterygomandibular space and the sublingual space. It is the superior boundary of the submandibular space.

Mandibular SCCA Has Complex Biology

As with all cancers, oral SCCA is a disease that starts at the molecular level through the accumulation of genetic and epigenetic changes. The accumulation of these changes leads to a cascade of cellular events that, over time, alters the behavior of the affected cells.

Discussion of the complex biology of oral SCCA is far beyond the scope of this chapter. However, it is important to review a few salient points. First, although several mutations have been identified to be commonly affected, by either genetic mutations or epigenetic modification, none of these genes are found in all, or even most, oral SCCA tumors. In addition, the fashion in which they are altered is highly variable.[5-7]

Second, the idea of "field cancerization" (sagely described by Slaughter before knowledge of DNA, genes, and their implications) has been used to describe oral SCCA.[8] This hypothesis suggests that broad fields of cells are exposed to the same insult or insults, leading to changes (at the genetic level) that predispose cells within the field to become cancer. This suggests that tumors and their recurrences (or second primaries) are at least partially clonal, sharing common genetic alterations. However, within the "field," and even with a single tumor, there is a tremendous amount of genetic heterogeneity between cells. Although it is tempting to imagine that within this "field" a dominant cell or a few dominant cells break through normal cellular controls and expand clonally, it is probably more accurate to think of a tumor and its surrounding microenvironment as an ecosystem of variously altered cells that separately contribute to the hallmarks of cancer growth.[9]

Third, although it is very appealing to think of oncogenesis as a linear path from normal to invasive cancer, the actual route is likely much more circuitous and variable. Many have attempted to define a succession of genetic alterations that lead early pre-cancers to evolve into late invasive, and possibly metastatic, cancers.[10,11] Unfortunately, none have accurately captured how tumor progression occurs in a way that is clinically helpful in predicting which lesions and tumors are progressive.

Clinical Presentation and Natural History of Mandibular SCCA

Mandibular cancers can present as leukoplakia, erythroleukoplakia, ulcers, verrucous lesions, or, rarely, as intraosseous lesions. These lesions may originate from the gingiva, from the buccal mucosa, from the retromolar trigone, the lip, or the floor of mouth. However, mandibular SCCA, like all oral

SCCA, rarely follows a linear course from leukoplakia to dysplasia to invasive carcinoma to metastatic disease. More commonly, a mandibular lesion is identified and biopsied when it already represents invasive SCCA. One of the most common locations for oral SCCA, and therefore oral SCCA affecting the mandible, is the floor of mouth, particularly the lingual gutter adjacent to the mandibular molars.

Progression of the disease at the primary site can occur along several avenues and at variable rates, depending on the biologic aggressiveness of the tumor. SCCA starts within the floor of mouth and then encroaches onto the mandible. The thick cortex of the mandible is an anatomic barrier to tumor progression. However, the tumor will eventually erode through cortical bone into the marrow space. Even in the absence of radiographic cortical destruction, SCCA can have microscopic infiltration into the cortical bone.

Alternatively, if the tumor originates or extends onto the attached gingiva that is surrounding the teeth, it can invade the periodontal ligament space and then into the alveolar bone. These tumors may extend from the buccal gingiva, through the papilla, onto the lingual gingiva, or vice versa. Tumors that extend into the periodontal ligament space and alveolar bone may result in loosening of teeth. This may lead to shifting of the dentition resulting in malocclusion or loss of teeth. Ulcers of the attached gingiva lead to exposure of tooth roots. This, especially when combined with tooth mobility and gingival bleeding, can be mistaken for gingival recession due to periodontal disease.

Once the tumor enters the marrow space, either through the periodontal ligament and alveolar bone or through destruction of cortical basal bone, the tumor can spread within this space. Although it is postulated that invasion within the marrow space proceeds more quickly, there is limited evidence to support this. Similarly, once the tumor extends into the inferior alveolar nerve canal, invasion can potentially spread along this canal beyond radiographically visible tumor involvement. However, again, there are limited data on the significance of the inferior alveolar canal involvement's effect on tumor invasion.[12]

One of the most common presenting symptoms is pain.[13-15] Although not all patients have pain associated with their tumor, the presence of pain is often the motivation that pushes patients to have their tumor evaluated. Also, tumors that are left untreated almost invariably will become painful as the disease progresses. A patient complaining of pain should raise the suspicion of the clinician, even when previously performed biopsies were negative or only demonstrated dysplasia. Dysplasia is not typically painful, so the development of pain is suggestive of a change in the trajectory of oncogenesis toward malignant transformation. Pain is not simply a by-product of tumor activity, but a component of tumorigenesis.[16] Oral SCCA is known to secrete nociceptive factors that trigger pain, which then lead to subsequent endogenous release of inflammatory mediators that promote tumor growth.[17,18]

Pain can manifest in a number of ways, but cancer pain primarily occurs with function. For example, mandibular SCCA extending into the floor of mouth will present with pain with eating and speaking. Extension posteriorly into the retromolar trigone will involve the superior pharyngeal constrictor, leading to odynophagia. Bony invasion may manifest with pain when chewing or even jaw movement, particularly if a pathologic fracture has occurred. Otalgia may also be a feature of mandibular cancer.

Cancer pain is known to be highly opioid refractory. Patients with untreated, painful mandibular SCCA may present with increasing opioid requirements, or abuse of other medications or drugs to try to reduce the pain. Also, as the pain is most notable with function, patients often present with a history of self-restricting certain behaviors. For example, a patient with a tumor extending into the floor of mouth may experience great pain with talking and eating. Such a patient would be observed to become much less talkative and to be losing weight.

Mandibular SCCA may also affect adjacent sensory nerves, such as the inferior alveolar nerve or lingual nerve. Unexplained paresthesia, although not a common presenting sign, is very concerning and requires thorough investigation.

Very advanced mandibular SCCA that extends outward into the soft tissues may lead to skin alterations. Skin involvement may present with erythema, induration, pain, and a peau d'orange texture.

Mandibular SCCA, like most oral SCCA, has a propensity for regional metastasis to cervical lymph nodes. However, unlike other head and neck SCCA sites, the primary site is often the dominant feature. It is uncommon for a patient to present with an isolated lymph node with an unknown primary that turns out to be from an oral site. However, it is not uncommon for a patient to present with both an obvious mandibular primary and palpable lymphadenopathy. The level IA and IIA nodal basins are the most frequently involved. Contralateral regional metastases are also seen, particularly with tumors that encroach on the midline.

The genetic alterations required that allow for distant metastases may occur at any time along tumor progression. However, distant metastases of mandibular SCCA are not generally seen until very advanced disease. Risk for distant metastases increases with the presence of nodal metastases, particularly at the lower levels of the neck (levels IV and V).[19,20]

Prognosis is most closely associated with the stage of the disease at the time of treatment. Of the features that are used to define the stage, the presence of either nodal or distant metastases is the most significant. The presence of nodal metastases halves the 5-year survival rate.[20] The presence of distant metastases is terminal, with average survival being less than a year.

Staging

The staging criteria and staging system for head and neck cancer in general and oral cavity cancer in particular, recently underwent substantive modification as published in the 8th edition of the *AJCC Staging Manual,* thereby more accurately representing the unique biologic, clinical, and epidemiologic features of oral squamous cell carcinoma (OSCC) (Table 24.1). The first modification is in the T stage, as it incorporates depth of invasion (DOI). In the 1980s, Spiro and colleagues identified the importance of tumor thickness as a prognostic indicator in oral cavity cancer. Depth of invasion

TABLE 24.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease
T4a	Moderately advanced local disease. (Lip) Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose). (Oral cavity) Tumor invades adjacent structures only (e.g. through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face). Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base or encases carotid artery
Regional Lymph Nodes: Clinical (cN)	Oropharynx (p16–) and hypopharynx
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node >3 cm but ≤ 6cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N3	Lymph node(s) >6 cm and ENE(–) or metastasis in any node(s) and clinically overt ENE(+)
N3a	Lymph node(s) >6 cm and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathologic ENE should be recorded as either ENE(–) or ENE(+)
Regional Lymph Nodes: Pathologic (pN)	Oropharynx (p16–) and hypopharynx
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
pN2	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+); or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2a	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+); or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–)
pN2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN3	Lymph node(s) >6 cm and ENE(–); or metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)

TABLE 24.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)—cont'd

Regional Lymph Nodes: Pathologic (pN)—cont'd Oropharynx (p16–) and hypopharynx

pN3a	Lymph node(s) >6 cm and ENE(–)
pN3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)

Distant Metastasis (M) Oropharynx (p16–) and hypopharynx

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Registry Data Collection Variables

1. Lip location (external or vermilion border)
2. ENE clinical: ENE(+) or (–)
3. ENE pathologic: ENE(+) or ENE(–)
4. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
5. Perineural invasion
6. Lymphovascular invasion
7. p16/HPV status
8. Performance status
9. Tobacco use and pack-years
10. Alcohol use
11. Depression diagnosis
12. Depth of invasion (mm)
13. Margin status (grossly involved, microscopic involvement)
14. Distance of tumor (or moderate/severe dysplasia) from closest margin
15. WPOI-5

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated

From Ridge JA, Lydiatt WM, Patel SG, et al: Lip and oral cavity. In Amin MB, Edge SB, Greene FL, et al, editors: *AJCC cancer staging manual,* ed 8, New York, 2017, Springer. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

is a more sophisticated and reproducible method of measuring a tumor. It is measured by first finding the "horizon" of the basement membrane of the adjacent squamous mucosa, and DOI is defined as the deepest point of tumor invasion from that line (in millimeters). Extrinsic muscle infiltration has been removed from the staging criteria because DOI is more representative of the clinical problem both clinically and pathologically. DOI assesses the invasiveness of the tumor rather than any exophytic component.

A second major modification in the new staging system is the recognition of extranodal extension in categorizing metastatic cancer to the cervical lymph nodes. Additional updates to this classification include the following:

1. Separate N category approaches for patients treated without cervical lymph node dissection (clinical N [cN]) and patients treated with cervical lymph node dissection (pathologic N [pN]).
2. Extranodal extension (ENE) is introduced as a descriptor in N categorization for all HPV-negative cancers, and its presence is designated pN2a for a single ipsilateral node <3 cm and pN3B for all other node(s).
3. Clinically overt ENE is classified as ENE and is considered ENE+ for cN.
4. Pathologically detected ENE is classified as either ENE_{mi} (<2 mm) or ENE_{ma} (>2 mm) for data collection purposes only, but both are considered ENE^{+} for definition of pN.

However, pathologic stage does not trump clinical stage, and assignment of ENE should be based primarily on physical examination, rather than on imaging studies.

The primary tumor stage remains essentially the same in the new system, with the exception that DOI will increase the T category by 1 for each 5 mm of tumor depth (until ≥10 mm). Pathologic ENE^{+} will increase the nodal category by 1. In addition, the AJCC recommends other prognostic factors be considered and recorded along with standard staging information, including Eastern Cooperative Oncology Group (ECOG)/Zubrod or Karnofsky performance measures, tobacco and alcohol use, tumor location, number and size of nodes, perineural invasion, and ENE.

Worst pattern of invasion (WPOI) is a validated outcome predictor for OSCC that is highlighted in the 8th edition of the *AJCC Staging Manual.* It is recommended that WPOI-5, defined as tumor dispersion of ≥1 mm between tumor satellites, be recorded as part of pathologic staging. Even in early-stage oral cancer, a DOI of >4 mm combined with a WPOI-5 increases the probability of recurrence to approximately 42%. Perineural invasion (PNI) or lymphovascular invasion constitute a WPOI-5 classification. When identified, PNI should be subclassified as either intratumoral or extratumoral. Named nerves should be specified, and PNI should be subclassified as focal or multifocal.

Focused Physical Examination

The focused examination of the patient with mandibular cancer should include an examination of the neck, face, and oral cavity (including teeth). Examination of the pharynx, larynx, and cranial nerves should also be performed as directed by the patient's presenting symptoms.

Neck

All levels of the neck should be palpated for lymphadenopathy. Level I is the most common site for regional metastasis from mandibular SCCA. Level II is the next most frequent site.[21] Special attention should be directed to these areas when performing a neck examination. When examining level I, the author asks the patient to place the tongue against the hard palate. This results in depression of the mylohyoid muscles, pushing the submandibular triangle inferiorly, making smaller lymph nodes here more easily palpable. When examining level II, the author will have the patient turn slightly to the ipsilateral side and flex the neck to relax the sternocleidomastoid. This muscle can then be slightly retracted to allow for palpation of the upper jugular chain of lymph nodes.

Face

Any asymmetries in the face should be noted. The mandible should be palpated for expansion or tenderness.

The examiner should record the maximal incisal opening. Normal maximal incisal opening is considered to range from 40 to 50 mm. Neoplasms of the temporomandibular joint, ramus of the mandible, and lateral pharyngeal space can all cause limitation of movement and pain. Trismus due to tumor invasion can make for a difficult intubation and should be noted preoperatively so a plan for a difficult airway management can be discussed.

Oral Cavity and Oropharynx

When examining the oral cavity, the buccal mucosa, vestibular mucosa, alveolar gingiva, palatal mucosa, lingual mucosa, floor of mouth, and all borders of the tongue should be inspected both visually and by palpation. If the patient is wearing any removable dental prostheses, these should always be removed prior to inspection. Examination of the mandible should be done by bimanual palpation to assess for swelling or cortical expansion. The characteristics of any swelling should be described. Pay special attention to assessing for extension of the tumor onto the buccal mucosa, floor of mouth and tongue, retromolar trigone, and oropharynx.

For advanced mandibular tumors, adjuvant radiation therapy should be expected. Therefore, one should perform a cursory dental exam, making note of any teeth with questionable prognoses. Extraction of compromised teeth can be performed at the same time as the ablative surgery to prevent delays in treatment. It is important to measure the maximal incisal opening, as well as make note of the Angle classification for the patient's occlusion, the position of the maxillary and mandibular dental midlines, and reproducibility of the patient's occlusion. This information will play a critical role in the reconstructive phase of any surgical treatment for malignancy provided.

Extremity

For advanced mandibular cancers, the examination should include examination of potential donor sites for reconstruction. Our unit favors the use of the fibula osteocutaneous flap for mandibular reconstruction. As part of the reconstructive surgical consultation, the lower legs are examined, starting with visual inspection. The examiner looks for scars from previous surgery and stigmata of arterial or venous insufficiency. Arterial insufficiency is characterized by loss of hair, shiny appearing skin, cool and pale skin, a mottled or marbled appearance, onychomycosis, and occasionally hyperemia when moved from a supine to dependent position. Severe arterial insufficiency results in areas of gangrenous changes and non-healing ulcers. The patient may also complain of pain that is relieved by placing the extremity in a dependent position. Venous insufficiency is characterized by edema and splotchy cyanosis that worsens when the extremity is placed in a dependent position. Venous insufficiency may also present with stasis ulcers. The examiner should palpate for pulses from the dorsalis pedis artery (located just lateral to the extensor tendon of the great toe) and the posterior tibial artery (located just posterior to the medial malleolus of the distal tibia). If the pulses cannot be palpated, a Doppler probe may be used. Ankle-brachial indices (ABIs) may be measured, which is an easily performed, noninvasive test for arterial insufficiency. However, we rarely perform this test, as the combination of our clinical exam and imaging studies provides enough information to indicate whether a lower extremity is a viable donor site. If there is any question whether or not three-vessel run off to the lower extremity is sufficient, another donor site is chosen.

Biopsy

Once a suspicious lesion is identified, a biopsy of the lesion is arranged. Often, this can be done under local anesthesia. Generally, mandibular SCCA begins within the soft tissue, so sampling using a biopsy punch or scalpel is fairly straightforward. Deeply infiltrative lesions or primary intraosseous lesions may present with greater difficulty in accessing the lesion. Biopsies of these may be performed with greater ease under general anesthesia. Regardless of the approach, the most critical aspect for proper pathologic diagnosis is to obtain sufficient amounts of representative tissue. This may require several biopsies if the lesions poorly defined.

Imaging

Imaging is an essential part of the initial diagnostic workup, staging, and surgical planning.

The first image that is obtained is a panoramic radiograph (orthopantomogram). This provides some preliminary information of extent of bony involvement and destruction by tumor. In addition, the panoramic radiograph provides essential information about the remaining dentition. As radiation therapy is likely to be a part of the treatment plan, it is important to perform a pre-radiation dental evaluation and remove any teeth that have poor prognoses.

For advanced mandibular squamous cell carcinoma, we order computed tomography (CT) of the face and neck with contrast, a non-contrasted maxillofacial CT using the 3D Systems Protocol (http://www.medicalmodeling.com), CT angiograms (CTA) of the lower extremities, and positron emission tomography combined with CT (PET/CT) to complete staging and rule out second primaries.

The rationale for the CT with contrast of the face and neck is its combination of utility and ease. Bony anatomy is much better and soft tissue characterization of the primary tumor and neck lymphadenopathy is reasonably demonstrated with CT when compared with magnetic resonance imaging (MRI). At our unit, it is much easier to schedule a CT than an MRI. In addition, patients find CT scans easier to tolerate than MRI. Of course, dental artifact often diminishes the quality of the soft tissue imaging in the oral cavity, which is less of an issue with MRI. MRI may have higher sensitivity for marrow invasion, although specificity is less than CT.[22]

In our unit, Virtual Surgical Planning (VSP) and 3D-printed cutting guides and models are used for every patient with advanced mandibular cancer. A higher resolution, finer cut, non-contrast CT of the face is a requirement for use with VSP.

As mentioned earlier, the fibula free flap is our reconstruction modality of choice. Part of the preoperative assessment of the viability of this option is clinical and radiographic assessment of the lower extremity for sufficient three-vessel arterial supply of the distal lower extremity. Either a CTA or magnetic resonance angiogram (MRA) would provide accurate assessment of blood supply. These help confirm three-vessel runoff in the lower leg, quantify peripheral vascular disease, and rule out problematic anatomic variations (long trunk, peronea magna, or absent posterior tibial artery). Actual angiograms have been replaced by these two modalities for the purposes of assessment for reconstructive surgery. We favor CTA, as it has the dual benefit of assessing the vasculature and providing data on the bony anatomy for VSP.

One can complete staging by imaging for distant metastases and second primaries in several ways. Our group favors PET/CT for several reasons. It is demonstrably superior to CT or MRI alone for detecting occult metastases, although the utility of this tool in altering treatment for this reason alone is debatable.[23,24] It serves as a baseline for comparison when obtaining post-treatment surveillance imaging for locoregional or distant recurrence. It includes areas most commonly affected by distant metastases or second primaries in the same scan. It can provide functional data when the anatomic characteristics of CT alone may be equivocal. It is, unfortunately, more expensive and is not quite as widely available as CT or MRI scanners, although this is rapidly changing. An alternative to PET/CT would be a chest CT, or even a chest plain film if the patient is at low risk for a second lung primary (when a patient is a never smoker).

Treatment Planning

In counseling patients on treatment of advanced mandibular SCCA, it is helpful to frame the discussion around current National Comprehensive Cancer Network (NCCN)

Guidelines.[25] The three traditional modalities for oncologic treatment are surgery, radiation, and chemotherapy. All have roles in the treatment of advanced mandibular SCCA. Patients with mandibular SCCA preferably have surgery as initial primary treatment.[26]

Primary treatment with radiation therapy may be considered in some settings when patients may not be good surgical candidates, although this scenario is exceedingly rare. Local control of disease in the oral cavity, particularly when there is bony invasion of the mandible, is less when compared to surgery.

Neoadjuvant chemotherapy, or chemotherapy prior to initiation of the primary treatment, is a modality that has been investigated by several clinical trials. Reasons for this approach include the following. Early chemotherapy provides early systemic therapy, which hopefully would decrease the incidence of distant metastases. Using chemotherapy when there is measurable tumor allows for biologic interrogation of the tumor. An induction regimen that yields a good response theoretically suggests a tumor that may be more responsive to definitive treatment. Similarly, it also helps select an adjuvant chemotherapy regimen in the postoperative setting. Third, neoadjuvant chemotherapy can occasionally reduce the size of the primary tumor, making a tumor that may have been either unresectable or resectable only with considerable morbidity into a potentially more easily resectable tumor. However, large, multicenter clinical trials have not shown improvements in either progression-free survival or overall survival.[27,28] Despite this, there may still be a role for neoadjuvant chemotherapy in the appropriate patient population, although that population is yet to be clearly defined.

There are several considerations to review when planning surgery for advanced mandibular cancer.

Airway

Locally advanced mandibular cancers, if involving the masticator muscles, can lead to significant trismus. The tumor itself may be obstructive and/or friable, resulting in obscuration of the airway from mass effect and bleeding. In the patient with recurrent tumor after surgery and/or radiation therapy, altered anatomy exacerbates these challenges. These factors may make securing the airway during anesthesia induction precarious.

The difficulty of the airway must be assessed jointly by the surgeon and anesthesiologist using physical examination, which may include a preoperative fiber-optic exam. A plan of action for securing the airway is discussed before induction, and all relevant preparations are made. When dealing with a difficult airway, the choices that our team deliberates between are: awake video laryngoscopy exam followed by induction and intubation, awake fiber-optic intubation, or awake tracheostomy. The decision is ultimately determined by the difficulty of the patient's airway and the comfort level of the anesthesiologist and surgeon with each of these techniques.

Regardless of the type of airway initially established, our group will create a tracheostomy for every patient treated for advanced mandibular cancer, with rare exceptions. This strategy is often debated, and there is published single institution data from a number of centers suggesting that patients do as well or better with a short period of intubation followed by extubation and close monitoring.[29,30] Our rationale for elective tracheostomy is primarily for safety, faster weaning from mechanical ventilation (often immediately), and improved pulmonary toilet. We do recognize that tracheostomies are not benign, with their own related complications. Ultimately, the decision to perform a tracheostomy depends greatly on specific institutional factors, one of which is the availability of an emergent airway team capable of establishing an airway on a difficult patient on the ward on a moment's notice.

Type of Resection for Primary

The standard surgery for resection of advanced mandibular SCCA is a composite resection of soft tissue (involved mucosa, periosteum, muscle, and bone) and a segmental mandibulectomy. As described earlier, the extent of the mandibulectomy is dictated as much by the size of the tumor as it is by which mandibular subunits are included.

For advanced mandibular SCCA that does not have frank bony invasion clinically or radiographically, a marginal mandibulectomy can be considered. Marginal mandibulectomy refers to a resection of the superior aspect of the mandible, the majority of which is the alveolar bone segment. The majority of the densely cortical basal bone along the inferior border of the mandible is preserved. When appropriate, this offers the considerable advantage of maintaining the natural mandibular contour and framework. The primary reconstructive surgery is then simplified considerably and can be directed to only replacing the missing soft tissue. Great caution should be taken when considering this approach, however. There is greater risk of having a positive or close margin, as early bone invasion is not always clearly discernible on CT. This technique is also not recommended if the patient has an atrophic mandible, as the remaining mandible after a sufficient margin has been taken is often inadequate and prone to pathologic fracture, especially if radiation is given postoperatively. If the tumor and resection in a dentate portion of the mandible, removal of the alveolar bone can actually make it more challenging to prosthetically reconstruct the missing teeth. As mentioned earlier, the basal bone is not always aligned directly below the dentate segment, making the angulation of dental implants placed into it suboptimal. In addition, the restorations have a longer distance between the occlusal plane and the height of the implant platform at the bone, which can lead to unfavorable levering forces if the angulation involves non-axial directed loading. For these reasons, the authors use this technique only in select circumstances.

The margin of resection should be 1 to 1.5 cm, with the ultimate goal of achieving a negative pathologic margin of 5 mm.[31] With mandibular gingival cancers, particularly those in the retromolar trigone, there can be a larger discrepancy between the margin that is determined by physical examination and imaging and the final pathologic margin.[32]

Management of the Regional Lymphatics

In management of oral SCCA, consideration must be given to how to address the regional lymphatics. There are essentially two scenarios to consider: the neck with clinical nodal metastasis (N+) and the neck without clinical nodal metastasis (N0).

The first scenario is the simplest to discuss. N+ disease requires definitive treatment. The two modalities available are surgery or radiation therapy. By and large, surgery in the form of a neck dissection is the most common. The rationale for surgery over radiation therapy is that surgery involving the neck is already part of resection of the primary. If the reconstruction involves a microvascular free flap, access to the neck vessels and a neck dissection are already required. Third, in certain circumstances where the resection is completed with no high-risk histopathologic features, treatment may conceivably limited to one modality (surgery only). The type of neck dissection for N+ disease is usually some iteration of a modified radical neck dissection, levels I-V. In modern head and neck surgery, traditional radical neck dissections are rarely required.

The second scenario of the N0 neck requires a detailed discussion outside of the scope of this chapter.[33] Despite a recently published large randomized controlled trial showing improved survival with elective neck dissection of the N0 neck, many surgeons still debate the merits of surgery versus a watch and wait approach.[34] The authors favor performing a selective neck dissection with all locally advanced mandibular SCCA in patients with N0 necks. The reasons are as follows. There is at least a 30–50% risk of nodal metastasis with advanced mandibular SCCA.[21,35] As already stated, a cervical approach is already required for a composite resection of the mandible (unless a marginal mandibulectomy is performed). Third, in our unit, most mandibular resection defects are reconstructed with some form of microvascular free flap. A neck dissection for vascular access is, therefore, already required. Expanding the surgery into a selective neck dissection of levels I through III (and/or IV) does not alter the surgery significantly.

Reconstructive Surgery Planning

Reconstruction of oral defects following oncologic surgery has been the one area within oral/head and neck surgery that has enjoyed the greatest evolution in the last few decades. The first major advance was the mastery of microvascular surgery and the ability to perform free-flap reconstructions with high reliability. The second major advance was the development of composite tissue flaps of both bone and soft tissue. The third major advance was the application of virtual surgical planning and 3D-printed cutting guides to bone flap surgery, which has simplified many of the technique-sensitive aspects of bone flap contouring and made precision mandibular reconstruction much more predictable and reproducible.

Numerous classification schemes exist that describe various defect-oriented approaches to mandibular reconstruction. Our preferred classification system is that described by Brown, which considers the dentate mandible in relation to the involvement of the canine teeth and mandibular condyle (Table 24.2).

TABLE 24.2 Brown Classification System Based on the Four Corners of the Mandible

Class I (angle)
Lateral defect not including ipsilateral canine or condyle

Class Ic (angle and condyle)
Lateral defect including condyle



Class I



Class Ic

Class II (angle and canine)
Hemimandibulectomy including ipsilateral but not contralateral canine or condyle

Class IIc (angle, canine, and condyle)
Hemimandibulectomy including condyle



Class II



Class IIc

Class III (both canines)
Anterior mandibulectomy includes both canines but neither angle



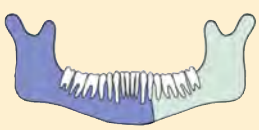
Class III

Class IV (both canines and at least one angle)
Extensive anterior mandibulectomy including both canines and one or both angles

Class IVc (both canines and at least one condyle)
Extensive anterior mandibulectomy including both canines and one or both condyles



Class IV



Class IVc

From Brown JS, Barry C, Ho M, Shaw R. A new classification for mandibular defects after oncological resection. *Lancet Oncol*. 2016;17(1):e23–e30.

There are several options that are available for mandibular reconstruction. Defects from mandibular SCCA resection will involve both soft tissue and bone. Choosing which reconstructive modality is most appropriate depends on the patient's defect and general health, the availability of a microvascular surgeon, and the surgeon's experience. The ideal reconstruction will restore the facial form in three dimensions as well as maintaining mandibular function for chewing, speech, and swallowing.

Soft Tissue Flap Combined With or Without Bone Graft

One approach to reconstructing composite mandibular defects is to consider the soft tissue and bony reconstruction separately. In this instance, a soft tissue flap is used to replace the resected gingiva, mucosa, and muscle bulk. This also creates a well-vascularized envelope that can be used as a recipient site for a bone graft. If a segmental mandibulectomy has been performed, a reconstruction plate is used to appropriately position the remaining native mandible in the preoperative occlusion, with adequate anterior-posterior projection and maintaining preoperative mandibular width. The portion of the plate that spans the defect does not need to have a contour that matches the natural curvature of the mandible. In fact, it is better to simplify the bending into straight segments for each subunit. The soft tissue flap is draped over the plate and sutured to the native mucosa to seal the plate off from the oral cavity. Several types of soft tissue flaps can be used, both regional and distant.

Regional soft tissue flaps include the submental island flap and the pectoralis major flap. The submental island flap is close and reliable. However, its proximity limits its usefulness, as the pedicle is often disturbed by lymphadenectomy of level IB and by the mandibulectomy itself. Taking the time to meticulously preserve the pedicle while sufficiently removing lymph node and cancer-bearing tissue negates the benefit. The pectoralis major myocutaneous flap is an excellent flap for this purpose. It provides both skin and muscle, the latter providing a particularly good vascular bed for protecting the hardware and nourishing a bone graft. However, it can be fairly bulky, and it is often difficult to close the skin flaps of the neck incision over the muscle, requiring an unsightly skin graft in the neck.

Depending on the size of the defect, there are several free flap options that may be of use. The most commonly used fasciocutaneous flap is the radial forearm free flap. It provides a large amount of skin; has a pedicle of large caliber and length for easy anastomosis; is pliable and flexible, which is ideal in the oral cavity; and has minimal donor site morbidity. For larger defects, an anterolateral thigh flap may also be considered, but it tends to be too bulky for mandibular soft tissue defects.

The bony portion can then be reconstructed using bone graft. The most commonly used source is a corticocancellous bone graft harvested from the iliac crest.

Having described this option, the authors rarely use this technique for mandibular reconstruction. Although some surgeons argue that bony reconstruction with the iliac crest bone graft is superior to that of a fibula free flap for implant placement, we have not found the bone quality to be the limiting factor. In addition, there are several disadvantages to this approach. As mentioned earlier, advanced mandibular SCCA is usually treated with radiation therapy started within 6 weeks of surgical resection. At that time, free bone graft placed primarily will have been revascularized, but incorporation into the native mandible will not be close to maturity. Radiation damage will almost certainly destroy any neovascularization as well as the tenuous osteocytes within the bone graft. If bone graft is placed secondarily, a second surgery is required that places free bone graft into a poorly vascularized tissue bed. Bone morphogenic protein-2 (BMP-2) mixed with harvested stem cells derived from bone marrow aspirate concentrate has been used; however, the safety of using a growth factor in a cancer patient is not well defined and seems counterintuitive.[36]

Osteocutaneous Free Flaps

The most common technique for mandibular reconstruction of composite bone and soft tissue defects following oncologic resection is using an osteocutaneous free flap. This has the advantage of placing healthy, vascularized bone and soft tissue into a defect that is assaulted by saliva, bacteria, and radiation.

There are a few different types of osteocutaneous free flaps that are used for mandibular reconstruction. They are the fibula free flap, the deep circumflex iliac artery (DCIA), and the scapula free flap. Each of these has advantages and disadvantages, as evidenced by the observation that different centers will prefer one to the others.

Fibula

The fibula flap is the one most frequently used by our group for mandibular reconstruction. It has several advantages. The site is distant from the head and neck, and flap harvest can be performed simultaneously with the ablation easily and comfortably. It has a reliable skin paddle of considerable size. Also, the skin paddle is based on septocutaneous perforators, making dissection straightforward. The septum is of a good length, allowing flexibility between placement of the bone and soft tissue. Up to 25 cm of bone can be harvested, which allows the surgeon to reconstruct angle-to-angle mandibular defects. It has a reliable periosteal supply that allows the surgeon to perform multiple osteotomies to contour the fibula into an ideal shape. It has a relatively long pedicle with good vessel diameter of both artery and vein. It can also be raised with a second muscle and skin flap based off of a perforator to the soleus muscle, although this shortens the pedicle length considerably.

There are some disadvantages. The bone is densely cortical, with a very fatty marrow space. Although this allows for good primary stability when implants are placed, this is not ideal bone stock for osseointegration. Having said that, the few long-term retrospective studies of implant survival in fibula flaps have shown favorable implant survival rates of 91–93%, although this decreases to 69% at 20 years.[37,38] The bone height is short compared to the vertical dimension of the mandible. Although this is of little consequence in the ramus and body region, when used to reconstruct to anterior mandible,

this often results in an appearance much like that of an atrophic mandible. Defects that include both oral mucosa and skin are difficult to reconstruct, as the number and location of skin perforators are not predictable, making planning for separate skin islands difficult. The donor site scar is also very visible and difficult to camouflage.

Deep Circumflex Iliac Artery (DCIA)

The DCIA flap is also very popular. The shape and size of the iliac crest is well matched for mandibular body and parasymphysis reconstruction (Fig. 24.5A,B). The bone is type III to type IV (more cancellous than cortical), theoretically making it more satisfactory for implant osseointegration (Fig. 24.6).

There are several disadvantages to the DCIA flap. The skin paddle is fixed to the iliac crest, limiting its versatility. As the crest is typically oriented to reconstruct the inferior border, the skin paddle is suitable only for reconstructing skin defects; it is unsuitable for oral defects. The internal oblique muscle is raised with the flap and can be used to line the oral defect and mucosalize by secondary intention, however. The length of the pedicle is shorter than for the fibula. The flap itself is shorter, so it can, at most, be used for hemimandibular defects.

Scapula

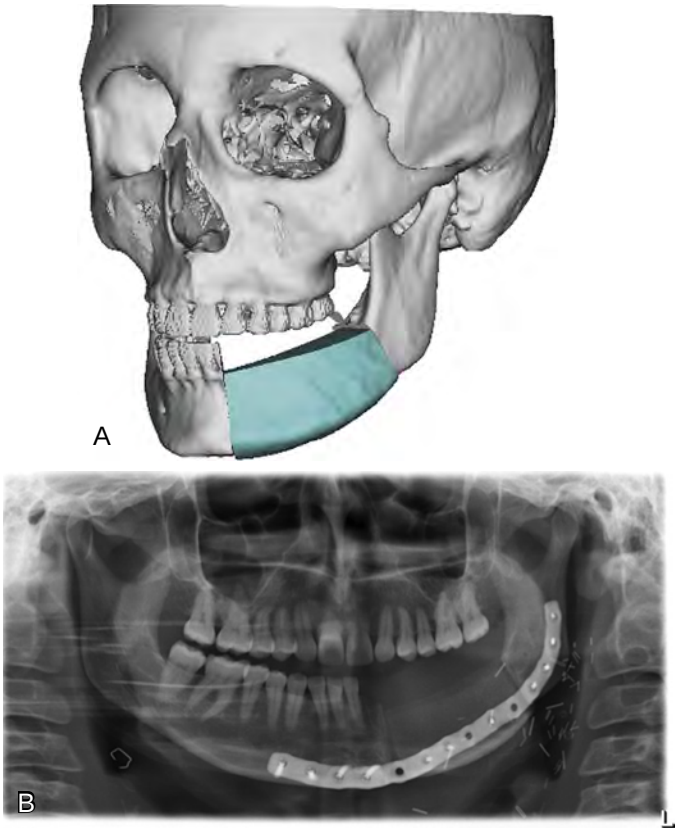
Our group rarely uses subscapular system flaps for mandibular reconstruction. The advantages are flexibility. The chimeric flaps that can be based off of the subscapular system make it ideal for complex composite defects involving soft tissue and bone (Fig. 24.7).

However, there are several disadvantages. For mandibular reconstruction, the bone thickness is not generally suitable for implant, although some have argued otherwise.[39] The length of bone is limited, and full-arch defects are difficult to reconstruct well. Finally, it is uncomfortable, albeit possible, to harvest the flap and perform the ablation simultaneously in a two-team approach.

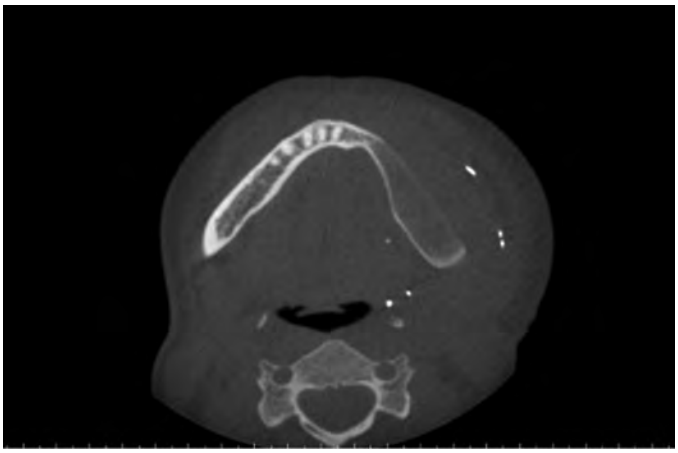
Computer-Assisted Surgical Planning (Virtual Surgical Planning)

As mentioned earlier, nearly all of our patients with mandibular cancer have their ablative and reconstructive surgeries planned using VSP. Once the requisite imaging data have been collected and uploaded to our third-party 3D planning company, a web-based VSP meeting is scheduled involving the ablative surgeon, reconstructive surgeon, and engineer.

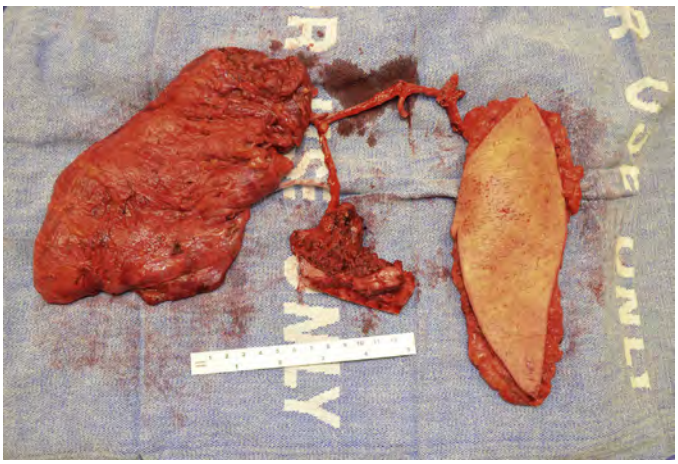
The ablation is planned first, using the mandibular subunit principles described earlier. The osteotomies are placed with a minimum of 1.5-cm margins, but often more generous to



• **Fig. 24.5** **A** and **B**, Deep circumflex iliac artery flap has ideal shape for mandibular body reconstruction.



• **Fig. 24.6** Deep circumflex iliac artery flap has type III to type IV bone.



• **Fig. 24.7** Subscapular system mega flap allows for flexibility in reconstruction.

include the entire mandibular subunit. This is initially done on a virtual 3D model reconstructed from the CT data. After the osteotomy is planned on the virtual 3D model, the same cuts can be viewed on traditional axial/coronal/sagittal views to make sure a sufficient margin has been planned for in all planes.

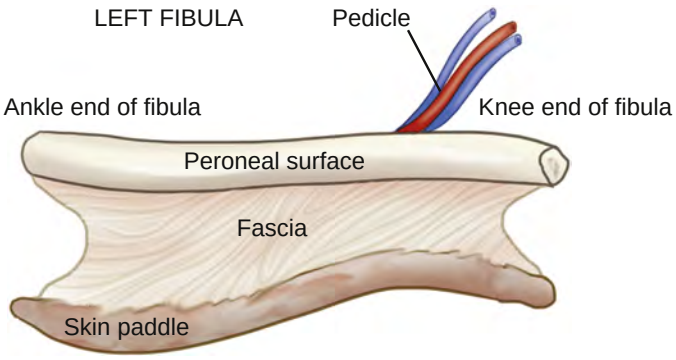
When planning the cuts, it is generally better to make the cuts straight butt joints to keep the junction between the reconstruction and native mandible simple and facilitate flap inset. Under some circumstances, it may be advantageous to make the osteotomy oblique. This can be done to increase the contact surface area between the reconstructed mandible and native mandible. This also can be done to make a segment of the reconstruction slightly longer, to facilitate periosteal blood supply to that segment. In dentate portions of the mandible, it is best to plan the osteotomy through a tooth socket rather than between tooth roots. This leaves sufficient alveolar bone housing around the tooth closest to the osteotomy.

Next is the planning of the reconstruction. Data from the CTA of the lower extremities are used to create virtual 3D models of the fibula (or other bony flap).

When choosing which fibula to use, there are three important questions. First, determine on which side of the neck the recipient vessels are most likely to be. In patients who have not had surgery before, the ipsilateral neck is most commonly used. Second, determine whether the pedicle is going to be coming off anterior or posterior. For body defects, body and symphysis defects, or angle-to-angle defects, we typically have the vessels run posterior, unless the contralateral neck is being used for the recipient vessels. For defects that include the condylar ramus subunit, particularly those that require condylar reconstruction, we typically have the vessels run anterior to avoid having a hairpin loop of the pedicle at the skull base. Third, determine where the soft tissue defect will be: intraoral, cutaneous, or both.

Once these factors are determined, assuming appropriate vascularity of both lower extremities, the leg most suited for the defect is chosen. Knowing that the skin paddle for the fibula flap is attached by its septum to the posterolateral aspect of the fibula, that the most reliable perforators are most commonly found between the middle and distal third of the fibula, and that the lateral side of the fibula is the most suitable for plating and is directed buccal, we choose the leg that will result in the skin paddle facing the direction of the soft tissue defect while the pedicle faces the planned direction. This arrangement leaves the pedicle running along the lingual side of the neo-mandible. For example, if we are reconstructing a right mandibular body defect including oral mucosa using vessels in the ipsilateral neck, we will use the contralateral fibula with the pedicle facing posterior. This will leave the skin paddle facing the oral cavity (Fig. 24.8).

The engineer then creates virtual osteotomies in the chosen fibula to replace each of the mandibular subunits. The most distal osteotomy is placed about 6 to 7 cm proximal to the lateral malleolus of the fibula. The fibula segments are then planned to fill the defect from posterior to anterior.

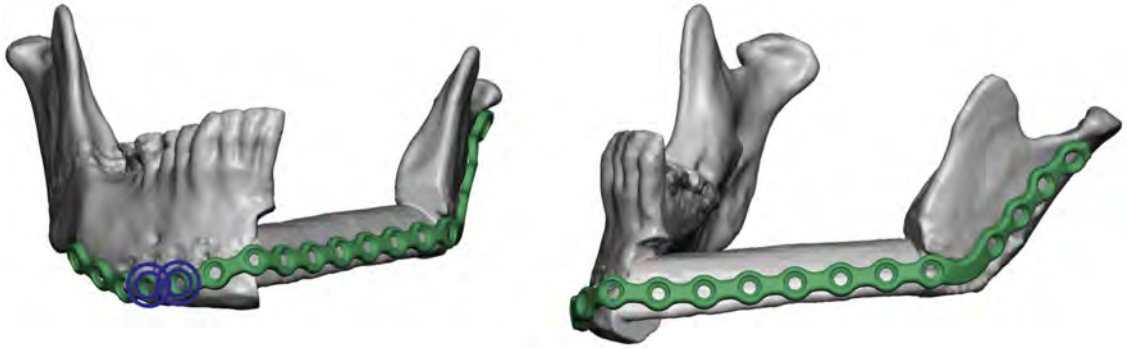


• **Fig. 24.8** Arrangement of fibula in relation to its pedicle, skin paddle, and the defect to be reconstructed.

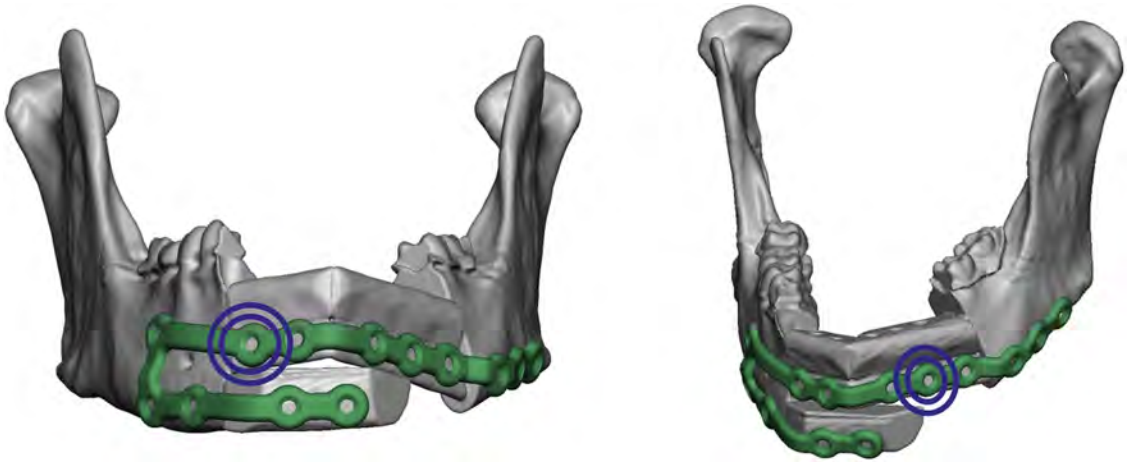
One of the challenges of using a fibula flap to reconstruct the mandible is the discrepancy in size and shape. Namely, the difference between the height of the mandible and the fibula and the dual arc configuration of the mandibular alveolus and inferior border can be difficult to match. For elderly patients with some amount of mandibular atrophy, this is not significant. This is most pronounced in young, slender patients with thin fibulas and no mandibular atrophy. Many surgeons place the fibula at the inferior border, which emphasizes the contour and skeletal framework of the lower face. This often leads to a fibula that is lateral and inferior in position to the ideal placement for implant reconstruction. Other surgeons prioritize placing the fibula at the position of the alveolus. This is optimal for implant placement, but often makes soft tissue closure more difficult and can potentially lead to an external contour deformity.

Several modifications of fibula planning have been used to mitigate this challenge. We often place the fibula in an intermediate position. At the angle, the fibula is placed at the inferior border and lateral. This creates symmetry of the facial contour at the angle region. As we move into the dentate area of the mandible, the fibula is placed halfway between the inferior border and alveolus. It is also planned medial to the mandibular border to correspond with the opposing dentition (Fig. 24.9). Translucent overlay of the existing teeth or opposing teeth can be used to help with this portion of the surgical planning. In our experience, this leaves the fibula in a position that can be easily used for definitive dental reconstruction with minimal compromise to the facial contour. Other groups have reported on their experience with similar findings.[4]

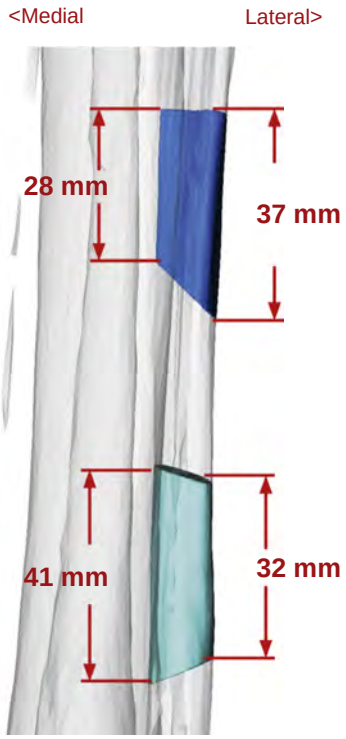
Another modification is using a double-barrel configuration for the fibula (Fig. 24.10). We find this helpful for isolated body defects, when the fibula is very thin, or for isolated symphysis defects. It does shorten the length of the pedicle and add complexity by creating hairpin turns in the pedicle. When planning for a double barrel, a minimum of 3 cm of bone between the two segments needs to be discarded to allow the turn in the pedicle to be as gentle as possible (Fig. 24.11). The proximal portion of the fibula showed be used as the superior segment, as this is the most critical to maintain (Fig. 24.12). Also, rigid fixation should be used on both segments to the native mandible. The two fibula segments do not form a bony union with each other.



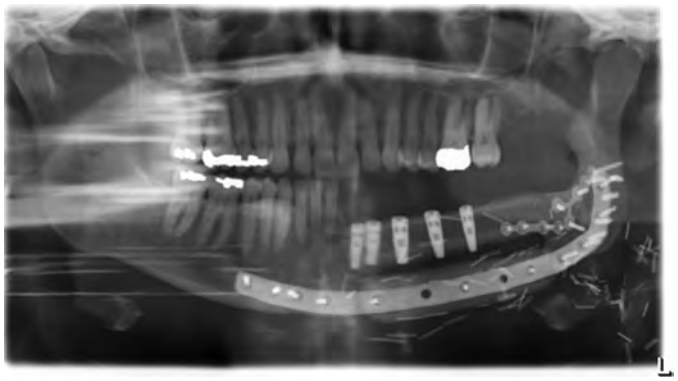
• **Fig. 24.9** Positioning of fibula in intermediate position for reconstruction of the mandibular body.



• **Fig. 24.10** Double-barrel arrangement of the fibula.

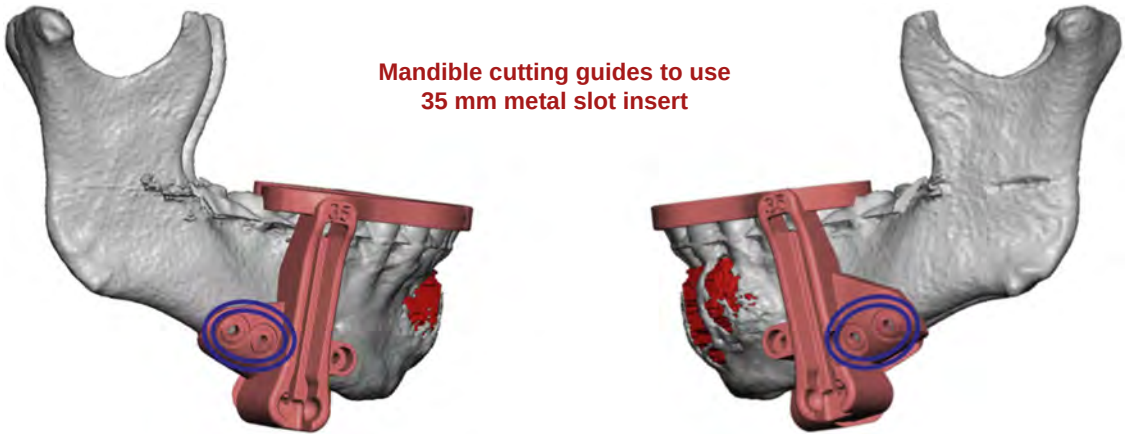


• **Fig. 24.11** Discarding 3 cm of fibula to allow for folding of the fibula into a double barrel.

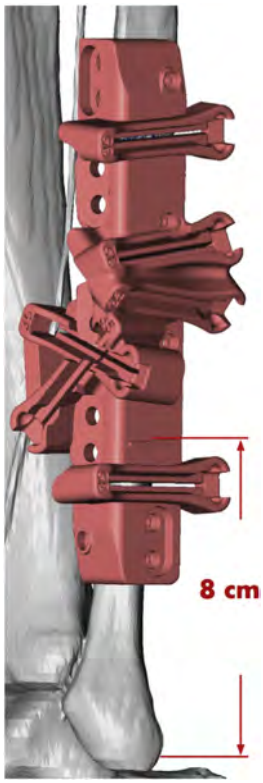


• **Fig. 24.12** Using the proximal segment as the alveolus in double-barrel arrangement.

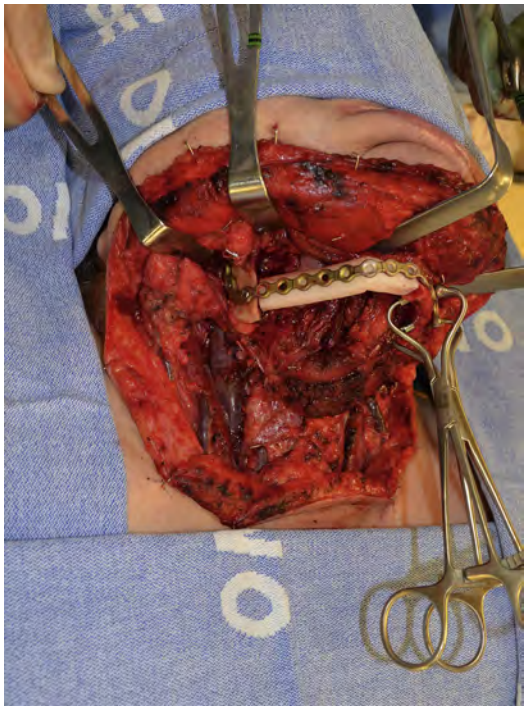
Once the reconstruction is planned, the engineers from the surgical planning company will design the cutting guides and 3D print them for use intraoperatively. The mandibular cutting guides are planned with predictive holes for the anticipated reconstruction plate (Fig. 24.13). The fibula cutting guide is designed to rest on the lateral side of the fibula, if possible. We ask for a mark to be placed on the cutting guide to designate an arbitrarily selected distance from the lateral malleolus, to aid in fitting the fibula guide at the appropriate position along the proximal-distal axis



• **Fig. 24.13** Predictive holes built into mandibular cutting guides that correspond with holes from reconstruction plate.



• **Fig. 24.14** Mark on fibula cutting guide corresponding to an arbitrarily selected distance from the lateral malleolus.

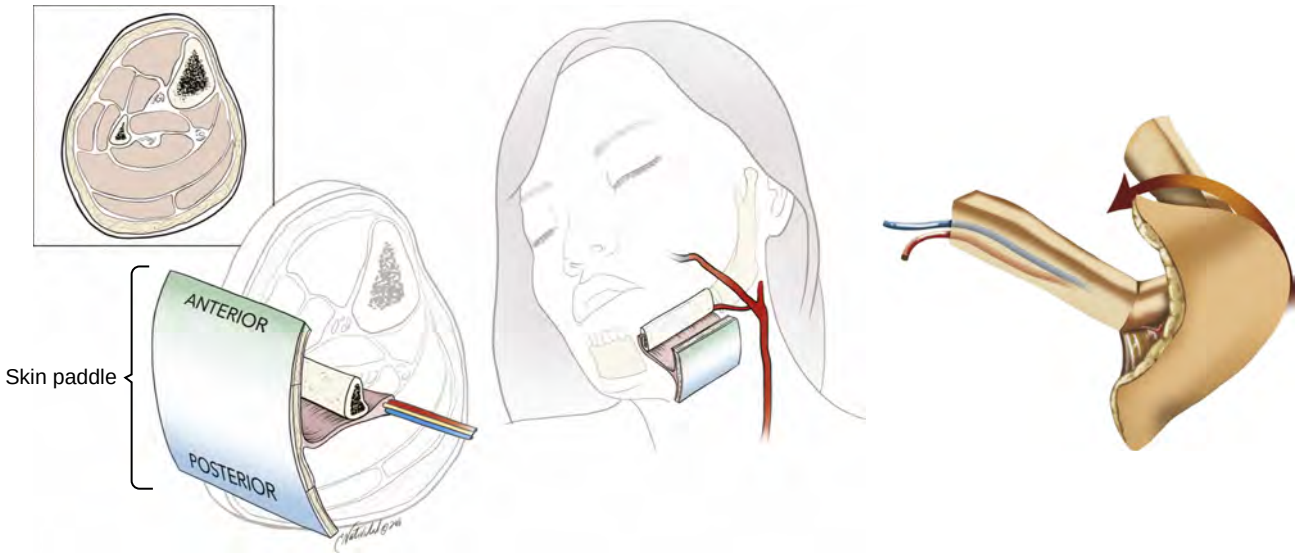


• **Fig. 24.15** Bone graft template used for confirmation of accuracy of surgical plan intraoperatively.

(Fig. 24.14). We ask for 0.5 mm of space in the fit of the fibula guide to the fibula to accommodate the soft tissue. We also ask for a bone graft template to be printed, to fit into the defect prior to bringing the flap to the head, to make sure the plan was executed appropriately (Fig. 24.15).

If there is enough time between the planning session and the surgery date, we will also ask for a custom plate made for the patient. Custom plates have advantages and disadvantages. The custom plate does not have the points of weakness caused by bending and shaping. The custom plates can be made thicker, either in parts or as a whole, to add strength. Because they are custom made, they can be made into custom arrangements and shapes to fit the defect. They are more expensive, take additional time to make, and are less adjustable. For dentate patients, if the registration of the occlusion is inaccurate on the CT used for planning, the close adaptation of the plate to the bone and the plate's rigidity can torque the native mandible, resulting in a malocclusion. Because these plates are thicker, they are more difficult to correct.

Dental implants can be also placed at the time of primary reconstruction. This can be computer planned, and drill guides can be built into the fibula cutting guide. When placing dental implants simultaneously, we typically choose the leg that results in the skin paddle facing externally. This allows the implants to be placed away from the septocutaneous perforators. This does



• **Fig. 24.16** Modification of the skin paddle to allow for flipping over the fibula. (Adapted from Hwang L, Natividad EM, Ellis M. Fibula flap harvest: How leg selection impacts inset for mandible defects. *Microsurgery*. Jul 1, 2016.)

require that the skin flap be widened anteriorly in the leg to allow it to wrap around and close the oral defect (Fig. 24.16). In patients with mandibular cancer who receive adjuvant radiation therapy, it is unclear whether it is better to place the implants primarily (i.e., before radiation) or secondarily. There are a few studies that have found increased risk of implant failure when placed secondarily after radiation therapy, although the success rates are still fairly high.[40] Interestingly, one study identified primary placement as a risk factor for implant failure.[38]

Preoperative Speech-Language Pathology Evaluation

The speech-language pathologist (SLP) plays an invaluable role in the evaluation of patients with newly diagnosed mandibular cancer. Prior to treatment, the SLP will provide assessment and counseling to the patient on the potential effect of treatment on both speech and swallowing.

At the initial visit, the SLP will also emphasize the patient's role in the successful rehabilitation course of care. The patient must be an active participant to achieve optimal rehabilitation of the speech and swallowing functions. Counseling also includes education regarding the role of post-treatment evaluation and the necessity of oral-pharyngeal exercises, when appropriate. Involvement of the patient's family or friends early in the process will help to provide encouragement and support throughout their care.

Counseling involves a comprehensive evaluation of the patient's swallowing function and diet tolerance using clinical swallowing evaluation or objective measure. An oral-pharyngeal clinical swallow evaluation involves a detailed history of the patient's medical status, as well as an oral-motor examination to assess the range of motion, strength, and coordination of the oral-pharyngeal system. The swallow evaluation will assess bolus manipulation, control, transfer, weakness, residue, and hyolaryngeal elevation and excursion and allow for possible determination of aspiration risk.

If there is question of silent aspiration, an instrumental examination of swallowing may be required. An instrumental evaluation may include flexible endoscopic examination of swallowing (FEES), or a fluoroscopic modified barium swallow study (MBS). The instrumental evaluations provide useful information about the structure and function of the swallowing mechanisms, as well as safety of the swallow.

Recommendations will be given to the patient regarding diet texture, aspiration precautions, and behavioral adjustments to reduce aspiration risk in order to maintain safe oral nutrition prior to treatment.

The examination will also include an evaluation of the patient's speech and voice systems. The SLP will examine the articulator's range of motion and strength, intelligibility of speech, and quality of the voice. Discussion may be necessary regarding the options for communicating during and after treatment. This will help by having the communication systems introduced and immediately available, as well as making a possible transition to other forms of communication easier for the patient.

Early therapeutic intervention by an SLP allows for appropriate patient expectations, and optimal plan of care. In addition, it can identify if there is a higher risk of dysphagia and articulation deficits. Patients who have dysphagia prior to treatment are at higher risk of long-term dysphagia and possibly permanent tube feeding.[41] Prediction of swallowing and speech outcomes is dependent on the plan of care, age, frailty, and size and location of the tumor.

Preoperative Workup

In addition to the general medical and surgical principles for the preoperative workup of a patient, there are several specific issues that deserve specific consideration.

All patients are evaluated for risk of cardiovascular complications and the need for preoperative medical or procedural cardiac optimization. The American Heart Association has published guidelines on the cardiac risk assessment of non-cardiac surgical patients, which they update periodically. Oral/head and neck surgery is not specifically mentioned, but is generally considered low to moderate risk surgery. This has been validated using Goldman's criteria and the Revised Cardiac Risk Index (RCRI).[42,43] It is important to remember, however, that there is a wide spectrum for oral/head and neck cancer surgery, and mandibular resection with free flap reconstruction would, at least intuitively, be higher on that risk scale. This should be factored in when using the RCRI, which calculates preoperative risk and determines the need for cardiology referral.

A preoperative nutrition assessment is essential. Quite frequently, because of the symptoms associated with advanced mandibular cancers, patients have struggled with eating and swallowing for months before presentation. This is accompanied by severe protein and caloric malnutrition. This predisposes these patients to elevated risk of wound healing complications, infection, and flap failure.[44] Patients with preoperative weight loss should have nutrition labs drawn. Consideration should be toward feeding tube placement and a period of nutritional optimization prior to surgery in the severely malnourished.

Surgery

Airway

As discussed previously, a discussion between surgeon and anesthesiologist prior to induction can avoid most airway complications. After the patient is induced and the airway is secured with an endotracheal tube, our group converts this to a tracheostomy. Initially, an armored (reinforced) endotracheal tube is used, which is lower profile than a tracheostomy tube and keeps it out of the way. If the anesthesiologist has any difficulty with intubation, an awake tracheostomy under sedation and local anesthesia is performed before excessive airway instrumentation leads to a "cannot ventilate" situation.

Vascular Access

Good peripheral intravenous accesses with large-bore catheters, accompanied by an arterial line for invasive monitoring, are usually sufficient for vascular access. We rarely require central venous access, unless otherwise dictated by the patient's comorbidities. If central venous access is required, a subclavian or femoral line is placed.

Room Setup

We typically perform the ablative surgery and flap harvest simultaneously. This requires two instrument setups, one sterile and one clean/contaminated; two scrub technicians; and one to two circulating nurses. The bed is not turned, but this would be dictated by the size and shape of the operating room.



• **Fig. 24.17** Patient leg positioning.

Patient Setup

The patient is kept in a supine position. We use a Mayfield with a horseshoe head rest to place the neck into extension. The donor leg is flexed at the hip and knee. Bumps are secured to the bed to keep the leg positioned in this fashion (Fig. 24.17).

Surgical Approaches

Several incision designs have been described and used. Most commonly, we use a straight-line apron cervical incision, placed roughly halfway between the clavicle and mandible, within a neck crease.[45] Posteriorly, the ipsilateral side extends just behind the sternocleidomastoid, curving slightly upward toward the mastoid process. Anteriorly, the incision extends onto the contralateral side so that sufficient access can be obtained to the mandible beyond the planned osteotomy.

Many surgeons incorporate lip-split incisions to facilitate access. This improves access substantially, but often leaves an unsightly scar and, occasionally, notching of the lip. We reserve lip splits for very advanced tumors that extend into the floor of mouth, tongue, skull base, and/or oropharynx, or for patients with recurrence who are undergoing a salvage operation.

The incision is taken through skin and platysma. In the midline, the platysma is absent, so the depth is kept in the same plane by visualizing the same thickness of the skin flap. Skin and muscle flaps are developed superiorly to the inferior border of the mandible, then inferiorly to the clavicle. Avoid communicating the neck wound with the tracheostomy site.

The marginal mandibular branch of the facial nerve is protected. The simplest way is to develop a flap of the superficial layer of the deep cervical fascia. A curvilinear incision is made at the level of the inferior edge of the submandibular gland. This incision is taken just deep to the capsule of fascia investing the submandibular gland. The flap is then raised superiorly in this plane to the inferior border of the mandible. Branches of the facial artery and vein are ligated. Alternatively, one can perform the Hayes Martin maneuver, by ligating the facial artery and vein two fingerbreadths below the mandible, and then raise a flap deep to this plane to the inferior border. A third method would be to identify the marginal mandibular branch of the facial nerve as it courses superficial to the facial vein, and protect it.

Segmental Resection Using Surgical Guides

At this point, the appropriate neck dissection is completed. This is described elsewhere in this text. This can be left in continuity with the mandibular resection or taken separately.

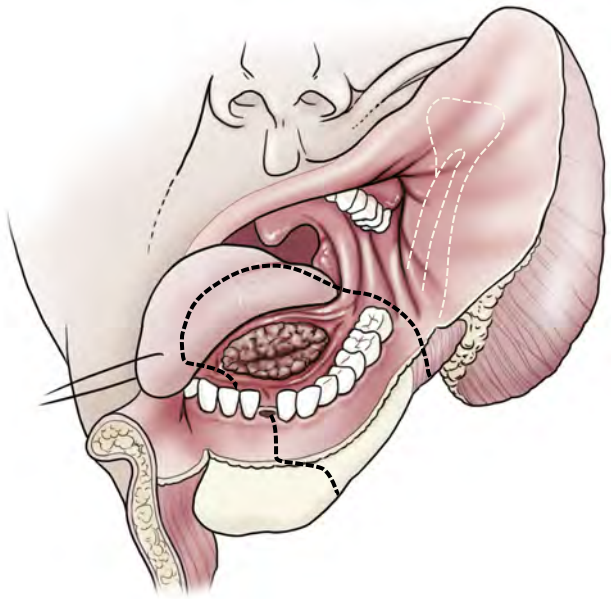
Army-navy retractors draw up the superior skin flap, exposing the palpable edge of the mandible. A malleable retractor is then paced just onto the inferior border to create some tension of the soft tissues overlying the mandible. Sharp dissection is then used to expose the inferior border of the mandible.

Periosteal elevators are used to skeletonize the mandible in the subperiosteal plane proximal and distal to the planned resection.

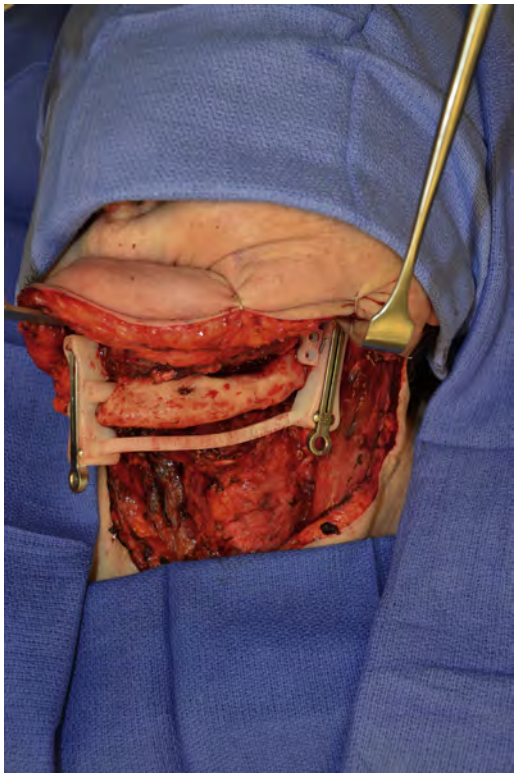
The surgery is then directed to the oral cavity. A 1- to 1.5-cm soft tissue margin is sharply incised around the tumor. Sharp dissection is used to maintain this margin three-dimensionally around the visualized and palpated tumor on the buccal side. This buccal dissection is connected with the transcervical dissection. On the lingual side, the dissection is carried sharply into the floor of mouth. The lingual artery and vein may be encountered, and should be ligated. Once the dissection approaches the mylohyoid muscle, visualization and inability to maintain adequate tension make sharp dissection more difficult (Fig. 24.18).

Once we reach this point, we then start with our mandibular osteotomies. The cutting guide or guides are fitted to the mandible (Fig. 24.19). If an osteotomy was planned through the dental arch, the tooth in the osteotomy is extracted. It is helpful to leave some attached gingiva around this extracted tooth so that the soft tissue closure between skin and gingiva does not lie directly over the bony junction between fibula and native mandible.

After the guides are fitted and secured with fixation screws, the predictive holes are also drilled. These will be used later. A reciprocating saw is then used to perform the osteotomies. Of note, if the osteotomy is in the ramus region and placed through the sigmoid notch, the guide will usually stop short of the notch. Because the superior part of this osteotomy is not part of the junction with the fibula, precision is less critical, and this cut can be made freehand without adversely affecting the reconstruction.



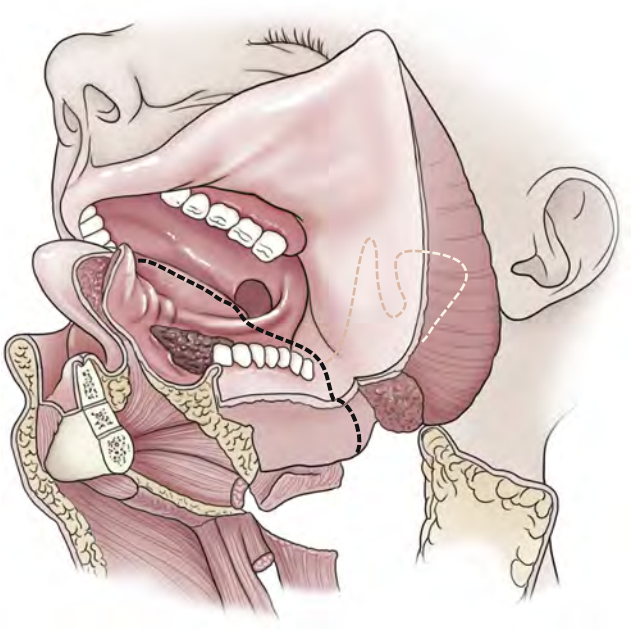
• **Fig. 24.18** Starting sharp dissection around the mandible from the buccal side. Notice soft tissue dissection on the lingual side has only been just started. (From Silver CE, Rubin JS: *Atlas of head and neck surgery*, 2e, London, 1999, Churchill-Livingstone.)



• **Fig. 24.19** Placement of cutting guides onto mandible.

Once the osteotomies are completed, the resection thus far is gently retracted laterally and through the neck incision (Fig. 24.20). This allows for visualization and palpation of the floor of mouth margin. The remainder of the resection is completed sharply. The facial artery and vein will be encountered and should be divided appropriately.

If the resection includes the condylar ramus unit, after the distal osteotomy performed, the lingual dissection proceeds



• **Fig. 24.20** The mandible bone osteotomies have been performed. The mandible is retracted laterally as the lingual soft tissue dissection is performed. From Silver CE, Rubin JS: *Atlas of Head and Neck Surgery*, 2e, London, 1999, Churchill-Livingstone.)

in a similar fashion, with gentle lateral retraction, proceeding from anterior to posterior superior. While working posteriorly, the specimen is also gradually drawn inferiorly. If possible, leaving some of the condyle can be helpful for reconstruction.

We typically take frozen section margins circumferentially from the resection bed. Additional margins are taken deep or in areas of concern. This is performed knowing that there is considerable controversy about the benefit of frozen section analysis and how it should be performed.

Reconstruction

Prior to surgery, we either have a reconstruction plate pre-bent to the patient's stereolithic model or have a patient-specific plate made by the surgical hardware vendor. When prebending the reconstruction plate, we typically use a 2.0 reconstruction plate. This is easier to bend than thicker plates and is of sufficient strength. Although some surgeons argue that reconstruction plates lead to stress shielding and bone atrophy, favoring smaller fixation plates, we have not found this to be the case. When bending the plate, start with the in-plane bends. These are much harder to do after out-of-plane bends are done. When doing the out-of-plane bends or twists, avoid doing so back and forth, which creates significant weaknesses in the plate. Finally, the plate needs to fit passively on the model. This is most important in dentate patients. A plate that snaps snugly to the model is too tight and will torque the native mandible into a malocclusion. It is preferable to have the plate slightly off of the mandible rather than too snug. If possible, have the plate fit onto the pegs for the predictive holes. It is often easier to reduce or remove these pegs off of the model, as they can get in the way (Fig. 24.21).

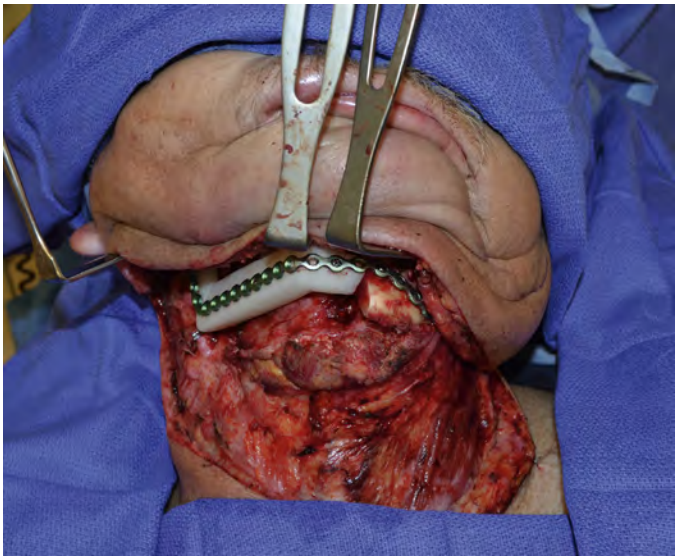


• **Fig. 24.21** Plate adapted to postop model. Notice that pegs have been reduced for ease of fitting.

At the start of the surgery, the planned soft tissue defect is estimated. This is not a two-dimensional measurement. The planned skin paddle should have enough skin to wrap over the fibula and fold into a buccal and lingual vestibule. Enough skin should also be harvested to reconstruct the tongue if a partial glossectomy is included as well, so as to not tether the tongue to the neo-mandible.

After the primary tumor has been removed, the prebent or custom-made reconstruction plate is fitted to the remaining native mandible using the predictive holes. This automatically establishes the appropriate condylar positioning, anterior-posterior projection, and mandibular width based on the virtual surgical plan. If the patient is dentate, the patient must be placed into maxillomandibular fixation (MMF). This can be done using MMF screws, embrasure wires, or arch bars. Of note, using MMF screws alone on floating mandibular segments will cause buccal torquing of the mandible, leading to tight intercuspation of the buccal cusps but opening of the lingual cusps. Once the patient's occlusion is placed into stable MMF, the reconstruction plate is fixated using locking screws. Because of the inherent inaccuracies and imperfections that accumulate with each step, the plate may not fit perfectly. Or, if it does, it may cause a disruption of the occlusion. The occlusion should be prioritized. This may require some adjustments in the plan. Usually, all that is required is accepting gaps between the bone and plate. Occasionally, this requires not using the predictive holes and drilling new holes. Once the reconstruction plate is secured, remove the patient from MMF and confirm that the occlusion is appropriate.

Next, we adapt the bone graft template to the defect (Fig. 24.22). This allows for a visual assessment of how accurate the plan is thus far. The information gathered from fitting the bone graft template is then communicated to the reconstructive surgeon harvesting the flap. If the defect is slightly bigger than the template, the reconstructive surgeon can correct the difference by preserving additional bone. If the defect is smaller, the template is adjusted. Either way, the template is then disinfected with Betadine and passed to the reconstructive surgeon to verify the shape and adjust the bone flap at the leg to the appropriate shape and size.

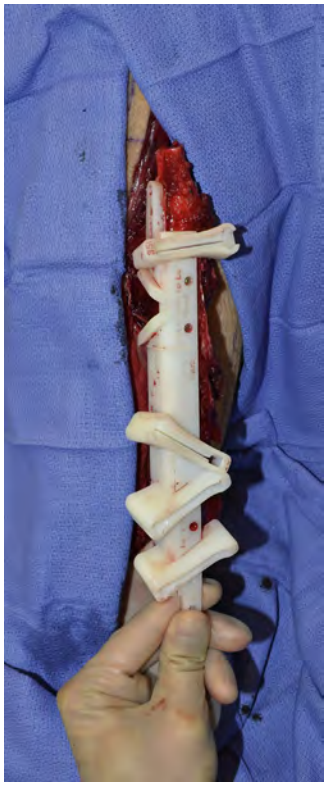


• **Fig. 24.22** Bone graft template fitted into defect.

Reviewing techniques for dissection and elevation of flaps is left for other dedicated texts. However, discussion of considerations specific to mandibular reconstruction is warranted. When planning the skin paddle, we usually center the skin flap over the perforators, which are found between the middle and distal thirds of the fibula within the lateral intermuscular septum. Because the number and location of the perforators are not entirely predictable, complex soft tissue defects require approaching the soft tissue flap elevation in a manner that allows for adjustability. We will often raise a soft tissue flap larger than required to accommodate for adjustments. When starting the flap harvest, we start with the anterior incision and approach the lateral compartment first. Because we harvest the flap in tandem with the ablative surgeon, we do not make the posterior skin incision until the primary has been removed. The posterior incision can be changed to accommodate any changes in the size of the soft tissue defect.

If the natural positioning of the skin paddle is going to be facing opposite that of the defect, the skin paddle needs to extend anterior toward the dorsum of the lower leg. This allows for the flap to be pulled over the fibula while minimizing compression on the delicate perforators (see Fig. 24.16).

Halfway through the fibula harvest, the fibula is sectioned proximally and distally. The proximal cut is placed arbitrarily at 6 cm distal to the fibular head to avoid injury to the common peroneal nerve that courses superficial to the neck of the fibula. Once the fibula has been completely elevated and vascular pedicle prepared, the cutting guide is fitted to the fibula (Fig. 24.23). It is important to note that the fibula cutting guide rarely locks onto the fibula in one place, because of the soft tissue around the bone and our computer correction for this. As a result, its proximal-distal positioning has considerable latitude. This has both advantages and disadvantages. Although the twist that occurs in the distal fibula creates irregularities in the contours, the width of the fibula is fairly uniform along its length. Therefore, the guide can be placed in a position slightly



• **Fig. 24.23** Cutting guide fitted to fibula after elevation of flap completed.

off from what was virtually planned in order to have the skin perforators ideally placed, centered on a given segment rather than between segments or off a discarded portion of the fibula. Alternatively, the guide can be placed more distal to maximize the length of the pedicle.

Once the guide is secured, careful sub-periosteal pockets are created in the areas of the planned closing osteotomies. Avoid stripping the fibula segments that are meant to be part of the neo-mandible. A malleable retractor is placed between the pedicle and bone to protect it when making the cuts.

If dental implants are to be placed primarily, do so before making the closing osteotomies (Fig. 24.24). It is important to dissect the soft tissue from the bone only minimally so as not to compromise the vascularity of the bony segments. The implant osteotomies must be over prepared and tapped. Be careful to keep the torque below 40 N-cm when seating the implants to avoid inadvertent splintering of the fibula.

Once the closing osteotomies are completed, the guide can be removed. Depending on the width and girth of the fibula, occasionally the osteotomies are only partially complete. This is due to the limitations of the length of the reciprocating saws that are used. Use great care in completing these osteotomies so as to avoid injury to the pedicle and to avoid creating new osteotomies that are at angles different than planned. After doing so, carefully removed the areas of discarded fibula.

Next, some initial modifications are performed to the bone flap before dividing the pedicle to bring the flap to the head. The bone graft template is compared to the bone flap. An egg-shaped burr is used to make minor adjustments, if necessary, so the flap has the same shape.



• **Fig. 24.24** Placement of implants prior to performing osteotomies.

The pedicle is divided and the flap is brought to the head. The flap inset starts with fitting the bone to the native mandible and plate. This usually requires additional adjustments to the bone. The skin paddle will have to be passed into the defect first, under the reconstruction plate before the bone flap fits. The skin paddle is closed to native mucosa using horizontal mattresses and 3-0 polyglactin sutures to ensure a watertight closure.

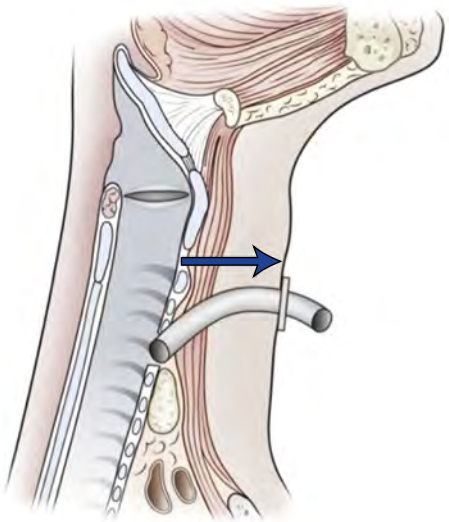
Postoperative Care

The postoperative care of a patient who has undergone composite resection of the mandible, neck dissection, and reconstruction with an osteocutaneous free flap requires multisystem management and multidisciplinary involvement. In our institution, the care team includes the team of oral and maxillofacial surgeons, critical care physicians and nurses, respiratory therapy, pharmacy, physical therapy, occupational therapy, dieticians, speech and language pathology, case management, and social workers. A complete discussion of the principles of management of the critically ill patient goes beyond the scope of this chapter. This section focuses on unique aspects of postoperative care as it relates to patients with mandibular cancer.

Airway Management

As previously mentioned, all of these patients receive tracheostomies. Besides providing a secure airway, this provides several advantages in the postoperative period.

The first major advantage is that a tracheostomy is much more comfortable and tolerable than an oral or nasal endotracheal tube. As a result, both sedation and mechanical ventilation can be quickly weaned. Most of our patients are off of ventilator support and are breathing spontaneously with a tracheal mask by the time of transfer to the ICU or by the morning after. Most of our patients have sedation completely weaned off by the morning after, if not sooner. Although many centers have protocols for sedation and immobilization for patients with flap reconstruction, recent studies have shown no advantage in flap survival while also showing increased risk of complications, in particular ventilator-associated pneumonias and need for prolonged ventilator support.[46]



• **Fig. 24.25** Dierks Type I slow displacement of tracheostomy. (From Dierks E: Tracheostomy: elective and emergent, *Oral Maxillofacial Surg Clin N Am* 20:513-520, 2008.)

The second advantage is improved ease of pulmonary toilet. Many patients with oral cancer have baseline chronic obstructive pulmonary disease. Respiratory therapy and pulmonary toilet is much easier to perform on patients with tracheostomies. Furthermore, these patients may require diagnostic or therapeutic bronchoscopy in the postoperative setting. Again, these are much more easily performed through a tracheostomy tube.

A third advantage is flexibility. If a patient develops any sort of setback during recovery that requires they be placed back on mechanical ventilation and/or sedation, re-intubation is not necessary. The cuff is simply inflated and the circuit connected.

We typically use a dual-lumen Shiley cuffed tracheostomy tube. This is downsized to a smaller, cuffless tracheostomy tube around the fifth postoperative day. The patient is decannulated around the sixth or seventh postoperative day after they tolerate capping trials.

The tracheostomy tube is secured using sutures. It is very important not to use tracheostomy ties, as the ties place compressive forces on the neck veins, which can lead to flap venous compromise.

Several complications can occur with tracheostomies, including mucous plugging, bleeding, and dislodgment (Fig. 24.25). These are covered later. However, the most common complication associated with tracheostomy tubes in this setting is pressure sores caused by the flange of the tracheostomy tube pressed against the edematous skin overlying the sternal notch. This can be avoided by securing the

tube using loose sutures and being fastidious about keeping the area clean and dry. Specialized sponge pads can be placed under and around the flange to prevent pressure sores.

Blood Pressure, Fluids, and Temperature Management

In addition to maintaining blood pressures for cerebral and end-organ perfusion, maintaining perfusion pressures to the flap reconstruction is essential for success. Perfusion pressure to the flap is important not only for blood flow and tissue oxygenation,[47] but also for decreasing vascular resistance and maintaining vasculature patency.[48,49] This is because within the flap, the vasculature has been denervated, losing its ability to respond to parasympathetic signaling and vasodilate. We aim to keep patient at or above the normotensive range, with the mean arterial pressure above 60 mm Hg and systolic blood pressure above 100 mm Hg in the immediate postoperative period. Although there are few data suggesting that this pressure is appropriate or necessary for improved flap survival, it falls above the lower limits of blood pressure where peripheral vasoconstriction sets in. In truth, there is considerable latitude with this. Much of the required pressure for flap perfusion depends on its proximity to the heart. Because mandibular reconstructions usually have anastomoses to branches of the external carotid artery, which have very high flow, even lower blood pressures are often tolerated. Hypotension must be avoided, as stimulation of the renin-angiotensin pathway would lead to unopposed vasoconstriction within the flap.

To maintain flap perfusion, adequate fluid resuscitation is necessary. Because of the length of the surgery, and the considerable insensible losses that occur from having an open neck and extremity, these patients can very easily be under-resuscitated. Liberal fluid resuscitation is recommended, with some studies recommending the upper limit of fluid given at 3.5 to 6 mL/kg/hour.[50-52] In our experience, this amount of fluid delivery is necessary only intraoperatively and perhaps the first day postoperatively to achieve euvolemia. Once they are euvolemic and hemodynamically stable, our patients are placed on maintenance levels of fluids, which are then weaned as enteral feeds are initiated. Hypervolemia should also be avoided, as it has been suggested that it may be related to increased risk of flap thrombosis from edema.

The type of fluid used is initially isotonic crystalloids (such as lactated Ringer, normal saline, or Plasma-Lyte). Colloids are used as well, but sparingly, as their use has been found to be an independent risk for negative outcomes.[50,52] Blood products are also used judiciously. Wax and colleagues reported on their use of a hematocrit of 25% as a transfusion trigger.[53] However, we follow the more restrictive triggers as recommended by the AABB (formerly American Association of Blood Banks) of transfusing around hemoglobin of 7 to 8 g/dL.[54] Exceptions, when we are more liberal with transfusion, include patients who are hypotensive, are still actively bleeding, or have cardiovascular disease. With blood products, there is a delicate balance between optimizing oxygen carrying capacity and detrimental increase in blood viscosity.

Vasopressors are often regarded as anathema by microvascular surgeons. However, this aversion has not been born out in the literature, nor has it been detrimental, in our experience, when used sparingly. A meta-analysis found no statistically significant difference in flap survival in patients who have received vasopressors compared with those who have not.[55,56] In that review, Levophed (norepinephrine) was found to more favorable.[57,58] In our practice, we typically use Levophed or Neo-Synephrine, either in small boluses or as low-level infusions. We use these drugs judiciously, only in patients who remain hypotensive and/or hemodynamically unstable despite adequate fluid resuscitation. We avoid vasopressin, as we have found observable peripheral vasoconstriction of the microcirculation of the flap when it is used.

Temperature control is also important as it affects both vascular resistance and viscosity. We keep our patients' rooms warmed to 75° F to prevent hypothermia, which has been associated with flap compromise.

Nutrition

To avoid providing substrate for infection, our patients have enteral feedings for the first week (2 weeks or longer if in the salvage setting after radiation therapy). For most patients, this means a nasogastric Dobhoff feeding tube that we place intraoperatively. As discussed earlier, in patients who are likely to have prolonged dysphagia or difficulty eating, we will arrange for a percutaneous gastric feeding tube be placed.

The nuances of tailoring nutrition to patients needs go beyond the scope of this chapter. All of our patients have a consultation with a registered dietitian and have their nutrition closely monitored both as an inpatient and as an outpatient.

Prophylaxis of Thrombosis

There is much debate, and a dearth of evidence, for type and timing of thrombosis prophylaxis. It is agreed that flap surgery is an independent risk factor for venous thromboembolism, and the vast majority of surgeons use some form of protocol to manage this.

Venous thrombi are primarily related to fibrin deposition and are, theoretically, better prevented by anticoagulants such as heparin. However, the use of heparin or low-molecular-weight heparin (LMWH) must be balanced by the risk of surgical site bleeding and hematoma formation, which is in of itself thrombogenic. Our protocol is to start prophylactic doses of LMWH starting on postoperative day 1 (i.e., 30 mg subcutaneous injections, twice daily).

Arterial thrombi are primarily related to platelet aggregation and are theoretically better prevented by anti-platelets, such as aspirin. Our practice is to use low-dose aspirin (81 mg) daily for a month. The combination of aspirin and prophylactic doses of LMWH has been found not to lead to a discernible increase in bleeding risk.[59,60]

Flap Monitoring

There is much debate about flap monitoring, how best to do it and whether or not it is even necessary. What is well established

is that most complications related to flap perfusion occur within the first 48 hours, the vast majority of which are within the first several hours after surgery (30% within the first hour).[61] Earlier detection and intervention does lead to improved salvage rates. Finally, although the most optimal form of flap monitoring (external Doppler, implanted Doppler, pin-prick/scratch, temperature, turgor, color, etc.) has not been demonstrated, it is agreed that the most critical factor is the experience of the clinician performing the monitoring evaluation.

Our protocol for flap monitoring starts with hourly checks by trained nursing staff for 48 hours. Each check consists of examining the color of the skin paddle, the suppleness of the neck, and external Doppler signal. During the first 48 hours, the patient remains in the intensive care unit. In our institution, there is no step-down unit with appropriate patient-nurse ratios for these flap checks. After 48 hours, the flap checks are decreased to every 2 hours. After 72 hours, the flap checks are decreased to every 4 hours, then every 6 hours the day after that. For the first 24 to 48 hours, the skin paddle of the flap is scratched periodically by one of our surgeons to verify capillary refill. The scratch is observed for bleeding time, color, and quality of the bleeding (gush of blood or a steady ooze).

Because there are so few data on the appropriate flap monitoring regimen, or whether or not it is even truly necessary, an institution's protocol should primarily be determined by the number of trained individuals who can perform checks accurately, keeping in mind that the first 48 hours (the first 12 hours, even) are the most essential.

Rehabilitation

Patients who have undergone mandibular resection and free flap reconstruction have considerable rehabilitative requirements. Our practice is to involve physical therapy, occupational therapy, and SLP as early as possible.

We prefer aggressive early mobilization, unless a flap is exceptionally tenuous during inset. The patient is kept on bed rest for the first 24 hours but allowed to be in a chair position. They are fitted for a CAM walker boot, which helps prevent drop foot. By the second postoperative day, physical therapy and occupational therapy begin with helping with transfers and strengthening exercises in bed. Patients who have undergone fibula flap transfer are kept on non-weight-bearing restrictions on their donor leg for 4 days. This restriction is more related to the desire to avoid mobility of the skin graft at the donor site. On the fourth day, physical therapy and occupational therapy work with the patient on partial weight bearing and transfers. On the fifth day, the physical therapist works with the patient on starting to walk with assistance. By the time of discharge, most patients are walking with an assist device (usually a walker).

Postsurgical Speech-Language Pathology

The inpatient SLP will typically be consulted immediately after surgery but, depending on the extent of the resection, may have limited intervention for the first few days. The clinical examination will include a thorough oral-motor exam with special consideration to the surgical site and, if present, flap. The SLP needs to confer with the surgeon for any limitations on range of motion to ensure that suture lines will not be compromised with active range of motion. Range of motion of the speech and swallowing structures should be assessed. Gentle range of motion exercises can improve healing, reduce swelling, and allow the patient to better understand their anatomic changes.[62]

The surgeon will indicate if and when the patient is appropriate for a swallow evaluation. The assessment may include a clinical swallow evaluation and, if necessary, an instrumental swallow evaluation. When a flap is not involved, swallow evaluations can often occur in the first few days after surgery; however, types of food trials would be limited. If there is need for a free flap, adequate time for healing will be required prior to oral trials (usually 5 days postoperatively, 14 days if the patient had prior radiation therapy). Swallowing can be impacted by reduced lip closure, swelling, slowed oral transit, oral residual, and reduced hyolaryngeal elevation as a result of surgery. Initial diet textures may be limited to non-chew items and liquids. The SLP will assess the risk of aspiration and safe diet tolerance and will advance the diet texture when appropriate. It may be necessary to introduce postures or maneuvers or to adjust the texture or viscosity of the food in order to improve safety and tolerance.

Initially, swelling may impact speech intelligibility, so there may be fluctuations in the first few days as swelling increases and decreases. Lip closure may be reduced, impacting labial sounds. Speech exercises to improve lip range of motion and speech precision should be introduced as soon as appropriate.

Once the patient's soft tissue wounds have healed, which typically takes several weeks, jaw range of motion exercises should also be introduced. Postoperatively, the patient may have reduced bite force and reduced jaw range of motion, and mastication may be impacted. Exercises will include jaw opening and lateralization. If the patient does not have appropriate jaw opening, jaw mobilization systems such as a TheraBite or OraStretch may be beneficial.

Surgical Complications

Regardless of the disease, all surgical patients are at risk for complications including cardiovascular (congestive heart failure, myocardial infarction), pulmonary (health care–acquired pneumonia), renal (poor renal perfusion, post-renal obstruction, renal toxicity), neurologic (cerebrovascular accident, acute delirium), and hematologic (venous thromboembolism).

This section focuses on complications specifically related to the surgery for mandibular cancer treatment.

Intraoperative Complications

Nerve Injury

There are several nerves that are routinely sacrificed or inadvertently injured during mandibular resection. Nerves that are routinely sacrificed include the inferior alveolar nerve, the branches of the cervical plexus, branches of the ansa cervicalis

(although the cervical plexus and ansa cervicalis can both be painstakingly preserved, on occasion), occasionally the marginal mandibular branch of the facial nerve, and occasionally the lingual nerve.

The spinal accessory nerve can be unintentionally injured in as many as 69% of patients.[63] There are two main parts of the neck dissection where this might occur: as it passes from anterolateral to the internal jugular vein into the sternocleidomastoid, or as a branch exits posteriorly to innervate the trapezius. Injury can be due to accidental division. In this instance, primary neurorrhaphy with coaptation of the epineurium should be performed. More commonly, weakness in the spinal accessory nerve is due to neuropraxic injury from excessive manipulation and/or retraction. Both of these situations should be carefully avoided, if possible. This nerve can be sacrificed in patients with bulky neck disease.

The hypoglossal nerve is a remarkably resilient nerve important for speech and swallowing. It is rarely injured unless intentionally sacrificed as part of a tumor resection. Despite considerable manipulation, dissection, and retraction, the hypoglossal nerve usually retains its function. If inadvertent injury occurs, it is usually from unintentional division of the nerve. This can occur if the vein associated with the hypoglossal nerve is torn and bleeding obscures the surgical field. Haphazard use of cautery or vascular clips to stop this bleeding can very easily cause hypoglossal nerve injury.

Hemorrhage

The mandible is enveloped in highly vascular tissue. The easiest way to avoid hemorrhage is to purposefully seek out the vessels that are prone to bleeding. Several vessels may need to be preemptively controlled during resection.

The facial artery and vein course superficial to the mandible at the antegonial notch, just anterior to the insertion of the masseter at the mandibular angle. During the transcervical approach, this should be identified and either ligated or freed to be retracted. The facial artery and vein have several branches that course to and around the submandibular gland, including the named submental artery and vein. These will need to be ligated.

The lingual artery and vein lie medial to the mandible, superior to the mylohyoid muscle. During the medial dissection, this should be intentionally identified and either ligated or dissected and retracted for protection. This is most easily performed after the osteotomies have been performed with outward traction of the resected mandible.

The masseteric artery is a branch of the maxillary artery, which courses from medial to lateral through the sigmoid notch. This artery is not well visualized from a transcervical approach, as it is quite high and deep within the wound. It is very easy to injure this artery while making a vertical osteotomy through the sigmoid notch. To avoid damaging this artery, the surgeon must always know the depth and location of the tip of the reciprocating saw when making the osteotomy.

The inferior alveolar artery runs within the inferior alveolar canal. This may cause vigorous bleeding following an osteotomy. The vessel is fairly small as it makes its intraosseous course. It can usually be stopped by electrocautery alone.

Malocclusion

In patients who have and are retaining their dentition, getting the final occlusion as close as possible to the preoperative occlusion is important. To do so requires correct positioning of the dentate native mandible and the free-floating condylar subunit in centric relation (fully seated within the glenoid fossa). The use of pre-bent plates and predictive holes is very helpful for achieving appropriate positioning. However, when virtual surgical planning has not been used, positioning the condylar ramus unit correctly can be challenging. Using a bone clamp, posterior and superiorly directed forces should be used on the condylar segment. Care must be taken not to cause rotation of the segment when seating the condyle. To avoid this, keep in mind that the mandibular angle, where the ramus joins the body, is typically obtuse. Use preoperative imaging or the opposite side as a reference.

Pre-bent or custom hardware can also be a double-edged sword. Because the plates are so rigid, slight inaccuracies can shift the mandible and teeth out of position. Therefore, it is important to use locking screws to avoid this. Also, the plate needs to fit passively on the preoperative model.

Correction of the malocclusion is easiest at the time of initial surgery. After the hardware has been secured, release the maxillomandibular fixation and check that the patient passively closes into a well-interdigitated maximum intercuspation consistent with the patient's preoperative occlusion. A malocclusion identified at the time of initial surgery will not improve with elastics. The plate must be taken off and the positioning corrected. If a "drop-back" is observed toward the ipsilateral side of the defect,[64] the problem is that the condylar segment was not fully seated in the glenoid fossa. If the mandible deviates to the contralateral side, the condylar segment was pushed too far posteriorly out of the glenoid fossa.

A malocclusion that did not exist intraoperatively but presents in the early postoperative period is due to alterations within the temporomandibular joint. This most often presents as deviation of the mandible to the contralateral side and is most likely due to ipsilateral joint effusion. This should be expected to resolve with time. Guiding elastics will help bring the mandible into an appropriate position.

A malocclusion that develops months or a year after surgery is likely due to alterations in the soft tissue envelope and the patient's muscular mechanics. This is secondary to scarring of the overlying soft tissue and/or to a relative imbalance of the muscle attachments of the native mandible compared to the reconstructed mandible. If gentle manual manipulation can bring the mandible into a reasonable occlusion, placing arch bars and guiding elastics may be able to retrain the patient. Otherwise, this may require mandibular osteotomies to correct.

Postoperative Complications

Surgical Site Infections

The oral cavity is the part of the human body most heavily colonized with bacteria. One would expect that mandibular surgery would be at significant risk for surgical site infections. Surprisingly, most patients do not develop infections, although the rate is certainly higher when compared to surgery in sterile

compartments. Yarlagadda and colleagues published a 13.3% risk of surgical site infection in 480 cases over 4 years.[65] Identified risk factors included advanced age (>65 years) and prior radiation therapy (only in patients with cancer). Our unpublished experience has been lower, but includes non-cancer patients. Interestingly, the average time for diagnosis of a postoperative infection was 30 days after surgery.

There is much debate about how best to use antibiotics as prophylaxis. Published guidelines recommend 24 hours of antibiotics in clean/contaminated cases.[66] Despite this, many oral/head and neck surgeons routinely use antibiotics for extended periods. A recent retrospective analysis by Mitchell and co-workers from the University of Washington examined risk factors for surgical site infections in the first 30 days after surgery.[67] Interestingly, identified risk factors included choice of clindamycin (compared to ampicillin/sulbactam as a control) as the antibiotic, hypothyroidism, and use of oral tobacco. Greater than 24 hours of antibiotics reduced risk of overall infections and surgical site infections among all patients, but this difference was not seen when looking specifically at clean-contaminated surgeries.

Given the lack of available data to draw from, it is difficult to make an evidence-based decision about choice and length of antibiotic prophylaxis. In our practice, we use cefazolin starting preoperatively and continued for 7 days postoperatively. Clindamycin is used in patients with penicillin or cephalosporin allergies. This period is extended if there are any signs of infection. At this point, coverage is broadened until cultures and sensitivity testing allow us to narrow our choice. Using this approach, our own internal review reveals infection rates around 3%, although these data are drawn from all of our patients, not all of whom were treated for cancer.

Vascular Compromise of the Flap

Flap failure is a specter that hovers in the background after every microvascular reconstructive surgery. Fortunately, it is a relatively rare phenomenon, generally felt to only occur around 1–5% of the time. However, when flap failure does occur, it is felt by the patient, family, and surgeon as a catastrophic loss that definitely results in a major setback in a patient's recovery.

Most of the time, flaps that are tenuous can be identified intraoperatively. Wei and colleagues observed that the majority of flaps in their center that failed had issues with perfusion soon after inset.[61] Therefore, the surgeon should not leave the operating room, assuming a stable patient, until the problem with the flap is identified and corrected, if possible.

During the early monitoring period, if signs of flap compromise are detected, the first step is determining the cause. Arterial insufficiency manifests as a pale flap that has slow capillary refill, slow bleeding on scratch testing, and difficult-to-find arterial Doppler signal. Venous insufficiency manifests as an engorged flap that appears cyanotic. On scratch testing, a gush of dark blood is seen. Mixed arterial and venous insufficiency can manifest as combination of these examination findings. For example, a pale flap that slowly bleeds dark blood can be seen with a flap that has arterial insufficiency and venous insufficiency. Finally, it is possible to have good arterial inflow and venous outflow while having poor perfusion of the microcirculation. This is manifested by poor perfusion to parts of the soft tissue flap despite normal Doppler signal and patency of the arterial and venous pedicle when explored in the operating room.

A detailed discussion of flap salvage is a topic that goes beyond the scope of this chapter. However, in our practice, insufficiency of any type requires urgent exploration. The neck is opened and any hematoma is washed out. The arterial and venous pedicles are examined. The venous anastomosis is divided first, to assess outflow. If no venous bleeding returns, the arterial anastomosis is also divided. Both the artery and vein are inspected. Any thrombus is gently removed if possible. The smallest size Fogarty catheter can be used in the artery to gently remove any thrombus too far distal to easily remove using forceps. The venous pedicle is gently cleaned. Thrombus located proximally in the vein is carefully milked out.

It is important to remove as much as thrombus as possible prior to the next step, which is to flush the system with heparin:saline (we use 10,000 units in 500 mL of saline). We flush the flap through until the venous outflow runs clear. We then flush the flap using alteplase, 2 mg diluted in 2 mL of injectable saline, administered intra-arterially with the veins left open.[68] Subcutaneous injection of alteplase (2 mg) into the soft tissue portion of the flap has been described in case reports.[69] Prior to re-anastomosis, the recipient vessels are inspected. If they remain suitable, they are prepared and the anastomosis is performed. If they are not suitable, either they are trimmed back to flowing vessels, or new recipient vessels are selected, if available.

After the anastomosis is complete, the geometry of the pedicle is meticulously examined. Any kinking or turn more acute than 90 degrees must be corrected. This may require further separation of the arterial and venous pedicle to allow greater degrees of freedom. We often will carefully tack the pedicle down with sutures to allow it to lie with a gentle curvature. This should be done with care because suturing the pedicle can also cause areas of kinking and constriction. The head is then positioned in different extremes while watching the pedicle. This is done to make sure no kinking occurs in other head positions.

Despite valiant attempts at salvage, flaps will fail. When faced with a failed flap, the natural inclination is to attempt to address the defect with a compromised solution, such as leaving the defect or using a less optimal but simpler reconstruction, such as a regional flap. However, the first-line therapy for a failed flap is to perform a second free flap. Before this is done, a hypercoagulable workup should be performed.[70] If any known source of hypercoagulability is identified, it is addressed medically and optimized. More often than not, this workup is negative. In this case, we use multiagent thromboprophylaxis (aspirin) with anti-platelets and therapeutic anticoagulation (heparin infusion for 3 days, then weight-based LMWH for 5 days). Although there are other published protocols, none are evidence based.[59]

Airway Embarrassment

One of the most catastrophic complications in oral/head and neck surgery is the loss of the airway and death. Preparation is the key to avoiding this complication. Because of this, we almost universally perform tracheostomies on our patients. However, tracheostomies are not infallible.

Tracheostomy dislodgment is one such failing. These can occur early after tracheostomy placement if the tube is poorly secured, if the tube is too short for the patient's neck, or if the patient is agitated and causes a forced dislodgment. This is an emergent situation when this occurs before the track becomes mature, as replacement can be very difficult for non-surgeons and the patient is still dependent on the surgical airway.

Dislodgment can also occur in a delayed fashion. Dierks described two types of slow displacement, one of which is worth highlighting here.[71] Type I slow displacement occurs when the distance between the skin and trachea increases as swelling increases, pushing the flange and causing the tip of the tube to come out of the trachea (see Fig. 24.25). An early sign of this is difficulty with passing a suction cannula. Once identified, the tube should be replaced with a longer tube as soon as possible. If this is not detected before complete displacement, this will descend into an emergent loss of airway.

Mucous plugging of the tracheostomy is a frequent and potentially fatal complication. Tracheostomy tubes are inherently irritating to the airway and will often stimulate increased secretions and coughing. In smokers and patients with chronic obstructive pulmonary disease, this is especially true. One potential nidus that can cause this increased sputum to form mucous plugs is an incompletely seated inner cannula. When using dual-lumen tracheostomy tubes, the inner cannula is designed so that when seated, the tip of the inner cannula is flush with the outer cannula. From the surface, this can be determined by noting that the wings of the inner cannula are full engaged on the lip of the outer cannula. When incompletely seated, there is a step between the inner and outer cannulas where mucus tends to accumulate. Given time, the lumen can become completely obstructed.

Fastidious tracheostomy care can prevent the scenarios just described. Humidification of the tracheostomy is essential to prevent drying of mucus and plugging. Frequent suctioning and changing of the inner cannula, particularly early on, can prevent plugging and help identify type I slow dislodgment. Careful inspection of the flange to ensure that it is adequately secured and the sutures remain intact can prevent early dislodgment. In new tracheostomies, an airway cart, which includes a tracheostomy surgical tray and intubation equipment, is kept in close proximity to the patient.

Adjuvant Therapy

Radiation Therapy

There are three cardinal rules in radiation therapy. Rule 1: put the tumor in the beam. Rule 2: put organs at risk out of the beam. Rule 3: put the tumor in the beam. Identifying the gross tumor volume and its draining lymph nodes is the first and most important step in radiation treatment planning. The technical aspects of radiation therapy are covered in detail in Chapter 13. Tumor target volumes and organs at risk (e.g., salivary glands, mandible, or spinal cord) are contoured on the CT images taking into account staging imaging, pathology reports, and physical exam. Target volumes have specific definitions recognized by all radiation departments: the gross tumor volume (GTV) defines the area(s) of known measurable tumor and grossly positive lymph nodes either on imaging or examination, and it receives the highest dose of radiation of 70 Gy. The clinical tumor volume (CTV) is an expansion of the GTV to cover subclinical spread of disease surrounding the GTV. Identifying the various lymph node groups on axial planning CT images is critical, but the CTV volume needs to be adjusted based on clinical judgment.[72] The ipsilateral (and contralateral) neck is considered intermediate risk if there is a clinically positive lymph node and is prescribed approximately 60 Gy (see Chapter 13 for details). The contralateral (and ipsilateral) neck, if clinically negative, is considered low risk and prescribed approximately 50 to 54 Gy. In the uncommon case when the ipsilateral neck is clinically negative but the contralateral neck is positive, bilateral necks should be considered intermediate risk because isolated contralateral lymph nodes are rare.[73] Understanding how tumor spreads locally is also regnant to determining the CTVs. CTVs are expanded after they are finalized to create a planning treatment volume (PTV). The PTV expansion accounts for daily variations of patient setup and anatomy and varies between treatment centers based on institutional certainty on the accuracy of the setup procedure, which may be affected by image guidance, immobilization devices, and so on.

The challenge of comparing the outcomes of one institution to another stems from the heterogeneity of the interpretations of what constitutes GTVs and CTVs, and how much to expand the volumes to generate the PTV—even whether or not to add chemotherapy.[74] There are no mandatory guidelines on how one should plan a radiation treatment, so each institution should develop a standard methodology, preferably adhering to a widely accepted published protocol, and make adjustments over time depending on their outcomes. It is also beneficial to have an internal review process of checking the contours among radiation oncologists to help preserve consistency and discover potential mistakes This should help improve the results of patient care.[75]

No contemporary treatment should use two-dimensional techniques based primarily on x-ray plain film imaging, surface anatomic landmarks, and manual dose calculations. At minimum, 3D-conformal radiation therapy (3D-CRT) should be used, and preferably intensity modulated radiation therapy (IMRT, photon or proton) if available. 3D-CRT and IMRT are discussed in detail elsewhere (Chapter 13). Compared to 3D-CRT, IMRT for head and neck cancer can better reduce treatment-related toxicity, resulting in improved quality of life.[76] A recent meta-analysis of five prospective phase III randomized controlled trials comparing IMRT with two-dimensional radiotherapy or 3D-CRT showed that IMRT reduced the incidence of grades 2 to 4 xerostomia without compromising locoregional control and overall survival.[77]

Image-guided radiation therapy (IGRT) is the process of near real-time imaging during a course of highly conformal radiotherapy, with the ultimate intent of improving target accuracy and precision by correcting for geometric and anatomic deviations. This is also covered in Chapter 13. This technology helps the treating physician adhere to the three cardinal rules of radiation therapy, because we can "see" the tumor volume at the time of treatment. The temptation arises, however, to make the GTV, CTV, and PTV volumes tighter in order to reduce side effects. Clinical judgment cannot be taught but must come from experience, often compelled by untoward outcomes; therefore a careful follow-up of the patients' outcomes is mandatory in order to develop a keen sense of where not to cut corners.

By default, treatment of advanced mandibular tumors will require a large volume of normal tissue to be exposed to bystander radiation. Any head and neck radiotherapy can cause temporary and/or permanent damage to the parotids, submandibular glands, mandible, and teeth, among other tissues. Studies have shown that parotid gland function is preserved if mean dose to the gland is kept lower than 24 to 26 Gy.[78] This often cannot be achieved without compromising tumor coverage on the ipsilateral side if the patient presents with large level II lymph nodes. In order to adhere to the three cardinal rules, the ipsilateral parotid may have to be sacrificed, which inevitably will lead to compromised quality of life. This underscores the importance of a team approach to radiation therapy.

The first step in the management of oral complications of head and neck radiotherapy begins with proper multidisciplinary assessment and dental consultation.[79] Careful examination and imaging are necessary prior to radiotherapy, with proper identification of teeth that need to be removed prior to treatment, and particular attention should be drawn to the ipsilateral molars (see Chapter 13 for detailed discussion of oral complications). Radiation therapy for all head and neck cancers should never be viewed as an isolated effort, but must be engaged in as part of a multipronged effort in collaboration with surgeons, medical oncologists, dentists, therapists, nurses, physical therapists, dietitians, and so on. A multidisciplinary approach leads to better adherence to best practice and to improved survival.[80,81]

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method that very precisely delivers a high dose of radiation to an extracranial target. SBRT is typically a complete course of therapy delivered in one to five sessions (fractions).[82] It usually combines IMRT, IGRT, and stable immobilization to target the gross tumor volume with tight margins in order to deliver high fractional radiation dose. The use of SBRT is emerging for salvage of treatment failures with definitive radiation or chemoradiation,[83,84] but surgical salvage should be considered if possible for recurrent tumors.

Chemotherapy

In treatment of mandibular SCCA with curative intent, chemotherapy is given in two clinical scenarios:

1. Induction chemotherapy (IC); also known as neoadjuvant therapy with chemotherapy given before definitive therapy
2. Postsurgical adjuvant therapy that includes concurrent chemoradiation (CRT) or RT alone

Induction Chemotherapy

Induction chemotherapy has been a controversial but attractive option for managing HNSCC patients in selected clinical situations, especially for patients with high risk of distant metastasis. MACH-NC meta-analysis on induction chemotherapy trials, which included patients with unresectable disease, showed a small improvement in survival (hazard ratio [HR]: 0.90; 95% confidence index [CI], 0.82 to 0.99) and distant failures for induction chemotherapy in those trials that used a platinum and 5-fluorouracil (PF) regimen.[85] However, because of differences in design between treatment protocols, a comparative and consistent statement of benefits still remains unknown.[86]

Quantitative results of sequential chemotherapy and radiotherapy are significantly different when compared to concurrent strategies. Chemotherapy leads to destruction of tumor at a constant fraction rather than a constant number of cancer cells and results in a fractional tumor decrease that is not larger than 1-2 log, leading to exponential survival curves. Therefore, chemotherapy alone results in tumor responses that are neither clinically nor pathologically complete.[87] These data explain the impressive tumor shrinkage often observed after induction chemotherapy but also highlights the importance of definitive treatment.[88]

A separate analysis of the MACH-NC Group was published in 2013 with studies that added taxanes into PF induction chemotherapy (IC). Five randomized trials, with median follow-up of 4.9 years and a total of 1772 patients enrolled, demonstrated that absolute benefit at 5 years was 7.4%, from 35% to 42.4% (HR 0.79; 95% CI, 0.70 to 0.89; $P < .001$) in favor of taxane-PF IC over PF.[89] The efficacy of docetaxel-based chemotherapy regimen (docetaxel, cisplatin, and 5-fluorouracil, TPF) in locally advanced head and neck cancer was evaluated in EORTC 24971, a phase III open-label randomized trial, involving 358 adult patients.[90] Patients in this study treated with TPF prior to surgery or radiation had a significantly longer median overall survival (OS) compared to a standard treatment of PF, with a 28% risk reduction of death, 18.6 versus 14.5 months ($P = .0128$). Patients also had a significantly longer time to disease progression of 11.4 months, compared with 8.3 months ($P = .015$) for the patients receiving standard therapy. Posner and colleagues reported the results of a large randomized phase III study (TAX 324) comparing TPF to PF IC.[88] The study showed TPF to be superior to PF for survival, leading to the approval of TPF by the U.S. Food and Drug Administration (FDA) for the induction treatment of patients with locally advanced HNSCC. The combination of the three compounds in the TPF regimen for advanced head and neck cancer in adults has been 75 mg/m^2, 75 mg/m^2, 750 mg/m^2 (Study TAX323) and 75 mg/m^2, 100 mg/m^2, 1000 mg/m^2 (Study TAX 324), respectively. Although MACH-NC showed a survival advantage for PF-based ICT over definitive RT

alone, it remained unclear whether TPF-based ICT improves OS over definitive CRT alone because neither of these studies were designed to address this question.

To answer this question, a three-arm phase III trial was conducted by the Spanish Head and Neck Cancer Cooperative Group, in which 439 patients with unresectable HNSCC were randomly assigned to CRT with cisplatin at 100 mg/m^2 given on days 1, 22, and 43, or IC with either PF+CRT or TPF +CRT. The intent to treat (ITT) analysis showed no difference between IC followed by CRT versus CRT alone in PFS, which was a primary end-point of the study.[91] Furthermore, in contrast to the two previous TAX 323 and 324 trials, the study failed to show a survival advantage of TPF over PF.[91] More recently, data were published from paired phase III trials (DeCIDE and Paradigm) assessing ICT plus CRT versus CRT alone, which again failed to demonstrate a clear advantage for ICT. Both studies showed no statistically significant differences in overall survival, the primary end-point of the study, but a difference in distant recurrence without prior locoregional recurrence was found ($P = .043$) favoring sequential therapy in the DeCIDE study and suggesting the benefit of a sequential approach in patients with high risk for distant metastases.[86]

Adjuvant Chemotherapy and Radiation

Risk-adapted adjuvant radiation therapy for patients who have undergone surgical resection of their primary tumor is dependent on known histopathologic risk factors that include advanced T status, two or more positive lymph nodes, PNI, lymphovascular invasion (LVI), positive or close resection margins, and extracapsular extension (ECE). The role of chemotherapy in the postoperative management of the patient with adverse prognostic risk factors has been clarified by two separate multicenter randomized trials and a combined analysis of data from those trials for patients with high-risk cancers of the oral cavity, oropharynx, larynx, or hypopharynx.[92-94] The US Intergroup trial RTOG 95-01 demonstrated statistically significant improvement in locoregional control and disease-free survival but not OS,[92] whereas the European EORTC trial found significant improvement in survival and the other outcome parameters.[93] There were some differences in design, primary end-point, and exclusion criteria between those two trials. To better define risk, a combined analysis of prognostic factors and outcome from the two trials was performed.[94] This analysis demonstrated that for patients in both trials, only those with ECE and/or positive resection margins benefited from the addition of cisplatin to postoperative radiotherapy. Thus, chemoradiation is clearly indicated for ECE and/or microscopic positive mucosal margins. There was a trend toward improved survival in favor of chemoradiotherapy in the group of patients who had stage III/IV disease, PNI, vascular embolisms, and/or clinically enlarged level IV/V lymph nodes secondary to tumors arising in the oral cavity or oropharynx, but the differences were not statistically significant. Interpretation of these results is limited by the fact that the data are derived from a post hoc subgroup analysis rather than from a prospective trial in which statistical analysis was adjusted for subgroup comparison.

Post-treatment Surveillance

In our institute, the patient returns to see the surgeon 2 months after completion of adjuvant therapy. At this appointment an oral/head and neck examination is performed looking for any signs of recurrence or second primaries. Inspection of the wounds in the oral/head and neck area as well as the donor site is performed.

The patient will still be suffering from the side effects of surgery and radiation therapy, so appropriate counseling is performed. Expected side effects include loss of taste or dysgeusia, xerostomia, fatigue, and depression. Dysphagia may also be present.

Loss of taste with or without dysphagia can lead to severe malnutrition. Dietary habits should be assessed and the patient's weight followed. Involving an outpatient dietitian is often helpful. At the first appointment, the patient's weight may still be declining, but the slope of this decline should be flattening out toward the patient's nadir for weight.

Depression and/or adjustment disorder is very common among patients with cancer diagnoses. Lydiatt and colleagues reported in a series of publications about the incidence of depression among patients with head and neck cancer, its negative effect on patient survival, and the benefit of prophylactic escitalopram in preventing depression in patients with head and neck cancer.[95,96] We do not routinely prescribe prophylactic antidepressants for our patients, but we do inquire about depressive symptoms and offer treatment options when appropriate.

The first post-treatment imaging PET/CT is performed 12 weeks after completion of adjuvant therapy. The timing is extrapolated from data showing the optimal timing for post-treatment scans in patients with SCCA in other head and neck subsites treated with primary radiation therapy. When interpreting the initial PET/CT, it is important to correlate findings carefully with the clinical examination. Asymmetric muscle activity (particularly in the tongue), which may be accentuated by compensatory physiologic muscle movement in patients with altered anatomy, can result in false positives.[97]

Subsequent surveillance visits are done every 3 months for the first 2 years. For high-risk patients, this interval is shortened to every month. The best surveillance interval is that which allows for early detection of recurrence without being overly burdensome on the patient. Just as important is educating the patient of signs and symptoms concerning for recurrence. In particular pain, ulceration, new lesions or masses, or neck swelling are essential signs and symptoms the patient should pay attention to.

After 2 years, the interval is increased to every 6 months up to 5 years. After 5 years, the patient is discharged from continued surveillance to return as needed.

Secondary Reconstruction and Revision Surgery

Although primary reconstruction for mandibular defects after oncologic resection using a fibula osteocutaneous free flap leaves most of our patients with a very reasonable result, taking

that same patient to a definitive reconstruction with intact and functional dentition requires revision surgeries.

This poses several challenges. One challenge is financial, in that dental reconstruction with implant-supported or implant-retained prosthetics is very expensive. Because of this, few patients continue on to receive secondary reconstruction.

The more formidable challenge is surgical. With any surgery to revise or manipulate the flap, especially after adjuvant radiation therapy, there is a difficult-to-quantify risk of causing partial or total flap failure. In addition, there is very little in the way of published protocols for how to best get the patient to an optimal dental reconstruction. We wait until at least 6 months after completion of treatment (more often up to a year) before proceeding with secondary surgery. The rationale for this delay is twofold. The first reason is to allow for collateral neovascularization of the flap. The second reason is to allow sufficient time for tumor surveillance. It would be unfortunate to begin a costly and time-consuming set of procedures only to scrap the entire endeavor if a recurrence requires surgical re-resection.

Managing the Soft Tissue

The first task is to refine the soft tissue. In implant dentistry, thick attached gingiva, which is resilient enough to resist the trauma of mastication and brushing and creates a seal around the prosthetic tooth to protect the implant and bone below, is the ideal. Unfortunately, this is exceedingly difficult to re-create in a post-resection mouth.

Although skin is keratinized, it is mobile and does not form any hemidesmosomal attachments to the implant or prosthesis. Furthermore, even in thin individuals, the thickness of the skin paddle is at least a centimeter or more from skin to bone.

One technique we use involves debulking the skin paddle. To do this, the skin is sharply elevated off the flap in a subcutaneous plane buccal and lingual from an incision centered over the bone. The blood supply to the skin will ideally be based on collateral neovascularization from the recipient buccal mucosa and floor of mouth. Subcutaneous fat overlying the bone is carefully removed using Metzenbaum scissors until periosteum is visible. During this approach, the septocutaneous perforators may be encountered and, if in the way, cauterized and divided. Ideally, the dissection can proceed toward the bone along the septum. The skin flaps that were elevated are then tacked down along the inferior border of the fibula on the buccal and lingual side, as if doing a vestibuloplasty.

A split-thickness skin graft harvested from a distant site is placed directly on the periosteum. A stent made from acrylic is secured to the screws through the graft into the fibula, holding the skin graft against the periosteum (Fig. 24.26). Alternatively, the wound can be allowed to heal by secondary intention, although this can result in excessively proud granulation tissue that can bury implants.

Another technique involves burying the skin graft. As described previously, skin flaps are developed and the subcutaneous fat removed down to the periosteum. A split-thickness skin graft is placed directly on the periosteum of the fibula. However, rather than using a stent, the skin flaps are approximated and closed, burying the skin graft. This is left buried for a month. At the second surgery, the skin flaps are elevated again and vestibuloplasty performed as described earlier.[98]



• **Fig. 24.26** Flap debulking and skin grafting.

For smaller soft tissue defects, gingival grafts harvested from the palate can be used instead of skin grafts. This results in better peri-implant soft tissues, but is limited by the quantity available for harvest.

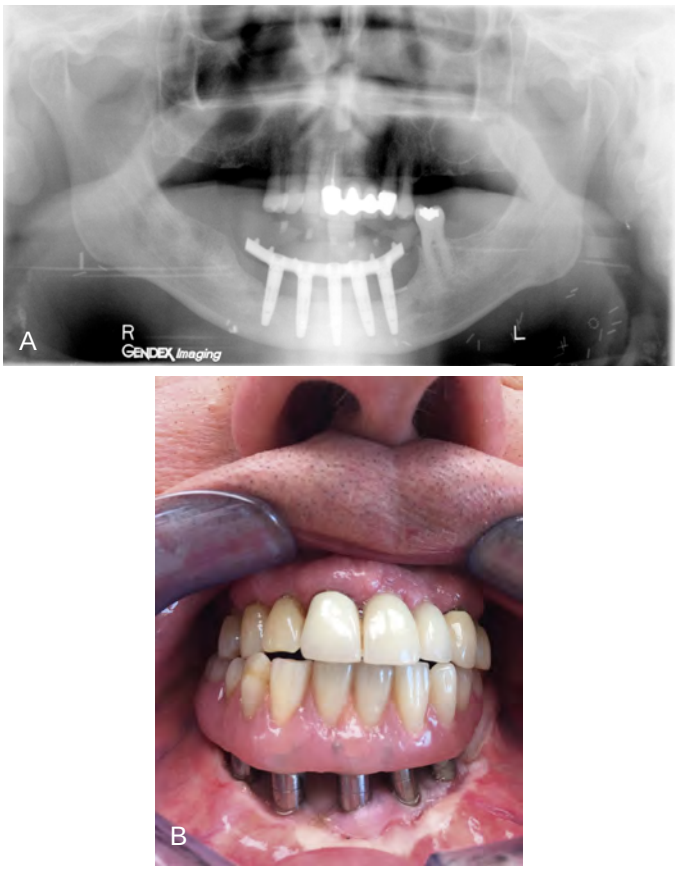
Implant Surgery

Once the soft tissue modifications have been completed and have taken, we can move onto the placement of dental implants, if an implant-supported or implant-retained prosthesis is planned. The patient should be evaluated by a prosthodontist or dentist who is comfortable with complex dental reconstructions. The number and location of implants to be placed will depend on the prosthetic plan. Because the primary reconstruction was planned with final dental reconstruction in mind, the position of the fibula should be set up for ideal placement.

When placing implants in fibulas, soft tissue dissection should be kept to a minimum. Soft tissue flaps are developed buccal and lingual in a supra-periosteal plane. Just enough elevation is performed to expose the crest of the fibula. When exposing the bone, take care to minimize the elevation of periosteum.

The standard sequence of twist drills is used to create the osteotomies for implants. As described earlier, the osteotomies need to be overprepared and tapped. Insertion torque should not exceed 40 N-cm. Because of the stability of implants within the fibula, these often can be done in a single stage with healing abutments. The tallest healing abutments available should be used.

Once the implants have been placed according to the prosthetic plan, the soft tissue flaps can be approximated around the implants. Because the soft tissue flaps can be thicker than gingival flaps, they may still cover the tops of the healing abutments. Ettinger and colleagues described a technique using



• **Fig. 24.27** Implant-supported prosthetic rehabilitation following composite resection for oral squamous cell carcinoma. **A,** Panoramic radiograph demonstrating implant placement with superstructure; **B,** intraoral view with fixed prosthesis in place.

interarch elastics over the healing abutments to hold the periimplant soft tissue down.[99] This technique can also be used to hold down the skin grafts.

Dental Prosthetics

Different prosthetic options are available, depending on the patient's reconstructed anatomy. These options include fixed bridges (Fig. 24.27), fixed hybrid prostheses (Fig. 24.28), or overdentures (Fig. 24.29). When choosing the type of prosthesis, the patient's ability to maintain hygiene around the implants and prosthesis should factor significantly into the decision. Although most patients prefer fixed options in terms of function, maintenance is much easier with removable options.

Summary

Advanced oral squamous cell carcinoma of the mandible is a complex disease that requires multidisciplinary input. Treatment starts with surgical resection. Free osteocutaneous flaps allow for primary reconstruction with high levels of predictability. Considerable preoperative preparation is imperative for successful results. The use of Virtual Surgical Planning has ushered in an era where excellent reconstruction outcomes are very reproducible. Postoperative rehabilitation requires multiple specialists. Most patients with advanced mandibular cancers will also receive adjuvant treatment in the form of radiation or chemoradiotherapy. Protocols for tumor surveillance vary among institutions, but patients should be followed closely for the first 2 years. Definitive dental reconstruction requires soft tissue revision and dental implant placement before a functional prosthesis can be realized. This requires coordination with an experienced dentist or prosthodontist.

Case A, Brown Class I Defect

Patient A (Fig. 24.30) is a 54-year-old man with a 30 pack-year smoking history who was referred to us complaining of increasing facial pain and difficulty swallowing over the prior 6 months. Physical examination revealed a large, indurated, and deeply ulcerated mass that appeared to start in his left retromolar trigone with extension to his floor of mouth, glossotonsillar sulcus, and tonsillar fossa with obvious mandibular invasion (see Fig. 24.30).

A biopsy was performed, confirming invasive squamous cell carcinoma. Preoperative imaging for surgical planning and staging purposes was obtained, which included a PET/CT, a CT maxillofacial using the 3D Systems protocol, a CT with contrast of the head and neck, and a CTA of the lower extremities.

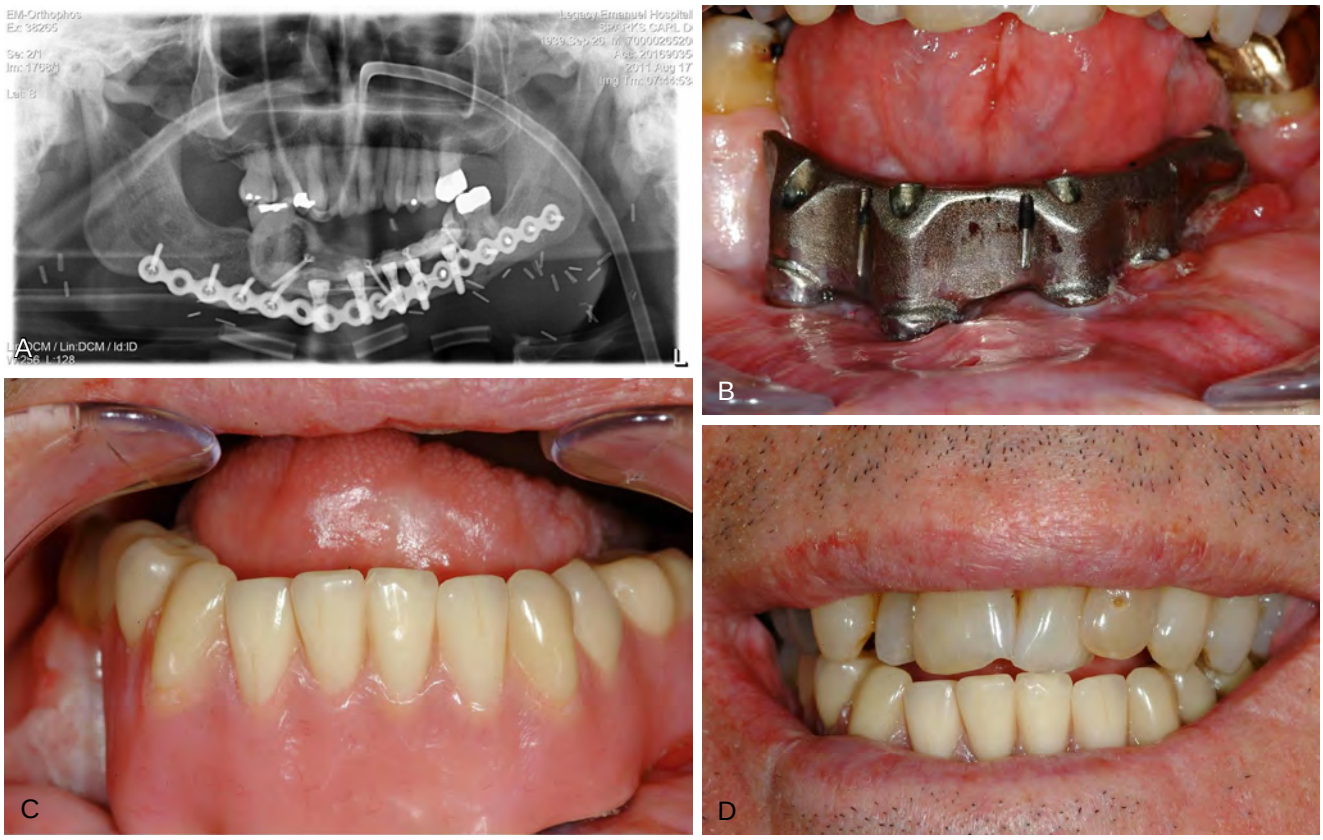
Imaging studies confirmed that the tumor had clearly destroyed the cortical bone of the mandible and had invaded into the marrow space (see Fig. 24.30A,B). The CTA showed good three vessel runoff to the feet (see Fig. 24.30C). The staging imaging demonstrated at least two enlarged, centrally necrotic level II and III cervical lymph nodes but no distant metastases. The patient was staged at cT4aN2bM0.

We recommended a composite resection including the floor of mouth and mandible with lateral oropharyngectomy. A right modified radical neck dissection was also recommended. This would leave a soft tissue defect of the oral cavity and oropharynx as well as a Brown type 1 defect of the lateral mandible. We recommended a fibular osteocutaneous free flap to restore mandibular continuity and oropharyngeal defect. He was referred to a tobacco cessation program. The patient was discussed at our multidisciplinary oral/head and neck tumor board. The board consensus agreed with our recommendations.

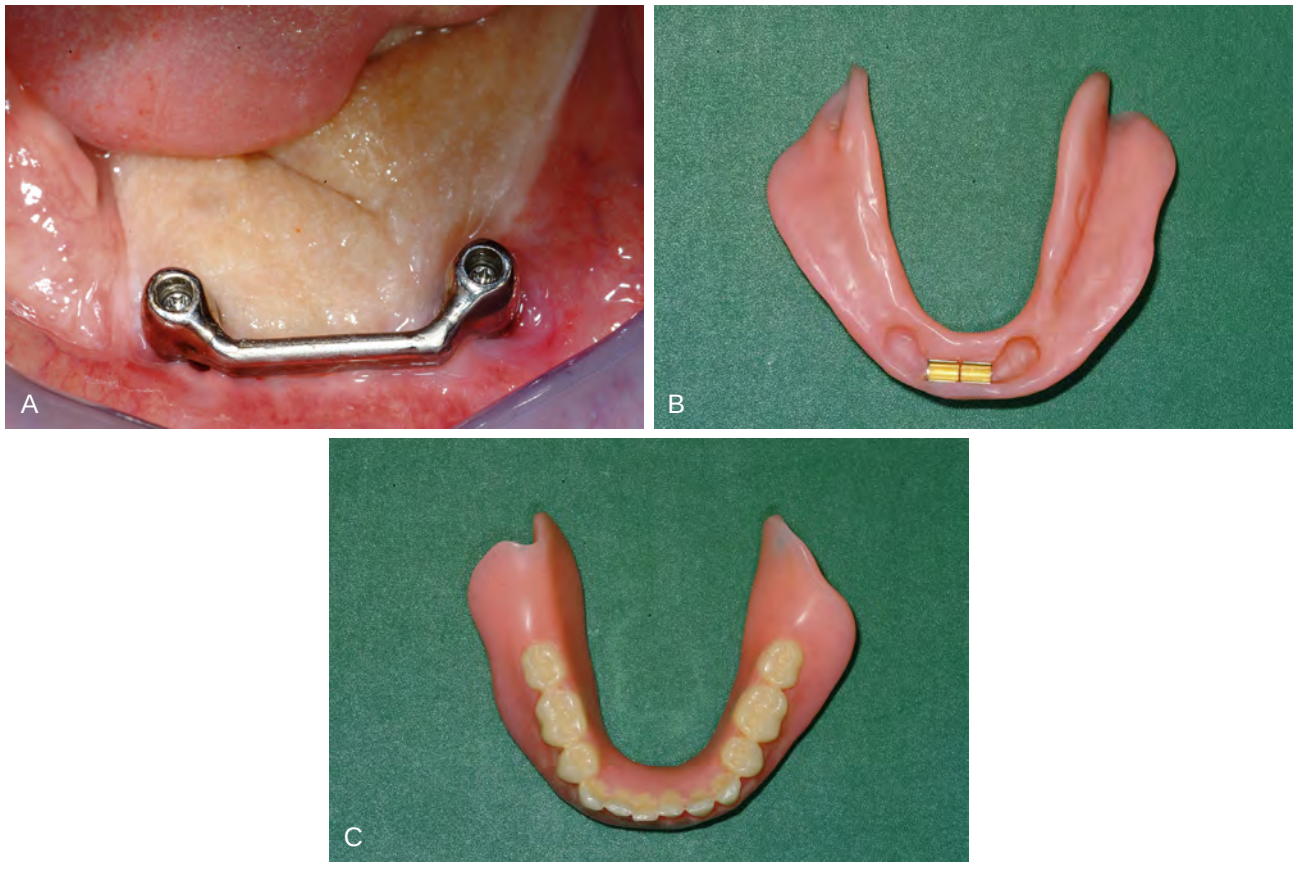
Preoperative medical workup was completed. Because of his severe protein and caloric malnutrition, he was scheduled for PEG placement and a nutrition consultation.

A web-based VSP meeting was scheduled. The meeting included the ablative surgeon, the reconstructive surgeon, the surgical hardware representative, a VSP engineer, and our trainees.

The first part of the VSP meeting involved planning the segmental resection. Using the mandibular subunit principles, the left body of the mandible and a portion of the mandibular ramus/angle were planned for removal (see Fig. 24.30D). On the ipsilateral side, the osteotomy was placed in the sigmoid notch.



• **Fig. 24.28** Implant-supported prosthetic rehabilitation following composite resection for oral cancer and fibular free flap reconstruction. **A,** Panoramic radiograph demonstrating implant placement; **B,** intraoral view of spark erosion appliance; **C,** intraoral view of fixed hybrid prosthesis in place; **D,** final postoperative result.

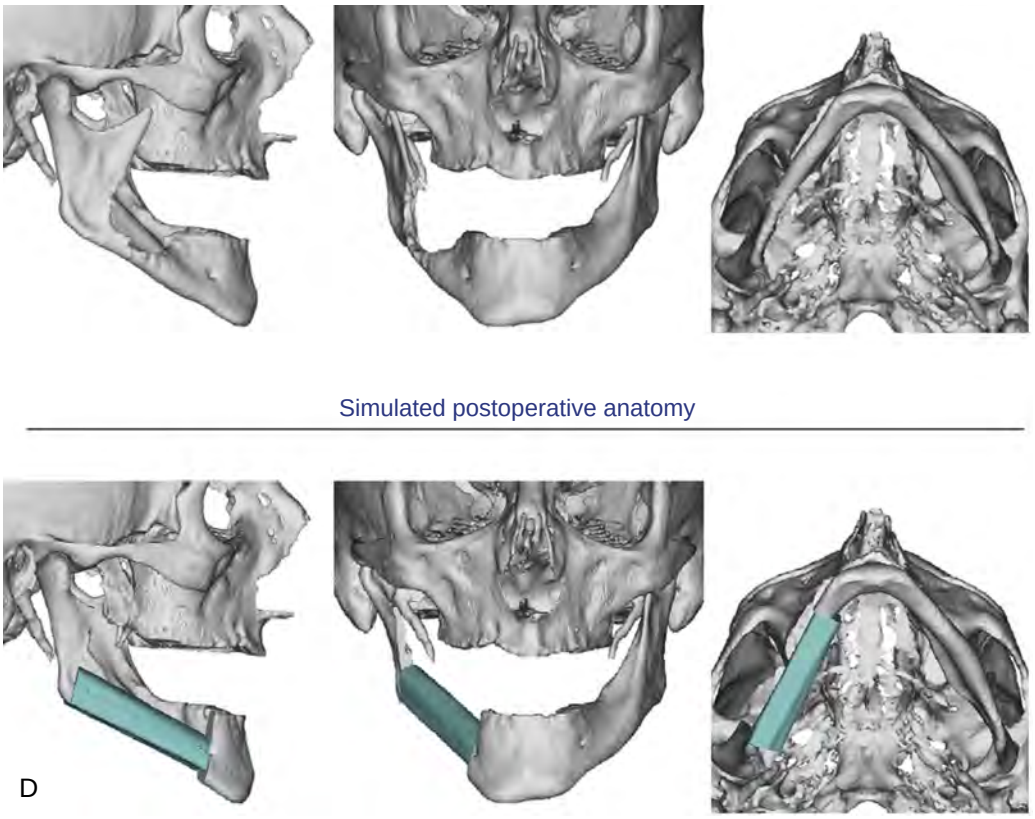


• **Fig. 24.29** Implant-supported overdenture following composite resection for oral cancer with fibular free flap reconstruction. **A,** Postoperative intraoral view demonstrating Hader bar for denture retention; **B,** denture with clasps; **C,** final overdenture.



• **Fig. 24.30** ***Case A:*** A 50-year-old man with cT4AN2bM0, Stage IVA squamous cell carcinoma of the retromolar trigone. **A** and **B,** CT imaging studies confirming that the tumor had clearly destroyed the cortical bone of the mandible and had invaded into the marrow space; **C,** Computed tomographic angiography (CTA) of the lower extremities showed good three-vessel runoff to the feet.

Continued



• **Fig. 24.30, cont'd** ***Case A:*** **D,** Virtual Surgical Planning (VSP) plan for segmental resection. Using the mandibular subunit principles, the left body of the mandible and a portion of the mandibular ramus/angle was planned for removal.

After the segmental resection had been performed digitally, the left fibula was adapted to the defect. We set the distal osteotomy at 7 cm proximal to the lateral malleolus, which avoided interruption of ligamentous attachments that would lead to ankle instability. The left lower leg was chosen with the plan to perform the anastomosis within the right neck. This would place the skin paddle facing intraorally to replace the mandibular gingiva and oropharynx.

Off-line, surgical cutting guides with predictive holes were designed and printed. As is often the case, our mandibular cutting guides were made in one piece to improve on accuracy of the cuts (see Fig. 24.30E). The fibula cutting guide was fabricated with a mark with an arbitrary distance from the lateral malleolus of the fibula for accurate placement along the fibula (see Fig. 24.30F). A postoperative model of the mandible was also printed. A reconstruction plate was adapted to the postoperative model, using the predictive holes (see Fig. 24.30G). Specific attention was paid to ensuring that the plate fitted passively. The cutting guides, models, and plate were then given to the central processing department at our hospital for sterilization.

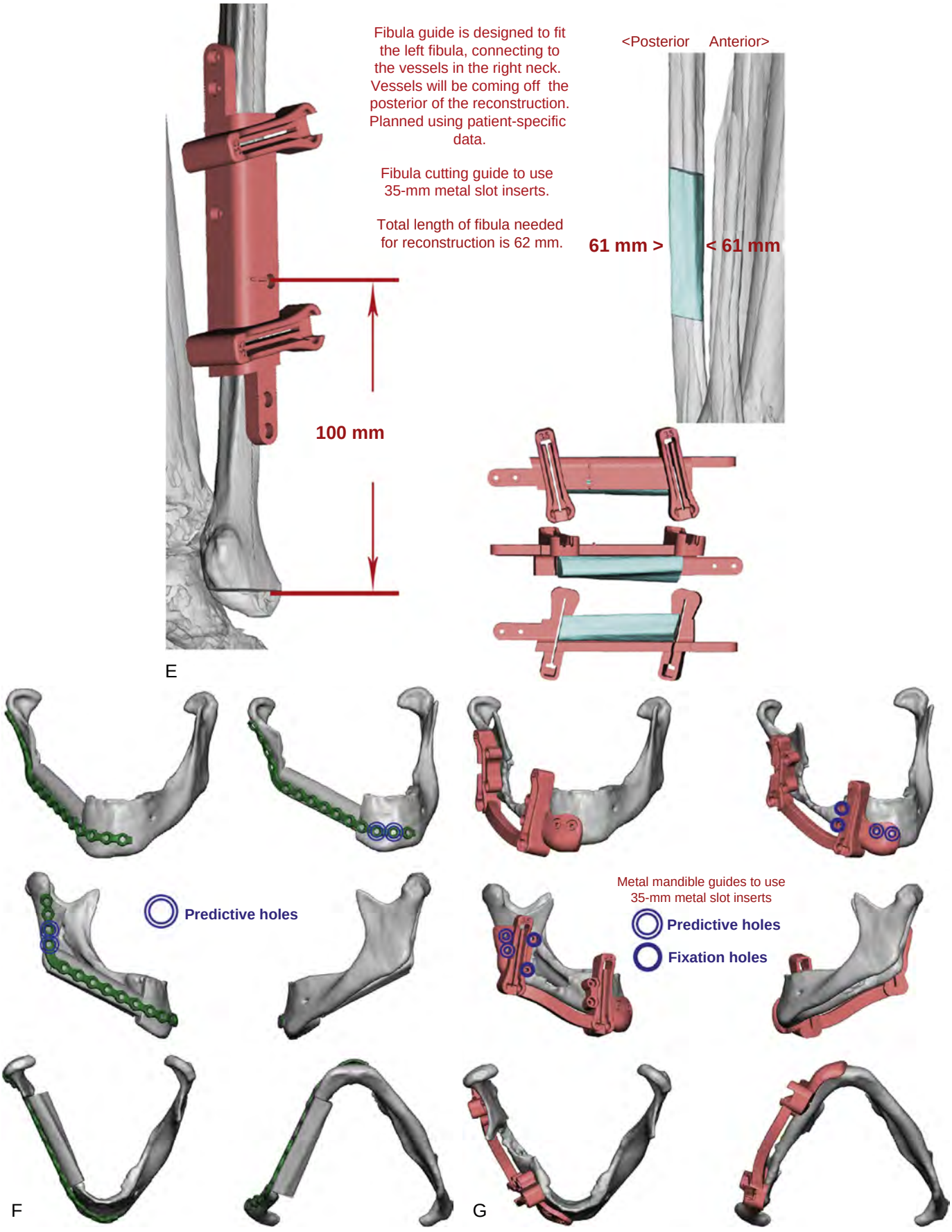
The patient was then taken to the operating room. A tracheostomy was created at the start of the procedure. The patient then underwent a composite resection of his floor of mouth, mandible and oropharynx, according to the virtual plan (see Fig. 24.30H). The specimen, removed en bloc with the bilateral modified radical neck dissections, is pictured in Fig. 24.30I.

A second team of surgeons simultaneously harvested the fibula flap with a large skin paddle. The fibula cutting guide was adapted to the fibula at the leg after the harvest was complete and osteotomies were performed.

Next, the pre-bent reconstruction plate was secured using the predictive holes (see Fig. 24.30J). The fibula was then brought up to the head and fitted to the mandible (see Fig. 24.30K). Note that intraoperatively the osteotomies replicated the virtual plan very closely from multiple views. The skin paddle was used to replace the mandibular gingiva and floor of mouth. A surveillance CT taken later shows excellent approximation of the virtual plan.

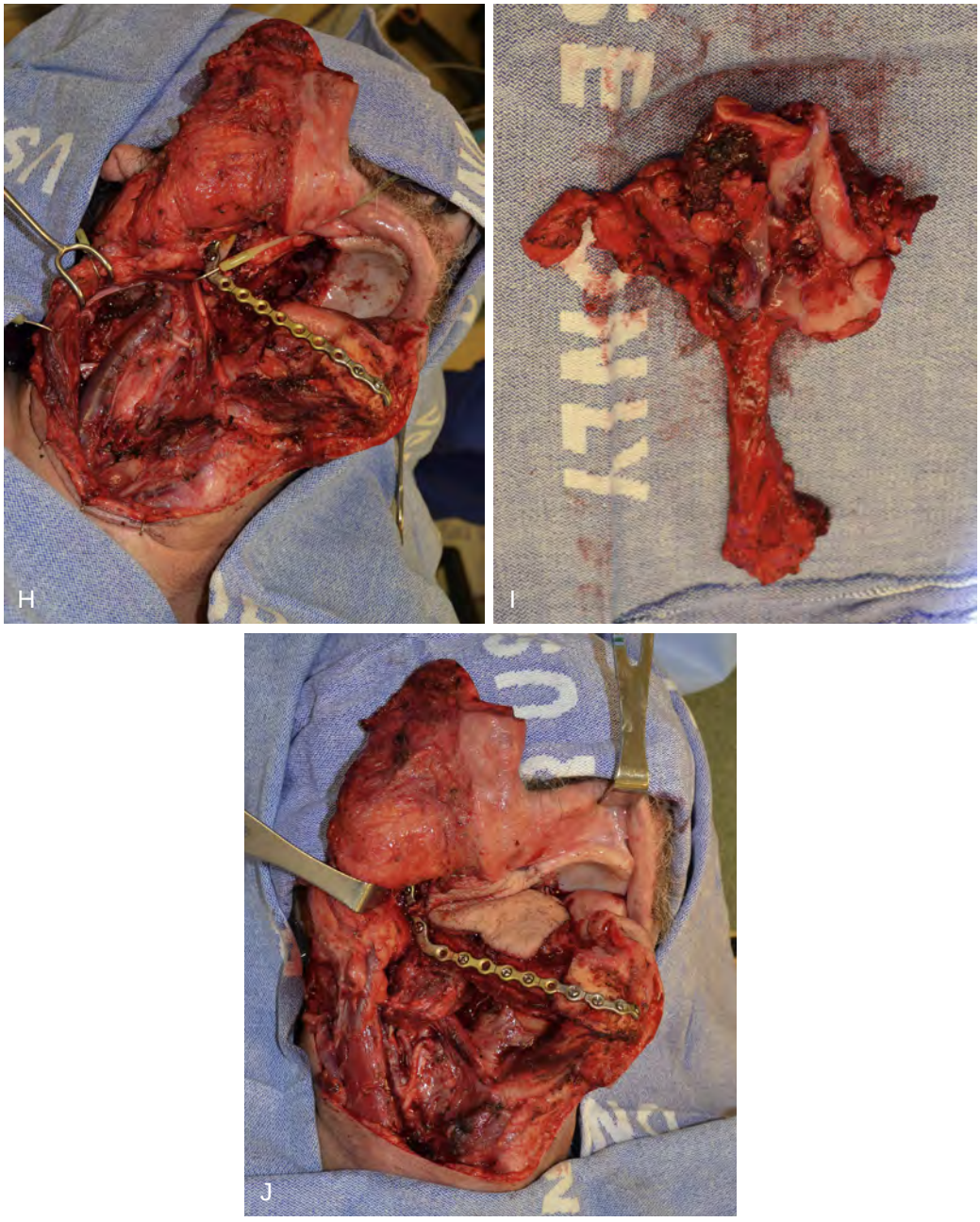
Final pathology revealed a 3.7 × 3.5 × 1.9 cm moderately differentiated squamous cell carcinoma, negative margins, with lymphovascular invasion, perineural invasion, and bone invasion. Nodal metastases were identified, with 2 of 30 nodes positive for metastatic cancer, with no extracapsular extension. He was staged at pT4aN2bM0 with intermediate risk features.

The patient was treated with adjuvant radiotherapy (see Fig. 24.30L–Q), based on NCCN guidelines. The patient's right retromolar tumor and neck were treated with an IMRT technique. A 9-beam angle step and shoot IMRT plan was used, treating at a dose of 200 cGy per fraction prescribed to the 97% isodose line using 6MV photons. A total of 6000 cGy was delivered to intermediate-risk tumor bed and ipsilateral regional nodes. The contralateral neck received 54 Gy.

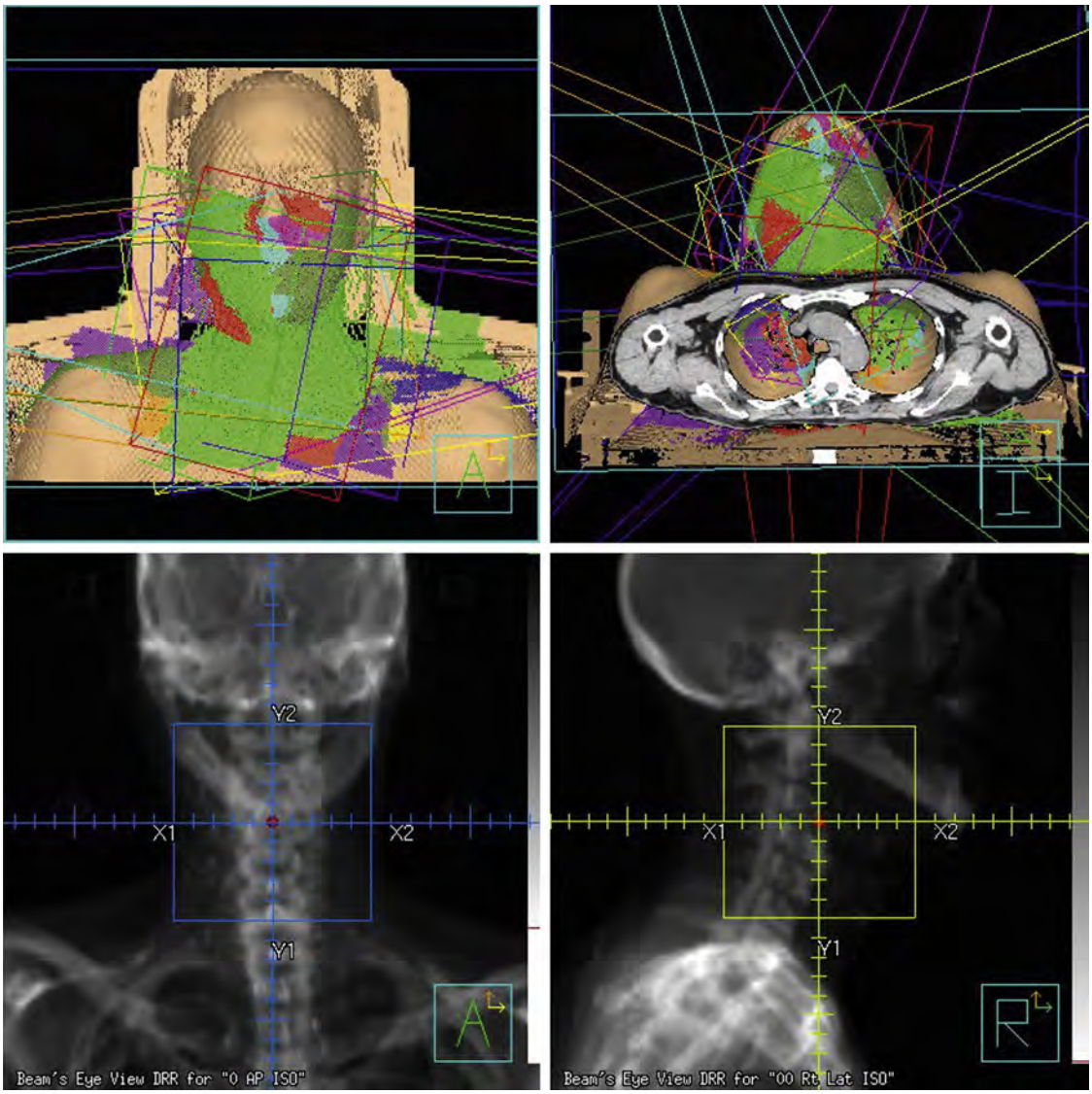


• **Fig. 24.30, cont'd** ***Case A:*** **E,** The fibula cutting guide was fabricated with a mark with an arbitrary distance from the lateral malleolus of the fibula for accurate placement along the fibula.**F,** Virtual reconstruction plate was adapted to the postoperative model, using the predictive holes. **G,** Mandibular cutting guides were made in one piece to improve accuracy of the cuts.

Continued



• **Fig. 24.30, cont'd** *Case A:* **H,** Intraoperative view of composite resection of the floor of mouth, mandible, and oropharynx, according to the virtual plan with pre-bent reconstruction plate in place. **I,** Oromandibular specimen with en bloc neck dissection. **J,** Fibular flap inset.



K

• **Fig. 24.30, cont'd** ***Case A:*** **K-O,** Case A's intensity-modulated radiation therapy (IMRT) isodosing plan for pT4aN2bM0 with intermediate risk features. The patient's right retromolar tumor and neck were treated with an IMRT technique. A 9-beam angle step and shoot IMRT plan was used, treating at a dose of 200 cGy per fraction prescribed to the 97% isodose line using 6-MV photons. A total of 6000 cGy was delivered to intermediate-risk tumor bed and ipsilateral regional nodes. The contralateral neck received 54 Gy.

Continued

He has been in structured surveillance and has remained disease free for 3 years. He has had relief of his pain, has quit tobacco, and is able to swallow (see Fig. 24.30R,S).

Case B, Brown Class II Defect

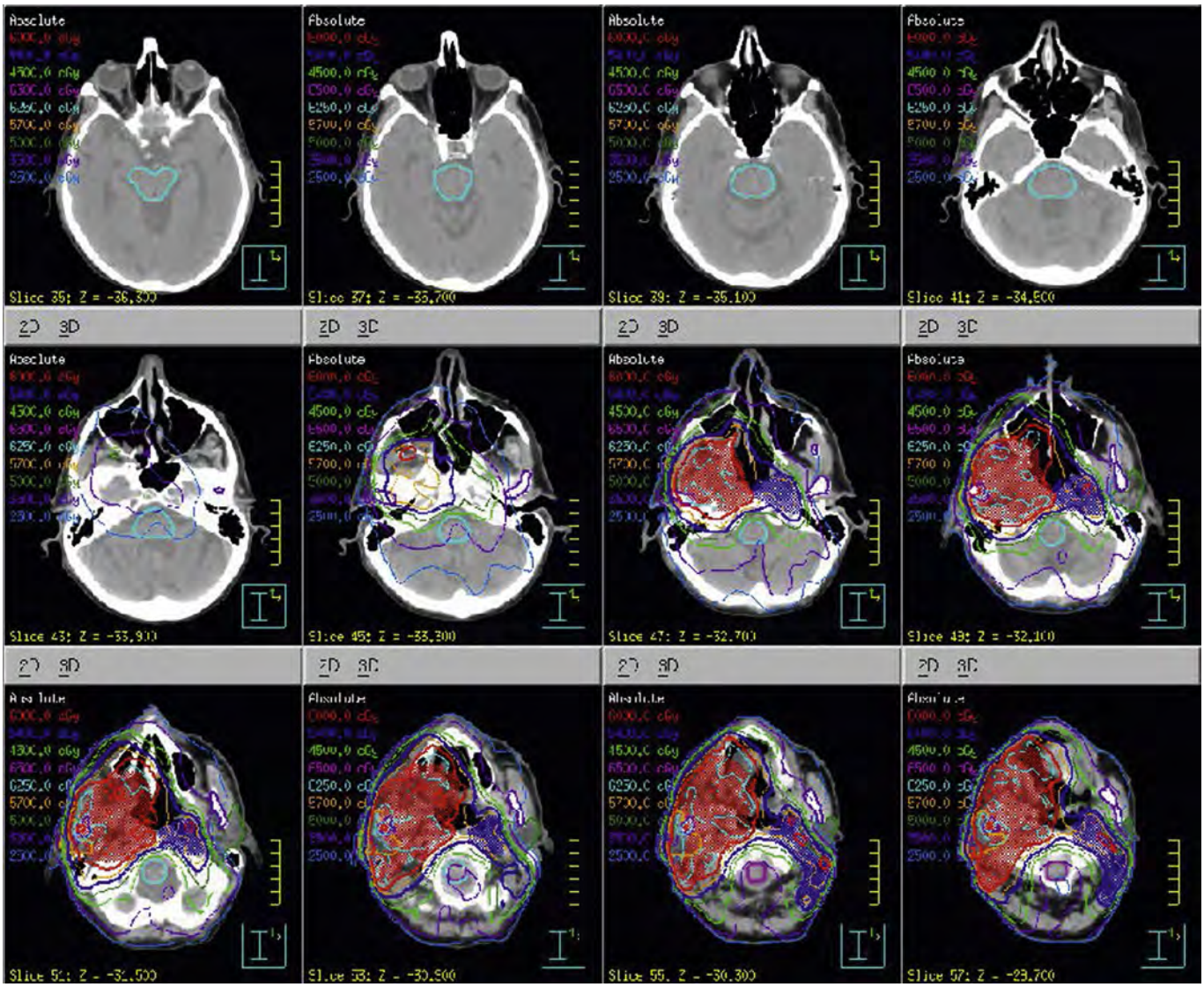
Patient B (Fig. 24.31) was a 76-year-old man with a 50 pack/year smoking history and history of alcohol dependence who was referred to us by his dentist for evaluation of an ulcerative lesion in the right mandibular gingiva. His chief complaint was that his dentures were not fitting well. His medical history included a history of coronary artery disease, hypertension, and hyperlipidemia.

Physical examination revealed an indurated, and deeply ulcerated mass that involved his right mandibular gingiva (see Fig. 24.31A,B). He was edentulous.

A biopsy was performed, confirming invasive squamous cell carcinoma. Preoperative imaging for surgical planning and staging purposes was obtained, which included a PET/CT, a CT maxillofacial using the 3D Systems protocol, a CT with contrast of the head and neck, and a CTA of the lower extremities.

Imaging studies confirmed that the tumor had clearly destroyed the cortical bone of the mandible and had invaded into the marrow space (see Fig. 24.31C,D). The CTA showed good three-vessel runoff to the feet (see Fig. 24.31E). The staging imaging demonstrated no evidence of cervical lymphadenopathy and no distant metastases. The patient was staged at cT4aN0M0.

We recommended a composite resection including the floor of mouth and mandible resection, extending from the right angle to the left parasymphysis. Because the tumor crossed the midline, bilateral selective neck dissections (levels I-IV) were



L

• **Fig. 24.30, cont'd** *Case A:* **L,** For legend see p. 511.

also recommended. This would leave a Brown type 2 mandibular defect. We recommended an osteocutaneous fibula flap to restore the mandibular form, the floor of mouth, and the mandibular gingiva. He was referred to a tobacco cessation program. The patient was discussed at our multidisciplinary oral/head and neck tumor board. The board consensus agreed with our recommendations.

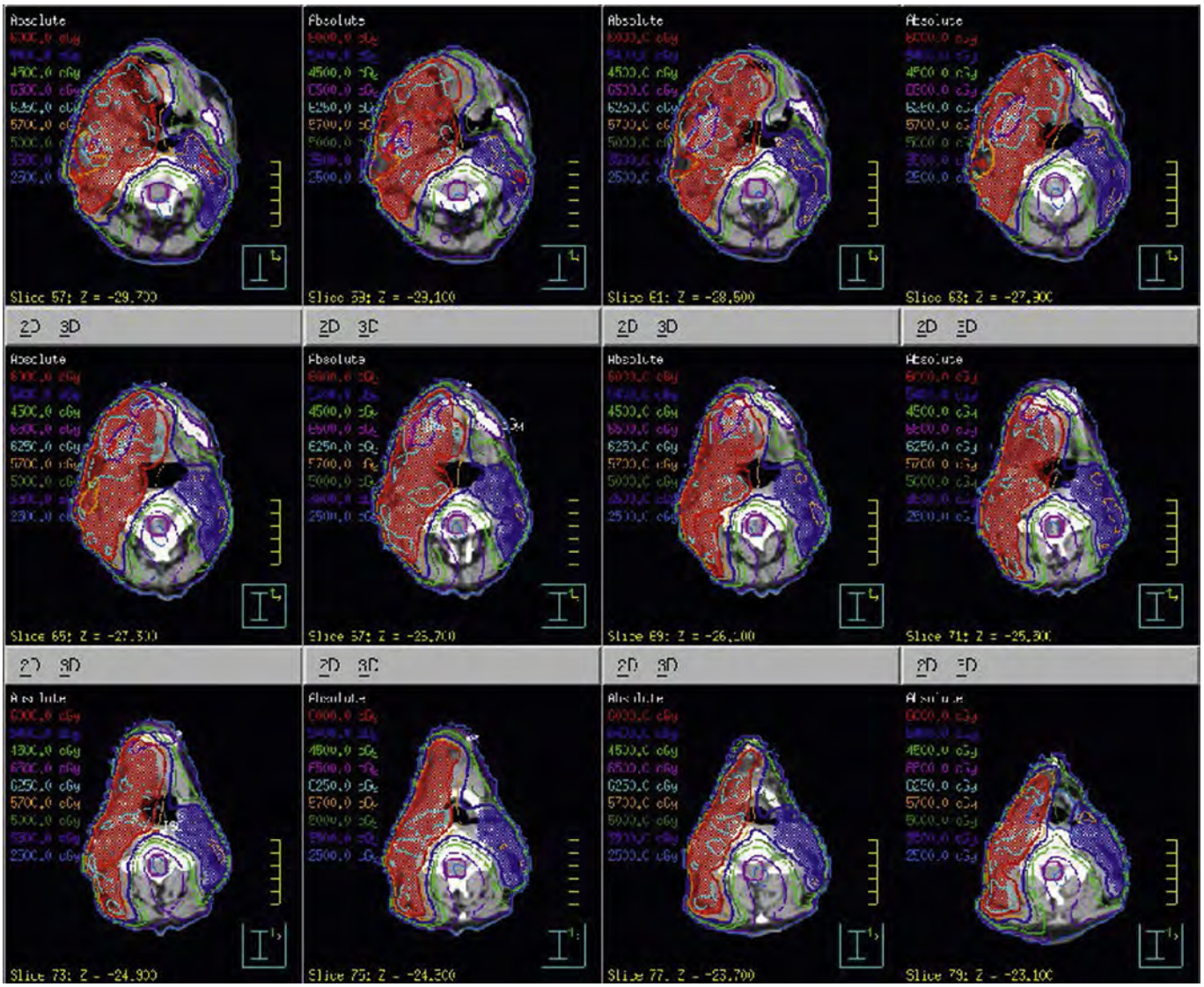
Preoperative medical workup was completed. Because of his severe protein and caloric malnutrition, he was scheduled for PEG placement and a nutrition consultation.

A web-based VSP meeting was scheduled. The meeting included the ablative surgeon, the reconstructive surgeon, the surgical hardware representative, a VSP engineer, and our trainees.

The first part of the VSP meeting involved planning the segmental resection. Using the mandibular subunit principles, the entire right body of the mandible and symphysis were planned for removal (see Fig. 24.31F). On the ipsilateral side, the osteotomy was placed in the sigmoid notch. On the contralateral side, the osteotomy was placed at the parasymphysis, as the margin did not necessitate removal of additional bone.

After the segmental resection had been performed digitally, the left fibula was adapted to the defect. We set the distal osteotomy at 7 cm proximal to the lateral malleolus, which avoided interruption of ligamentous attachments that would lead to ankle instability. The left lower leg was chosen with the plan to perform the anastomosis within the right neck. This would place the skin paddle facing intraorally to replace the mandibular gingiva. Closing osteotomies were planned to shape the fibula into three segments to replace the left body and symphysis.

Off-line, surgical cutting guides with predictive holes were designed and printed. As is often the case, our mandibular cutting guides were made in one piece to improve accuracy of the cuts (see Fig. 24.31G,H). The fibula cutting guide was fabricated with a mark with an arbitrary distance from the lateral malleolus of the fibula for accurate placement along the fibula

M 

• **Fig. 24.30, cont'd** *Case A:* **M,** For legend see p. 511.

Continued

(see Fig. 24.31K). A postoperative model of the mandible was also printed (see Fig. 24.31J). A reconstruction plate was adapted to the postoperative model, using the predictive holes (see Fig. 24.31I,J). Specific attention was given to ensuring that the plate fitted passively. The cutting guides, models, and plate were then given to the central processing department at our hospital for sterilization (see Fig. 24.31L,M).

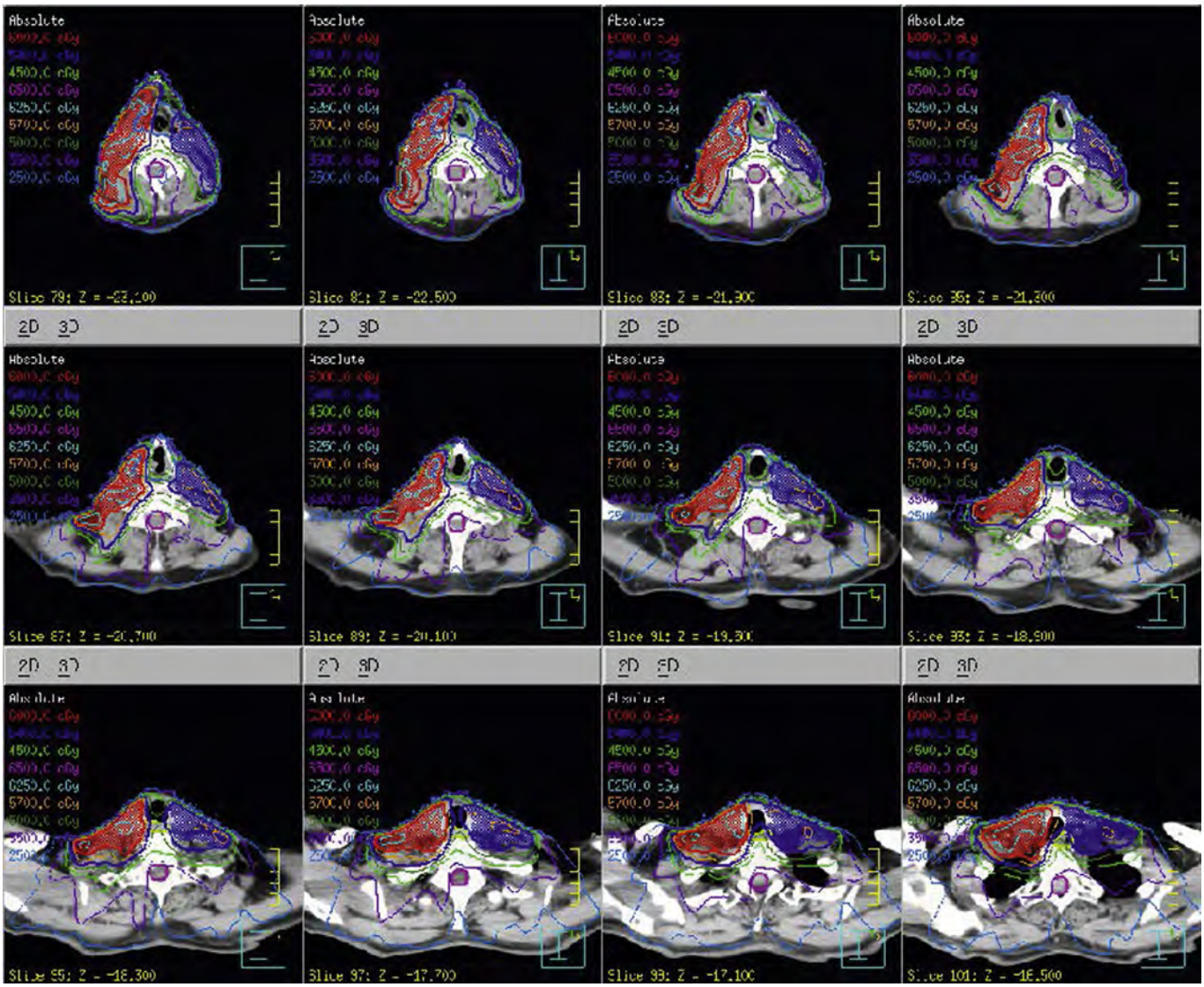
The patient was then taken to the operating room. A tracheostomy was created at the start of the procedure. The patient then underwent a composite resection of his floor of mouth and mandible according to the virtual plan (see Fig. 24.31N). The specimen, removed en bloc with the bilateral selective neck dissections, is pictured in Fig. 24.31O.

A second team of surgeons simultaneously harvested the fibula flap with a large skin paddle. The fibula cutting guide was adapted to the fibula at the leg after the harvest was complete and osteotomies were performed.

Next, the pre-bent reconstruction plate was secured using the predictive holes. The fibula was then brought up to the head and fitted to the mandible (see Fig. 24.31P). Note that intraoperatively the osteotomies replicated the virtual plan very closely from multiple views. The skin paddle was used to replace the mandibular gingiva and floor of mouth (see Fig. 24.31Q). A surveillance CT taken later shows excellent approximation of the virtual plan, and he had an excellent functional and esthetic outcome (see Fig. 24.31R).

Final pathology revealed a 4.0 × 3.5 × 1.9 cm moderately differentiated squamous cell carcinoma, negative margins, with perineural invasion and bone invasion. Bilateral nodal metastases were identified with 2/50 nodes positive for metastatic cancer, with no evidence of extracapsular extension. He was staged at pT4aN2cM0, stage IVA with intermediate risk features.

The patient was treated with adjuvant radiotherapy, based on NCCN guidelines. He was in structured surveillance and remained disease free for nearly 3 years. He achieved relief of his pain, quit tobacco, and was able to swallow. Unfortunately, he developed distant metastasis 2 years after treatment and entered hospice, where he succumbed 26 months following treatment.



N

• **Fig. 24.30, cont'd** *Case A:* **N,** For legend see p. 511.

Case C, Brown Class III

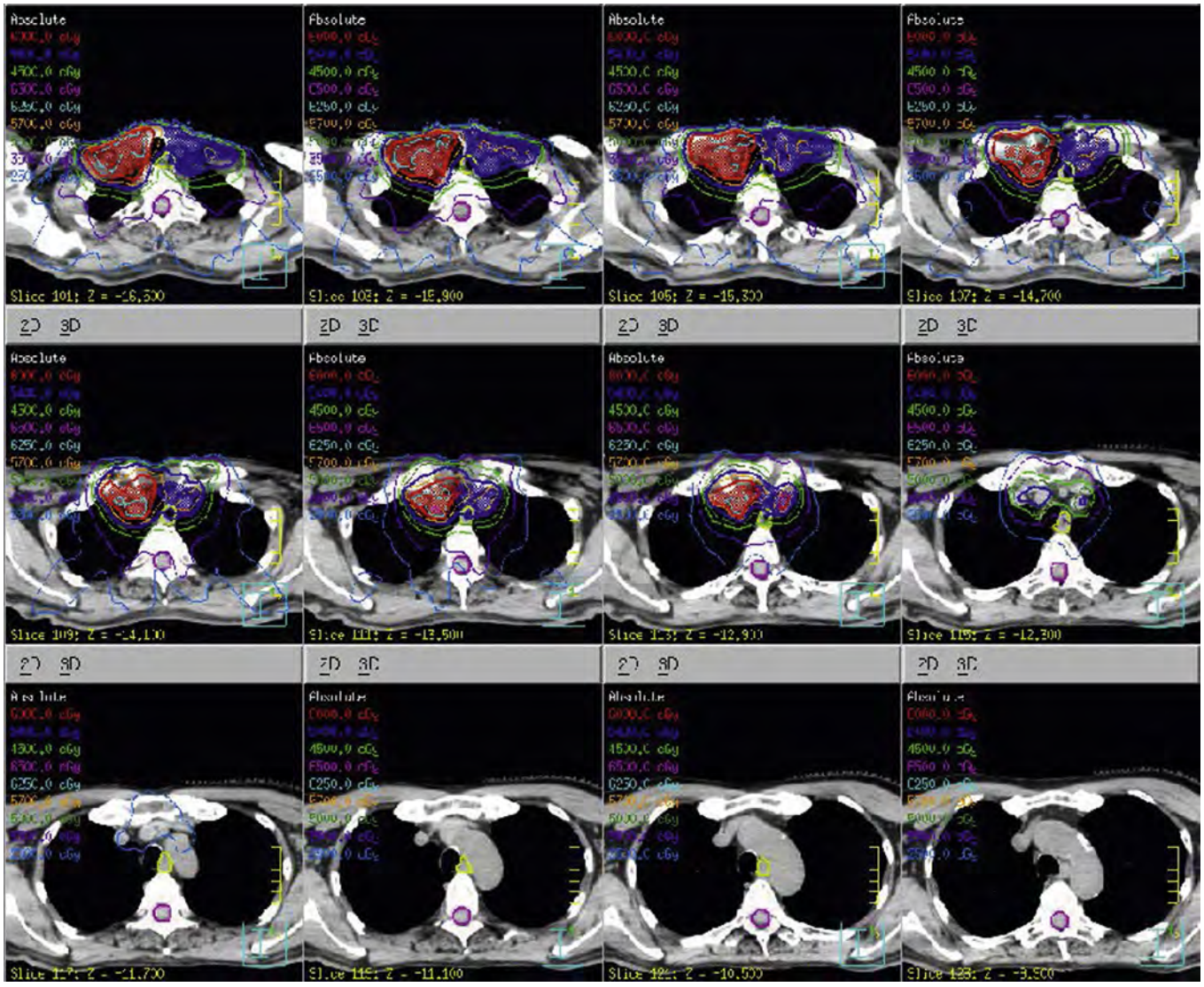
Patient C (Fig. 24.32) is a 60-year-old man who was referred to us for neck swelling and mandibular gingival lesions concerning for malignancy. He reported first noticing a lump developing in his left neck 1 year before he presented to us. At the time, he ignored it. He then began to notice a painful sore in the gums around his lower left teeth. The discomfort progressed to include his tongue, affecting both speech and swallowing. Because of this, he had lost 20 pounds over the previous 6 months. Eventually, after dealing with this for close to a year, he went to see a local dentist, who promptly referred him to an oral and maxillofacial surgeon. Examination revealed a large ulcerative lesion in his floor of mouth, tongue, and gingiva that was highly suspicious for malignancy, and he was then quickly referred to our group.

His medical history was sparse, given the lack of consistent medical care. He did endorse ongoing heavy tobacco use, approximately 60 pack years, along with a past history of heavy alcohol abuse.

Physical examination revealed a large, indurated, and deeply ulcerated mass that appeared to start in his left oral tongue and encompass his floor of mouth and mandibular gingiva (see Fig. 24.32A). The lesion insinuated itself around the left mandibular posterior teeth, but extended and included the lingual surfaces of his right mandibular premolars. In addition, his dentition suffered from generalized dental caries.

A biopsy was performed, confirming invasive squamous cell carcinoma. Preoperative imaging for surgical planning and staging purposes was obtained, which included a PET/CT, a CT maxillofacial using the 3D Systems protocol, a CT with contrast of the head and neck, and a CTA of the lower extremities.

Imaging studies confirmed that the tumor had clearly destroyed the cortical bone of the mandible and had invaded into the marrow space (see Fig. 24.32B,C). The CTA showed



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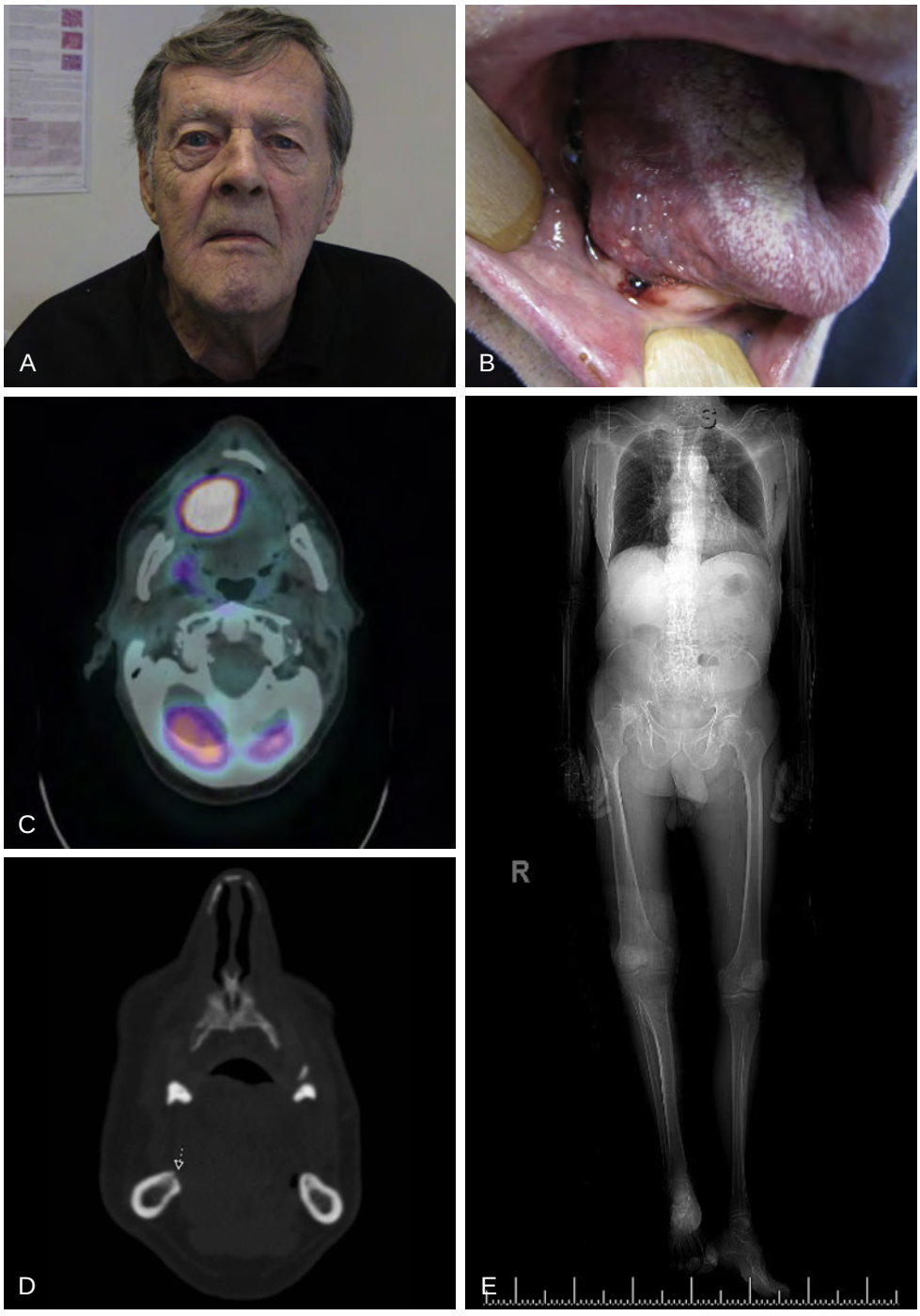


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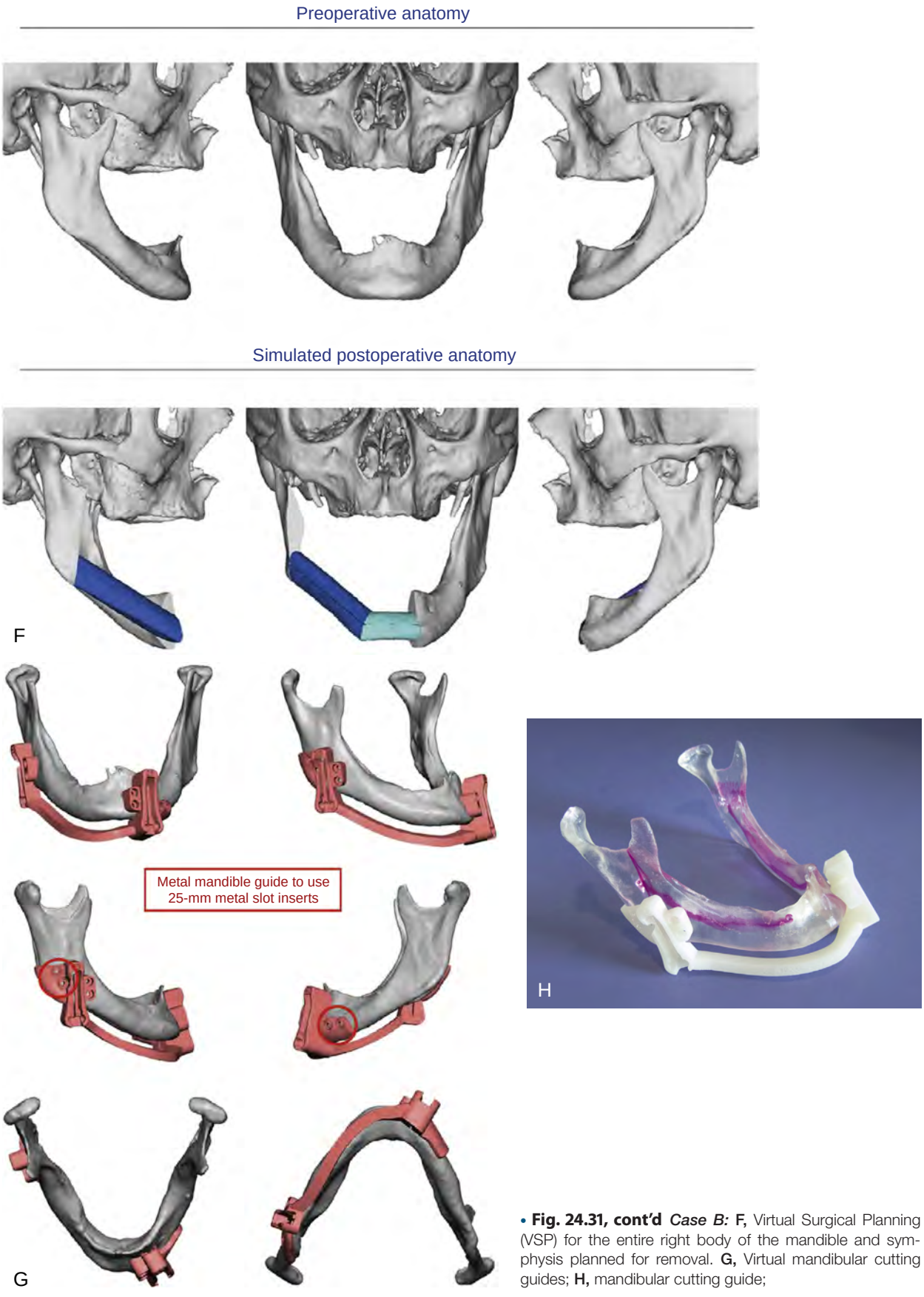
• **Fig. 24.30, cont'd** *Case A:* **P,** Intraoral view following adjuvant radiation. **Q,** Postoperative appearance following adjuvant radiation therapy.



• **Fig. 24.31** ***Case B:*** A 76-year-old man with pT4AN2bM0, Stage IVA squamous cell carcinoma of the mandibular gingiva. **A,** Pretreatment facial appearance. **B,** Intraoral appearance of mandibular gingival lesion. **C,** Positron emission tomography (PET)/CT. **D,** CT demonstrating cortical invasion into the marrow space; **E,** Computed tomographic angiography (CTA) of the lower extremities shows good three-vessel runoff to the feet.

good three-vessel runoff to the feet. The staging imaging demonstrated bilateral cervical lymphadenopathy but no distant metastases. The patient was staged at cT4aN2cM0.

We recommended a composite resection including a hemiglossectomy, floor of mouth resection, and a subtotal mandibulectomy, from angle to angle. Bilateral modified radical neck dissections were also recommended. This would leave a soft tissue defect of the tongue and mandibular gingiva along with a long bony defect. We recommended two flaps to reconstruct this: a radial forearm flap to restore the shape and maintain the mobility of the tongue, and an osteocutaneous fibula flap to restore the mandibular form, the floor of mouth, and the mandibular gingiva. Because he would likely require adjuvant radiation therapy, we also recommended extraction of all of his remaining teeth. He was referred to a tobacco cessation program. The patient was discussed at our multidisciplinary

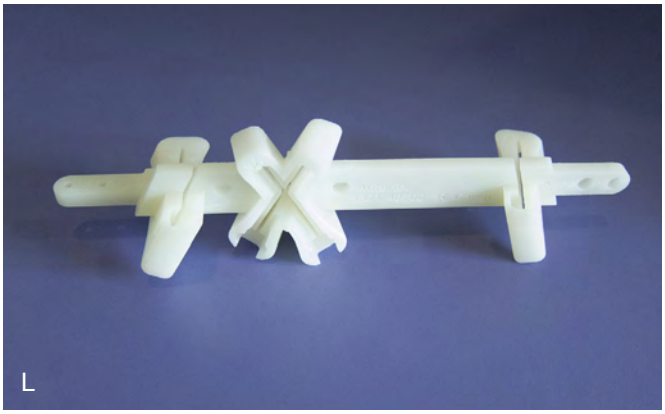


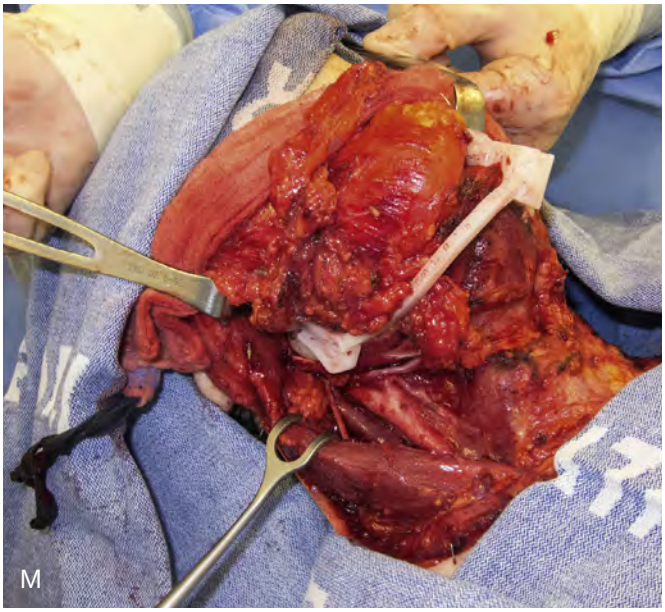
• **Fig. 24.31, cont'd** *Case B:* **F,** Virtual Surgical Planning (VSP) for the entire right body of the mandible and symphysis planned for removal. **G,** Virtual mandibular cutting guides; **H,** mandibular cutting guide;

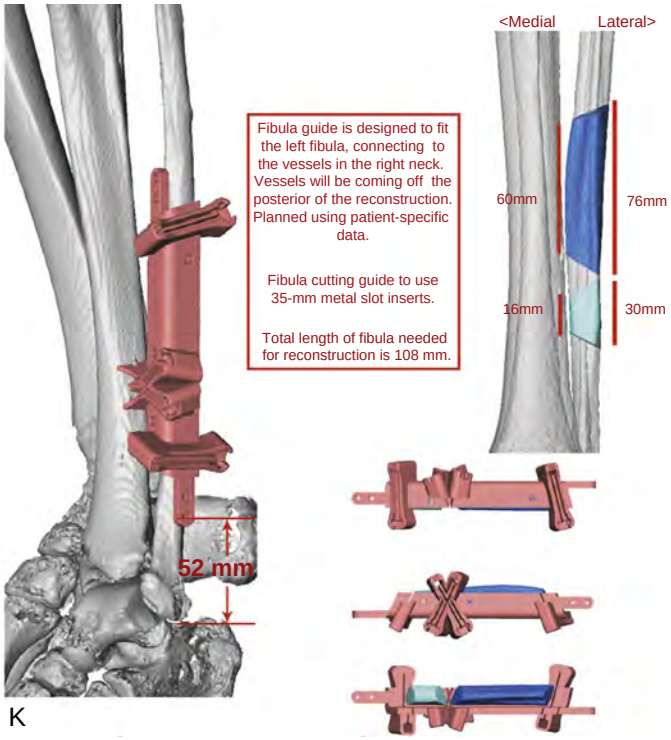
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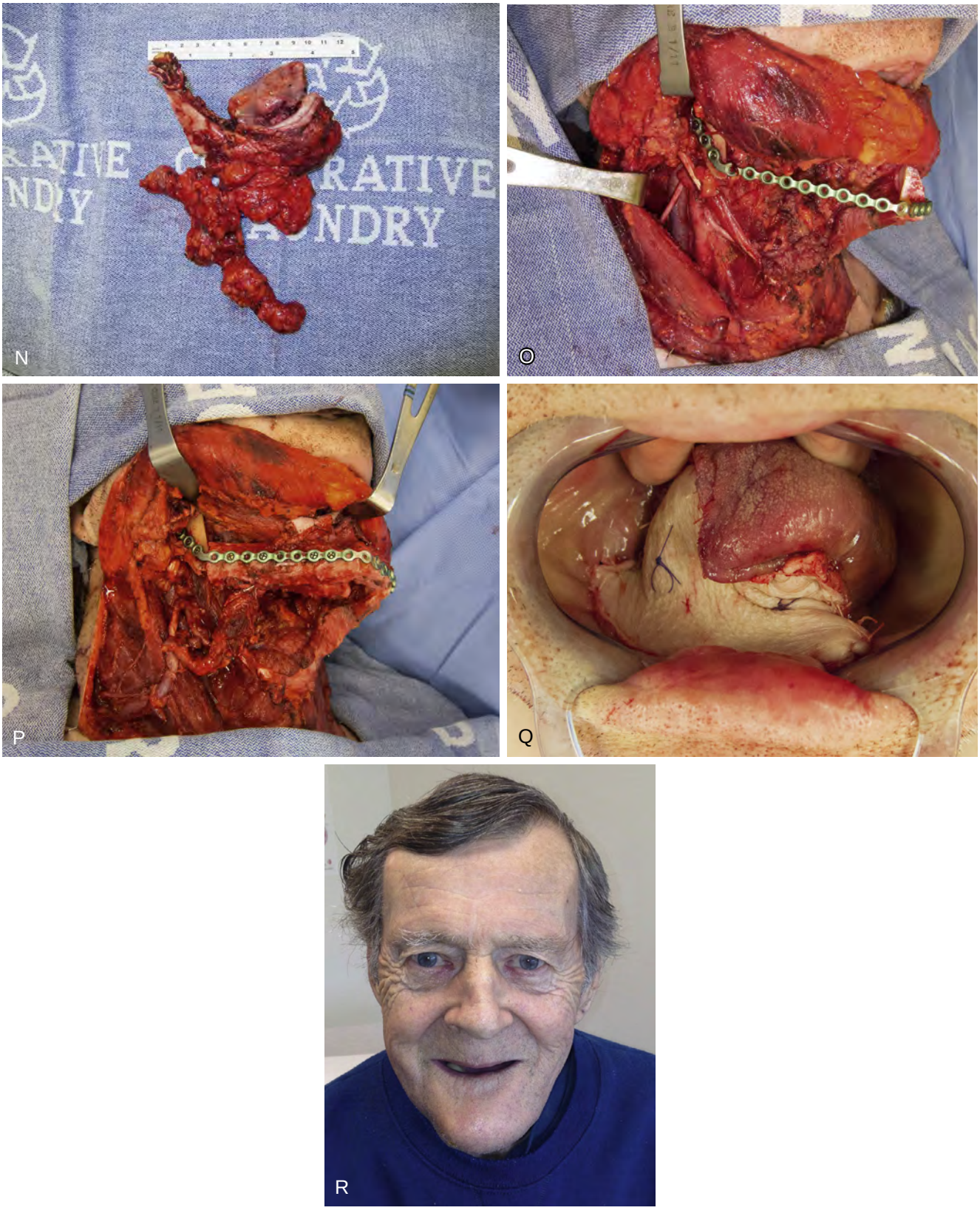




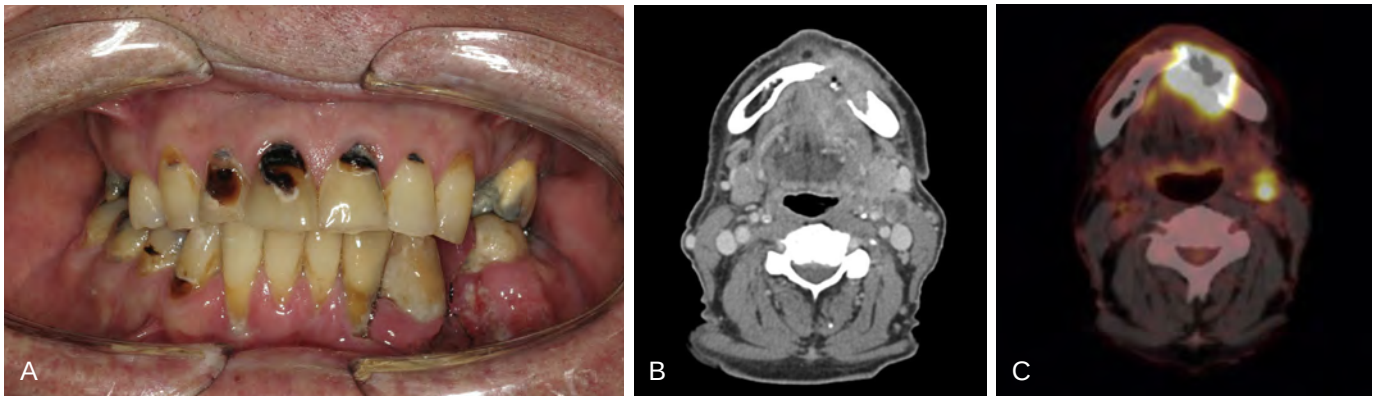




• **Fig. 24.31, cont'd** *Case B:* **I,** virtual reconstruction plate. **J,** Reconstruction plate was adapted to the postoperative model, using the predictive holes. **K,** Virtual fibula cutting guide. **L,** Fibula cutting guide. **M,** Composite resection of patient's floor of mouth and mandible with selective neck dissection according to the virtual plan; mandibular cutting guide secured with screws.



• **Fig. 24.31, cont'd** *Case B:* **N,** Specimen. **O,** Reconstruction plate inset. **P,** Fibula inset. **Q,** Skin paddle to reconstruct oral cavity. **R,** One-year postoperative appearance.



• **Fig. 24.32** ***Case C:*** A 60-year-old man with pT4AN3cM0, stage IVB squamous cell carcinoma of the mandibular gingiva. **A,** Image of a left oral tongue and floor of mouth squamous cell carcinoma that has invaded into the mandible. In this image, notice the lesion insinuating itself around and destroying the alveolar bone around the left mandibular premolar teeth. **B,** CT with contrast, axial cut, shows a large enhancing mass causing bony destruction of the left mandible; **C,** positron emission tomography (PET)/CT, fluorodeoxyglucose (FDG) avid area encompassing the left and anterior mandible.

oral/head and neck tumor board. The board consensus agreed with our recommendations.

Preoperative medical workup was completed. Because of his severe protein and caloric malnutrition, he was scheduled for PEG placement and a nutrition consultation.

A web-based VSP meeting was scheduled. The meeting included the ablative surgeon, the reconstructive surgeon, the surgical hardware representative, a VSP engineer, and our trainees.

The first part of the VSP meeting involved planning the segmental resection. Using the mandibular subunit principles, the entire left body of the mandible, symphysis, and right body of the mandible were planned for removal, from the ipsilateral mandibular angle to the contralateral mandibular angle (see Fig. 24.32D). On the ipsilateral side, the osteotomy was placed in the sigmoid notch. On the contralateral side, the osteotomy was placed at the angle, as the margin did not necessitate removal of additional bone.

After the segmental resection had been performed digitally, the right fibula was adapted to the defect. We set the distal osteotomy at 7 cm proximal to the lateral malleolus, which avoided interruption of ligamentous attachments that would lead to ankle instability. The left lower leg was chosen with the plan to perform the anastomosis within the right neck, which had less nodal disease burden. This would place the skin paddle facing intraorally to replace the mandibular gingiva. Closing osteotomies were planned to shape the fibula into three segments to replace the left body, symphysis, and right body.

Off-line, surgical cutting guides with predictive holes were designed and printed. As is often the case, our mandibular cutting guides were made in one piece to improve accuracy of the cuts (see Fig. 24.32E,F). The fibula cutting guide was fabricated with a mark with an arbitrary distance from the lateral malleolus of the fibula for accurate placement along the fibula (see Fig. 24.32G). A postoperative model of the mandible was also printed (see Fig. 24.32H,I). A reconstruction plate was adapted to the postoperative model, using the predictive holes. Specific attention was paid to ensuring that the plate fitted passively. The cutting guides, models, and plate were then given to the central processing department at our hospital for sterilization.

The patient was then taken to the operating room. A tracheostomy was created at the start of the procedure. The patient then underwent a composite resection of his mandible and hemiglossectomy, according to the virtual plan (see Fig. 24.32J,K). The specimen, removed en bloc with the bilateral modified radical neck dissections, is pictured in Fig. 24.32L.

A second team of surgeons simultaneously harvested the radial forearm free flap (see Fig. 24.32M) and fibula flap with a large skin paddle (see Fig. 24.32N). The fibula cutting guide was adapted to the fibula at the leg after the harvest was complete, and osteotomies were performed.

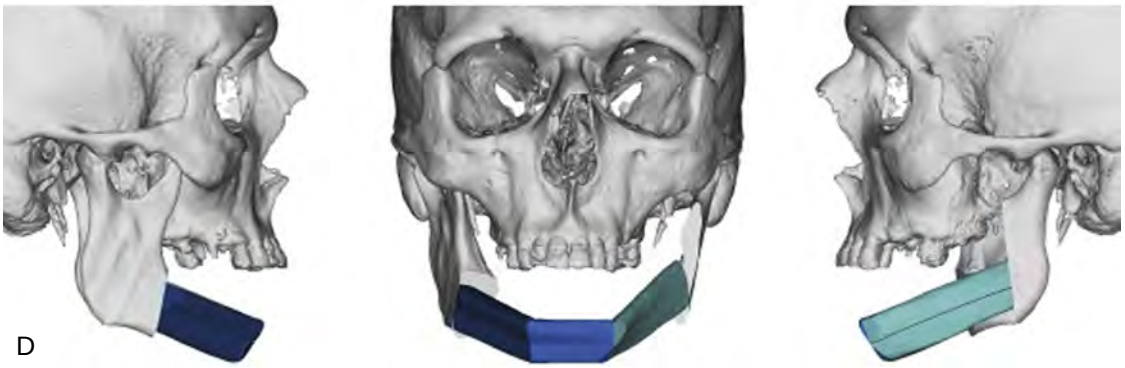
The radial forearm flap was used to reconstruct the tongue first. Next, the pre-bent reconstruction plate was secured using the predictive holes (see Fig. 24.32O). The fibula was then brought up to the head and fitted to the mandible (see Fig. 24.32P-R). Note that intraoperatively the osteotomies replicated the virtual plan very closely from multiple views. The skin paddle was used to replace the mandibular gingiva and floor of mouth (see Fig. 24.32S). A surveillance CT taken later shows excellent approximation of the virtual plan (see Fig. 24.32T).

Final pathology revealed a 3.7 × 3.5 × 3.2 cm moderately differentiated squamous cell carcinoma, negative margins, with lymphovascular invasion, perineural invasion, and bone invasion. Bilateral nodal metastases were identified, with 7 of 64 nodes positive for metastatic cancer, some of the nodes showing evidence of extracapsular extension. He was staged at pT4aN3cM0, Stage IVB with high-risk features.

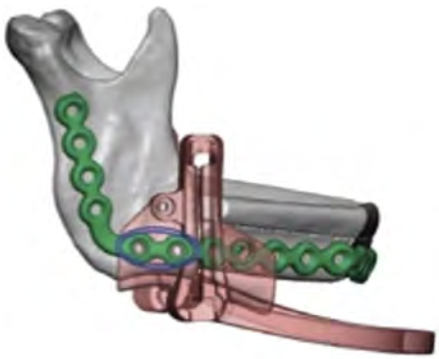
The patient was treated with adjuvant chemoradiotherapy, based on NCCN guidelines. He has been in structured



Simulated postoperative anatomy

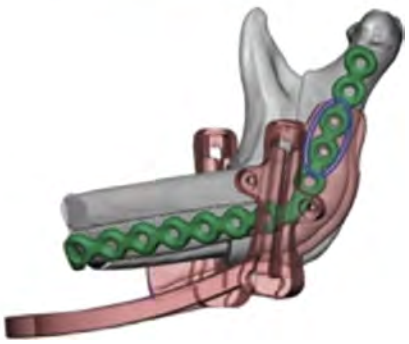


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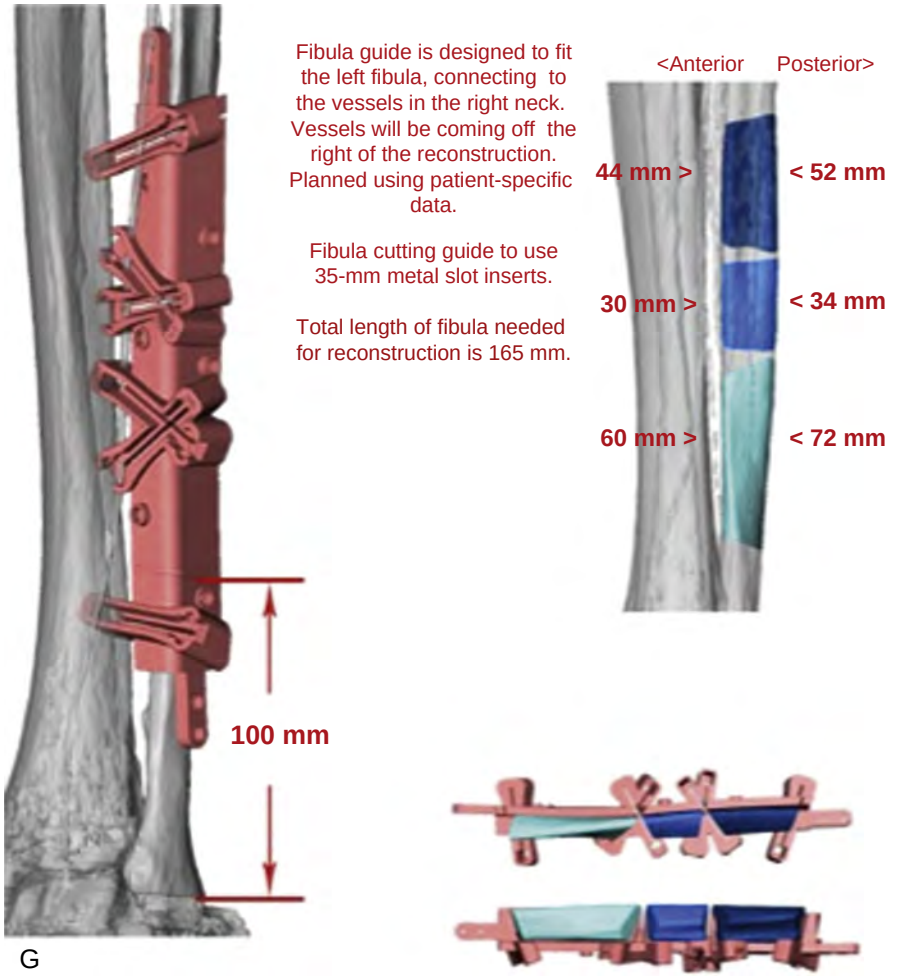
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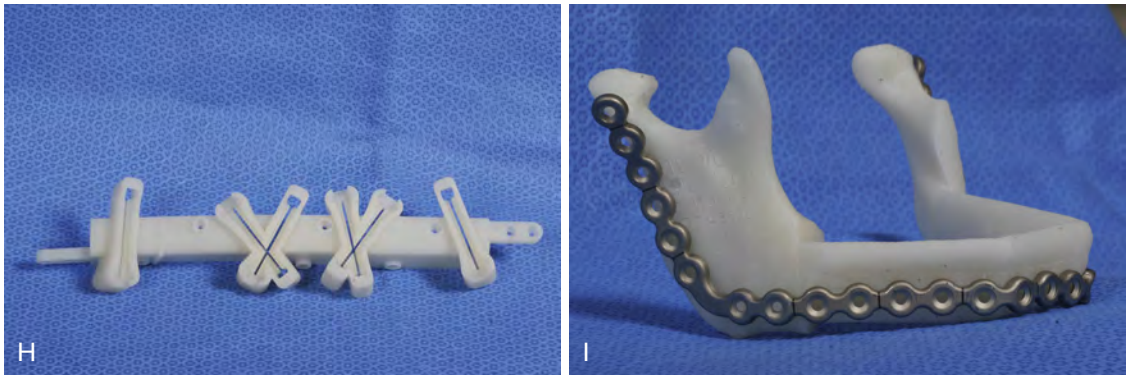


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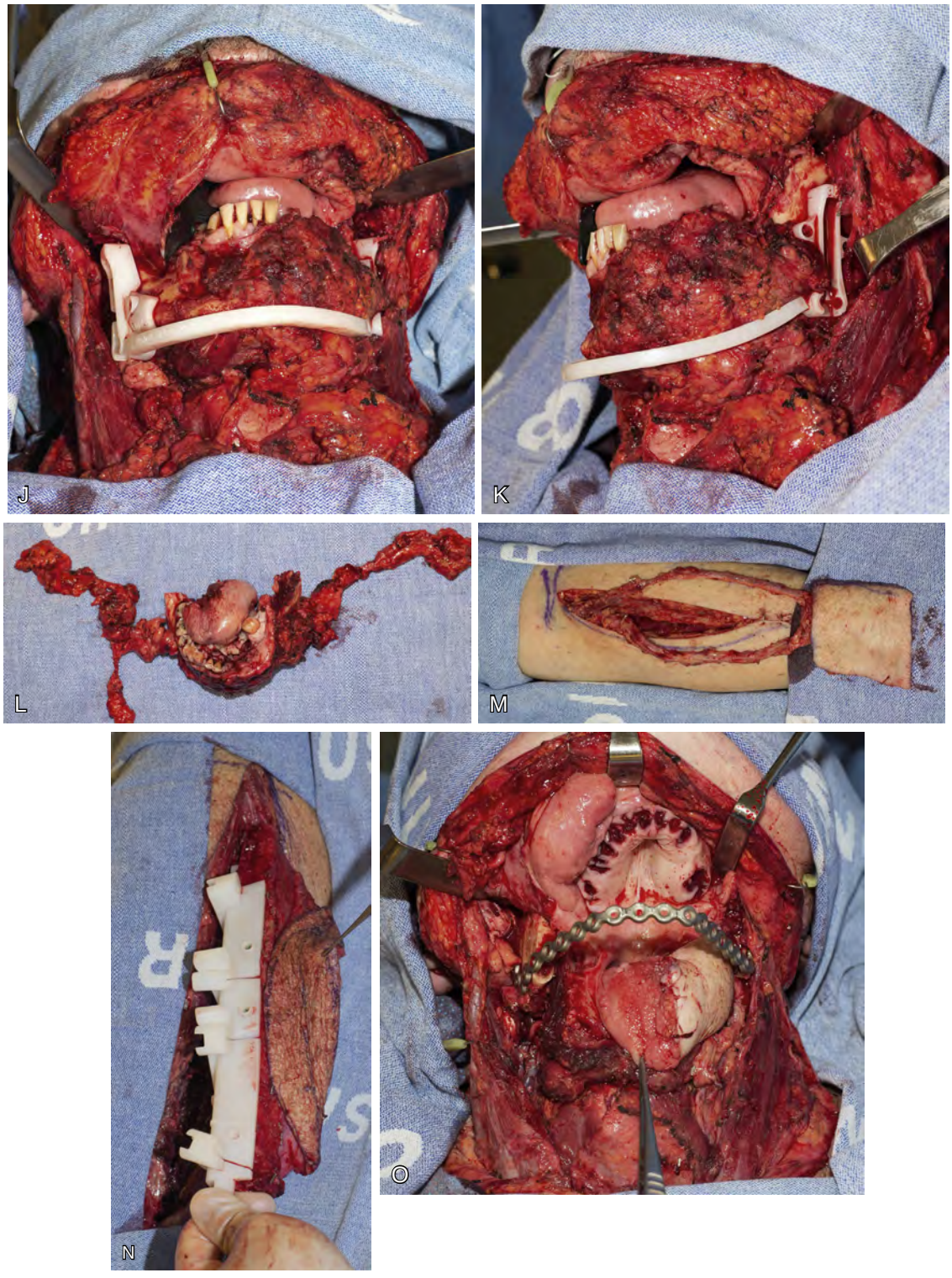
• **Fig. 24.32, cont'd** ***Case C:*** **D,** Virtual Surgical Planning (VSP) images showing pre- and postoperative views of the mandible; **E,** VSP images of the planned mandibular cutting guide. Notice the strut connecting both sides of the cutting guide and the predictive holes. **F,** Mandibular cutting guide. Notice the strut connecting both sides of the cutting guide.

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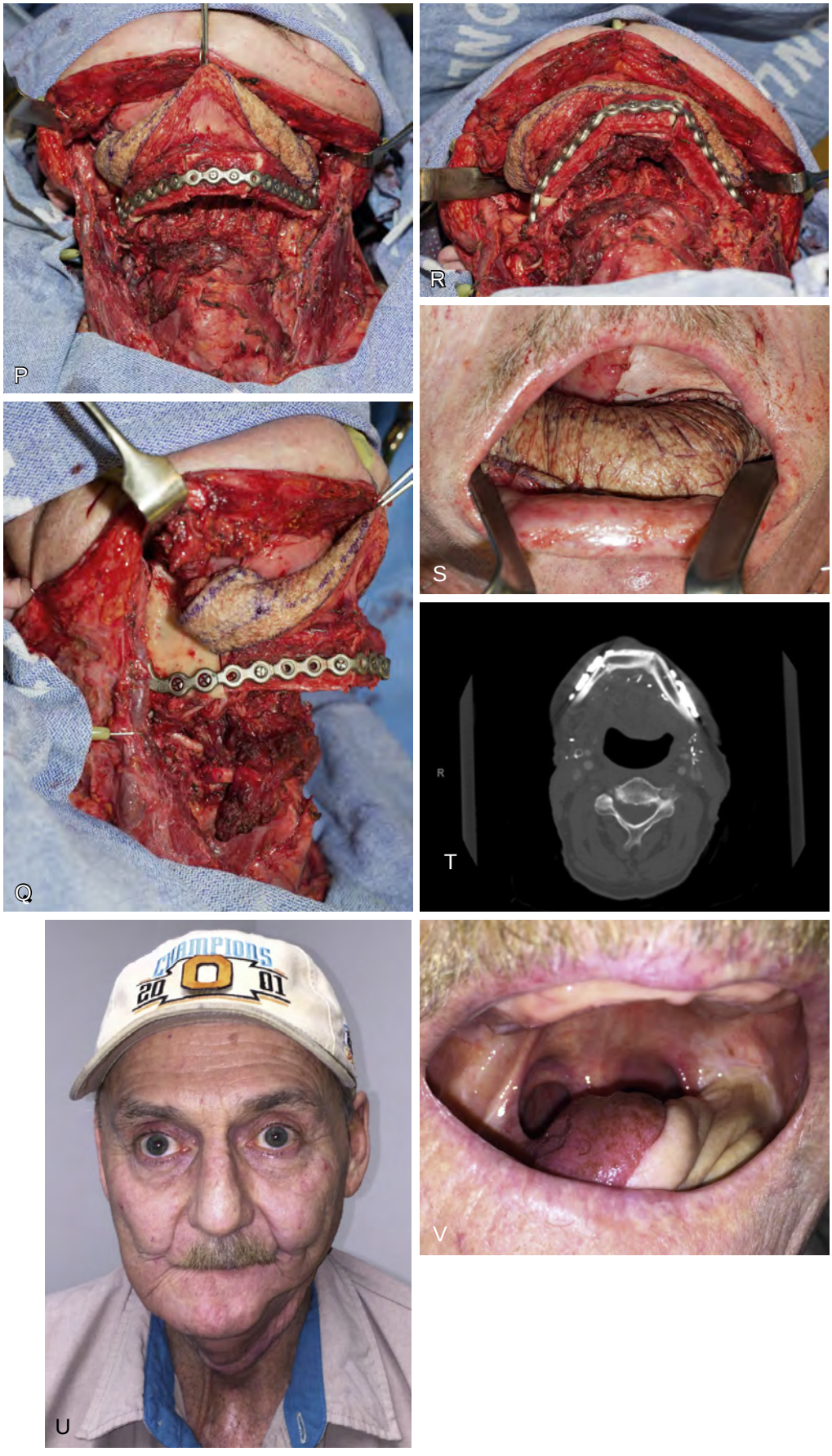


• **Fig. 24.32, cont'd** ***Case C:*** **G,** VSP images of the planned fibula cutting guide. Notice the 10-cm mark denoting the appropriate positioning of the guide relative to the lateral malleolus of the fibula. **H,** Planned fibula cutting guide. **I,** Postoperative model, with reconstruction plate fitted to it. Notice the passive fit of the plate.



• **Fig. 24.32, cont'd** *Case C:* **J,** The mandible with the cutting guide secured, viewed from the front and **(K)** from the left. **L,** En bloc resection specimen of left tongue, floor of mouth, mandible, and bilateral modified radical neck dissections. Notice the large, ulcerated mass that is centered in the left oral tongue and floor of mouth, extends and invades through the left mandible, and encroaches upon the lingual gingiva of the right mandible. **M,** Harvested radial forearm free flap, prior to pedicle division. **N,** Harvested left fibula flap prior to closing osteotomies. Notice the long, elliptical skin paddle that spans the entire length of the fibula. Also notice that the cutting guide is secured to the fibula. **O,** The radial forearm free flap has been used to reconstruct the tongue first. The pre-bent reconstruction plate has not been secured to the remaining native mandible, using the predictive holes made from the cutting guide.

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• **Fig. 24.32, cont'd** *Case C:* **P,** The osteotomized fibula, shaped and adapted to the reconstruction plate, according to the virtual plan, viewed from the front; **Q,** from the right; and **R,** from below. **S,** Intraoral view of the final inset of the fibula skin paddle to reconstruct the mandibular gingiva and floor of mouth. Notice that proper positioning of the bony segment relative to the lip allows for creation of a labial vestibule. **T,** CT with contrast, axial cut, shows excellent approximation of the virtual plan, with good bony contact between fibula segments and the native mandible. **U,** Patient seen 3 years after his initial surgery and completion of his adjuvant chemo-radiotherapy. He now wishes to proceed with dental prosthetic reconstruction. **V,** Intraoral view.

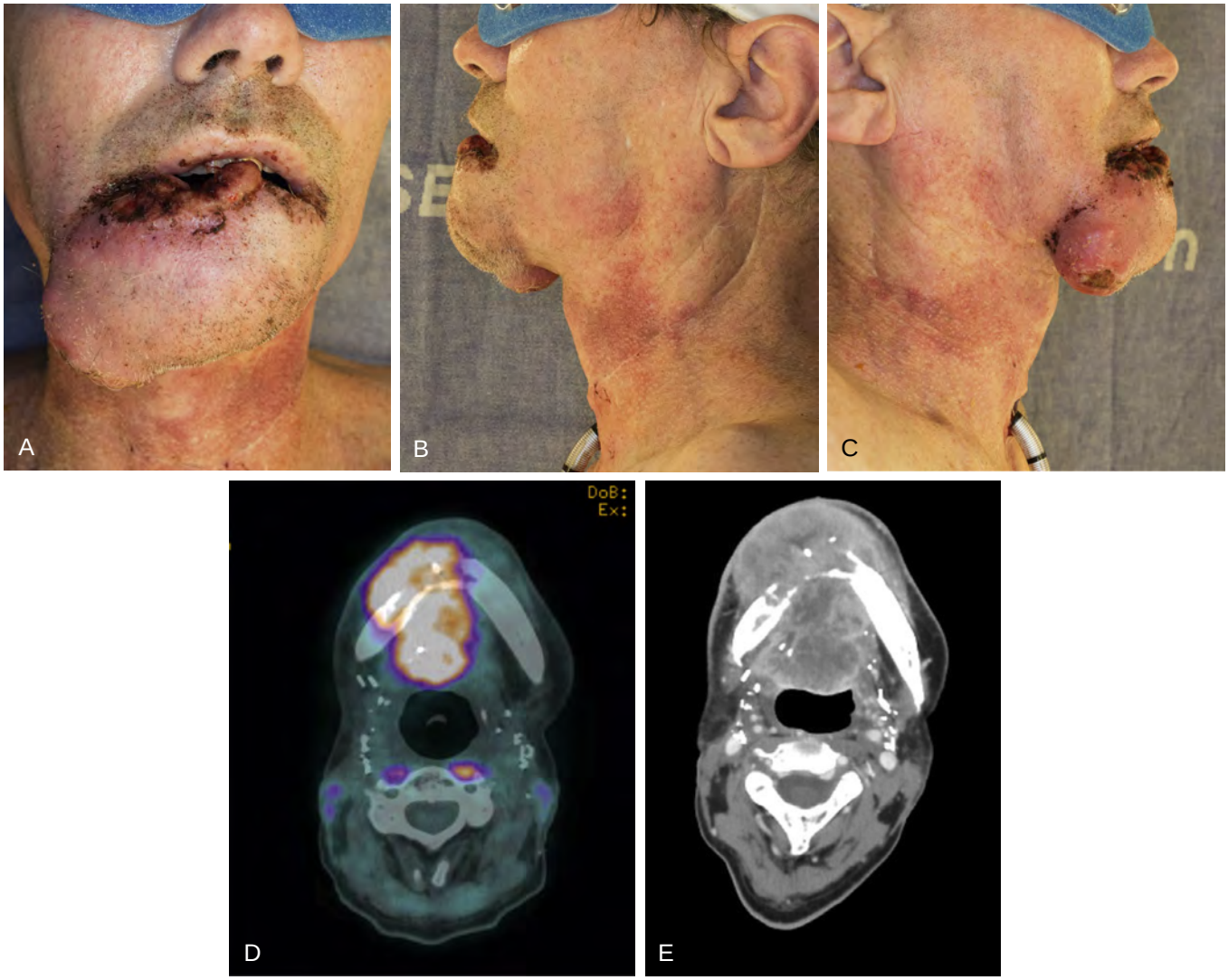
surveillance and has remained disease free for nearly 3 years. He has had relief of his pain, has quit tobacco, and is able to swallow (see Fig. 24.32U,V). He is now beginning prosthetic rehabilitation to replace his dentition.

Case D, Brown Class III Defect, Angle to Angle Resection with Total Glossectomy and Laryngectomy

Patient D (Fig. 24.33) was an unfortunate patient of ours who was plagued with what has been described as "field cancerization," an oral cavity lined with genetically abnormal mucosa fertile for the growth of cancer after cancer. He was a 46-year-old man when he was first seen in our department. At the time of his initial presentation, he was diagnosed with oral squamous cell carcinoma of the tongue. He underwent a partial glossectomy and neck dissection. He was staged as a pT1N2bM0 with high-risk features. He was then treated with adjuvant chemoradiotherapy.

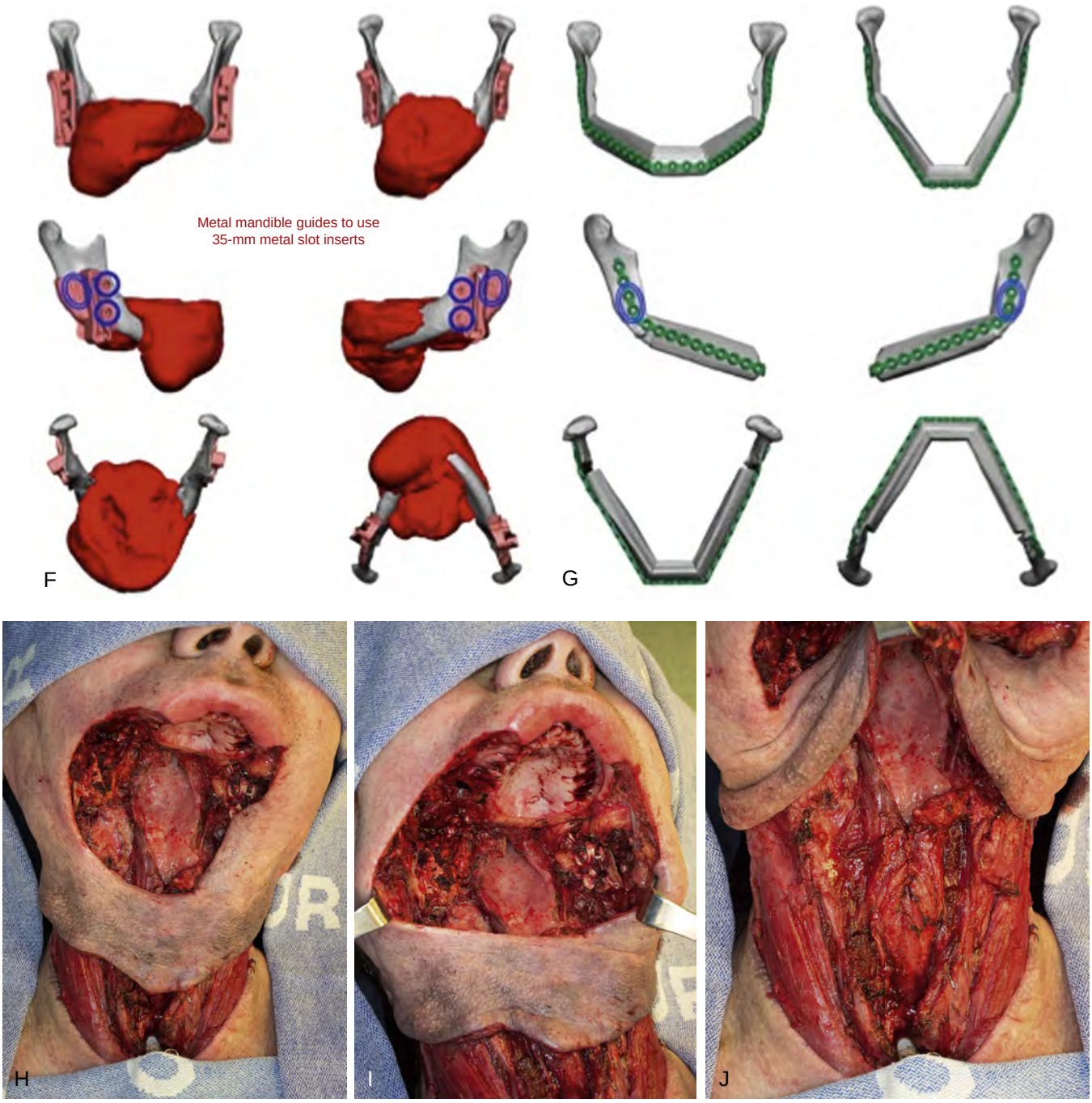
He remained without evidence of disease for 7 years. After being discharged from structured follow-up, he returned with new oral-cavity lesions. Field biopsies revealed new primaries in the mandibular gingiva and floor of mouth. We recommended composite resection of his mandible and floor of mouth. He sought a second opinion, and, at another institution, was offered a partial resection followed by additional radiation therapy.

He was not seen again in our department for another 3 years. During that time, he had completed the partial resection, a second round of radiation therapy, and multiple laser ablations. Physical examination at that time revealed ulcerated erythroleukoplakia that encompassed all of his tongue, his buccal mucosa, his mandibular gingiva, and his floor of mouth (see Fig. 24.33A). Field biopsies were performed that identified squamous cell carcinoma primaries in his left floor



• **Fig. 24.33** ***Case D:*** Recurrent T4AN0M0, stage IVA squamous cell carcinoma of the mandibular gingiva. **A,** Disease progression through palliative chemotherapy and clinical trial immunotherapy, viewed from front, **B,** from left, and **C,** from right. **D,** Positron emission tomography (PET)/CT showing extensive disease progression encompassing the entire tongue, mandible, and chin. **E,** CT with contrast shows degree of bony destruction.

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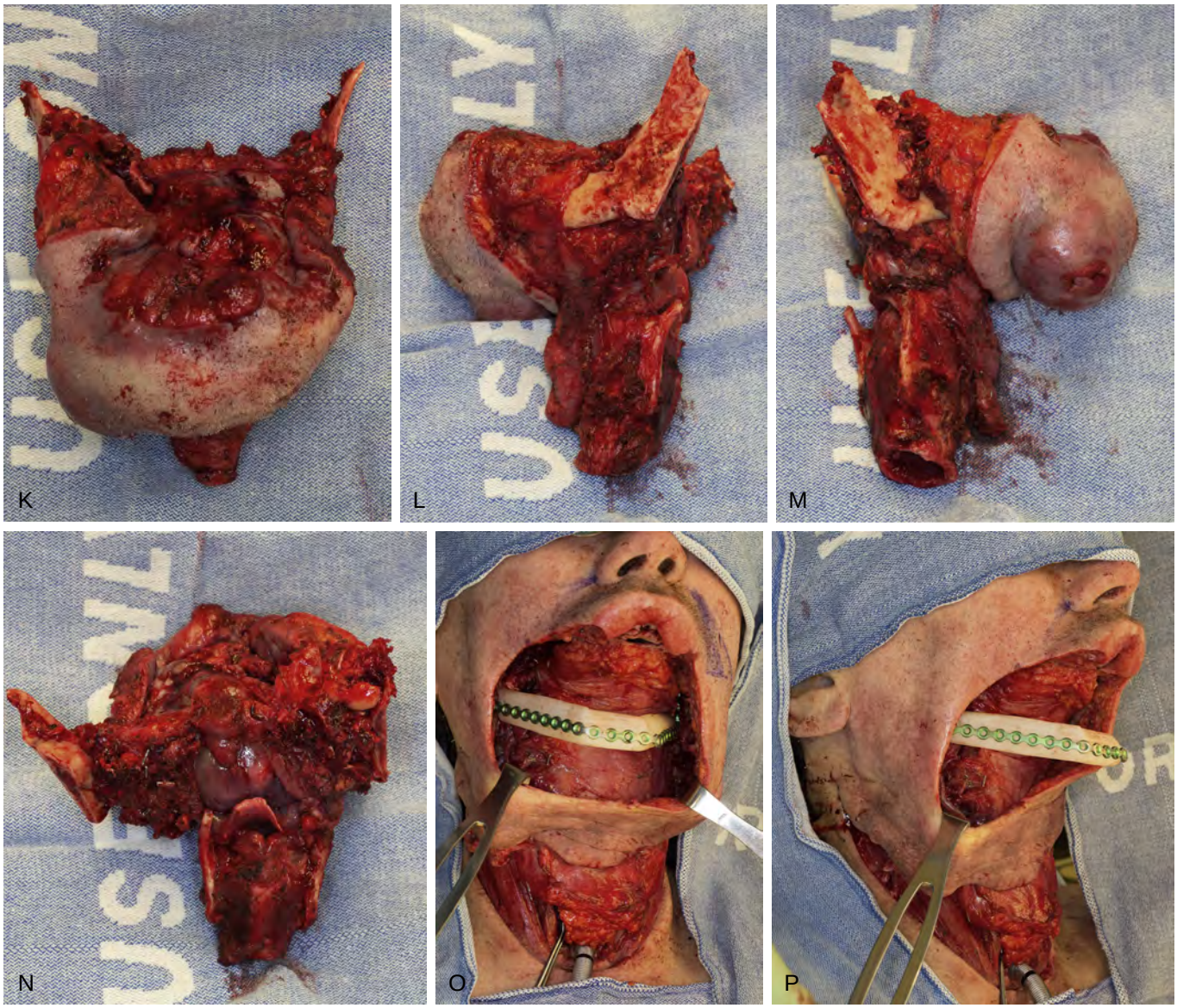


• **Fig. 24.33, cont'd** *Case D:* **F,** Virtual Surgical Planning (VSP) image of the mandible with virtually created tumor. **G,** VSP image of the reconstructed neomandible using the fibula. **H,** The composite defect of total glossectomy, total laryngectomy, bilateral buccal mucosa resection, subtotal mandibulectomy, total lower lip and chin resection when viewed from the front, **I,** below, and **J,** the pharyngeal defect (after pharyngotomy closure) with the cervical flaps retracted superiorly.

of mouth, left tongue, and anterior mandibular gingiva. He was recommended and was treated with a composite resection of his floor of mouth, partial glossectomy, marginal mandibulectomy, and reconstruction with a radial forearm free flap (see Fig. 24.33B,C).

Unfortunately, he developed new primaries in his left lower lip and right mandibular gingiva. He was offered a composite resection with mandibulectomy at that time, but declined. He was started on palliative chemotherapy with 8 weeks of cetuximab to bridge him until we could enroll him into a clinical trial. He progressed during treatment but was able to be enrolled into a clinical trial using a 4-1BB agonist (immunotherapy).

His locoregional disease continued to progress, resulting in constant and unremitting pain. The tumor, at this point, had grown to include his entire tongue, destroyed his anterior



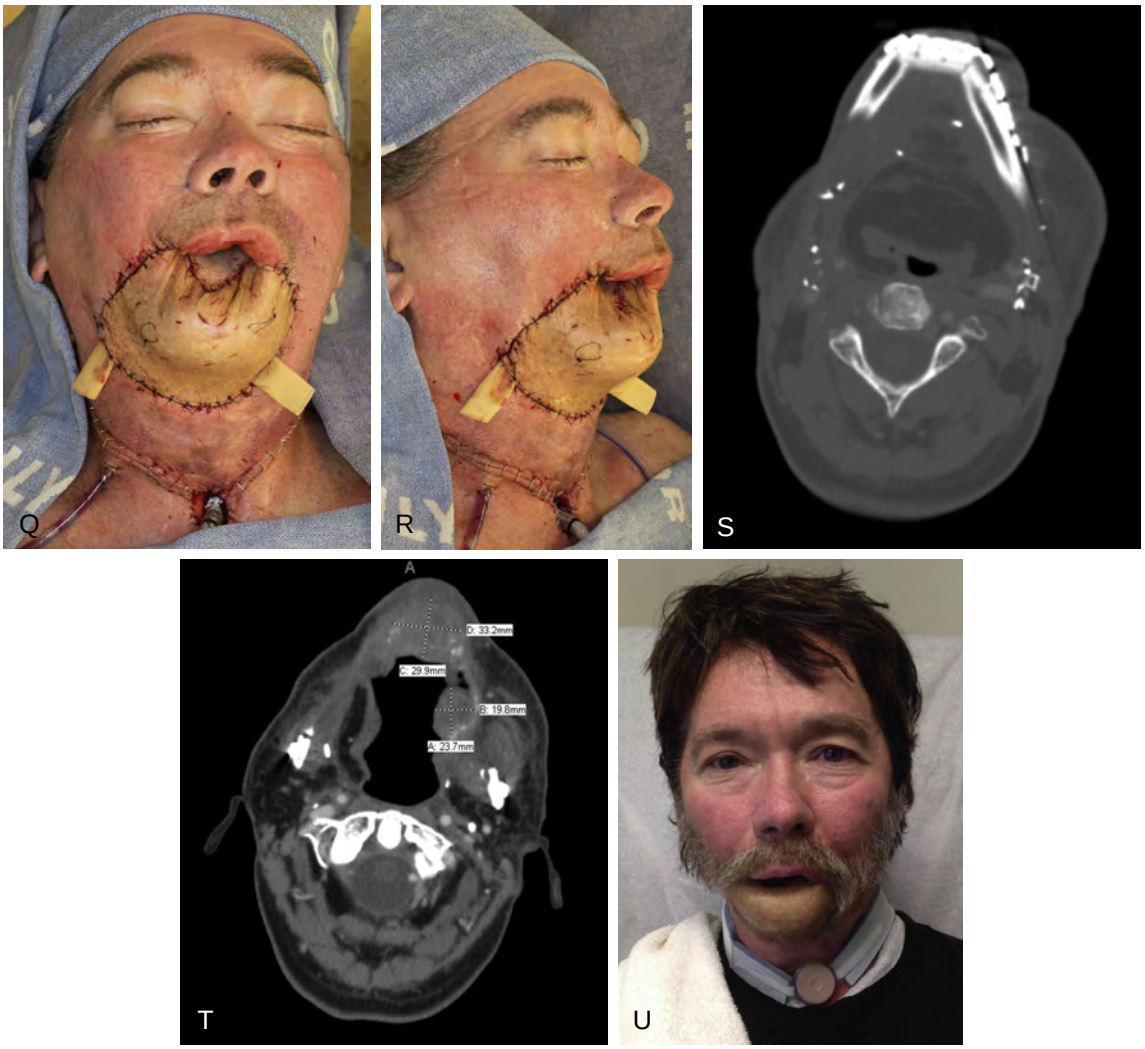
• **Fig. 24.33, cont'd** *Case D:* **K,** The en bloc specimen of total glossectomy, total laryngectomy, bilateral buccal mucosa resection, subtotal mandibulectomy, total lower lip and chin resection when viewed from the front, **L,** the left, **M,** the right, and **N,** posteriorly. **O,** After inset of the anterolateral thigh flap to reconstruct the floor of mouth, bilateral buccal mucosa, and pharyngeal defect, the reconstruction plate is secured to the remaining mandible and the fibula bone graft template is tried in to verify accuracy, viewed from the front and **P,** the right.

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mandible, and invaded into the skin of his chin and lower lip (see Fig. 24.33A-C). A repeat PET/CT scan and CT with contrast were obtained that showed extensive local disease but no evidence of distant metastases (see Fig. 24.33DE).

We recommended salvage surgery in the form of a composite resection including a subtotal mandibulectomy (from angle to angle), lower lip resection, chin resection, total glossectomy, total laryngectomy, and bilateral buccal mucosa resection. This would leave him with a large soft tissue defect, long bony defect, and a permanent stoma. To reconstruct this we recommended using two flaps: a fibula free flap to reconstruct the mandible and soft tissue of the lip and chin and an anterolateral thigh flap for floor of mouth, buccal mucosa, and pharyngeal reconstruction. His case was discussed at our multidisciplinary oral/head and neck tumor board. The consensus agreement was that surgery remained the only viable option for palliation and treatment with curative intent. Hospice was also discussed, but the patient had declined.

A maxillofacial CT using the 3D Systems protocol and a CTA of the lower extremities were obtained. A web-based VSP meeting was scheduled. Our ablative surgeon, reconstructive surgeon, surgical hardware representative, a VSP engineer, and trainees participated. The tumor was virtually highlighted in three dimensions, using data taken from the contrasted scans (see Fig. 24.33F). Using the principle of mandibular subunits, resection of the left body, symphysis, and right body were planned.



• **Fig. 24.33, cont'd** *Case D:* **Q,** The fibula inset to reconstruct the mandible, with the skin paddle replacing the soft tissue of the chin and lower lip, viewed from the front and **R,** the right. **S,** A surveillance CT scan, axial cut, showing good approximation of the virtual plan with strong bony contacts between the fibula segments and native mandible. **T,** CT scan with contrast, axial cut, 3 months after composite resection, showing three new primaries within the maxilla. **U,** Our patient, prior to his death.

Because the previous neck dissection was in the left neck, the right neck was deemed more appropriate for a recipient site. The right fibula was selected so that the skin paddle of the fibula would face externally to reconstruct the skin of the chin. Segments of fibula were designed to replace the left body, symphysis, and right body in sequence (see Fig. 24.33G). Osteotomies were planned through the sigmoid notches on either side.

After the segmental resection had been performed digitally, the right fibula was virtually adapted to the defect. We set the distal osteotomy at 7 cm proximal to the lateral malleolus, which avoided interruption of ligamentous attachments that would lead to ankle instability. Posteriorly, the fibula was set along the inferior border. As the fibula approached the anterior mandible, the height of the fibula was set slightly higher and opposing the maxillary arch. The chin projection was decreased, to avoid problems with soft tissue coverage and closure.

Off-line, surgical cutting guides with predictive holes were designed and printed. Pre- and postoperative models were also printed. A reconstruction plate was adapted to the postoperative models, using the predictive holes. Specific attention was paid to ensuring that the plate fitted passively. The cutting guides, models, and plate were then given to the central processing department at our hospital for sterilization.

The patient was taken to the operating room. He underwent the composite resection of the mandible, chin, lip, total glossectomy, buccal mucosa, and total laryngectomy. The mandibulectomy osteotomies were made according to the virtual plan using the surgical guides. Predictive holes were drilled prior to the resection osteotomies. The extent of the defect is shown in Fig. 24.33H-J, where the lower face, lower half of the oral cavity, and upper airway are now gone. The specimen is shown in Fig. 24.33K-N.

A large anterolateral thigh flap was harvested and used to reconstruct the neopharynx, the tongue/floor of mouth, and buccal mucosa (not pictured). Using the predictive holes, the pre-bent reconstruction plate was adapted to the native mandible on both sides. The fibula template was placed into the defect to verify the appropriate fit and size (see Fig. 24.33O,P).

The fibula was then harvested and secured into a place, using monocortical screws. A large enough skin paddle was harvested to allow for replacing the skin of the chin rolling over to the fibula to join the anterolateral thigh flap (see Fig. 24.33Q,R). The stoma was then matured. A surveillance CT demonstrated good approximation of the virtual plan with excellent bony contact between the fibula segments and the native mandible (see Fig. 24.33S).

Final pathology demonstrated a large (9 cm) well-differentiated squamous cell carcinoma. All of the margins were negative. Extensive lymphovascular and perineural invasion was observed. This primary was staged at pT4aN0M0.

Unfortunately, 3 months later the patient developed three new primaries in the maxilla (see Fig. 24.33T). Shortly after, he developed paratracheal lymphadenopathy. He progressed through additional chemotherapy, which was given in hopes of bridging him to another clinical trial. He succumbed to his disease later that year. However, prior to his death, he was pain free and was able to return to his favorite pastime, golfing (see Fig. 24.33U).

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25

Early Buccal Mucosa Cancer

JONATHAN SHUM, ANGEL BLANCO, SHAN GUO, JOANN MARRUFFO, JAMES C. MELVILLE

Buccal squamous cell carcinoma is an aggressive cancer requiring multimodal treatment due to its high rate of reoccurrence.[1,2] It is relatively uncommon in North America and Western Europe, accounting for only 10% of all carcinomas of the oral cavity[3] (Fig. 25.1). However, it is one of the most common forms of oral cancer in central and Southeast Asia (30%), primarily related to the popularity of chewing tobacco and betel quid (betel nut and slaked lime) in this geographic region.[4] In contrast, tobacco and alcohol use are considered to be the major risk factors for buccal squamous cell carcinoma in the United States.[5] Buccal carcinoma in the United States and Europe is most frequently diagnosed in individuals older than 60 years of age, whereas in studies from India and Taiwan the average age is younger than 50 years.[6]

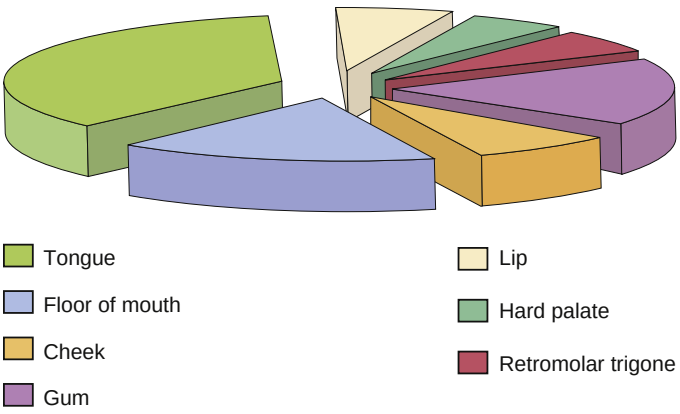
Relevant Anatomy

The buccal mucosa is defined by the epithelium lining the inner surface of the cheeks and lips from the line of contact of the opposing lips to the line of attachment between the alveolar ridge (upper and lower) and the pterygomandibular raphe. The buccinator muscle provides the main structural and functional component of the cheek. This muscle originates from the pterygomandibular raphe as well as from the lateral aspect of the maxillary and mandibular alveolus. The ligamentous raphe separates the buccinator from the superior constrictor muscle, and extends from the hamulus of the pterygoid to the mylohyoid ridge of the mandible. Anteriorly, the buccinator muscle extends to contribute to the orbicularis oris. Lateral to the buccinator is the buccal fat pad, which also extends between the masseter and temporalis muscles. The parotid duct pierces the buccinator muscle and enters the oral cavity adjacent to the second maxillary molar. The buccal mucosa contains approximately 40 cm^2 of mucosal surface on each side of the oral vestibule. Fig. 25.2 illustrates the location of the buccal mucosa within the oral cavity.

This intimate anatomic relationship between the buccal mucosa, buccinators, and buccal space allows for the potential for cancer to progress unimpeded by any anatomic barriers once it penetrates the buccinator muscle. Once into the buccal space, cancer may spread to neighboring intraoral subsites and structures, such as the infratemporal fossae, external skin, and adjacent maxilla and mandible. Involvement of the maxilla, mandible, cheek skin, parotid gland, and lips leads to varied and morbid resections including through-and-through resection of the skin and composite resections of the mandible and/or maxilla resulting in complex defects. Also, tumors of the buccal mucosa may involve multiple subsites, which may lead to ambiguity of the site of origin.[7]

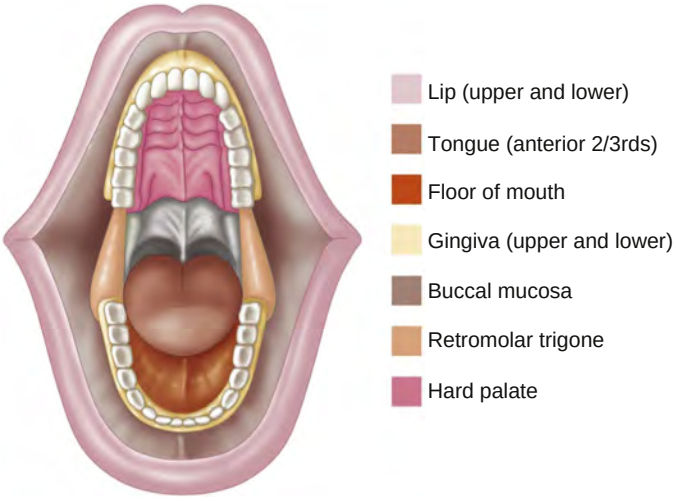
Presentation

Almost half of all leukoplakias are identified on the buccal mucosa, 80.1% of which are microscopically benign and approximately 3.1% are squamous cell carcinoma.[8] Due to the likelihood of benign etiology, leukoplakia of the buccal mucosa can often be ignored by dentists and attributed to trauma such as denture irritation. Buccal carcinoma often presents as an asymptomatic leukoplakia or erythroplakia, often adjacent to the retromolar trigone and third molar region. The common chief complaint for a suspected buccal carcinoma is of an intraoral mass (55%), a non-healing oral ulcer (39%), or intractable pain (28%)[4]



• **Fig. 25.1** Distribution of primary oral cancer sites in the mouth. (From Shah JP, Patel SJ, Singh B: *Jatin Shah's head and neck surgery and oncology.* 4th ed. Philadelphia; Elsevier Mosby, 2012, p 233.)

(Fig. 25.3). Other signs and symptoms include lymphadenopathy and trismus. Facial paralysis and skin ulceration have been reported more commonly in advanced stages, that is, T3 and T4 lesions. Dysfunction of the facial nerve indicates deep invasion through both the buccinator muscle and buccal space, and suggests perineural invasion, an adverse prognostic factor.



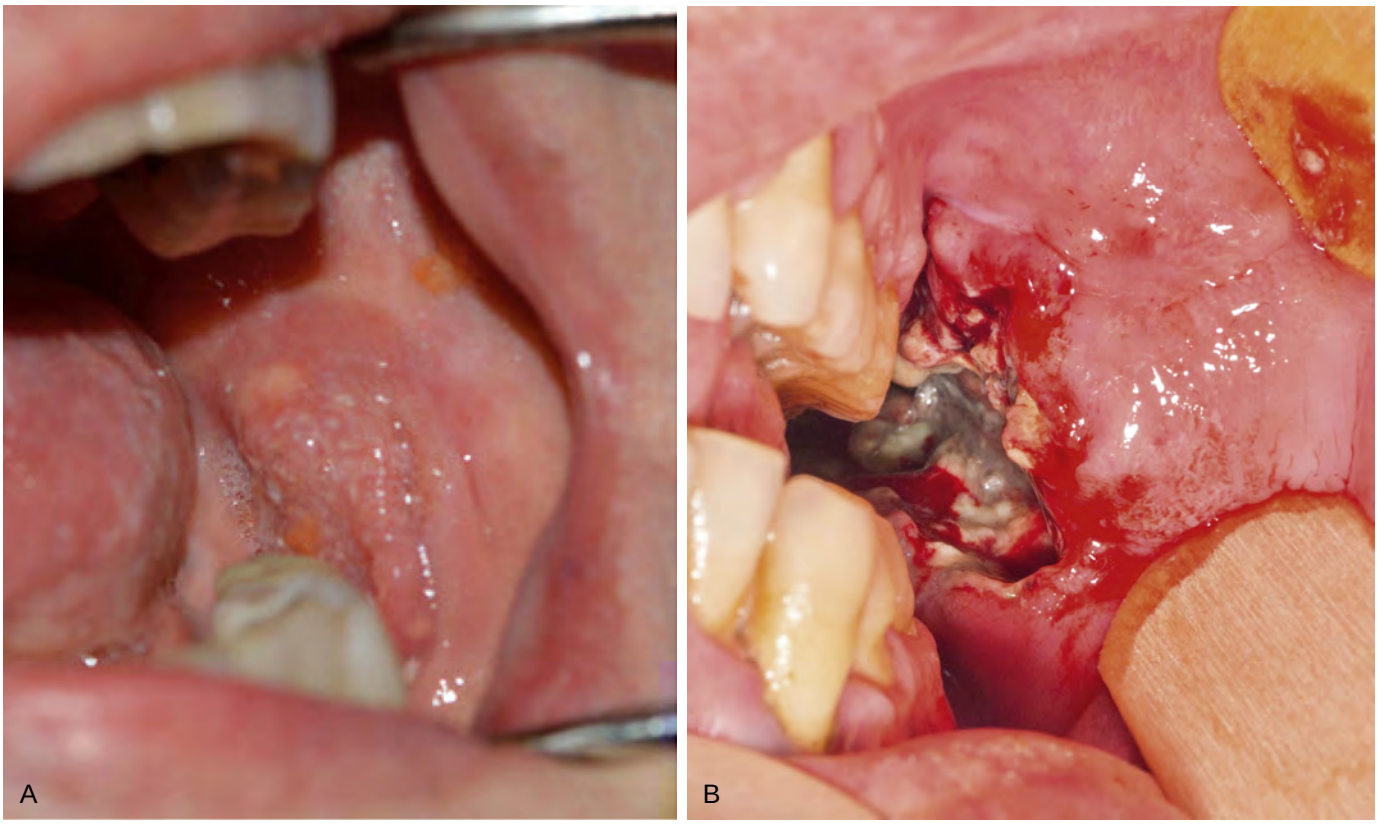
• **Fig. 25.2** Regional anatomy of the oral cavity. (From Shah JP, Patel SJ, Singh B: *Jatin Shah's head and neck surgery and oncology.* 4th ed. Philadelphia; Elsevier Mosby, 2012, p 232.)

Staging

The National Comprehensive Cancer Network (NCCN) outlines the criteria for tumor staging of the buccal squamous carcinoma within the section for oral cavity tumors.

The identification of a biopsy proven squamous cell carcinoma should prompt a thorough head and neck examination with care to obtain the necessary information to complete an accurate staging of the cancer. The clinical examination includes a detailed description of the lesion in terms of location, dimension, texture, and associated symptoms. In terms of staging for buccal carcinoma, the T category requires the greatest dimension of the tumor and is also dependent upon the structures involved by the lesion; for example, the invasion of bone or of adjacent structures such as the external skin would upstage a tumor to T4 regardless of size. The only feature that defines T1 and T2 lesions is based on the lesion's greatest dimension. T1 lesions are less than 2 cm in greatest dimension, and T2 lesions are greater than 2 cm but less than 4 cm in greatest dimension. Fiber-optic evaluation of the larynx and hypopharynx should be considered in the work-up of the patient with traditional risk factors such as tobacco and alcohol use.

Imaging studies further enhance the accuracy of staging due to the ability to evaluate a lesion and their respective lymphatic drainage basins in the neck. Computed tomography (CT) and magnetic resonance imaging (MRI) are ideal



• **Fig. 25.3** **A,** Various patterns of presentation. T2 exophytic squamous cell carcinoma of the buccal mucosa. Note the raised, granular lesion arising from the buccal mucosa. **B,** T2 ulcerative squamous cell carcinoma of the buccal mucosa. On examination this lesion demonstrates ulceration, necrosis, and induration.

for the work-up of T1 and T2 lesions of the buccal mucosa. These two modalities, CT and MRI, provide good soft tissue definition to interpret the dimensions and proximity to vital structures at the primary and regional sites (Fig. 25.4). Image clarity and resolution can be affected by dental hardware and restorations and in some cases can be modified by patient positioning or by the gantry tilt angle to reposition metal artifacts away from the area of interest. The imaging studies should also assess the possibility of bony invasion. Current techniques with CT, MRI, cone beam CT, and positron emission tomography/CT, have high diagnostic accuracy for detection of mandibular bone tissue invasion by squamous cell carcinoma: 83% to 94% sensitivity and 91% to 100% specificity.[9] MRI is the modality of choice if no bony invasion is suspected. It allows for superior soft tissue resolution and can detect the presence of perineural spread.[10] Nodal evaluation is completed by the combination of the physical examination and radiographic findings to determine the number, greatest dimension, and laterality of any suspected nodal disease.

Management Principles and Known Outcomes

Squamous cell carcinoma of the buccal mucosa has traditionally been treated surgically, with postoperative therapy in the forms of radiation and/or chemotherapy reserved for high risk features such as positive or close margins, bone invasion, and late T stage, and if a neck dissection is performed, the identification of nodal disease and extracapsular extension.



• **Fig. 25.4** Axial CT image of a T2 ulcerative squamous cell carcinoma of the buccal mucosa.

A review of the literature on buccal carcinoma demonstrated a predominance of studies from areas of the world where betel nut habits are endemic. These areas include Southeast Asia, with India being a predominant contributor to the current studies. Although buccal carcinoma associated with betel nut usage and cancers occurring in North America are clinically similar, they have been described to have a different molecular pathogenesis. A high-frequency of HRAS mutation is detected in Asian populations associated with betel nut chewing.[11,12] Only less than 6% of HRAS mutations are identified in samples in North America.[13] The tumor suppressor gene, *p53,* is the predominant mutation identified in the tobacco-associated oral squamous cell carcinomas in North America.[14] A comparison between patients at Cancer Care Manitoba, Canada, and Tata Memorial Hospital, India, treated for buccal carcinoma revealed significant differences in 5-year overall survival and disease-free survival of 57.4% versus 80.1% and 42.9% versus 66.4%, respectively.[15] Although the oncogenic pathways may differ between the two types of buccal carcinomas, Pathak and colleagues[15] concluded that the significant discrepancy in the survival outcomes was due to the difference in the age of presentation and not to different biologic behavior.

With regard to NCCN management of buccal squamous cell carcinoma, the initial step is the work-up and clinical staging. Following completion of the medical history and physical examination, the dimensions of the primary tumor are evaluated to determine the T stage of the lesion. T1 lesions are less than 2 cm, whereas T2 lesions are 2 to 4 cm in greatest dimension. Nodal status of N0 denotes no clinical or radiographic concern for regional metastasis. Management strategies for stages I and II include resection of the primary lesion with consideration for ipsilateral neck dissection. If contralateral nodal disease is present, a bilateral neck dissection is indicated. In an N0 scenario, T2 to T4 lesions warrant an elective neck dissection due to the increased risk for occult metastasis. Tumor thickness is the main determinant for an elective neck dissection in T1 lesions. Sentinel lymph node biopsy is an alternative to elective neck dissection for the evaluation of occult cervical metastasis, for which the reported sensitivity is 0.93 and the negative predictive values range from 0.88 to 1.[16-18] The identification of tumor invasion of the buccinator muscle, Stensen's duct involvement, skin involvement, perineural invasion, lymph node involvement, and extracapsular extension are poor prognostic features for which to consider addition of adjuvant therapy. For patients who are not candidates for initial surgical therapy, definitive radiation therapy is a viable option.

Surgical intervention is the preferred initial therapy for T1 and T2 lesions at our institution. In multiple studies examining stage I and II buccal carcinoma, all cases were treated primarily with surgical intervention, with 60% to 80% undergoing a unilateral elective neck dissection and 10% to 35% receiving adjuvant radiotherapy.[3,19,20] Despite aggressive initial therapy, T1 and T2 buccal carcinomas carry a poor local recurrence rate. Despite aggressive initial therapy, T1 and TE buccal carcinomas carry a poor local recurrence rate ranging from 38% to 45%.[3,20,21] Five-year overall survival for T1- and T2-sized tumors was 78% and 66%, respectively.[21]

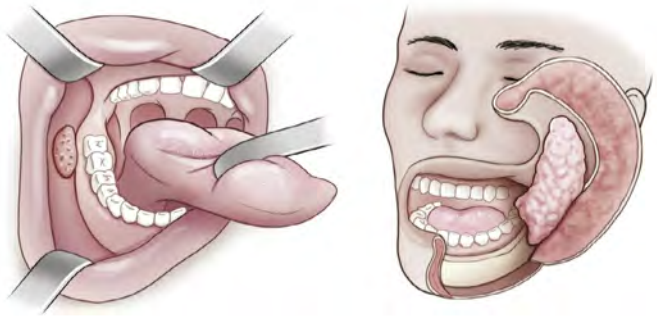
Surgical Management

In preparation for surgery, wide exposure is essential to avoid unnecessary contamination of the wound by unintentional dislodgment of surgical towels that outline the field. If a neck dissection is performed, landmarks of the ipsilateral mastoid tip, clavicle, and midline are necessary. Placement of a nasal endotracheal tube avoids inadvertent damage to the airway circuit and increases the working room for excision of an oral lesion. Care should be taken to ensure there is no pressure over the alar cartilage, eyes are protected, and the anesthesia circuit is padded to prevent pressure sores. Whether to use neuromuscular blockade is surgeon preference. Perioperative antibiotics are administered routinely because access is gained via a combination of transoral and transcervical approaches.[22] Single and combination antibiotic regimens have been studied and recommended for head and neck oncologic surgery.[22,23] Clindamycin and ampicillin-sulbactam are commonly used as sole agents; whereas, cefazolin and metronidazole are administered as a combination.[24,25] Duration for antibiotic coverage is generally 24 to 48 hours after surgery.[26]

Approach

Depending on the extent of the lesion, the approach to surgical resection of squamous cell carcinoma of the buccal mucosa varies. The majority of T1 and T2 lesions of the buccal mucosa can be removed via a transoral access (Fig. 25.5). Common instrumentation to augment this approach is a bite block and mouth prop to maintain the mouth open during the procedure. For buccal lesions above the occlusal plane, a Weber-Ferguson approach may facilitate the removal of a lesion that encroaches onto the maxillary gingiva or bony substructure. A mandibular lip split/cheek flap may also facilitate removal of a buccal lesion that incorporates the inferior half of the buccal mucosa (Figs. 25.5 and 25.6).

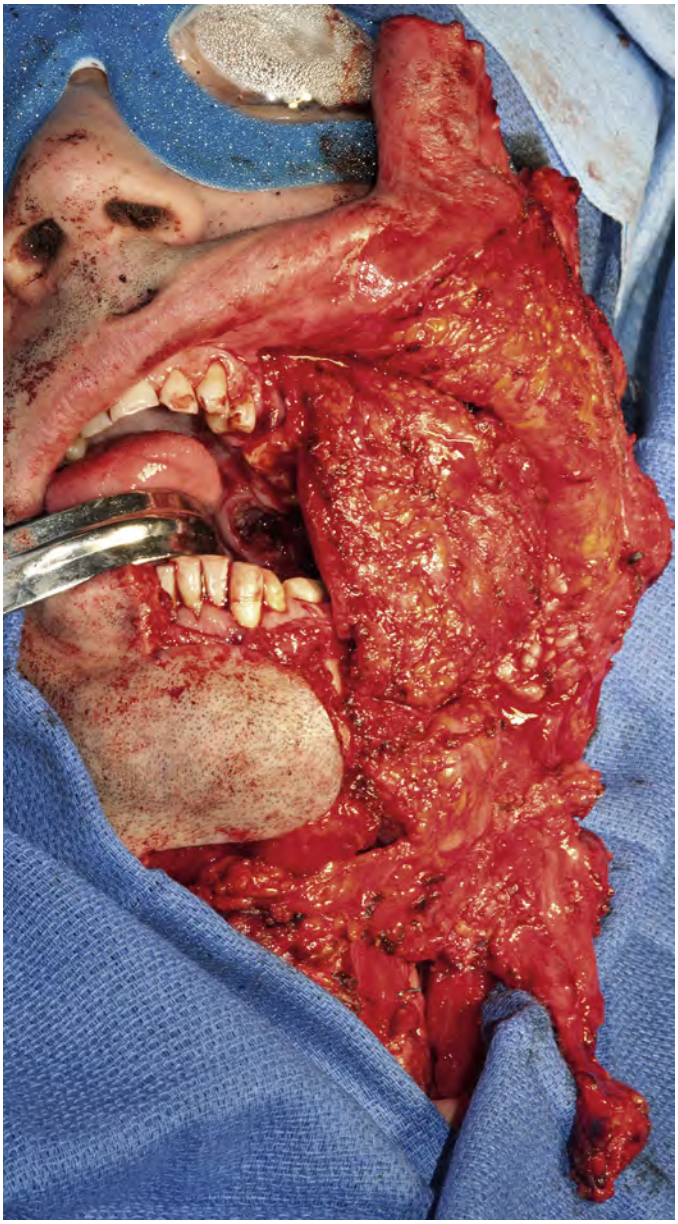
A lip split incision may be performed for larger lesions that prevent adequate transoral visualization of the tumor. Factors such as trismus, microstomia, or posterior buccal location are indications for lip split access. The more common lip split incisions include a midline incision (Roux-Trotter) and a chin crease incision (McGregor), which attempts to conceal the wound around the contours of the chin. In either approach, it is beneficial to create a superficial hash mark along the vermillion border of the lip to facilitate accurate closure. A full-thickness incision through the lower lip is performed and can be extended to the mandible depending on the location of the surgical margins. Closure of the wound is in a layered fashion with care to ensure approximation of the vermillion border.



• **Fig. 25.5** Access procedures. *Left:* Transoral approach. *Right:* Lip split exposure. (Redrawn from Hao S-P, Cheng M-H: Cancer of the buccal mucosa and retromolar trigone, *Oper Tech Otolaryngol-Head Neck Surg* 15:239-251, 2004.)

Management of the Primary

Evaluation of the primary tumor includes both the clinical examination and review of imaging studies. The lesion is first outlined followed by the delineation of the resection margin



• **Fig. 25.6** Clinical photograph of a lip split with preservation of chin pad and exposure of left squamous cell carcinoma of the buccal mucosa.

approximately 1.5 to 2 cm around the primary tumor with care to avoid stretching the mucosa while marking the tissue. An adjunct technique for identifying the extent of lesion is the application of Lugol's iodine. The predominant lining of the oral cavity is non-keratinizing stratified squamous epithelium, which allows for the use of Lugol's iodine to aid in the identification of dysplastic mucosa. In the normal epithelium, the intermediate and superficial layer cells contain glycogen in their cytoplasm. Cancer and dysplastic cells contain little or no glycogen due to the increased glycolysis consequent to a dysfunctional cellular cycle.[27] This observed effect of a higher rate of glycolysis relative to most normal cells is called the Warburg effect.[28] Iodine is glycophilic and forms tri-iodide molecules within glycogen molecules, resulting in a brown staining of normal nonkeratinized oral mucosa. A lack of stain is observed in areas of dysplasia and carcinoma.

The margins surrounding the planned resection are sent for frozen margin analysis. Care is taken to obtain a frozen margin specimen of adequate size, approximately 3 mm in width along the remaining mucosal margin surrounding the resection specimen. The tissue margin is placed on a non-adherent dressing and sent for pathology review with the mucosal surface facing upward for frozen section analysis. This assists the pathologist in the orientation of the specimen. To facilitate the removal of the mucosal margins for frozen section, the posterior margin is obtained first, followed by the anterior margins. When specimens are obtained from the anterior wound margins before the posterior margins, bleeding can be a nuisance.

Several anatomic landmarks should be considered in the resection of T1 and T2 lesions, including the dentoalveolar complex of the mandible and maxilla, Stensen's duct, buccinator, and external skin.

The proximity of the tumor to adjacent bony structures, such as the dentoalveolar complex of the mandible and/or maxilla, should be examined for the presence of erosions in the cortices, which would suggest bony involvement by tumor. Of note, the erosion of the alveolar bone or tooth socket is not sufficient to classify the lesion as a T4 lesion. Medullary involvement of the mandible or erosion into the sinus is an indication for a segmental resection and/or maxillectomy. If the projected resection margin incorporated the mandible/maxillary complex, without identified gross bony involvement, it is possible to consider a marginal resection in order to maintain a 1.5- to 2-cm clear margin. Use of a marginal resection depends on the viability of residual basal bone, with mandibular bone less than 10 mm being an indication for reinforcement with a reconstruction plate. Plate thickness of 2.5 mm and greater are standard for the reconstruction and reinforcement of mandibular defects. The nerves located in this area are generally removed as part of the specimen. These can include the inferior alveolar nerve, buccal nerve, and infraorbital nerve. For lesions with erosion into the maxillary sinus, the sinus lining should be sent as a specimen. The design of a marginal resection should incorporate smooth lines, with an effort to avoid the placement of acute angles that could act as potential sites for stress/strain fractures to occur. The marginal resection will have an anterior boundary commonly requiring the extraction of teeth at the planned osteotomy site. A horizontal osteotomy is performed below the roots of the teeth with special consideration to the amount of residual bone on the mandible. For the mandible, the posterior osteotomy generally travels through the sigmoid notch in a gentle curve. A maxillectomy may require separation of or osteotomy through the pterygoid plates to clear the posterior margin. Osteotomies can be created with a saw blade or fissure burr under copious irrigation. Following the marginal resection, sharp edges are smoothed with a burnishing burr or bone rasp to facilitate healing and closure.

The extent of Stensen's duct involvement should be considered in the tumor resection. If the resection margin violates the duct orifice without significant involvement of the length of the duct, it is possible to truncate Stensen's duct at the resection margin and to perform a sialodochoplasty following frozen margin analysis. Sialodochoplasty allows one to reposition the duct into uninvolved mucosa. The duct can be spatulated and secured to the mucosa with a non-resorbable suture, such as 6-0 nylon. The alternative is to clip the duct and to chemo-denervate the parotid gland, for example, with Botox injections.[29] Without ligation of Stensen's duct, it is common for sialoceles to develop, which may compromise reconstruction of the resection defect and result in a salivary fistula.

The buccinator muscle is a significant landmark for lesions of the buccal mucosa, in that 60% of superficial cancers that do not clinically appear to involve the muscle actually do have muscle involvement.[30] T1 lesions identified as superficially invasive squamous cell carcinoma, that is, those thinner than 3 mm, have a low potential for violation of the buccinator muscle, and generally the deep surgical margin will spare the muscle. Studies have demonstrated no significant reduction in survival by preserving the buccinator when the tumor thickness does not grossly violate the submucosal layers.[31] In contrast, T1 lesions more than 3 mm thick and T2 lesions should be resected to include the buccinator muscle as a deep surgical margin. It is believed that the buccinator is an anatomic barrier for the containment of cancerous cells, and the risk of local recurrence is increased when the buccinator demonstrates signs of invasion by cancer. Penetration of the buccinator potentially places cancer cells into the buccal fat pad, enabling spread via unpredictable patterns in this area that has no significant anatomic barriers. This aspect of buccal carcinoma is believed to contribute to the increased risks of local and regional recurrence.

The external skin should be examined for the possibility of tumor involvement, which would manifest as induration and lack of mobility of the subcutaneous and skin layers. These features indicate the necessity for a full-thickness resection of the buccal mucosa and cheek. Lesions that encroach on 1 cm of the oral commissure risk development of microstomia because involvement of the lip results in contracture and immobility of the lip and mouth movements.

The buccal artery is generally encountered for lesions of the buccal mucosa and should be ligated to prevent postoperative bleeding. Branches of the facial nerve are situated along the lateral aspect of the buccinator and effort to salvage the nerve

may be considered if there is no dysfunction of the nerve or no suggestion of clinical tumor invasion.

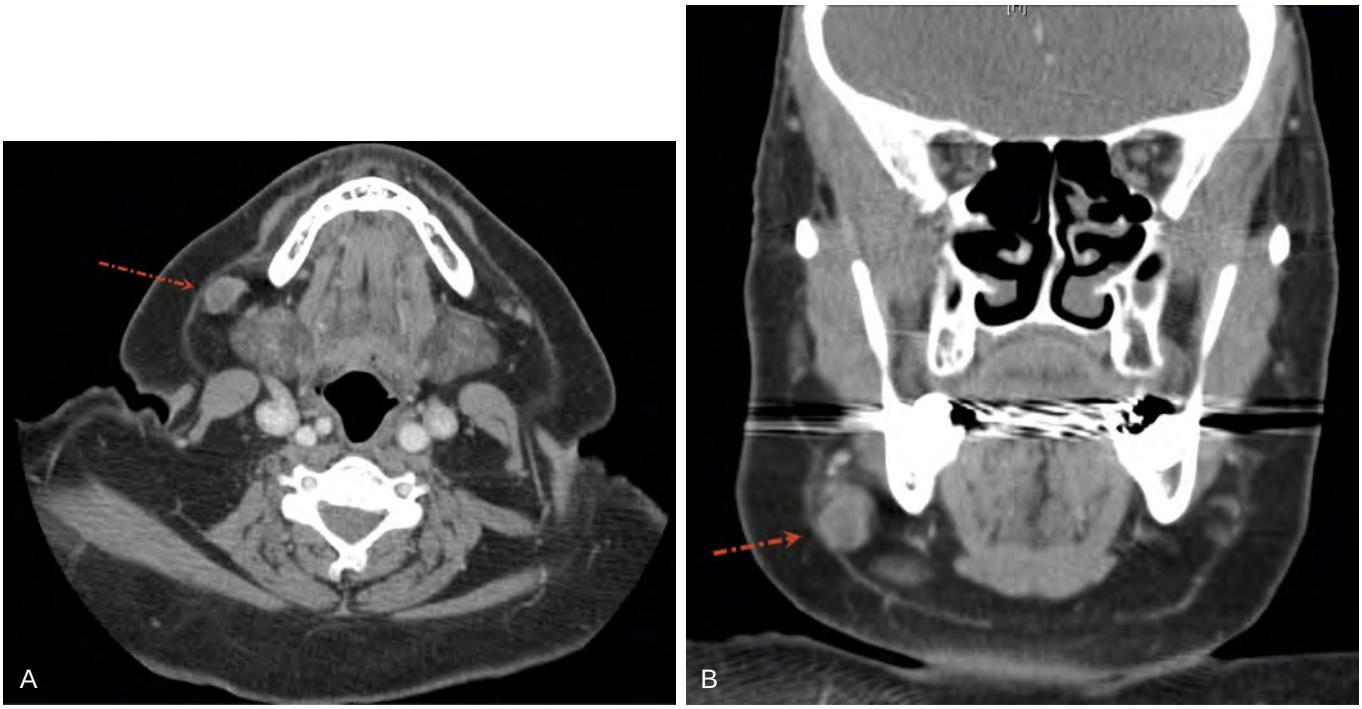
Management of the Neck

Management of the neck is based on the likelihood of occult metastasis in lesions staged T1 and T2. Patients with a clinically negative N0 neck are indicated for neck dissection if the primary buccal lesion is of T2 to T4 size. With T1 lesions that are less than 2 cm in greatest dimension, the most accessible predictor of occult metastasis is tumor thickness.[21,32] Current literature has defined this feature to be an established predictor for occult metastasis in the oral cavity for the tongue and floor of mouth. Due to limited data on cancers of the buccal mucosa, recommendations are generally extrapolated from studies of more common subsites such as the tongue. Debate exists regarding the threshold for an elective neck dissection: lesions less than 2 mm thick are commonly observed, and lesions thicker than 4 mm are generally indicated for elective neck dissection. These thresholds vary among institutions and range from greater than 3 mm to 5 mm.[21,32] Additional features with a strong association to tumor aggressiveness and propensity for occult metastatic spread include the identification of tumor budding, presence of perineural invasion, pattern of the infiltrating front, and poorly differentiated tumors.[21,32-34]

Patterns of lymphatic drainage that commonly filter to levels I, II, and III of the neck are well described for the oral cavity.[35,36] Lesions of the buccal mucosa adhere to these described general patterns, with the addition of having predictable ipsilateral drainage and being less likely than cancers of the tongue to develop skip metastasis.[37,38] In an N0 neck with T1 or T2 lesions, the supraomohyoid neck dissection at levels I, II, and III are commonly completed and sufficient for node sampling. The presence of nodal disease by clinical or radiographic examination would indicate the need for a selective neck dissection or modified radical neck dissection whereby structures that are not adjacent to or involved in the nodal disease are preserved. Fig. 25.7 highlights the identification of nodal disease in level Ib from an ipsilateral T2 squamous cell carcinoma. In bulky nodal disease, a radical neck dissection may be needed to remove gross disease when the internal jugular vein, spinal accessory nerve, or sternocleidomastoid muscle cannot be separated without disruption of the nodal disease.

Reconstruction

Reconstruction for T1 and T2 buccal carcinoma resection defects falls into three categories that include primary closure via local flap advancement, non-vascularized grafts, and microvascular free tissue transfer. Lesions of T1 size are generally amenable to primary closure. Local regional flaps can be raised or mucosal margins undermined to obtain tension-free closure. Buccal fat pad advancement is commonly obtained because resection alone can draw out the buccal fat pad lobules. Gentle dissection and guidance can delivery the fat pad to cover areas of the buccal mucosa for wound coverage. The buccal fat pad has five lobes with a rich vascular supply for a reliable source for wound coverage. It is a delicate structure and meticulous care is required to ensure the blood supply is not disrupted or fat lobules and septae are not separated when



• **Fig. 25.7** **A,** Axial CT image of nodal disease associated with a T2 squamous cell carcinoma of the buccal mucosa. *Arrowhead* points to the level Ib regional metastasis. **B,** Coronal CT image of nodal disease associated with a T2 squamous cell carcinoma of the buccal mucosa. *Arrowhead* points to the level Ib regional metastasis.

manipulating the tissue into the desired location. The use of the buccal fat pad as an oncologically viable reconstruction platform for buccal mucosal defects has not demonstrated an increase in local recurrence compared with alternative means of reconstruction.[3]

Skin grafts can be used to reline the resection wound, most commonly for superficially invasive carcinomas. Even with the loss of the buccinator muscle, the underlying buccal fat pad and/or subcutaneous tissues of the face are rich in vascular supply and collaterals and can support a graft. Common practice is to obtain a split-thickness skin graft of 0.015 to 0.018 inches, ideally from the upper thigh. This graft would be applied directly onto the wound bed and secured with chromic gut suture to eliminate dead space. A bolster is placed to ensure direct contact of the graft to underlying tissue.

Microvascular free flap reconstruction is also a viable option in areas of the buccal mucosa. For T2 lesions, resections involving only soft tissue are reconstructed with fasciocutaneous or myocutaneous flaps. The radial forearm fasciocutaneous free flap would serve this purpose well in that it is a relatively thin and pliable soft tissue reconstruction that can reline the buccal mucosal defect if the buccinator muscle is removed. In reconstruction of the anterior buccal mucosa in which the commissure of the mouth is compromised, the radial forearm flap can include the harvest of the palmaris longus tendon to suspend the corner of the mouth for improved lip competence and symmetry. Alternative donor sites include lateral arm, ulnar, and anterior lateral thigh free flaps. In a mandibular discontinuity defect, the fibula osteocutaneous flap would provide bony and soft tissue reconstruction. Vascular anastomosis is commonly completed between the facial artery and vein, with the vascular pedicle delivered into the neck on the medial or lateral aspect of the mandible.

Complications

Complications encountered in the resection of T1 and T2 buccal carcinomas include collateral injuries that occur as a result of cancer resection or that occur secondary to wound healing. Collateral damage can include injury to the terminal branches of the facial nerve, specifically the marginal mandibular branches, and the buccal branches. Marginal mandibular branch weakness manifests as a lack of animation for the depressor muscles of the lower lip, depressor anguli oris, depressor labii inferioris, and mentalis. The buccal branch of the facial nerve innervates the buccinator, levator labii, anguli oris, and orbicularis oris. Resection margins can also affect drainage of saliva from Stensen's duct, accessory ducts, and the parotid gland, which may create salivary leaks, fistulae, and sialoceles.

Late complications such as wound contracture of the buccal mucosa can lead to trismus if portions of the posterior buccal mucosa are resected and become fibrotic. Trismus induced by surgical fibrosis can be improved with vigorous jaw stretching and physiotherapy. Oral appliances can be used to help facilitate mouth opening. Oral incompetence and microstomia may result if the lesion involves the anterior buccal mucosa or oral commissure.

Fracture of the residual mandible may result after marginal resection if insufficient bone remains without adequate support. A reconstruction plate can reinforce residual mandible bone if the bone is less than 10 mm in height. Care is taken to design a marginal resection with curved osteotomies to avoid sharp angles in the native mandible because these are areas of stress and tension, and can propagate a fracture more readily than with curved line angles.

Radiation Therapy

General Principles

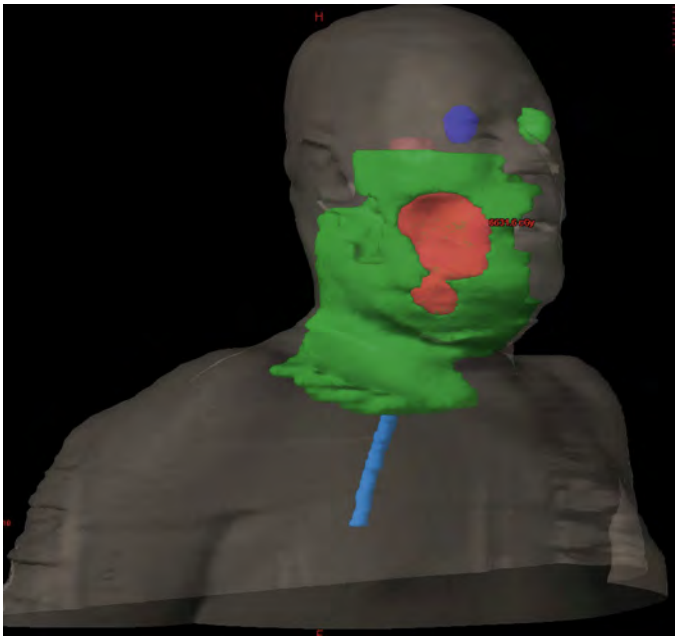
Radiation therapy is the therapeutic application of ionizing radiation to treat cancer by damaging the DNA necessary for cellular functions. It is an effective modality for the treatment of oral cavity carcinomas such as the location on the buccal mucosa and can be used as a single definitive treatment alone or more commonly after surgery with or without the addition of chemotherapy. With respect to T1 and T2 lesions of the buccal mucosa, radiation treatment is reserved as additional treatment following surgical resection. Indications for postoperative radiation include positive margins, bone involvement, perineural invasion, poor histologic differentiation, multiple nodal involvement, and extracapsular spread. Application of radiation therapy as initial treatment for T1 and T2 buccal cancer is reserved for patients who choose the treatment or for those who would not be able to tolerate surgical intervention because of medical comorbidities or instability. Although radiation therapy is effective, it is associated with a significant acute and late toxicity profile, including dehydration, dermatitis, fatigue, osteoradionecrosis, fibrosis, xerostomia, mucositis, dysphagia, weakness, and relative prolonged treatment time.

Treatment strategies correspond to guidelines defined by the NCCN. Surgery is generally indicated as initial therapy for T1 and T2 buccal carcinomas. Indications for adjuvant therapy are dictated by the final pathologic analysis, and in the absence of adverse histopathologic features there is no requirement for radiation therapy. Adjuvant treatment in the form of postoperative radiation therapy alone is the identification of additional high-risk features, such as one positive lymph node in the absence of extracapsular spread. The presence of multiple adverse features such as extracapsular spread, positive margin, and perineural invasion would be considered for the combination of radiation therapy and chemotherapy. Re-resection is attempted if a positive margin is resectable. An ipsilateral neck dissection is completed as part of the resection in all T2 lesions and in select T1 lesions based on tumor depth. Radiation is typically completed bilaterally with a decreased dose to the contralateral site, although unilateral radiation therapy is sometimes offered.

After receipt of final pathology results, it is prudent to facilitate the recovery of the patient from surgery and to ensure the wounds are adequately healed for adjuvant therapy. The overall treatment time—surgery plus indicated adjuvant treatment—should be completed in less than 100 days. Studies have demonstrated improved tumor control and survival when radiation therapy begins within 6 weeks of surgery.[39,40]

Imaging for Treatment Planning and Setup

Intensity modulated radiation therapy is used at the authors' institution and in preparation for radiation therapy; mouth guards are fabricated to protect areas of the jaw or non-target tissues from collateral radiation. Planning and treatment are done with the patient in a consistent supine position; a custom thermoplastic mask and the aforementioned mouth guard help with immobilization. The planning CT scan is conducted with intravenous contrast and using a multislice CT scanner and 2.5-mm slices. Information gathered from the final pathology report, surgeon, and preoperative and postoperative imaging is considered when the radiation oncologist completes the target volume delineation. Targeting is completed through axial CT images and three-dimensional reconstruction, and care is taken to protect vital structures in the field to limit complications associated with radiation treatment (Figs. 25.8 and 25.9).

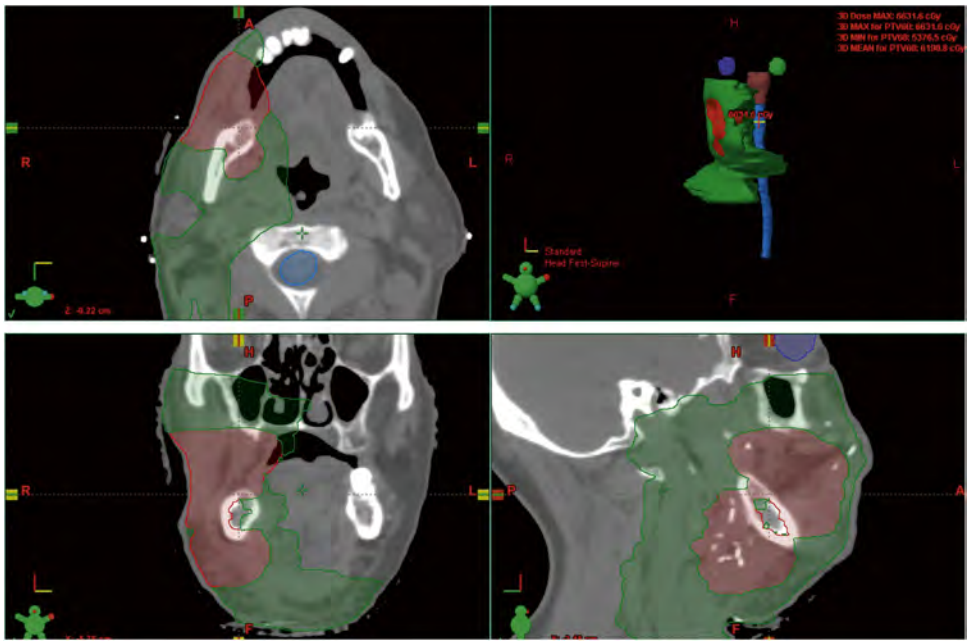


• **Fig. 25.8** Three-dimensional representation of target volume for a primary buccal carcinoma and regional sites. Red shading outlines target zone of primary surgical bed and area of detected nodal disease.

The indication for radiation therapy in T1 and T2 buccal cancers is based on the identification of high-risk factors of the primary tumor; these include close and/or positive margins, perineural invasion, lymphovascular invasion, and cellular differentiation. Following discussion by the multidisciplinary tumor board, the decision for adjuvant therapy is commonly made because buccal carcinoma is notorious for increased risk for local regional recurrence.

The typical radiation dose prescribed for the postoperative bed and the dissected neck is 60 Gy (2 Gy/fraction) in 30 fractions. Low-risk sites, such as the contralateral neck, receive a minimum of 54 Gy in 30 fractions. High-risk sites, such as extracapsular spread and/or focally positive surgical margin, would receive 66 Gy in 33 fractures.[41] Fig. 25.10 outlines the dose-volume histogram that summarizes radiation dose at vital structures of the head and neck.

Adaptive radiotherapy is used in treatment of buccal carcinomas to provide accurate and optimal treatment delivery, in addition to limiting collateral injury during the course



• **Fig. 25.9** Radiation therapy treatment planning with CT imaging. Post-resection CT images in the axial *(top left)*, coronal *(bottom left)*, and sagittal *(bottom right)* planes with outline demonstrating planned treatment dosage. Red areas will be treated with approximately 66 Gy; included is the area of the primary buccal carcinoma and associated regional lymphatic basin with nodal disease. *Top right* window demonstrates three-dimensional reconstruction of planned target volumes.

of adjuvant treatment. Multiple factors can alter the anatomy upon which an initial radiotherapy plan is established. These factors include postoperative edema and fluctuations in weight. Following surgery, the surgical bed can undergo significant changes, generally involving postoperative edema followed by a reduction in edema as tissues recover. Microvascular reconstructions can place a combination of tissues into the recipient site, and the properties of those tissues dictate the amount of contraction and volume loss to be expected. For example, bone and adipose tissue generally demonstrate less significant volume loss compared with muscle. Fluctuations in weight are also a significant factor in postoperative anatomic changes because one's diet is generally limited by access via the oral cavity and/or dependence on a percutaneous gastrostomy tube. Also, tumor response to radiotherapy leads to deviations from the initial treatment plan.

These concepts have led to the practice of adaptive radiotherapy, which is generally applied to all sites of the head and neck, including buccal mucosa. Indications for replanning include greater than 10% weight loss from initial planning and immobilization issues, such as an ill-fitting radiation mask. Replanning is scheduled about halfway through treatment, in the 20- to 30-fraction period. Treatment response specifically in buccal carcinoma sites has demonstrated an apparent anterior migration of the parotid gland toward the high-dose radiation field. With adaptive radiotherapy, the amount of excess radiation to the parotid glands can be controlled and thereby reduce the effects of xerostomia.[42] Without replanning, treatment sequences have been shown to significantly reduce doses to target volumes and increase doses to critical structures.[43]

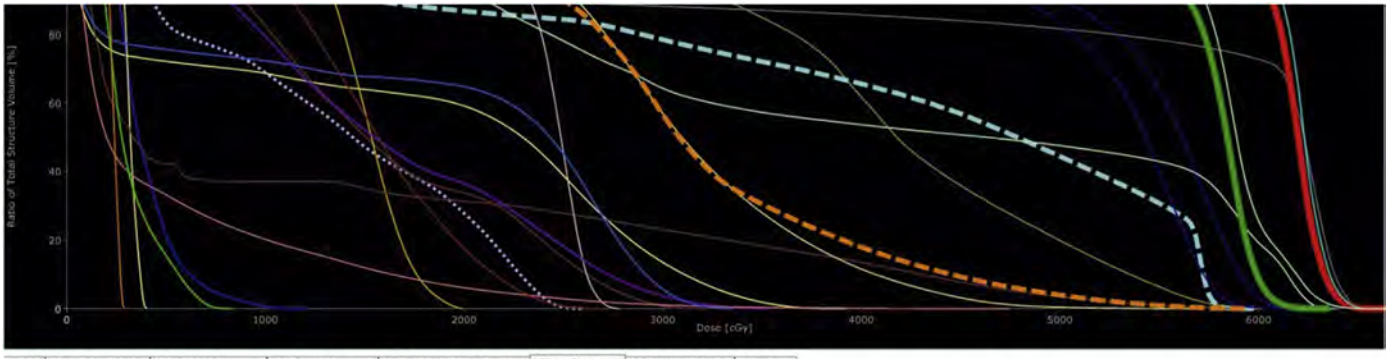
Complications

General complications associated with radiation therapy to the oral cavity include mucositis, radiation-induced fibrosis, radiation caries, osteoradionecrosis, xerostomia, radiation dermatitis, fatigue, and delayed wound healing.

Radiation-induced complications more common to the buccal carcinoma include radiation-induced fibrosis leading to trismus, osteoradionecrosis, and xerostomia.

A thorough oral examination should be done by a dentist and all questionable dentition should be extracted due to the significant dose of external beam radiation (>60 Gy) and associated risk for osteorradionecrosis. Patients are also fitted for fluoride trays and consulted on effects of radiation mucositis, xerostomia, and overall oral health. Radiation-induced trismus is another morbidity associated with the treatment of buccal squamous cell carcinoma. If the trismus is due to tight and resilient mucosal fibrosis in the tonsillar and/or retromolar areas (typically the pterygoid musculature), a significant increase in opening may be achieved by excising this tissue and replacing it with a viable skin paddle from either a myocutaneous or a free microvascular flap. Modest gains can be achieved with bilateral coronoidectomies or partial excisions of the fibrosis in the masseter or medial pterygoid muscles.[44] An alterative to excision is the use of CO_2 laser ablation of the fibrotic cicatrix. Scar bands are released and the post-laser ablation wound is manipulated with extensive physical therapy to avoid the recurrence of dense scar. Success of the procedure appears to be closely associated with compliance with physical therapy and mouth-opening exercises and less so with the type of procedure for scar lysis.

Positive results have been achieved using physical therapy rehabilitation devices such as TheraBite and Dynasplint systems. At our institution we have developed a protocol of



Fields | Dose Prescription | Field Alignments | Plan Objectives | Optimization Objectives | Dose Statistics | Calculation Models | Plan Sum

View	DVH Line	Structure	Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
☑		BrainStem	Approved	AHN	C1	29.7	100.0	99.9	513.6	3220.2	1660.6
☑		rEye	Approved	AHN	C1	9.2	100.0	100.2	222.9	1219.2	409.7
☑		Cord + 0.7cm	Approved	AHN	C1	177.6	100.0	100.0	29.8	3930.5	1798.7
☑		rLens	Approved	AHN	C1	0.1	100.0	99.6	272.9	403.7	324.5
☑		rParotid	Approved	AHN	C1	26.7	100.0	100.1	3956.4	6169.2	5527.9
☑		lBrachialPlexus	Approved	AHN	C1	15.1	100.0	100.1	292.5	2605.1	1409.7
☑		Larynx	Approved	AHN	C1	36.1	100.0	100.0	2182.4	6019.8	4264.9
☑		rBrachialPlexus	Approved	AHN	C1	17.5	100.0	100.1	458.6	5975.6	4252.8
☑		PreopGTV	Approved	AHN	C1	38.3	100.0	100.0	0.0	6554.3	5427.1
☐		Body-3mm	Approved	AHN	C1						
☑		lCochlea	Approved	AHN	C1	0.3	100.0	99.5	1226.3	1998.4	1543.2
☑		PTV60	Approved	AHN	C1	167.6	100.0	100.0	5376.5	6631.6	6190.8
☑		Esophagus	Approved	AHN	C1	1.7	100.0	100.1	63.4	5900.1	1416.5
☑		rCochlea	Approved	AHN	C1	0.3	100.0	100.2	2176.6	2777.6	2480.7
☑		rParotid-PTV	Approved	AHN	C1	15.6	100.0	99.9	3956.4	6169.2	5344.6
☑		Mandible	Approved	AHN	C1	89.9	100.0	100.0	1325.0	6385.7	4273.5
☑		Brainstem+0.3cm	Approved	AHN	C1	51.6	100.0	99.9	384.3	3541.3	1687.0

• **Fig. 25.10** Dose-volume histogram. Summary of treatment dosage to vital structures in the vicinity of a right T2 squamous cell carcinoma of the buccal mucosa.

prophylactically performing coronoidectomies at the time of pre-radiation extractions or at initial surgery. Patients who will undergo radiation therapy are examined to have teeth with questionable prognosis extracted with particular attention given to posterior mandibular dentition. The first and second molars are commonly the site of trauma and initial osteoradionecrosis. Coronoidectomies are also performed in patients who have undergone surgery in the area of the coronoid and who will undergo radiation on the premise that the release of the temporalis attachment will reduce the amount of scarification that can occur on the temporalis.

Chemotherapy

Systemic therapy can be integrated in the management of buccal mucosa squamous cell carcinoma in adjuvant, neoadjuvant, and palliative settings. In the adjuvant or postoperative setting, chemotherapy is administered with radiation after surgical resection. The survival benefit of adjuvant chemotherapy when used with radiation was demonstrated in two prospective randomized studies (RTOG 9501 and EORTC 22931).[45-47] For patients with early-stage (T1/2N0M0) buccal mucosa cancer after R0 resection, the benefit of chemotherapy is not established; however, it should be considered for T2 disease with positive margins. For those patients with node-positive T1/2 buccal mucosa cancer, chemotherapy can be considered for those with adverse features that include N2/3 disease, nodal disease at level IV or V, lymphovascular invasion, perineural invasion, extracapsular extension of nodal disease, and positive margins after resection. The two subsets of patients who benefit most from the addition of chemotherapy are those with positive margins and those with evidence of extracapsular spread.[46]

Various chemotherapy agents with radiosensitizing properties have been used in the management of buccal mucosa squamous cell carcinoma. Among them, cisplatin is the most established and most commonly used agent. Cisplatin cross-links DNA, which makes DNA more susceptible to radiation damage and blocks cellular DNA repair after sublethal or lethal damage. The most common potential side effects of cisplatin include nausea, tinnitus, hearing impairment, cytopenia, electrolyte imbalance, and renal insufficiency, which can all be well managed with supportive care. Carboplatin and taxanes can be used as alternatives for those who cannot tolerate cisplatin. Cetuximab, an EGFR (epidermal growth factor receptor) inhibitor, has demonstrated survival benefit when used with radiation treatment in oropharyngeal and laryngeal squamous cell carcinoma. The benefit of cetuximab in the adjuvant setting for oral cavity cancer is not well established despite its use in clinical practice due to its favorable tolerability.

Rehabilitation

Prosthetic dental rehabilitation options should be addressed with the patient before surgical treatment to establish realistic patient expectations. Depending on the oral health status of each patient, the restorative dentist and the surgeon can create the foundation for the final prosthesis. The size of tumor and location would determine the amount of resection and type of reconstruction needed. Implants are a valuable tool that are used to aid in the retention and stability of the final restoration. Ideally, implants should be placed at the time of surgical removal of the tumor and extraction of nonrestorable teeth. However, this is not always possible because tumor removal, reconstruction, and control of disease take priority. Implant placement after radiation treatment has been linked to a reduction in functional osseointegration, which in turn increases the risk of osteoradionecrosis and the need for prophylactic treatments such as hyperbaric oxygen and pentoxifylline and vitamin E.[44,48,49] Studies have shown that implants placed in bone irradiated at doses lower than 45 Gy have a higher implant success rate.[50] Despite the risks associated with surgery on irradiated bone, some would consider implant placement 2 years after the completion of radiation treatment.[51]

Like for other carcinomas of the oral cavity, treatment of buccal carcinoma should be aimed at restoring function, esthetics, and quality of life. Maintenance of masticatory and swallowing functions, prevention of trismus, and establishing the groundwork for a prosthetic rehabilitation should be the main goals of the reconstructive surgeon. A microvascular free flap, such as a radial forearm flap or an anterolateral thigh flap, is ideal for such reconstruction, except such flaps provide too much bulk, which impedes the patient's functions. In some cases, this is a minor problem for patients who undergo external beam radiation because the flap frequently has fibrosis and diminution of this tissue. Patients who are not candidates for external beam radiation, however, can undergo modification procedures as early as 6 months without compromising viability of the reconstruction.

The use of an osteocutaneous flap, such as a fibula flap, allows the surgeon to place endosseous dental implants immediately or at a later stage. The use of traditional avascular bone grafting is another option but requires a secondary procedure and the presence of adequate well-vascularized soft tissue.

The management of bulky soft tissue reconstructions, scar tissue, and decreased mouth opening encompass the most challenging issues for the restorative dentist.[49] Debulking of skin paddles is necessary when excess tissue encroaches into the interarch space, which should be reserved for the final dental prosthesis. Ideally, a minimum of 8.5 mm of vertical space and 9 mm of horizontal space of denture base is required for an implant-supported overdenture with Locator attachments. An implant bar restoration requires approximately 13 to 14 mm of vertical space.[52,53] The type of implant restoration should be determined before implant placement if possible. Vertical soft tissue excess overlying the native mandible or bony reconstruction also needs to be reduced to obtain a fixed keratinized tissue interface for implant placement and maintenance. It is common for soft tissue reconstructions of the buccal mucosa to obliterate the vestibule. Through a process of soft tissue debulking, vestibuloplasty, and placement of a split thickness skin graft or AlloDerm the area can be prepped for a dental prosthesis. Generally, the soft tissue overlying the mandible and/or fibula should be thinned to the level of the periosteum.

If a bony microvascular reconstruction is placed, care is taken to be aware of the side of the vascular pedicle and to prevent inadvertent injury to the periosteum. An acrylic splint can be used to bolster a graft along an open surgical wound to guide soft tissue healing and create a vestibule.

Scar release should also be considered if inadequate mouth opening is caused by scar formation. Areas of dense scar bands are located in the region of the ascending ramus and coincide with the fibers of the temporalis muscle. Palpation of the buccal soft tissues generally identifies locations of the restrictive soft tissue scars. Following scar release, aggressive postoperative jaw opening exercises facilitate the maintenance of a functional mouth opening greater than 30 mm. Devices such as the TheraBite and Dynasplint have demonstrated increased patient compliance and maintenance of functional mouth opening following the identification of postsurgical and radiation-induced trismus.

Dental implants in patients who underwent resection of mandible, maxilla, or both aid in the retention and stabilization of the prosthesis. If possible the use of tools such as virtual implant planning should be used to improve the outcome of the final prosthesis. Due to the high reoccurrence rate of buccal squamous cell carcinoma, the authors advocate a prosthesis that allows for accessible visualization of the site, such as a removable implant retained denture. Also, the use of a removable prosthesis is considered most cost effective, provides for better oral hygiene, requires fewer implants, and creates better distribution of forces between implants and tissue.[49]

Patients with remaining dentition who receive radiation therapy should have fluoride carriers fabricated for daily fluoride treatment and be informed of overall oral health care as well as the side effects of irradiation, such as mucositis, xerostomia, increased risk for dental caries, loss of taste, trismus, and osteoradionecrosis. It is important for the patient to have frequent dental visits, at least every 4 to 6 months, after cancer treatment to address any complications that may arise due to the side effects of radiation and to reinforce the importance of oral health care. After the first year of treatment, it is common for patients to move forward with their lives and become noncompliant with oral hygiene and fluoride treatments that are vital to the overall success of treatment and quality of life.

Surveillance

Among oral cavity subsites of carcinoma, the buccal carcinoma is understood to have an aggressive tendency for local and regional recurrence. Multiple studies have demonstrated a pattern for tumor recurrence within 2 years, with the majority recurring in less than 1 year of surgery.[20,21,54] Furthermore, the identification of recurrence is a poor prognostic feature associated with a 50% salvage rate, which is similar to that of other sites in the oral cavity. Close surveillance is essential to the overall success. Follow-up recommendations vary by year following treatment and are defined in the NCCN guidelines. Generally, follow-up is recommended every 2 to 4 months for the first 2 years and every 6 months during the third to fifth years. Annual examinations are suggested after 5 years.

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26

Advanced Buccal Mucosa Cancer

ADAM P. FAGIN, MARK K. WAX, DANIEL PETRISOR

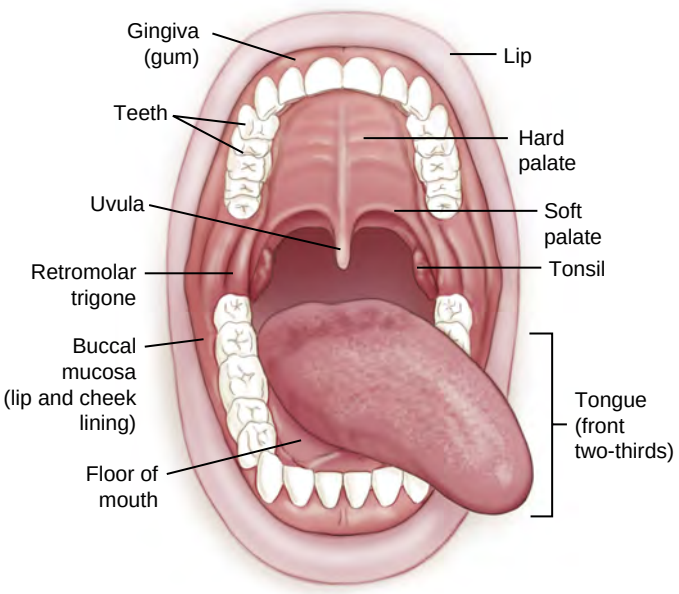
The most recent report from the American Cancer Society found the incidence of oral cancer to be 46,000 cases a year.[1] Of those, the vast majority are oral squamous cell carcinoma. In order to better characterize oral squamous cell carcinoma, the American Joint Committee on Cancer (AJCC) has divided the oral cavity into seven subcategories: mucosal lip, alveolar ridge, retromolar trigone, floor of mouth, maxillary hard palate, oral tongue, and buccal mucosa[2] (Fig. 26.1). Buccal mucosa squamous cell carcinoma (buccal cancer) is a rare subtype of oral squamous cell carcinoma accounting for only 5–10%[3-7] of all lesions in regions outside of Central and Southeast Asia, where buccal cancer accounts for up to 70% of all oral cavity cancers.[8] This large difference in prevalence of buccal cancer between the two regions has been attributed to the prevalence of "pan" chewing. "Pan" is a combination of tobacco, betel nut, and slaked lime (calcium hydroxide).

This chapter focuses specifically on the presentation and management of T3 and T4 buccal cancer, defined as primary tumors larger than 4 cm and with evidence of invasion into adjacent structures, respectively.[2] The summary of the authors' recommendations and supporting evidence for the management of T3/T4 buccal cancer can be found in Fig. 26.2. Unfortunately, primary tumors of that size are not uncommon. Retrospective studies within the past 15 years reported rates of T3/T4 lesions between 33% and 38%.[9-11]

Clinical Anatomy

The AJCC defines the anatomic borders of the buccal mucosa as the lining of the inner surface of the cheeks and lips from the line of contact of the mucovermilion junction to the line of attachment of mucosa to the alveolar ridge and the pterygomandibular raphe[2] (see Fig. 26.1). The borders have been more rigorously described by Rodgers and colleagues.[12] The medial wall of the buccal space is formed by the buccinator muscle and its overlying fascia, which extends from the mandible inferiorly to the zygomatic arch superiorly. The deep portion of the lateral wall is formed by the muscles of facial expression and their fascia (risorius, zygomatic major, and quadratus labii superioris). More superficial to these muscles lies the superficial fascia, subcutaneous fat, and skin. The orbicularis oris muscle forms the anterior border. The posterior border is the anterior border of the masseter muscle. Superior and inferior limits are formed as fascia attaches to the periosteum of the zygomatic arch and mandible, respectively.

The significant anatomic contents of this region include Stenson's duct, the facial artery and vein, buccal fat, facial nerve branches, and the muscles that control the oral sphincter. The facial nerve provides motor innervation to the muscles in this space while the third branch of the trigeminal nerve provides sensory innervation. Muscles in this region, including the buccinator, orbicularis oris, risorius, levator anguli oris, and depressor anguli oris, are integral to daily function because they control the patency of the oral sphincter and lower facial expression. Large defects in this area resulting from the resection or denervation of these muscles cause difficulty in maintaining the integrity of the oral sphincter. Often the oral sphincter aperture is reduced secondary to a loss of tissue in this area, post resection. With modern reconstructive surgical techniques we can often restore the volume of tissue lost; however, the lack of muscular innervation and/or control often still results in a loss of



• **Fig. 26.1** Anatomic regions of the oral cavity including the buccal mucosa.

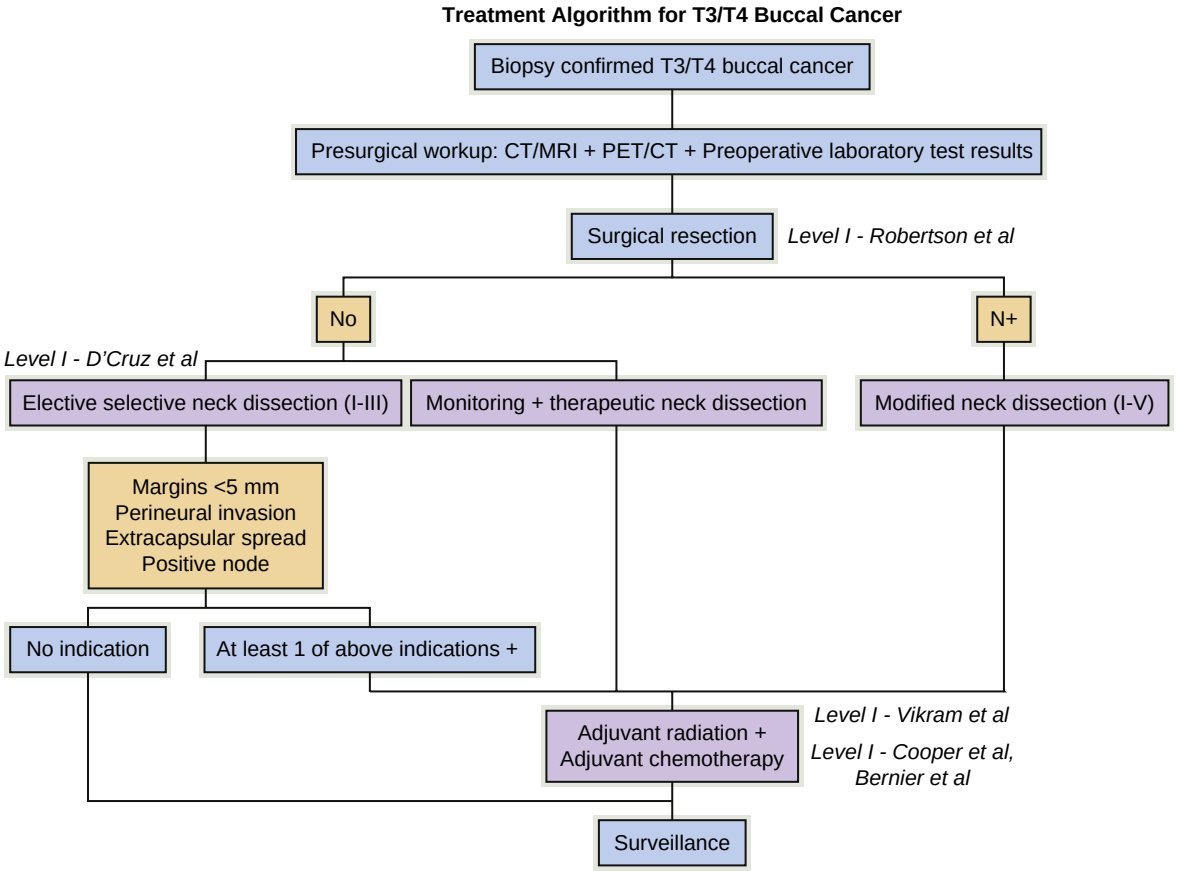
oral sphincter integrity. Functionally for patients, this manifests as difficulty chewing and controlling oral secretions, and asymmetry of facial expression. Disturbance of these three functions not only has a huge impact on daily activities, but can be quite distressing socially and cosmetically. The region receives vascular supply anteriorly from the facial artery and its tributaries, the inferior and superior labial arteries. The posterior vascular supply is derived primarily from the buccal artery, a branch of the internal maxillary artery.[13] Lymphatic drainage is provided by the submental, submandibular, and jugulodigastric nodes.[14]

Buccal cancer has historically been described as a subsite of the oral cavity with a high rate of locoregional recurrence. It is hypothesized that this is due to the lack of anatomic barriers to spread in the buccal space. The buccinator muscle and its overlying fascia are the only barrier to the spread of buccal cancer. Once the tumor has invaded beyond the buccinator muscle and encroaches on the buccal fat, there is no good anatomic barrier to prevent further spread. The pattern of nodal progression has been described by Shah and colleagues and typically progresses in a linear fashion from level I to II to III, with rare involvement of IV and V.[15] Further details and clinical implications of nodal progression are discussed in the management of the neck section of this chapter.

Epidemiology and Predisposing Factors

It has been well established that the two most common predisposing factors to oral cancer are tobacco and alcohol use.[16-19] It has also been shown that these two have a synergistic effect with one another.[20,21] While the use of tobacco products and alcohol increases the risk of buccal cancer, in an analysis by anatomic subsite, Jovanovic and colleagues[17] reported that the increase in relative risk for smoking and alcohol consumption was least in buccal cancer in comparison to any other anatomic site. The largest risk factor associated with buccal cancer is the chewing of betel nut products, endemic in South East Asia. This risk factor is so profound that it completely changes the overall anatomic subsite prevalence of oral cancer in these regions.

Buccal cancer prevalence is the highest where the betel nut product, "pan," is traditionally chewed behind the cheek or lower lip (Fig. 26.3). There has been some discussion in the past whether buccal cancer in the West is comparable to that seen in endemic "pan" chewing regions, given the possibility that the etiology could potentially alter the pathogenesis and clinical behavior of the disease. However, a study comparing buccal cancer patients from Canada to matched controls from India showed no difference in survival when the authors controlled for age at presentation.[22]



• **Fig. 26.2** Summary treatment algorithm for T3/T4 buccal cancer with level of supporting evidence cited in *italics* at decision points.[35,40,48,53,55]

The median age for buccal cancer is similar to that of other oral squamous carcinomas with median reported ages between 54 and 70 most in the late 1960s.[4,9-11,14] There does not appear to be a strong gender predilection in Western nations. Previously, studies have reported a slight female predilection up to 60%[4,10,14,23] or no predilection.[11] However, in Southeast and Central Asia, where there is a cultural male predilection for "pan" chewing, there is an associated male predilection for buccal cancer.[24,25]

Premalignant Lesions

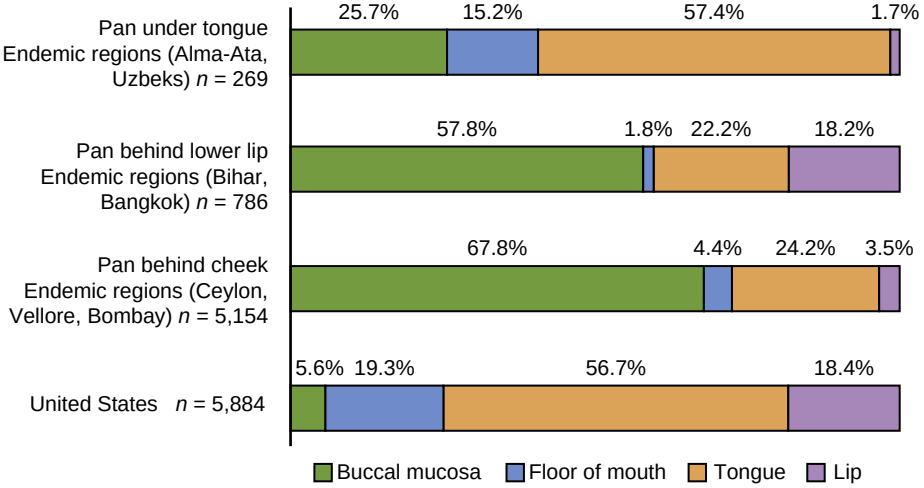
Leukoplakia is defined as a white patch or plaque that cannot be ascribed to any other clinical disease. Leukoplakia has long been known to be a precancerous lesion for oral squamous cell carcinoma. The rate of malignant transformation is not definitively known, but reports in the literature range widely from 0.13% to 17.5%. This variance is attributed to variation in risk factors, population, timing at presentation, and follow-up between reporting studies.[26-28] One study by Silverman and co-workers with 257 cases and an average follow-up of 7.2 years reported that the buccal mucosa was the most common anatomic site for leukoplakia to occur, accounting for 46% of all leukoplakias observed. However, the buccal mucosa also had a relatively lower rate of malignant transformation, 11.1% over the average 7-year follow-up period, with other anatomical subsites ranging between 28.9% for the tongue and 8.9% for the lip.[28] A related lesion to leukoplakia is erythroplakia, defined as a red patch that cannot be scraped off or ascribed to any other pathologic disease. These lesions are much more concerning, with more than 90% of biopsies revealing invasive squamous cell carcinoma or carcinoma in situ.[29]

Presentation

Buccal cancer can be mistaken for occlusal trauma on the buccal mucosa. This confusion can sometimes lead to delay in appropriate referral and subsequent treatment. To distinguish occlusal trauma of the buccal mucosa from buccal cancer, it is important to take an appropriate history. Patients often chronically traumatize their buccal mucosa without realizing, resulting in hyperkeratinization, which is characterized by thickening of the mucosa with ill-defined boarders absent any open ulceration. In contrast, on close examination, the borders of leukoplakia or buccal cancer tend to be well demarcated with distinct borders. If an ulceration is present, the duration of the ulcer is important. Anything over 2 weeks without clear history and mechanism of reinjury warrants a biopsy. In general the authors recommend a low threshold for biopsy. While the incidence of buccal cancer is low, the impact of delaying treatment is significant.

Unfortunately, it is not uncommon for patients to present with T3/T4 disease. In a large study in the United States by Diaz and colleagues,[11] 45% of patients presented with T3/T4 tumors. According to a retrospective study by Chhetri and co-workers,[9] the three most common presenting chief complaints for patients with buccal cancer were buccal mass, pain, and mucosal ulcer regardless of the T stage at presentation. Although leukoplakia was a less common presentation, it was also specific to the presentation of T1 or T2 lesions. In contrast, skin ulcer, trismus, and facial paralysis were uncommon, but specific for T3 or T4 lesions. In addition, patients with these advanced lesions can present with a neck mass or dysphagia.

When a patient presents with a lesion concerning for buccal cancer, the clinician should first perform a complete head and neck physical examination focusing on the depth and extension of tumor involvement. It is not uncommon for T3/T4 buccal cancers to have invaded adjacent structures including the orbit, ear, oropharynx, or other anatomic subdivisions of the oral cavity. This examination should include a complete and thorough examination of the oral cavity with the removal of any intraoral prosthetic devices and adequate mobilization of the tongue with aid from the clinician using a piece



• **Fig. 26.3** A comparison of the prevalence of oral squamous cell carcinoma by anatomic location and geographic region/cultural quid chewing practices. Demonstrates the correlation between oral cancer frequency and placement of betel nut products seen in South East Asian countries, especially its impact on buccal cancer.[7,8]

of gauze, noting any masses, swellings, ulcerations, leukoplakias, or erythroplakias. If a mass exists in the buccal mucosa, careful bimanual palpation of the mass is important, noting its mobility within the submucosal structure. The presence of adhesions to adjacent submucosal structures is more concerning than a freely mobile mass. If the tumor extends deep into the oropharynx, laryngoscopy is often required to fully visualize the extent of the tumor. Next, a thorough examination of the neck for palpable nodes and evidence of possible metastasis should be conducted. Special attention should be paid to areas I and II, where buccal cancer nodal metastasis is most common.[6] Finally, a complete history should be taken, including risk factors such as alcohol use, tobacco history including betel nut chewing, family history of cancer, and past medical history. Once a thorough history and physical is complete, an incisional or punch biopsy is necessary for definitive diagnosis. If the diagnosis of buccal cancer is confirmed, the authors recommend immediate referral to a tertiary care center that routinely manages malignancy with possible regional involvement, where a thorough evaluation and staging can be performed.

Staging and Presurgical Work-up

With a biopsy-confirmed diagnosis of buccal cancer, the clinician should begin the staging and presurgical work-up. The first step is either magnetic resonance imaging (MRI) or computed tomography (CT), to fully assess the extent of local spread into adjacent anatomic areas such as the overlying skin, masticator space, submandibular space, retropharyngeal space, and adjacent bony structures including the zygoma, maxilla, and mandible. With the local extent of the tumor fully defined, the next step is to evaluate for nodal involvement. This is arguably the most important aspect of staging for prognosis, and historically the most difficult. The MRI or CT already obtained should be examined for nodal involvement, but this modality has historically shown poor sensitivity. Positron emission tomography (PET)/CT can be obtained, which has been shown to be more sensitive and specific than MRI/CT alone. In a study looking at necks that had no evidence of nodal involvement on CT or MRI, the PET/CT demonstrated a sensitivity and specificity of 67% and 85%, respectively.[30] The authors of this study attribute the low sensitivity to the PET/CT's inability to detect nodes smaller than 3 mm. If the patient is found to have nodal involvement, a full-body PET/CT can be considered to evaluate for distant metastasis. Once these tests have been conducted, the patient can be staged using the standard criteria defined by the AJCC[2] (Table 26.1). An accurate staging will not only help guide future treatment, but also guide an appropriate PARQ discussion (procedures, alternatives, risks, and questions) with patients before embarking on a treatment path.

The American Joint Committee on Cancer (AJCC) recently made substative modifications to the TNM staging criteria and staging system for head and neck cancer in general and oral cavity cancer in particular. These changes more accurately represent the unique biologic, clinical, and epidemiologic features of oral squamous cell carcinoma (OSCC) (see Table 24.1 in Chapter 24). In the first modification, the T stage now incorporates depth of invasion (DOI). In the 1980s, Spiro and colleagues identified the importance of tumor thickness as a prognostic indicator in oral cavity cancer. Depth of invasion is a more sophisticated and reproducible method of measuring a tumor. It is measured by first finding the "horizon" of the basement membrane of the adjacent squamous mucosa, and DOI is defined as the deepest point of tumor invasion (in mm) from that line. Extrinsic muscle infiltration has been removed from the staging criteria because DOI is more representative of the clinical problem both clinically and pathologically. DOI assesses the invasiveness of the tumor rather than any exophytic component.

In the second modification, extranodal extension is now recognized when categorizing metastatic cancer to the cervical lymph nodes. Additional updates to this classification scheme include the following:

1. Separate N category approaches are given for patients treated without cervical lymph node dissection (clinical N [cN]) and patients treated with cervical lymph node dissection (pathological N [pN]).
2. Extranodal extension (ENE) is introduced as a descriptor in N categorization for all HPV-negative cancers, and its presence is designated pN2a for a single ipsilateral node <3cm and pN3b for all other node(s).
3. Clinically overt ENE is classified as ENE and is considered ENE(+) for cN.
4. Pathologically detected ENE is classified as either ENE_{mi} (<2 mm) or ENE_{ma}(>2 mm) for data collection purposes only, but both are considered ENE(+) for definition of pN.

However, pathologic stage does not trump clinical stage, and assignment of ENE should be based primarily on physical examination, rather than on imaging studies.

The primary tumor stage remains essentially the same in the new system, with the exception that DOI will increase the T category by 1 for each 5-mm of tumor depth (up to ≥10 mm). Pathological ENE(+) will increase the nodal category by 1. In addition, the AJCC recommends that other prognostic factors be considered and recorded along with standard staging information, including Eastern Cooperative Oncology Group (ECOG)/Zubrod or Karnofsky performance measures, tobacco and alcohol use, tumor location, number and size of nodes, perineural invasion, and ENE.

The new AJCC TNM staging highlights the worst pattern of invasion (WPOI) as a validated outcome predictor. It is recommended that WPOI-5, defined as tumor dispersion of ≥1 mm between tumor satellites, be recorded as part of pathologic staging. Even in early-stage oral cancer, a DOI of >4 mm combined with a WPOI-5 increases the probability of recurrence to approximately 42%. Perineural invasion (PNI) or lymphvascular invasion constitute a WPOI-5 classification. When identified, PNI would be subclassified as either intratumoral or extratumoral. Named nerves should be specified and PNI should be subclassified as focal or multifocal.

TABLE 26.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor ≥2 cm and ≤4 cm in greatest dimension
T3	Tumor ≥4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease.
T4a	Moderately advanced local disease. (lip) Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose); (oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face). Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
T4b	Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base or encases carotid artery

Regional Lymph Nodes: Clinical (cN) Oropharynx (p16-) and hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N3	Lymph node(s) larger than 6cm and ENE(–) or metastasis in any node(s) and clinically overt ENE(+)
N3a	Lymph node(s) >6 cm and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L).* Similarly, clinical and pathological ENE should be recorded as either ENE(–) or ENE(+)

Regional Lymph Nodes: Pathological (pN) Oropharynx (p16-) and hypopharynx

NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
pN2	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2a	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–)
pN2b	metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN3	Lymph node(s) >6 cm and ENE(–); or metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)
pN3a	Lymph node(s) >6 cm and ENE(–)
pN3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)

TABLE 26.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)—cont'd

Distant Metastasis (M) Oropharynx (p16–) and hypopharynx

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Registry Data Collection Variables

1. Lip location (external or vermilion border)
2. ENE clinical: ENE(+) or (–)
3. ENE pathological: ENE(+) or ENE(–)
4. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
5. Perineural invasion
6. Lymphovascular invasion
7. p16/HPV status
8. Performance status
9. Tobacco use and pack-years
10. Alchohol use
11. Depression diagnosis
12. Depth of invasion (mm)
13. Margin status (grossly involved, microscopic involvement)
14. Distance of tumor (or moderate/severe dysplasia) from closest margin
15. WPOI-5

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L).* Similarly, clinical and pathological ENE should be recorded as either ENE(–) or ENE(+).

Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In Amin MB et al, eds. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

Prognosis

Buccal cancer has long been described as an aggressive cancer with high rates of locoregional recurrence compared to other sites in the oral cavity. This has historically been a difficult statement to validate in Western populations, given the rarity of buccal cancer and variation in treatment regimen. However, the two largest retrospective studies conducted in the West in the past 20 years, when surgical treatment with or without adjuvant radiation therapy had become the standard, can now offer more definitive insight. In these two studies, the average 5-year recurrence rates for buccal cancer were slightly higher than the rest of the oral cavity, 45% by Diaz and associates[11] and 42% by Bachar and co-workers,[10] compared to 36% by Boysen and colleagues,[31] respectively. This difference has been attributed to the lack of anatomic barriers to spread in the buccal space discussed earlier.

Prognostic factors vary significantly from study to study, which is likely due to varying study designs and populations. Only nodal involvement has been shown across multiple studies to consistently be associated with 5-year survival.[10,11,32,33] T stage has had conflicting reports of correlation with survival. One study reported a decrease in survival associated with advanced T stage,[32] whereas others have reported a lack of correlation between T stage and survival.[10,11,32] Other factors that have been shown to sporadically correlate with survival include extracapsular spread,[11,33] tumor thickness >4 mm,[34] skin involvement,[32,34] bone involvement,[32] and tumor grade[32,33] (Table 26.2).

Management of the N0 Neck

As long as diagnostic imaging fails to reach 100% specificity, clinicians will be faced with the dilemma of how to manage the clinically N0 neck. The decision between potentially ignoring metastatic spread, which is associated with a sharp decline in survival, versus the comorbidities associated with an elective neck dissection has plagued clinicians for years.

Any discussion of the N0 neck would be amiss without mentioning a recent randomized controlled clinical trial out of India by D'Cruz and colleagues[35] that randomized 596 patients with N0 T1/T2 tumors to elective neck dissection or clinical monitoring with therapeutic neck dissection if indicated. The study showed an improvement in 3-year survival rate for the elective dissection group compared to therapeutic dissection, 80% and 67.5%, respectively. Patients in the elective neck dissection group were given a selective neck dissection, levels I–III, unless positive nodes were found on frozen section during surgery, in which case a modified neck dissection was performed, levels I–V. It is worth noting that this study failed to show a survival benefit for the 78 patients with buccal cancer who were randomized. However, this may be because the study became underpowered when this subdivisional analysis was conducted. Although the study looked at T1/T2 tumors and was not specific to buccal cancer, the authors believe that it still provides strong evidence that patients presenting with T3/T4 buccal cancer and an N0 neck should undergo a selective

TABLE 26.2 Five-Year Survival Rates Reported by Multiple Studies Based on Prognostic Factor

Study	Early Overall Stage (I-II)	Late Overall Stage (III-IV)
Lin et al, 2006*†	52	23
Liao et al, 2006‡	83	66
	Early T-Stage (I-II)	**Late T-Stage (III-IV)**
Diaz et al, 2003§	*72*	*63*
Lin et al, 2006*†	50	22
Liao et al, 2006‡	84	65
Bachar et al, 2012¶	74	64
	Negative Nodal Involvement	**Positive Nodal Involvement**
Diaz et al, 2003*§	70	49
Lin et al, 2006*†	47	14
Liao et al, 2006*†	84	40
Bachar et al, 2012*¶	87	51
	Negative Extracapsular Spread	**Positive Extracapsular Spread**
Diaz et al, 2003*§	69	24
Liao et al, 2006*†	84	40
	Negative Bone Invasion	**Positive Bone Invasion**
Lin et al, 2006*†	40	22
Liao et al, 2006‡	76	70
	Negative Skin Invasion	**Positive Skin Invasion**
Lin et al, 2006*†	40	13
Liao et al, 2006‡	78	62
	Good/Moderate Differentiation	**Poor Differentiation**
Lin et al, 2006*†	45	27
Liao et al, 2006*‡	21	79

*Denotes that the study reported statistical significance ($P < .05$).
†Lin C-S, Jen Y-M, Cheng M-F, et al: Squamous cell carcinoma of the buccal mucosa: An aggressive cancer requiring multimodality treatment. *Head Neck* 2006;28(2):150-157.
‡Liao C-T, Wang H-M, Ng S-H, et al: Good tumor control and survivals of squamous cell carcinoma of buccal mucosa treated with radical surgery with or without neck dissection in Taiwan. *Oral Oncol* 2006;42(8):800-809.
§Diaz EM, Holsinger FC, Zuniga ER, Roberts DB, Sorensen DM. Squamous cell carcinoma of the buccal mucosa: One institution's experience with 119 previously untreated patients. *Head Neck* 2003;25(4):267-73.
¶Bachar G, Goldstein DP, Barker E, et al: Squamous cell carcinoma of the buccal mucosa: Outcomes of Treatment in the modern era. *Laryngoscope* 2012;122(7):1552.

neck dissection. This is because only patients with occult nodal involvement benefit from neck dissection, and the rate of occult metastasis is greater among patients with T3/T4 disease than the patients with T1/T2 in this study. Thus, patients with T3/T4 disease would be more likely to benefit from selective neck dissection than those in this study with T1/T2 disease.

Prior to this recent study, a study by Weiss and associates[36] was often cited when weighing the risks and benefits of elective neck dissection. This study used complex decision tree analysis to calculate that if the risk of nodal metastasis was greater than 20% than the benefits of elective neck dissection outweighed the risks. To apply this study to the specific case of T3/T4 buccal cancer discussed here, one of the largest and most recent Western retrospective studies on buccal cancer by Diaz and coworkers[11] reported that 26% of N0 patients undergoing elective neck dissection had positive nodes upon histopathologic evaluation. Additionally, Shah and colleagues[15] reported on 501 patients undergoing neck dissection and found buccal cancer to have the highest rate of occult metastasis at 56%. However, this rate should be interpreted cautiously, because of the total of 501 patients, only 9 were N0 patients with buccal cancer undergoing elective neck dissection. Therefore, the decision tree analysis by Weiss and associates would support selective neck dissection in clinically N0 patients with T3/T4 buccal cancer.

Finally, the morbidity associated with neck dissection has come a long way since the radical neck dissection was originally described by Crile in 1906. Now, modified neck dissection and selective neck dissection are much more popular options because of their decreased morbidity. In fact, recent studies have shown that patients undergoing selective neck dissection (levels I–III) have no statistically significant difference in quality-of-life scores when compared to those who did not undergo surgery.[12,37-39] In addition, selective neck dissection has proven quite effective at sampling nodes in the N0 neck. Shah and colleagues reported that only 3.5% of patients who presented with an N0 neck had any nodal metastasis outside of levels I–III.[6] Therefore a selective neck dissection in conjunction with frozen section can provide invaluable intraoperative staging with minimal morbidity.

In light of this evidence, the authors recommend selective neck dissection of levels I–III for patients presenting with T3/T4 buccal cancer and an N0 neck after appropriate diagnostic imaging work-up has been performed.

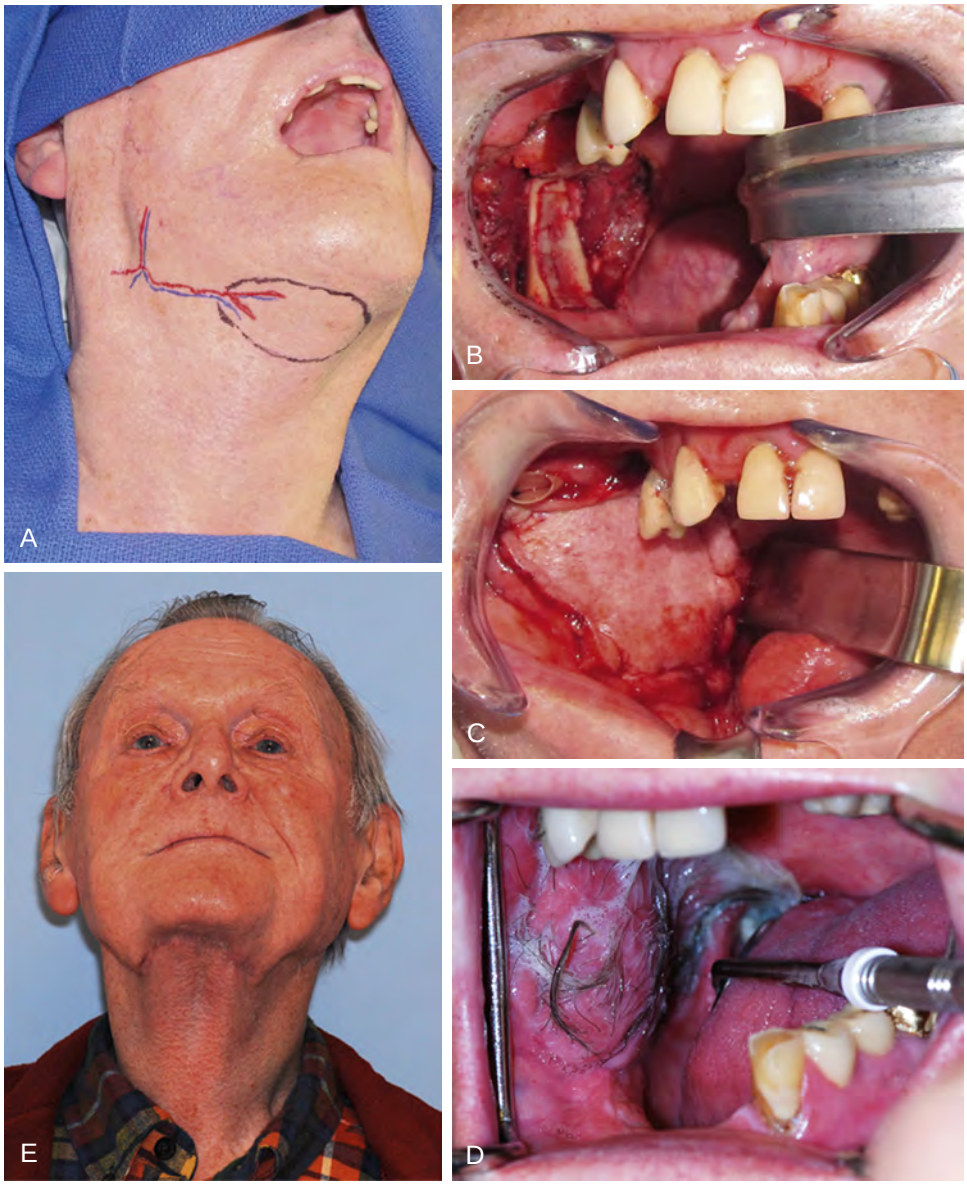
Surgical Treatment Options

Ever since the landmark trial by Robertson and colleagues, which randomized patients with squamous cell carcinoma of the oral cavity to receive surgical resection plus radiation therapy versus radiation alone, surgery with or without adjuvant radiation therapy has been the standard of care for patients with buccal cancer.[40] The study closed early as a result of ethical concerns due to a significant survival benefit for those in the combination arm.

By definition T3/T4 buccal cancer are large or invasive, if not both. Complete resection of such lesions often results in large, complex defects typically requiring a regional or free flap for adequate reconstruction. Anatomically, if the tumor spreads beyond the buccal space, it can reach sensitive areas including the parotid and facial nerve laterally, pterygoid space posteriorly, maxilla superiorly, and mandible inferiorly. Several different approaches exist for these patients. The best surgical and reconstructive option will vary based on the specific clinical presentation and goals of the patient. The authors describe several common approaches along with the advantages and disadvantages of each, so that the clinician may choose the best option for the individual patient from least invasive to most invasive.

When adequate resection margins can be obtained without involving the skin, it leaves a single surface defect for reconstruction. However, these defects are not without their own challenges. When only the mucosa is resected, significant scarring of the remaining tissue can occur, resulting in functionally significant postoperative trismus. This can be further exacerbated if postoperative radiation therapy is indicated; see the later discussion of adjuvant radiation therapy. To minimize postoperative scarring, reconstruction with adequate pliable tissue is essential. There are several donor options for the reconstruction of these defects. When the defect is small, regional flaps can be considered. Regional flaps minimize donor site morbidity and often reduce reconstruction time because they do not require microvascular anastomosis. In select cases, when the patient has adequate submental laxity and the defect is small enough (Fig. 26.4A and B), the submental flap can offer an excellent source of regional soft tissue for reconstruction. Fig. 26.4C shows the defect immediately postoperatively after the submental flap has been harvested and rotated into position. Figs. 26.4D and E show the patient with an excellent recovery 2 months postoperatively. When the defect is too large for a submental flap, given the amount of donor tissue available, a free flap should be considered. In the authors' experience, the thin, pliable tissue found in the radial forearm is excellent for mucosal reconstruction. Fig. 26.5A and B show a larger T3 buccal cancer preoperatively and the resultant defect after adequate margins have been obtained. Fig. 26.5C shows the marked donor site, and Fig. 26.5D displays the completed reconstruction immediately postoperatively. In the unusual case where the radial artery cannot be sacrificed, the lateral arm may also be considered, since the posterior radial collateral artery harvested with the lateral arm is not essential to the survival of the distal extremity. In addition, the lateral thigh can be an option in leaner patients.

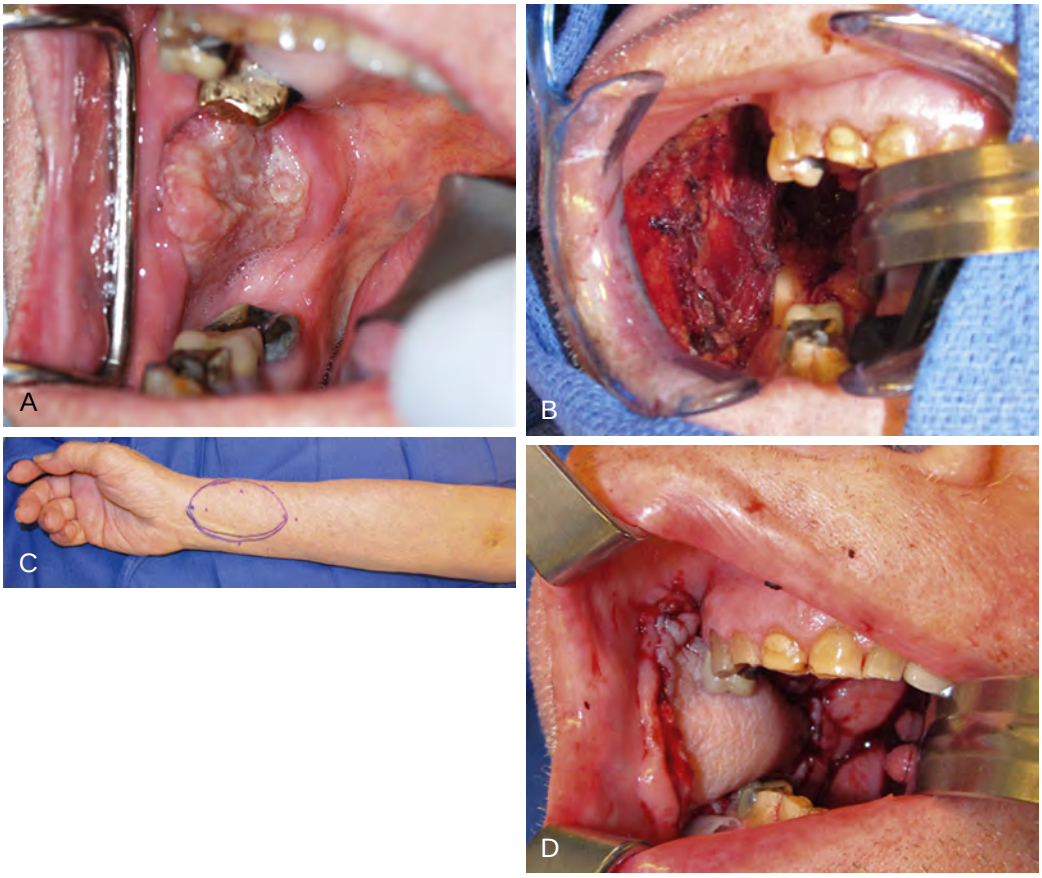
Often resection of T3/T4 tumors will result in through-and-through defects. These lesions are typically the easiest to resect, because the surgeon does not need to be concerned about the depth of resection on the mucosal side. However, the resultant defect requires a donor site capable of recreating both a mucosal and skin surface. This necessitates either a free flap designed with two separate skin paddles or a larger, folded paddle. For this style of defect, the authors recommend the use of a scapula free flap, which can be harvested with two large, separate skin paddles to reconstruct the entire defect. Downsides to the scapula flap are the need to reposition the patient intraoperatively and a relatively shorter vascular pedicle.



• **Fig. 26.4** T3 buccal cancer reconstructed with a regional submental island flap. **A,** Preoperative photo demonstrating adequate submental laxity for harvest with artery, vein, and donor soft tissue panel marked. **B,** Resultant mucosal defect after resection with adequate margins obtained. **C,** Immediately postoperative with the submental flap harvested, rotated, and sutured into position. **D,** Two-month postoperative intraoral photo demonstrating integration and mucosalization of the skin panel. **E,** Two-month postoperative extraoral photo demonstrating excellent healing and cosmetically improved submental contour.

Unfortunately, it is not uncommon for a T3/T4 buccal cancer to require the resection of a bony component, either maxilla or mandible. Because of the extent of disease, it is usual practice to not immediately reconstruct a composite defect of the maxilla with a bony free flap. The soft tissue component is by far the more important tissue for reconstruction. Loss of the posterior maxilla is not very functionally debilitating in these patients. The increased distance between the maxilla and the anastomosing vasculature in the neck can pose a problem during reconstruction. Therefore a radial forearm is often a convenient option, with its long pedicle, if the defect is small enough. In the case of larger defects, a scapula flap can be required.

When the composite defect involves only soft tissue and the mandible, a fibula free flap is typically the first option. The fibula free flap has several advantages that make it uniquely suited to reconstruct the mandible. First, it has excellent periosteal circulation, which allows for multiple osteotomies to reconstruct the contour of the mandibular body. Second, it can provide enough bone to reliably support dental implants. Third, it can be harvested with the patient supine, allowing for a two-team approach. However, in patients with significant atherosclerotic disease, the fibula might not be an option because of concern for post-harvest vascular insufficiency of the lower extremity. In such cases,

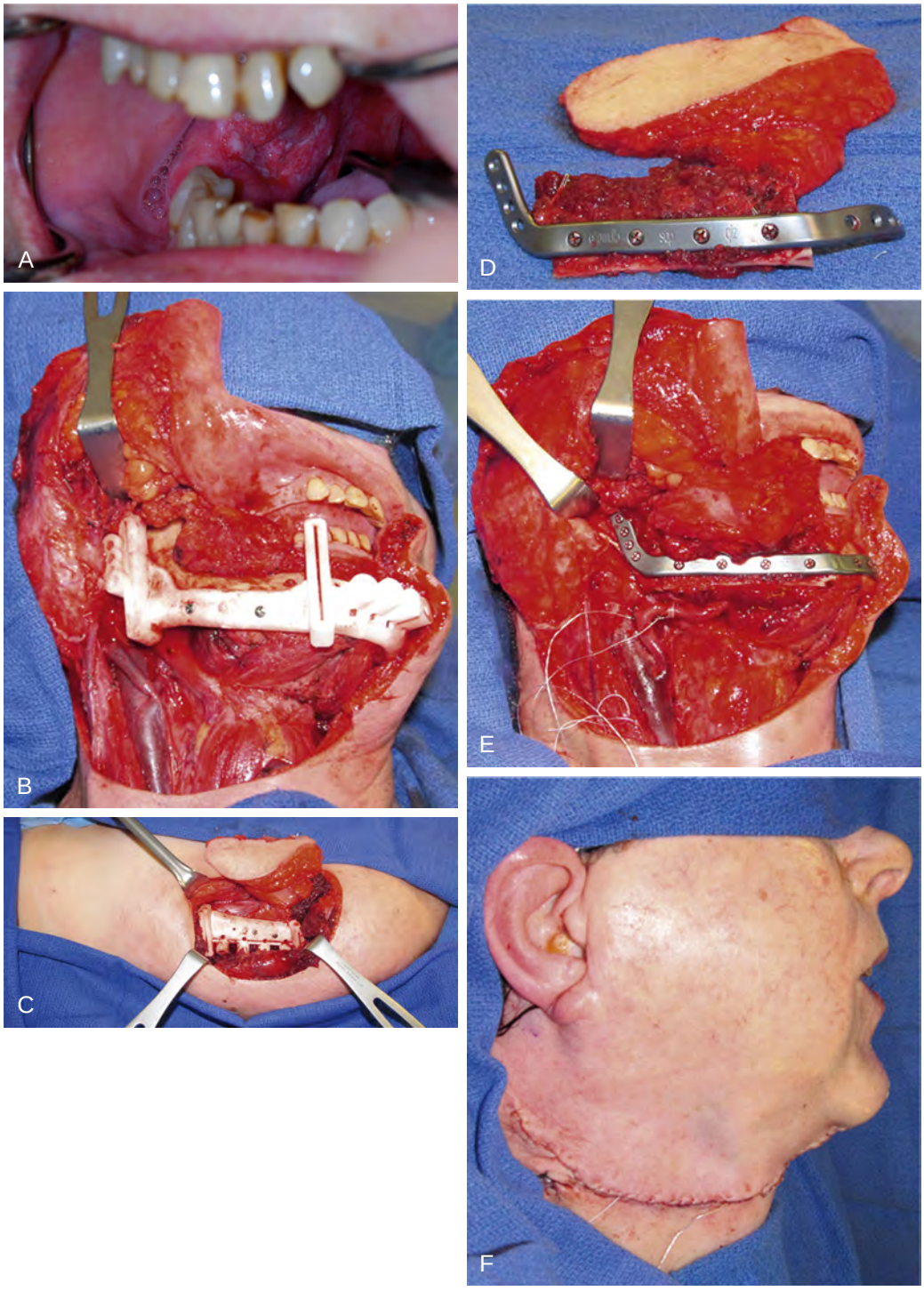


• **Fig. 26.5** T3 buccal cancer reconstructed with a radial forearm free flap. **A,** Preoperative T3 buccal cancer. **B,** Intraoperative photo of resultant defect after lesion was resected with adequate margins. **C,** Preoperative marked radial forearm donor site. **D,** Immediate post-reconstruction image with radial forearm free flap.

the scapula is becoming a near-equivalent alternative for segmental defects with the recent advances in preoperative CT-guided surgical planning. Fig. 26.6A shows a T4 buccal cancer involving the mandible in a patient with significant lower extremity atherosclerosis. Fig. 26.6B shows the buccal soft tissue excised with adequate margins and the patient-specific cutting guide secured in place, which was preoperatively planned to obtain adequate surgical margins for the bony resection. Fig. 26.6C shows the scapula skin paddle dissected with the patient-specific cutting guide in place marking the osteotomy sites. Fig. 26.6D shows the prefabricated reconstruction plate screwed into the graft positioning the lateral border of the scapula superiorly which is wide enough to support future dental implants. Fig. 26.6E shows the scapula inset with the reconstruction plate lining up with the pre-drilled screw holes from the ablative patient-specific cutting guide. Note the seamless bony abutment between the distal segment of the graft and the remaining mandible. The authors hypothesize that this tight bony fit will reduce the rate of plate extrusion. With this guided graft and reconstruction, the surgeons are able to maintain excellent mandibular projection postoperatively (Fig. 26.6E).

Although in many cases reconstruction of a defect involving the mandible with bony support is preferred due to the possibility of long-term dental rehabilitation, it is not always the case. In salvage cases with known metastatic disease, basic function and ease of postoperative recovery take precedence. Fig. 26.7A demonstrates a large recurrent buccal cancer involving the mandible in a patient who desired control of his oral sections and cosmetic improvement. In such cases where a large soft tissue defect is anticipated without the need for bony support, a rectus abdominis flap is a viable option. Fig. 26.7B shows the volume of excised tissue that must be reconstructed. One month postoperatively, the patient has an improved cosmetic appearance and has regained integrity of the oral sphincter (Fig. 26.7C).

Finally, the largest of T3/T4 buccal cancers can require resection of portions of both the maxilla and mandible. The resultant defects require extensive and often creative surgical reconstructive approaches. Perhaps counterintuitively, in resections that result in two bony defects, it is often the resultant soft tissue defect that is most difficult to manage simply because it is so large. As a result, it is not uncommon for the defect to require two separate free flaps such as a fibula and scapula or radial forearm to provide adequate tissue.



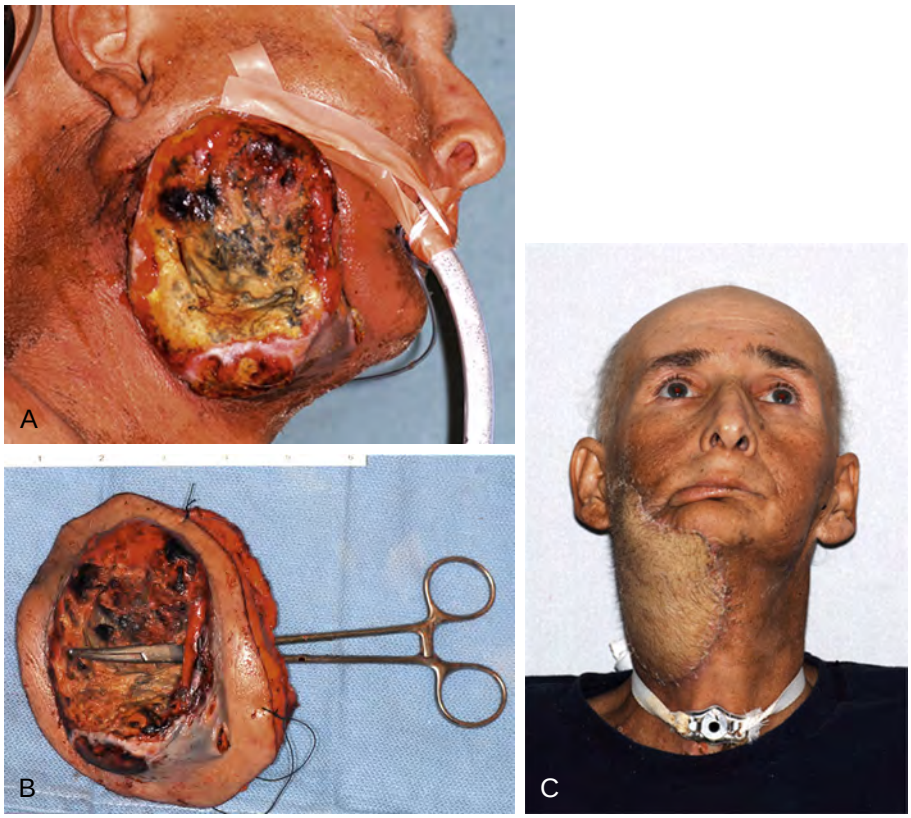
• **Fig. 26.6** T4 buccal cancer involving the mandible resected and reconstructed with a scapula flap using CT-guided preoperative planning and guide fabrication. **A,** Intraoral preoperative photo of T4 buccal cancer involving the mandible in a patient with significant lower extremity atherosclerosis. **B,** The buccal soft tissue excised with adequate margins and the patient-specific cutting guide secured in place, which was preoperatively planned to obtain adequate surgical margins for the bony resection. The vertical slits in the proximal and distal aspects of the guide are used to position the saw. The screw holes marked on either side will line up with the prefabricated plate shown in **D** and **E**. **C,** Scapula skin paddle dissected with the patient-specific cutting guide in place marking the osteotomy sites. **D,** The prefabricated reconstruction plate screwed into the graft positioning the lateral border of the scapula superiorly which is wide enough to support future dental implants. **E,** The scapula inset with the reconstruction plate lining up with the pre-drilled holes from the patient-specific cutting guide. Note the seamless bony abutment between the distal segment of the graft and the remaining mandible. **F,** Immediate postoperative image highlighting the maintenance of mandibular projection obtained with this technique.

Surgical Margins

Historically, some of the difficulty in discussing "positive" margins has been the heterogeneity of two key aspects that define the term. First is the width of the margin. One of the first papers to examine margins was Looser and colleagues in 1978, who somewhat arbitrarily used 5 mm as a cutoff for their analysis and reported a decrease in local recurrence and increase in overall survival.[41] Second, there was a lack of consensus on whether or not carcinoma-in-situ or dysplasia within the conventional 5-mm margins was considered "positive." More recently, based on critical analysis by pathologists, the community has decided that there is strong evidence to support that only frank tumor within the defined margin should be counted as "positive."[42] A recent survey by Meier and co-workers[43] revealed that there was still a lack of consensus in the field. They reported that most surgeons have adopted the 5-mm cutoff, but there was lack of agreement on whether or not carcinoma-in-situ within the 5-mm zone represented a positive margin. Perhaps the most important thing in this discussion is not finding the "right" definition, but finding the uniform definition, so that research in the future can report on congruent topics.

More recently, several studies have called into question the dogma of the 5-mm margin. The only study looking specifically at buccal cancer, by Chiou and associates in 2010,[44] reported that, locoregional recurrence rates were significantly different using a 3-mm margin as a cutoff, but not when looking at a cutoff of a 5-mm margin. This finding would suggest that a ≥3-mm margin may be adequate. Brandwein-Gensler and co-workers[45] have further called into question the significance of the evaluation of the margin entirely. These authors reported a greater correlation with local recurrence and a composite histologic scoring system using lymphatic invasion, perineural invasion, and histologic appearance. Sutton and colleagues[46] reported a similar finding: Although they found 5-mm margins to increase disease-free survival and decrease local recurrence, they also found that failing to obtain a 5-mm margin was correlated with the "histological aggressiveness" of the tumor seen on pathology. The authors go on to hypothesize that "margins" may be a histologic marker for tumor aggression rather than an important factor unto themselves. Because no surgeon will intentionally leave positive margins on resection, the presence of histologically positive margins could indicate that the tumor cells are more rapidly invading what appears to be clinically normal tissue in the operating room. This leads to the suggestion of critically evaluating the biopsy specimen for the markers of aggressiveness outlined earlier, and treating these tumors intraoperatively with slightly greater margins than the surgeon typically would anticipate. Although there has been no trial to validate this suggestion, the authors feel that clinicians should use every piece of evidence at their disposal, including histologic clues provided on the biopsy, to help guide management of the patient.

Despite this evidence, for the management of T3/T4 buccal cancer the authors still use the standard convention of a 5-mm



• **Fig. 26.7** Large recurrent buccal cancer reconstructed with rectus abdominis flap. **A,** Preoperative photo demonstrating lack of integrity of oral cavity and significant cosmetic defect. **B,** Large volume of soft tissue excised, instrument highlighting preoperative through-and-through nature. **C,** One month post-op demonstrating regained integrity of oral sphincter and improved cosmesis.

margin in their clinical practice. However, the authors think that the field needs further research to determine the necessity of these margins. Although there is only a 2-mm difference between the two proposed definitions, when this 2 mm is applied to the radius of a hypothetical tumor, the overall volume resected becomes quite clinically significant for patients and their subsequent reconstruction.

Adjuvant Radiation Therapy

As discussed earlier, surgery is the definitive treatment of choice for T3/T4 buccal cancer. However, adjuvant radiation therapy has proved to be beneficial in select patients, especially those with frankly positive or close (<5 mm) surgical margins. Multiple studies have demonstrated a significant decrease in local recurrence rates when comparing patients with positive margins who undergo adjuvant radiation to those who undergo surgery alone.[47-50] One other indication that has been described in the literature is the presence of a single positive node in a T1/T2 tumor. Shrime and associates[51] showed an increase in survival for floor-of-mouth and oral-tongue cancers when adjuvant radiation was provided in the setting of one lymph node <3 cm. However, it is worth noting that the paper did not report a significant result in the combined analysis, which would contain buccal cancer.

Timing has been another topic of discussion. Several historic studies have shown an improvement in local recurrence rates when the radiation therapy is initiated within 30 days of surgical resection. The first study to do so was by Vikram and colleagues.[48] More recently, a retrospective study looking specifically at buccal cancer corroborated this finding with an increase in local recurrence in those patients who initiated radiation more than 30 days after surgery, when compared to those with an earlier initiation date.[49]

Unfortunately, additional indications for adjuvant radiation therapy have not been as well defined in the literature, though many of been proposed. Commonly used criteria include primary tumor depth greater than 10 mm, extracapsular spread of lymph nodes, perineural invasion, and T3/T4 tumors. Many institutions including our own still use consensus expert opinion on a case-by-case basis to decide which patients will best benefit from adjuvant radiation therapy. At our institution, all patients with T3/T4 buccal cancer receive adjuvant radiation therapy within 30 days of surgery.

The recommendations for dosage and duration of postoperative radiation therapy are based on the landmark large prospective randomized controlled trial by Peters and co-workers.[50] All patients who meet the criteria given earlier, which include T3/T4 disease, should receive 1.8 Gy per day, 5 days per week, to a total dosage of 58 Gy to the surgical site and neck. High-risk areas, namely areas with nodes exhibiting extracapsular spread, should receive a boosted dose of 60 to 63 Gy.

Adjuvant Chemotherapy

Adjuvant chemotherapy, often combined with radiation therapy, has shown promising results in recent years. However, no studies have looked specifically at adjuvant chemotherapy for the treatment of buccal cancer, and so the evidence and recommendations provided here are all generalized from literature looking at squamous cell carcinoma of the head and neck. There is now strong evidence for adjunctive chemoradiation therapy in comparison to adjunctive radiation therapy alone for select patients. Two large prospective phase III trials, Bernier and colleagues and Cooper and associates, showed benefit in local recurrence rates and disease-free survival with adjuvant chemoradiation consisting of cisplatin 100 mg/m^2 given at 1, 22, and 43 days plus concurrent adjuvant radiation when compared to adjuvant radiation alone.[52,53] Additionally, Bernier and co-workers showed an improvement in overall survival with the chemoradiation regimen, which Cooper and colleagues failed to show. A meta-analysis of the two trials totaling 739 patients who were considered to be "high risk" due to positive margins, stage III–IV disease, 2+ nodal involvement, extracapsular spread, perineural disease, or vascular embolisms demonstrated an improvement in overall survival, local control, and disease-free survival.[54] Recently, 10-year follow-up results from the Cooper trial were published.[55] The trial still failed to show any benefit in overall survival, but did demonstrate a persistent benefit in local recurrence and disease-free survival only in the subset of patients with microscopically involved surgical margins or extracapsular lymph node spread.

The decision to recommend adjuvant chemotherapy to a patient is made on consensus expert opinion on a case-by-case basis. However, the authors feel that the trials just presented are generalizable to the management of T3/T4 buccal cancer. These trials provide strong evidence for the use of adjuvant chemoradiation therapy for these patients because they are, by definition, advanced stage. This was one of the inclusion criteria for the Bernier trial, which demonstrated benefit in local recurrence, disease-free survival, and overall survival.[54]

Definitive Radiation and Chemotherapy

Although surgical treatment is undoubtedly the first option for patients with T3/T4 buccal cancer, definitive radiation or radiochemotherapy can be considered in circumstances where surgery is not an economic option or is contraindicated because of other comorbidities of the patient. This has been especially important in Central and Southeast Asia, where the rate of buccal cancer is much higher because of the prevalence of "pan" chewing and surgery is not as readily available an option as it is in the West.

There have been several studies looking at definitive radiation therapy as a treatment option. The largest of these trials was a retrospective review of 234 cases conducted in India by Nair and co-workers.[24] This trial reported 3-year disease-free survival rates for patients with stage I and II disease, 85% and 63%, respectively. These rates are comparable to those of similarly staged patients who underwent surgery elsewhere. However, for patients with stage III and IV disease, 3-year survival rates were 41% and 15%, respectively, which is much lower than desired. To put this in perspective, the heavily cited retrospective study on buccal cancer by Diaz and colleagues,

offering surgery plus adjunctive radiation when indicated (extracapsular spread or positive margins), reported 3-year survival rates of 78%, 75%, 72%, and 50% for stages I, II, III, and IV, respectively.[11] These results show that definitive radiation therapy may be a reasonable option for patients with stage I or II disease, but for those with T3/T4 tumors, as discussed in this chapter, definitive radiation therapy is not an adequate substitute for surgery.

In 2015, Iqbal and associates published a retrospective study of 63 patients on definitive chemoradiation therapy for patients with buccal cancer.[56] The regimen provided was gemcitabine + cisplatin + 55 Gy. Overall, the study reported a 5-year overall survival, disease-free survival, and progression-free survival rates of 30%, 49%, and 30%, respectively. Specifically looking at patients with T3/T4 lesions, the study reported an 18% complete response, 73% partial response, and 9% stable disease or progression. Unfortunately, the results of this study are also not promising for advanced stages of buccal cancer.

However, a study by Vedasoundaram and colleagues in 2014 has shown some promise for local control of even advanced buccal cancer using definitive radiation therapy in the form of high-dose-rate interstitial brachytherapy.[57] This 33-patient study, with an average follow-up time of 26 months, reported local control rates of 100%, 85%, and 80% for stage I, II, and III disease, respectively. This is a preliminary study, and further research would be required to offer a definitive comparison between this option and the gold standard of definitive surgical management with or without adjuvant radiation therapy. It is worth noting, however, that this therapy is highly complex and, in the authors' opinion, does not help solve the problem that Nair and co-workers were initially trying to address, of a more economically feasible option for the management of buccal cancer in resource-poor regions.

Chemoradiation is sometimes selected for patients who are thought to be too frail to undergo surgical therapy. However, radiation therapy is still a treatment based on the mechanical destruction of cancerous tissue. As a result, many patients have significant post-radiation scarring that can result in clinically significant trismus and cosmetic defects, especially if the skin is involved. There are certainly patients who are not suited for prolonged surgical resection and reconstruction, but radiation therapy is a taxing treatment for patients as well, with potentially greater functional impairment than modern surgery and reconstruction.

Overall, the authors acknowledge the fact that not all patients have the option to undergo surgery with or without adjuvant radiation therapy, the current standard of care for T3/T4 buccal cancer. When this treatment option is not available, patients and clinicians must try other options. The evidence presented here supports the use of definitive radiation or chemoradiation therapy for early-stage lesions, which have shown comparable results to surgery. Unfortunately, for advanced disease there is no effective, proven alternative to surgery at this time.

Surveillance

Buccal cancer has been reported to have some of the highest rates of recurrence by anatomic subsite. It is hypothesized that this is due to the lack of anatomic barriers in this region once the cancer penetrates the buccinator muscle and fascia.[12] Thus, continued postoperative surveillance is of paramount importance with T3/T4 buccal cancer. In the recent literature, 5-year local control and overall control rates for buccal cancer have ranged between 57.5% and 86%[10,33] and between 36.3% and 78%,[10,32,33] respectively. It is also important to note that recurrence usually occurs relatively early. The largest study in the United States, that by Diaz and colleagues, reported the median time to recur was 8 months, with the majority within 1 year.[11] Although recurrence can certainly occur at any time, the first year following surgical resection is perhaps the most important.

As a result, the authors recommend a follow-up visit every month for the first year, every second month for the second year, every third month for the third year, and every six months for the fourth and fifth years in accordance with the National Comprehensive Cancer Network guidelines. After 5 years without evidence of recurrence, it is the surgeon's choice whether to continue yearly follow-up or discharge the patient. At these follow-up visits it is important that a thorough examination be performed, focusing on the local area of tumor resection and level I–III nodes where regional recurrence is most likely, given the anatomic drainage patterns. Often complete visualization of the tumor resection site is difficult because of bulky flaps or scarring and resultant trismus, especially if adjunctive radiation therapy is indicated. In situations where complete visualization cannot be obtained, the authors recommend CT or MRI imaging to better assess for recurrence. Smit and associates reported on a cohort of postoperative oral squamous cell carcinoma patients and found that 70% of patients with recurrence reported pain as their first symptom.[58] Therefore, pain is an important warning sign of possible recurrence and should be thoroughly evaluated.

In patients who do experience local recurrence, salvage surgery offers the best chance at increased survival. Koo and colleagues reported an improved survival after recurrence for patients who received reoperation with or without adjuvant radiation therapy when compared to patients who received salvage chemoradiation therapy alone.[59] The management of regional recurrence depends on whether or not the level of recurrence has already undergone neck dissection. In the previously undissected neck, a neck dissection should be performed. However, the management of regional recurrence in a previously dissected neck is more complex because the recurrence is often in the surrounding soft tissue and can be intimately involved with the great vessels of the neck. In this case, imaging should be performed to evaluate the resectability of the lesion. If resection is possible, the authors recommend surgical resection with adjuvant radiation therapy. If the recurrence does not appear resectable, chemoradiation is best option. Unfortunately, in studies specific to buccal cancer, the reported rates of successful salvage are low, ranging between 9% and 22%.[11,32] Although this chance of success is low, salvage surgery still offers a chance at survival. These data can help guide PARQ discussions with our patients.

Regular follow-up and surveillance does more than just check for recurrence and offer a chance at salvage surgery. It

helps build a long-term relationship of trust, which is perhaps more important. As we are well aware, most of these patients will eventually succumb to their disease. With regular follow-up, we can continue to provide support and information throughout this process. We should be reminded to always educate our patients on all treatment options, including palliative care if it is appropriate, so that we can best empower our patients in a joint decision-making approach.

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27

Early Palatomaxillary Cancer

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Squamous cell carcinoma (SCC) of the maxillary gingiva, maxillary sinus, hard palate, and alveolar ridge is rare, comprising approximately 66% of maxillary malignancies and 3% to 5% of all head and neck cancers.[1] Compared with SCC of other intraoral sites, maxillary SCC is a diagnostic challenge because its diverse clinical presentations often mimic benign disease processes such as sinusitis, periodontal disease, lichen planus, inflammatory reactive tumor-like lesions, and nonspecific granulation tissue[2] (Figs. 27.1 and 27.2). Because the region's overlying mucosa is so thin, underlying bone and associated structures are affected earlier.[3] This type of malignancy most often presents after the fifth decade of life and has a predilection for males.

Clinical and Radiographic Features

Maxillary malignancies generally remain asymptomatic or present with non-specific sinonasal symptoms until invasion into adjacent structures occurs. Common symptoms include facial or dental pain, loose teeth, nasal obstruction, and epistaxis. Less common presentations include new onset facial asymmetry, displacement or protrusion of the globe with superior extension, and midface paresthesia with involvement of the trigeminal nerve. Clinical presentations of maxillary gingival SCC vary from case to case; they can often appear as ulcerated, exophytic, leukoplakic, erythroplakic, or erythroleukoplakic lesions (Fig. 27.3). Plain dental radiographs, such as a panoramic radiograph, may show a "moth-eaten" destruction of lamina dura and surrounding bone, as well as cloudy maxillary sinuses. However, computed tomography (CT) and magnetic resonance imaging (MRI) provide comprehensive visualization of the tumor and depict the pertinent prognostic factors: tumor thickness, depth of invasion, and bony involvement. While CT shows bone involvement, MRI delineates the tumor and perineural invasion and discriminates between tumor and mucus in an obstructed maxillary sinus (Fig. 27.4). The proximity of oral mucosa of the vestibule to the alveolar bone creates a challenge for radiologic evaluation, thus methods have been developed to differentiate between such structures. The "puffed cheek" method works well for CT scans but cannot be maintained for lengthy magnetic resonance imaging. Thus, Dillon and colleagues[4] described placing a 2- × 2-cm gauze pad in the vestibule to provide adequate displacement of oral mucosa. The gauze is of low signal intensity on both T1 and T2 images and enables improved visualization by the neuroradiologist[4] (Fig. 27.5). Additionally, positron emission tomography (PET) imaging is a useful adjunct for detecting regional nodal metastasis, distant metastases, and other primary tumors. It is most commonly obtained for patients with T3 and T4 tumors or when metastasis is suspected.



• **Fig. 27.1** Left maxillary gingival ulcerative lesion consistent with clinical picture of periapical abscess, granulation tissue, or malignancy. Biopsy of lesion revealed squamous cell carcinoma.



• **Fig. 27.2** Lesion of the right maxillary palate treated as periodontal disease for 3 months before biopsy revealed squamous cell carcinoma.



• **Fig. 27.3** Ulcerated and exophytic erythroleukoplakic gingival lesion of the right maxilla involving teeth #1-4, noted to be squamous cell carcinoma.



• **Fig. 27.4** Noncontrast CT image (axial view) of right maxillary posterior squamous cell carcinoma indicating the associated bony erosion and subtle soft tissue thickening in the region of teeth #1 to 4 consistent with the clinical picture shown in Fig. 27.3.

Variants of Squamous Cell Carcinoma

SCCs account for more than 90% of oral cavity malignancies.[4] Variants and subtypes include adenosquamous cell carcinoma, basaloid SCC, spindle cell carcinoma, verrucous carcinoma, and maxillary sinus carcinoma.

Adenosquamous Carcinoma

Adenosquamous carcinoma was first identified by Gerughty and colleagues in 1968. Controversy existed over the definition of this entity, in that many people originally believed it was an aggressive variant of mucoepidermoid carcinoma. Histologically, these tumors are comprised of SCC in addition to glandular abnormalities, with or without mucin. This entity has a higher propensity for distant metastases, specifically to the lung.[5]



• **Fig. 27.5** T1-weighted MRI (axial view) depicting gauze placement in the right buccal vestibule extending from the first molar to the midline for improved visualization of involved planes.

Basaloid Squamous Cell Carcinoma

The World Health Organization recognized basaloid as an aggressive variant of SCC in 2005. Even though its incidence in the head and neck regions is a mere 2%, basaloid SCC is most commonly found in the upper aerodigestive tract.[3] These tumors have a predilection for men in the sixth to eighth decades of life. Histopathologic analysis reveals basaloid-appearing nests with comedonecrosis and dysplastic surface mucosal epithelium.[6]

Verrucous Carcinoma

Verrucous carcinoma is a low-grade variant of SCC, comprising less than 5% of SCCs. Intraorally it most commonly affects the maxillary and mandibular vestibule, gingiva, buccal mucosa, tongue, and hard palate. The site of chronic tobacco placement most often corresponds to the exact site of lesion development. Treatment modalities for verrucous carcinoma of the oral cavity are the same as those for SCC, although neck dissection may not be indicated because verrucous carcinoma typically is slower to metastasize.[7]

Spindle Cell Carcinoma

In the head and neck region, spindle cell carcinomas are most commonly found in the larynx. This is another aggressive

variant of SCC and histologically contains an SCC component as well as a spindle cell with sarcomatous appearance.[8]

Maxillary Sinus

Maxillary sinus malignancies are extremely rare and comprise 0.2% to 0.5% of all carcinomas and 3% of head and neck carcinomas; the incidence is higher in Asia. In the United States and Europe, 80% of paranasal sinus carcinomas involve the maxillary sinus.[9]

Risk Factors

Smoking is a well-established etiologic factor for SCC of the maxilla and sinonasal tract. Evidence suggests a dose-response relationship to wood dust exposure and adenocarcinoma of the sinuses.[10] Antral carcinomas are identified with risk factors involving chemicals associated with the farming, metal, leather, and construction industries. Human papillomavirus as a causal agent of maxillary carcinoma is also documented.

Principles of Management

According to the National Comprehensive Cancer Network (NCCN) 2014 guidelines, SCC of the maxillary gingiva, as well as other malignancies of the head and neck, should be managed by a comprehensive team of specialists. This team includes a head and neck surgeon, reconstructive surgeon, dentist/prosthodontist, radiologist, medical oncologist, radiation oncologist, speech and swallow therapist, nutritionist, and social worker. Additional medical subspecialties may be needed depending on the structures affected by the malignancy. These include neurosurgery, ophthalmology, and/or audiology. The expertise of psychologists, addiction services, and palliative care providers should also be an integral part of the head and neck cancer team. In the 2014 guidelines, comprehensive pain management was added as a consulting subspecialty, because the pain from these malignancies can severely affect one's quality of life.[11]

Surgical Management

TNM Staging

Tumor staging is important in determining treatment. Table 27.1 lists the classification for determining staging of the primary maxillary tumor.[11]

The American Joint Committee on Cancer (AJCC) recently made substative modifications to the TNM staging criteria and staging system for head and neck cancer in general and oral cavity cancer in particular. These changes more accurately represent the unique biologic, clinical, and epidemiologic features of oral squamous cell carcinoma (OSCC) (see Table 27.1). In the first modification, the T stage now incorporates depth of invasion (DOI). In the 1980s, Spiro and colleagues identified the importance of tumor thickness as a prognostic indicator in oral cavity cancer. Depth of invasion is a more sophisticated and reproducible method of measuring a tumor. It is measured by first finding the "horizon" of the basement membrane of the adjacent squamous mucosa, and DOI is defined as the deepest point of tumor invasion (in mm) from that line. Extrinsic muscle infiltration has been removed from the staging criteria because DOI is more representative of the clinical problem both clinically and pathologically. DOI assesses the invasiveness of the tumor rather than any exophytic component.

In the second modification, extranodal extension is now recognized when categorizing metastatic cancer to the cervical lymph nodes. Additional updates to this classification scheme include the following:

1. Separate N category approaches are given for patients treated without cervical lymph node dissection (clinical N [cN]) and patients treated with cervical lymph node dissection (pathological N [pN]).
2. Extranodal extension (ENE) is introduced as a descriptor in N categorization for all HPV-negative cancers, and its presence is designated pN2a for a single ipsilateral node <3cm and pN3b for all other node(s).
3. Clinically overt ENE is classified as ENE and is considered ENE(+) for cN.
4. Pathologically detected ENE is classified as either ENE_{mi} (<2 mm) or ENE_{ma}(>2 mm) for data collection purposes only, but both are considered ENE(+) for definition of pN.

However, pathologic stage does not trump clinical stage, and assignment of ENE should be based primarily on physical examination, rather than on imaging studies.

The primary tumor stage remains essentially the same in the new system, with the exception that DOI will increase the T category by 1 for each 5-mm of tumor depth (up to ≥10 mm). Pathological ENE(+) will increase the nodal category by 1. In addition, the AJCC recommends that other prognostic factors be considered and recorded along with standard staging information, including Eastern Cooperative Oncology Group (ECOG)/Zubrod or Karnofsky performance measures, tobacco and alcohol use, tumor location, number and size of nodes, perineural invasion, and ENE.

The new AJCC TNM staging highlights the worst pattern of invasion (WPOI) as a validated outcome predictor. It is recommended that WPOI-5, defined as tumor dispersion of ≥1 mm between tumor satellites, be recorded as part of pathologic staging. Even in early-stage oral cancer, a DOI of >4 mm combined with a WPOI-5 increases the probability of recurrence to approximately 42%. Perineural invasion (PNI) or lymphovascular invasion constitute a WPOI-5 classification. When identified, PNI would be subclassified as either intratumoral or extratumoral. Named nerves should be specified and PNI should be subclassified as focal or multifocal.

Treatment Planning

Maxillary resection and reconstruction is challenging because of the functional and esthetic complexity of the midface. Removal of the malignancy with adequate margins (1 to 2 cm) must be considered in conjunction with preservation of the patient's oral nutritional, speaking, and visual competencies. Functional sequelae of a maxillectomy include soft tissue prolapse, deglutition deficiencies, and visual changes due to orbital

TABLE 27.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor ≥2 cm and ≤4 cm in greatest dimension
T3	Tumor ≥4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease.
T4a	Moderately advanced local disease. (lip) Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose); (oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face). Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
T4b	Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base or encases carotid artery
Regional Lymph Nodes: Clinical (cN)	Oropharynx (p16-) and hypopharynx
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N3	Lymph node(s) larger than 6cm and ENE(–) or metastasis in any node(s) and clinically overt ENE(+)
N3a	Lymph node(s) >6 cm and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L).* Similarly, clinical and pathological ENE should be recorded as either ENE(–) or ENE(+)
Regional Lymph Nodes: Pathological (pN)	Oropharynx (p16-) and hypopharynx
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
pN2	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2a	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–)
pN2b	metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN3	Lymph node(s) >6 cm and ENE(–); or metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)
pN3a	Lymph node(s) >6 cm and ENE(–)
pN3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)

TABLE 27.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)—cont'd

Distant Metastasis (M)

Oropharynx (p16-) and hypopharynx

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

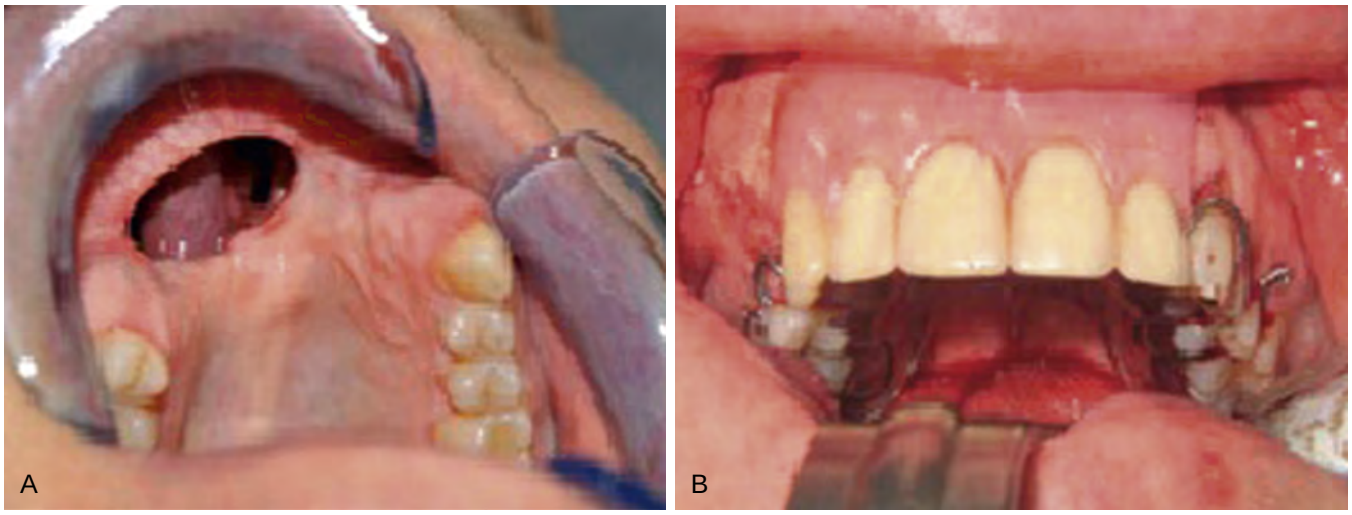
Registry Data Collection Variables

1. Lip location (external or vermilion border)
2. ENE clinical: ENE(+) or (–)
3. ENE pathological: ENE(+) or ENE(–)
4. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
5. Perineural invasion
6. Lymphovascular invasion
7. p16/HPV status
8. Performance status
9. Tobacco use and pack-years
10. Alchohol use
11. Depression diagnosis
12. Depth of invasion (mm)
13. Margin status (grossly involved, microscopic involvement)
14. Distance of tumor (or moderate/severe dysplasia) from closest margin
15. WPOI-5

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated

From Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In Amin MB et al, eds. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017. http://dx.doi.org/10.1007/978-3-319-40618-3_10.



• **Fig. 27.6** **A,** Postoperative image 1 year after resection of right maxillary squamous cell carcinoma lesion. **B,** Obturator fabricated for defect closure and tooth replacement.

volume loss and removal of the orbital floor and rim. Esthetic difficulties of the facial reconstruction include color and texture matching of free flap skin, symmetry, and scarring.[12]

Before the resection, the options of an obturator versus a local rotational or microvascular free flap must be discussed with the patient in detail. Planned reconstruction with an obturator generally results in shorter operating room times and affords direct vision to the resection site during routine follow-up visits (Fig. 27.6). Despite the ability of modern imaging modalities to directly survey the tumor bed, literature suggests that they provide no increased ability to identify recurrence earlier in unreconstructed patients.[13] Radiation oncologists may prefer to have a removable obturator placed for improved targeted therapy versus treatment through bulky reconstruction. The addition of teeth on the obturator at the outset is a consideration for those patients in whom missing dentition would present an additional physical or psychologic burden. Obturator design, fit, and comfort require skilled technique on the part of the prosthodontist, and meticulous hygiene and sufficient dexterity on the part of the patient.[8] Conversely, free flap reconstruction is usually performed at the time of surgical ablation. Immediate dental reconstruction that allows for masticatory rehabilitation using dental implants has been presented in the literature but this is often performed as a subsequent procedure. Although research outcomes vary, Yetzer and Fernandez[14] performed a retrospective chart review of 21 patients with orbitomaxillary defects and found there was a better quality of life in patients who underwent free flap reconstruction compared with those who received prosthetic obturation.

Patients with locally advanced SCC should be evaluated for the presence of distant metastases before surgical intervention. This includes basic laboratory work-up, specifically liver function tests. Preoperative chest CT or radiography to screen for lung metastasis and a PET/CT scan for more advanced tumor stage should be considered to rule out distant spread of disease. All patients should also have a preoperative panoramic radiograph to assess the quality of the dentition (in preparation for potential radiation treatment) and to assess the sites for resection osteotomies. Medical optimization by the patient's primary care physician should be performed to ensure the best prognosis.

Surgical Resection

In 2012, Cordeiro and Chen[15] classified maxillectomies based on the extent of the resection, when considering the maxilla as a six-sided geometric shape. The type I, or partial, maxillectomy is resection of one to two walls of the maxillary sinus (usually the anterior and medial). A type II, or subtotal, maxillectomy involves removal of the inferior five walls of the maxillary sinus, but the orbital floor remains intact. The subtotal maxillectomy is further subclassified into type IIA, which includes less than 50% of the hard palate, and type IIB, which includes more than 50% of the transverse palate and/or the anterior maxillary arch. Type III (total) maxillectomy is defined as resection of all six maxillary sinus walls, with (type IIIA) or without (type IIIB) removal of the orbit. A type IV maxillectomy involves the superior five maxillary sinus walls and orbit, rendering exposure of the dura and brain.

A second classification system for maxillary defects was created for ease of discussion between the surgeon and the maxillofacial prosthodontist. Brown's classification describes the maxillary defect, as well as the likely functional and esthetic result[16] (Fig. 27.7). The defects are classified according to the vertical and horizontal dimensions of the defect. The vertical component is assigned a number: class I (maxillectomy with no oro-antral fistula), class II (low maxillectomy), class III (high maxillectomy), and class IV (radical maxillectomy).

Classes II to IV are further specified by a letter component defining the horizontal component of the resection: *a,* unilateral alveolar maxilla and hard palate not involving the nasal septum or crossing the midline; *b,* bilateral alveolar maxilla and

hard palate and may include the nasal septum; and *c,* entire alveolar maxilla and hard palate.

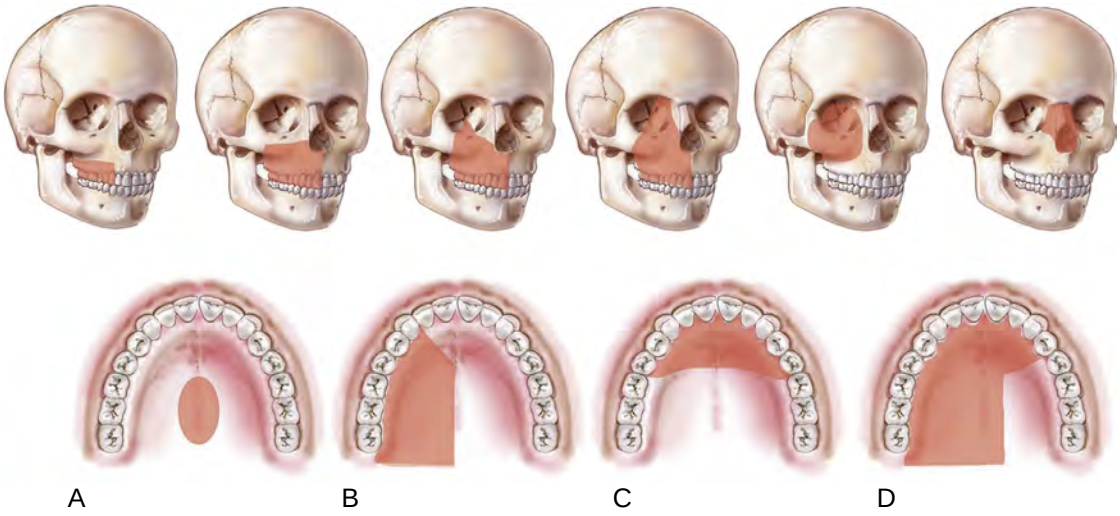
Brown and Shaw[16] further specify that the number classification dictates the esthetic effect of surgery on a patient whereas the letter classification specifies the increasing difficulty of oral and dental rehabilitation (Fig. 27.8).

Access to the maxilla can be via a transoral or a transfacial approach usually in the form of Weber-Ferguson access, with or without some form of modification depending upon the posterior extent of tumor and involvement of the orbit.

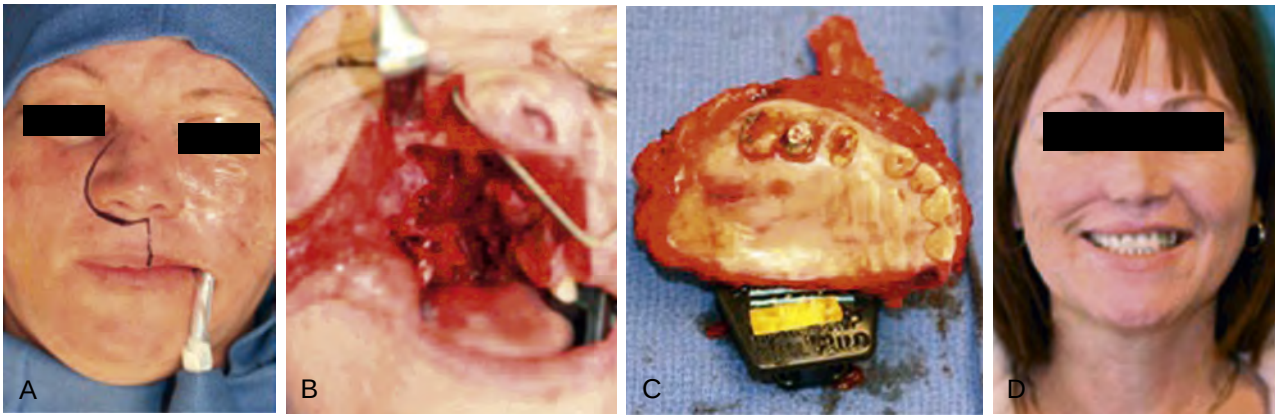
Neck Dissection

The role of an elective neck dissection for patients with SCC of the maxilla with a clinically negative neck remains somewhat controversial, although recent literature supports this treatment. Historically, the rate of cervical metastasis of SCC from the maxillary gingiva was considered to be lower than that of other oral sites. Recent retrospective studies have shown that the rate of cervical metastasis is higher, ranging from 21.5% to 66.7%.[17] The pathway of metastasis involves lymph drainage from the maxillary gingiva through the buccal lymphatic system into the submandibular lymph nodes. Due to the rich lymphatic vessels in the gingival buccal sulci, lesions extending into the mucosa of the sulcus have increased rates of metastasis when compared with that of isolated maxillary gingival lesions. In a study by Zhang and colleagues,[17] all lesions involving the gingival-buccal sulcus were noted to have advanced tumor staging (at least T3).

Morris and colleagues[18] performed a retrospective study of 139 patients (1985 to 2006) with SCC of the hard palate and maxillary alveolus to evaluate incidence of neck metastasis and lymph node involvement. They found that there was high incidence of regional recurrence (30%) in patients who were clinically N0 occurring in a mean time of 6 months. Patients with advanced stage (pT2 to T4) primary tumors were at the highest risk. Elective treatment of the neck (selective neck dissections of levels I to III) was

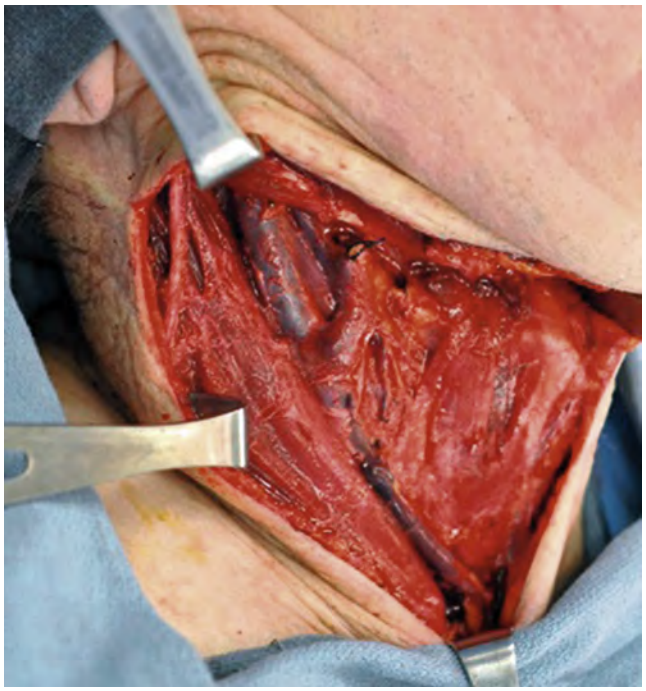


• **Fig. 27.7** Brown's classification of maxillectomies.



• **Fig. 27.8** **A,** Planned Weber-Ferguson incision. **B,** Right maxillary resection via Weber-Ferguson access. **C,** Resected right maxillary specimen. **D,** Postoperative facial photograph. (Photographs courtesy of Brian Schmidt, DDS, MD, PhD, FACS.)

recommended in all patients with locally advanced maxillary gingival SCCs. Additionally, Yang and colleagues[19] performed a retrospective cohort study of 31 patients with SCC of the maxillary gingiva and 31 with SCC of the hard palate. The incidence of an occult neck node in this group was 27.5% (32.1% for the patients with a maxillary gingival malignancy alone). Based on this study, the authors recommended elective neck dissection for all patients with stage T2 or higher SCC of the gingiva or hard palate. Zhang and colleagues[17] also confirmed these findings, reporting that most lymph node involvement was detected at levels I to III with low rates of metastasis to levels IV and V. His group also studied risks factors for cervical metastasis for maxillary gingival SCC. Pathologic staging was noted to be the most important factor, followed by involvement of the gingival-buccal sulcus.[17] Thus, selective neck dissections from levels I to III for T4 maxillary SCC are strongly recommended, especially when there is gingival-buccal sulcus involvement[17] (Fig. 27.9).



• **Fig. 27.9** Right ipsilateral neck dissection at levels I to IV with concurrent resection of a right maxillary gingival squamous cell carcinoma lesion.

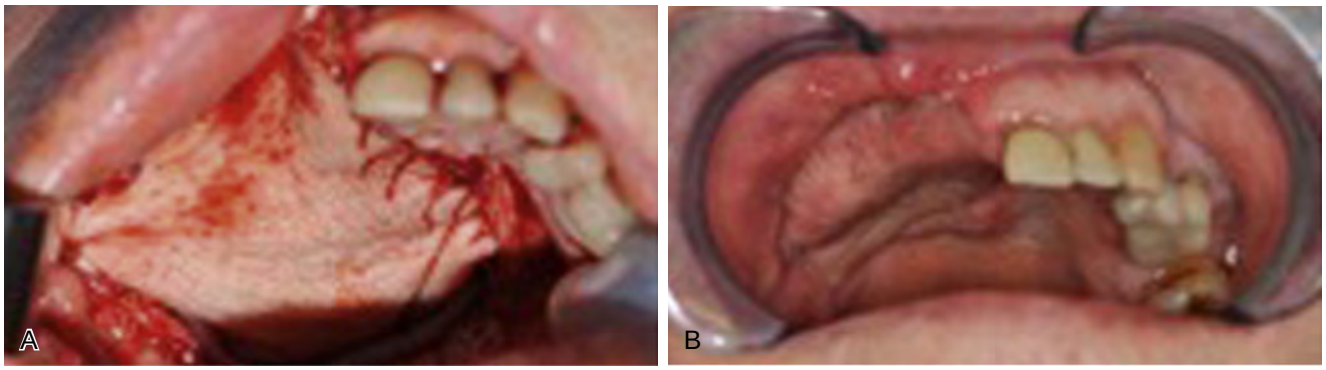
Reconstruction

The goals of maxillary reconstruction include appropriate wound closure, elimination of the surgical defect, support of the globe or elimination of the orbital volume loss defect, preservation of the partition between the maxillary sinus and adjacent structures, maintenance of the esthetic facial projections, and palatal reconstruction.[20] Cordeiro and colleagues fabricated an algorithm for facial reconstruction after maxillectomy, based on their experience with 100 flaps performed at Memorial Sloan-Kettering Cancer Center.[20] The authors recommended a radial forearm flap for the type I maxillectomy, because it provides sufficient skin for such low volume yet high surface area defects, and affords a long pedicle for neck anastomosis. A radial forearm fasciocutaneous free flap is recommended for type IIA maxillectomies, whereas a radial forearm osseocutaneous flap is recommended for type IIB defects (Fig. 27.10). In either situation, dental implants can be placed for prosthetic retention. Due to the complexity of type III defects, multiple flaps may be indicated—a split calvarial, iliac crest, or rib graft to re-create the orbital floor, and a rectus abdominis myocutaneous flap for replacement of the mucosa and skin. Alternatively, a temporalis rotational flap and obturator is a non–free flap option.[20] Kosutic and colleagues[21] describe reconstruction of a radical maxillectomy with orbital exenteration with a latissimus dorsi flap in conjunction with a scapula/teres muscle/infraspinatus muscle flap for bony reconstruction of the orbit. A rectus abdominis flap is recommended for a type IV maxillectomy reconstruction[21] (Fig. 27.11).

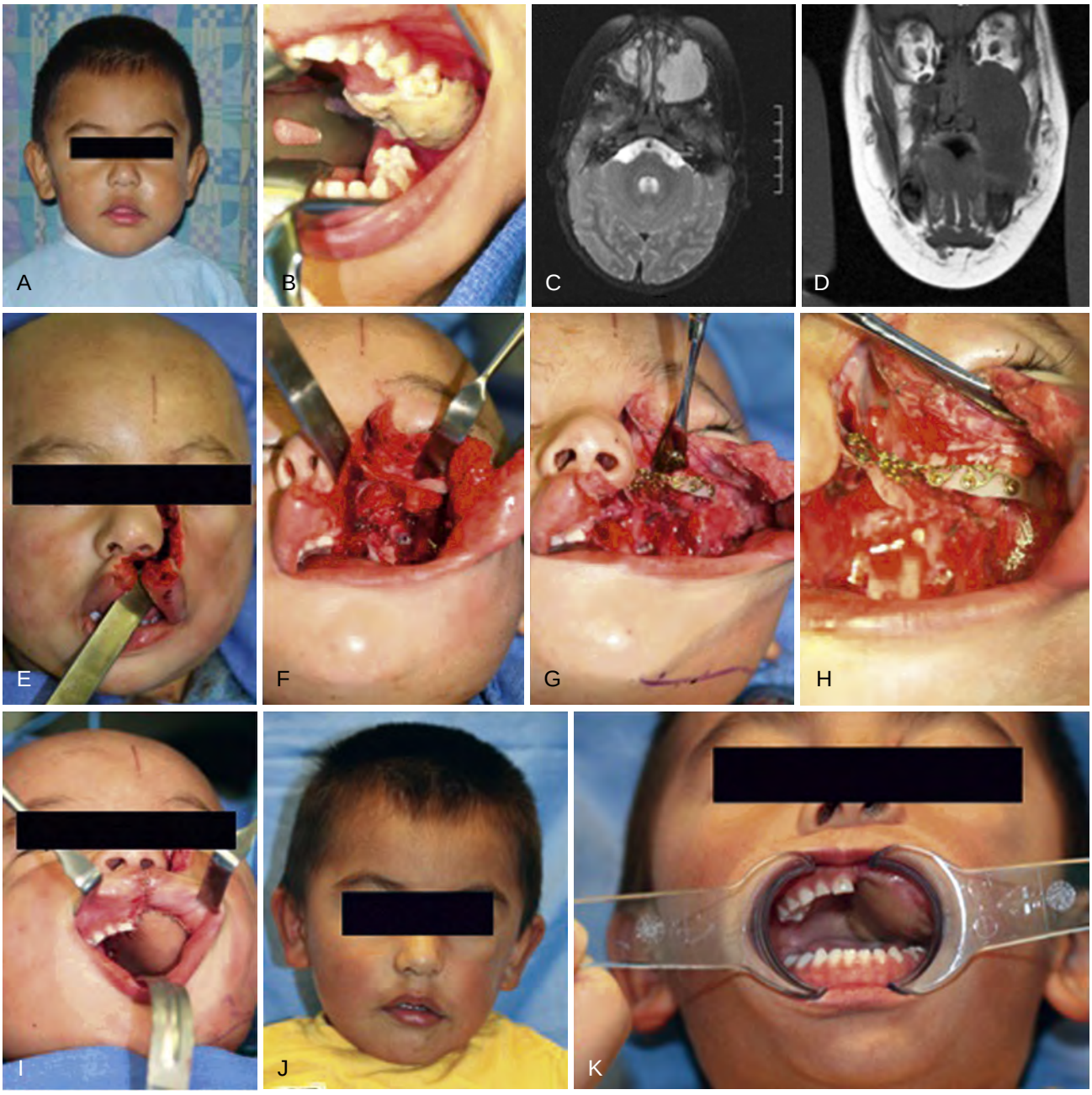
Adjuvant Therapies

Radiation Therapy

Surgical resection with partial or total maxillectomy is widely accepted as the most effective treatment for palate-maxillary



• **Fig. 27.10** Radial forearm free flap after immediate inset into maxillary defect **(A)** and 2 months postoperatively **(B).**



• **Fig. 27.11** **A,** Clinical photograph of patient with moderate left-sided facial edema. **B,** Intraoral photograph of left maxillary tumor. **C,** Axial T1-weighted MRI of left maxillary neoplasm. **D,** Coronal T2-weighted MRI of left maxillary neoplasm. **E** and **F,** Tumor resection via Weber-Ferguson approach. **G** and **H,** Left maxillary reconstruction. **I,** Flap inset. **J,** Clinical photograph after free flap reconstruction. **K,** Intraoral photograph after free flap reconstruction. (Photographs courtesy of Brian Schmidt, DDS, MD, PhD, FACS.)

SCC. In cases in which free resection margins are unobtainable, patient condition is poor, or the patient refuses surgical intervention, radiation therapy should be considered.

The efficacy of radiation therapy in the treatment of maxillary SCCs has been studied. Poeschl and colleagues[21] performed a retrospective review of 93 patients with alveolar, gingival, or palatal maxillary SCC treated with resection and/or radiation therapy.[22] The majority of patients (66%) presented with stage T4. Patients who did not receive surgical treatment due to unresectable lesions (T4b) or significant medical comorbidities died subsequently of tumor-related causes. For patients who received adjuvant therapy after surgical resection, the authors noted an overall 5-year survival rate of 71%. In this study, prognosis for patients without surgical resection was poor. However, surgical intervention with adjuvant radiation therapy for cases in which margins were involved or deemed close provided a better overall prognosis. Radiation therapy is recommended to begin within 6 weeks of surgical resection.

The consequences of radiation therapy and their effects on patient quality of life should be a part of the treatment planning discussion. Side effects of radiation therapy vary based on the anatomic area of treatment, cumulative dose, dose per fraction, and proximity to vulnerable tissues and organs. Acute side effects include edema, mouth sores, and xerostomia. Long-term sequelae include dysgeusia, mucositis, trismus, infection, and pain. Additionally, radiation-induced trismus inhibits insertion and removal of an obturator, as well as speech and eating. Subsequently, jaw exercises to increase the patient's maximal incisal opening are imperative.

Chemotherapy

High-risk patients with locally advanced SCC of the head and neck have been shown to benefit from postoperative concurrent chemotherapy compared with receiving radiation therapy alone. Risk factors associated with increased recurrence rates include extracapsular nodal spread, positive resection margins, perineural or vascular invasion, N2 or N3 nodal disease, and level IV or V nodal involvement; all are indications for chemoradiotherapy. Cooper and colleagues[23] also described improved locoregional control and disease-free survival with concurrent chemotherapy administration in patients with microscopically involved resection margins and/or extracapsular spread of disease. Patients with T4 maxillary gingival SCC without these additional risk factors may consider radiation therapy alone.

Surveillance and Assessment of Recurrence

Regular follow-up and cancer surveillance are essential both for the detection of recurrent disease and to diagnose new primary tumors that may develop. Approximately 90% of all recurrences occur within the first 2 years after treatment; therefore, vigilant follow-up visits should occur frequently during this timeframe. Thereafter, 6-month to yearly follow-ups are recommended. There are no set guidelines for interval imaging during this period, but periodic CT, MRI, and PET/CT scans should all be considered.

Prognosis

Bhattacharyya[24] performed a retrospective review of 650 patients afflicted with maxillary sinus cancer in the National Cancer Institute's Surveillance, Epidemiology, and End Results database from 1988 to 1998.[24] This study found the mean survival time to be 52 months and the overall 5-year survival rate to be 35%. The author attributed this finding to the late presentation of most patients with nonspecific symptoms. In this group, 67% presented with nasal obstruction, 69.3% with nasal discharge, and 47.8% with cheek pain. Subsequently, more than 50% of the patients in this study presented with T3 or T4 tumors.[24]

Summary

Maxillary gingival SCC is a rare entity that provides a diagnostic and treatment challenge to clinicians due to its diverse presentation and proximity to underlying bone and associated structures. Locally advanced disease lends itself to subtotal or total maxillectomy with selective neck dissection of levels I to III. Adjuvant radiation and chemotherapy should be considered in high-risk patients. Regular post-treatment follow-up visits and cancer surveillance screens are essential in early diagnosis of disease recurrence and detection of secondary malignancies.

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28

Advanced Palatomaxillary Cancer

JAMES MURPHY, JOSEPH I. HELMAN, SEAN P. EDWARDS, BRENT B. WARD

The process of surgically removing large tumors involving the maxilla is challenging. The ablative defect resulting from the extirpation of locally advanced tumors results in a potentially disfiguring and challenging reconstructive defect. The first recorded successful maxillectomy was performed by Joseph Gensoul in 1827. He published a case series of his maxillectomy procedures entitled "Lettre chirurgicale sur quelques maladies graves du sinus maxillaire" in 1833.[1] He described his first procedure consistent with a total maxillectomy on a 17-year-old boy, Jean-Marie Vericel, which he performed in May 1827. The patient had a tumor of the left maxilla that had been present since the patient was 4 years old. The operation was performed with chisels after a cheek flap had been raised. No pathologic diagnosis was given but a desmoid fibroma or a fibro-osseous lesion would be reasonable guesses. The patient reportedly did well postoperatively, was able to eat and drink, but had a speech deficit. This was an ambitious procedure to perform, and considering it was the era before anesthesia and prior to Semmelweis publishing his work, the eventual outcome is impressive. Maxillectomy in the modern era has evolved significantly from that described by Gensoul. The advances in modern anesthesia, antisepsis, and equipment allow maxillectomies to be performed routinely without significant risk of mortality or excessive morbidity.

Ohngren's line defines an imaginary line connecting the medial canthus of the eye to the angle of the mandible. Maxillary tumors found postero-superior to this line are believed to have a poor prognosis due to the proximity to the orbit, the pterygopalatine fossa and the infratemporal fossa. The clinical applicability of Ohngren's line is of questionable value but the authors suggest that any tumor found postero-superior to it should be investigated with magnetic resonance imaging (MRI) with contrast to assess for perineural involvement at the skull base and beyond. Squamous cell carcinoma is the predominant pathology necessitating maxillectomy, but sarcomas, salivary gland tumors, melanoma, inverted papilloma, ameloblastoma, and other odontogenic tumors are pathologies where an aggressive maxillectomy may be required. This chapter focuses on the management of locally advanced, T3/T4 epithelial origin malignancies as defined by the American Joint Committee on Cancer. The surgical defect resulting from the resection of other large pathologic processes involving the maxilla and subsequent reconstruction follows the same principles as described in this chapter, but the need for neoadjuvant treatment, the surgical management, and the adjuvant treatments vary depending on the primary pathology.

With regard to maxillary squamous cell carcinomas, a distinction needs to be made between those originating from the maxillary sinus and those originating from the maxillary gingiva. Three percent of head and neck carcinomas are known to originate from the paranasal sinuses, with the majority arising within the maxillary sinus.[2,3] Because of the anatomic nature of the maxillary sinus, malignancy can grow quite large before diagnosis, explaining the frequency of late presentation.[4] The majority of maxillary carcinomas though arise from the gingiva/soft tissues overlying the maxillary alveolus/palate. The close proximity of these tumors to the underlying bone means that they can quickly invade into medullary bone or the maxillary sinus, resulting in upstaging to stage IV malignancy on the basis of local spread. It is not currently known if these stage IV malignancies have a prognosis different from that of malignancy that grew to a large size without significant symptoms in the confines of the maxillary sinus. It is plausible to think the former would have a better prognosis, but there are no data to support such a statement.

Pertinent Anatomy

In essence the maxilla is the cornerstone of the upper facial skeleton. Each maxilla articulates with the following bones of the facial complex: the zygoma, palatine, nasal, inferior concha, vomer, lacrimal, frontal, ethmoid, the contralateral maxillary bone, and sometimes the lateral pterygoid plate of the sphenoid bone. Each maxilla contributes to the formation of the infratemporal fossa, the pterygopalatine fossa, the inferior orbital fissure, and the pterygomaxillary fissure. The maxilla houses the upper dentition in its alveolar process, and the maxillary sinus is predominantly contained within it in the majority of people. The maxilla is the critical structure of the inferior orbital rim and forms an important component of the orbital floor. It forms the roof of the oral cavity/floor of the nose and lateral wall of the nasal cavity. The maxilla serves as a site of origin/insertion of many muscle groups including muscles of facial expression, muscles of the velar complex, and the inferior oblique muscle, together with some fibers of origin of the lateral and medical pterygoid muscles. The

maxilla has a rich neurovascular supply. The third part, or pterygopalatine portion, of the maxillary artery is the predominant blood supply to the maxilla, although there is a rich vascular anastomosis between other vascular networks and the maxilla. The posterior superior alveolar, infraorbital, greater palatine, and sphenopalatine branches contribute the greatest vascular supply to the maxilla. The greater palatine nerve travels with the greater palatine artery through the pterygopalatine canal to its respective foramen in the hard palate, and the nasopalatine branch of the posterior superior nasal branch of the maxillary nerve, which emerges from the incisive canal, innervates the palate and associated alveolus of the maxilla. The infraorbital groove is found at the posterior part of the orbital surface of the maxilla and transmits the infraorbital nerve and vessels. Just prior to entering the groove, the posterior superior alveolar nerve branches off the trunk of the maxillary nerve to supply the posterior maxilla. The infraorbital groove ends anteriorly as a canal and subdivides into the larger infraorbital canal, which opens as a foramen below the margin of the orbit, and a smaller canal that runs down the anterior wall of the maxillary sinus, transmitting the anterior superior alveolar nerve and vessels. Occasionally a middle superior alveolar nerve branches off the posterior part of the infraorbital canal to the premolar teeth. Orbital branches, posterior inferior nasal branches, external nasal branches, and superior labial branches of the maxillary nerve also contribute to the neural supply of the maxilla.

Staging

The American Joint Committee on Cancer (AJCC) recently made substantive modifications to the TNM staging criteria and staging system for head and neck cancer in general and oral cavity cancer in particular. These changes more accurately represent the unique biologic, clinical, and epidemiologic features of oral squamous cell carcinoma (OSCC) (Table 28.1). In the first modification, the T stage now incorporates depth of invasion (DOI). In the 1980s, Spiro and colleagues identified the importance of tumor thickness as a prognostic indicator in oral cavity cancer. Depth of invasion is a more sophisticated and reproducible method of measuring a tumor. It is measured by first finding the "horizon" of the basement membrane of the adjacent squamous mucosa, and DOI is defined as the deepest point of tumor invasion (in mm) from that line. Extrinsic muscle infiltration has been removed from the staging criteria because DOI is more representative of the clinical problem both clinically and pathologically. DOI assesses the invasiveness of the tumor rather than any exophytic component.

In the second modification, extranodal extension is now recognized when categorizing metastatic cancer to the cervical lymph nodes. Additional updates to this classification scheme include the following:

1. Separate N category approaches are given for patients treated without cervical lymph node dissection (clinical N [cN]) and patients treated with cervical lymph node dissection (pathological N [pN]).
2. Extranodal extension (ENE) is introduced as a descriptor in N categorization for all HPV-negative cancers, and its presence is designated pN2a for a single ipsilateral node <3 cm and pN3b for all other node(s).
3. Clinically overt ENE is classified as ENE and is considered ENE(+) for cN.
4. Pathologically detected ENE is classified as either ENE_{mi} (<2 mm) or ENE_{ma} (>2 mm) for data collection purposes only, but both are considered ENE(+) for definition of pN.

However, pathologic stage does not trump clinical stage, and assignment of ENE should be based primarily on physical examination, rather than on imaging studies.

The primary tumor stage remains essentially the same in the new system, with the exception that DOI will increase the T category by 1 for each 5-mm of tumor depth (until ≥10 mm). Pathological ENE(+) will increase the nodal category by 1. In addition, the AJCC recommends other prognostic factors be considered and recorded along with standard staging information, including Eastern Cooperative Oncology Group (ECOG)/Zubrod or Karnofsky performance measures, tobacco and alcohol use, tumor location, number and size of nodes, perineural invasion, and ENE.

The new AJCC TNM staging highlights the worst pattern of invasion (WPOI) as a validated outcome predictor. It is recommended that WPOI-5, defined as tumor dispersion of ≥1 mm between tumor satellites, be recorded as part of pathologic staging. Even in early-stage oral cancer, a DOI of >4 mm combined with a WPOI-5 increases the probability of recurrence to approximately 42%. Perineural invasion (PNI) or lymphovascular invasion constitute a WPOI-5 classification. When identified, PNI would be subclassified as either intratumoral or extratumoral. Named nerves should be specified and PNI should be subclassified as focal or multifocal.

Classification of Maxillectomy Defects

The three-dimensional shape of the maxillary complex and its multiple bony articulations make it difficult to create a succinct, unified classification scheme for maxillectomy defects. Terms such as *partial, limited, medial, subtotal, radical,* and *extended* are used frequently, but most do not have a widely agreed definition. A universal classification scheme would be helpful, as it would allow more efficient communication of the resultant defect which would hopefully lead to easier dissemination of knowledge. Currently no such classification scheme exists with regard to maxillectomy defects. Broadly speaking, three widely accepted classifications are used, which individually may have greater applicability to the ablative surgery, the reconstructive surgeon, or the maxillofacial prosthodontist. Spiro and colleagues[5] introduced a classification scheme, which was subsequently refined by Cordeiro and Santamaria.[6] They divided maxillectomies into:

Type I (limited maxillectomy): Resection of one or two walls of the maxilla excluding the palate

Type II (subtotal maxillectomy): Resection of the maxillary arch, palate, and anterior, posterior, medial, and lateral walls (lower five walls), but the orbital floor is preserved

TABLE 28.1 **American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)**

Primary Tumor (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease
T4a	Moderately advanced local disease. *(Lip)* Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (ie, chin or nose). *(Oral cavity)* Tumor invades adjacent structures only (eg, through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face) NOTE: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4.
T4b	Very advanced local disease; tumor invades masticator space, pterygoid plates, or skull base or encases carotid artery

Regional Lymph Nodes: Clinical (cN)

Oropharynx (p16–) and hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes, ≤6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes, ≤6 cm in greatest dimension and ENE(–)
N3	Lymph node(s) >6 cm and ENE(–) or metastasis in any node(s) and clinically overt ENE(+)
N3a	Lymph node(s) >6 cm and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
	NOTE: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L).* Similarly, clinical and pathological ENE should be recorded as either ENE(–) or ENE(+)

Regional Lymph Nodes: Pathological (pN)

Oropharynx (p16–) and hypopharynx

NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(–)
pN2	Metastasis to a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(+); or metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2a	Metastasis to a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(+); or metastasis in a single ipsilateral lymph node, >3 cm but ≤6 cm in greatest dimension and ENE(–)
pN2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN3	Lymph node(s) >6 cm and ENE(–); or metastasis in a single ipsilateral node, >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)
pN3a	Lymph node(s) >6 cm and ENE(–)
pN3b	Metastasis in a single ipsilateral node, >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)

Continued

TABLE 28.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)—cont'd

Distant Metastasis (M) Oropharynx (p16–) and hypopharynx

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

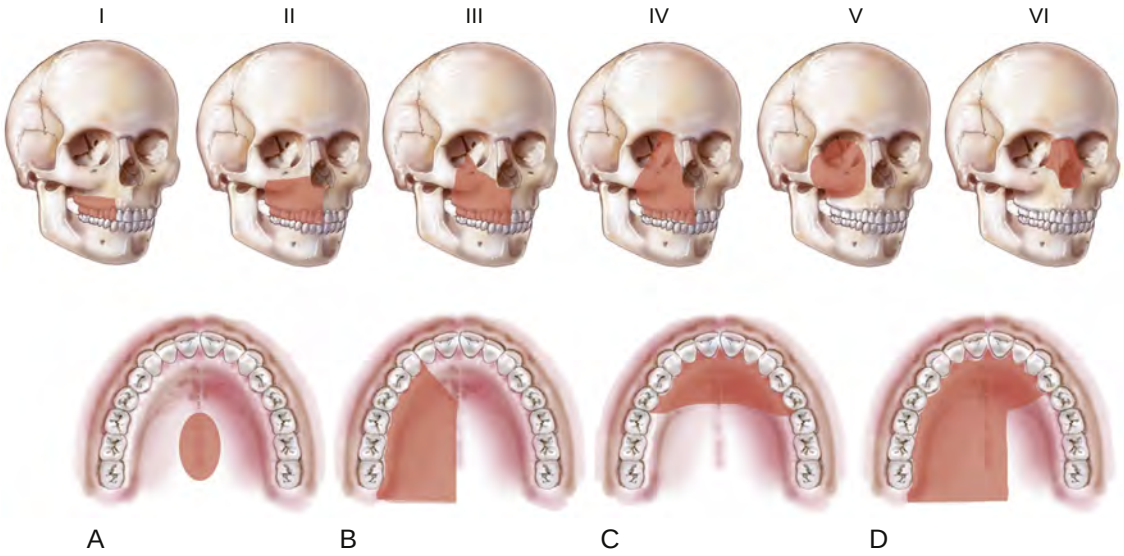
Registry Data Collection Variables

1. Lip location (external or vermilion border)
2. ENE clinical: ENE(+) or ENE(–)
3. ENE pathological: ENE(+) or ENE(–)
4. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
5. Perineural invasion
6. Lymphovascular invasion
7. p16/HPV status
8. Performance status
9. Tobacco use and pack-years
10. Alchohol use
11. Depression diagnosis
12. Depth of invasion (mm)
13. Margin status (grossly involved, microscopic involvement)
14. Distance of tumor (or moderate/severe dysplasia) from closest margin
15. WPOI-5

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated

Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In Amin MB et al, eds. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017. http://dx.doi.org/10.1007/978-3-319-40618-3_10.



• **Fig. 28.1** Brown's maxillectomy classification. (Adapted from Brown JS, Shaw RJ. Reconstruction of the maxilla and the midface: Introducing a new classification. Lancet Oncol. 2010;11;1001–1008.)

Type III (total maxillectomy): Resection of all six walls of the maxilla. Type III was subdivided into "a" or "b" depending on the preservation or exenteration of the orbital contents, respectively

Type IV (orbitomaxillectomy): Exenteration of the orbital contents and upper five walls, but preservation of the palate

This classification was a welcome addition but was biased toward the ablative surgeon.

Okay and colleagues[7] introduced a classification scheme weighted toward the maxillofacial prosthodontist in its design.

Ia: Defect of the hard palate not involving the alveolus

Ib: Defect limited to premaxilla or maxillary alveolus and dentition without canine involvement

II: Defect of any portion of the hard palate and tooth-bearing maxillary alveolus and only one canine with anterior margin of defect lying within premaxilla, or anterior transverse palatectomy that involves less than 50% of the hard palate

III: Defects involving any portion of the hard palate and alveolus including both canines or transverse palatectomy that involves greater than 50% of the hard palate

Subclasses "f" and "z" were added when the defect involved the inferior orbital rim and body of zygoma respectively

Brown and associates[8] appreciated the need to better describe the maxillectomy defect in the horizontal plane (Fig. 28.1). The authors subsequently refined the originally reported classification to its current guise[9]:

- Vertical component
  - I: Maxillectomy not causing an oronasal fistula and not involving the orbit or nasal structures
  - II: Low maxillectomy not involving the orbit
  - III: Maxillectomy removing palate/alveolus and involving the orbital adnexae without orbital enucleation or exenteration
  - IV: Maxillectomy removing the palate/alveolus with orbital enucleation or exenteration
  - V: Orbitomaxillary defect not involving palate/alveolus
  - VI: Nasomaxillary defect
- Horizontal component
  - a: Palatal defect only not involving the alveolus
  - b: Less than or equal to half unilateral palate/alveolus
  - c: Less than or equal to half bilateral or transverse anterior palate/alveolus
  - d: Greater than half maxillectomy involving the palate/alveolus

This classification scheme introduced a greater complexity that enables a better definition of the ablative defect without being overly complex. Even though it is biased toward the surgeon, it is probably the most complete classification, as it has applicability for the surgeon and prosthodontist alike. This will be the maxillectomy classification scheme used in this chapter.

Management

The management of locally advanced malignancies of the maxilla requires a multidisciplinary approach. According to the National Comprehensive Cancer Care Network (NCCN), patients with T3/T4a malignancies are recommended to have multimodality therapy. Once a thorough history and physical exam, pathologic diagnosis, and appropriate radiologic examination have been performed, a discussion should be held with the patient regarding the options available. Current consensus favors surgical extirpation of the malignancy followed by adjuvant radiation or chemoradiation, depending on the pathologic findings. It is important to inform the patient of these recommendations soon after diagnosis. This helps them to begin to appreciate the likely protracted nature of the treatment required. Furthermore, it allows them to begin making preparations to undergo such treatment. Patients with T4b malignancies are by definition surgically unresectable. Management

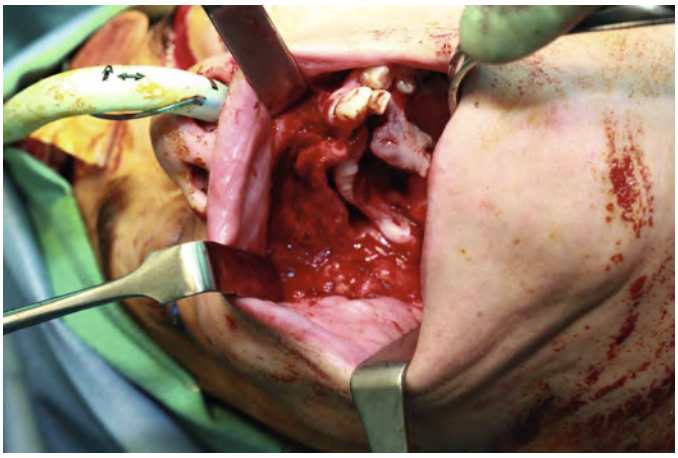
strategies to treat these patients include chemoradiation with therapeutic or palliative intent, single modality radiation that may be given at a therapeutic or palliative dose, palliative chemotherapy, or hospice care.

Patients frequently ask the treating provider for a survival prognosis. This can be a difficult question to answer with any degree of accuracy, as patient comorbidities, tumor biology, and tolerance of treatment will affect this. Nomograms are available to help guide a more informed discussion on preoperative cancer-specific mortality, preoperative locoregional recurrence-free survival, and preoperative overall survival relative to oral squamous cell carcinoma.[10] Quality of life is assuming increasing importance in relation to the treatment of head and neck cancer. With regard to locally advanced malignancies of the maxilla involving surgery as a treatment, a decision regarding reconstruction needs to be reached and has potential implications for quality of life.

The primary aim of surgery is to remove the tumor with clear margins. Locally advanced malignancies of the maxilla generally have invaded into the maxillary sinus. As a result, the superior portion of the resection specimen may be positive for malignant cells. This is not a true positive margin, as the malignancy is projecting into the space of the maxillary sinus without compromising surrounding tissues. The reading pathologist needs to appreciate this in order to accurately document the pathology. Frozen section analysis is an important aid in the quest to achieving negative final margins. Achievement of a negative resection margin is important in predicting the risk of locoregional recurrence in head and neck malignant processes. Obtaining a negative surgical margin becomes more difficult with increasing tumor burden. Sensitivity of frozen section analysis in locally advanced malignancies of the maxilla has been reported to be less than 40%.[11,12] Byers and co-workers support the use of frozen section analysis in all but T4 tumors because of the poor prognosis regardless of margin status.[13] Despite this, the prognostic factor the surgeon has potential control over is the final surgical margin. Therefore, the majority of ablative surgeons will continue to use frozen section analysis as an aid in locally advanced maxillary malignancies.

Surgical Management of the Primary

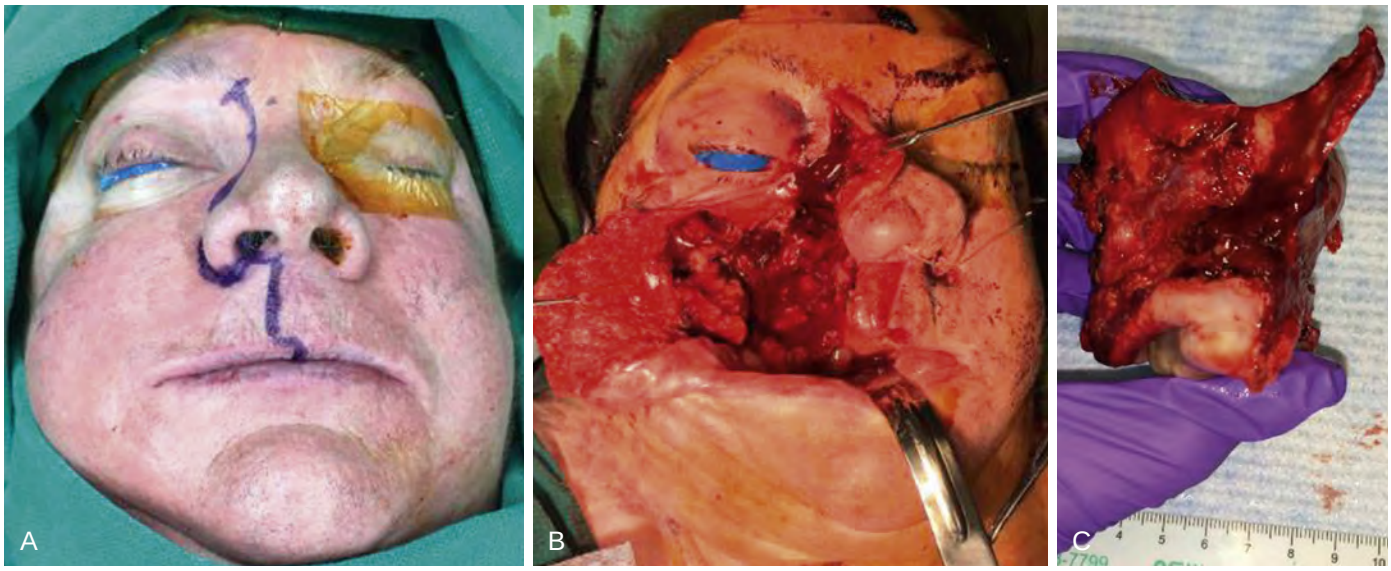
Management of the patient's airway needs to be considered initially before embarking on resection of the malignancy. Small-volume tumors defined as locally advanced, secondary to bone invasion, can be resected and the resultant defect (Brown IIa, IIb, IIc) restored with an obturator or local tissue rearrangement without the need for a surgical airway. A nasotracheal airway or even an orotracheal airway is sufficient in this scenario, but the surgeon needs to be mindful of the airway, especially when the osteotomy cuts are being made, so as to minimize the risk of compromising the airway tube. The anesthesiologist should be advised to place the airway tube to the contralateral side to reduce the risk. If a free flap reconstruction is to be undertaken to reconstruct the maxillectomy defect, strong consideration should be given to placing a surgical airway, even for those with a Brown V defect. This is to facilitate the surgical procedure and the ability to get the patient mobilized quickly after the procedure without excessive worry about surgical edema compromising the airway.



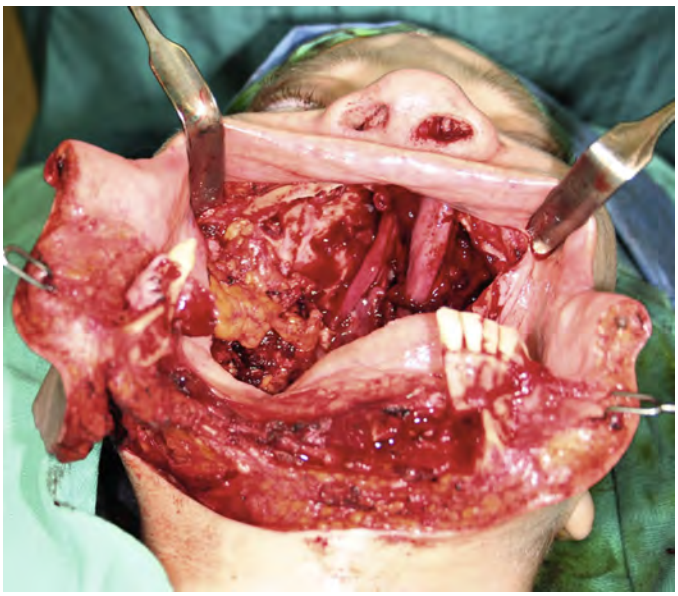
• **Fig. 28.2** Peroral access for a maxillectomy with the aid of retractors.

The access for the surgical procedure needs to be assessed. Small to moderate-size T4a malignancies of the maxilla can be resected via a peroral approach if they are confined the maxillary bone. Appropriately placed von Langenback retractors facilitate access to perform a maxillectomy that would result is a Brown IIa, IIb, IIc defect (Fig. 28.2). For large tumors, a peroral approach is generally inadequate to allow safe complete extirpation and facilitate subsequent reconstruction. A Weber Fergusson incision can be combined with Dieffenbach's subciliary incision modification or a Lynch incision to aid unrivaled access to the anterior maxilla and orbital floor and side walls (Fig. 28.3A–C). The disadvantage of this approach is facial scarring and the potential for ectropion with Dieffenbach's modification. An alternative strategy to increase surgical access without using an incision on the facial skin is a midface degloving approach. This provides improved access to the anterior maxilla and inferior orbit, but access is not as optimal as can be achieved with a Weber Fergusson. A lip split mandibulotomy may be indicated to increase access to the pterygoid plates/skull base when treating locally advanced malignancies of the maxilla (Fig. 28.4).

Achieving adequate access is a critical component to allow the surgeon the ability to remove the malignancy. The principles of extirpation of locally advanced tumors of the maxilla follow basic oncologic principles. With the aid of visual cues and palpation, the surgeon should make mucosal and soft tissue incisions at least 1 to 1.5 cm away from the clinical gross tumor margin. Osteotomies can be created with the use of a power saw, osteotomes, a Gigli saw, or a combination thereof. In the dentate patient, the alveolar osteotomy should be created through an extraction socket rather than through interdental bone. This is critically important when an obturator is used for the reconstruction, but it should also be considered even when a bone-containing free flap is used to reconstruct. The logic behind this is to minimize the risk of excessive bone loss that is critical in the support and maintenance of the tooth closest to the osteotomy site. The maxillary artery and pterygoid venous



• **Fig. 28.3** Weber Fergusson incision. **A,** Outline of Weber Fergusson incision with Lynch extension to aid access. **B,** Ablation performed with the aid of Weber Fergusson incision. **C,** Resection specimen of showing maxillectomy and external ethmoidectomy.



• **Fig. 28.4** Lip split mandibulotomy to aid access for a maxillectomy.

plexus can lead to troublesome bleeding when performing a maxillectomy. The final osteotomy created should be along the pterygomaxillary junction or the osteotomy to detach the pterygoid plates from the skull base depending on the extent of the maxillectomy. This allows swift access to the maxillary artery, which is frequently lacerated as part of this procedure. Control of hemorrhaging vessels can be obtained using suture ligatures, surgical clips, or a combination. Retraction of the lacerated artery can create difficulty in locating it. Initial spasm of the artery as result of the trauma may allow a relative hemostasis, but this may present as a delayed hemorrhage once the spasm resolves. Therefore attention should always be directed to trying to locate the proximal end of the maxillary artery and tying it off.

Encroachment of locally advanced maxillary malignancies on the orbit may necessitate an orbital exenteration. Iannetti and associates defined three distinct stages in sinonasal malignancies with respect to orbital involvement[14]:
Stage I: Bony orbital wall erosion
Stage II: Periorbital breach
Stage III: Penetration into the periorbital fat and beyond

Traditional ideology considered periorbital involvement in the malignant process as an indication to perform orbital exenteration. The logic behind performing orbital exenteration with extension of the malignancy to this anatomic boundary is being questioned and evidence is emerging in the literature to suggest that orbital preservation can be achieved even when a sinonasal malignancy extends to the periorbita without gross infiltration beyond it.[15,16] Adopting this approach will mean the margins will likely be close (<5 mm) or even positive, and adjuvant radiation will be required with its attendant risks to the orbit. Advancements in radiation oncology make this a feasible option with the prospect of maintaining a functional eye after radiation. The surgical management of locally advanced maxillary malignancies extending to or past the periorbita will result in a Brown III or IV defect, respectively. Brown V defect rarely results from malignancies originating within the maxilla and will not be discussed in this chapter. Large sinonasal malignancies can progress to involve the maxilla, necessitating the removal of the nose together with the maxilla, resulting in a Brown VI defect.

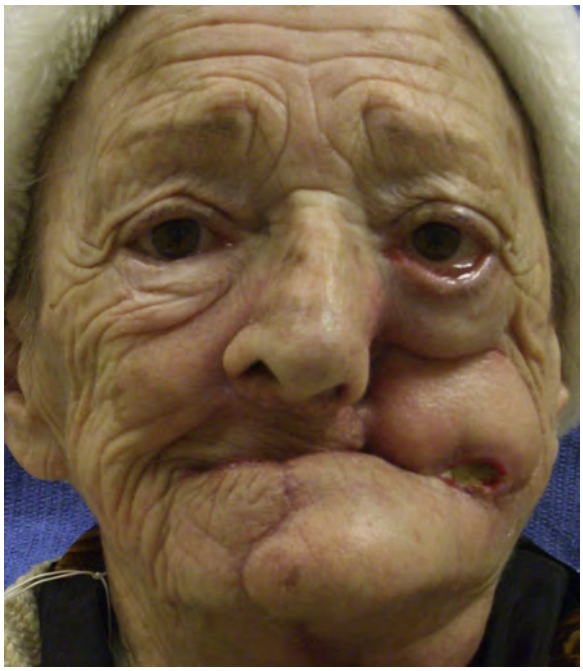
Management of the Neck

Relative to other oral cavity subsite malignancies, there was an element of confusion as to when to perform elective neck dissection in those with maxillary carcinomas. With regard to squamous cell carcinomas of the tongue, floor of mouth,

mandibular gingiva, and buccal mucosa, relatively well-defined guidelines exist as to when to perform an elective neck dissection in the clinically negative neck. The decision tree analysis reported by Weiss and colleagues [17] argues for an elective neck dissection when a 20% or greater risk of occult metastasis exists. Until recently there was a paucity of data to aid in determining what factors were associated with a 20% or greater risk of regional metastasis from maxillary carcinoma. A multiinstitutional study by Montes and associates and a single institution study by Brown and co-workers supported elective neck dissection levels I to III in patients with T2, T3, and T4 squamous cell carcinoma of the maxilla.[18,19] The current highest level of evidence supporting an elective neck dissection levels I to III in those with a T2 or greater squamous cell carcinoma of the maxilla is a meta-analysis by Zhang and colleagues.[20] A complicating factor with locally advanced carcinomas of the maxilla is the potential for encroachment of the malignancy on the soft palate. This leads to the possibility of involvement of the retropharyngeal lymph nodes. Guan and associates reported that 18 of 59 patients in a Chinese population had regional lymph node involvement from a maxillary squamous cell carcinoma at the time of referral, with the retropharyngeal lymph nodes involved in 66% of the patients with regional disease.[21] This is an alarmingly high incidence of retropharyngeal lymph node involvement that is not replicated in the majority of reports on maxillary squamous cell carcinoma, but it does highlight the potential for regional metastasis to this site from maxillary malignancies. The difficulties with regard to surgical access and the potential for significant morbidity associated with extirpation of retropharyngeal lymph nodes precludes it being performed routinely. With regard to locally advanced malignancies of the maxilla, especially those extending to the soft palate, radiation therapy should be directed toward this lymphatic system.

Reconstruction

Reconstruction of the maxilla is somewhat more complex than mandibular reconstruction. The reconstructive options for the surgical defect include a locoregional pedicled flap, an obturator, or a free vascularized flap, with the majority of locally advanced malignancies of the maxilla requiring one of the latter two reconstructive options. Opinion is divided regarding the best reconstructive option. Obturators have long been used to reconstruct maxillary defects. The advantages of using an obturator to reconstruct an appropriately sized defect include a less complex, shorter operation, potentially quicker recovery, the lack of donor site morbidity, simultaneous obturation of the oroantral/oronasal defect and provision of a prosthetic dentition for mastication, and the ability to visually monitor the operative site for tumor recurrence. A claim has been made that obturators have a cost advantage; however, this statement needs to be qualified by considering the long-term maintenance required with obturators, which necessitates frequent visits to a prosthodontist for maintenance and adjustments. One can cynically conclude that for an appropriate-size defect, an obturator is cost effective in those with locally advanced tumors when patient prognosis is taken into account.



• **Fig. 28.5** Poor nasal and soft tissue support with an obturator resulting in facial distortion.

A key determinant in assessing the feasibility of an obturator to reconstruct is the size of the ablative defect. Brown IIa or IIb defects, especially when the maxillectomy does not encroach on the canines, are good candidates for obturators. Brown IIc defects can also be considered obturator candidates, but the implications of nasal support should be assessed (Fig. 28.5). With the involvement of a canine or the two canines in a Brown IId defect, an obturator will encounter significant problems with retention and resistance. Zygomatic implants have been used to overcome these issues but add to the cost burden and place the patient at risk of osteoradionecrosis as locally advanced carcinomas meet the criteria for adjuvant radiation. Another issue with the use of an obturator for reconstructing large maxillary defects is the compromise to the vascular supply to the surrounding tissues, especially the facial drape. This becomes critically important if radiation therapy is planned, as breakdown of the facial soft tissues can occur (Fig. 28.6A–C). After performing the maxillectomy and achieving hemostasis, the remaining tissue on the soft palate should be examined. In unilateral maxillectomies where an obturator is planned for reconstruction, if less than half the soft palate tissue remains, strong consideration should be given to complete removal of the ipsilateral soft palate. This will allow the obturator to extend posteriorly and obliterate the defect without being compromised by the remnant of soft palate tissue, which will inevitably scar and contract.

Muneuchi and colleagues stated that filling the defect with a soft tissue free flap to meet minimum reconstruction requirements was best.[22] This option will inevitably affect the patient's quality of life, especially with regard to cosmetic result and mastication. For patients undergoing orbital exenteration



• **Fig. 28.6** **A,** Preoperative clinical photo of a patient with a T4a squamous cell carcinoma maxilla. An obturator was planned because of patient comorbidities despite the fact the defect would be a Brown IId. **B,** Intraoperative photo of the obturator in place to reconstruct the ablative defect. **C,** Postoperative photo showing soft tissue breakdown overlying the obturator.

and those with a poor long-term prognosis who are not good candidates for an obturator, a soft tissue–only free flap may be the best option to reconstruct the defect. Soft tissue free flap options for the maxillectomy defect patient include the anterolateral thigh flap, the rectus abdominis, the latissimus dorsi, and the radial forearm fasciocutaneous flap. For large ablative defects of the maxilla through an osteomyocutaneous free flap provides the best opportunity to maximize cosmetic and functional results. A fibula free flap, circumflex scapular artery (CSA) flap, or a scapula tip with or without the latissimus dorsi are the authors' preferred osteomyocutaneous free flaps to reconstruct the maxilla in those with locally advanced disease. The radial forearm osteocutaneous free flap and the deep circumflex iliac artery free flap with the internal oblique are other alternative bone-containing free flaps documented in the literature for the reconstruction of the maxilla.[6,9] The primary objective of the free flap is to provide a partition between the oral cavity and the nasal cavity and also to support the orbit if applicable. The relative advantages and disadvantages of each are shown in Table 28.2. The decision of which flap to choose is dependent on the geometry of the proposed ablative defect, presence of peripheral vascular disease or vascular variations/anomalies, potential need to place osseous dental implants, and patient and surgeon preference.

The fibula free flap contains a good length of bone and an adequate pedicle length for the reconstruction of the majority of maxillectomy defects. Virtual surgical planning has proved to be a tremendous aid in preoperative planning and as an aid intraoperatively in such cases. For Brown IIb, IIc, IId defects, the fibula is probably the osteomyocutaneous flap with the best properties for reconstruction. Osteotomies should be created to aid reproduction of a canine eminence in the neomaxilla. This will help improve facial cosmesis and ultimate restoration of a functional dentition. The pedicle can be placed on the buccal or palatal aspect of the fibula in the maxilla. If it is placed palatally, consideration should be given to harvesting a generous amount of flexor hallucis longus to protect the pedicle from desiccation from the passage of air through the nasal apertures. Depending on the positioning of the pedicle either buccally or palatally, harvesting the fibula free flap from either the contralateral or ipsilateral leg will aid orientation of the

TABLE 28.2 Comparison of Bone Containing Free Flaps to Reconstruct the Maxilla

	Bone Stock	Pedicle Length	Orientation Complexity	Low Donor Site Morbidity	Ease of Two-Team Harvest
Fibula flap	+++	+++	++	+++	++++
CSA flap	++	++	+++	+++	+
Scapula tip	++	+++	+++	++++	+
Scapula tip with LD	++	++	+++	+++	+
DCIA	++++	+	+++	+	+++
ORFF	+	++++	+++	+	+++

CSA, Circumflex scapular artery; *DCIA,* deep circumflex iliac artery; *LD,* latissimus dorsi; *ORFF,* osteocutaneous radial forearm flap.

skin paddle to drape optimally to close the palatal defect. For a Brown III defect, orientation of the fibula can make it challenging to reconstruct the defect and orient the skin paddle to separate the oral cavity from the ablative defect. Some have proposed creating two osteotomies resulting in three separate bone segments. Each segment can then be used to reconstruct the orbital rim/floor, medial sinus wall, and alveolus, respectively; however, positioning the skin paddle can be difficult using this system. An alternative strategy is to use a vascularized segment of the fibula to reconstruct the alveolus and to use a nonvascularized portion to reconstruct the inferior orbital rim (Fig. 28.7). The nonvascularized bone reconstructing the orbital rim has been shown to be able to survive even when adjuvant radiation is used. An alternative strategy is to perform a coronoidectomy and to use this to support the orbit as shown in Fig. 28.8. Alloplastic material can be used in conjunction with an autograft to help prevent enophthalmos and orbital dystopia in these cases.

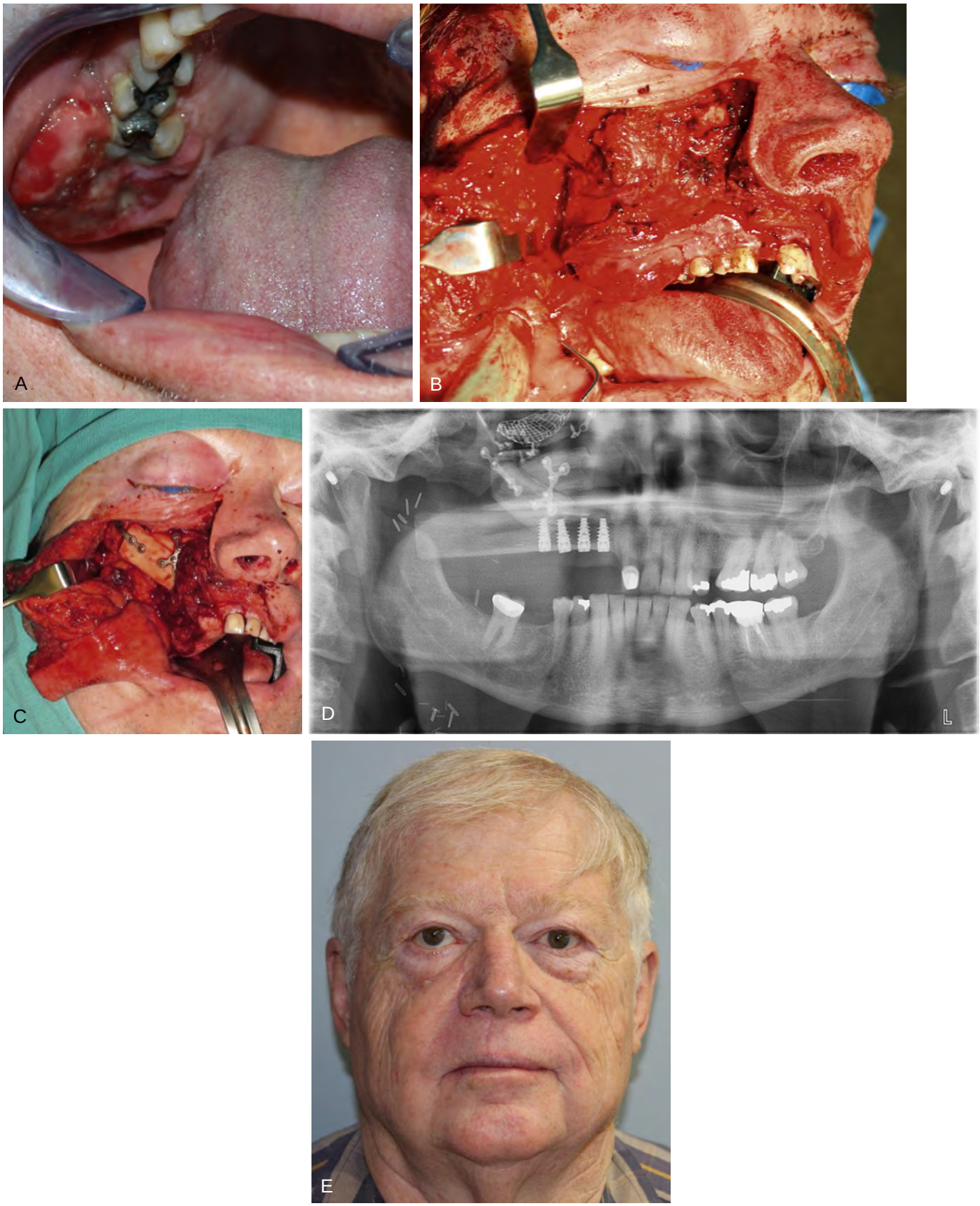
The CSA can be used successfully to reconstruct a maxillary defect. Pedicle length is not as good as with a fibula, so consent should be obtained for a vein graft. Dissection of the pedicle proximally to the subscapular artery can enhance pedicle length but can create vessel size mismatch for microvascular anastomosis. Even though the bone stock of a CSA is not as good as that of a fibula, by orienting the lateral aspect of the flap toward the alveolus, dental implants can be placed (Fig. 28.9). The scapula tip, supplied by the angular artery branch of the thoracodorsal, can also be harvested and used to reconstruct the maxilla (Fig. 28.10). The advantage of good pedicle length must be weighed against the poor bone stock with this free flap.

Adjuvant Therapy

Locally advanced (T3/T4) maxillary malignancies meet the criteria for adjuvant therapy as defined by the NCCN. The NCCN guidelines on adjuvant therapy are heavily influenced by the RTOG 9501 and EORTC 22931 trials.[23,24] Based on these trials, the NCCN guidelines recommend adjuvant chemoradiation for those with positive margins or regional lymph nodes with extracapsular extension and single-modality adjuvant radiation for those with any of the following on final pathology: locally advanced disease (T3/T4), N2 or greater disease, lymphovascular invasion, or perineural invasion. Arguments have been made that N1 disease and depth of invasion greater than 5 mm should be considered for adjuvant radiation. Regardless, all patients with locally advanced disease of the maxilla will be advised to undergo adjuvant radiation. Radiation is not without its side effects. The deterministic side effects, such as mucositis and dermatitis are bitterly complained about by most patients. The patient also should be advised of potential stochastic side effects, with radiation-induced sarcoma being the most common. It should be acknowledged that this is a secondary concern in those with locally advanced disease. The potential for osteoradionecrosis and radiation-induced trismus, the increased risk of carotid stenosis due to radiation-induced endarteritis, dysphagia, and hypothyroidism when adjuvant radiation is used in the head and neck must be understood. The risk of dysphagia is particularly high with locally advanced malignancy of the maxilla due to the importance of irradiating the retropharyngeal lymph node basin. At the authors' institute, volumetric modulated arc therapy is used in preference to intensity-modulated radiation therapy (IMRT) in the treatment of locally advanced maxillary malignancies. This is because it provides equivalent conformal radiation dosage to the proposed target volume (PTV) of the tumor but with a shorter treatment time to deliver an equivalent dose compared with IMRT, and with fewer monitor units.[25] The reduction in monitor units leads to a reduction in scatter and exposure of the non-PTV tissue to low-dose radiation, which would subsequently reduce the risk of radiation-induced malignancy.

Quality-of-Life Factors

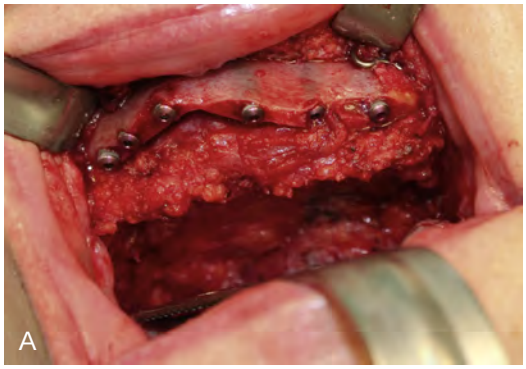
Maxillectomy for locally advanced disease can have a significant impact on appearance, mastication, speech, swallowing, activity related to employment and recreation, and pain level. This can have a negative impact on quality-of-life factors. When the maxillectomy encroaches on the pterygoid plates, trismus can result. This trismus can be compounded with the administration of radiation therapy. In this cohort of patients,

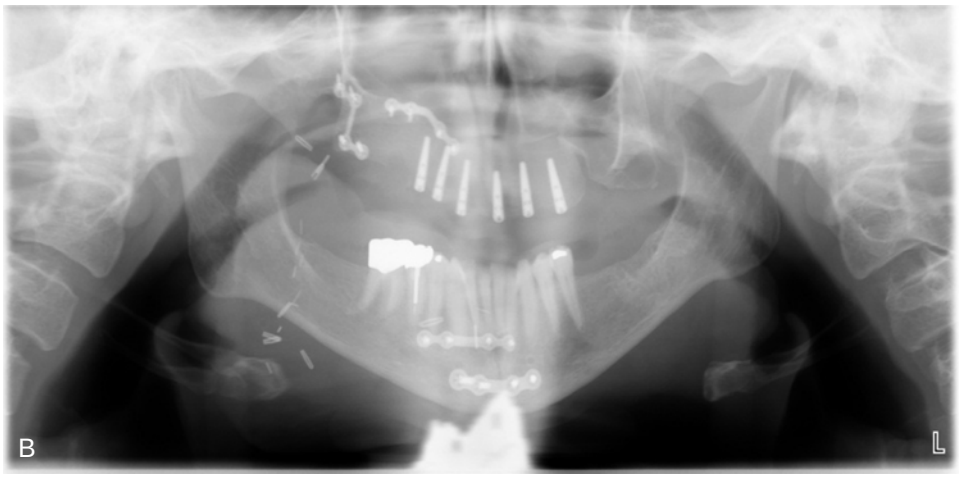


• **Fig. 28.7** **A,** Preoperative clinical photo. **B,** Resection specimen. **C,** Nonvascularized bone to support the orbit in the resulting Brown IIIb defect. **D,** Panorex showing orbital floor autograft and fibula free flap in place. **E,** Postoperative appearance.



• **Fig. 28.8** 3D CT reconstruction showing coronoid and anterior ramus of mandible used to support orbit and to form inferior orbital rim in a Brown IIIb defect. The patient declined a free flap reconstruction. An obturator was used.









• **Fig. 28.9** **A,** Dental implants placed in CSA flap to aid dental rehabilitation. **B,** Panorex showing implants in place. **C,** Implant superstructure in place. **D,** Implant retained denture in place.

preoperative referral to an occupational therapist/physical therapist should be considered. Early and diligent postoperative use of a jaw motion rehabilitation device, of which there are many on the market, can minimize the degree of resultant trismus. Severe trismus affects the ability to meet nutritional requirements, and a nasogastric feeding tube in the short term and a gastrostomy tube long term may be required.

Creating a partition between the oral cavity and the nasal cavity in the post-maxillectomy patient is key to preventing hypernasal speech and nasal leakage of oral cavity contents. Free flaps have an advantage over prosthetic obturation in precluding nasal leakage. As the size of the ablative defect increases beyond a Brown IIb, this becomes an increasing problem. Preemptive consultation with a speech and language therapist can help identify patients who have baseline swallowing deficits. Identification of such patients may help determine the most appropriate reconstructive option.

It is widely assumed that free flaps as a reconstructive method for the maxillectomy defect patient lead to improved quality of life compared to those who receive a prosthetic obturator. However, there are no strong data in the literature to support this. Rogers and colleagues examined this but found no statistically significant difference in health-related quality of life between a prosthetic obturator and a free flap to obliterate the maxillectomy defect in the patient population they analyzed.[26] A trend for obturator patients to be more concerned about their appearance and report a higher level of discomfort was appreciated, though. It is difficult to definitively answer which reconstructive method maximizes quality of life because, as the defect size increases, the practicality of using an obturator diminishes, making it difficult to match patients in studies. The morbidity of a free flap in patients with a smaller maxillectomy defect compared to an obturator and the minimal potential improvement in quality of life means many surgeons and patients alike opt for an obturator. Dental implants placed in free flaps give patients the potential to have fixed dentition on a bone-containing free flap; however, an understanding of the possible risks of osteoradionecrosis, poor characteristics of the soft tissue associated with the free flap leading to excessive granulation around the implants, and the financial burden together with time needed to achieve a fixed restoration must be acknowledged.



• **Fig. 28.10** **A,** Preoperative T1 MRI image of a T4a sinonasal SCC invading the maxilla. **B,** Intraoperative ablative Brown VId defect. **C,** Resection specimen. **D,** Intraoral view showing mucosalization of muscle on scapula tip flap.

Continued



• **Fig. 28.10, cont'd** **E,** Postoperative appearance using scapula tip free flap to reconstruct in frontal and lateral views. Prosthetic nasal reconstruction planned. **F,** 3D CT demonstrating bony reconstruction.

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29

Advanced Palatomaxillary Cancer (Special Considerations Related to Reconstruction)

JAMES BROWN, CHRIS J. BUTTERWORTH, CAROLINE BRAMMER

Clinical Presentation

Gingival or alveolar squamous cell carcinoma (SCC) of the upper alveolus or maxilla presents with ulceration and loosening of teeth in the dentate patient. In the edentulous patient there may be problems retaining the upper denture, and sometimes malignant changes may be confused with denture stomatitis or oral thrush. In general the presentation is earlier than with tumors arising in the maxillary sinus growing into the oral cavity, although the staging of clinical T4a tumors is still high, as early bone invasion is typical [1,2] (Table 29.1 and Fig. 29.1). Epistaxis and nasal congestion or blockage is much less likely, and so many patients will present to their dentist in the first instance with oral ulceration, loosening of teeth, and/or ill-fitting dentures.

Anatomy

The hard palate and alveolus are static structures of thin bone covered with attached gingival and palatal mucosa except buccally, as the reflected mucosa allows the movement of the cheeks and lips. The alveolus supports the dentition, and the height and anatomy change dramatically with the loss of teeth and the need to wear a dental prosthesis. This is well illustrated through Cawood and Howell's classification of the jaws.[2] The maxilla tends to lose bone anteriorly as well as in height, thus changing the relationship with the lower jaw, which maintains its position. With the loss of bone, the maxillary sinus can become very close to the palatal mucosa and so can be breached in early invasion for edentulous patients. Because the palate and alveolus form a fixed structure, this facilitates reconstruction because the soft tissue component requires no mobility.

Staging

At Aintree University Hospital, in our series of 43 patients with SCC of the maxillary alveolus the majority pathologic T stage was T4a[1,2] (see Table 29.1)—very much as expected, as the tumor arises adjacent to the bone and so invades through the cortex at an early stage. In fact there were no pathologic T3 tumors at all, as a tumor greater than 4 cm in the maxillary alveolus is very likely to be infiltrating the bone. It is very important to distinguish between tumors arising in the paranasal sinuses, which in this case is virtually always the maxillary sinus. These tumors have a different etiology and presentation and require more radical surgery and complex reconstruction. We were the first to report the outcome of selective neck dissection for this tumor group, and the comparison of the two sites in terms of T size is interesting (see Table 29.1). Almost without exception the tumors that invade the oral cavity from the maxillary sinus will be larger on computed tomography (CT) or magnetic resonance imaging (MRI) than the measurement in the oral cavity and so can easily be separated and managed in the appropriate category.

We have published a series of 18 patients with SCC of the maxillary sinus.[3] The tendency for these tumors to metastasize and/or recur in the neck is less, although they are nearly all stage IV in view of their late presentation. Of 13 selective neck dissections, only 1 was positive (8%) compared to 3 of 11 cases (27%) for SCC of the maxillary alveolus. This compares to a conversion rate of clinical N0 to pathologic N+ of 79/254 (31%) for the rest of the oral cavity sites, which is a similar result.[1] We tended to do less selective neck surgery for the maxillary alveolus in cN0 necks: 11 of 43 (26%) compared with 254 of 465 (55%) in the rest of the oral cavity, because we reconstructed this patient group with less free tissue transfer and so did not need to enter the neck for microvascular anastomoses.

Our standard work-up for a patient with any oral cancer including the maxillary alveolus is an MRI scan, CT thorax, and Panorex. In some cases we may decide to include a CT head and neck for more information on bone destruction for maxillary tumors.

TABLE 29.1 Comparison of T Stage Between Gingival Maxillary and Maxillary Sinus Squamous Cell Carcinoma

T Stage	Clinical T (No. Cases)	Pathologic T (No. Cases)
Maxillary Alveolus (n = 43)		
1	5	7
2	10	5
3	3	—
4a	25	31
Maxillary Sinus (n = 18)		
1	—	—
2	2	—
3	2	3
4a	14	15

Management Principles

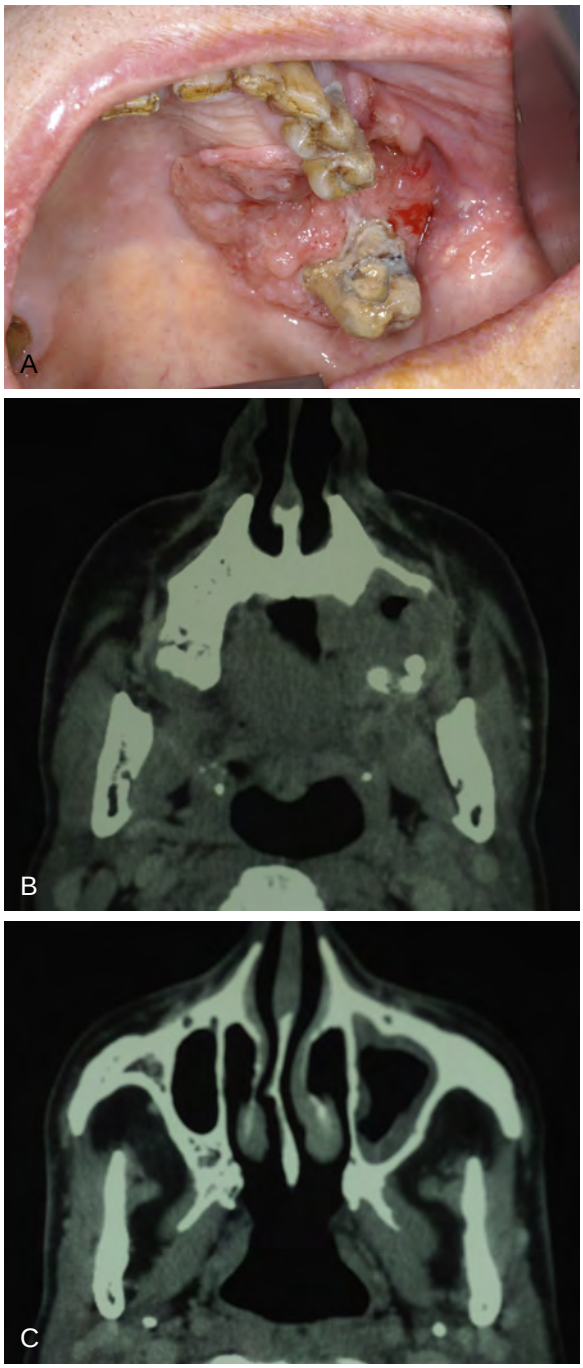
The standard of care should be available for protocols based on national and international recommendations and verified by a tumor board or multidisciplinary team (MDT) meeting of specialists and associated workers involved in the management of head and neck cancer. The patient's level of comorbidity requires careful assessment by the medical and anesthesiology team prior to the decision to offer curative surgery, which is usually the preferred option for any patient with a squamous cell carcinoma arising from the oral gingiva or mucosa and situated in the upper palate and/or alveolus. If the tumor is not considered operable, then neoadjuvant chemotherapy with or without concurrent radiotherapy could be considered prior to re-scanning and assessment for surgery if there is a reasonable response to this initial treatment. There will be patients who will be offered only palliative treatment because the chances of a cure are considered very unlikely. If there are already distant metastases, then palliative treatment is usually the only option available.

Our protocols agree strongly with those from the NCCN guidelines for Head and Neck Cancer, including cancer of the oral cavity.

NCCN Guidelines

T3 or T4a—Resective surgery with unilateral or bilateral neck dissection (ND)
No adverse factors—consider radiotherapy (RT)
Extracapsular spread (ECS) and/or involved margins—Chemotherapy/RT and consider further resection for involved margins

The NCCN guidelines for T1/T2 squamous cell carcinoma of the oral cavity do emphasize the role of sentinel node biopsy for cN0 cases. In our own practice we would either do a sentinel node biopsy (SNB) or a selective neck dissection to reduce the risk of regional recurrence. SNB is very useful for smaller cancers when a selective neck dissection is likely to be negative.



• **Fig. 29.1** Clinical photograph of right maxillary alveolus squamous cell carcinoma **(A)** with CT scans confirming the likely site with no high involvement of the maxillary sinus **(B,C)**.

A tumor board or MDT may decide to advise a watch and wait policy for regional recurrence, but the quality of life and morbidity following SNB now make this option very difficult to withhold after due discussion with the patient and family.

The chief role of selective neck dissections in these NCCN guidelines is to determine which patients are candidates for possible adjuvant therapy (chemotherapy/radiotherapy [RT] or RT alone), although selective neck dissection (SND) may be used as treatment when neck tumor burden is low.[1] In general patients undergoing SND should not have clinical nodal disease; however,

TABLE 29.2 Reported Outcomes Following Primary Surgery and Adjuvant Treatment as Prescribed

Author	No. Cases	SND for cN0	Converted to pN+	cN+ and pN+	Local	RR	LRR	Overall Survival
Simental et al, 2006[9]	26	4 (17%)	0/4 (0%)		7 (29%)	7 (29%)	0	13 (50)
Montes & Schmitt, 2008[10]	14	3	0	3	1 (7%)	4 (29%)	1 (7%)	NS
Kruse & Gratz, 2009[11]	30	2	0	4	NS	7 (23%)	NS	NS
Mourouzis et al, 2010[12]	17	0	0	4 (24%)	2 (12%)	6 (35%)	0	9 (53)
Morris et al, 2011[13]	139	8 (6%)	2 (25%)	14 (10%)	NS	34 (24%)	7 (5%)	NS
Brown et al, 2013[1]	43	12 (28%)	3 (25%)	12 (28%)	8 (19%)	11 (26%)	0	17 (40)

cN+, clinically node positive; *LRR,* locoregional recurrence; *NS,* not stated; *pn+,* pathologically node positive; *RR,* regional recurrence; *SND,* selective neck dissection.

SND may prevent morbidity in patients with nodal disease and may be appropriate in certain patients with N1 or N2 disease.[1,4-7]

The NCCN guidelines indicate that postoperative chemoradiotherapy should be considered where extracapsular spread (ECS) of the lymph nodes is present and/or there is an involved surgical margin where no further resection is possible. Guidance for the use of radiotherapy or intensity modulated radiation therapy (IMRT) is much less clear:

- Advanced T stage, which is assumed to be T3/T4
- Depth of invasion (not clarified in the guideline)
- Multiple positive nodes without ECS
- Perineural or lymphovascular invasion
- The omission of close margins (>1 mm but <5 mm from tumor edge to tissue margin) is a surprise, as this is often the concern of the tumor board and a common reason for adjuvant radiotherapy, especially in the presence of a close margin.

Outcomes

Our results in Liverpool have been published, and they are disappointing when compared to other sites in the oral cavity,[1] from which we conclude that the lower rate of SND and hence regional recurrence (26% in this site compared to 7% in the rest of the oral cavity) is the main contributor to the lower overall survival in this group—40%, compared to 57% for the other oral sites. Joshua Lubek[8] and colleagues, from Baltimore, described 37 cases involving the maxillary gingiva with an overall survival of 38%, similar to the Liverpool results of 40%. Other reports[1,9-13] (Table 29.2) show better outcomes, although regional recurrence does seem to be poorly controlled.

Surgical Management

Access

The standard access for the maxilla is an upper lip split, which is simple and quick but has the disadvantage of leaving a midline scar. An alternative for a class II level maxillectomy according to the Lancet classification[14] is the facial degloving approach[15,16] when bilateral intercartilaginous incisions are made and then extended inferior to the septum and laterally through the alar region so that the lateral sulcus incisions can be extended and the lower part of the nasal tissue retracted superiorly to allow good access to the septum and the maxilla. It is also sensible to consider a lower lip split and mandibulotomy to access the maxilla, especially if the tumor is more posterior and the difficulty is considered to be the protection of the internal carotid artery during the resection. After a neck dissection, the access is ideal, and the most problematic part of this procedure, the posterior resection, is rendered more safe.

Management of the Primary (Based on the Lancet Classification)

Class I

Class I maxillectomy can normally be done without access, and the only decision is whether to include the full-thickness alveolus. If taken, this converts the maxillectomy to a class II. On occasion, the hard palate separating the mouth from the nose requires resection, usually with some part of the soft palate. In this situation the lower part of the nasal septum is part of the resection, but the inferior turbinates can usually be spared.

Class II

This defect implies removal of the full-thickness alveolus to form an oroantral fistula. If this extends laterally or anteriorly, it will result in loss of part of the nasal septum, lower turbinates, and nasal support, especially if bilateral. Often it is best to start in the midline with head and neck resection and work laterally, but it is preferable to make a safe buccal incision with a 1.5-cm margin from the tumor edge. This can then be developed up to the inferior orbital nerve and nasal piriforms and pterygoid plates, similar to the dissection for a Le Fort I osteotomy. Anteriorly it may be helpful to do a facial degloving procedure or a lip split to ensure a safe margin more superiorly if needed. We usually prefer to delineate all the oral cavity cuts with unipolar diathermy at this stage.

After exposing the maxilla and deciding the extent of the maxillectomy bilaterally and in height, it is time to make the lateral bone cuts initially at the Le Fort I level as far as the pterygoid plates. If the tumor involves the posterior maxilla and tuberosity region, then we prefer to make a saw cut through the

pterygoid plates as superior as we dare, remembering that the skull base is higher at the anterior part of the plates and lower in the more posterior region. This cut may be completed with a chisel, and this technique is useful to ensure the bone cuts are through and likely to allow down-fracture and delivery of the specimen.

The next part of the operation is completion of the oral cavity incisions, which were delineated earlier and will result in the separation of the soft palate and bone cut through the palate from posterior to anterior. At this point it is usually possible to down-fracture the maxillary resection. The use of a large curved chisel is sometimes helpful.

Having delivered the specimen out of the oral cavity, it is important to examine the margins of resection carefully and take more tissue from areas that may be doubtful in terms of clearance. It is not our practice to do frozen sections, as the evidence that they will reduce the risk of local recurrence has not been established, and of course there is no guide to closeness of the margin, which must be either positive or negative.

There were no class III resections required in our series of gingival squamous cell carcinomas. We think that if such cases arise, it is likely that they arose in the paranasal sinuses if the orbital floor is part of the resection.

Management of the Neck

It is clear from the literature and our study comparing gingival maxillary tumors to the rest of the oral cavity that there is just as high a potential for recurrence if the neck is not addressed.[1] This study showed that a positive neck at presentation, after neck dissection, or recurrence from an untreated neck was 37% in the gingival maxilla compared to 40% in the rest of the oral cavity. Regional recurrence was reported at 26% for gingival maxillary tumors, which compared to 7% in the rest of the oral cavity, with a conclusion that the lower propensity for neck dissection for maxilla was resulting in poor neck control. We now would recommend an SNB for small gingival maxillary tumors, an SND if free tissue transfer is preferred for T4 primaries, or an SNB if obturated. SNB is particularly useful in this site, as the neck is farther from the primary site, reducing the confusion between potentially involved nodes and the spread of radioactive positivity to the neck from the injected primary site. This technique will also cover both sides of the neck and avoid the need for bilateral neck dissection. If the patient has a T4 gingival maxillary tumor crossing the midline, which we will often reconstruct, then we prefer an SND on the most likely side to be invaded following an SNB investigation to check the contralateral neck.

Reconstruction

The classic hemimaxillectomy (class IIb)[14] on one side of the maxilla can usually be obturated with some success. If the defect crosses the midline but is still less than half the defect, this is termed a class IIc, and reconstruction may give a better result depending on the loss of alar and nasal support. When more than half of the alveolus is removed, this is termed a class IId, and here we recommend either an implant-retained prosthesis or reconstruction. This approach is clarified in the section on rehabilitation.

For the low type of maxillectomy, a fibula flap can work well, with the skin island replacing the attached mucosa of the hard palate. This form of reconstruction can give very good results and may be preferred by the prosthodontist for implant security, but the soft tissue interface is a disadvantage compared to bone and muscle such as the iliac crest with internal oblique. We also prefer this option if the piriform and nasal bone loss is high anteriorly, as without full support there can be facial collapse not entirely compensated by the successful dental rehabilitation.

Complications

Surgical complications in the immediate scenario include bleeding, airway, and aspiration in the early postoperative phase. Bleeding in the neck can occur, especially in the intermediate phase, and requires early and appropriate intervention. Flap loss, on the other hand, is less of a concern, especially if obturation is a reasonable option, as the patient can recover and return for another attempt at biologic reconstruction if he or she wishes.

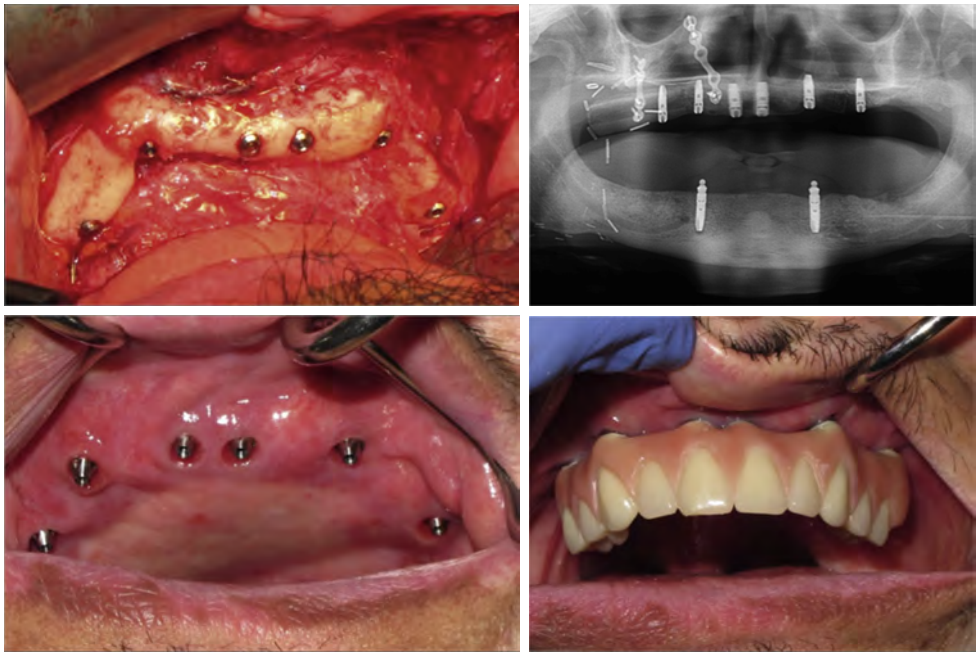
One of the main problems we have encountered is a higher involved and close margin rates for these resections, which reflect the often late presentation and misjudgment of the extent of the spread into the soft tissues. Our results[1] show an involved margin and local recurrence rate of 42% and 19% for the maxilla compared to 17% and 10% for the rest of the oral cavity cohort. As a result, it is worth considering immediate obturation and SNB for those patients with clinically negative neck, followed by reconstruction with a free flap if desired, allowing an opportunity to ensure clear margins with further resection at the time of the change of obturator. If reconstruction is the team's and the patient's choice for a positive neck, then immediate reconstruction is preferred so as to be able to use the operated recipient vessels at the optimum time.

Rehabilitation of the Maxillary Class II Defect

The Reconstructed Patient

Preplanned Approach

With the advent of stereolithographic techniques and computerized planning, there is the possibility of placing implants into the bony reconstruction being used for the maxillary reconstruction. This is been best described in the use of the fibula flap, with appropriate computerized preplanning and with surgery being guided with appropriate stereo lithographic cutting guides, templates, and custom-design osteosynthesis plates.[17] In the management of new oral malignancy, where time is of the essence, the use of such techniques requires significant in-house technical support and financial investment, and it carries the ultimate risk that rehabilitation does not occur in any case due to inadequate disease control or other factors.



• **Fig. 29.2** Conventional dental implants used to support a screw-retained fixed prosthesis in a patient following resection and fibula flap reconstruction for a IId maxillectomy defect.

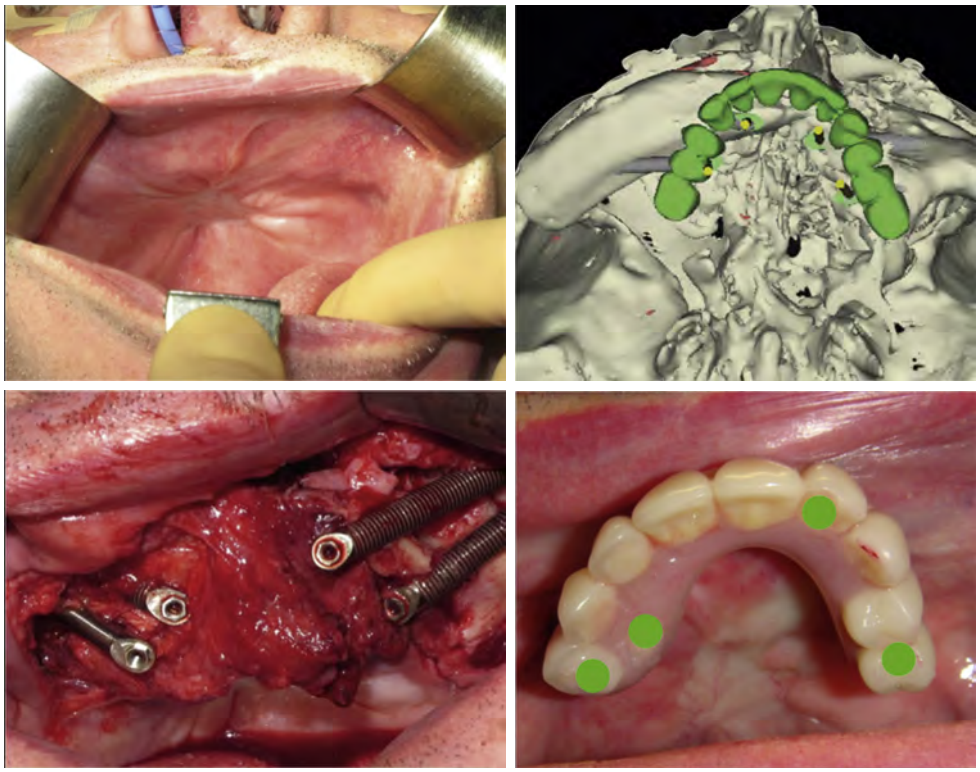
Delayed Dental Rehabilitation

In our unit, we prefer a delayed dental rehabilitation approach following reconstruction of the maxilla for malignant disease. A joint decision is made prior to surgery between the operating microvascular surgeon and the maxillofacial prosthodontist regarding the most appropriate free-flap reconstruction for the individual patient, taking into account all the appropriate factors that will contribute to the overall success of the treatment approach. Where the defect is mainly posterior, a soft tissue flap will often suffice, but if the defect requires the loss of a greater part of the maxillary alveolus (especially class IIc and IId, where the defect crosses the midline), a composite flap is likely to be recommended, as long as the patient is fit for such a procedure. The dental motivation of the patient is also extremely important and contributes significantly to the decision-making process preoperatively. Following successful surgical and oncology treatment, the patient is assessed for an implant-supported prosthesis. Prosthodontic planning is undertaken with mounted study casts and a removable trial prosthesis where possible. Usually a diagnostic CT scan will be arranged to ensure that the bony component of the reconstruction is well healed to the native bone and to obtain an accurate picture of the 3D bony reconstruction in relation to the planned prosthesis. Scans also reveal the presence and position of the osteosynthesis plates and whether this will interfere with the planned implant surgery. In general terms, where no radiotherapy has been used, dental rehabilitation often begins 4 to 6 months following treatment. If postoperative radiotherapy or chemoradiotherapy has been used, treatment is often delayed until after the first year post-treatment. Hyperbaric oxygen therapy is not routinely used in such cases.

Computerized dental implant planning software is an excellent adjunct to determine the appropriate number, type, and angulation of implants into both the reconstructed bone and the native remaining bone. Standard dental implants can often be used, as long as the bony reconstruction is in an ideal position with respect to planned tooth position (Fig. 29.2). Where the position of the composite flap is lateral to the dental arch (as often occurs with a deep circumflex iliac artery [DCIA] reconstruction [iliac crest and internal oblique]), or if the remaining maxilla is severely atrophic, the use of angled zygomatic and zygomatic oncology implants can often provide an excellent way of supporting the dental reconstruction, bringing the screw access holes within the body of the dental prosthesis (Fig. 29.3). Implant surgery is carried out under general anesthesia, generally in a two-stage approach with appropriate management of any intraoral skin flaps, which are debulked and tailored to form a vestibule wherever possible and ensuring that the peri-implant tissues are immobile. Where radiotherapy is not being used, more aggressive soft tissue reduction is employed together with peri-implant soft tissue grafting with palatal tissue[18] or split skin graft. Where fixed dental prostheses are provided, a screw-retained approach is always used to ensure that ongoing surveillance is not hampered and so that future maintenance of the prosthesis is straightforward.

The Obturated Patient

In patients for whom surgical reconstruction is deemed unsuitable, the provision of a maxillary obturator is a useful alternative. As for all oral cancer patients, a full clinical examination of the dentition and periodontium is crucial in the provision of a successful prosthesis, especially where retention of maxillary teeth is envisaged as part of the support and retention for the obturator.



• **Fig. 29.3** Fixed dental prosthesis retained by four zygomatic implants. The use of zygomatic implants compensated for the laterally placed deep circumflex iliac artery bone graft on the defect side and the severe atrophy on the nondefect side.

The horizontal component of the class II defect places an ever-increasing requirement for the concomitant insertion of osseointegrated implants as the amount of residual maxilla decreases, in order to supply much-needed retention and support for the prosthesis. The edentulous patient is routinely treated with implants to provide retention for what otherwise would be a poor obturator prosthesis.

For small unilateral posterior defects, a conventional non-implant solution is often well tolerated and retained. In a fully dentate individual, especially where the posterior defect only extends up to the premolar tooth on the affected side, a tooth-retained maxillary obturator with or without prosthetic teeth can provide an excellent solution.

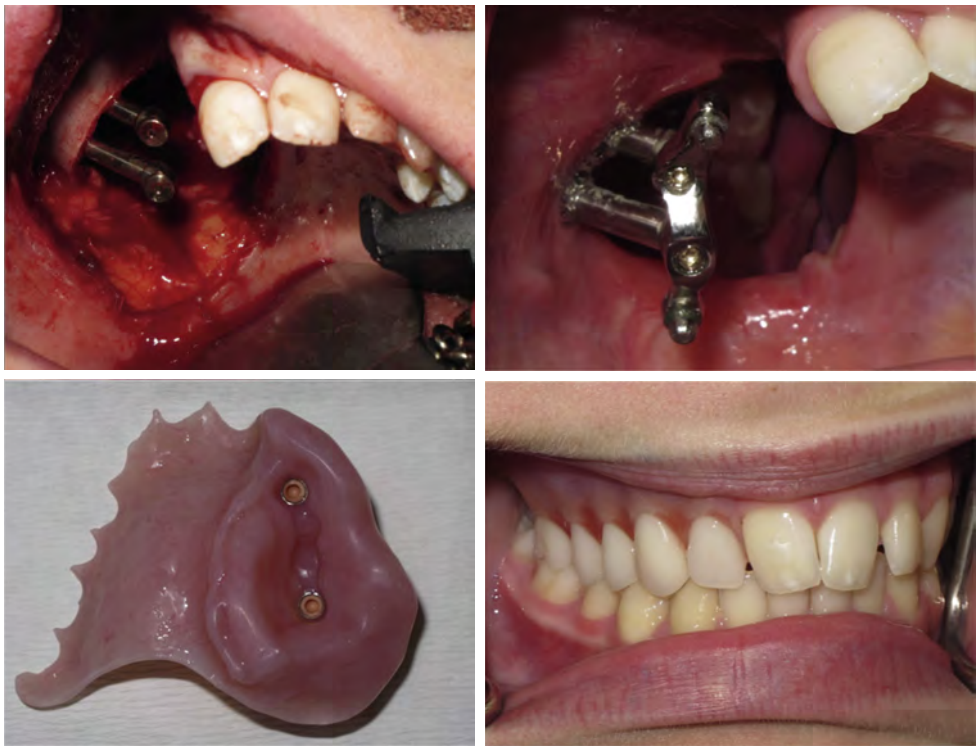
Once the surgical defect extends into the anterior segment, our preference is to attempt the placement of zygomatic oncology implants into the affected side at the time of resection. Often we are able to place two such implants, which can be used to support the obturator with a splinted bar-type reconstruction (Fig. 29.4). Such an approach provides valuable in-defect retention and support and can virtually eliminate any prosthesis movement in function, which standard prostheses are unable to provide. The use of implants also removes the need for an unsightly dental clasp on maxillary incisor teeth or the use of soft silicone materials to engage undercuts within the defect, with their high maintenance requirements. The height of the obturator component can also be kept to a minimum, which is of great advantage to a patient struggling with post-surgical trismus. Where only a single zygomatic implant can be placed because of anatomical restrictions, further immediate dental implants can be placed with the concomitant loss of anterior teeth to provide a splinted implant framework replacing the anterior teeth as a fixed dental prosthesis with distal support and retention for a simple acrylic obturator (Fig. 29.5). The framework is usually placed 2 weeks post resection in an immediate loading protocol.

In the larger Brown class 2d defects where very little alveolus remains, a quad-zygomatic approach is taken, again with loading of a definite obturator at 2 weeks' post resection (Fig. 29.6).

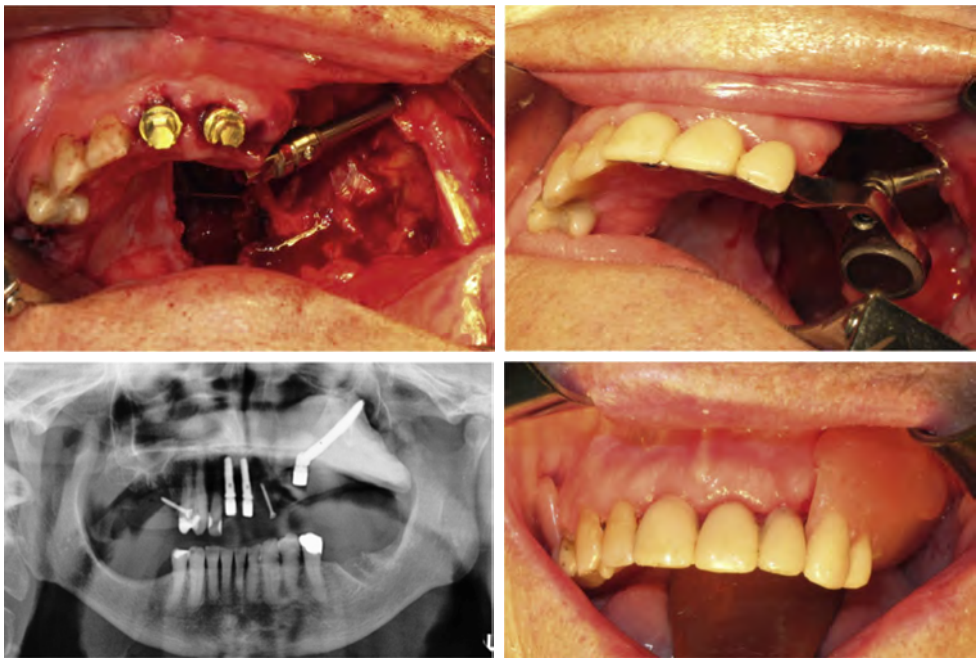
Zygomatic implant survival in this group of patients has been variably reported[19-24] on small institutional experiences, which may represent the steep learning curve in this type of treatment. The largest published series, by Boyes-Varley and colleagues,[19] reported 100% survival on a group of 20 patients with 40 zygomatic implants. Our own, as yet unpublished, data on 102 consecutively placed implants in 38 patients demonstrated 92% survival.

Radiotherapy and Chemotherapy

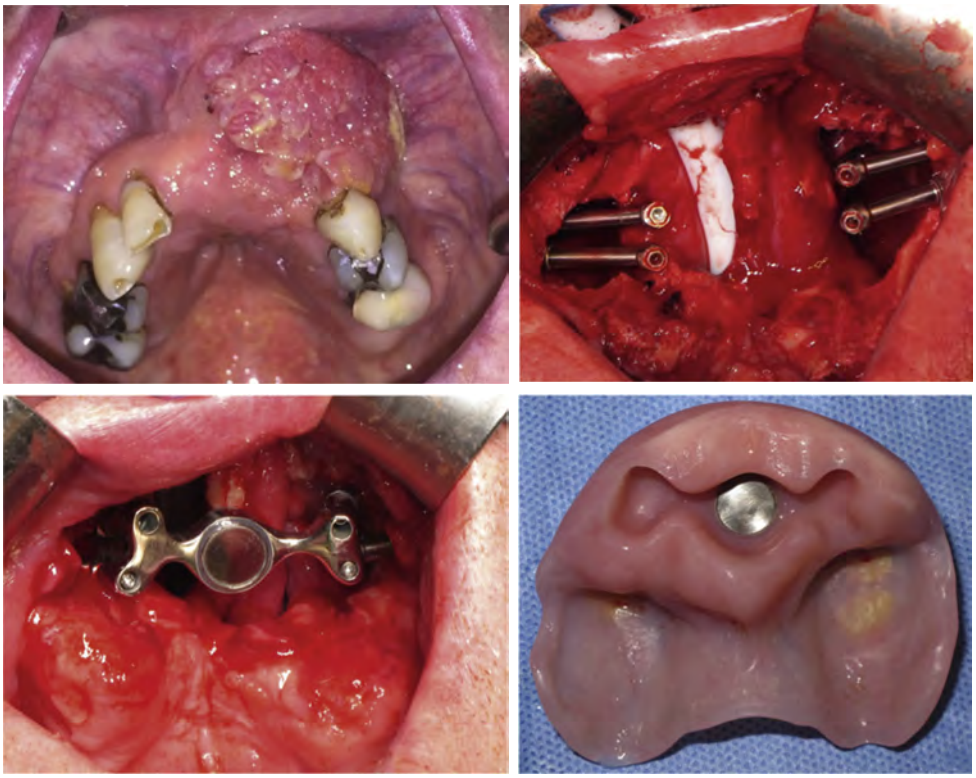
Radiotherapy and chemoradiotherapy for locally advanced (T3/T4) tumors of the oral cavity, including those of the maxillary alveolus, have a major role as an adjunctive therapy following potentially curative surgery. For locally advanced tumors, published series reporting outcomes of definitive radiotherapy alone for tumors of the maxillary alveolus indicated poor 5-year survival, although comorbidity precluding surgery and inoperability due to the extent of disease are confounding factors. For smaller localized tumors (T1/T2), however, radiotherapy is a safe and effective treatment.[25,26] Series for chemoradiotherapy in this context are generally small, but have reported 5-year



• **Fig. 29.4** Splinted zygomatic oncology implants (Southern Implants, South Africa) supporting a simple acrylic obturator in a 14-year-old patient following resection of a class IIb maxillary sarcoma.(From Dattani A, Richardson D, Butterworth CJ. A novel report on the use of an oncology zygomatic implant-retained maxillary obturator in a paediatric patient. *Intl J Implant Dent.* 2017. Retrieved from https://journalimplantdent.springeropen.com/articles/10.1186/s40729-017-0073-7.)



• **Fig. 29.5** Maxillary obturator supported by a fixed hybrid implant-supported prosthesis consisting of anterior fixed bridge and posterior support and retention for a simple acrylic obturator.



• **Fig. 29.6** A quad-zygomatic approach for a large class IIc defect. A definitive immediate load maxillary obturator is fitted 2 weeks following resection.

overall survival rates of 56–76% in selected cases.[27,28] Bone invasion in T4 tumors is a risk factor for osteoradionecrosis; however, some authors have reported that rates of osteoradionecrosis are no higher in those patients treated with chemoradiotherapy with bone invasion than in those without.[27] The extent of bone invasion would, however, be a contributory factor. Other factors include the delivered radiation dose to the mandible and parotids, which increases the risk of dental caries and the requirement for extractions.[29]

In the postoperative setting, radiotherapy is given to reduce the risk of local recurrence and thereby increase the overall chances of cure. In the absence of significant postoperative medical or surgical complications, radiotherapy should commence within 42 days of surgery, as delay is known to be detrimental to outcomes. There are significant toxicities associated with radiotherapy, so benefits must outweigh the risks. Although these risks are always evaluated in the context of the individual, published guidelines are generally in agreement on the indications for postoperative adjuvant therapy. Radiotherapy is indicated postoperatively for locally advanced tumors T3/T4, nodal involvement (two or more nodes), and extracapsular nodal spread (ECS) and close or positive surgical margins, although the definition of a close margin is not absolute and needs to be take in clinical context. When evaluating a close margin, the presence or absence of perineural or lymphovascular invasion would also be taken into consideration.

Chemoradiotherapy is advised in fit patients (WHO 0 or 1) under the age of 70, in the presence of postoperative positive margins or where extracapsular lymph node spread is present. This practice is based on the results of the EORTC 22931 and RTOG 9501 studies, both of which revealed an improvement in disease-free survival following delivery of cisplatin-based chemoradiotherapy compared to radiotherapy alone for patients at high risk of recurrence following definitive surgery.[30,31] Long-term follow-up confirms the benefit in patients with positive surgical resection margins or ECS; patients without these features did not benefit from the addition of chemotherapy.[32,33] Both of these studies recruited in the era before intensity modulated radiation therapy (IMRT), radiation portals covering the entire surgical field, and all draining lymph nodes at risk, delivering a dose of 60 to 66 Gy in 33 fractions to areas at particularly high risk (ECS or positive margins), plus cisplatin 100 mg/m^2 on days 1, 22, and 43 of radiotherapy. In these studies only 57–61% received the full intended dose of chemotherapy; renal toxicity, thrombocytopenia, and neutropenia limited delivered doses. Intermediate-dose weekly cisplatin is being investigated in the postoperative chemoradiotherapy setting by some groups as an attempt to reduce toxicity while maintaining dose intensity.[34] IMRT has been shown to reduce xerostomia when compared to conventional radiotherapy[35] and in retrospective series has been shown to improve disease-free survival for oral cancers.[36] Treatment volumes using IMRT for postoperative radiotherapy are controversial and not clearly defined. Irradiated volumes covering postoperative surgical fields are by their nature larger than those used to treat undissected areas, and care must be undertaken when employing an IMRT technique to fully cover the surgical bed. Some studies have shown a high marginal recurrence

rate, particularly after flap reconstruction from tumors of the oral cavity. Care must be taken to include an adequate margin around the flap,[37] the area at high risk being the tissues around the flap rather than the flap itself. T4 tumors of the hard palate and maxillary alveolus have a high propensity for lymph node spread, and prophylactic neck dissection in the clinically node-negative neck is advised accordingly.[38,39] If prophylactic neck dissection has not been performed in the clinically node-negative neck, then the radiotherapy fields should cover the ipsilateral neck. The lymphatic drainage of the maxillary alveolus and the hard palate is generally predictable and flows via two routes: via the submandibular nodal group (level Ib) and then to the superior jugular chain (level IIa) or via the retropharyngeal plexus (level VIIa) and again on to the superior jugular chain.[40,41] These nodal groups should be included in the clinical target volume in the node-positive or undissected neck; level III nodes may also be included as the next station in the chain of predicted nodal involvement. Contralateral nodal chains should be included if the primary tumor crosses or encroaches upon midline, or in the presence of significant ipsilateral nodal invasion.

Surveillance

The NCCN guidelines do not include the timing of surveillance but emphasize the importance of teamwork.

NCCN Guidelines

A physician and other health care professionals with expertise in the management and prevention of treatment sequelae should review the patient's:

- General medical care
- Pain and symptom management
- Nutritional support
- Dental care for radiation therapy effects
- Xerostomia care
- Smoking and alcohol cessation
- Speech and language therapy
- Audiology
- Tracheotomy care
- Wound management
- Depression and anxiety management
- Social work and supportive care

In the United Kingdom, we generally review patients monthly in the first year, every 2 months in the second, and every 3 months in the third, then subsequently 6 monthly until 5 years have been completed.

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Advanced Palatomaxillary Cancer (Special Considerations Related to Nasal Involvement)

PHILLIP PIRGOUSIS, RUI P. FERNANDES, ROI DAGAN

Epidemiology

Squamous cell carcinoma of the oral gingiva constitutes 25% of all oral cavity carcinomas, yet only approximately 3% affect the maxillary gingiva.[1,2] Despite this being a relatively uncommon subsite, a significant volume of literature exists describing the specific biologic behavior of carcinomas in this area as well as their clinicopathologic features and prognosis.[3-7]

Approximately 34,360 cases of oral cancer are reported annually in the United States. Age-adjusted incidence rates are 15.6% per 100,000 for men and 6.1% per 100,000 for women. Higher rates are observed among African American males in the United States, particularly for cancer of the oropharynx.[8]

Overall survival rates for carcinoma of the maxillary gingiva and hard palate are fair. The 3- and 5-year survival rates in 62 patients from 2003 to 2012 from a single institution were 66.6% and 57.3%, respectively.[5] Statistically significant associations were also shown between survival rates and tumor differentiation, tumor stage, margin status, and lymph node involvement. These associations have also been demonstrated in other similar outcome studies.[1,2,4,6]

Much attention has been devoted to the appropriate management of the clinically node negative neck in maxillary gingival carcinoma. Occult nodal disease varies among published retrospective reports, ranging from 21.5% to 66.7%.[9-14] It is well accepted now that tumors staged T2-T4 warrant elective neck dissection given the relatively high incidence of occult nodal disease.

Maxillectomy Classifications

Historically, Ohngren[15] in 1993 was the first to distinguish between tumors arising from the nasal cavity and paranasal sinuses from those arising in the maxilla. He was also the first to identify topographically that antero-inferior tumors had a more benign behavior compared to postero-superior tumors with a more malignant aggressive behavior.

Since this time, numerous maxillectomy classifications have been proposed. Generally, all have attempted to describe the horizontal and vertical extent of the maxillectomy defect, and some have expanded their classification to include the complex 3D anatomy of the maxillary defect.[16-20] Okay and colleagues[19] and Brown and Shaw[20] have critically included the defect involving the dentate maxilla and its implications on microsurgical reconstruction and/or prosthetic rehabilitation.

Maxillary Reconstruction With Nasal Involvement

Over the past 15 years, significant attention has been devoted to reconstructive algorithms and microsurgical reconstructive options for maxillary and mid-face defects.[17,21] Much of this relates to the complex anatomic region faced by the reconstructive surgeon together with the specific facial subunits requiring reconstruction.

Furthermore, the microsurgical reconstructive repertoire has steadily increased with various donor sites and free flap options available, both soft and composite flaps, enabling a more tailored defect-specific reconstruction with superior esthetics and functional outcomes.[22-26]

The importance of the central portion of the face including the maxilla, palate, upper lip, and nasal complex cannot be overemphasized. This component of the face comprises the functional and esthetic cornerstone of the mid-facial unit and is integral to every key mid-facial feature.[27] This portion of the maxilla provides the structural framework and bony buttresses of the central mid-face, allowing resistance to forces of mastication, anchoring the dentition, supporting the upper lip and nasal complex, and providing points of origin of the mimetic musculature. Hence, it is clearly evident that ablative defects in this area have a critical impact on nasal respiration, deglutition, speech, mastication, and esthetics.

Reconstructive Considerations Specific to the Central Mid-face

The central mid-face or nasomaxillary complex demands unique attention to functional and esthetic concerns specific to this anatomic subsite. These include:

- Restoration of facial projection
- Provision of upper lip support
- Skeletal support for the nasal complex
- Separation of oral and nasal cavities
- Separation of oral and maxillary sinus cavities
- Bony reconstruction allowing for dental rehabilitation
- Esthetic restoration of facial soft tissue defects

Given the complex and varied nature of the reconstructive requirements above, it is obvious that a single microvascular flap is incapable of providing all these fundamental components and realistically requires the use of a combination of microvascular free flaps, autologous grafts, and local flaps for optimal reconstructive outcomes.[28]

Location and availability of recipient vessels are critical in central mid-face reconstruction because these factors will frequently dictate flap selection due to pedicle length.[29] Often 10 to 12 cm of pedicle length is required to achieve an anastomosis between the mid-face and ipsilateral neck. For some free flaps this is not possible. Alternatively, recipient vessels such as the superficial temporal artery and vein negate the challenge of reaching the neck for vessel anastomosis and have proven to be useful and reliable in both mid-face and scalp reconstruction.[29] Cordeiro et al[29] showed 96% overall flap survival in 71 reconstructed patients. They did make reference to potential drawbacks of the superficial temporal system, notably the susceptibility to vasospasm, vessel tortuosity, and small caliber.

Additionally, the retromandibular vein is another alternative large caliber recipient vein that can be used.

The vessel-depleted and irradiated neck poses further reconstructive challenges, frequently requiring the need for interpositional vein grafts to reach the closest available recipient vessels. Such cases are associated with increased risk for thrombosis and potential flap failure.[30,31] Creation of arteriovenous loops using harvested vein grafts have been successfully used to reduce the incidence of thrombosis by minimizing vein graft ischemia and endothelial damage in this setting.[32] Free flap reconstruction may then be performed immediately or delayed with no difference in flap survival. Cephalic vein transposition also provides adequate recipient venous drainage when the jugular venous system is compromised.[33]

Reconstructive Options for the Maxilla

The radial forearm free flap remains the workhorse soft tissue flap for head and neck reconstruction and has been successfully used in maxillary reconstruction either as a composite osteocutaneous flap or in conjunction with autologous nonvascularized bone grafts. Its thin, pliable soft tissue component allows it to conform well to the maxillary defect specifically allowing for both nasal and oral re-lining. Primary or delayed autologous bone grafts such as a "sandwich" technique allow for restoration of both hard and soft tissue elements. This technique should be used with caution in patients undergoing adjuvant radiation therapy because the risk for bone graft loss and extrusion is greater.

Cordeiro and colleagues[24] reported the use of the osteocutaneous radial forearm flap for this purpose wherein the vascularized radius was used to reconstruct the bony maxilla.

However, the volume of bone harvested is insufficient for prosthetic implantation, making dental rehabilitation impossible without additional grafting. Also, risk for radial fracture is high if prophylactic plating is not performed, but it remained in the range of 23–31% in various series.[34]

The subscapular system of free flaps has become increasingly popular for mid-face reconstruction since its initial description[35] and popularization.[36] The subsequent description of the "angular branch" and the rich periosteal supply of the lateral border of the scapula[37] enabled its use as a myo-osseous or osteocutaneous flap in maxillary and mid-face reconstruction, enabling ease of anastomosis in the neck due to its long vascular pedicle. Depending on patient body habitus, a thin skin flap may be harvested that can be used for intra-oral or nasal lining. In contrast, the myo-osseous flap harvested from the scapula tip bears great resemblance in shape to the maxilla and is well suited for palatomaxillary reconstruction, allowing for mucosalization of the muscle bed. Prosthetic implantation is possible but may require secondary bone graft augmentation.[38] The overriding disadvantage remains the inability to perform simultaneous tumor resection and flap harvest.

The deep circumflex iliac artery (DCIA) internal oblique iliac crest osteomyocutaneous free flap has been well described by Urken and colleagues[39] and Brown.[40] Various orientations of the iliac crest have been described. The iliac crest can be placed horizontally in low maxillectomy defects or vertically in high maxillectomy defects. Also, Brown[40] showed that harvesting a skin paddle was unnecessary in that the internal oblique used to reconstruct the palate epithelializes rapidly, retaining the qualities of oral mucosa. Perforator-based composite DCIA flaps with skin have been described; however, the skin paddle is unreliable and frequently too bulky for maxillary reconstruction.[41]

The fibula osteocutaneous free flap is arguably the workhorse bone flap for both maxillary and mandibular reconstruction.[42,43] Its long bony segment, thin pliable skin paddle, adequate bone volume for implant placement, ability to osteotomize and contour, long vascular paddle, and good vessel caliber make it well suited for mid-face reconstruction.[44] Similar to the sandwich technique, a large skin paddle can be harvested to provide both oral and nasal lining as well as cover the fibula bone.[24]

Simultaneous flap harvest can occur with tumor ablation and the donor site morbidity is negligible. Futran and colleagues[44] also reported excellent results in terms of facial projection, speech, swallowing, and dental rehabilitation.

It is thus evident from the abundance of literature pertaining to mid-face reconstruction that various microvascular flap options enable safe, reliable, and reproducible esthetic and functional maxillary reconstruction.

The procedure for addressing the associated nasal defect varies among institutions and reconstructive surgeons, and most would delay definitive nasal reconstruction.

Reconstructive Options for the Total or Subtotal Rhinectomy Defect

Large ablative defects of the nasal complex–associated maxillectomy should be addressed after maxillary reconstruction. For ideal and stable nasal reconstruction, the underlying structural support provided by the maxilla must be restored first. Provision of an intact nasal floor is vital, and so is ensuring a stable bony infrastructure from the anterior maxillary reconstruction upon which upper lip support, nasolabial angle, and nasal projection can be optimally restored (Fig. 30.1).

The structural subunits of the nose are arguably the most complex within the face to reconstitute when absent, a fact that complicates nasal reconstruction. Complex 3D architecture, multilayer construction, and functional importance highlight the difficulties associated with rebuilding nasal defects.[45]

Extensive nasal defects frequently require reconstruction using both microvascular free flaps and adjacent tissue together with autologous grafts such as cartilage and bone. Reconstruction of such through-and-through defects must employ an inside-out approach, addressing the internal lining, bony and cartilaginous supportive framework, and finally skin resurfacing of the external nose.[46]

When reconstructing the inner lining, the reconstructive surgeon has numerous options including skin grafts, mucosal flaps, local skin flaps, and free flaps.[47-49] The choice of flap is often dictated by the extent of the defect and the local tissue available for use. When available mucosal flaps are preferred so as to replace like with like within the nasal cavity. Pedicled "turn-in" flaps when available are simple and extremely reliable for this purpose. For the total nasal defect, the fasciocutaneous or osteocutaneous radial forearm free flap is ideal.[50,51] The osteocutaneous radial forearm flap provides the additional advantage of immediate structural support for the nose, obviating the need for subsequent split calvarial bone grafts (Fig. 30.2).[52]

Structural support follows reconstitution of the internal lining and provides the foundation upon which esthetic and functional nasal reconstruction is based. This can be achieved with the use of autologous split calvarial bone and cartilage[52] with the calvarial bone fashioned into an L-strut or with the use of the osteocutaneous radial forearm free flap.[50,51] This sequence of reconstruction most reliably reestablishes nasal tip projection, as well as dorsal and midvault support, and recreates distinct anatomic lateral subunits and alae.[50]

The final layer in nasal reconstruction is the cutaneous nasal envelope. Options here include full- and split-thickness skin grafts, both of which have poor skin color match and inferior tissue quality. The gold standard and most well-described method for skin resurfacing of the nose remains the paramedian forehead flap.[53,54] The flap is harvested based on the supratrochlear artery and vein and inset into the defect. Donor sites that cannot be fully primarily closed are dressed with Xeroform and allowed to heal secondarily.

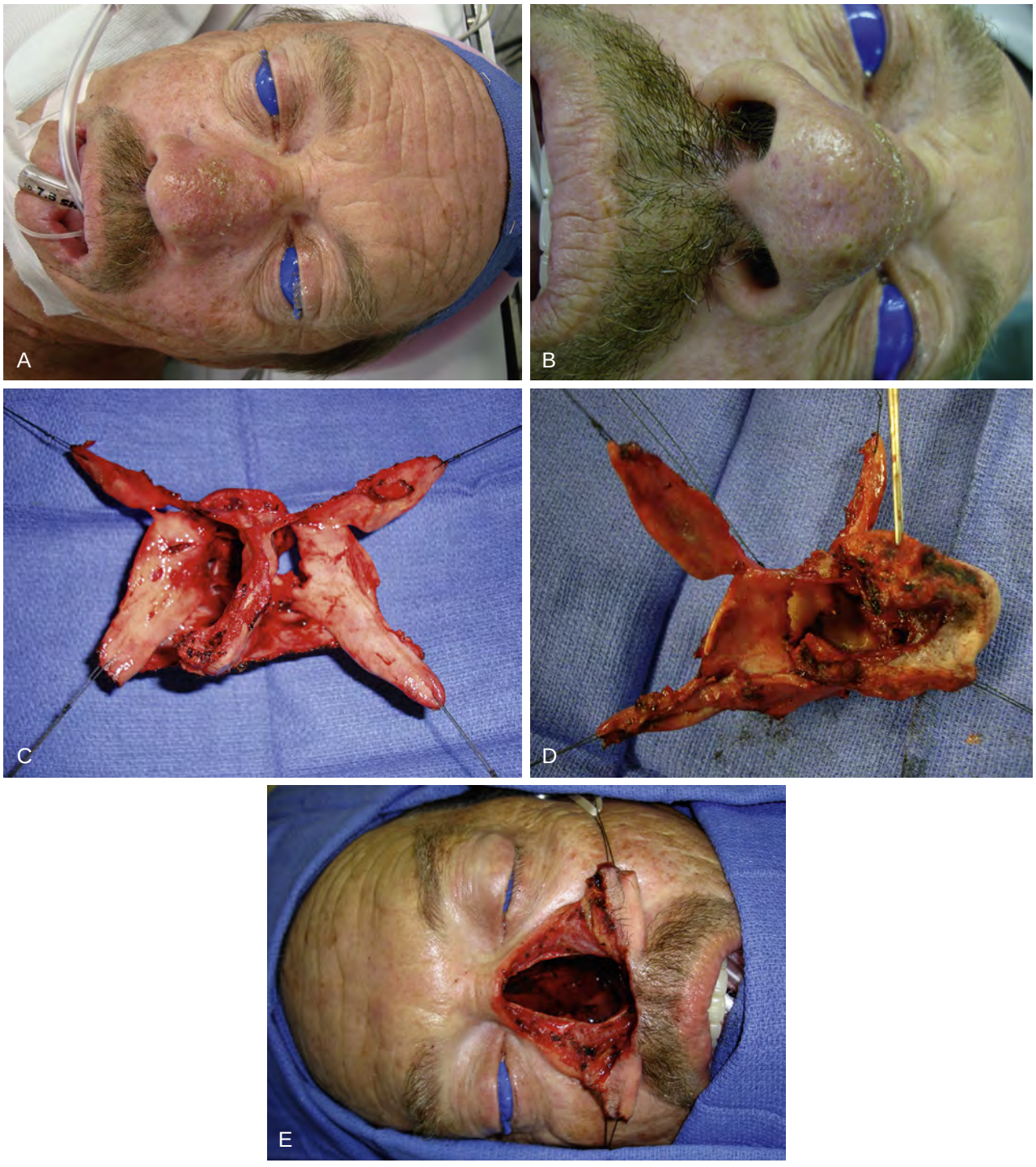
Takedown of the forehead flap generally occurs at 3 weeks from time of harvest, ensuring adequate time for neovascularization from the recipient bed (Fig. 30.3).

It is the authors' preference that complex ablative defects involving the nasomaxillary complex should be addressed in stages for superior functional and esthetic results. Ideally, the maxillectomy defect is addressed first with the necessary and appropriate composite flap reconstruction and, once stable, proceed with secondary nasal reconstruction, particularly where total and subtotal nasal reconstruction are needed (Fig. 30.4).

Radiation Therapy Technique

Radiotherapy is indicated in all curative cases of T4 carcinoma of the maxilla with invasion of the sinonasal region, either as primary therapy or in the adjuvant setting. Adjuvant therapy should be initiated within 6 weeks of surgery, allowing for sufficient healing of surgical wounds. Computed tomography (CT) simulation should be performed with head and neck immobilization and depression and leveling of the shoulders. Oral stents, when tolerated, can be helpful in displacing the tongue from the irradiated volume. In locally advanced or perineural disease that extends to the skull base, magnetic resonance imaging can be helpful for treatment planning in both delineation of target volumes and intracranial normal tissue structures such as the brain, brainstem, visual pathways, temporal lobes, hippocampi, and hypothalamus-pituitary complex. Co-registering of presurgical imaging can also be helpful in delineating target volumes.

After CT simulation is completed, target and normal tissues are defined. Gross residual tumor is called the *gross tumor volume.* The *clinical target volume* (CTV) is defined as the volume at risk for harboring residual microscopic disease. For T4 tumors of the maxilla, the CTV should include the entire primary resection bed, and adjacent subsites of the sinonasal region are included to account for occult microscopic disease. In cases of perineural extension, the skull base nerve tracts are often included in the CTV.[55] The neck should be irradiated electively when it is not dissected, and postoperative neck radiotherapy is recommended for patients with positive neck dissections. For lateralized tumors, ipsilateral neck radiotherapy is acceptable, as long as the primary tumor did not extend within 1 cm of midline, there is no bulky adenopathy in the involved neck placing the contralateral neck at risk from backup lymphatics, and the contralateral neck has been adequately staged and is negative. Nodal CTV delineation has been standardized in both the primary and postoperative settings in published guidelines.[56,57] CTVs are subsequently expanded for planning target volumes by a margin of 3 to 5 mm to account for residual uncertainties in planning and delivery. These margins are designed to ensure that the CTVs will receive their prescribed doses with 95% certainty. The margins can be minimized by improving the reproducibility of treatment setup through secure immobilization



• **Fig. 30.1** **A,** Preoperative view. **B,** Bird's eye view. **C,** Specimen after tumor resection. **D,** Superior view of specimen. **E,** Resection defect.



• **Fig. 30.2** **A,** Preoperative view of nasal tumor. **B,** Bird's eye view. **C,** Result following tumor resection and defect closure with nasal stenting.



• **Fig. 30.2, cont'd** **D,** Late postoperative result. **E,** Appearance with nasal prosthesis, left view. **F,** Appearance with nasal prosthesis, right view. **G,** Frontal view. **H,** Right lateral view. **I,** Right lateral view without prosthesis.



• **Fig. 30.3** **A,** Preoperative view with paramedian forehead flap outlined. **B,** Preoperative frontal view. **C,** Post resection defect, left lateral view. **D,** Tumor specimen. **E,** Internal lining reconstructed with septal hinge flap. **F,** Inset of septal hinge flap.



• **Fig. 30.3, cont'd** **G,** Elevated paramedian forehead flap. **H,** Inset paramedian forehead flap. **I,** Postoperative result prior to second stage. **J,** Preoperative view prior to second stage flap division. **K,** Postoperative view after second stage. **L,** Left lateral view.



• **Fig. 30.4** **A,** Preoperative frontal view of nasal tumor. **B,** Right oblique view. **C,** Preoperative view prior to resection. **D,** Post-ablative defect. **E,** Tumor specimen. **F,** Defect dressed with xeroform and nose stented.



• **Fig. 30.4, cont'd** **G,** Postoperative view.

and on-board image-guided radiotherapy using daily cone-beam CT.[58] The critical normal tissues include the brainstem, spinal cord, salivary glands, larynx, cochlea, brachial plexuses, cervical esophagus, and mandible.

Doses of 66 to 70 Gy are prescribed to the primary site and high-risk regions of the neck (regions of extracapsular extension), doses of 60 Gy are prescribed to the positive region of the neck, and 45 to 50 Gy are prescribed to lower risk regions of the neck over 6 to 7 weeks of radiotherapy delivered once daily using 2-Gy fractions. Hyperfractionation is also useful when the target volume lies close to the optic structures, which are at lower risk for toxicity when radiotherapy is delivered at a lower dose per fraction.[59]

Currently, most patients are treated with advanced radiotherapy techniques such as intensity modulated radiation therapy (IMRT).[60] Proton therapy may further improve the therapeutic index.[61,62]

Concurrent chemotherapy is indicated for cases of gross residual disease, positive margins, or when ECE is present in the neck.[63] For many years the standard regimen has been cisplatin delivered intravenously at 100 mg/m^2 every 3 weeks. Many centers have recently adopted weekly cisplatin at 30 to 40 mg/m^2 as an alternative.[64] Alternatively patients who are not suitable for cisplatin-based chemotherapy can be treated with carboplatin or cetuximab, a monoclonal antibody targeting the epidermal growth factor receptor.

During therapy patients are monitored weekly for management of nutritional status, hydration, mucositis, infection, skin reactions, and other acute effects of therapy. Intense supportive care is required, including the use of feeding tubes in many patients, and treatment breaks should be minimized because increasing the overall treatment time has been associated with decreased locoregional disease control.

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31

Lip Cancer

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Lip cancer is a frequently diagnosed and highly curable cancer of the head and neck region due to its ability to be detected in early stages. In the United States the overall incidence of lip cancer is 1 per 100,000 population, although in higher sun exposure areas of the United States the incidence of lip cancer is approximately 12.7 per 100,000.[1] The prognosis associated with early-stage lip cancer management is quite favorable, with 5-year survival statistics typically exceeding 90%.[1] Even so, some lip cancers have been observed to exhibit aggressive behavior with recurrence or mortality noted in up to 15% of cases.[2,3] Lymph node metastases have been observed to occur in 5–20% of cases, with an overall incidence quoted as 10%.[4] The prognosis for upper lip cancer has historically been noted to be less favorable than that of lower lip cancer.[3,5] In particular, Zitsch and colleagues[3] found a 5-year cause-specific survival rate of 77% for cancer of the upper lip and 90% for the lower lip, but these statistics included both squamous cell carcinoma and basal cell carcinoma of the lips. More recently, Pietersma and colleagues[6] reported similar survival rates for 126 upper and 979 lower lip squamous cell carcinomas with a 94% 10-year relative survival rate for upper lip and a 90% 10-year relative survival rate for lower lip squamous cell carcinomas. The frequency of lip cancer varies internationally with an incidence of 25–30% of all cases of oral cancer.[1,7] Approximately 95% of lip cancers occur in men, typically older than 50 years of age.[8,9] The most common age range at diagnosis is 54 to 65 years, although these cancers occasionally occur in patients younger than age 30 years.

Although lip cancer has most often been categorized as an oral cancer, the authors choose to consider lip cancer one of the facial skin cancers for anatomic and biologic reasons. Anatomically, the most common location for lip cancer is the vermilion or mucocutaneous junction. Biologically, the behavior of squamous cell carcinoma of the lip is similar to that of squamous cell carcinoma of the facial skin rather than the oral mucosa, both in terms of survival and the incidence of lymph node metastases. Finally, the most commonly identified carcinogen of squamous cell carcinoma of the lip is ultraviolet radiation. Like other head and neck skin cancers, patients with lip cancer typically have light complexions, freckles, blue eyes, and fair colored hair. The lower lip is at a higher risk for skin cancer than the upper lip due to the prominence of the lower lip and the inherently greater sun exposure. This anatomic feature accounts for the discrepancy between the incidence of upper and lower lip cancers. The prevalence of lip cancer is at least 10 times higher in whites than in those with darker skin, and is very rare in black people, with statistics similar to those for facial skin cancers.[1] For these reasons, lip cancer should be considered a skin cancer rather than an oral cancer. Other risk factors for lip cancer include the traditional carcinogens for head and neck cancer such as cigarette and pipe smoking, lip trauma, and immunosuppression. Ohman and colleagues[10] identified 34 lip cancers (0.7%) in their retrospective study of 4,950 solid organ transplanted patients. These authors indicated that the risk for lip cancer increased 44 times in their cohort and the relative survival for patients in whom lip cancer developed following solid organ transplant was significantly decreased compared with non–solid organ transplant patients. While numerous risk factors may be related to the development of lip cancer, the overwhelming anecdotal evidence points to prolonged and cumulative sun exposure as the most significant carcinogen involved in the development of squamous cell carcinoma of the lip.

Approximately 90% of lip cancer occurs on the lower lip with nearly 2–7% of cases occurring on the upper lip and 2–4% noted at the commissure.[8] Squamous cell carcinoma is clearly the most common histologic variant, with basal cell carcinoma, melanoma, and minor salivary gland cancers of mucosal origin comprising the other histologic variants of lip cancer. The latter diagnosis is certainly an exception to the previous statement that lip cancer should be considered a skin cancer rather than an oral cancer.

Pertinent Anatomy

The upper lip is formed embryologically by the fusion of the lateral maxillary processes and a central nasofrontal process. Due to the anatomic separation of the lateral segments, contralateral lymphatic cervical metastases are quite rare from upper lip cancers. This anatomic feature is in contradistinction to the lower lip that forms by fusion of two lateral mandibular processes in the midline. Lower lip



• **Fig. 31.1** Actinic keratosis of the lower lip with ulcerations. Geographic incisional biopsies were performed that identified moderate dysplasia.

cancers, therefore, are at higher risk for contralateral metastasis. Blood supply to the lips is from the superior and inferior labial arteries.

Lymphatic drainage of the lips follows a predictable course of metastatic dissemination. Lymph node metastases related to lip cancers occur in fewer than 10% of patients with cancer of the lower lip and up to 20% of patients with cancer of the upper lip and commissure.[1] Cancers of the lateral aspect of the upper lip preferentially metastasize to the buccal, periparotid, and preauricular regions overlying the body of the mandible.[1] Secondary metastases occur to the cervical lymph nodes in the submandibular triangle. Cancers of the lower lip preferentially drain into cervical lymph nodes of the submental and submandibular triangles of level I cervical lymph nodes.[11] Subsequent metastases can occur in level II and III lymph nodes. Dissemination to level IV and V lymph nodes is quite rare, although when cervical metastases do occur from lower lip cancers, bilateral level I metastases are not uncommon.

The sensory nerve distribution of the upper and lower lips is provided by the maxillary and mandibular divisions of the trigeminal nerve, respectively. The lower lip neurosensory innervation is of significance in the work-up of patients with lower lip cancer, specifically with regard to obtaining a screening panoramic radiograph to rule out mandibular involvement by the cancer as occurs through perineural spread.

Staging

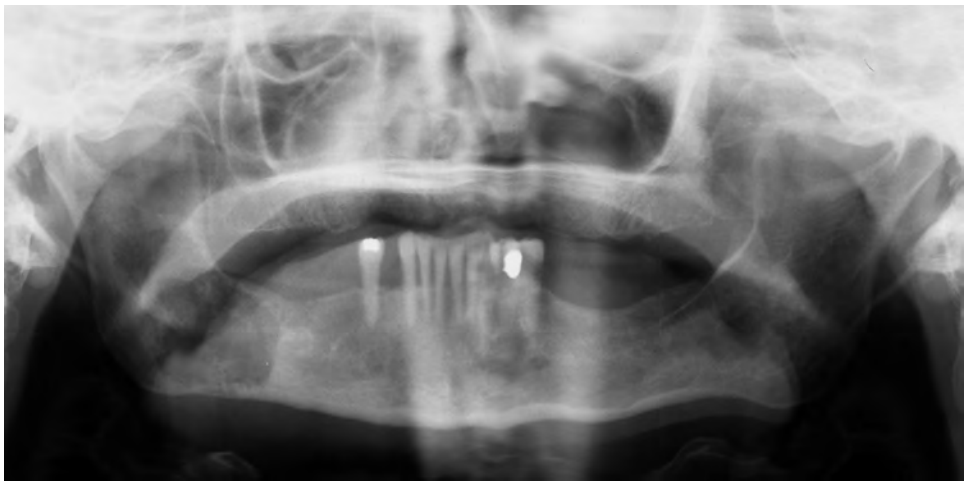
History, physical examination, and incisional biopsy are the most valuable tools in establishing a diagnosis of lip cancer. A discussion of cancer undoubtedly warrants a discussion of pre-cancer. The most common pre-cancer of the lower lip is actinic keratosis (Fig. 31.1). Actinic keratosis involves ultraviolet radiation damage of the lower lip. It is named due to the white color of the vermilion of the lower lip that is affected by actinic



• **Fig. 31.2** A large squamous cell carcinoma of the lower lip.

keratosis. The lip is also characteristically dry in its appearance. Ulcerations may be present but a mass is not noted in actinic keratosis. The histologic evaluation of actinic keratosis may reveal signs of dysplasia or carcinoma in situ. When a mass is present, an invasive cancer diagnosis is almost certainly to be established through a required incisional biopsy. Actinic keratosis is a clinical diagnosis that does not require a preoperative incisional biopsy but certainly requires histologic confirmation following excision.

A history of a non-healing crusted mass of the lip that persists for several months is typical of an invasive cancer diagnosis (Fig. 31.2). The incisional biopsy should be performed within the center of the lesion in order to establish the diagnosis. Once a diagnosis of squamous cell carcinoma of the lip has been made it is most important to obtain a panoramic radiograph to investigate for a widened mental foramen and/or erosion of the mandible that could occur by perineural spread by a lower lip cancer (Fig. 31.3). Subsequently, the cancer can be staged (Table 31.1). In general terms, special imaging studies such as computed tomography (CT) or magnetic resonance imaging of the primary site and the neck are obtained as part of the preoperative work-up of all patients with lip cancer. Positron emission tomography CT (PET-CT) may be obtained when the patient presents with an N+ designation. This is especially the case when unilateral adenopathy exists in association with a lower lip cancer and imaging with a PET CT scan will image the contralateral neck. Distant metastases, including those of the axillary lymph nodes and bone, are identified in approximately 1–2% of patients at the time of initial evaluation of a previously untreated lip carcinoma.[8,12,13] In preparation for ablative surgery performed in an operating room setting, routine blood work, electrocardiogram, and chest radiographs are obtained according to standards set by the surgeon's operating room and attending



• **Fig. 31.3** Metastatic squamous cell carcinoma of the right mandible in a patient who was previously treated for a stage II squamous cell carcinoma of the right lower lip. The metastatic focus reflects proximal perineural spread of the lip cancer to the mandible.

TABLE 31.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor ≥2 cm and ≤4 cm in greatest dimension
T3	Tumor ≥4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease
T4a	Moderately advanced local disease. (lip) Tumor invades through cortical bone or involves the inferior alveolar nerve, floor of mouth, or skin of face (i.e., chin or nose); (oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone of the mandible or maxilla or involves the maxillary sinus or skin of the face). Note: Superficial erosion of bone/tooth socket (alone) by a gingival primary is not sufficient to classify a tumor as T4
T4b	Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base or encases carotid artery
Regional Lymph Nodes: Clinical (cN)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N3	Lymph node(s) larger than 6 cm and ENE(–) or metastasis in any node(s) and clinically overt ENE(+)
N3a	Lymph node(s) >6 cm and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L).* Similarly, clinical and pathological ENE should be recorded as either ENE(–) or ENE(+)

TABLE 31.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)—cont'd

Regional Lymph Nodes: Pathological (pN)

NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
pN2	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2a	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–)
pN2b	metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN3	Lymph node(s) >6 cm and ENE(–); or metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)
pN3a	Lymph node(s) >6 cm and ENE(–)
pN3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+)

Distant Metastasis (M)

Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Registry Data Collection Variables

1. Lip location (external or vermilion border)
2. ENE clinical: ENE(+) or (–)
3. ENE pathological: ENE(+) or ENE(–)
4. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
5. Perineural invasion
6. Lymphovascular invasion
7. p16/HPV status
8. Performance status
9. Tobacco use and pack-years
10. Alcohol use
11. Depression diagnosis
12. Depth of invasion (mm)
13. Margin status (grossly involved, microscopic involvement)
14. Distance of tumor (or moderate/severe dysplasia) from closest margin
15. WPOI-5

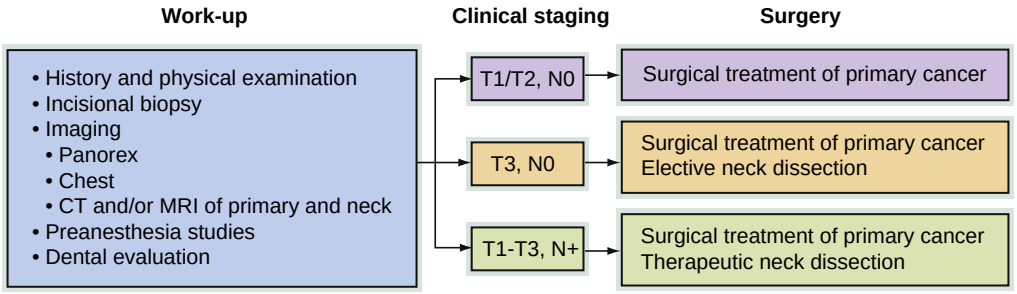
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TABLE 31.1 American Joint Committee on Cancer Staging for Lip and Oral Cavity Cancer (8th Edition)—cont'd

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated

From Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In Amin MB et al, eds. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017. http://dx.doi.org/10.1007/978-3-319-40618-3_10.



• **Fig. 31.4** The work-up, staging, and surgical strategy associated with squamous cell carcinoma of the lip. (Adapted from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Head and Neck Cancers, Version 2.2017.)

anesthesiologists. With all of this information, the surgeon determines the strategy of ablative surgery (Fig. 31.4).

Surgical Treatment

The management of T1-T3 squamous cell carcinoma of the lip should include the objectives of ablation of the patient's cancer with curative intent and the creation of a functionally and esthetically acceptable immediate biologic reconstruction of the lip. The surgical management of lip cancer is unique in that there is no utility in providing a delayed biologic reconstruction. This statement represents a departure from the management of some head and neck cancers in which delayed biologic reconstructive surgery of a segmental defect of the mandible is acceptable. Lip cancer must be managed with immediate soft tissue reconstruction. In so doing, the reconstruction must be performed so as to avoid microstomia that is cosmetically and functionally unacceptable. Esthetic goals of lip reconstruction include restoration or preservation of anatomic landmarks, reconstruction of facial subunits, acceptable color and texture match, and lip symmetry. Functional goals of lip reconstruction include the maintenance of oral competence, sufficient oral access, preservation of sensation, mobility, and proper phonation.

Soft tissue flaps, as may be used in these reconstructions, are local in terms of their anatomy and random or axial pattern flaps in terms of their blood supply. Random pattern flaps, typically local in terms of their anatomy, are those in which specific pedicles are not identified or necessarily preserved within the flap. In contrast, an axial pattern flap, anatomically described as either local or regional, is one wherein the pedicle is identified and intentionally preserved within the flap that is rotated into the recipient tissue bed.

Specific Treatment and Techniques

Ablative and reconstructive surgery of the lips is performed in an operating room setting with a nasoendotracheal intubation. An oral intubation may distort the anatomy of the lips and may, therefore, alter the geometry of the reconstruction. The design of the excision is determined by the type of reconstruction that will be performed. The determination of the most adequate linear margin in the management of lip cancer is a topic of speculation and controversy. Some authors have indicated that the size of the primary cancer dictates the magnitude of the linear margin.[14] Small lip cancers measuring less than 1 cm in diameter can often be managed with linear margins of 5 mm,[15] while larger cancers require 8 to 10 mm linear margins.[14] De Visscher and colleagues[16] have determined that a 3-mm linear margin is acceptable in the management of early-stage squamous cell carcinoma of the lower lip as long as intraoperative frozen sections are obtained to confirm cancer-free margins. In the final analysis, it would seem prudent to include a 5- to 8-mm linear margin of normal-appearing skin and mucosa as part of the excision of lip cancer with frozen section analysis of those margins. This approach is consistent with the general consensus that appears in the literature as well as an understanding of the biologic behavior of lip cancer.

Vermilionectomy (Lip Shave) and Mucosal Advancement Flap

The vermilionectomy, also known as a lip shave, is primarily indicated for the management of actinic keratosis with or without dysplasia. That said, microinvasive squamous cell carcinoma may be successfully managed with a vermilionectomy

as long as the excision of the cancer is accomplished with a negative deep margin in the vermilionectomy. Frankly invasive cancer based on incisional biopsy represents a contraindication for the vermilionectomy. The vermilionectomy must be performed from commissure to commissure due to the diffuse nature of the lower lip actinic keratosis. In addition, the cosmetic result of the mucosal advancement flap is enhanced by a complete lower lip mucosal reconstruction. A partial vermilionectomy with isolated mucosal advancement flap will create a stark color difference in the reconstruction that will be esthetically unacceptable. Following vermilionectomy and frozen section analysis of the specimen, the remaining lower lip mucosa is undermined and advanced in a uniform fashion so as to permit closure in a single layer without tension and with a smooth contour (Fig. 31.5).

Wedge Excision and Primary Closure

Invasive cancers of the upper and lower lip require full thickness excision and immediate reconstruction according to the magnitude of the excision. When the excision involves up to one third of the lower lip, a wedge excision may be performed with a linear primary closure (Fig. 31.6). Some authors have recommended a wedge excision and primary closure for defects measuring up to one half of the lower lip. Perhaps the most important decision in whether to use this technique is the laxity of the remaining tissues of the lower lip and face. An older patient with relatively greater tissue redundancy may be able to undergo primary closure of a relatively large defect that would require local flap reconstruction in a younger patient with less laxity of the surrounding soft tissues. One contraindication to the wedge excision and primary closure is when the lip cancer extends to involve the oral commissure. The wedge excision should not cross the labiomental fold because hypertrophic scars tend to occur in this location.

Block Excision With Karapandzic Flap Reconstruction

Cancer excisions involving between one half and two thirds of the upper or lower lip cannot be reconstructed with primary closure without introducing microstomia. Under these circumstances, local flap reconstruction is required. The surgeon may wish to implement local flap reconstruction of the lower lip when excising less than half of the lower lip. The Karapandzic flap is such a reconstruction (Fig. 31.7). These flaps were originally described in 1974 and based on the facial artery.[17] Block excision of the lip is designed to accommodate the Karapandzic flap reconstruction. Following excision of the lip cancer and frozen section analysis of the margins of the specimen, the flap design is accomplished. In so doing, an assessment is made as to the need for bilateral flaps. As the magnitude of the excision increases, the need for bilateral Karapandzic flaps becomes indicated. This is particularly the case for those excisions that cross the midline of the lower lip. The relaxed skin tension lines of the nasolabial folds are used for development of the flaps. These flaps are created through skin and muscle, but do not communicate with the oral cavity. When an upper lip cancer is excised, the reconstruction is accomplished with reverse Karapandzic flaps (Fig. 31.8). As previously discussed, some small cancers may be excised with reconstruction using Karapandzic flaps in younger patients who do not have acceptable surrounding soft tissue laxity so as to permit primary closure. As such, if any doubt exists as to the possibility of postoperative microstomia, the surgeon should perform excision of the lip cancer with local flap reconstruction rather than wedge excision with primary closure. As with the wedge excision, the Karapandzic flap reconstruction is contraindicated when the commissure is excised with the specimen.

Wedge Excision With Abbe Flap or Abbe-Estlander Flap Reconstruction

The Abbe flap was originally described by several authors in the 19th century before Abbe's description, after which time the technique took his name. The flap is a two-staged procedure that represents a cross-transfer of full-thickness tissue from one lip to the other, and is limited in the amount of tissue that can be reconstructed. When used to reconstruct an upper lip defect, a flap of one quarter of the lower lip is used to reconstruct as much as one third of the upper lip. The height of the defect and the height of the flap must be coincident. The flap is based on the labial artery that exists in the vermilion of the lip. Advantages of the Abbe flap include acceptable skin texture and color match with the surrounding tissue of the recipient tissue bed. Following primary closure, the pedicle crosses the oral stoma and may be severed in 2 to 3 weeks. The Abbe-Estlander flap was originally designed to reconstruct defects near the oral commissure. The medial pedicle of the flap is used to reconstruct the commissure. Disadvantages of the Abbe flap include the required two-stage approach to this flap. This feature, as well as the straightforward and predictable nature of other techniques of lip reconstruction, has largely resulted in replacement of the performance of the Abbe flap.

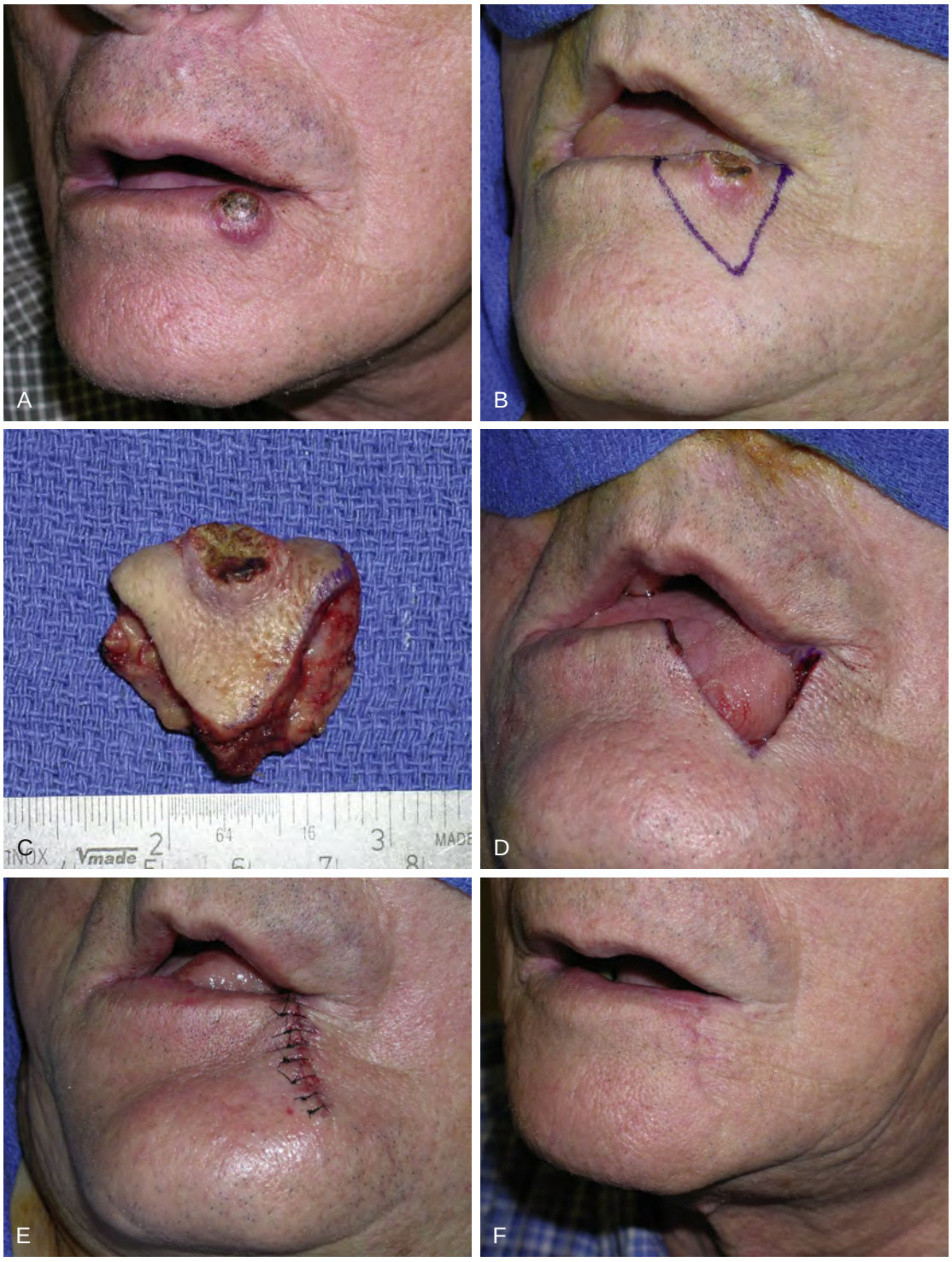
Block Excision With Webster Modification of the Bernard Cheiloplasty

Cancer excisions involving more than two thirds of the lower lip may be reconstructed with Webster modification of the Bernard cheiloplasty. First described in 1960, this technique is random pattern in its nature and requires the development of Burow's triangles in its implementation[18] (Fig. 31.9). The Burow's triangles are designed so that the medial vertical limb is incorporated into the nasolabial fold. The width of the base of the triangle is calculated so that the distance from the oral commissure to the lateral portion of the base equals half the width of lip tissue excised. This type of reconstruction is suitable to reconstruct the lower lip when a neck dissection is not being performed. Laxity of the buccal region as occurs in older patients is required so as to advance bilateral cheek tissue in the reconstruction. The Webster modification of the Bernard cheiloplasty is particularly suited to reconstruction of the oral commissure and should be considered first in such circumstances.

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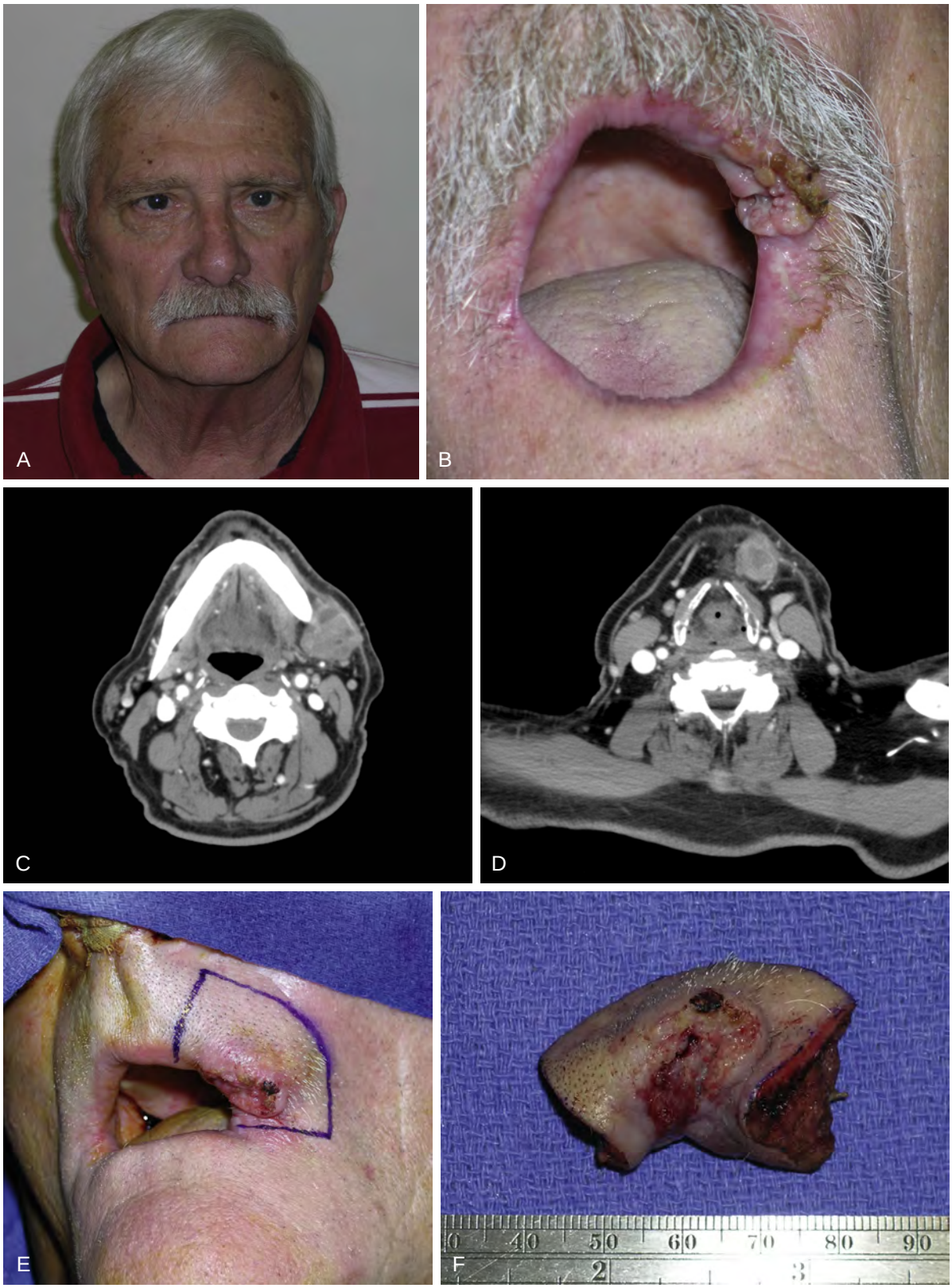
• **Fig. 31.5** **A,** A non-healing ulcer of the midline lower lip that has been present in an immunocompromised patient for 6 months. An incisional biopsy was performed that identified carcinoma in situ. **B,** A vermilionectomy (lip shave) is planned from commissure to commissure so as to create symmetry in the immediate reconstruction with mucosal advancement. **C,** The vermilionectomy specimen. **D,** Final histopathology identified a microinvasive squamous cell carcinoma with negative margins. (Hematoxylin and eosin, original magnification ×10.) **E,** The defect is noted. Care is taken to preserve the anatomic location of the terminal portions of the mental nerves. **F,** The lower lip mucosa is undermined, advanced, and closed primarily in a single layer fashion. **G,** The cosmetic result of this patient's vermilionectomy is noted at 1 year postoperatively.



• **Fig. 31.6** **A,** This biopsy-proven stage I squamous cell carcinoma of the left lower lip can be managed with a wedge excision with primary closure because the cancer excision with margins sacrifices approximately one third of the lower lip. **B,** The wedge excision is demarcated with a skin marking pen. Note that the commissure is preserved in the excision, the inferior aspect of the excision does not cross the mentolabial fold, and the dimensions of the excision do not exceed one third of the lower lip. All three issues must be observed in performing a wedge excision. **C,** The specimen is examined by frozen sections for complete excision. **D,** The resultant defect is noted. **E,** A primary closure of the defect is able to be performed in anatomic layers so as to preserve function of the lower lip. Attention is also given to properly reconstructing the vermilion border so as to preserve the cosmetic appearance of the lower lip. **F,** An excellent 1-year postoperative appearance of the patient's lip closure is noted without signs of recurrent disease.



• **Fig. 31.7** **A,** This stage II biopsy-proven squamous cell carcinoma of the lower lip occupies approximately one half of the lower lip. As such, a wedge excision and primary closure cannot be performed because it would likely result in microstomia. **B,** A block excision of the lower lip is outlined with the intention of performing an immediate reconstruction with bilateral Karapandzic flaps. **C,** The specimen should be examined for the adequacy of excision with frozen sections. The permanent sections identified perineural invasion such that postoperative radiation therapy was planned (see Fig. 31.12A). **D,** The resultant defect of the lower lip is noted. **E** and **F,** Reconstruction is performed with bilateral Karapandzic flaps that maintain the esthetics of the lower lip.

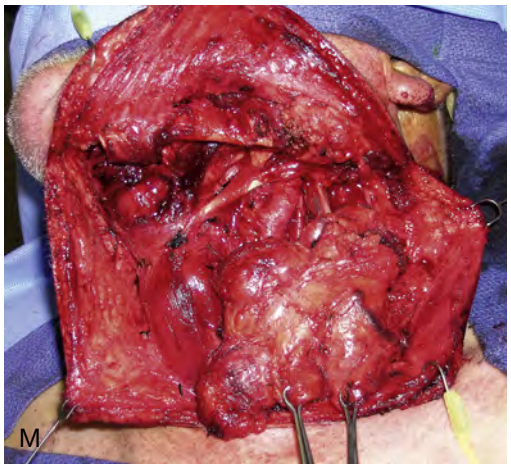


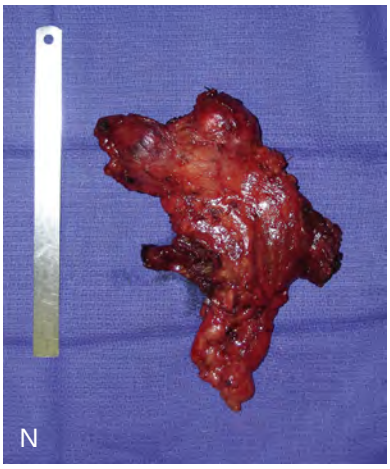
• **Fig. 31.8** **A** and **B,** A 72-year-old man with a squamous cell carcinoma of the left upper lip. Physical examination found adenopathy at levels I and II of the left neck. Clinical staging was T2N2bM0. **C** and **D,** CT scans demonstrate metastatic adenopathy at levels I and II of the left neck. A therapeutic neck dissection was planned. **E** and **F,** The location and size of the primary cancer of the lip led to planning with a block excision and reconstruction with a left reverse Karapandzic flap.

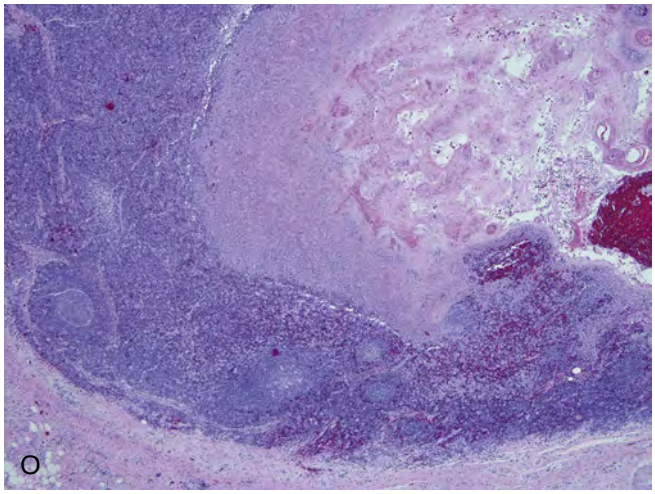
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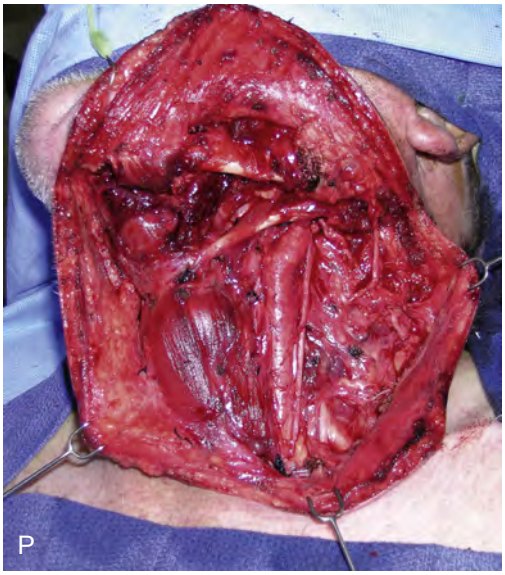


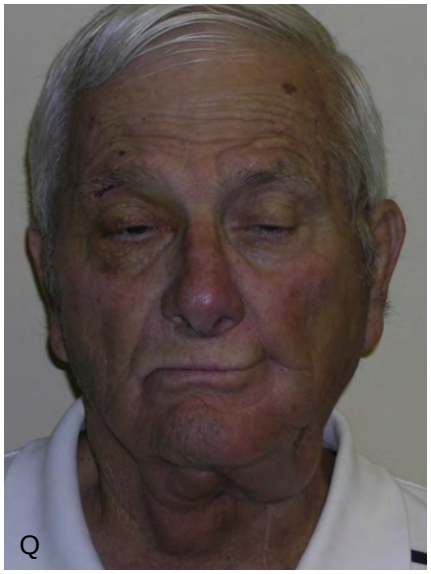
• **Fig. 31.8, cont'd** **G,** Final histopathology of the specimen revealed the presence of perineural invasion. **H,** The resultant defect of the left upper lip. **I-K,** Reconstruction is performed with unilateral reverse Karapandzic flaps. **L** and **M,** A left type I modified neck dissection is also performed.



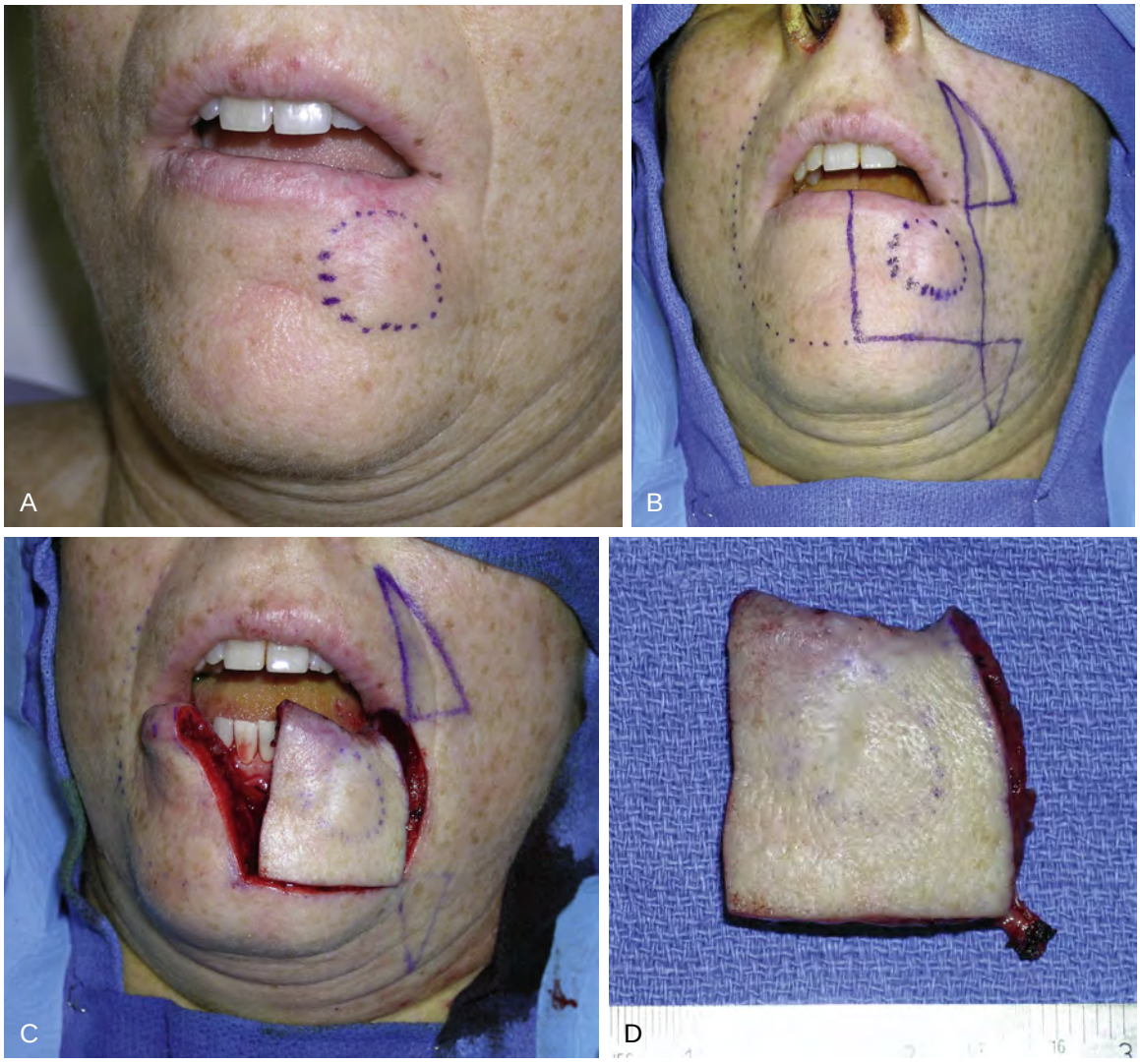








• **Fig. 31.8, cont'd** **N** and **O,** The neck dissection specimen. Final histopathology identified five of 40 lymph nodes with metastatic disease, three of which exhibited extranodal extension of the metastatic cancer. **P,** The resultant defect is noted in the left neck. **Q,** The patient underwent postoperative radiation therapy due to the extent of his disease. Resultant lymphedema in the left neck is noted at 6 months postoperatively.



• **Fig. 31.9** **A,** The subcutaneous extent of a recurrent desmoplastic melanoma of the left lower lip and chin. **B,** The margin required to remove this recurrent melanoma will sacrifice the left oral commissure. As such, a block excision is planned with immediate reconstruction using a right Karapandzic flap and a left Webster modification of the Bernard cheiloplasty. Burow's triangles are outlined as are required for this reconstruction. **C** and **D,** The excision of the cancer is performed and the specimen is delivered.

Management of the Cervical Lymph Nodes in Lip Cancer

The incidence of cervical lymph node metastases associated with lip cancer is reported in 3-8% of patients.[19] Location of the tumor on the lip may predict occult neck disease. Tumors involving the upper lip may show a higher rate of metastasis to cervical lymph nodes than lower lip cancers and may metastasize directly to level I and level IIA lymph nodes. The tumor grade and the tumor thickness appear to be the most important predictive factors for lymph node involvement by lip cancer. Most early-stage lip cancers are diagnosed as well-differentiated squamous cell carcinoma. These low-grade tumors rarely metastasize to the cervical lymph nodes, and Szewczyk and colleagues[20] determined that only two of 22 neck dissections contained lymph node metastases from low-grade tumors. In high-grade tumors, however, the incidence of nodal spread was doubled with four out of 24 patients found to demonstrate lymph node metastases in neck dissection specimens.

The depth of invasion by a lip cancer or the tumor "thickness" also predicts the risk of spread to regional nodes. In findings similar to that for melanoma, the deeper a squamous cell carcinoma of the lip penetrates the normal lip, the greater the risk of nodal disease. Several groups have found that a tumor thickness of more than 4 mm places the patient at a significant risk for lymph node involvement.

A large German study of lip cancer reviewed the influence of tumor grade and depth of invasion on the risk for node involvement.[21] The study examined 326 patients treated between 2001 and 2011 for T1 or T2 lip squamous cell carcinoma. The researchers found that patients who were node-negative had predominantly low-grade tumors (76% World Health Organization grade 1, 21% WHO grade 2, and only



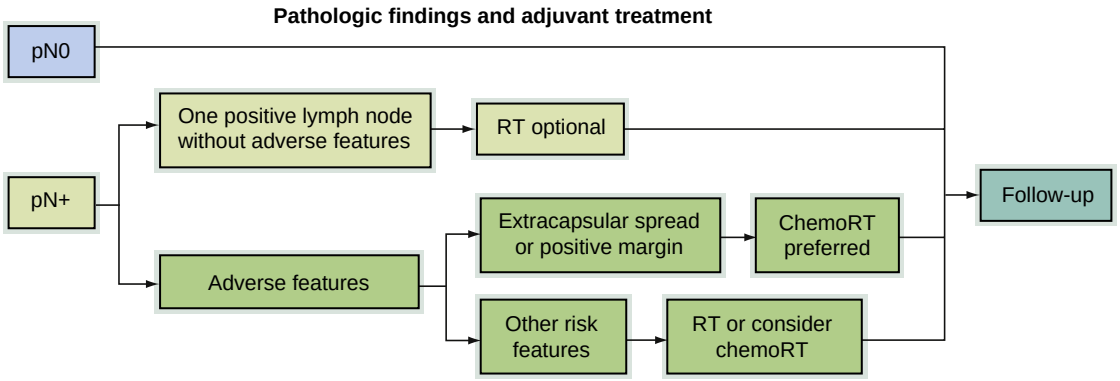
• **Fig. 31.9, cont'd** **E,** The resultant defect is noted. **F** and **G,** The flaps are developed and advanced so as to create an anatomic closure. **H,** A 5-year postoperative appearance of the patient shows an esthetic reconstruction with minimal microstomia.

1.7% WHO grade 3). In contrast, patients with node-positive disease were more likely to have high-grade lesions (only 11% WHO grade 1, 61% WHO grade 2, and 27% WHO grade 3). The study also found that tumor thickness correlated with node positivity. The mean tumor thickness in patients who were node-negative was 2.8 mm. The mean thickness in patients with node-positive disease was 7.1 mm. Superficial tumors (<2.5 mm tumor thickness) rarely involved the regional nodes. However, tumors thicker than 4 mm had a significant risk for nodal spread. Based on these findings the authors proposed a method for predicting lymph node involvement. Patients with well-differentiated grade 1 squamous cell carcinoma of the lip with a tumor thickness greater than 5 mm carry a significant nodal risk and should be treated with neck dissection or irradiation of the regional nodes. Alternatively, patients with grade 2 or 3 tumors with a thickness greater than 2.5 mm carry a significant node risk and benefit from neck dissection or nodal irradiation.

Radiation Therapy

Most squamous cell carcinomas of the lip present as surgically resectable tumors with effective control in 90–94% of patients.[6] Even so, some patients in whom lip cancer develops carry significant medical comorbidity and are at high risk for complications related to general anesthesia and surgical resection. In these poor surgical candidates, definitive radiation therapy is an effective treatment option with results identical to resection. In addition, some patients who have undergone effective removal of their lip cancers require adjuvant radiation therapy because adverse histologic features are present in the specimen (Fig. 31.10).

A large study in the Netherlands examined 256 patients with stage I lip cancer.[22] Some patients underwent margin-negative local resection. Other patients were treated with definitive radiation targeting only the involved lip. With a median follow-up of 55 months, excellent local control was achieved in both groups, with local recurrences in only 3.6% of resected



• **Fig. 31.10** The role of adjuvant therapy in the management of lip cancer as a function of the pathologic stage of lymph nodes. *RT,* radiotherapy; (Adapted from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Head and Neck Cancers, Version 2.2017.)

patients and in 4.4% of radiation patients. The disease-free survival was not significantly different between patients who underwent surgery or received definitive radiation, and radiation therapy appeared to be more frequently used in higher risk patients with larger tumors and high-grade lesions.

A more recent Australian study[19] examined 93 patients with T1 or T2 lip cancer between 1980 and 2012. Patients were treated with definitive radiation therapy with local control reported at 95%, regional nodal failure reported in only 5%, and with a 10-year disease-free survival of 90%. In this study only 3 of 93 patients treated by radiation therapy died as a result of lip cancer. Thus definitive radiation therapy offers an attractive treatment option for squamous cell carcinoma of the lip in patients who are poor surgical candidates.

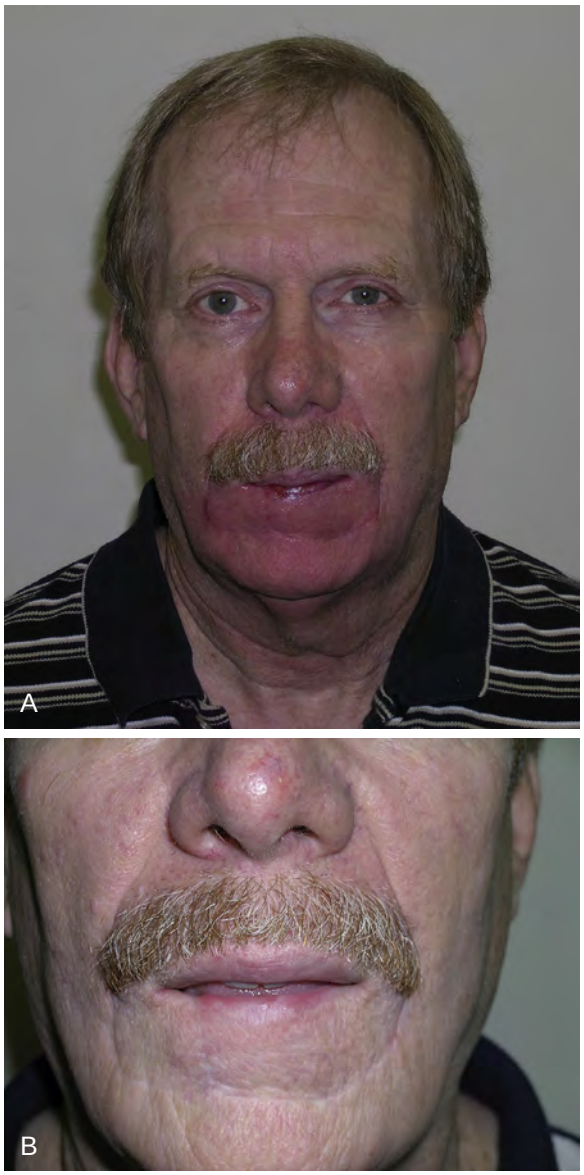
Finally, definitive radiation therapy may be the preferred treatment for large superficial squamous cell carcinomas that involve more than one third of the lip (Fig. 31.11). Resection offers excellent local control in large lip tumors but must be balanced against the functional and cosmetic outcomes. Tumors longer than 3 cm are difficult to resect with widely negative margins while still leaving a functional lip. Older patients may have more tissue laxity that allows resection of slightly larger tumors. However, anesthesia of the reconstructed lip limits full function, and radiotherapy has been thought to offer a better cosmetic and functional outcome.[23] Even larger lesions involving more than one third of the lower lip respond well to radiation therapy. Thanh Pham and Cross[19] showed local recurrence in only 5% of patients treated with definitive radiation and 40% of those patients presented with T2 lesions. As a result, current National Comprehensive Cancer Network treatment guidelines recommend consideration of definitive radiation for tumors that occupy most of the lower lip.



• **Fig. 31.11** **A,** A stage II (T2N0M0) squamous cell carcinoma of the lower lip in a 35-year-old man. The patient chose definitive radiation therapy over a surgical procedure. **B,** The tumor responded well to definitive radiation therapy.

Radiation Technique

Squamous cell carcinoma of the lip is a locally invasive disease that rarely spreads to the regional lymph nodes. Definitive radiation thus targets the gross tumor within the lip with a 1.5- to 2-cm margin to account for any submucosal spread. Definitive radiation to the node regions can be delivered by intensity modulated radiation therapy (IMRT). Most commonly, lateral lower lip tumors are treated along with ipsilateral cervical lymph nodes in levels IA and IB. More midline tumors carry a risk of bilateral lymph node metastases such that both left and right levels IA and IB lymph nodes are treated with IMRT (Fig. 31.12). Tumors of the upper lip are rare but carry a risk for skip metastases to the submandibular nodes and as a result IMRT should cover levels IA, IB, and IIA. Adjuvant radiation with IMRT to bilateral levels IA, IB, and IIA is standard. Neck dissection or comprehensive



• **Fig. 31.12** **A,** The patient in Fig. 31.7 required postoperative radiation therapy to the lower lip and bilateral upper cervical lymph nodes due to perineural invasion in the primary specimen. **B,** At 5 years postoperatively, he showed no evidence of local or regional recurrent disease.

neck radiation is necessary if the level IIA submandibular nodes are involved clinically or radiographically. Extrapolation of results from other head and neck sites is used to justify the addition of concurrent chemotherapy in locally advanced lip cancers with close or positive margins, with extracapsular extension of nodes, or when multiple or bulky lymphadenopathy is present. In these patients, IMRT is used, covering the at-risk node stations with 1.8 to 2 Gy per fraction to a dose of 50 to 54 Gy. The sites of higher risk are treated with higher doses of 66 to 70 Gy.

Literature has been published by several groups[24-26] supporting the efficacy of brachytherapy for the treatment of lip cancer, with achievement of local control reported in 94–98% of cases. A discussion of brachytherapy for lip cancer is beyond the scope of this chapter that will rather focus on external beam radiation as definitive treatment.

Lip cancer can be effectively treated with supervoltage, orthovoltage, or now more commonly focal electron therapy. The visible primary tumor is identified as a gross tumor volume, which is expanded by 1.5 to 2 cm along the length of the involved lip to account for submucosal spread to create a clinical target volume. A radiation field is developed to cover the entire clinical target volume. An intraoral lead shield is commonly used to protect the uninvolved gingiva and oral cavity from the radiation dose passing through the treated lip. Custom lead surface blocking can be used to protect the skin of the chin, face, and uninvolved lip.

The standard radiation treatment is delivered at 2 Gy per fraction as daily treatment over 7 weeks to a total dose of 70 Gy. As long as 3 months may be required following treatment for the treated tumor to completely resolve but local tumor control can be expected in up to 95% of patients, as discussed previously. Regional nodal failure is rare and disease-free survival at 10 years can be expected in 90% of patients. The dose of radiation can be slightly increased to 2.2 Gy per fraction, thereby resulting in definitive treatment in only 6 weeks. However, the higher dose in our experience can increase acute toxicity, and decreasing treatment by 1 week does not seem a significant benefit.

In older patients and those who live a long distance from a radiation treatment center, a more hypofractionated radiation treatment protocol can be delivered. A dose of 3 Gy per fraction over 17 days to a dose of 51 Gy has been reported.[19] This 3.5-week treatment is more convenient and offers the same 95% control in small superficial lip tumors. However, the larger dose per fraction can result in severe dermatitis and mucositis requiring more than 1 month to resolve and leaving the patient at increased risk for epithelial atrophy and telangiectasia.

Margin Status and Adjuvant Radiation Therapy

The issue of margin status and the need for adjuvant radiation therapy after resection is one of the most complicated issues surrounding the management of lip cancer. Additional measures must be taken when a margin is positive after initial resection of a squamous cell carcinoma of the lip (see Fig. 31.10). A repeat excision can be attempted; however, the surgical target may be difficult to define and the additional loss of lip tissue threatens cosmesis and function. If additional resection is not feasible, then adjuvant radiation can control a positive margin. No treatment failures were seen in a recent study in which lip cancer was treated with surgical resection followed by adjuvant radiation to 66 Gy.[27] An Australian study found that patients with a positive margin treated with adjuvant radiation showed only a 6% recurrence rate at 5 years, and these recurrences often occurred in the lymph nodes and not in the lip itself.[28]

Achieving a "close" margin is the greatest quandary in management of lip cancer. No randomized trials have been conducted and no consensus exists as to the precise definition of a clear margin for lip cancer. Results from oral cavity cancer treatments support a 5-mm surgical margin in order to be considered clear.[29-31] Other authors have suggested that a margin of less than 3 mm is adequate for lip cancer, demonstrating only a 2.8% local recurrence rate with this small linear margin.[16] These authors used intraoperative frozen sections to confirm negative

margins, which may explain their excellent outcomes. However, a recent Chinese study found an increase in local recurrence and a decrease in overall survival in patients with close margins (less than or equal to 2 mm).[32] Other groups have found similar links between margin status and poor outcomes. An Australian report found that patients with lip cancer with a surgical margin less than 2 mm had increased recurrence rates.[28] In this report, there was a 51% recurrence-free survival rate at 5 years when surgical margins were less than 2 mm, leading the authors to conclude that a 2-mm negative excision is inadequate. However, adjuvant radiation was able to control disease in these patients with close margins, increasing the recurrence-free survival to 92%.

The surgical ablation of lip cancer should be attempted with negative margins while still preserving the optimal function and cosmesis of the lip. If the margin is negative by more than 5 mm, it seems clear that the patient can be safely observed with low risk of failure. Patients fall into an equivocal zone when the resection margin is between 2 and 5 mm. In the absence of randomized trials, clinical judgment and local experience are required. Additional resection with reconstruction can be attempted in these patients. However, it may often be best in these "close" margin patients to refer them for adjuvant radiation treatment with the knowledge that, with proper technique, irradiation can prevent recurrence and maintain lip function in approximately 95% of patients.

Chemotherapy

Systemic therapy has a limited role in the treatment of lymph node-negative early-stage squamous cell cancers of the lip. In patients with stages I and II lip squamous cell cancers, surgical resection or radiotherapy remain the primary treatment choices.

The role for adjuvant chemoradiotherapy after primary resection in patients with high-risk oral cavity, oropharynx, larynx, or hypopharynx squamous cell cancers has been evaluated in two large randomized clinical trials,[33,34] the results of which may be extrapolated for treatment of the patient with lip cancer. The US Intergroup trial (RTOG 9501) randomized patients with positive margins, two or more positive lymph nodes, or extracapsular spread to receive radiotherapy alone or radiotherapy with concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43. The Intergroup trial did not show improvement in overall survival but there was a statistically significant improvement in locoregional control and progression-free survival. The European Organisation for Research and Treatment of Cancer (EORTC 22931) trial also compared the same treatments in patients with resected high-risk head and neck squamous cell cancers. High risk was defined as T3 or T4 tumors with any nodal stage but it also included additional high-risk features such as perineural invasion, vascular invasion, and level IV or V lymph node involvement in patients with oral or oropharyngeal squamous cell cancers. The EORTC 22931 trial reported significant improvement in all survival outcomes. Combined analysis of these two trials identified the addition of cisplatin to radiotherapy to result in improved overall survival only in patients with extracapsular nodal spread or positive margins.[35] The findings from the combined analysis are considered exploratory, but at present, to our knowledge, there are no data to support the use of adjuvant chemoradiotherapy in patients with resected node-negative T1, T2, or T3 lip cancers.

In patients with stage I or II lip squamous cell cancer who are not candidates for surgical resection, radiotherapy alone is recommended. The 5-year survival for these patients is greater than 90% and therefore the addition of systemic therapy is not required. The benefit of adding concurrent chemotherapy with radiation was evaluated in the MACH-NC (Meta-analysis of chemotherapy in head and neck cancer) analysis. The analysis included 93 randomized studies with more than 16,000 patients with locally advanced head and neck squamous cell cancers; a small but significant improvement in overall survival (absolute benefit of 4.5% at 5 years) for concurrent chemoradiotherapy versus radiotherapy alone was reported.[36] Subsequent updated analysis confirmed that the benefit of adding concurrent chemotherapy to radiation was seen in all tumor sites of head and neck squamous cell cancers, including oral cavity squamous cell cancers.[37] Concurrent high-dose cisplatin with radiation remains the standard treatment,[38,39] but other treatment regimens that incorporate carboplatin, 5-fluorouracil (5-FU), and taxanes can also be considered.

Surgical resection remains the treatment of choice for patients with T1, T2, or T3 node-negative squamous cell cancers, and adjuvant chemoradiotherapy is limited to those patients with positive margins after resection. Also, concurrent chemoradiotherapy is a treatment option for patients with T3, N0 lip squamous cell cancers who are not surgical candidates. However, the decision to proceed with concurrent chemoradiation versus radiation alone must be guided by the treating physician's clinical judgment. Moreover, these conclusions are limited by the fact that clinical trials evaluating chemotherapy include lip squamous cell cancers as a subsite in the general category of oral cavity cancers and outcomes specific to patients with lip squamous cell cancers are generally unavailable.

Systemic chemotherapy plays a much greater role in patients with locally advanced and distant metastatic disease. In patients with early-stage disease, careful multidisciplinary evaluation is essential to identify those few patients who might benefit from the addition of systemic chemotherapy to their treatment plan.

Surveillance

Post-treatment surveillance of patients with lip cancer centers on history and physical examination and imaging, as clinically indicated. Clinical evaluation of these patients typically occurs every 1 to 3 months in the first postoperative year, every 2 to 6 months in the second year, every 4 to 8 months in years 3 to 5, and once annually thereafter. The exact time frames are specifically tailored to patients based on their most recent physical examination as well as the histopathologic status of their tumor. For example, patients with metastatic cervical lymphadenopathy are followed more closely due to the higher rate of recurrent disease. Cure is anticipated for those patients with margin-negative T1-T3 lip cancer excisions with no evidence of cervical lymph node metastasis who undergo postoperative radiation therapy as indicated.

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Early HPV-Related Tonsil Cancer

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Approximately 15,000 new cases of oropharyngeal squamous cell carcinoma (SCC) are diagnosed annually in the United States with 50–60% originating in the palatine tonsillar complex.[1] Historically, these cancers were most prevalent in older men with significant tobacco and alcohol exposures.[2] More recently, the rise of human papillomavirus (HPV)–associated oropharyngeal SCC has resulted in an epidemiologic shift with an increasing incidence of tonsillar SCC among younger patients who lack the traditional risk factors.[3,4] The prognosis and treatment of tonsil SCC is based on tumor (T) and nodal (N) classification, which correlates with the largest single-dimension size of the primary cancer and the size, number, and location of lymph nodes, respectively. In general, single modality therapy is advocated for stage I-II (T1-2N0) tonsillar SCC, reserving multimodality therapy for more advanced stage disease.

Early tonsil tumors (T1-T2) are limited to the tonsillar complex without involvement of adjacent structures. In addition to primary tumor classification, other pathologic features such as the perineural spread and lymphovascular invasion may affect treatment response and prognosis. Early-stage tonsil cancers can usually be managed using either surgery or radiation therapy with excellent oncologic results. Over the past several decades, radiation therapy has been the dominant approach to treating early-stage tonsillar SCC. However, recent advances in minimally invasive surgical techniques, namely transoral robotic surgery (TORS), have sparked a resurgence in the role of surgery for oropharyngeal SCC. Rapid advances in technology for both surgery and radiation are enabling further evolution in the treatment of early-stage oropharyngeal SCC, especially in the growing cohort of HPV-positive patients. This chapter focuses specifically on the clinical presentation, diagnostic evaluation, and contemporary management of T1-T2 tonsillar SCC from a multidisciplinary perspective.

Anatomy of the Tonsillar Complex

The oropharynx is a multifaceted anatomic structure that is further subdivided into the soft palate, base of tongue, and tonsillar complex. The tonsillar complex is located along the lateral pharyngeal wall and is bounded anteriorly and posteriorly by the palatoglossal and palatopharyngeal muscles, respectively. Bilaterally, the tonsillar complex is composed of the palatine (faucial) tonsils—large aggregates of lymphoid tissue that function as part of the mucosal-associated lymphoid tissue (MALT) system—and the associated tonsillar fossae in which they are encased. Along the lateral surface of each tonsil there is a thin, fibrous capsule that is an extension of the pharyngobasilar fascia. The intratonsillar extensions of this fascial layer form the tonsillar septa that encase the associated neurovascular supply. The medial free surface of the tonsil is lined by non-keratinized stratified squamous epithelium and projects into the oropharynx. Invaginations of squamous epithelium from the tonsillar surface form tonsillar crypts, which give the medial surface an irregular, pitted appearance.

Neurovascular Supply

Arterial blood supply to the tonsillar complex is provided by the external carotid system by way of tonsillar branches of the lingual, ascending palatine, ascending pharyngeal, and facial arteries. Venous drainage is through the peritonsillar plexus, which drains into the internal jugular vein via the lingual and pharyngeal veins. The tonsils are innervated by tonsillar branches of both the maxillary nerve (V2) and the glossopharyngeal nerve (IX).

Lymphatics

Efferent lymphatic drainage of the oropharynx is complex, but in general it is primarily to the jugulodigastric nodes and the upper deep cervical lymph nodes. These nodal basins correspond to levels II, III, and IV, as has been described extensively in prior studies.[5,6] Other potential routes of metastatic spread involve the parapharyngeal and retropharyngeal lymph nodes. Although the phenomenon of skip metastasis to other neck levels has been described in oropharyngeal SCC,[7] this is rare, especially in cases of early-stage tumors.

Parapharyngeal Space

For patients who are node negative, the parapharyngeal space represents the first echelon of nodal and direct tumor spread. Consequently, the careful surgical or radiation oncologist—being an expert anatomist—should be intimately familiar with the boundaries and demarcations of this potential route of dissemination. The parapharyngeal space (Fig. 32.1), represents the conceptual stereotypic boundaries of the traditional MD Anderson "anatomic volume at risk" for early-stage tonsil cancers (see later). The parapharyngeal space is a potential space occupied by adipose tissue, cranial nerves V, IX, XI, and XII, the deep cervical lymph nodes, and the ascending pharyngeal and maxillary arteries.[8] This "inverted pyramid" is bordered superiorly by the base of skull (including the hypoglossal canal and foramen lacerum), anteriorly by the pterygomandibular raphe (fascia covering the pterygoid muscles and the mandible), posteriorly by the carotid sheath and the retropharyngeal space, medially by the deep cervical fascia investing the pharynx, and inferiorly by the greater cornu of the hyoid bone. The lateral border changes composition as the space descends and includes the ramus of the mandible, the deep lobe of the parotid gland, the medial pterygoid muscle, and the posterior belly of the digastric muscle. This space also has a direct relationship with all but one of the other six deep compartments of the head and neck, separated from these areas by thin membrane.[8] These relationships may serve as conduits for non-hematogenous, non-lymphatic spread of tumor that violates the parapharyngeal space. Therefore, tonsillar SCC that transgresses the superior constrictor muscle layer and buccopharyngeal fascia carries an increased intrinsic risk for local failure.

Clinical and Diagnostic Evaluation

Etiology

The dominant risk factors historically associated with tonsillar SCC are tobacco and alcohol consumption, and their synergistic oncologic effects on the mucosa of the aerodigestive tract have been well established. However, the last several decades have seen an epidemiologic and etiologic shift in tonsillar SCC as smoking rates decrease while the prevalence of HPV-associated oropharyngeal SCC has steadily risen. A recent retrospective analysis of current Surveillance, Epidemiology, and End Results (SEER) data indicates that the prevalence of HPV-associated oropharyngeal SCC increased by more than 200% between 1988 and 2004 while cases of HPV-negative cancers declined by nearly 50%.[4] The oncogenic effects of HPV subtypes 16 and 18 are well known in several types of cancer such as cervical, skin, and anorectal. Their role in oropharyngeal SCC is now clear as well. Several recent studies have demonstrated that HPV DNA sequences, especially HPV 16, may be found in 50–70% of cases of tonsillar SCC.[4,9] Moreover, this emerging epidemic of HPV-associated tonsillar SCC has affected a distinct, younger cohort of patients who often lack appreciable exposure to traditional risk factors.

Clinical Presentation

Tonsillar SCC is the most common affected subsite of the oropharynx. Patients with early-stage tonsillar SCC are frequently asymptomatic or may present with poorly localized symptoms. The most common presenting symptom is a painless neck mass. This is often the case with HPV-associated tumors, which have a propensity for early nodal metastases.[10]

Other common initial presenting symptoms include globus sensation, mild otalgia, or mild odynophagia. More severe symptoms such as dysphagia, weight loss, trismus, and bleeding are less common and are often harbingers of more advanced disease.

Tumor Staging

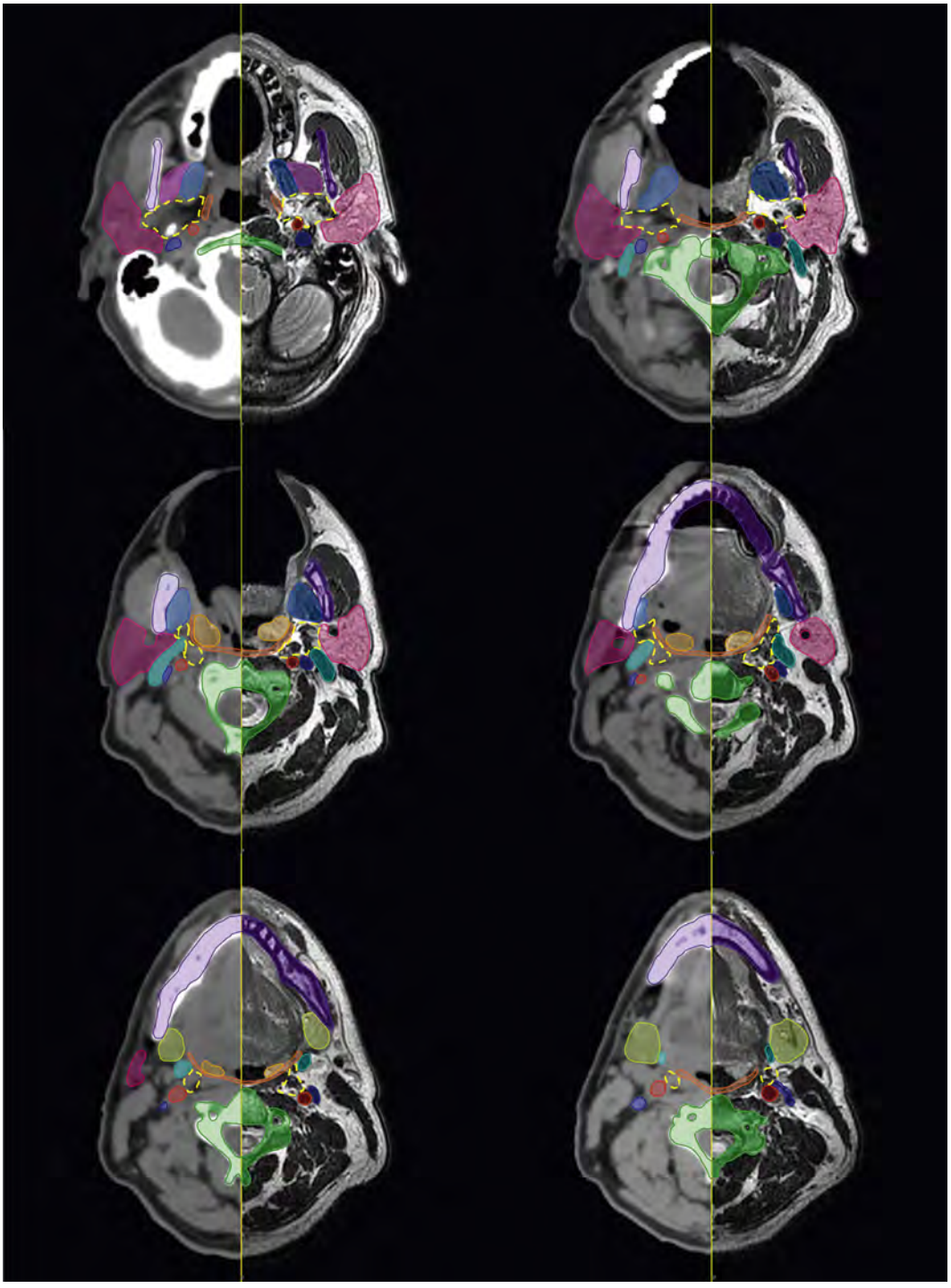
The current staging of oropharyngeal cancers including tonsillar SCC is outlined in the American Joint Committee on Cancer (AJCC) *Cancer Staging Handbook*[11] (Tables 32.1 and 32.2). Based on clinical examination and diagnostic imaging, an accurate assessment and estimation of the size and local extent of the tumor, as well as any associated cervical adenopathy, should be made. Early-stage tonsillar SCC encompasses T1 and T2 cancers that are no larger than 4 cm in greatest dimension and without involvement of other pharyngeal subsites. Accurate clinical staging of tonsillar SCC is of high importance because it has implications for treatment, clinical outcomes, and, most importantly, prognosis. This assessment is predicated on a thorough and systematic clinical evaluation including physical examination, diagnostic imaging, and airway endoscopy.

Physical Examination

Even with contemporary advancements in medical imaging, physical examination remains foundational in the work-up of any head and neck cancer. Patients with a suspicious tonsillar mass should undergo a thorough head and neck examination. The tonsillar fossae and the surrounding tissues of the lateral pharyngeal wall should be closely inspected and palpated. This will give the clinician a sense of the size and extent of any suspicious lesion as well as its relationship to surrounding structures. The oral tongue, tongue base, and soft palate should also be thoroughly evaluated for signs of tumor involvement that would indicate a more advanced staged lesion. Careful examination of the neck should also be performed to assess for concomitant adenopathy. Finally, a complete head and neck examination must include a comprehensive evaluation of the nasopharynx, oropharynx, hypopharynx, and larynx that provides not only a more complete assessment of the primary lesion but also assists in ruling out any secondary malignancies. This is usually best performed using endoscopic methods.

Diagnostic Imaging

High-resolution imaging has become a standard component in the work-up of patients with newly diagnosed tonsillar SCC. Imaging augments the clinical examination, facilitates accurate tumor staging, and often guides subsequent decisions regarding



• **Fig. 32.1** Identification of the parapharyngeal space in cross-sectional imaging. The right half of each image shows non-contrast CT scan obtained during radiation treatment simulation. Left half shows T2 fast spin echo MR sequence collected in the treatment position and matched to CT using deformable registration. Images proceed from cranial to caudal. Yellow dashed line denotes borders of parapharyngeal space. Contoured regions show structures forming the border of the space as follows: *dark purple,* mandible; *light purple,* lateral pterygoid; *medium blue,* medial pterygoid; *magenta,* parotid gland; *dark orange,* superior pharyngeal constrictors; *light orange,* tonsils; *green,* vertebrae; *dark blue,* internal jugular vein; *red,* internal carotid/common carotid artery; *light blue,* posterior belly of the digastric muscle; *yellow-green,* submandibular gland.

TABLE 32.1 American Joint Committee on Cancer (AJCC) Staging System for Oropharynx Cancer (8th Edition)

Primary Tumor (T)	
T0	No primary tumor identified
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease; tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, mandible or beyond*
Regional Lymph Nodes: Clinical (cN)	
NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none >6 cm
N2	Contralateral or bilateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension
Regional Lymph Nodes: Pathological (pN)	
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present

*Mucosal extension to lingual surface of epiglottis from primary tumors of the base of tongue and vallecula does not constitute invasion of the larynx.
From O'Sullivan B, Lydiatt WM, Haughey BH, et al. HPV-mediated (p16+) oropharyngeal cancer. In Amin MB et al (eds). *AJCC cancer staging manual,* 8th edition, New York: Springer; 2017.

further diagnostics and treatment approach. Imaging studies are most helpful for evaluating status of regional lymph nodes. Imaging can also be useful for evaluating the primary tumor site but this is highly dependent on technique and anatomic limitation (e.g., dental artifact). Imaging of the oropharynx can easily overestimate or underestimate the extent of disease.[12] Therefore, imaging is not a substitute for a thorough clinical examination.

Although the choice of imaging is often based on clinician preference and/or institutional availability, in general computed tomography (CT) or magnetic resonance imaging (MRI) are used most frequently. Each has its own particular advantages and disadvantages in evaluating tonsillar neoplasms. Contrasted CT imaging of the head and neck is the preferred imaging modality in many centers, including MD Anderson Cancer Center (MDACC), given the relative rapid image acquisition, low cost, and ease of interpretation compared to MRI. Conversely, MRI may be complementary to CT in distinguishing tumor margins from normal surrounding tissue and deep soft tissue involvement, particularly for cancers that traverse the glossotonsillar sulcus and base of tongue.[13] Moreover, MRI remains a good diagnostic alternative to contrasted CT in patients with an allergy to iodine.

Whether using CT or MRI, imaging criteria that suggest pathologic lymphadenopathy include irregular borders (extracapsular extension of disease), abnormally enlarged size (i.e., greater than 1.5 cm at level I and II; greater than 1 cm at levels III-V) as measured in the axial plane, or evidence of necrotic/cystic change.[12] While there is variability in the literature, the reported sensitivity and specificity of CT and MRI in the detection of nodal disease are as high as 95-100% and 81-92%, respectively.[14]

Finally, positron emission tomography (PET) combined with CT (PET/CT) may be helpful in the work-up of early-stage tonsillar SCC. Several studies have attempted to compare the efficacy of PET in the detection of nodal metastasis compared with CT and/or MRI with mixed findings. For instance, using the histologic results of associated neck dissections as reference, Hannah and colleagues[15] demonstrated significantly higher specificity of PET (100%) compared with CT (81%), but both had similar sensitivity in detecting nodal disease. Conversely, a similar study of 124 patients comparing PET with combined CT/MRI found higher sensitivity with PET (75% vs. 53%) with similar diagnostic specificity between the two modalities (93% and 95%, respectively).[16] Finally, in a retrospective analysis of 67 patients, Yoon and colleagues[14] showed similar sensitivity and specificity of CT, MRI, and PET/CT in the detection of nodal metastasis. However they advocate using a combined approach to diagnostic imaging due to an overall improvement in accurately assessing nodal stage in their cohort.[14] However, tissues with high levels of baseline metabolic activity, including the lymphoid tissue of the oropharynx, can produce false-positive results. As such, PET/CT can overestimate the extent of primary disease. PET/CT can also miss occult metastatic disease. For these reasons, it is not a preferred imaging modality for early-stage tonsillar SCC at MDACC except in the work-up of an unknown primary carcinoma or in cases of suspected recurrence or second primary malignancy.

Surgical Endoscopy and Biopsy

Definitive diagnosis of tonsillar SCC requires a biopsy for histopathologic confirmation. Although this can be performed in select cases with local anesthesia in an in-office setting, many patients benefit from an operative endoscopy under general anesthesia. Traditionally, a "triple" or "pan" endoscopy consisting of direct laryngoscopy, bronchoscopy, and rigid esophagoscopy was advocated, not only for obtaining a tissue biopsy but also for primary tumor staging and ruling out the presence of synchronous lesions of the aerodigestive tract. However, with improved imaging and in-office fiber-optic endoscopic techniques, the extent of the operative endoscopy can often be tailored based on clinical necessity. The primary benefit of operative endoscopy is that it affords the clinician the opportunity to better assess the full extent of a lesion of interest as well as its mobility, depth of invasion, and relationship with adjacent tissues. Any suspicious lesions can be biopsied and sent for

TABLE 32.2 American Joint Committee on Cancer Staging for HPV+ Oropharyngeal Squamous Cell Cancer (8th Edition)

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T0, T1, or T2	N0, N1	M0	I
T0, T1, or T2	N2	M0	II
T3	N0, N1, N2	M0	III
T4	N0, N1, N2, N3	M0	III
Any T	Any N	M1	IV

Pathological Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T0, T1, or T2	N0, N1	M0	I
T0, T1, or T2	N2	M0	II
T3 or T4	N0, N1	M0	II
T3 or T4	N2	M0	III
Any T	Any N	M1	IV

Registry Data Collection Variables

1. Tumor location
2. Lymph nodes
3. Perineural invasion
4. Extranodal extension
5. Smoking history

From O'Sullivan B, Lydiatt WM, Haughey BH, et al. HPV-mediated (p16+) oropharyngeal cancer. In Amin MB et al, eds. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

frozen section analysis, which aligns with the final pathologic diagnosis in more than 90% of cases.[17] However, false-positive and -negative results can occur, even when the pathologist is experienced, and as a result, definitive treatment should be based on the final histopathologic findings.

At MDACC, confirmation of regional metastatic disease by fine-needle aspiration (FNA) biopsy or ultrasound-guided FNA can obviate the need for a direct biopsy of an obvious primary tumor. Endoscopy with biopsy is warranted if the primary tumor is less obvious and confirmation of the primary will influence management (e.g., impact the extent of surgery or fields of radiation therapy). Tonsillectomy may be beneficial in the work-up of the unknown primary cancer. However, endoscopy with biopsy is usually adequate for diagnosis and is far less morbid and much less likely to impact treatment (e.g., alter the margins of surgery or delay the initiation of radiation therapy).

Current Management Principles and Outcomes

The foundational principle of successful management of tonsillar SCC is achieving locoregional control because the success of salvage treatment of recurrent disease remains poor. For early-stage tonsillar SCC, effective treatment generally consists of single modality therapy with either surgery or definitive radiotherapy. Current National Comprehensive Cancer Network (NCCN) guidelines (2014)[18] recommend single modality therapy for both T1 and T2 tumors without concomitant neck disease and reserve multimodality therapy for stage III and IV disease (i.e., T1-2, N1-3). Beyond successful oncologic outcomes, treatment selection must also take into consideration each patient's baseline functional status, associated medical comorbidities, and the anticipated impact on post-therapeutic quality of life. To that end, multidisciplinary evaluation and treatment planning is critical to achieving the best possible oncologic and functional outcomes. At MDACC, all patients with early-stage tonsillar SCC are evaluated in a multidisciplinary fashion.

Both surgery and radiation therapy have demonstrated equivalent and excellent rates (i.e., >80–90%) of locoregional control and disease-free survival as definitive treatment modalities.[19-21] For the past several decades, primary radiation therapy has been the treatment of choice for early-stage tonsillar SCC due to its decreased short-term complication rates and improved functional outcomes compared with traditional surgical approaches.[1,21] Transoral surgical approaches as primary treatment have become increasingly popular as a means of

TABLE 32.3 Comparison of Surgery and Radiation as Single-Modality Treatment for Early-Stage Tonsillar Squamous Cell Carcinoma

	Transoral Robotic Surgery	Radiation
Staging	Pathologic	Clinical
Cost	Less expensive	More expensive
Length of treatment	<1 day	6-7 weeks
Risks		
Bleeding	+	
Xerostomia		+
Osteoradionecrosis		+
Outcomes		
Survival	Excellent	Excellent
Quality of life	?	?

+, risks present, ?, unknown or poorly defined.

potentially reducing long-term toxicity. We are not aware of any reported randomized controlled studies comparing radiation and surgery for early-stage tonsillar SCC.[19] As a result, recommendations regarding primary treatment for stage I and II lesions remain controversial and often reflect institutional biases. A comparison of primary surgery and radiation therapy as single-modality treatment for early-stage tonsillar SCC is provided in Table 32.3.

In contrast to early-stage tonsillar SCC, T1-T2 primary tumors associated with advanced nodal disease (i.e., stage III and IV) require multimodality therapy. For patients with advanced nodal disease (i.e., N2/N3), the addition of platinum-based chemotherapy or biologic therapy has been shown to provide a significant survival advantage.[22,23] The optimal strategy for the delivery of multimodality therapy for advanced-stage tonsillar SCC has yet to be defined. Over the past several decades non-surgical approaches have been favored, primarily because of the morbidity associated with traditional open approaches to the oropharynx. A shifting demographic and an increased focus on quality of life have led to a recent resurgence of primary surgical approaches using TORS. A study of 42 patients by Chung et al[24] compared surgery with adjuvant radiation versus chemoradiation therapy in the treatment of patients with early T classification (T1-T2) and advanced N classification (N2-N3) tonsillar SCC. The authors reported similar survival rates between the groups, and significantly improved quality of life outcomes for patients treated with primary surgery. However, this study is limited by the small sample size and differences in the total doses of radiation received between study groups, highlighting the need for high-quality, prospective functional outcomes data.

HPV and smoking status have a significant impact on treatment recommendations. The improved prognosis of patients with HPV-associated oropharynx cancer is well established.[25,26] Therefore, regardless of treatment approach there is a movement toward de-escalation to reduce iatrogenic complications and improve long-term quality-of-life. Although preliminary results of several studies seem to support treatment de-escalation as a viable alternative, there is currently a lack of evidence to support altering current practice patterns outside of a clinical trial.[27] At MDACC, it is strongly preferred to treat all patients with tonsillar SCC via clinical trials.

Surgical Management of the Primary Tumor

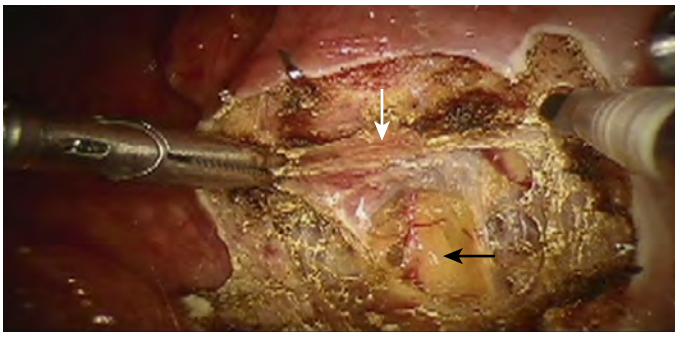
Historically, surgical excision was the primary treatment modality for tonsillar SCC. Although transoral approaches had been described, more radical open approaches were favored for wider surgical margins.[28] Traditional, open approaches often resulted in marked functional deficits. Following the Veterans Affairs Study in 1991,[29] the treatment paradigm shifted to "organ" preservation strategies with radiation and chemoradiation therapy being used extensively in the treatment of tonsillar and other oropharyngeal SCC.[1,22] More recently, growing concerns about the long-term effects of radiation therapy, coupled with a shifting demographic and changes in technology (e.g., robotics), have led to a renewed interest in the role of surgery in the treatment of tonsillar SCC.

Transoral Approaches

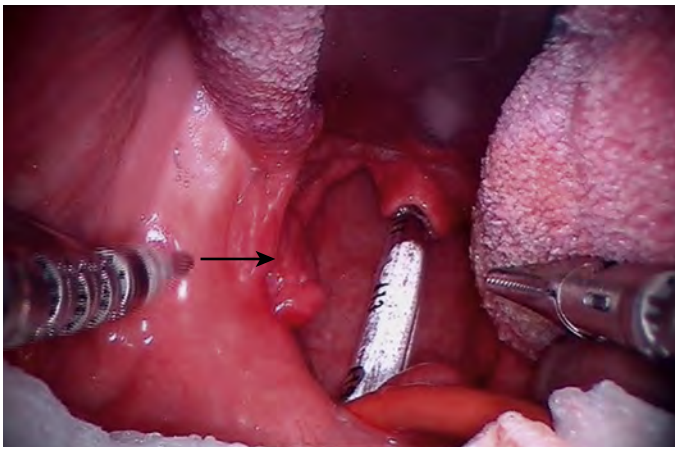
The majority of early-stage tonsillar SCC can be managed using a transoral approach. Achieving adequate exposure is crucial to surgical success in these cases, and can be facilitated by employing one of several different oral retractors including the McIvor, Crowe-Davis, Dingman, or Feyh-Kastenbauer (FK). This decision is based on patient anatomy, tumor size and location, and surgeon preference.

The approach and technical considerations for transoral resection of a tonsillar SCC (called *radical tonsillectomy, partial pharyngectomy,* or *transoral lateral oropharyngectomy*) have been thoroughly described.[30] The superior constrictor muscle layer with the buccopharyngeal fascia serves as a robust deep oncologic margin (Fig. 32.2). The deep parapharyngeal fat pad serves as a landmark for the internal carotid artery, which generally lies posterolaterally to the plane of dissection. Using a direct (non-robotic) technique, 5-year control rates of 89% and 82% were reported for T1 and T2 tonsillar SCC, respectively with an overall complication rate of 6%, and no patients required prolonged tracheostomy or gastrostomy feeding tube placement.

In recent years, modified techniques that employ newer technologies including transoral laser microsurgery (TLM) and TORS have been described. The primary value proposition of these contemporary techniques is the enhanced ability to perform oncologically sound resections via improved visualization and precision. TLM was first described by Steiner in 1988,[31] and since then indications have been expanded



• **Fig. 32.2** Superior surgical view from robotic console of deep margin of resection for a right tonsillar squamous cell carcinoma. The buccopharyngeal fascia deep to the superior constrictor muscle serves as a distinct anatomic boundary and oncologically effective surgical margin. *Black arrow,* parapharyngeal space fat; *white arrow,* superior constrictor muscle layer.



• **Fig. 32.3** Panoramic operative exposure of left tonsillar carcinoma *(black arrow)* provided by transoral robotic surgery (TORS). Improved visualization using TORS allows for excellent control of margins.

to include both early and advanced stage tumors of multiple subsites of the aerodigestive tract. TLM allows for precise tumor excision with decreased surgical morbidity and improved functional outcomes compared with traditional surgical approaches.[32] Disadvantages of TLM include the need for direct line of sight of the tumor and a protracted learning curve for the procedures.

TORS is a contemporary surgical technique that builds upon the foundational principles of transoral endoscopic surgery. TORS is increasingly used in the surgical management of head and neck malignancies[33,34] and is presently cleared by the U.S. Food and Drug Administration for the treatment of T1 and T2 oropharyngeal tumors. Compared with traditional transoral techniques, TORS offers several potential advantages including high-resolution, 3D operative view, improved operative precision, movement scaling, and dynamic multiplanar and true 360-degree rotational motion.[35] Compared with TLM, TORS is not limited by a need for direct line of sight.

A detailed discussion of the components and operative setup for TORS has been well summarized in a recent review.[36] The improved visualization afforded by TORS allows for precise oncologic control of margins similar to direct transoral resection of oral cavity SCC (Fig. 32.3). One-centimeter mucosal margins are planned for a final pathologic margin of 5 mm. The deep margin is invariably less than 5 mm after resection of a tonsillar SCC because of the short distance between the constrictor muscle layer and the parapharyngeal fat. Yet a narrow surgical margin (>1 mm) is oncologically acceptable if the buccopharyngeal fascia is preserved.

Early oncologic outcomes and functional data are promising for the use of TORS for oropharyngeal SCC. TORS has been shown to be feasible and safe.[37] Studies comparing TORS with historical surgical and non-surgical controls have demonstrated comparable disease control rates for early-stage tonsillar SCC.[38-40] However, many studies are limited by their retrospective nature, potential selection bias, and heterogeneity with regard to HPV status. Functional outcomes after TORS have been favorable compared with other surgical and non-surgical treatments. Postoperative enteral feeding rates and rates of dysphagia at 12 months are significantly reduced after TORS compared with traditional open surgery.[41] In a recent systematic review of more than 400 patients in 12 studies, Hutcheson and colleagues[42] found improved swallowing outcomes and decreased feeding tube utilization with primary TORS versus historic intensity-modulated radiation therapy (IMRT) cohorts. However, the authors noted that post-TORS functional outcomes appear to be dependent on a patient's baseline function and T stage and that long-term prospective data are lacking. Prospective studies with long-term functional outcomes are needed to better elucidate the ideal role for TORS in tonsillar SCC.

Traditional Open Approaches

Open approaches to the oropharynx are rarely used in the primary treatment of early-stage tonsillar SCC and are typically reserved for surgical salvage after radiation or chemoradiation therapy, or for the treatment of second primary tumors. Salvage surgery after definitive radiation therapy is associated with high morbidity, prolonged hospitalization, and functional deficits. TORS or TORS-assisted approaches can be beneficial in these cases. White and colleagues[43] showed TORS to be a viable alternative to open surgery in patients with recurrent oropharyngeal carcinoma, demonstrating decreased operative times, decreased intraoperative blood loss, less need for tracheostomies, and less need for postoperative feeding tubes. Thus, TORS is the preferred approach to small-volume salvage surgery or resection of early-stage second primary tonsillar SCC.

Management of the Neck

For patients with tonsillar SCC, the clinical stage of the neck lymph nodes is important for deciding overall treatment. As a general rule, management of the neck depends on the presence and extent of metastatic nodal disease and typically

mirrors the treatment of the primary tumor. Similar to other oropharyngeal tumors, tonsillar carcinoma carries an appreciable risk of nodal disease. Early-stage tonsillar SCC may have up to a 30% risk of occult nodal spread.[1] As such, concurrent treatment of the neck is warranted in all patients with tonsillar SCC.

At MDACC, treatment of the neck mirrors the treatment used for the primary tumor. For patients receiving primary radiation therapy, the at-risk nodal basins (i.e., levels II-IV) are included in the planned radiation fields. Conversely, an elective neck dissection is the preferred approach for patients whose primary tumors are to be managed surgically. The primary goal of selective neck dissection is to detect occult nodal disease and to guide subsequent adjuvant treatments based on final histopathologic findings (e.g., number of metastatic nodes, extracapsular nodal spread). A neck dissection can be safely performed at the time of TORS or in a staged fashion. Despite increasing popularity, sentinel lymph node biopsy is not recommended for early-stage tonsillar SCC outside of a clinical trial setting.

Given the rich lymphatic supply of the oropharynx, it is not uncommon for patients with early T-stage tonsillar SCC to present with advanced nodal disease at the time of initial diagnosis. If chemoradiation therapy is the primary treatment modality, then a post-treatment neck dissection is reserved for patients with clinical and/or radiographic evidence of persistent or progressive neck disease as seen on PET/CT imaging.[44,45] For patients with advanced nodal disease who are undergoing primary surgery, the neck should be addressed concurrently. Selective neck dissection has been shown to be effective in the setting of non-bulky metastatic nodal disease.[46] Patients with positive nodal disease frequently require adjuvant radiation following neck dissection with concurrent chemotherapy added for patients with pathologic evidence of extracapsular spread or positive surgical margins.[47] However, the prognostic significance of advanced nodal disease in the setting of HPV-associated oropharyngeal SCC is becoming better understood and may have implications regarding the need for and intensity of adjuvant treatments. For example, a recent review of SEER data for tonsil cancer demonstrated a reduced impact of nodal disease on survival among HPV-positive versus HPV-negative patients.[48] Furthermore, overall nodal stage and the presence of microscopic extracapsular spread do not necessarily portend a poorer prognosis in patients with HPV-associated oropharyngeal SCC treated with surgery.[49] Such findings are prompting calls for further changes to the nodal staging system for oropharyngeal SCC.

Surgical Complications

Complications associated with the surgical treatment of early-stage tonsillar SCC are similar to other oropharyngeal tumors and are best categorized as perioperative or postoperative. Complications that occur at the time of surgery are primarily related to iatrogenic damage to surrounding neurovascular structures. This can include inadvertent injury to important nerves such as the marginal mandibular (CN VII), glossopharyngeal (IX), vagus (X), spinal accessory (XI), or hypoglossal (XII) during the primary surgery or neck dissection. Also given the close proximity of the tonsillar fossa to the parapharyngeal and carotid spaces, a surgical complication can result in violation of the carotid artery system and/or its major branches (e.g., ascending pharyngeal artery, lingual artery).

The incidence of complications after TORS has been reported to be around 10% with the most common complications being hemorrhage, tooth injury, dehydration, and aspiration pneumonia. Complications after TORS have been shown to significantly decrease with surgeon experience.[50] In the immediate postoperative phase, oral hemorrhage is perhaps the most feared major complication because severe bleeding can be fatal due to aspiration, airway compromise, or hemorrhagic shock. Retrospective reviews have cited bleeding rates following TORS of 1.5% to around 13%.[51,52] These risks of vascular injury and postoperative hemorrhage have led some surgeons to advocate prophylactic ligation of branches of the external carotid artery during neck dissection. Finally, a unique risk of any transoral oropharyngeal resection is the formation of a salivary fistula between the pharynx and the adjacent compartments of the neck. However, despite concerns that concurrent neck surgery may increase the risk of fistulation, neck dissection has been shown to be safe at the time of primary surgical resection.[53]

Radiation Therapy

Radiation has successfully been used in the control of cancers arising from the tonsil since the mid-20th century with the dual goals of cure and functional organ preservation.[54] Appropriately administered radiation therapy is now expected to provide local control and overall survival in excess of 80% of patients with early-stage (T1-2, N0-1) tonsillar SCC according to large-scale multi-site series with some centers reporting more than 90% 5-year survival.[54a] Furthermore, radiation with concurrent chemotherapy remains a preferred treatment option for many patients with advanced-stage tonsillar SCC, including those demonstrating either advanced infiltrative primary tumors (T3-T4b) or nodal progression (N2-3).

General Principles

Effective radiation treatment planning utilizing radiation is dependent upon three primary factors: dose, overall treatment time, and target coverage. Excellent control of early-stage tonsillar SCC can be gained from radiation alone.[55] For well-lateralized tumors, toxicities can be minimized by limiting treatment to unilateral fields,[56,57] although this applies to a limited subset of patients without risk factors for contralateral spread (e.g., base of tongue, soft palate, or pharyngeal wall extension). On the basis of an analysis of dose fractionation parameters used in the treatment of tonsillar SCC at

MDACC between 1954 and 1968, Shukovsky and Fletcher[58] recommended doses of 65 Gy for T1 disease and 70 Gy for T2 disease, delivered over 6 to 7 weeks in 2-Gy fractions.[58] To minimize radiation-associated acute and long-term toxicities, the full definitive dose is, in modern practice, prescribed to a smaller volume using conformal approaches, which encompasses the primary and nodal gross tumor volume with margin within a larger volume that is treated to a lower dose to control microscopic disease.[59] There are two strategies for delivering this boost: (1) sequential delivery (after a larger volume has received the elective dose) or (2) concomitant boost, in which the additional dose is administered during the initial treatment period. Concomitant boost technique decreases the total duration of treatment, but increases the daily dose to these tissues, theoretically increasing the risk for long-term toxicity.

The Radiation Therapy Oncology Group trial 9003 compared three different fractionation schedules against standard fractionation (70 Gy in 7 weeks at 2 Gy/fraction) for patients with locally advanced head and neck cancer, the majority of whom had tumors arising from the oropharynx. An 8% improvement in locoregional tumor control with no increase in toxicities was observed in both the concomitant boost and hyperfractionation schedules, which are marked by shorter overall treatment time or increased total dose.[60] Results from the Danish Head and Neck Cancer Study Group (DAHANCA) trials demonstrated a similar benefit in locoregional control for accelerated radiotherapy, as compared to conventional fractionation.[61] Based on the results of these trials, many centers have adopted altered fractionation for control of head and neck cancers. Long-term follow-up of the RTOG 9003 trial shows persistent, but numerically smaller improvements in locoregional control in the altered fractionation arms, when compared with standard fractionation.[62] Given the logistic challenges that hyperfractionation presents in the age of IMRT, integrated concomitant boost has become the preferred treatment schedule at many centers.[63]At MDACC, T1 and early T2 cancers are often treated with a total dose of 66 Gy at 2.2 Gy per fraction or 70 Gy in 6 weeks at six fractions per week as described in the DAHANCA protocol. In the postoperative setting, in the absence of risk features necessitating chemotherapy (e.g., T4 disease, margin positivity, extracapsular extension), the dose is reduced to 60 Gy to control microscopic disease in the surgical bed, although the field is often extended to fully encompass surgically manipulated tissue.[47,64,65]

Control of the primary disease is dependent upon adequate coverage of grossly identifiable disease with an understanding of the patterns of spread. The palatine tonsil has a surface mucosa consisting of stratified squamous epithelium and is bordered laterally by a fibrous capsule. Beneath this capsule lies the superior pharyngeal constrictors, the parapharyngeal space, the pterygoid muscles and the mandible. Approximately 2 cm deep and lateral to the tonsil runs the internal carotid artery, through the parapharyngeal space.

With regard to invasive spread, Remmler and colleagues[66] reported the pattern of local disease extension among 160 patients referred to MDACC between 1968 and 1979. Most commonly tumors arising from the tonsil were found to extend to the tongue base (38%), lateral pharyngeal wall (31%), soft palate (23%), and retromolar trigone (10%). Fewer than 5% of tumors were also found to spread to the oral tongue, posterior pharyngeal wall, buccal mucosa, lateral floor of mouth, pterygoid muscles, and mandibular or maxillary bone, although this represents locally advanced disease. This study population may differ from modern patients, due largely to increasing incidence of HPV-associated SCC arising from the oropharynx.[4]

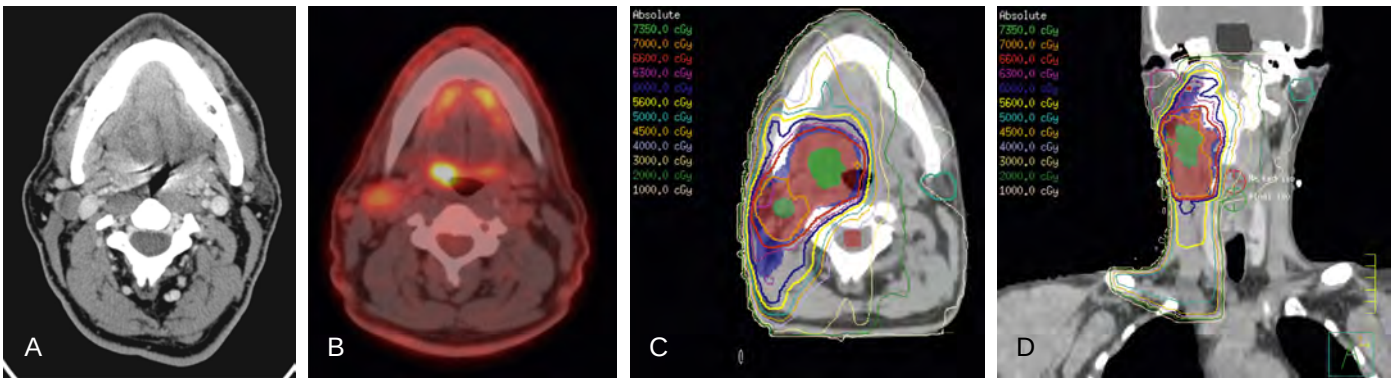
Based on the requisite coverage of the parapharyngeal space, at MDACC the anatomic coverage for subclinical disease encompasses, at minimum, tumoricidal dose to predefined regions of potential microscopic spread. The clinical target volume (CTV) for tonsillar SCC should include the lateral pharyngeal wall, the tonsillar fossa, and the anterior tonsillar pillar. The field should also include, superiorly, the lower aspect of the maxillary tuberosity, and, inferiorly, the tip of the epiglottis. More advanced disease should be covered to the hyoid or below. Physical examination can reliably and accurately assess extension onto the soft palate to guide coverage.

Pretreatment Imaging and Planning

CT Simulation

The purpose of simulation is threefold: (1) to place the patient in a reproducible and anatomically appropriate position for treatment; (2) to localize the tumor through high-quality imaging and integration with staging imaging and physical examination; (3) to evaluate and optimize the feasibility of high-quality treatment. Before simulation, all patients should be evaluated by a dental oncologist for evaluation and pretreatment oral care. To minimize the risk of osteoradionecrosis, complete extractions should be considered if the dose to the mandible will exceed 50 Gy, if there is concern for poor adherence to a strict post-radiotherapy dental hygiene regimen, or if patients are young or expected life span is long. Individual teeth should be extracted if there are caries or infection, periodontal disease, root canals, or any other pathology that would lead to a questionable prognosis. At least 10 days should be allowed for healing after extraction and before starting radiotherapy.[67]

Most patients are treated in the supine position with a neutral spine. Slight extension of the neck can move the chin out of the beam path for anterior-posterior beams. This is of particular importance if a matched half-beam block technique is to be used, in which case careful attention should be paid to ensure the chin is above the isocenter. Shoulders should be pulled downward, if necessary, to avoid interference with lateral beam angles. A thermoplastic mask that extends down through the neck and over the shoulders, preferably with reinforcement over the chin and brow, is used for immobilization and reproducibility. Before placing



• **Fig. 32.4** Treatment plan for unilateral intensity-modulated radiation therapy. **A,** Contrast-enhanced CT shows a well-lateralized 1.4 cm mass in the right palatine tonsil. **B,** FDG-avidity of the primary mass and necrotic jugulodigastric node seen on staging PET/CT scan. **C** and **D,** Isodose distribution of planned treatment. The tonsillar bed received 66 Gy in 30 fractions. A 4-Gy boost was delivered to the gross nodal disease using 9 MeV electrons to a total dose of 70 Gy.

the mask, a scout film should be obtained to ensure alignment. A tongue-lateralizing stent, if treating unilaterally, or a tongue-depressing stent, if the soft palate is involved, can be used to limit oral toxicity. Thermoplastic cushions may also be used under the head, neck, and shoulders to improve reproducibility and encourage appropriate neck position.

Axial CT images are then collected from the vertex through the heads of the clavicles with a slice thickness of 2.5 to 5 mm. At most centers, non-contrast CT images are collected, reinforcing the importance of high-quality staging imaging for target delineation. Some centers administer intravenous contrast for simulation scans, which can improve resolution for visualization of primary and nodal disease. Images are then uploaded into treatment planning software, where they can be fused with previously obtained contrast CT, PET, or MRI for improved target delineation. One limitation of imaging fusion is that patients are not in the same position and slices may be oblique, which can lead to inaccuracies due to reconstruction as well as position. MRI can be performed in treatment position using the immobilization devices described earlier, minimizing the motion of key target structures used in planning.[68]

MR Simulation

Because of its improved resolution of soft tissue and fascial planes, there is considerable interest in the utility of MR-based simulation in head and neck radiation. Adoption of MR simulation into routine practice has been limited by availability, apprehension regarding geometric distortions related to distance from magnet isocenter and chemical shift and susceptibility, and inexperience with MR quality assurance practices.[69] Recent studies show that geometric distortion in head and neck MRI yields a mean error of less than 2 mm compared with CT imaging[70] and that such distortion should be stable within a patient and thus correctable.[71] At this time MR-only simulation for head and neck cancers remains investigational; however, the integration of advanced MRI simulation with CT is commonly used at MDACC.

Current Techniques

Intensity Modulated Radiation Therapy

Advances in treatment planning systems and beam collimation have allowed for improved 3D conformality through the use of non-uniform beam intensities delivered through multiple beams of different shape and intensity. This technique, known as intensity modulated radiation therapy, or IMRT, allows treatment to be planned based on target and avoidance structures that are manually drawn on cross-sectional images and reconstructed into 3D representations of the patient's anatomy (Fig. 32.4). The delivery of more conformal radiation dose with the ability to avoid critical structures that might otherwise fall within a beam path offers the theoretic advantage of maintaining adequate disease control while reducing radiation-associated morbidities. Furthermore, concomitant boost can be administered in the form of a simultaneous integrated boost, in which the higher dose is attained by increasing the dose per fraction of once daily treatments, thereby obviating the need for twice daily treatments to administer the boost.

As described earlier, the usual approach is to deliver 66 to 70 Gy over 6 weeks to the high-dose CTV, including the primary tumor and any grossly involved nodes with a margin of at least 1 to 1.5 cm. A lower subclinical elective dose, usually 50 to 59 Gy, is delivered to the tissues surrounding the tumor and clinically uninvolved lymph nodes. At MDACC, nodal stations included in elective dose treatment for tonsillar SCC include the retropharyngeal nodes, all of levels II-V, and level IB, if the patient is node-positive. A third intermediate dose of 60 to 63 Gy may be included around the high-dose CTV to increase dose to high risk, but clinically uninvolved areas, and to improve conformality. Target volume delineation should integrate any pre-chemotherapy evaluation (if applicable), simulation imaging, staging imaging, and physical examination. Patterns of local extension and nodal drainage should also be considered when designing CTVs.

One of the primary advantages of being able to better shape the dose distribution using IMRT is the sparing of the parotid glands. Using conventional plans, the parotids were often within the beam path and thus received full treatment dose. The PARSPORT trial, a multi-institutional, randomized phase III trial comparing IMRT to conventional radiotherapy for pharyngeal cancer confirmed an improvement in xerostomia and patient quality of life with IMRT.[72] Such encouraging results were also reported by Eisbruch and colleagues[73] in the RTOG trial 0022, which evaluated accelerated hypofractionated IMRT for oropharyngeal cancer and showed xerostomia in only 16% of patients at 2 years. Another advantage is the ability to selectively spare the swallowing apparatus to minimize dysphagia. Feng and colleagues[74] reported on the ability to avoid dysphagia with IMRT and demonstrated (1) a relationship between the dose to the superior pharyngeal constrictors and both objective and subjective measures of swallowing dysfunction, and (2) that sparing of these structures is feasible using IMRT.

Confirming the effectiveness of IMRT for disease control, Garden and colleagues[55] reported on outcomes for small primary oropharyngeal carcinomas measuring less than 4 cm treated with IMRT at MDACC between 2000 and 2002. Most of the 51 patients received 63 to 66 Gy to the high-dose CTV and 54 Gy to the elective CTV. The 2-year actuarial local control rate for this patient population was 96% with a 100% control rate for T1/TX disease, compared with 88% for T2 disease. The 2- and 3-year overall survival rates were 93% and 87%, respectively. Parotid glands were significantly spared with 95% of patients receiving a mean dose of less than 30 Gy to at least one parotid gland.

In a larger series, Garden and colleagues[75] reported results of 776 patients treated with IMRT between 2000 and 2007 for oropharyngeal cancer at MDACC. The majority of patients in this study had T1/TX or T2 disease (75.5%) with tonsillar SCC making up 48% of the study population. The most common fractionation schedules were 66 Gy in 30 daily fractions or 70 Gy in 33 daily fractions. Actuarial 5-year survival and recurrence-free survival for T1 and T2 cancers were both 90%. The mean dose to at least one parotid gland was less than 26 Gy in 84% of patients and less than 26 Gy in both glands in 35% of patients. Despite the parotid sparing, no recurrences were seen in the parotid area.

In a study of 1046 patients with locally advanced (stage III-IVB) oropharyngeal SCC, Garden and colleagues[76] at MDACC chronicled the transition from conventional radiotherapy to IMRT in a single institution. The 5-year locoregional control for patients treated with IMRT was 92% compared with 77% in those treated using 3D conformal technique. The 5-year locoregional control rate for the 217 patients with early-stage (T1-2, N1-2a) oropharyngeal SCC treated with radiotherapy alone was 98%, higher than the control for concurrent chemoradiation therapy (90%). Although this study included patients with advanced cancer, it demonstrates improved local control and some evidence of improved toxicity with IMRT compared with conventional radiotherapy. Furthermore, these data support the use of single modality radiotherapy in the treatment of T1-T2 disease, even with significant regional involvement.

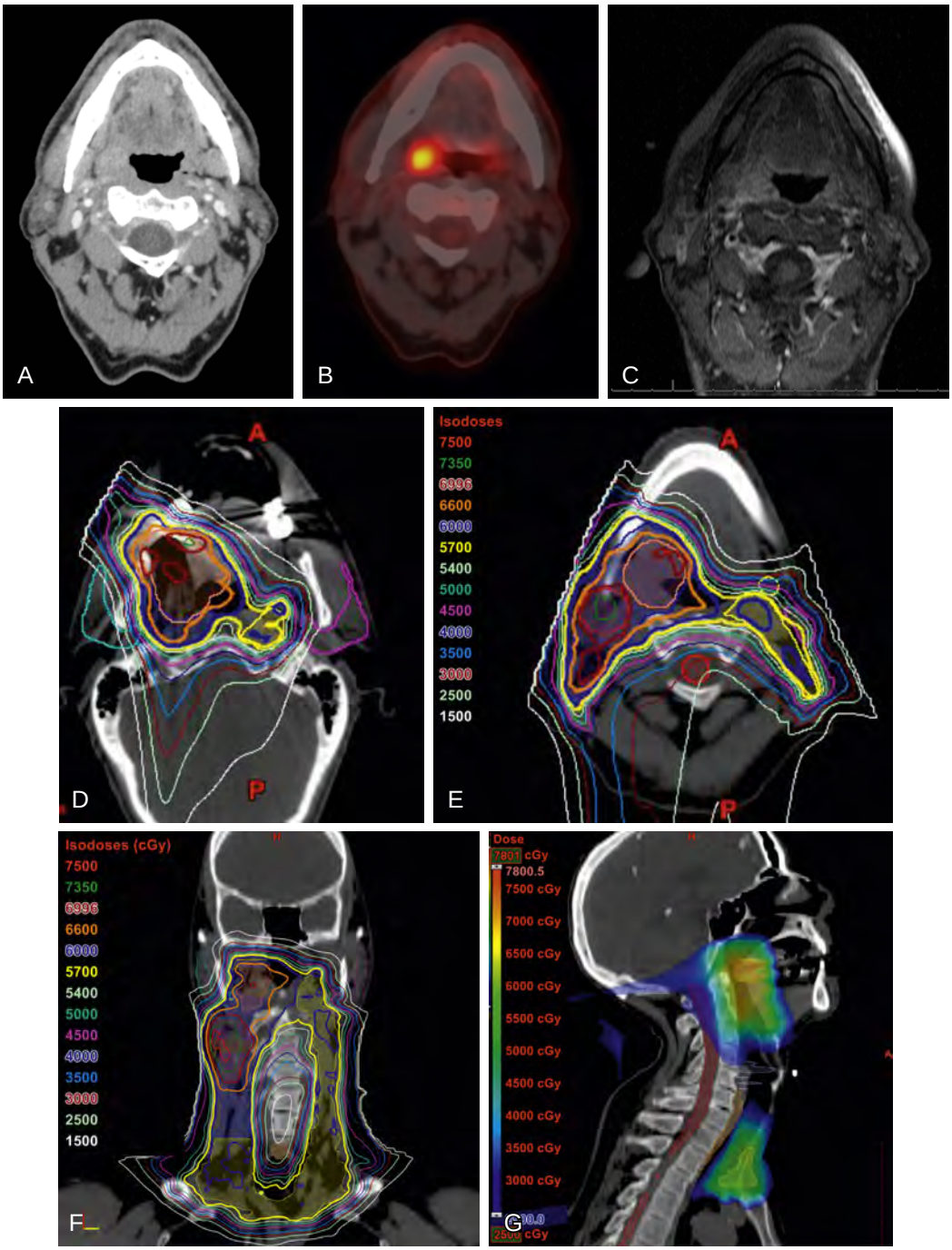
Unilateral irradiation may be considered for well-lateralized early-stage tonsillar SCC that does not approach midline. For these tumors, the risk of contralateral nodal drainage is very small, prompting some physicians to treat unilaterally. Initial reports from Princess Margaret Hospital and Vancouver Cancer Center demonstrated contralateral neck failure in 3.5% and 2.6% of early-stage patients, respectively.[57,77] In a study of 102 patients with early-stage tonsil SCC treated with unilateral radiation at MDACC, Chronowski and colleagues[56] reported a 5-year freedom from contralateral nodal recurrence rate of 96%. The 5-year overall survival and disease-free survival rates in this study were 95% and 96%, respectively.

Although IMRT provides superior tumor control with an improved xerostomia profile, the inclusion of multiple beams to treat the tumor distributes low and intermediate radiation dose throughout the head and neck. In a retrospective study, Rosenthal and colleagues[78] correlated increased occipital alopecia, nausea, and vomiting to increased scalp and brainstem doses from IMRT. They also correlate anterior oral mucositis to far anterior mandibular dose. Increased dose to skin and esophagus leading to increased acute toxicities has also been described. These reports highlight the importance of field design and patient selection when using IMRT to anticipate and minimize intermediate dose and to non-critical structures.

Proton Beam Radiation

The physical properties of protons offer another potential avenue to improve conformality and decrease dose to critical structures. Unlike the photons used in conventional radiotherapy and IMRT, which deposit a higher entrance dose at the skin surface as well as deposit an exit dose, protons have a finite stopping distance within tissue and deposit the majority of dose at the end of the beam (i.e., the Bragg peak phenomenon). Therefore, protons should theoretically deposit less dose than IMRT in non-target tissues both through diminished entry dose and absent exit dose. Proton treatment can be delivered via multiple techniques, including "passive scatter" irradiation, wherein two or three custom-collimated beams are scattered to deliver uniform dose throughout a field. Alternatively, scanning-beam technique can be used to deliver intensity modulated proton therapy (IMPT), in which magnets are used to direct multiple very narrow beams (pencil beams) to cover the target in layers, such that "spots" of protons of different energy are deposited. The ability of IMPT to deliver non-uniform energies to different depths aligns well with the complex and densely organized anatomy of the head and neck (Fig. 32.5).

Initial treatment planning studies have borne out this potential dosimetric advantage of IMPT over IMRT.[79,80] One concern for implementation has been ongoing uncertainty with regard to range and dose delivered using protons. This



• **Fig. 32.5** Treatment plan for bilateral intensity-modulated proton therapy. **A,** CT, **B,** PET/CT, and **C,** MRI of the neck demonstrating a right tonsillar carcinoma. The patient was enrolled in a clinical trial and randomized to receive bilateral proton beam radiation. **D** through **F,** Isodose distribution of planned treatment. The tonsillar bed received 66 Gy in 33 fractions. Gross nodal disease was treated to 69.96 Gy. **G,** Heat map showing restriction of high-dose radiation to tonsil region. Note that larynx is completely spared.

uncertainty increases with depth, meaning that the distal end of the proton beam has the greatest uncertainty with regard to depth and dose. The magnitude of uncertainty depends on the dose, beam range, and tissues.[81] Therefore, robust quality assurance practices are needed at any facility implementing protons in the treatment of head and neck cancers. Inter-facility standardization of quality assurance and treatment evaluation practices remains in development.

Frank and colleagues[82] reported 2-year results for the first 50 patients treated with IMPT between 2011 and 2014 for oropharyngeal SCC at MDACC. The majority of patients had stage IVA disease and 88% were HPV positive. After treatment with 66 to 70 cobalt-60 Gray equivalents, only one local failure and one neck failure were reported at 12 months. The 2-year actuarial disease-free survival was 94%, and there were no grade 4 or grade 5 toxicities. Based on these findings, investigators at MDACC have initiated a phase II/III randomized trial of IMRT versus IMPT for advanced stage oropharyngeal cancer with a primary end-point of reduced beam-path toxicities. Therefore, early reports suggest efficacy and safety, however, longer term follow-up is needed to see whether clinical results mirror the advantages seen with in silico dosimetric modeling.

Complications

Complications secondary to radiation treatment for tonsillar SCC are the direct consequence of two modifiable variables: the dose and volume of normal tissue that is irradiated. Radiation-related toxicities seen in initial experience were due to the large volume of tissue treated to a full 70 Gy using conventional techniques. With advances in 3D treatment planning and the development of IMRT, comparisons of dosimetric variables with recorded adverse effects have confirmed the association between dose, volume, and toxicity[83] and have led to a standardized set of dose constraints, which are published in the QUANTEC reviews.[84] Radiation toxicities can be divided into acute effects, those experienced during and shortly after treatment, and late effects, which may occur months to years after treatment. Acute toxicities are generally the result of the local inflammatory response to tissue damage, whereas late toxicities reflect the cytotoxic and pro-fibrotic properties of radiation, leading to a loss of local precursor cells, chronic vascular damage, and deposition of scar. Because acute reactions are generally transient and resolve after radiation is discontinued, this review focuses on late toxicities.

Dysphagia

Long-term dysphagia following radiation can be a potentially life-threatening complication, leading to chronic feeding tube dependence and aspiration. The incidence of dysphagia has decreased since the incorporation of IMRT in treating tonsillar SCC. In Garden and colleagues' recent series[75] of 776 patients treated with IMRT at MDACC, therapeutic feeding tube use during therapy remained high (47%); however, only 18 patients (2.3%) remained feeding tube dependent and five patients (0.6%) required dilation for esophageal stricture. A larger MDACC series including patients with advanced stage oropharyngeal cancer also demonstrated a 2% rate of chronic feeding tube dependence in patients with T1-2 tumors.[85] Long-term feeding tube use was associated with increased T stage, N stage, use of conventional radiation techniques, and inclusion of induction or concurrent chemotherapy. The incidence of feeding tube complications is further decreased by the use of unilateral radiation.

Xerostomia

Xerostomia can severely impact patients' quality of life and dental hygiene after radiation therapy. Generally, the incidence of xerostomia is related to the volume of irradiated salivary glands. The proximity of the tonsils to the parotid glands places at least the ipsilateral gland at high risk for chronic dysfunction. As with the swallowing apparatus, a dose-effect relationship has been described for the parotid glands with the publication of dose-volume constraints for the preservation of salivary flow from these glands.[81,83] The submandibular gland is also important for minimizing xerostomia,[78] accounting for almost 95% of salivary flow. Preservation of salivary flow generally requires a dose less than 39 Gy,[86] although at MDACC doses to the contralateral submandibular gland are restricted to less than 26 Gy, when possible. Ipsilateral submandibular sparing is generally unattainable with adequate coverage of the level II nodes, which receive at least 54 Gy.

Mandibular Osteonecrosis

One of the most severe complications of head and neck radiation is mandibular osteoradionecrosis. Exposure of the mandible to high doses of radiation causes changes in the vascular bed, thereby limiting the ability of the tissue to respond to normal wear and trauma and leading to bone necrosis, which typically develops within 1 to 3 years of radiation treatment. In a series of 100 patients irradiated for head and neck cancer at University of California, San Francisco, between 1971 and 1977, there was a 22% rate of osteoradionecrosis following treatment with 50 to 75 Gy.[86] Risk factors for osteoradionecrosis include the need for post-radiation tooth extractions, volume of the mandible receiving at least 60 Gy, alcohol and tobacco use, and advanced stage cancers.[87] It is absolutely vital that a patient have full dental evaluation with extraction of at-risk teeth before radiation treatment to minimize risk.

IMRT techniques can minimize radiation dose to the jaw, although greater dose heterogeneity and resultant "hotspots" can be seen. Ben-David and colleagues[88] reported no cases of mandible osteonecrosis in 176 patients treated with parotid-sparing IMRT at University of Michigan. All patients had full dental evaluations with extraction in only 3%. One hundred fifty-seven patients (89%) were dentulous during radiation. Maximum dose to the mandible was limited to

72 Gy. Although these results are early, they are encouraging with regard to limitation of osteonecrosis with IMRT. Osteonecrosis was observed in only one of 51 patients with early-stage oropharyngeal tumors treated with IMRT at MDACC between 2000 and 2002.[75] An additional 30 of 776 (3.9%) patients treated between 2000 and 2007 with IMRT for oropharyngeal cancer at MDACC developed osteoradionecrosis. The latter cohort included patients with advanced stage tumors, 54% of whom received induction and/or concurrent chemotherapy. Together, these data suggest that the risk for osteoradionecrosis has dramatically reduced with IMRT, and for single modality treatment in early-stage tonsillar SCC, the risk should not be expected to exceed 5%.

Chemotherapy

General Principles and Chemotherapeutic Agents

Definitive surgery and radiation therapy provide excellent locoregional control and survival for patients with early-stage tonsillar carcinoma. For patients with advanced local or regional disease, however, multimodality strategies incorporating chemotherapy are often required to improve locoregional control and survival. Chemotherapy in head and neck cancer including tonsillar carcinoma is used in multiple settings: (neoadjuvant) chemotherapy, definitive chemoradiation therapy, and adjuvant chemoradiation therapy. In this chapter, we briefly discuss the role of chemotherapy in tonsillar cancer; see Chapter 14 for further details regarding chemotherapy and specific agents and see Chapter 15 for the latest data regarding immunotherapy.

Combination Chemotherapy in the Definitive Setting

Although patients with T1/T2 tumors and minimal nodal disease can be managed with single modality radiation therapy, those presenting with advanced nodal disease should be considered for concurrent therapies. Concurrent chemoradiation therapy has demonstrated improvement in overall survival versus radiotherapy alone in patients presenting with locoregionally advanced head and neck SCC and has become the standard of care.[89-91] The Meta-Analysis of Chemotherapy in Head and Neck Cancer (MACH-NC), which pooled data from clinical trials in which patients with resectable or unresectable disease were randomized to receive definitive local therapy (surgery or radiation) or definitive local therapy plus chemotherapy, showed a 5-year survival benefit of 6.5% with concurrent chemoradiation therapy.[90,91]

Multiple different chemotherapeutic regimens have been used in this space. The most evidence-based concurrent regimen includes high-dose cisplatin (100 mg/m^2) given on days 1, 22, and 43 of daily radiation therapy.[92,93] This regimen is difficult for many patients to tolerate and carries risks, including nephrotoxicity, ototoxicity, and neurotoxicity. Alternative concurrent regimens that have been studied include cetuximab,[94] carboplatin with infusional 5-fluorouracil,[95] and weekly cisplatin.[96] All appear to be effective but have not been compared to high-dose cisplatin, which is considered the gold standard. They are reasonable options for patients who cannot tolerate high-dose cisplatin. RTOG 1016, a phase III trial randomizing patients with HPV-positive oropharyngeal cancer to either high-dose cisplatin or weekly cetuximab concurrently with radiation, recently completed accrual and results are pending (NCT01302834).

Patients with HPV-related oropharyngeal cancer have excellent outcomes following chemoradiation therapy.[97] There has been interest in trying to de-escalate therapy for these patients with the intention of preserving high cure rates while sparing toxicity. Retrospective data from our institution show that patients with T1 or T2 oropharynx tumors, even those with N2b or N2c nodal disease, have locoregional control greater than 90% at 5 years after radiation alone.[76] Further research is needed before de-escalation of therapy is routinely recommended for these patients.

Induction Chemotherapy

The use of induction chemotherapy for tonsillar cancer is controversial. There are a number of theoretical benefits of chemotherapy in this setting. More intense chemotherapy can be administered as part of an induction strategy than can be given concurrently, which could potentially eradicate micrometastatic disease and reduce distant recurrence. Also, chemotherapy is often better tolerated when given sequentially rather than concurrently. Clinical trials, however, have failed to show consistent benefit of induction chemotherapy over concurrent treatment.

Early trials showed that patients with locally advanced oropharyngeal cancer had better outcomes when receiving induction chemotherapy with cisplatin and infusional 5-fluorouracil (PF) followed by radiation versus radiation alone (median overall survival 5.1 vs. 3.3 years).[98] Other similar trials showed similar results; induction chemotherapy improved outcomes compared with radiation alone.[99,100] The TAX323 and TAX324 studies showed that an induction regimen of cisplatin, docetaxel, and 5-fluorouracil (TPF) is superior to PF for locoregional control and overall survival when given before either radiation alone (TAX323) or radiation with concurrent weekly carboplatin (TAX324).[101,102]

A large meta-analysis, MACH-NC, described earlier, showed that induction chemotherapy with PF led to an absolute improvement in 5-year survival of 2.4%.[90] This is less than the benefit with concurrent chemotherapy (6.5% improvement in 5-year survival). The same meta-analysis showed that induction chemotherapy reduced the rate of distant metastases by 4.3%, while improving locoregional failure by only 1%.

Because concurrent chemoradiation therapy has become the standard of care for locally advanced head and neck cancer,

the trials described earlier have been criticized for treating patients with radiation alone or with suboptimal concurrent chemotherapy (e.g., weekly carboplatin) following induction. It is not clear whether induction chemotherapy adds additional benefit to optimal chemoradiation therapy. Two recent studies, the PARADIGM and DECIDE trials, compared induction followed by chemoradiation therapy with chemoradiation therapy alone. In the phase III PARADIGM trial, patients with locally advanced head and neck cancer (defined as those with advanced tumor stage, T3 or T4, or advanced nodal stage, N2 or N3) were randomized to either standard chemoradiation therapy with cisplatin or induction chemotherapy with TPF followed by concurrent chemoradiation therapy with either carboplatin or docetaxel.[103] The trial was stopped early due to slow accrual, but there were no benefits seen in the induction arm. Rather, 3-year overall survival was numerically (although not significantly) better in patients who did not receive induction (78% vs. 73%, $P = .77$). In an analysis of only patients with oropharynx cancer, induction chemotherapy looked even worse when compared with chemoradiation therapy alone (3-year overall survival 83% vs. 73%, $P = .47$), while there was a small trend toward benefit in patients with non-oropharynx primaries. Similarly, the DECIDE trial randomized patients with head and neck cancer and N2 or N3 disease to either chemoradiation therapy alone (with a rather unconventional regimen of concurrent docetaxel, 5-fluorouracil, and hydroxyurea) or induction chemotherapy with two cycles of TPF followed by chemoradiation therapy with the same regimen.[104] This trial, like PARADIGM, did not reach its accrual goals, but analysis after 285 randomized patients showed no significant differences between the arms with respect to overall survival, locoregional control, or distant metastases.

After many years of research into induction chemotherapy, no study has convincingly shown a benefit over concurrent chemoradiation therapy, and there are obvious costs, both in terms of toxicity and length of treatment course. Even though it has been proposed that induction chemotherapy could be used in patients with advanced nodal disease to reduce distant recurrence, there are no level 1 data to support this approach. Concurrent chemoradiation therapy remains the standard of care, and induction chemotherapy should only be used after careful discussion with a multidisciplinary group. If induction chemotherapy is selected, TPF is the preferred regimen.

Combination Chemotherapy in the Adjuvant Setting

For patients with locally advanced head and neck cancer, recurrence after surgical resection is high. For patients with adverse features, including perineural invasion, multiple positive lymph nodes, and T3 or T4 primary tumors, postoperative radiation therapy can improve outcomes.[105] In patients with positive margins or with nodal extracapsular spread, postoperative concurrent chemoradiation therapy with high-dose cisplatin improves locoregional control and overall survival.[47,106,107] As discussed earlier, high-dose cisplatin can be difficult to tolerate, and alternative regimens are frequently used, although these have not been rigorously studied.

Patients with HPV-positive tumors have been shown to improve outcomes after definitive chemoradiation; recent data suggest that there is also excellent disease control following surgery and postoperative chemoradiation therapy in these patients.[108] Ongoing research is focused on the possibility of de-escalating therapy for these patients, especially those with only minimal extracapsular extension. Current guidelines, however, do not support the use of HPV status in selecting postoperative therapy.

Treatment Selection

The goal in treating tonsillar SCC, as in treatment of all other SCCs, is to maximize tumor control while minimizing functional impairment and toxicity. For early-stage tonsillar SCC (T1 or small T2 N0-1), either primary radiation or surgery (with appropriate adjuvant treatments as indicated) yields approximately equivalent rates of local control and survival.[20] Prospective randomized studies comparing radiation therapy with surgery for oropharyngeal SCC are lacking and may not be feasible. Proponents of a primary surgical approach highlight the potential benefits of pathologic staging, which can help tailor, and in some cases, deintensify treatment. A recent retrospective analysis of SEER data suggested a potential benefit even with non-oncologic tonsillectomy in patients with early-stage tonsillar SCC treated with radiation therapy.[109] However, primary radiation therapy is the preferred treatment approach for early-stage tonsillar SCC in many cases. For example, radiation is the preferred treatment for tumors that extend significantly onto the soft palate because extensive resection of the soft palate can severely impair speech and swallowing.

Given the overall excellent oncologic outcomes for early-stage tonsillar SCC, the choice of treatment is largely based on functional considerations, cosmetic results, and anticipated complication probabilities. These considerations become ever more important in the context of the present HPV-associated oropharyngeal SCC epidemic. For selected T1-2 tumors arising from the tonsil, a surgical approach can be ideal as a mechanism of evading radiotherapy entirely. Surgery in these cases can result in decreased disturbance of underlying superior pharyngeal constrictor muscles, which may improve long-term swallowing outcomes. However, if a primary surgical approach is selected, then clear microscopic margins are critical because gross residual disease requires definitive radiation dose and consequent toxicities. For this reason, TORS is most appropriate for small-volume, early-stage (T1-2) tonsillar SCC. Even among well selected patients with tonsillar SCC, a high proportion of patients will require postoperative radiation with or without concurrent chemotherapy because these patients often present with advanced stage disease. A primary surgical approach may still be beneficial in these patients by allowing for a reduced dose of radiation with fewer radiation-associated side

effects.[110–112] To ensure optimal individualized care, a multidisciplinary approach including surgical, radiation, and medical oncology should be involved in the initial assessment and treatment planning for every new case of tonsillar SCC, taking into account such factors as age, comorbidities, HPV status, and smoking history. The approach to treatment depends on site, stage, and expertise of the treating physicians, and should be discussed on an individual basis in a multidisciplinary setting.

Rehabilitation

Dental Rehabilitation

Dental care and rehabilitation in the management of early-stage tonsillar SCC is focused primarily on the prevention of post-radiation sequelae such as dental caries and osteoradionecrosis. Pretreatment dental screening to identify potential odontogenic issues and routine follow-up during and after treatment is crucial in preventing more serious complications. A dental practitioner who is trained and experienced in care of head and neck cancer patients is an integral member of a multidisciplinary treatment team.

Patients undergoing treatment for tonsillar SCC—especially radiation and chemoradiation therapy—are at increased risk for development of odontogenic complications. Dental caries and infections can result from a combination of xerostomia, alteration of the natural oral flora, and poor dental hygiene. Radiation doses of only 20 Gy have been shown to damage salivary gland tissue, which results in decreased salivary flow and progressive xerostomia[113] with increased susceptibility to dental caries and periodontal disease. Newer treatment modalities such as IMRT and proton therapy have been effective in reducing salivary glandular damage and the severity of radiation-associated xerostomia, although these remain common side effects. Therefore, the clinician must remain cognizant of these sequelae and proactive in addressing them. The use of sialagogues such a sucrose-free lemon lozenges or cholinergic medications to promote salivation during treatment may be useful. Oral rinses and gels can help alleviate the symptoms of hyposalivation, but their protective effects against odontogenic complications have not been established. Finally, daily fluoride treatments with a 1% neutral sodium fluoride gel have also been strongly recommended to prevent dental caries during and after radiation therapy. This can be applied by either daily brushing or via pre-fabricated dental appliances.

The most significant and feared complication of radiation therapy for tonsillar SCC is osteoradionecrosis. This condition is heralded by the development of chronic oral wounds, mucosal dehiscence, and, in advanced stages, exposed, necrotic bone. It can present within weeks of therapy but frequently occurs as a late complication years after completing radiation. Pathophysiologically osteoradionecrosis results from the creation of a hypoxic, hypovascular microenvironment brought on by radiation-induced tissue changes. Poor dental hygiene and underlying dental infections greatly increase the risk of osteoradionecrosis, and a thorough dental evaluation by a trained dental practitioner should be considered standard of care before initiating radiation therapy. This evaluation should include full mouth radiographs (e.g., Panorex films), diagnosis of underlying dental and periodontal diseases, and dental treatments including extractions as needed. Routine follow-up with a dental professional and maintaining strict dental hygiene should be stressed to the patient.

Speech and Swallowing Rehabilitation

The oropharynx is critical for normal speech and swallowing, and both the primary tumor as well as surgical and non-surgical treatments of tonsillar SCC can have marked effects on these crucial functions. As such, early and aggressive rehabilitation is an important aspect of postoperative care and can dramatically impact patients' quality of life. Close collaboration between the treatment team and a speech-language pathologist throughout all stages of treatment can maximize a patient's functional outcomes.

Maintaining and/or restoring swallowing is perhaps the most important functional concern for tonsillar SCC survivors, regardless of treatment approach. Patients treated with TORS have substantial short-term dysphagia that requires intensive rehabilitation for swallowing. Concurrent chemoradiation therapy can cause marked functional impairments with around 60% of patients with oropharyngeal SCC requiring a gastrostomy feeding tube during treatment.[85] It has been shown that reliance on a feeding tube and decreased oral intake during and after treatment may increase the risk of prolonged or permanent feeding tube use.[114] Thus, accurate assessment of pretreatment functional status, identification of those at an increased risk of functional impairment, and implementation of early speech and swallow rehabilitation are crucial.

Pretreatment functional assessment of baseline functional status is important in that it can be predictive of post-treatment outcomes and guide clinical decision making. Beyond a thorough clinical speech and swallow evaluation, an instrumental evaluation (i.e., modified barium swallow) should also be considered, especially in patients presenting with baseline symptoms of dysphagia, dysarthria, and/or aspiration.[115] Data obtained from this assessment can then be used to determine the risk for functional impairment during and after treatment and to prescribe preventive treatments. The early implementation of preventive swallow therapy and exercise has been shown in several clinical studies to be highly effective in maintaining oral intake and reducing the risk for swallow dysfunction.[114,116] The goal of early prophylactic swallow therapy is to maintain some level of oral intake during and after treatment to promote positive quality of life and functional outcomes. Finally, in patients in whom functional impairment develops following surgery or radiation therapy, an individualized rehabilitation strategy should be formulated by the clinician and speech pathologist. Again, standardized instrumental evaluations can help identify the pathophysiologic basis and extent of the dysfunction and

MD Anderson Cancer Center

Continuity of Care Patient Report Card

Head and Neck Center

Patient , MDA #
ACCT# Print Date
DOB FC SEX Location

Date: _____ Time: _____

Diagnosis: Squamous Cell Carcinoma of: ☐ Larynx ☐ Oropharynx ☐ Hypopharynx ☐ Nasopharynx ☐ Unknown

Treatment given: ☐ Chemotherapy ☐ Radiation ☐ Chemotherapy / Biochemotherapy

Congratulations! You have completed your treatment of your head and neck cancer. You will now transition into the recovery an follow-up phase for your cancer.

You will be having routine follow up appointments at the Head & Neck Center in MD Anderson Cancer Center for the next 2 years You will be alternating between your treating physicians each time. While there may be the need for other appts or testing along t way, here is the basic expected schedule of follow up appointments:

Date After Treatment	Date	Appointments	Physician	Testing
3 months	_____	☐ Radiation Oncology ☐ Medical Oncology ☐ H & N Surgery	_____ _____ _____	☐ MRI ☐ CT scan ☐ Blood Work
6 months	_____	☐ Radiation Oncology ☐ Medical Oncology ☐ H & N Surgery	_____ _____ _____	☐ MRI ☐ CT scan ☐ Blood Work
9 months	_____	☐ Radiation Oncology ☐ Medical Oncology ☐ H & N Surgery	_____ _____ _____	☐ MRI ☐ CT scan ☐ Blood Work
12 months	_____	☐ Radiation Oncology ☐ Medical Oncology ☐ H & N Surgery	_____ _____ _____	☐ MRI ☐ CT scan ☐ Blood Work
16 months	_____	☐ Radiation Oncology ☐ Medical Oncology ☐ H & N Surgery	_____ _____ _____	☐ MRI ☐ CT scan ☐ Blood Work
20 months	_____	☐ Radiation Oncology ☐ Medical Oncology ☐ H & N Surgery	_____ _____ _____	☐ MRI ☐ CT scan ☐ Blood Work
24 months	_____	☐ Radiation Oncology ☐ Medical Oncology ☐ H & N Surgery	_____ _____ _____	☐ MRI ☐ CT scan ☐ Blood Work
Survivorship	_____	☐ Radiation Oncology ☐ Medical Oncology ☐ H & N Surgery	_____ _____ _____	☐ MRI ☐ CT scan ☐ Blood Work

Provider's Signature/Credentials/ID# Print Name

Continuity of Care Patient Report Card
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• **Fig. 32.6** Continuity of care (COC) patient report for patients with advanced stage oropharynx cancer requiring multimodality therapy. The COC pathway allows for improved coordination of care. (Source: MD Anderson Cancer Center, Houston, TX.)

assist in selecting appropriate therapies to maximize swallowing ability and prevent aspiration events. Such therapies can include compensatory swallowing techniques (e.g., chin tuck, head rotation) and/or dietary modifications.[115]

Post-Treatment Surveillance

Patients with tonsillar SCC require regular, consistent follow-up and surveillance after treatment. However, the ideal surveillance schedule remains an area of controversy. Although several studies have suggested that survival is not related to the intensity of post-treatment follow-up,[117] current NCCN guidelines recommend a graduated follow-up schedule that decreases in frequency each year after treatment. At MDACC, patients are seen every 3 months for the first year after completing their primary and adjuvant treatments, then every 4 months during the second year, every 6 months during the third year, and then yearly after that. At each follow-up, a focused head and neck examination should be performed, which often includes indirect mirror laryngoscopy or fiber-optic laryngoscopy. Moreover, the clinician should inquire about new pain, swallowing function, oral intake, and any recent weight changes. New or changing symptoms can be a key indicator of disease persistence or recurrence. Patients should be asked about current tobacco use and appropriately counseled about cessation if needed. Finally, patients who have undergone radiation therapy should have thyroid function studies performed every 6 to 12 months to screen for subclinical hypothyroidism.[118]

The role and timing of surveillance imaging studies is also an area of ongoing debate and controversy. A baseline CT scan performed 4 to 6 months after completion of treatment is the current recommendation of the NCCN. This initial post-treatment scan allows the clinician to evaluate treatment response and has been shown to be predictive of long-term prognosis.[119] However, while the importance of obtaining baseline post-treatment imaging has been well established, the value of serial surveillance imaging of asymptomatic patients is nebulous. This practice is not currently recommended by the NCCN but is nonetheless part of routine follow-up care at numerous institutions including MDACC. While CT and PET/CT can be effective at detecting subclinical recurrence, a recent review found that routine surveillance imaging did not meaningfully impact patient survival.[120] However, current studies are limited by their size and heterogenous results, and larger prospective studies are needed to help define which subsets of patients would benefit from surveillance imaging.

Finally, patients who have undergone multidisciplinary treatment frequently have multiple follow-up appointments with a head and neck surgeon, radiation oncologist, and medical oncologist. This can result in unintentional redundancy of screening tests and imaging. In order to prevent duplicate examinations and streamline the surveillance schedule, at MDACC a continuity of care pathway has been established that coordinates follow-up examinations and testing into a consistent sequence that is shared among all providers involved in treatment. Using this approach, the post-treatment surveillance process has become more efficient and effective. A schematic flowchart of this surveillance pathway is demonstrated in Fig. 32.6.

Summary

Multidisciplinary management of early-stage tonsillar SCC is highly effective and offers patients excellent rates of cure and long-term prognosis. Although non-surgical treatment with primary radiation therapy has become the gold standard over the past couple of decades, newer surgical approaches such as TORS may be leading to a shift in paradigm. Moreover, the rise in HPV-associated tonsillar SCC among younger patients has prompted increased focus on de-escalated treatment strategies. In the end, patients are best served by a comprehensive treatment approach that incorporates a multidisciplinary team in the diagnosis, treatment, rehabilitation, and post-treatment surveillance of their cancer.

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33

Early HPV-Related Base of Tongue Cancer

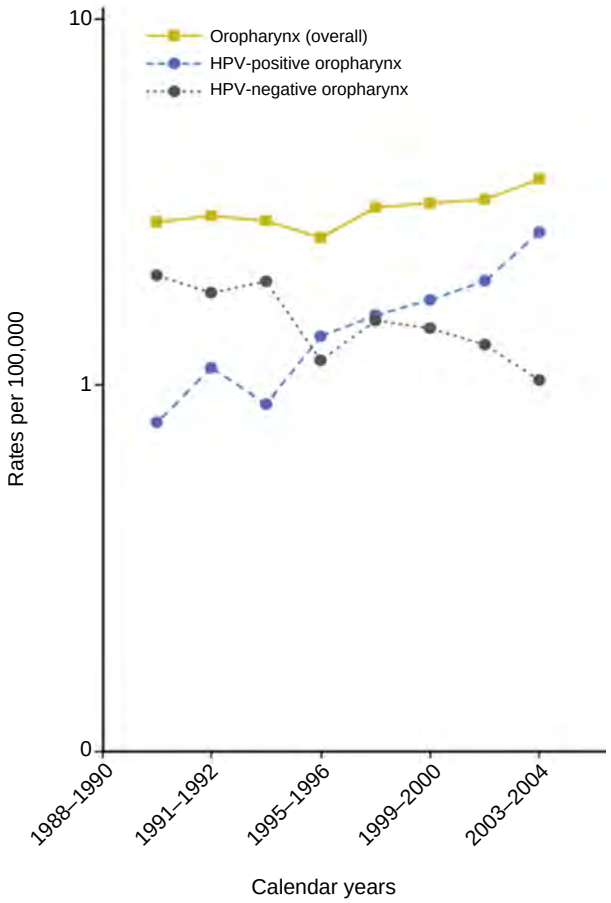
ASHISH A. PATEL, ALLEN CHENG, ROM LEIDNER, MARKA R. CRITTENDEN, AMBER L. WATTERS, MEGAN J. HYERS, R. BRYAN BELL

Approximately 15,000 new cases of oropharyngeal squamous cell carcinoma (OSCC) are diagnosed annually in the United States, with 40–50% originating in the base of the tongue.[1] As with most head and neck squamous cell carcinomas (HNSCCs), tobacco and alcohol use are significant risk factors for the development of base of tongue cancer. Recently, human papillomaviruses (HPVs), especially HPV type 16, have also been shown to be an important independent risk factor for the development of cancer of the tongue base, with the number of sexual partners being a contributing risk factor. D'Souza demonstrated an increased likelihood of oropharyngeal HPV infection in patients having either 10 oral sex partners (odds ratio, 5.2) or 25 vaginal sex partners (odds ratio, 3.9) during their lifetime.[2]

Although the overall incidence of HNSCC has declined in the last three decades owing to declining smoking rates among Americans, the incidence of oropharyngeal cancer has risen sharply, particularly in the 40- to 55-year-old male subgroup[3] (Fig. 33.1). Surveillance, Epidemiology, and End Results (SEER) data indicate a 13% increase in incidence from 1973 to 2004, with approximately 60% resulting from HPV-positive infection. Predictive modeling findings from the National Institutes of Health (NIH) project that within the decade the incidence rates of oropharyngeal cancers due to HPV will surpass that of cervical cancer.[4]

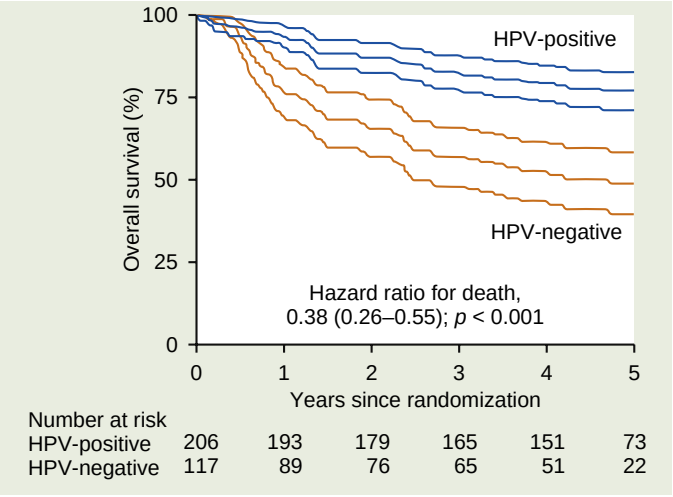
HPV-related OSCC is biologically and clinically distinct from HPV-negative tumors, which respond much less favorably than HPV-positive carcinomas to conventional therapies.[5,6] Three-year overall survival (OS) rates of 40–50% for patients with local regionally advanced HPV-negative OSCC treated with radiation and chemotherapy have been reported, as opposed to 80% survival for those with HPV-positive carcinomas treated with similar regimens (Fig. 33.2). A meta-analysis by O'Rorke and colleagues that included 42 studies and 4843 patients documented that HPV-positive oral head and neck squamous cell carcinoma (OHNSCC) patients had a 54% OS benefit compared with HPV-negative patients and also showed significantly improved progression-free and disease-free survival.[7]

Early base of tongue tumors (T1/T2) are limited to the tongue itself and do not involve adjacent structures. In addition to primary tumor classification, other pathologic features such as perineural spread, lymphovascular invasion, and extracapsular extension may affect treatment response and prognosis. Early-stage base of tongue cancers can usually be managed with either surgery or radiotherapy (RT) with excellent oncologic results, particularly in the HPV-positive population. Over the last several decades, RT has served as the dominant approach to treating early-stage OSCC. However, recent advances in minimally invasive surgical techniques, such as transoral robotic



• **Fig. 33.1** Cancers of the oral cavity and pharynx. (From Sturgis EM, Cinciripini PM: Trends in head and neck cancer incidence in relation to smoking prevalence. *Cancer,* 2007;110[7]:1429–1435.)

surgery (TORS), have resulted in resurgence of the role of surgery for OSCC. This chapter focuses specifically on the clinical presentation, diagnostic evaluation, and contemporary management of T1/T2 base of tongue squamous cell carcinoma (SCC) from a multidisciplinary perspective.



• **Fig. 33.2** Survival of oropharyngeal cancer patients according to human papillomavirus *(HPV)* status. In a Kaplan-Meier analysis, patients with HPV-positive cancer had better overall survival and progression-free survival rates than patients with HPV-negative cancer ($P < .001$ for both end-points, by the log-rank test). The 3-year rates of overall survival were 82.4% (95% confidence interval [CI], 77.2–87.6) in the HPV-positive subgroup and 57.1% (95% CI, 48.1–66.1) in the HPV-negative subgroup, and the 3-year rates of progression-free survival were 73.7% (95% CI, 67.7–79.8) and 43.4% (95% CI, 34.4–52.4), respectively. Patients with HPV-positive tumors had a 58% reduction in the risk of death as compared with patients with HPV-negative tumors (hazard ratio [HR], 0.42; 95% CI, 0.27–0.66) and a 51% reduction in the risk of relapse or death (HR, 0.49; 95% CI, 0.33–0.74). (Adapted from Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24–35.)

Anatomy of the Base of Tongue

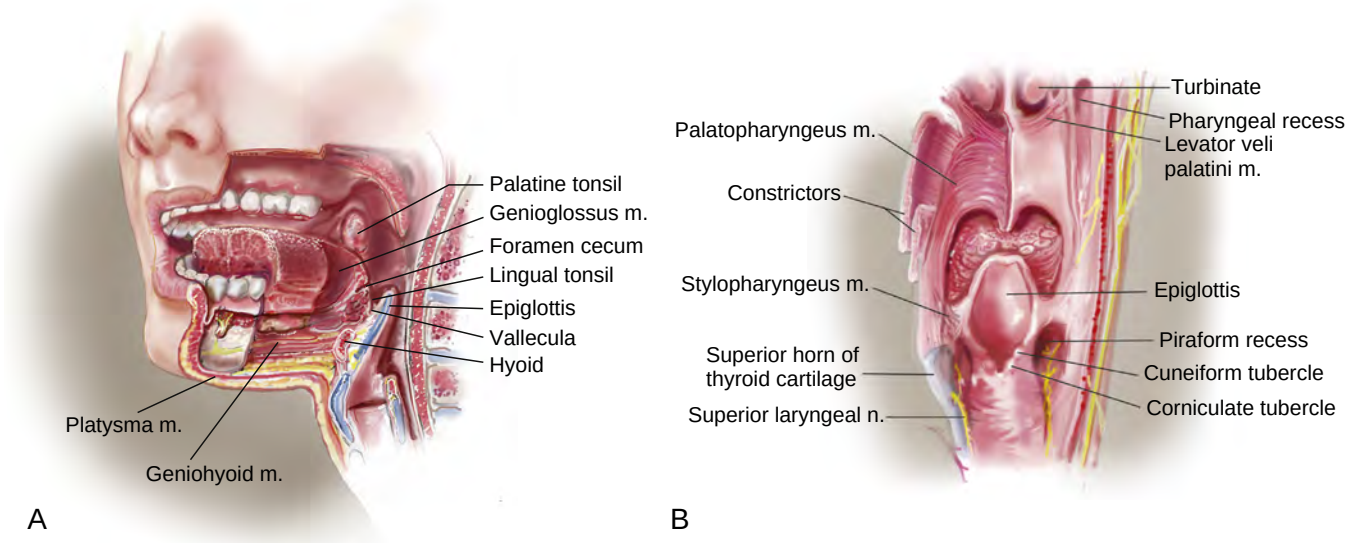
The oropharynx is divided into four clinical subsites: the anterior wall, posterior wall, lateral wall, and superior wall (Fig. 33.3). The anterior wall is further divided into the vallecula and base of tongue. The base of tongue consists of the posterior third or root of the tongue anteriorly bound by the circumvallate papilla, posteriorly by the vallecula, laterally by the glossotonsillar sulci, and inferiorly by the hyoid bone. The base of tongue is rich in lymphatics and contains aggregates of lymphoid tissue—the lingual tonsils—which contribute to the Waldeyer Ring. Unlike the palatine tonsils, the lingual tonsils are unencapsulated and are lined by nonkeratinized squamous mucosa that forms numerous crypts or invaginations on its surface.

As previously described, lymphatic drainage of the base of tongue is relatively predictable and includes levels II, III, and IV, with the first echelon of nodes being the upper deep cervical nodes and frequently the jugulodigastric node.[8,9] Tumors that encroach on the midline of the base of tongue are more likely to have bilateral lymphatic drainage. Other potential routes of metastatic spread involve the parapharyngeal and retropharyngeal lymph nodes. Cervical lymphadenopathy is commonly the first presenting sign of base of tongue carcinoma.[10]

The neurovascular anatomy of the base of tongue is derived from the lingual artery and its branches, the lingual veins, and tributaries, and the 5th, 7th, 9th, and 12th cranial nerves.

Clinical and Diagnostic Evaluation

The clinical presentation, natural history, risk factors, demographics, and outcomes are distinctly different for HPV-related and HPV-unrelated disease. The incidence of HPV-driven oropharyngeal cancer increased 225% between 1988 and 2004, whereas the incidence of HPV-negative oropharyngeal cancer



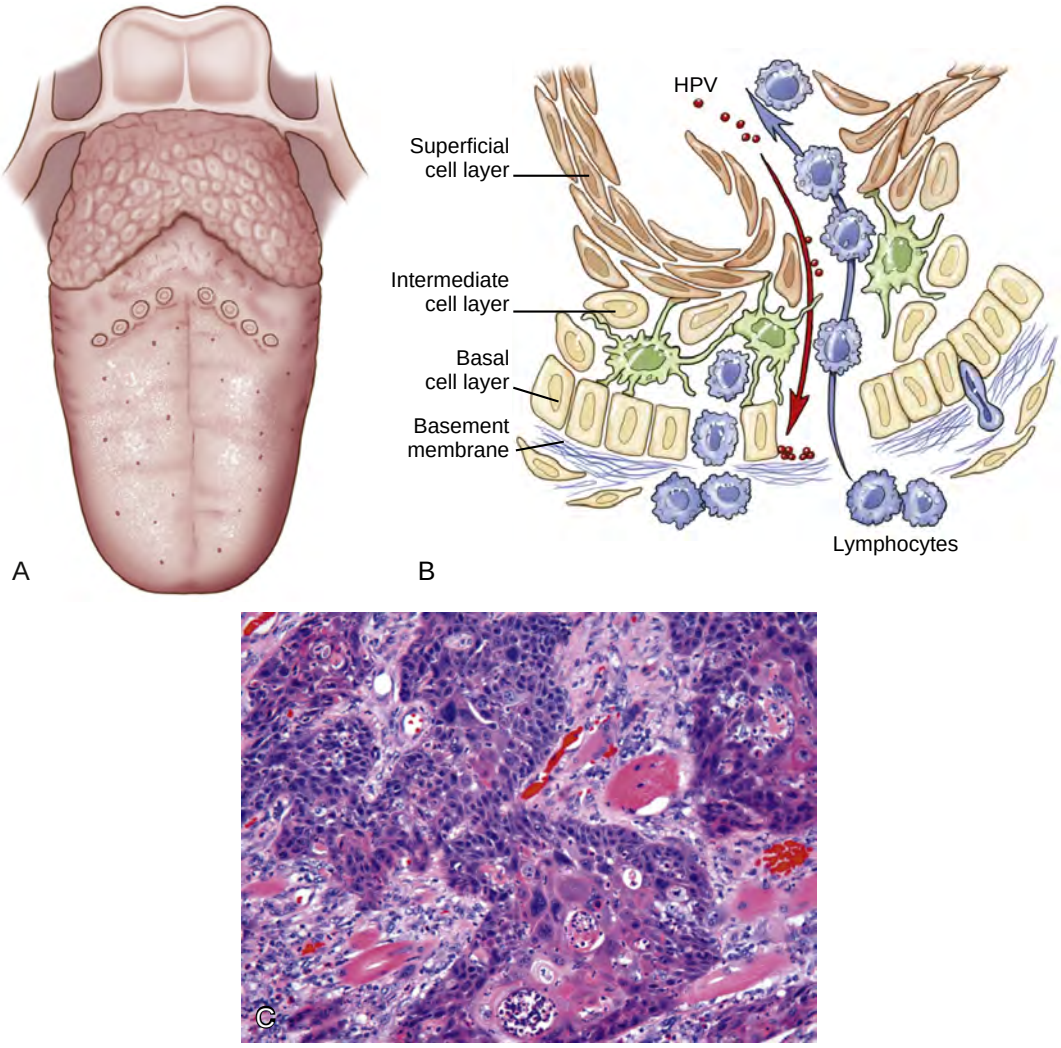
• **Fig. 33.3** Oropharyngeal anatomy. The oropharynx is divided into four clinical subsites: the anterior wall, posterior wall, lateral wall, and superior wall. **A,** Sagittal view; **B,** coronal view. The anterior wall is further divided into the vallecula and base of tongue. The base of tongue consists of the posterior third or root of the tongue anteriorly bound by the circumvallate papilla, posteriorly by the vallecula, laterally by the glossotonsillar sulci, and inferiorly by the hyoid bone.

decreased by 50%.[4] More than 100 HPV subtypes are known to exist, with over 15 having oncogenic potential,[11] but 60% of OSCCs are positive for HPV16.[12]

In the United States, it is estimated that about 40–80% of oropharyngeal cancers are associated with HPV, whereas in Europe the proportion varies from 20% to 90% depending on the prevalence of tobacco use. It is a rising epidemic in the 40- to 55-year-old male population.

Unlike conventional base of tongue HPV-negative, keratinizing SCC, HPV-related SCC arises within epithelial-lined crypts of lymphoid tissue—in general, either the palatine or the lingual tonsils (Fig. 33.4). Its pathogenesis is that of an oncovirus. After infection of lingual tonsillar tissue, the virus integrates its genome into the host cell DNA. This in turn upregulates oncoproteins E6 and E7, which are responsible for degrading p53 and retinoblastoma protein (pRb) tumor suppressor genes.[13] The tumors are generally characterized as nonkeratinizing, poorly differentiated, basaloid carcinomas (Fig. 33.4C). Early primary tumors involving the base of tongue are usually asymptomatic. The first presenting sign of T1 or T2 base of tongue cancer is usually painless cervical lymphadenopathy. In some patients, even with small primary tumors, mild symptoms of dysphagia, dysarthria, odynophagia, or globus sensation may be present. Significant dysphagia, weight loss, and hemoptysis may be signs of more advanced disease. These presenting signs, in the absence of heavy cigarette smoking with or without alcohol use, are most characteristic of HPV-associated base of tongue cancer.

The Radiation Therapy Oncology Group (RTOG) trial 0129 demonstrated prospective evidence that HPV positivity independently predicts improved OS and progression-free survival (PFS) among patients with OSCC.[9] In addition,



• **Fig. 33.4** Base of tongue anatomy and human papillomavirus (HPV)–related head and neck squamous cell carcinoma. **A,** The base of tongue comprises the region posterior to the sulcus terminalis and circumvallate papillae. It includes the lingual tonsils and intrinsic and extrinsic muscles of the tongue. **B,** Surface epithelium of the lingual tonsils deeply invaginates into a lymphoid stroma, creating crypts that increase the surface area of the tonsil by nearly 700%. The zones of squamous epithelium—the basal, intermediate, and superficial layers—are interrupted by migrating non-epithelial cells including lymphocytes and antigen-presenting cells (APCs). Loss of structural integrity leaves the basement membrane exposed to deposition of viral particles. **C,** Histophotomicrograph of typical HPV-related oropharyngeal cancer, characterized by basophilic, nonkeratinizing, poorly differentiated tumor cells in a stroma heavily infiltrated with lymphocytes.

HPV-associated oropharyngeal cancer responded favorably to RT when compared with the HPV-negative cohort. The 3-year OS for HPV-positive patients treated with concurrent chemoradiotherapy (CCRT) was 82.4% (for all patients, stages I–IV), compared with 57.1% for the HPV-negative group[5] (see Fig. 33.2).

Non–virally associated SCC of the base of tongue most commonly occurs in patients with significant tobacco history. Tobacco and alcohol use have a synergistic effect on upper aerodigestive tract tumorigenesis. These patients are slightly older[4] and tend to have more advanced signs and symptoms at presentation. Although the risk of cervical metastasis remains high in this group, primary tumors may be more symptomatic and are frequently a cause for alarm in patients.

Staging

The staging criteria and staging system for HPV-related oropharyngeal cancer recently underwent substantive modification as published in the eighth edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual, thereby more accurately representing the unique biologic, clinical, and epidemiologic features of HPV-related HNSCC compared with HPV-unrelated disease (Table 33.1). The revised system was initially proposed in 2015 based on a cohort of 573 patients with HPV-related oropharyngeal squamous cell carcinoma (OPSCC) treated with radiation or chemoradiotherapy over a 10-year period and by using recursive partition analysis (RPA) and adjusted hazard ratios (AHRs) of the current TNM staging criteria to reclassify patients into stage I, II, III, or IV. Two refined staging systems (RPA stage and AHR stage) were proposed based on the current TMN metrics, both of which were superior in prognosticating oncologic outcomes when compared with the current AJCC system.[14]

After this discovery study, the results of a seven-center study aimed at validating this model were published, with the new HPV OPSCC staging system proposed by the International Collaboration on Oropharyngeal cancer Network for Staging (ICON-S). This was essentially a modified version of the previous AHR system; the authors proposed that smoking and age should be excluded from an anatomically based prognosticating system. In addition, they found no difference in survival between T4a and T4b disease, leading the consolidation of T4 staging and ICON-S stage IV for patients with metastatic disease.[15]

Immunohistochemistry for p16 overexpression has emerged as an important surrogate biomarker for HPV-mediated disease; p16 is upregulated with HPV16, and oncoproteins degrade p53 and pRb, leading to HPV-mediated carcinogenesis. All oropharyngeal cancer should be tested for p16, and those cancers that do not overexpress p16 should be staged by use of the p16-negative staging system. The cut-point for determining p16 by immunohistochemistry is nuclear expression with greater than +2/+3 intensity and greater than 75% distribution, under which tumors should be staged with the p16-positive system.

The primary tumor stage remains essentially the same in the modified p16-positive staging system as in the traditional p16-negative system, with the exception that the p16-positive classification does not include a Tis category and there is not a T4b subcategory within the T4 group (Fig. 33.5). With these criteria, T1 tumors are less than or equal to 2 cm in greatest dimension, whereas T2 tumors are greater than 2 cm but less than or equal to 4 cm in greatest dimension. T1/T2 tumors by definition should be limited to the base of tongue and its intrinsic musculature and should not involve the extrinsic tongue muscles, muscles of mastication, mandible, or other pharyngeal subsites. Careful physical examination with endoscopic assistance and critical assessment of staging imaging is of paramount importance in accurately staging base of tongue carcinoma because treatment and prognosis are stage dependent.

Nodal staging in the eighth edition of the AJCC Staging Manual has changed considerably, as a reflection of ICON-S data which showed that traditional N0–N2b nodal stages are homogeneous for outcome within T1 and T2 categories (creating stage I). N2c and T3 have an intermediate stage (stage II), and T4 and N3 are the least favorable group (stage III). Stage IV is reserved for distant metastasis. The revised p16-negative system includes extranodal extension (ENE) as an important prognostic variable; however, the role of ENE is less well defined in p16-positive oropharyngeal cancer and it is not a factor in staging this disease.

Pathologic staging is modified for p16-positive oropharyngeal cancer to reflect data that indicate that metastatic node number, rather than ENE, laterality, or nodal size, is the prognosticator in surgically resected, neck-dissected p16-positive disease. Another finding in the surgically managed patient is that N3 disease behaves unusually well and is equivalent to N1; therefore N3 is eliminated from pN categorization. The favorable outcome for N3 is not apparent in patients treated non-surgically. Unlike with other head and neck sites, ENE does not appear to have the same prognostic significance in surgically treated patients, provided that adjuvant treatment is administered according to conventional practice.

Any p16-positive cervical lymph node metastases to level II or /III from an unknown primary are staged according to the p16-positive classification. In addition, the AJCC recommends other prognostic factors be considered and recorded along with standard staging information, including Eastern Cooperative Oncology Group (ECOG)/Zubrod or Karnofsky performance measures, tobacco and alcohol use, tumor location, number and size of nodes, perineural invasion, and ENE. There is no grading system for HPV-mediated oropharyngeal tumors.

Focused Physical Examination

The first step in evaluation and staging of cancer of the base of tongue remains a thorough but focused physical examination. Careful oral inspection and palpation of all subsites of the oral cavity and oropharynx should be completed with a headlight or other suitable focused light source. Care should be taken to properly dry the mucosa with gauze sponges before examination. Traction of the oral tongue anteriorly and bilaterally with a gauze sponge is particularly important to determine the anterior extent of the tumor. Retraction of the tongue

TABLE 33.1 American Joint Committee on Cancer Staging for Human Papillomavirus–Positive Oropharyngeal Squamous Cell Cancer, 8th Edition

Primary Tumor (T)

T0	No primary identified
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, mandible or beyond. (Mucosal extension to lingual surface of epiglottis from primary tumors of the base of tongue and vallecula does not constitute invasion of the larynx.)

Regional Lymph Nodes: Clinical (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none >6 cm
N2	Contralateral or bilateral lymph nodes, none >6 cm
N3	Lymph node(s) larger than 6 cm
N3	Metastasis in a lymph node ˃6 cm in greatest dimension

Regional Lymph nodes: Pathological (pN)

NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T0, T1, or T2	N0 or N1	M0	I
T0, T1, or T2	N2	M0	II
T3	N0, N1, or N2	M0	III
T4	N0, N1, N2, or N3	M0	III
Any T	Any N	M1	IV

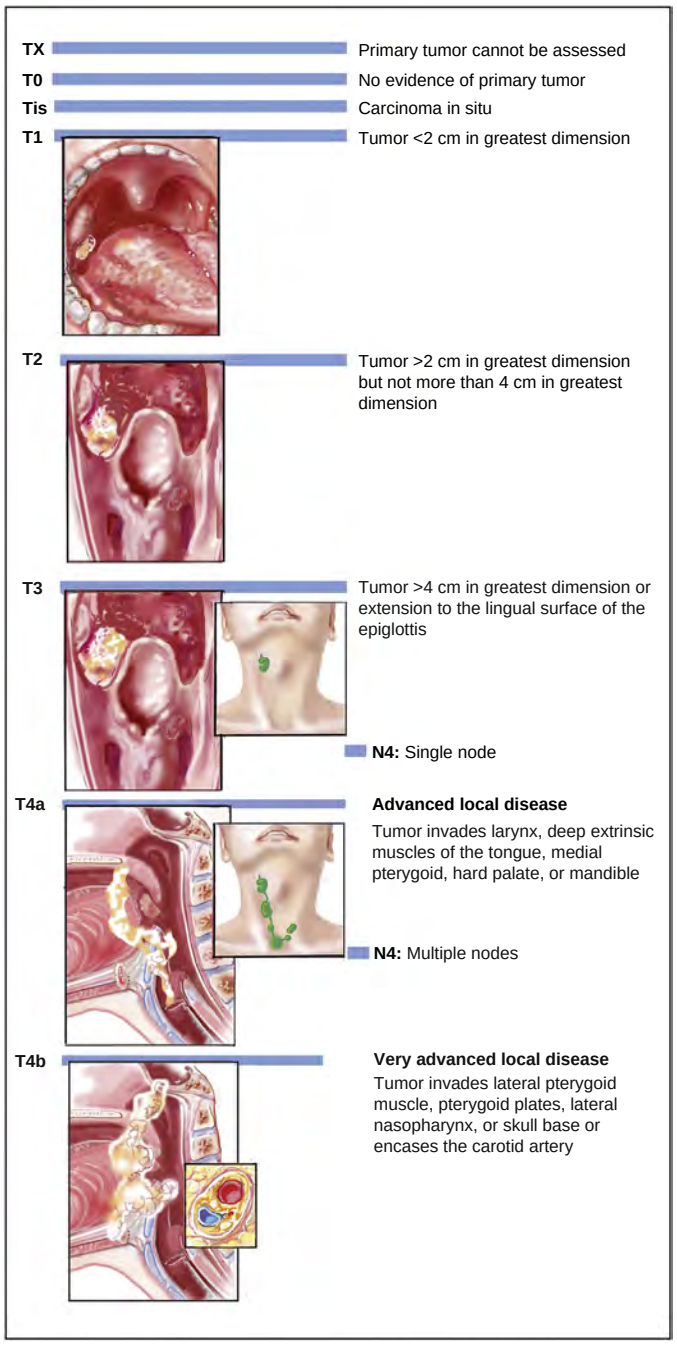
Pathologic Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T0, T1, or T2	N0, N1	M0	I
T0, T1, or T2	N2	M0	II
T3 or T4	N0, N1	M0	II
T3 or T4	N2	M0	III
Any T	Any N	M1	IV

Registry Data Collection Variables

1. Tumor location
2. Lymph nodes
3. Perineural invasion
4. Extranodal extension
5. Smoking history

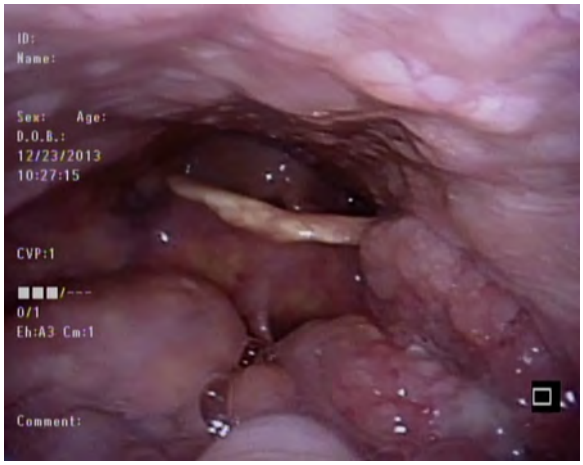
From O'Sullivan B, Lydiatt WM, Haughey BH, et al: HPV-mediated (p16+) oropharyngeal cancer. In Amin M, Edge S, Greene F, et al, editors: *AJCC cancer staging manual,* ed 8, New York: Springer; 2017. DOI 10.1007/978-3-319-40618-3_10.



• **Fig. 33.5** Staging diagram for oropharyngeal cancer.

medially with a tongue depressor should be completed bilaterally to examine the lingual gutter and glossotonsillar sulci. The aforementioned sites should be bimanually palpated bilaterally because many base of tongue tumors are endophytic or have an endophytic component. The tonsillar fossa, anterior and posterior tonsillar pillars, and soft palate should also be carefully visually inspected and manually palpated to determine if these subsites are involved or have signs of a co-synchronous primary tumor.

In-office flexible fiber-optic examination is necessary in all patients being evaluated for oropharyngeal cancer (Fig. 33.6). The nasopharynx, oropharynx, hypopharynx, and larynx should be examined in a sequential and systematic fashion.



• **Fig. 33.6** Nasopharyngoscopy for visualization of the oropharynx. Note left base of tongue tumor.

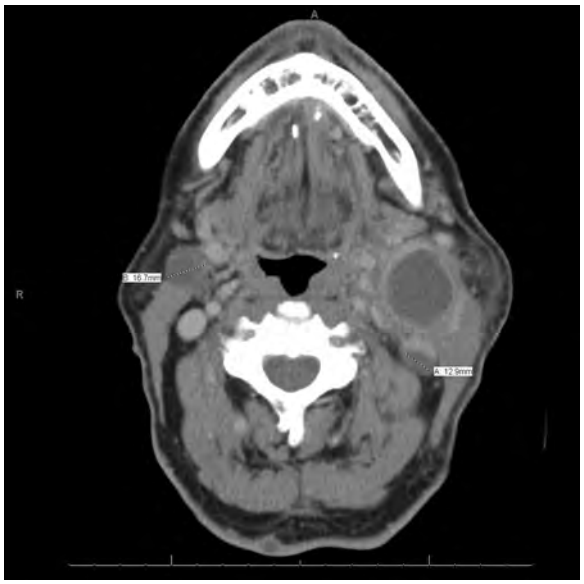
For base of tongue cancer, this is usually the only method of visualizing the primary site. It is important to note involvement of adjacent structures from this view, particularly the glossotonsillar sulcus, inferior tonsillar poles, vallecula, and lingual epiglottis. Careful examination of the remainder of the upper aerodigestive tract is important to evaluate for a co-synchronous mucosal primary.

One of the most important physical examination maneuvers is digital palpation of the base of tongue to estimate depth, thickness, surrounding tissue fixation, and laterality. HPV-related primary tumors may be imperceptible on endoscopic examination and require digital palpation to identify. This is difficult if not impossible to perform thoroughly and effectively in the office because it elicits the patient's gag reflex and can be quite painful or uncomfortable.

Examination Under Anesthesia or Operative Endoscopy

Although not always necessary, examination under anesthesia with operative rigid endoscopy serves many purposes. First, it allows for comprehensive digital palpation of the oropharynx, which in many patients cannot be completed without general anesthesia. Second, the use of a rigid laryngoscope allows for direct biopsy of the lesion to obtain a tissue diagnosis. Although this can be done in the office with a flexible endoscope with an internal port, it may be cumbersome for the surgeon and uncomfortable for the patient. In addition, obtaining a positive biopsy with flexible wire tissue forceps can be challenging with endophytic tumors because the base of tongue needs to be "unroofed" in order to enter the tumor.

Rigid endoscopy also allows for palpation of the tumor and base of tongue under direct vision with use of a suction cannula or cup forceps. This is of particular importance when evaluating patients for transoral resection. In patients with T1 and small T2 base of tongue tumors deemed transorally resectable with robotic assistance, operative endoscopy and tumor mapping may be performed immediately before surgical extirpation with the use of frozen pathology if necessary.



• **Fig. 33.7** Computed tomography (CT) scan of neck with contrast for staging of the neck in patient with T1N2cM0, stage IVA squamous cell carcinoma of the base of tongue. Note bilateral cervical lymphadenopathy.

Rigid esophagoscopy and bronchoscopy may also be used at this stage to assess for co-synchronous primary tumors, although positron emission tomography–computed tomography (PET-CT) has replaced elective panendoscopy for oropharyngeal cancer in our practice. Suspicious lesions or those with fludeoxyglucose F 18 (FDG) uptake on PET-CT warrant further evaluation with esophagoscopy or bronchoscopy and biopsy.

Evaluation of the neck also begins with physical examination and comprehensive palpation of the regional lymphatics. Although computed imaging techniques are more sensitive in detecting clinical metastatic lymphadenopathy, palpation allows the oncologist to characterize involved lymph nodes. The degree of fixation to the underlying tissue and overlying skin is helpful in neck dissection planning.

Imaging

Computed Tomography and Magnetic Resonance Imaging

High-definition computed tomography (CT) scan or magnetic resonance imaging (MRI) is instrumental in the staging process for most head and neck cancers. These imaging techniques allow the oncologist to assess the extent of the primary tumor and, combined with proper physical examination, are necessary for the accurate staging of base of tongue carcinoma. For T1/T2 base of tongue SCC, these studies allow for three-dimensional tumor mapping and are useful in determining if the disease is resectable via a transoral robotic-assisted approach.

Assessment of the regional lymphatics via CT or MRI is also an important component in clinically staging the neck. Although either study may be used, contrast-enhanced CT is the preferred method for most cases at our cancer center because it is more cost-effective, faster, and better tolerated by most patients (Fig. 33.7). MRI does have a distinct advantage in select cases because it may better delineate cancer in the base of tongue from surrounding unaffected soft tissue and does not require the use of iodinated intravenous contrast in patients with renal failure or iodine allergies. The sensitivity and specificity are comparable in detecting cervical adenopathy, although there is a wide range in the published literature.[16] Both are superior to physical examination alone.

Positron Emission Tomography–Computed Tomography

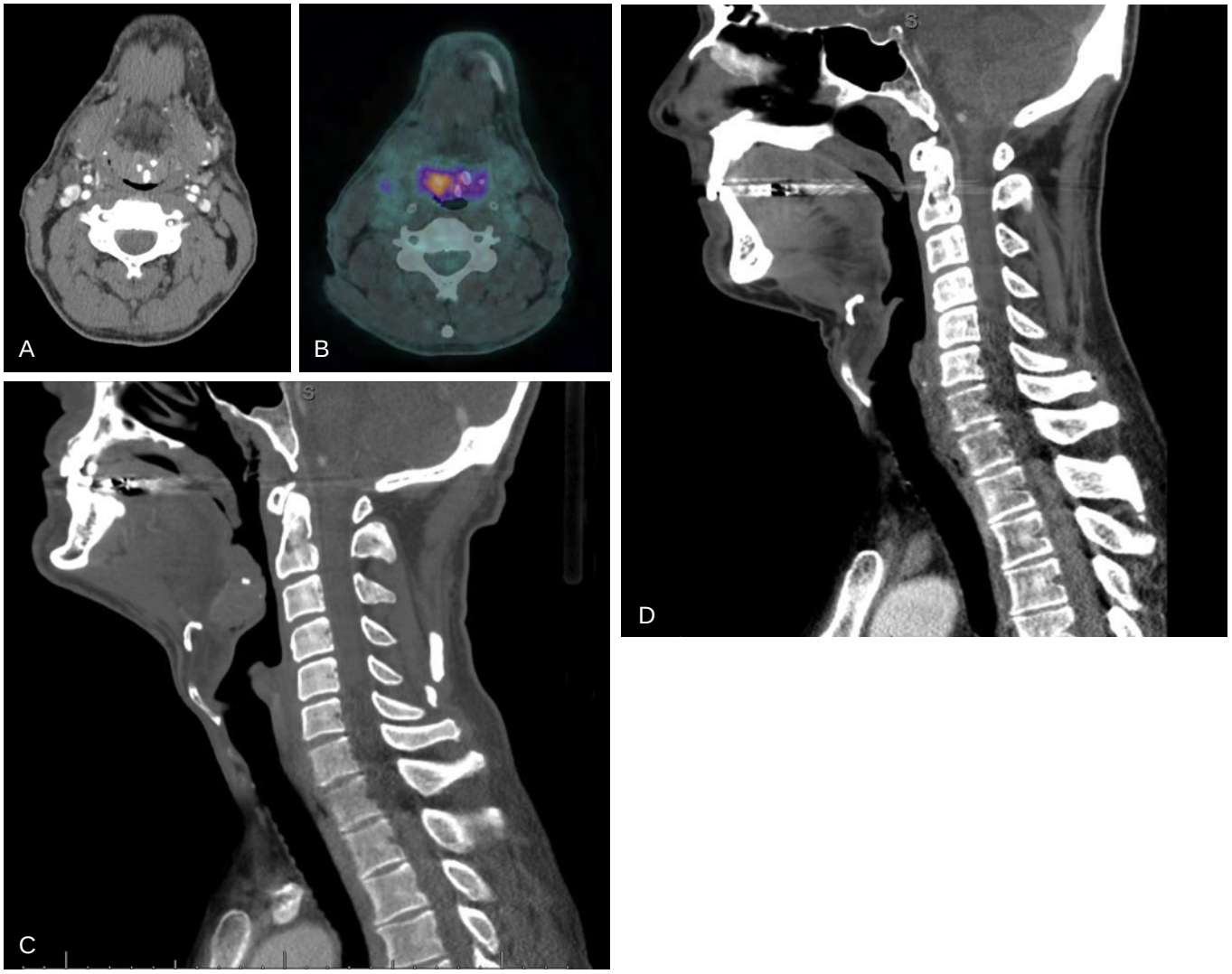
Positron emission tomography (PET) is useful in identifying metabolically active tissues in the work-up and staging for head and neck cancer. Combined with traditional CT scan, PET-CT offers the advantage of fusing anatomic tomographic images to correspond to areas of FDG uptake. Although perhaps best suited for advanced-stage disease and assessment of regional and distant metastasis, PET has an important role in patients with oropharyngeal cancer as an aid in the detection of the primary tumor or in cases of an unknown primary. The majority of patients with HPV-related T1/T2 base of tongue SCC will have a neck mass at presentation. A portion of these patients will have no obvious lesion on clinical examination or CT or MRI. Although fine-needle aspiration (FNA) of the metastatic lymph node can confirm a cytologic diagnosis and even HPV status, detecting the primary tumor may prove to be difficult. PET-CT may reveal a hypermetabolic focus in the oropharynx where no obvious or subtle structural abnormality exists. This allows for PET-directed biopsies instead of diagnostic tonsillectomy and multiple blind biopsies. Although lymphoid tissue in the tonsil and base of tongue, as well as pharyngeal muscle, may demonstrate some baseline FDG uptake, the keen eye of an oncologist can pick up subtle differences between left and right. Careful interpretation of PET-CT scan in the search for an occult primary tumor may guide therapy (Fig. 33.8).

False-positive PET imaging is a well-recognized phenomenon in association with acute inflammation or tonsillitis. However, false-negative findings can also occur, particularly within necrotic lymph nodes, which are commonly associated with HPV-related oropharyngeal cancer (Fig. 33.9).

HPV-related oropharyngeal cancer has somewhat less predictable patterns of distant metastases when compared with its HPV-negative counterpart.[17] Although the presence of distant metastases at initial presentation is uncommon, PET-CT remains valuable in detecting stage IVC disease, particularly in cases of extrapulmonary metastasis. In addition, this provides a baseline study for post-treatment comparison. We routinely advocate for combined PET with high-resolution iodinated contrast-enhanced CT for initial staging of patients with T1/T2 base of tongue cancer with any cervical metastasis (stage III and IV disease).

Ultrasound-guided Fine-Needle Aspiration

Although ultrasound alone has limited value in staging base of tongue carcinoma, ultrasound-guided FNA is a valuable tool in characterizing the cervical lymphatics. A 2007 meta-analysis of 17 articles and 25 data sets comparing various methods of lymph node metastasis detection demonstrated that

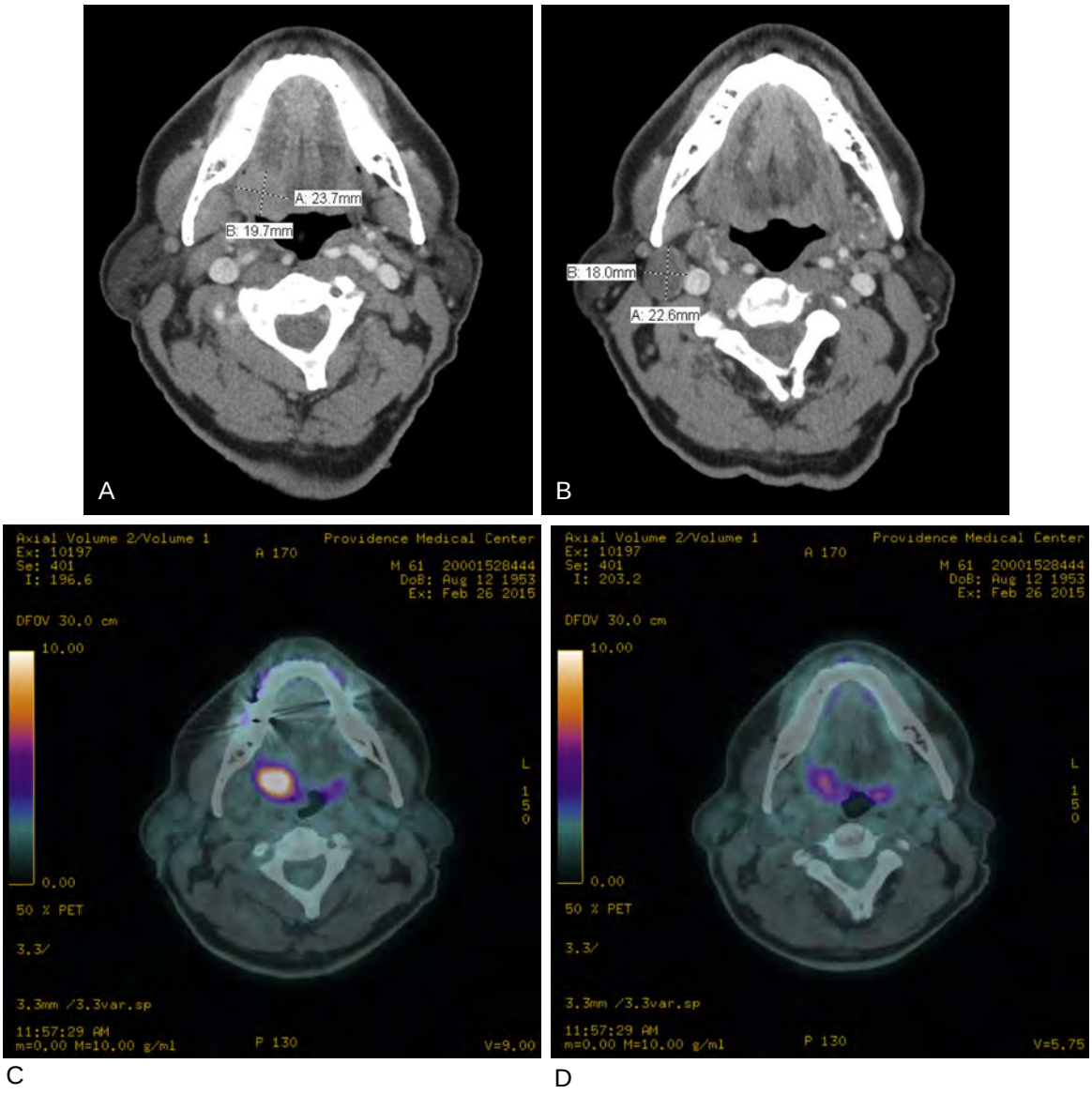


• **Fig. 33.8** Human papillomavirus–related base of tongue cancer in 48-year-old with T1N2bM0, stage IVA. Note that computed tomography (CT) evaluation and nasopharyngoscopy failed to detect primary lesion. However, on positron emission tomography–computed tomography (PET-CT) imaging, the small right base of tongue primary was noted to be embedded within hypertrophied lingual tonsillar tissue, and the patient was treated with transoral robotic surgery. **A,** Preoperative CT scan, axial view. **B,** Preoperative PET-CT scan, axial view. **C,** Preoperative CT scan, sagittal view. **D,** Postoperative CT scan, sagittal view.

ultrasound-guided FNA had the highest diagnostic odds ratio when compared with ultrasound alone, MRI, or CT scan. This meta-analysis also showed that specificity did not suffer with increased sensitivity when ultrasound-guided FNA was used to detect metastatic lymphadenopathy. Although the sensitivity of this modality had a wide range depending on the study (48–90%), specificity remained at 98–100%.[18] This requires an experienced and suitable sonographer or operator because careful sonographic evaluation of suspicious-appearing nodes as well as accurate needle aspiration are necessary in producing a representative sample. This technique is not practical in comprehensive clinical evaluation of the neck because the examinations are lengthy and somewhat invasive if procedures at multiple sites or multiple biopsies are to be performed. It is best suited to confirm a positive diagnosis of SCC in a patient with an obvious base of tongue mass to potentially obviate the need for surgical endoscopy and biopsy under anesthesia.

Pretreatment Patient Discussion

Once all the relevant diagnostic data have been obtained and staging studies have been completed, pretreatment consultation with the patient and his or her support system is appropriate. At our cancer center this consultation takes the form of a multidisciplinary forum, which requires the input of the surgeon, radiation oncologist, dental oncologist, medical oncologist, speech-language pathologist (SLP), dietitian, social worker, and nurse navigator. The National Comprehensive Cancer Network (NCCN) has guidelines and algorithms published annually based on the available data to help guide treatment for OSCC; these recommendations are strongly considered and generally followed. However, special circumstances such as poor performance status may necessitate deviation from NCCN guidelines on occasion. Clinical trials should be a priority in all patients with HNSCC, particularly those with advanced-stage disease.

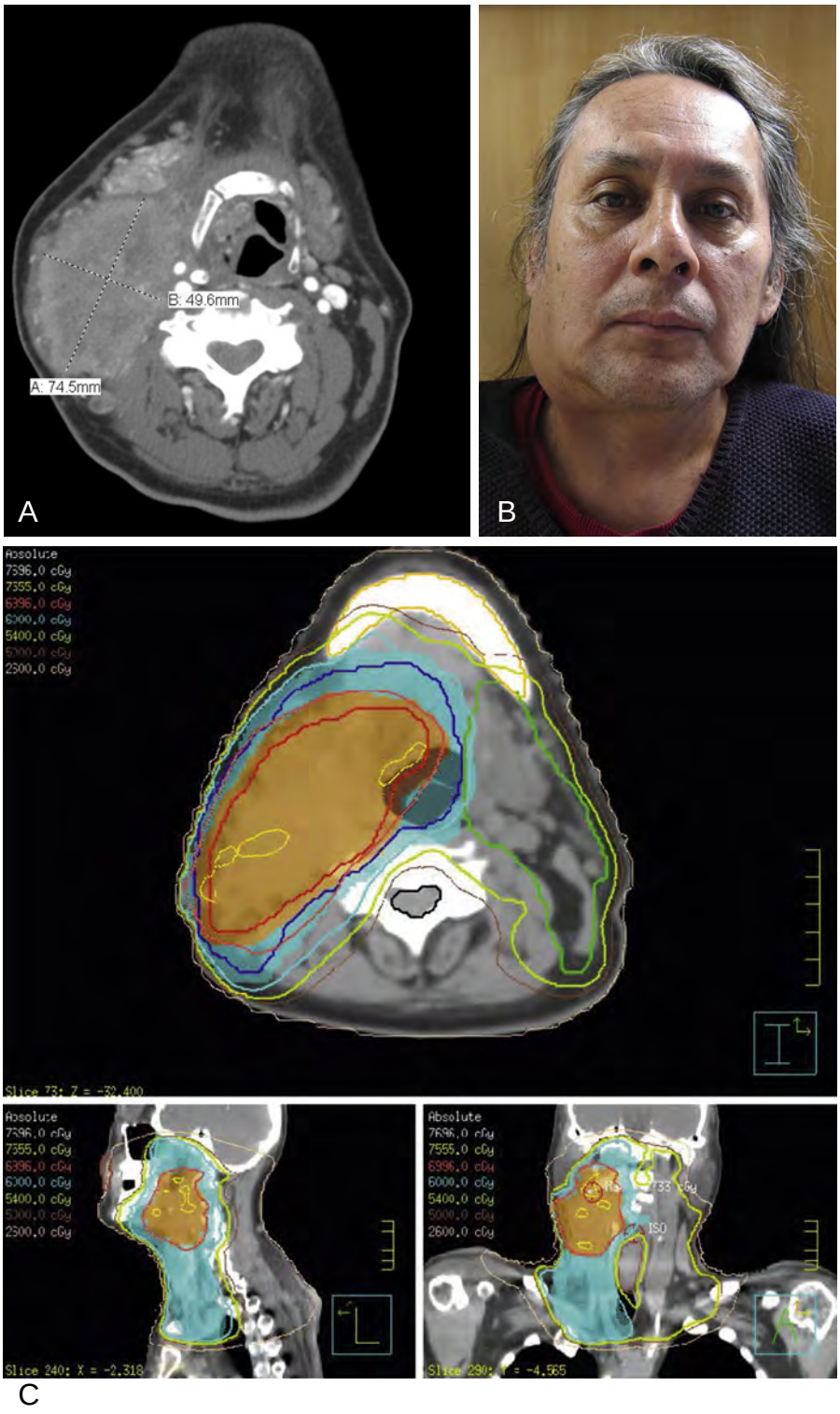


• **Fig. 33.9** T2N2 base of tongue squamous cell carcinoma (SCCA) in a 58-year-old man. Note false-negative finding on positron emission tomography–computed tomography (PET-CT) image of the metastatic lymph node demonstrated on contrasted computed tomography (CT) scan. **A,** CT scan of neck with contrast demonstrating primary lesion in base of tongue, axial view. **B,** CT scan of neck with contrast demonstrating metastatic lymph node in level II of the right neck, axial view. **C,** PET-CT, axial image. **D,** PET-CT, axial image.

Principles of Management—Surgery Versus Primary Radiotherapy or Chemoradiotherapy

Current NCCN guidelines advocate single-modality therapy for T1/T2 base of tongue squamous cell carcinoma (SCCA) without evidence of cervical metastases. This may include definitive radiation or surgical resection with or without neck dissection. At our institution, the majority of T1/T2 base of tongue carcinomas, over 90% of which are HPV positive, are treated primarily with TORS followed by risk-adapted adjuvant therapy. Patients also receive simultaneous, elective, selective level II–IV neck dissection at the time of TORS. Patients with high-risk features, such as bulky neck disease (N2c or N3) or obvious extracapsular nodal extension, are usually treated with definitive chemoradiation (Fig. 33.10).

Operative patients are currently stratified into risk groups based on various histopathologic features related to margin status, cervical metastasis, extracapsular extension, perineural invasion, or lymphovascular space invasion (Table 33.2). Low-risk patients have negative resection margins and N0–N1 disease without adverse histopathologic features and are observed after surgery; intermediate-risk patients have negative resection margins and more than one metastatic lymph node, perineural invasion, or lymphovascular invasion and are treated with adjuvant RT to 60 Gy; high-risk patients are those with positive resection margins or extracapsular extension and are treated with adjuvant radiation to 66 Gy with concurrent cisplatin. Patients



• **Fig. 33.10** A 59-year-old man with a diagnosis of a stage IVA T1N3M0 right base of tongue squamous cell carcinoma with bulky adenopathy treated with induction chemotherapy followed by concurrent chemoradiotherapy with cetuximab and radiation to 7000 cGy. **A,** Pretreatment CT scan of neck. **B,** Frontal view of patient. **C,** Intensity-modulated radiotherapy treatment fields.

with multiple cervical lymph node metastases or level IV or V adenopathy are also considered for adjuvant chemoradiotherapy because they may have a higher risk of treatment failure.[19]

Since the 1990s, the mainstay of treatment for T1/T2 base of tongue SCC has been definitive RT or definitive concurrent chemoradiotherapy. Compared with traditional open surgical approaches that employ mandibulotomy or transcervical pharyngotomy, definitive radiation was better tolerated with lower short-term morbidity, but with similar oncologic control. The paradigm shift toward "organ preservation" with non-surgical primary management of early-stage oropharyngeal cancer resulted in part from results of the Veterans Administration laryngeal cancer

TABLE 33.2 Postoperative Risk Stratification for Human Papillomavirus–Positive Oropharynx Squamous Cell Carcinoma

	Low Risk	Intermediate Risk	High Risk
T	T1/T2	T3/T4	Any
N	N0/N1	N2a/b/c	N3 or >4 nodes
Margins	Negative	Negative/close	Positive
ECE	Negative	Negative or micro <1 mm	Positive
PNI	Negative	Positive	Any
LVI	Negative	Positive	Any

ECE, extracapsular extension; *PNI,* perineural invasion; *LVI,* lymphovascular invasion.

trial, RTOG 91-11. However, since U.S. Food and Drug Administration (FDA) approval of TORS in 2009 for surgical treatment of oropharyngeal cancer, an increasing number of patients have been treated with a transoral surgical approach in an effort to tailor and de-escalate therapy where possible. There are now 2- to 5-year follow-up data indicating that locoregional control with TORS and risk-adapted adjuvant therapy is at least not inferior to control with definitive radiation or chemoradiation for the treatment of HPV-associated T1/T2 base of tongue SCC.[20–23] Although survival outcomes are excellent with either modality, the major benefit of surgery in this setting is that it allows the treatment to be tailored based on histopathologic interrogation and risk stratification, thereby eliminating the need for RT or chemotherapy in some patients and potentially resulting in a lower incidence of dysphagia and long-term gastrostomy tube dependence as well as better quality of life indices.[21,24] Furthermore, early data regarding the use of the da Vinci surgical robot (da Vinci Surgical System, Intuitive Surgical, Sunnyvale, California) for oropharyngeal cancer resections demonstrate safety with low morbidity and mortality, which continue to improve as surgeon experience and training progress.[20,25–28]

Since the initially published data demonstrating improved OS and favorable treatment response of HPV-positive oropharyngeal cancer compared with HPV-negative cohorts, oncologists have expressed interest in de-escalating therapy to reduce short- and long-term morbidity associated with treatment. The use of TORS for early-stage OSCC has almost certainly driven this enthusiasm, as early data suggested improved quality of life when compared with definitive non-surgical therapy. Several clinical trials—both surgical and non-surgical—are currently accruing patients in an attempt to answer that question. Currently, the treatment for HPV-positive and HPV-negative T1/T2 base of tongue SCC is identical outside of a clinical trial setting.

Radiation and Chemotherapy

Before the advent of TORS, in the last two decades, RT was the backbone of treatment for most oropharyngeal cancer. There has not been a randomized prospective clinical trial comparing surgery versus radiation for base of tongue cancer. A cooperative group trial aiming to compare RT and transoral resection of HPV-negative oropharyngeal cancer, RTOG 1221, was terminated owing to poor accrual. To help compare the two outcomes, Parsons and colleagues published a 30-year retrospective review of 51 studies reporting on 6400 patients with OSCC treated with surgery with or without RT, or primary radiation with or without neck dissection.[29] The majority of these patients underwent open surgical resection with mandibulotomy and radical neck dissection followed by possible adjuvant RT, or conventional external beam RT with possible salvage radical neck dissection. Intensity-modulated radiotherapy (IMRT), TORS, and advanced microsurgical reconstruction were not available during the three decades before this review. The results for patients with SCC of the base of tongue who underwent surgery with or without RT, and RT with or without neck dissection, respectively, were demonstrated to be nearly equal with regard to local control (79% vs. 76%; $P = 0.087$); locoregional control (60% vs. 69%; $P = .009$); 5-year survival (49% vs. 52%; $P = .2$); and 5-year cause-specific survival (62% vs. 63%; $P = .4$). However, there were significant differences between the groups with respect to severe complications (32% vs. 3.8%; $P = .001$) and fatal complications (3.5% vs. 0.4%; $P = .001$), favoring the cohort that underwent RT with or without neck dissection. The authors concluded that non-operative therapy was preferable to operative therapy for oropharyngeal cancers, regardless of stage, because it was associated with significantly lower morbidity and mortality.

RT for early-stage base of tongue cancer may be used as single-modality therapy in the absence of clinically apparent cervical metastases and is routinely used in the adjuvant setting after surgical resection of an intermediate- to high-risk base of tongue carcinoma.

Indications for RT in the definitive setting include patients who are not medically fit for surgery and cases in which surgery may result in trimodality therapy (predicted difficulty obtaining clear margins or radiographs suspicious for extranodal tumor extension).

Principles of Radiotherapy

IMRT is now the standard of care for treatment of most head and neck malignancies, including the base of tongue. Advanced imaging techniques, cone-beam CT, and computed localization allow for precise delivery of radiation with the ability to minimize collateral tissue damage. Standard fractionation is used in the majority of patients, with once-daily treatments, 5 days per week, with treatment breaks as needed because of acute toxicity. Altered fractionation has been studied prospectively in advanced head and neck cancer and T2N0 base of tongue cancer. RTOG trial 9003 randomized patients with stage II–IV head and neck cancer to a control standard fractionation arm and three arms of altered fraction radiation—hyperfractionation, accelerated fractionation with continuous treatment, and accelerated fractionation with split. Final results of this trial published in 2014 demonstrated that patients undergoing hyperfractionation (81.6 Gy/68 twice-daily fractions) had improved survival and locoregional control when compared with standard fractionation (70 Gy/35 daily fractions) with a hazard ratio of 0.79. This translates to a reduction in locoregional failure rate by 19%.[30] Nevertheless, altered fraction therapy is seldom used in early-stage oropharyngeal cancer because locoregional control is excellent (88–98%) with standard fractionated IMRT alone.[31,32]

In a typical IMRT plan for base of tongue cancer, known tumors, including the primary and metastatic adenopathy, are treated to 70 Gy. The remainder of the node-positive neck is treated at 59.4–63 Gy; a clinically negative neck is treated prophylactically at 54–56 Gy. This is done in 33–35 fractions depending on final dosage.

Indications for RT in the adjuvant postoperative setting include advanced primary lesions (pT3/pT4), N2 or greater nodal disease, nodal disease in levels IV or V, perineural invasion, or lymphovascular invasion. The primary and involved neck are treated to 60 Gy. If there is uninvolved neck, this is treated to 54–56 Gy. Positive margins or extranodal tumor extension are high-risk adverse pathologic features and are treated to 66 Gy. Furthermore, these patients benefit from the addition of platinum-based chemotherapy concurrently with radiation. The results of two large cooperative group trials, European Organisation for Research and Treatment of Cancer (EORTC) trial 22931 and RTOG trial 9501, published in 2004, comparing postoperative radiation and postoperative concurrent chemoradiation for advanced head and neck cancer demonstrated a survival benefit in the concurrent chemoradiation arm.[33,34] A 2005 post hoc analysis of the paired studies teased out that a select group of patients, namely those with ENE or positive surgical margins, benefitted from the addition of platinum-based chemotherapy, with an absolute survival benefit of 8%.[35] This led to the NCCN recommendation for addition of cisplatin to radiation in the adjuvant setting for those particular high-risk features.

Surgery

There is a wide variety of surgical approaches to the base of tongue, but they can be broken down into two distinct classifications—open versus transoral. Although many T1/T2 cancers of the base of tongue may be treated via transoral approaches, such as TORS or transoral laser microsurgery (TLM), some tumors still require wide, open access via more traditional approaches. These include access mandibulotomy, transcervical lateral pharyngotomy, or transcervical suprahyoid pharyngotomy. The transcervical lingual degloving or "pull-through" approach is generally reserved for larger tumors requiring total or subtotal glossectomy.

Management of the airway is critical for all operations involving the upper aerodigestive tract, and surgery of the base of tongue is no exception. The tongue, rich in vascularity and lymphatics, is prone to significant edema after instrumentation. Furthermore, the use of transoral retractors such as the Feyh-Kastenbauer, McIvor, Crowe-Davis, or other mouth gags for extended periods of time may result in significant venous congestion of the tongue. For patients undergoing transoral resection for base of tongue cancer, endotracheal intubation is preferred. It is imperative to communicate with the anesthesia team before induction and formulate an intubation plan. Although intubation may be accomplished via the nasal or oral route, our institutional preference is oral intubation with a reinforced or armored endotracheal tube. This is secured to the buccal mucosa opposite the side of the tumor by using heavy silk horizontal mattress sutures. In general, T1/T2 tumors of the base of tongue are not obstructive, but if clinic fiber-optic examination demonstrated airway compromise, awake fiber-optic intubation may be indicated. After base of tongue resection, clinical judgment dictates whether or not it is preferable to leave the patient intubated and transfer him or her to the intensive care unit. In our experience, the majority of patients can be safely extubated after TORS. However, if tongue edema and venous congestion are substantial, we will leave the patient intubated overnight. Extubation on postoperative day 1 is routinely accomplished after the patient passes a cuff leak test and spontaneous breathing trial.

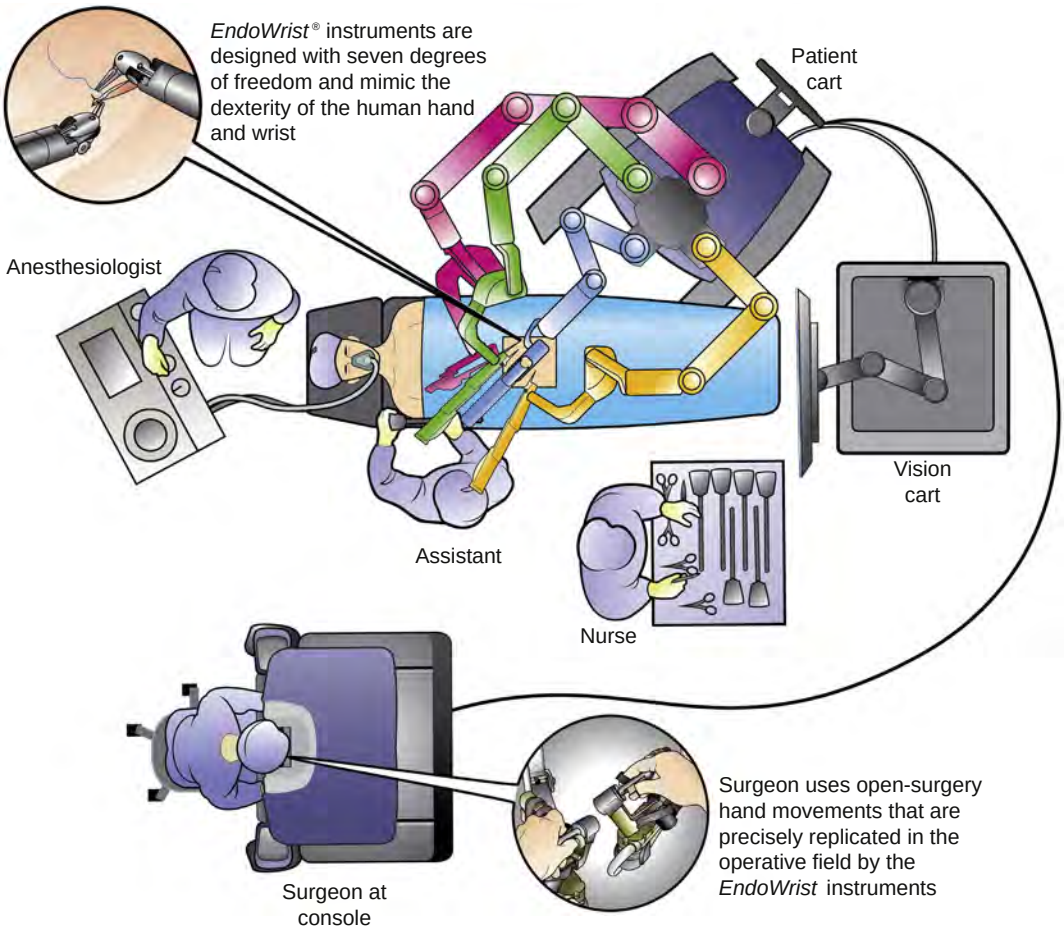
For patients undergoing open surgery for base of tongue cancer, tracheostomy is the preferred airway. Whether this is preceded by endotracheal intubation or performed as an awake tracheostomy is dictated by the amount of airway compromise from the tumor. Nonobstructive base of tongue cancers are generally amenable to oral endotracheal intubation before tracheotomy. Almost all patients undergoing open base of tongue resection require flap reconstruction of the defects, particularly if they have been previously irradiated or have undergone transcervical pharyngotomy. This necessitates tracheotomy for perioperative airway edema, but most patients can be decannulated before discharge from the hospital. Patients undergoing total glossectomy and flap reconstruction may require long-term or permanent tracheostomy or laryngectomy, in the case of chronic aspiration.

Transoral Robotic Surgery

Transoral robotic-assisted base of tongue resection has become the preferred minimally invasive method for the surgical treatment of T1/T2 tonsil cancers at high-volume institutions. Compared with traditional transoral techniques, such as TLM, TORS offers several potential advantages including high-resolution, three-dimensional operative view, improved operative precision, movement scaling, and dynamic multiplanar and true 360-degree rotational motion.[36,37] Although this technique has an associated learning curve, complication rates are inversely related to surgeon experience. A 2013 survey of 45 U.S. TORS surgeons reported a 0.3% mortality rate, all related to postoperative hemorrhage, with a statistically significant decrease in complication rate with surgeon operative volume greater than 50 cases.[38]

After securing the airway as outlined earlier, room setup, anesthesia collaboration, and robotic docking are critical to the success of a TORS operation[39] (Fig. 33.11). The table is turned 180 degrees away from the anesthesiologist, arms are tucked, and head is positioned on a Mayfield horseshoe headrest to allow for ideal neck extension and linear access to the oropharynx. The upper teeth are protected with a soft tooth guard, and an oropharyngeal retractor is placed under headlamp visualization. We prefer the Feyh-Kastenbauer-Weinstein-O'Malley (FK-WO) retractor because it is maximally adjustable (Fig. 33.12). The ability to control the pitch and depth of the retractor is particularly helpful in accessing the base of tongue. A variety of tongue blades for the FK-WO are available.

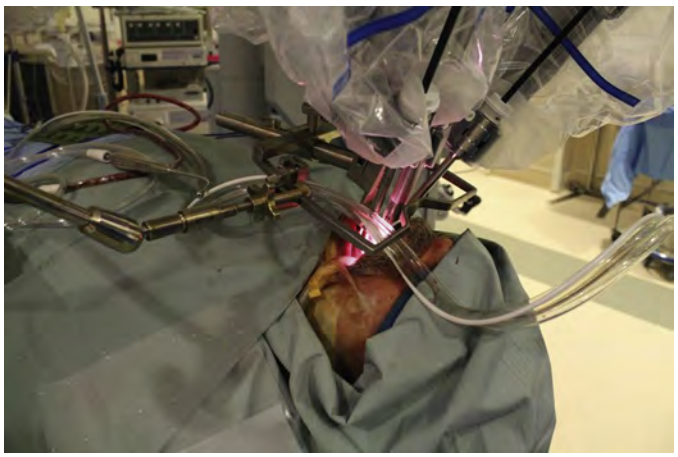
Once the FK-WO retractor is adequately positioned, the retractor is placed into suspension using StrongArm devices (MediFlex, Islandia, NY) latched to the operative table (Fig. 33.13). The da Vinci Si robot (Intuitive Surgical, Sunnyvale, CA) is then docked to the patient at a 30- to 45-degree angle. We prefer a 30-degree endoscope through the central cannula and 5-mm EndoWrist (Intuitive Surgical, Sunnyvale, Calif.) monopolar cautery and Maryland dissectors through the



• **Fig. 33.11** Transoral robotic surgery room setup. (From Park ES, Shum JW, Tuan GB, et al. Robotic surgery: a new approach to tumors of the tongue base, oropharynx, and hypopharynx. *Oral Maxillofac Surg Clin North Am*. 2013 Feb;25[1]:49–59.)



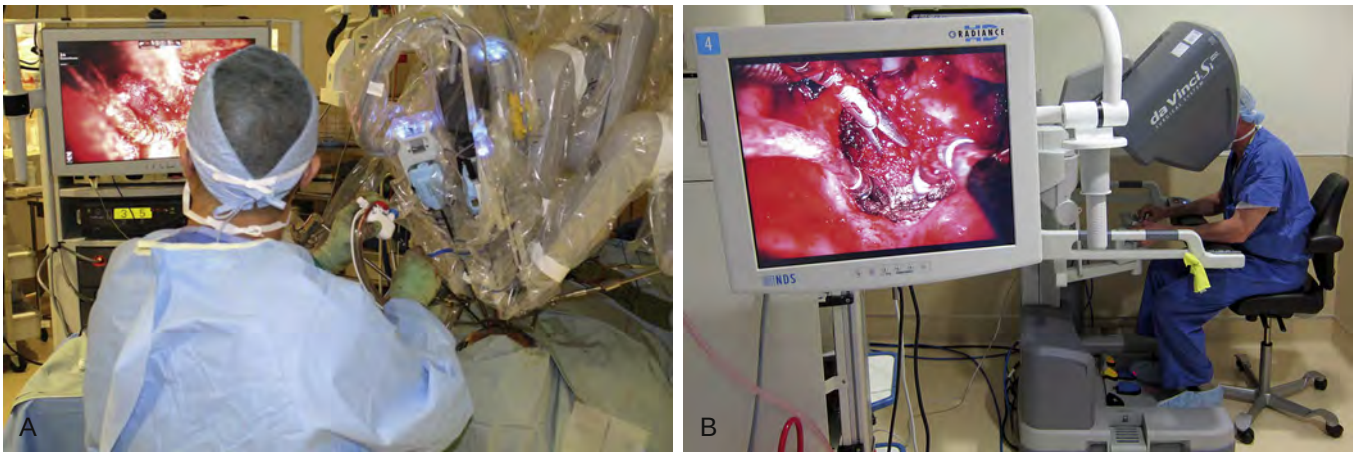
• **Fig. 33.12** Instrumentation for transoral robotic surgery.



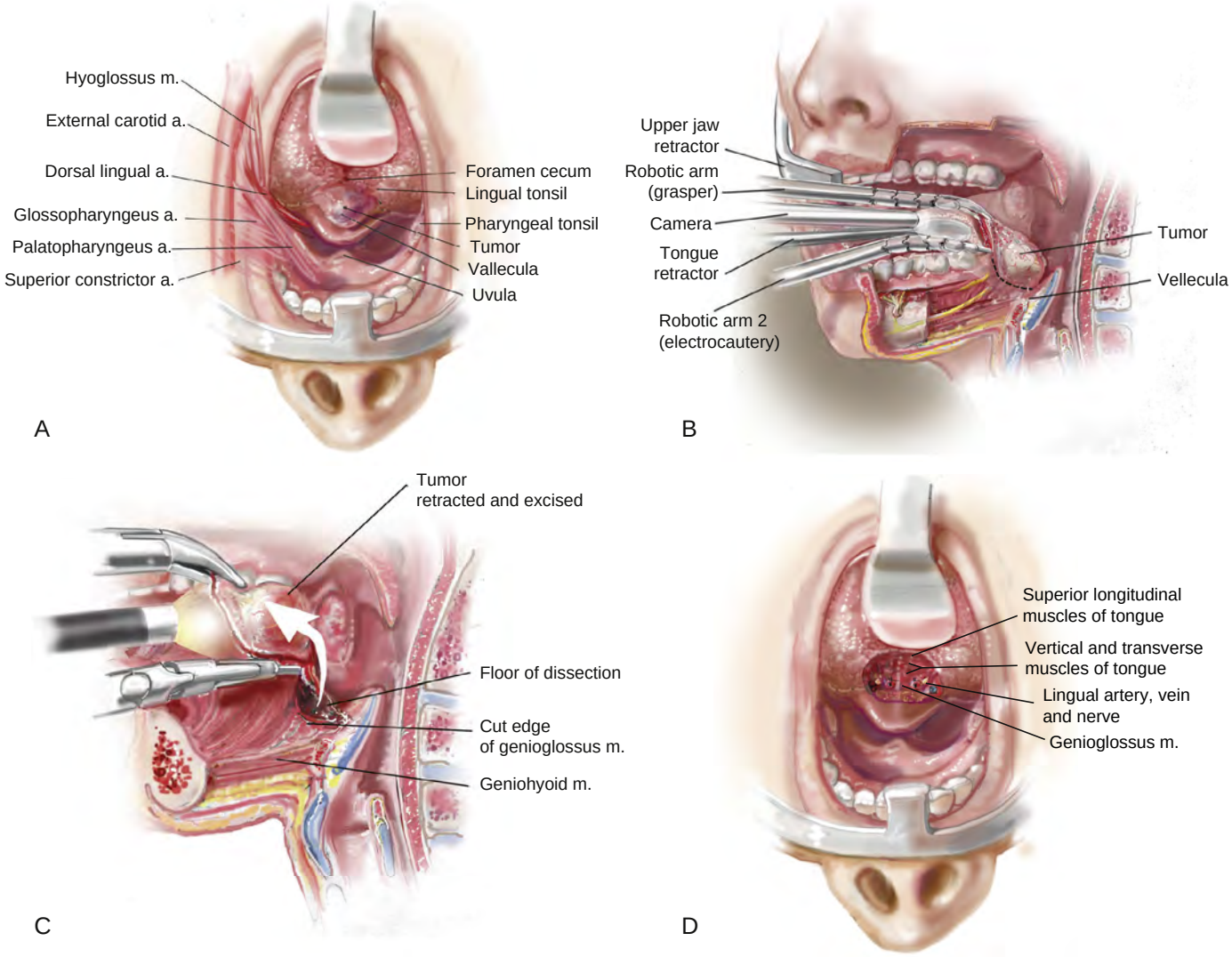
• **Fig. 33.13** Robotic arm setup for transoral robotic-assisted oropharyngectomy.

working cannulas. Care should be taken to position the distal ends of the cannulas just outside the oral introitus with sufficient inter-instrument width to avoid collisions during the operation. A bedside assistant is armed with two tonsillar suction catheters to evacuate smoke, blood, and saliva as well as to retract soft tissue for the console surgeon (Fig. 33.14).

Because early-stage base of tongue cancers may be small and difficult to visualize, it is oncologically favorable to resect the hemi–base of tongue as an entire unit to ensure en bloc resection. The operation begins with a horizontal incision, using monopolar cautery at the level of the circumvallate papilla—this should be positioned just posterior to the edge of the tongue blade (Fig. 33.15).



• **Fig. 33.14** View stations for transoral robotic surgery. **A,** Assistant's view.; **B,** Operating surgeon at the robotic console.



• **Fig. 33.15** Surgical view for transoral robotic-assisted base of tongue resection and oropharyngectomy. **A,** Intraoperative view. **B,** Sagittal view. **C,** Tumor resection. **D,** Postoperative view.

Dissection is carried medially to the midline and laterally to the glossotonsillar sulcus. The cut edge is grasped with Maryland dissectors, and the plane of dissection is sharply deepened in a broad front by using a deliberate sweeping motion to open the optical space between the specimen and tongue, as well as to cauterize the highly vascular muscle bed. As dissection proceeds posteriorly, the specimen is grasped and retracted posteriorly and superiorly to allow for adequate visualization. Dissection is carried posteriorly to the level of the vallecula. The armored endotracheal tube is an excellent guide to approximate depth and anteroposterior position as it passes just behind the epiglottis. Laterally, the lingual artery or its branches may be encountered; the application of hemoclips by the bedside assistant may be required for control. A 5-mm endoscopic clip applier is preferable in this situation because it allows for 360-degree motility. The specimen is then cleaved off through the mucosa of the vallecula and carefully delivered to the bedside assistant while correct orientation is maintained. At our institution, the entire specimen is oriented and sent to the pathology department fresh for specimen-driven frozen-section margin analysis. If close or positive margins are identified, these areas are re-resected to negative margins.

Concomitant elective or therapeutic neck dissection has been shown to be safe, with less than a 5% rate of persistent pharyngocutaneous fistula, and is our preferred method for surgical treatment.[25,27,40] Our institutional preference is to perform TORS and neck dissection during the same operation, in that order; however, for large tumors involving the glossotonsillar sulcus, neck dissection can be performed immediately before TORS resection in order to ligate the lingual artery or gain proximal carotid control. Our experience with T1/T2 tumors is that this is not usually required and that operative time may be reduced when the primary is resected first because the neck dissection can commence while one waits for margin status from the pathology department.

The extent of neck dissection is not universally agreed on, but most U.S. centers have gone to use of a level II–IV selective neck dissection, which has been shown to be safe and efficacious and to minimize morbidity (Fig. 33.16). Although we initially performed comprehensive neck dissection, we have evolved to use of a small-incision, level II–IV selective neck dissection unless there is clinical or radiographic evidence of level I or V lymph node metastasis (Fig. 33.17).

Salvage Surgery

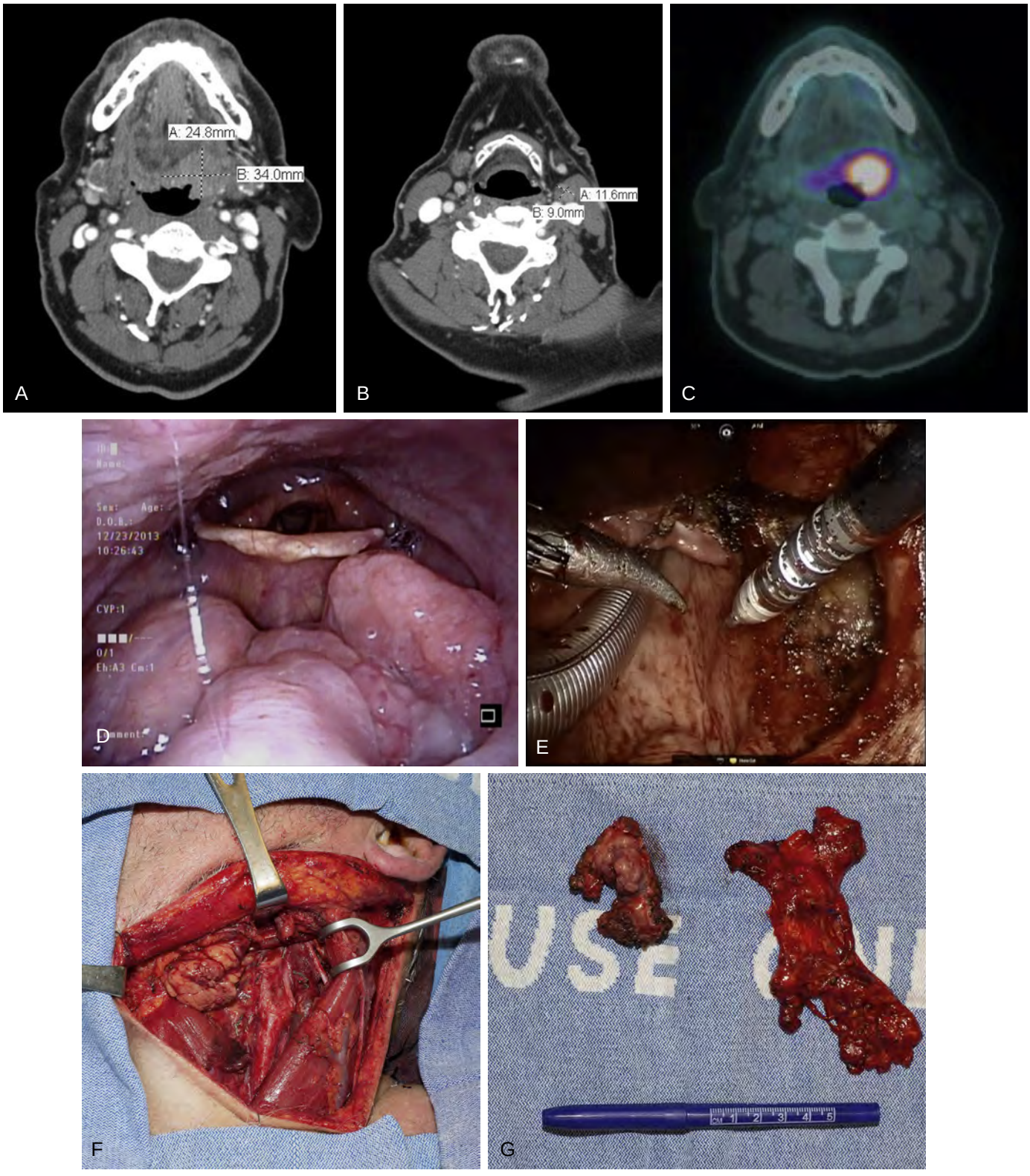
Before the era of non-surgical organ-preserving therapy, early-stage base of tongue carcinomas were routinely treated with open surgical approaches. Although locoregional control for T1/T2 oropharyngeal carcinoma is excellent with this approach, it does not come without morbidity. The use of access mandibulotomy or transcervical pharyngotomy is associated with pharyngeal leaks or fistulas, mandibular non-union, osteonecrosis, and facial incisions or scars, and these procedures more likely to require vascularized flap reconstruction when compared with transoral approaches, although many retrospective reviews have suggested that these approaches are well tolerated and accepted by patients.[41–43] These techniques are now primarily reserved for advanced-stage oropharyngeal cancer in which organ-sparing therapy is contraindicated or in the salvage setting for treatment failure. As stated previously, it is our practice to employ transoral minimally invasive approaches for early-stage base of tongue cancer for patients who may require only single-modality therapy or surgery with adjuvant RT alone. The role for open surgery for T1/T2 base of tongue carcinomas is limited to patients in whom non-surgical treatment has failed or patients with absolute contraindications to RT or chemoradiotherapy. Both transcervical and transmandibular open approaches to the base of tongue allow for wide access, en bloc resection, and ability to functionally reconstruct the pharynx with free tissue transfer; however, decreased rates of postoperative fistula, temporomandibular joint dysfunction, and esthetic morbidity have been reported with transcervical approaches.[44,45]

As described earlier in this manuscript, tracheostomy is the airway of choice when transcervical or transmandibular surgery is combined with free flap reconstruction. Unlike TORS approaches, open approaches routinely require the creation of a sizable pharyngo-cervical communication. Historically, these were managed with regional flaps, such as the pectoralis major myocutaneous flap; however, free flap reconstruction provides excellent results with regard to functional restoration of the base of tongue, prevention of aspiration, and separation of the pharyngeal and cervical compartments.

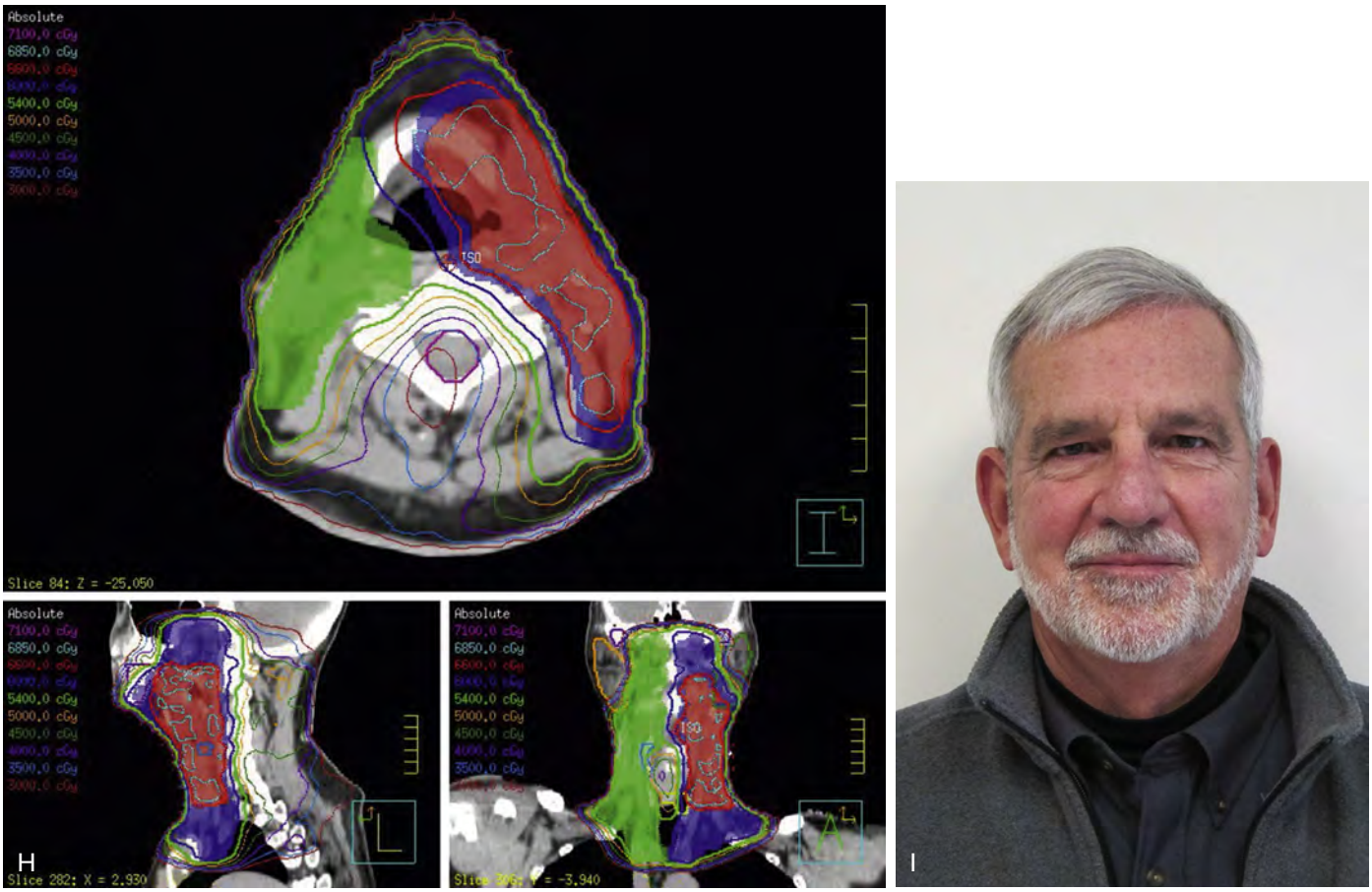
Transcervical Pharyngotomy

The majority of patients undergoing this operation will require elective or therapeutic neck dissection, so it is preferable to complete this immediately before accessing the pharynx. This allows for proximal vascular control and a surgical field that is clear of lymph node–bearing fibro-adipose tissue. The suprahyoid musculature is sharply separated from the hyoid bone, working from the midline out laterally. Completion of the neck dissection also allows for prior identification of the hypoglossal nerves, which may be prone to injury adjacent to the greater cornu of the hyoid bone. Once the submucosal surface of the pharynx is visualized from the cervical approach, a long toed-in Langenbeck retractor is placed into the vallecular space transorally. A suprahyoid pharyngotomy is created with cautery against the tip of the retractor, and the oropharynx is entered. Deaver or Sewell curved retractors are placed superiorly and inferiorly through the pharyngotomy to identify the base of tongue tumor (Fig. 33.18). A central segment of hyoid bone can be excised or divided for improved access. In addition, separation of the inferior constrictor from the thyroid cartilage and extension of the pharyngotomy laterally toward the piriform recess may be required to enter the pharynx laterally for wider exposure[46] (Fig. 33.17B). This is particularly helpful in larger tumors with hypopharyngeal involvement. At this point, the specimen can be carefully grasped and resected with sharp dissection using monopolar cautery. The lingual artery is commonly encountered and should be ligated.

Patients with larger T2 tumors or who have a previous history of radiation should undergo reconstruction with vascularized tissue, preferably a radial forearm free flap, to provide an adequate tongue mound to reduce aspiration and to close the pharyngocervical communication with reliable tissue. Smaller tumors may be left to heal by secondary intention, but impeccable closure of the pharyngotomy with local tissue rearrangement is critical in reducing the rate of salivary leaks and fistulas. This



• **Fig. 33.16** A 68-year-old male with pT2N2bM0, stage IVA, human papillomavirus (HPV)–positive squamous cell carcinoma of the left base of tongue treated with transoral robotic surgery and risk-adapted adjuvant radiation therapy. **A,** Pretreatment computed tomography (CT) scan of neck with contrast demonstrating base of tongue tumor, axial view. **B,** Pretreatment CT scan of neck with contrast demonstrating metastatic lymph node, axial view. **C,** Pretreatment positron emission tomography–computed tomography (PET-CT) scan. Carcinoma was initially staged as cT2N1M0, stage III. **D,** Nasopharyngoscopy revealed left base of tongue tumor. **E,** Intraoperative view after transoral robotic-assisted oropharyngectomy. **F,** Intraoperative view of simultaneous selective neck dissection, level II–IV, preserving submandibular gland, spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle. **G,** Resection specimens, which generated negative resection margins and three positive lymph nodes, resulting in upstaging to pT2N2bM0, stage IVA.



• **Fig. 33.16, cont'd** **H,** Adjuvant radiation dosimetry and treatment fields. **I,** Appearance of patient 1 year after completion of treatment.

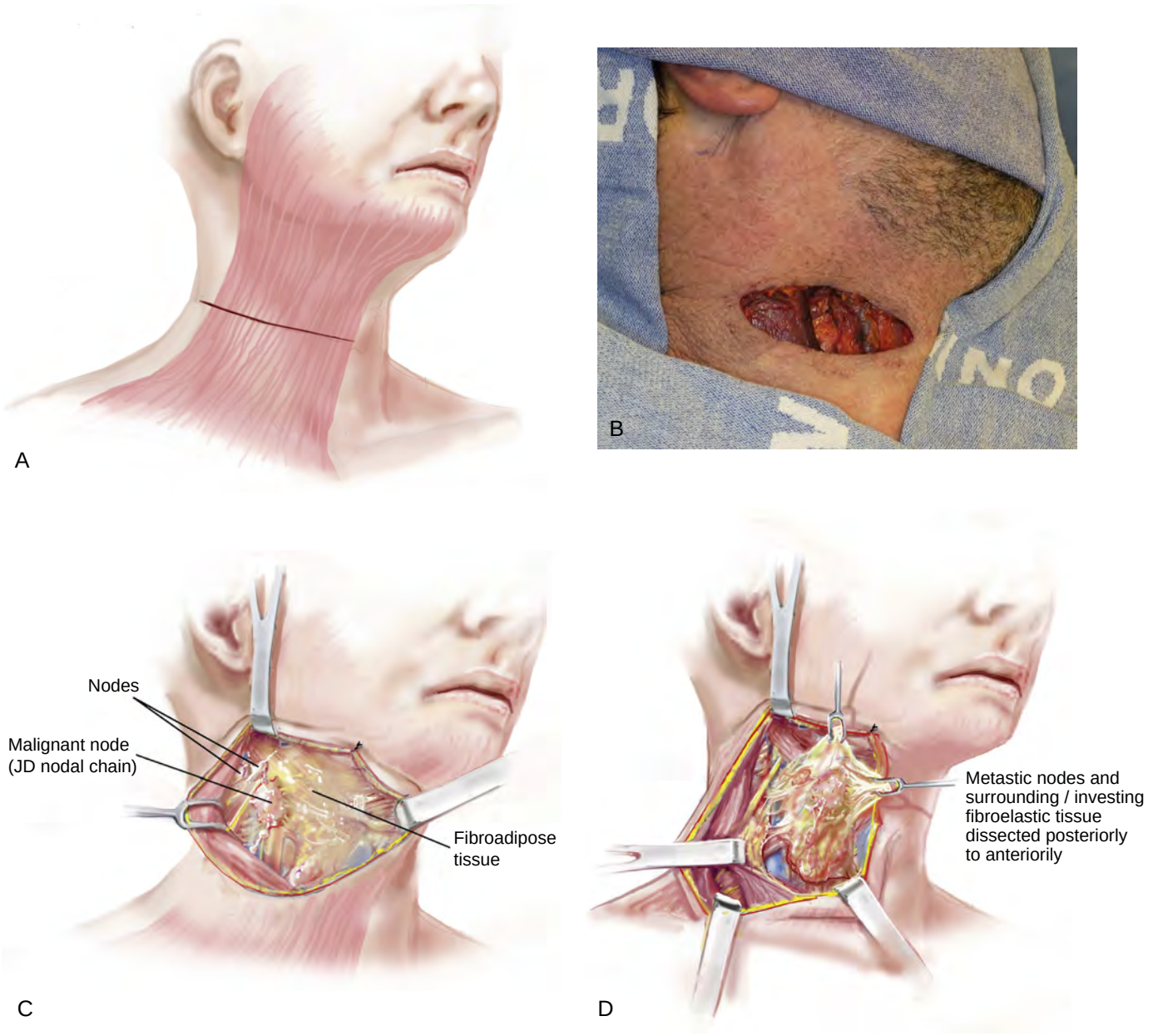
is accomplished by closing the pharyngeal mucosa with heavy slow resorbing sutures in large bites around the base of tongue and circumferentially around the hyoid. The lateral portion of the pharyngotomy in the hypopharynx should be closed with inverting mattress sutures in a Connell fashion. The suprahyoid and infrahyoid musculature can be raised as pedicled flaps to bolster to suture lines as a second layer of closure.

Transmandibular Approach

Similar to the transcervical approach, the transmandibular approach is best accomplished after completion of the regional lymphadenectomy (Fig. 33.19). The difference is in incision design, because this procedure will require a cutaneous lip-split. A fine-tipped marking pen is used to design a lower-lip midline split with a 90-degree stair-step at the vermillion border to help reorient the lip on closure. This is carried vertically to the labiomental crease and then followed in a wide semicircle around the chin pad back to the midline and the cervicomandibular junction. We prefer a modified Z-plasty design on the anterior neck to break up the scar and reduce the length of incision against lines of resting tension. This is then carried horizontally through a natural neck crease posteriorly past the border of the sternocleidomastoid.

During completion of the skin incision, the sharp angles designed in the lip and anterior neck can be accomplished by "stabbing" a No. 15 blade through each corner, with the back side of the blade creating the angle. This permits precise incisions, which will be important for esthetic closure. Skin flaps are elevated in a subplatysmal plane in the neck and full thickness overlying the chin. At this point, a mandibular vestibular mucosal incision should be designed based on the location of the planned mandibulotomy. Preoperative orthopantomogram is useful in selecting the osteotomy location. Midline or paramedian osteotomy is dictated by interdental spacing; care must be taken to avoid injury to dental roots. The gingival incision should be placed two teeth away from the planned osteotomy to avoid a suture line over the bone closure. This is carried through the vestibule on the ipsilateral side of the tumor, leaving an adequate cuff of unattached gingiva to close to. Subperiosteal dissection is completed on the buccal surface of the mandible to allow for plate adaptation. It is not required to develop a large cheek flap because this does always not improve access to the tongue base and unnecessarily compromises the periosteal blood supply to the mandible.

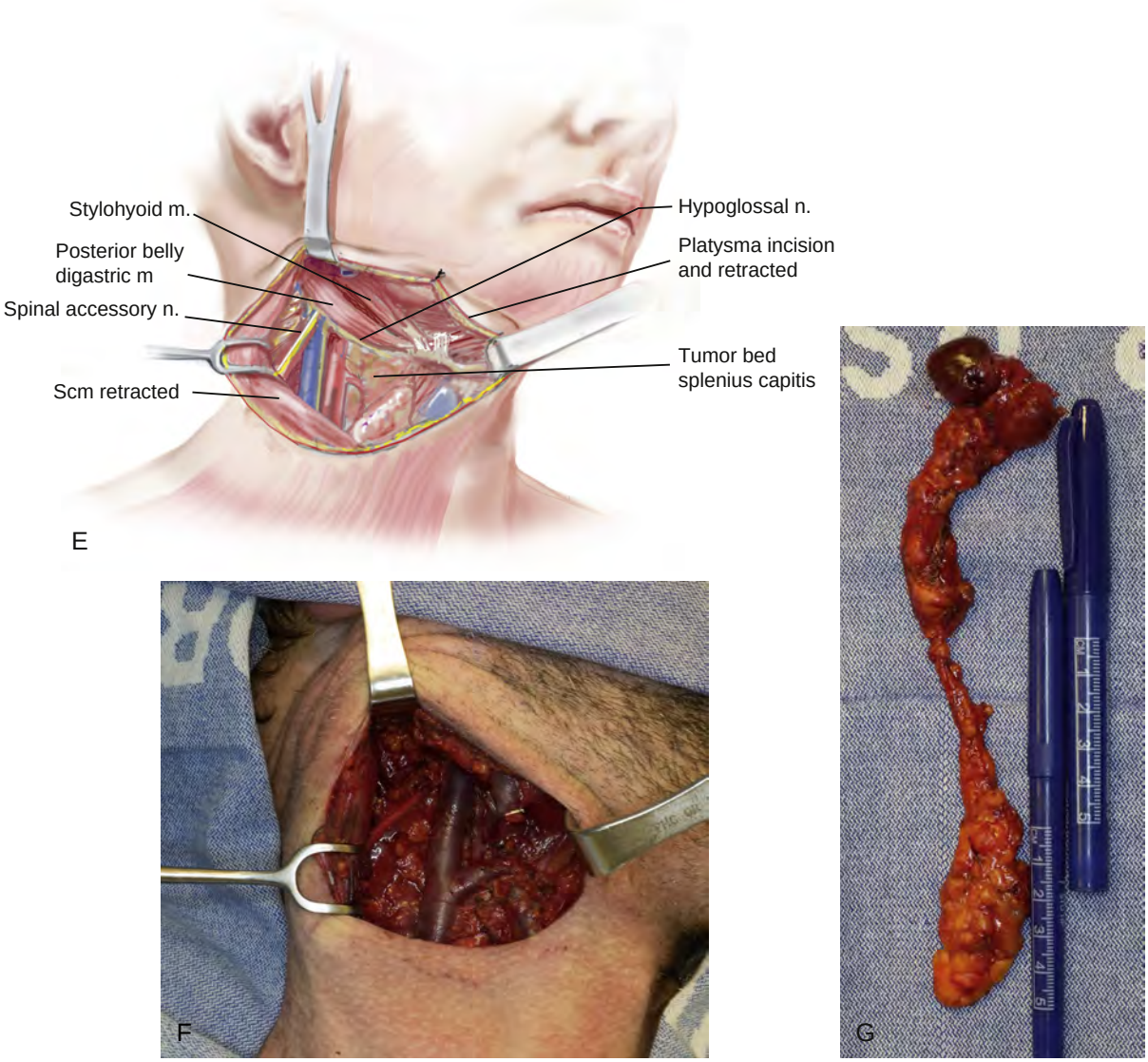
The planned mandibulotomy is scored with a reciprocating saw, and plates are prebent to the mandible. Arbeitsgemeinschaft für Osteosynthesefragen (AO) principles are followed for mandibular osteosynthesis, which requires an inferior border plate and superior tension band. Bicortical screw fixation at the inferior border is preferred, with a four- to six-hole plate and monocortical fixation at the tension band four-hole miniplate to avoid dental injury. It is imperative to carefully and



• **Fig. 33.17** Surgical management of the neck for oropharyngeal cancer: selective neck dissection, clearing levels II–IV. **A,** Incision design. **B,** Small incision design in prominent neck crease, intraoperative view. **C,** Superior and inferior skin flaps elevated in subplatysmal plane exposing fibro-adipose lymphatic-containing tissue (FALT) from the digastric muscle superiorly, the clavicle inferiorly, the trapezius posteriorly, and the thyroid cartilage anteriorly. **D,** FALT from levels II, III, and IV is mobilized off the paraspinal musculature, over the internal jugular vein and carotid artery, with preservation of the cervical rootlets and spinal accessory nerve.

accurately bend the plates to follow the contours of the mandible because even a small amount of plate torquing and elastic deformation may result in a malocclusion. Once the plates have been adapted and the mandible has been pre-drilled, the plates and screws are oriented and set aside. The osteotomy is completed with a reciprocating saw from the alveolus to the inferior border. If the interdental space is tight, it is advisable to compete the superior aspect of the osteotomy with a small sharp osteotome.

Once the mandible is split, dissection proceeds through the floor of the mouth toward the base of tongue. A cuff of lingual mucosa should be left attached to the mandible if oncologically permitted to aid in closure. The floor of mouth muscles are released and portions of them may be included in the specimen for margins. A cuff of mylohyoid may be left attached to the lingual aspect of the mandible for later re-suspension. During this maneuver, the lingual nerve may be dissected free and protected as it crosses from lateral to medial into the body of the tongue. As the dissection approaches the base of tongue mass, 1- to 1.5-cm oncologic margins are observed. The mandible is retracted bilaterally with the aid of large self-retaining Adson-Beckmann retractors or an assistant with a bone hook. Countertraction on the tongue is best accomplished with a penetrating towel clamp through the oral tongue. As dissection and resection proceeds



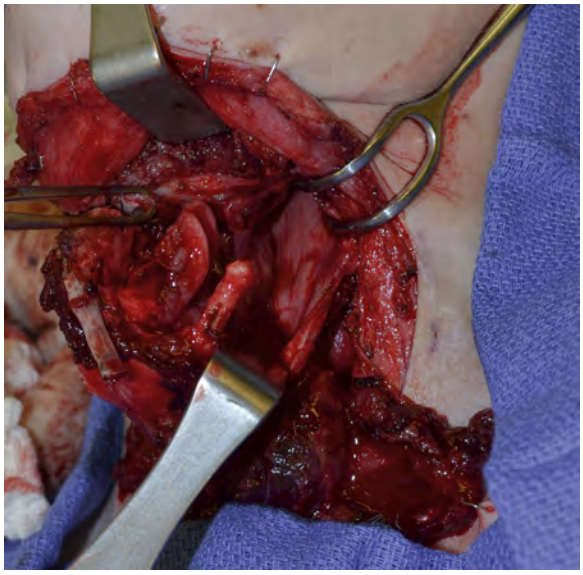
• **Fig. 33.17, cont'd** **E,** FALT from levels II–IV is delivered en bloc with preservation of the spinal accessory nerve, internal jugular vein, and sternocleidomastoid muscle. **F,** Intraoperative view after removal of FALT. **G,** Pathologic specimen.

posteriorly, the medial pterygoid is released and the working space opens so complete visualization of the base of tongue and oropharynx is possible. The lingual artery is ligated (or may have been previously ligated during neck dissection) and the tumor is resected with monopolar cautery. Careful visualization and digital palpation are of utmost importance during tumor resection to ensure adequate gross margin status.

Reconstruction of the tongue base is often necessary after resection, particularly in the salvage setting. For T1/T2 tumors, the radial forearm flap provides adequate soft tissue bulk to form a tongue mound. Thin patients with large T2 tumors may require thicker tissue such as an anterolateral thigh free flap or pectoralis major myocutaneous flap. Patients undergoing mandibulotomy and resection for primary treatment of early-stage tongue base carcinoma can simply undergo reconstruction with an oral tongue sliding flap, or foreshortening of the oral tongue to close the base of tongue defect. The remainder of the wound is closed in layers, with care taken to suspend the mylohyoid and hyoid bone.

Rationale for Elective Regional Lymphadenectomy

SCC of the base of tongue has a high propensity for cervical metastasis. In HPV-driven carcinomas, at presentation the majority of patients have advanced-stage disease due to clinically positive adenopathy.[47] T1/T2 base of tongue carcinomas with cN0 necks have occult metastasis rates ranging from 21% to 26%.[47a,48] For this reason, clinically N0 patients being treated with a surgery-driven approach should be considered for at least ipsilateral elective selective neck dissection to levels II–IV.[8,9] A retrospective analysis of 352 patients undergoing bilateral neck dissection for OSCC demonstrated a 28% incidence of pathologic bilateral cervical metastasis for T1/T2 base of tongue primaries (n = 78).[49] This is likely biased based on surgeon selection of "high-risk" patients being prescribed bilateral rather than ipsilateral neck dissection and does not take into account early-stage tumors that encroached on the midline. These data also suggest that

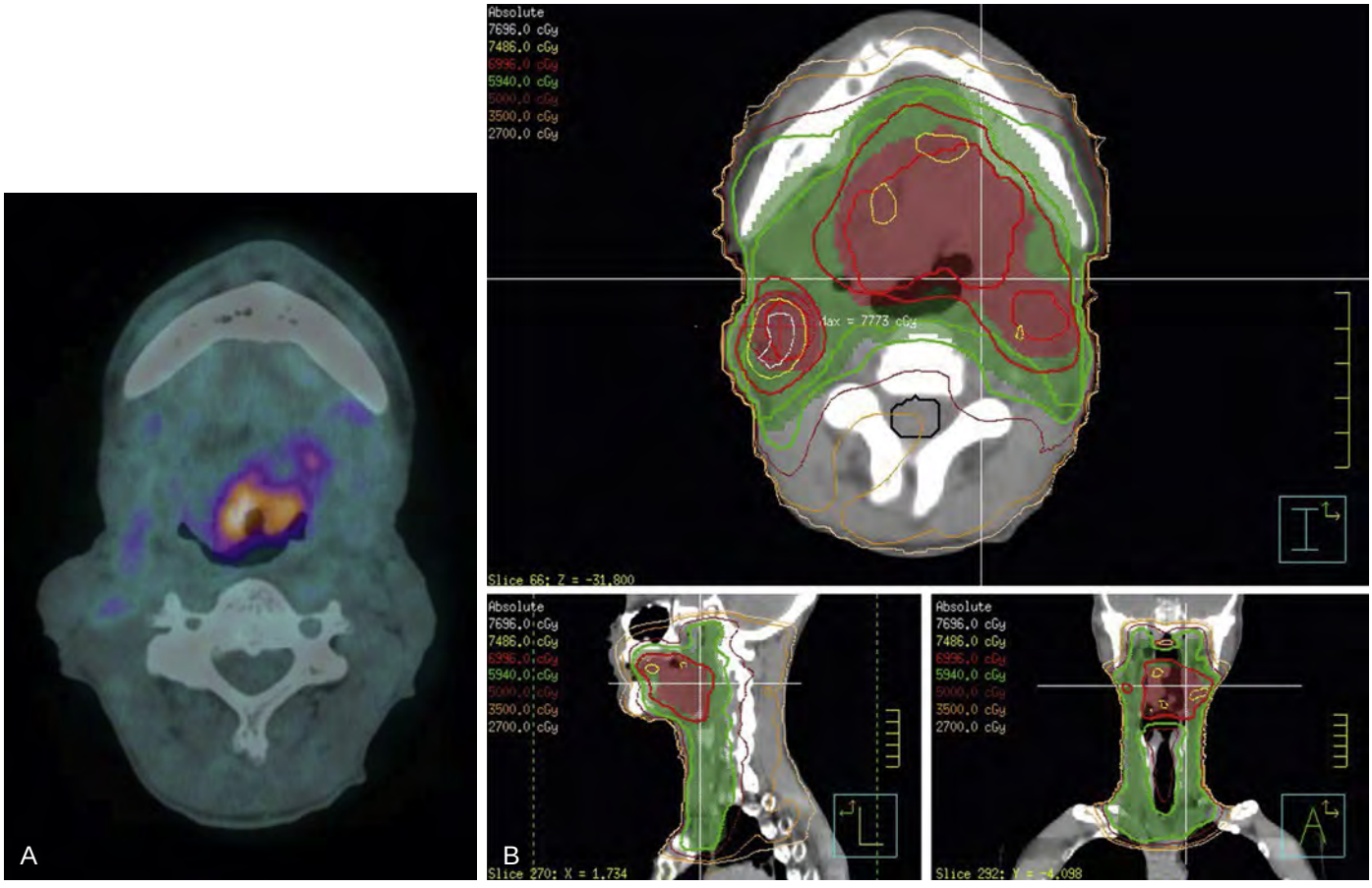


• **Fig. 33.18** Lateral pharyngotomy, intraoperative view.

base of tongue tumors were more likely to have bilateral cervical metastases when compared with tonsillar cancers ($P = .004$), but this has never been studied in a well-powered prospective clinical trial. Based on the current data, there is no absolute recommendation for contralateral elective neck dissection in base of tongue tumors that do not encroach on the midline.

Postoperative Care

After TORS base of tongue resection, patients will receive a nasogastric (NG) feeding tube and remain intubated overnight for airway protection. If not otherwise contraindicated, patients will receive 125 mg of intravenous methylprednisolone and 80 mg of intramuscular methylprednisolone depot to aid in alleviation of surgical edema. Maintenance fluids are initiated, taking care not to over-resuscitate. The head of bed is elevated 30 degrees or more to allow for dependent drainage, and most patients can be extubated within 24 hours if they pass

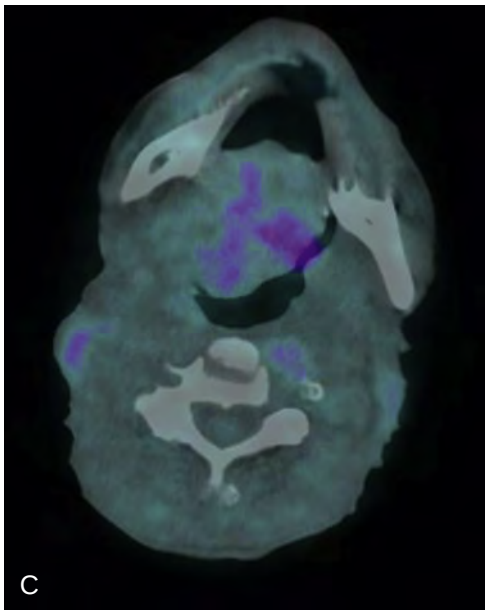


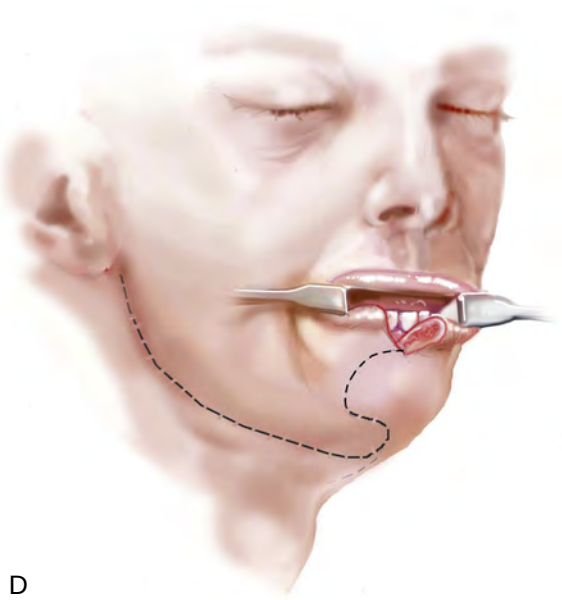
• **Fig. 33.19** A 48-year-old male with cT2N2cM0, stage IVA human papillomavirus (HPV)–negative squamous cell carcinoma of the base of tongue treated with primary chemoradiation. Twelve months after treatment, patient developed local recurrence and underwent salvage oropharyngectomy via mandibulotomy approach and reconstruction using a radial forearm free flap. **A,** Pretreatment positron emission tomography–computed tomography (PET-CT) demonstrating 4 cm ulcerated base of tongue tumor. **B,** Intensity-modulated radiotherapy (IMRT) plan.

a spontaneous breathing trial and cuff leak test. Tube feeds are initiated once the patient has been extubated and is stable and after a bedside swallowing evaluation by an SLP. All patients are encouraged to advance their oral diet with the guidance of an SLP and work toward maintaining all nutrition by mouth. Postoperative dysphagia is common. It is sometimes necessary to discharge patients from the hospital with an NG tube if oral intake remains inadequate, although almost all patients will regain meaningful swallowing within 2 weeks.

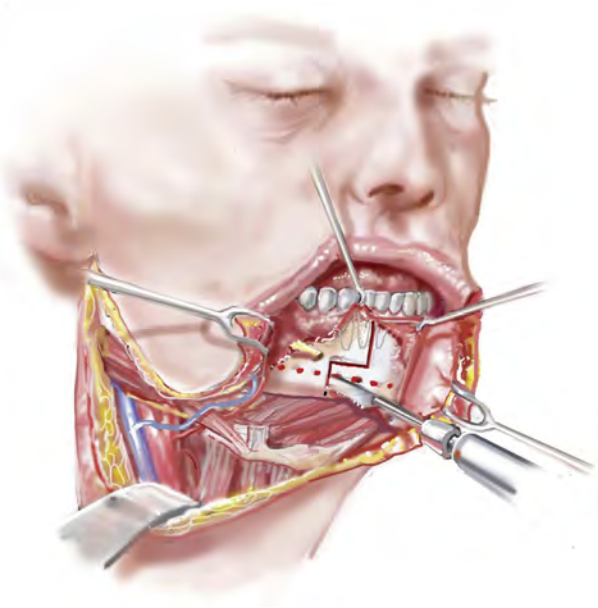
For open surgical resection, the postoperative course is variable. For patients undergoing larger resection or salvage resection, a gastrostomy tube may be considered if long-term dysphagia is predicted. Otherwise, NG tube placement is necessary for enteral feeding. In non-irradiated patients, oral intake may be initiated at postoperative day 5–7 if internal and external wounds are healing well. In the salvage setting, our preference is to wait 2–3 weeks before initiation of oral intake. This should also be done with the assistance and guidance of an SLP. If pharyngeal leak is suspected, a Gastrografin video swallow study may be useful, although most pharyngocutaneous fistulas are obvious on clinical evaluation.

Regarding tracheostomy management, most patients can be decannulated before hospital discharge. The tube cuff is deflated by postoperative day 2–3 when the patient can manage and



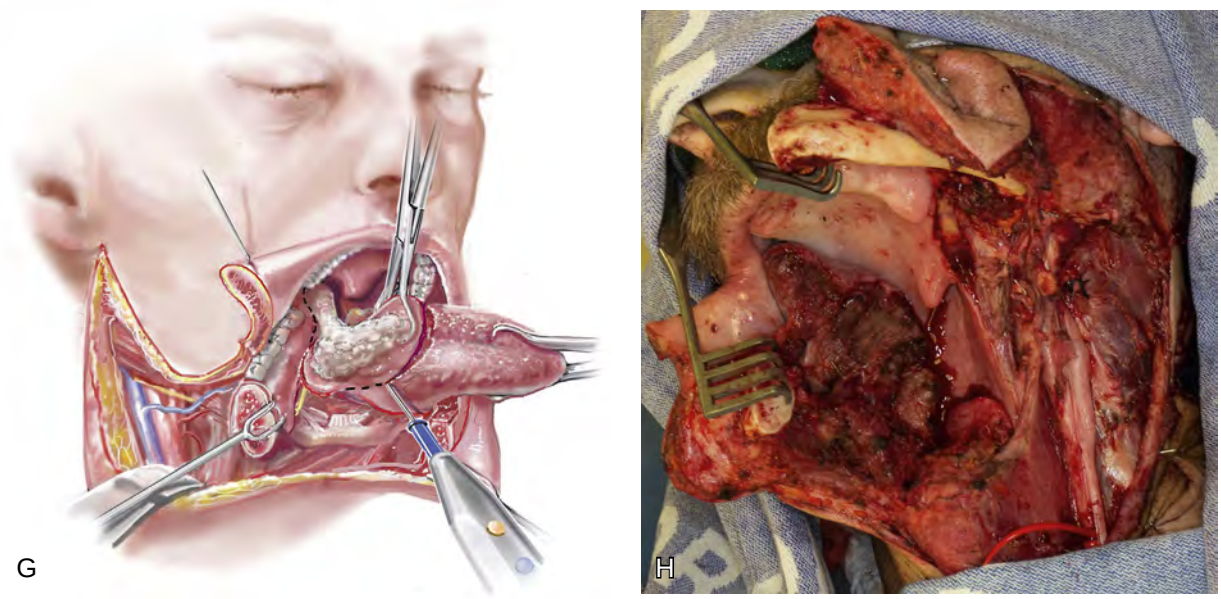






• **Fig. 33.19, cont'd** **C,** Surveillance PET-CT 1 year after chemoradiation, demonstrating local recurrence in the base of tongue. **D,** Incision design for salvage oropharyngectomy via lip-splitting approach. **E,** Incision design, intraoperative view. **F,** Paramedian stepped mandibulotomy.

Continued



• **Fig. 33.19, cont'd** **G,** Mandibulotomy and swing exposing the latero-posterior oropharynx and base of tongue to facilitate resection. **H,** Oropharyngectomy, intraoperative view.

swallow his or her own secretions. Patients should be explicitly instructed to practice swallowing saliva and use maneuvers demonstrated by the SLP. Between postoperative days 4 and 5, tracheostomy can be downsized in preparation for decannulation. Our preference is to use Jackson metal tracheostomy tubes with a 2-mm internal diameter drop from the previous tube. The outer diameter of Jackson tubes are lower profile and smooth and less irritating to the tracheal mucosa. This is helpful in reducing tracheal secretions and discomfort. The decreased bulk is also less obtrusive to swallowing mechanisms. A capping trial follows, and if the patient can remain plugged for 24 hours (including overnight), decannulation is appropriate.

Reconstruction

The primary goal of reconstruction of the oropharynx is to provide coverage and protect vital structures. More specifically, it is to protect the carotid artery and prevent salivary leakage into the danger space (if the tumor requires a resection deeper than the retropharyngeal space). A secondary goal is to preserve function. The muscles of the base of tongue, lateral pharyngeal walls, posterior pharyngeal wall, and soft palate are critically important for both speech and the oral and oropharyngeal phases of swallowing. These two goals create unique challenges. To understand these properly, it is helpful to review the anatomy.

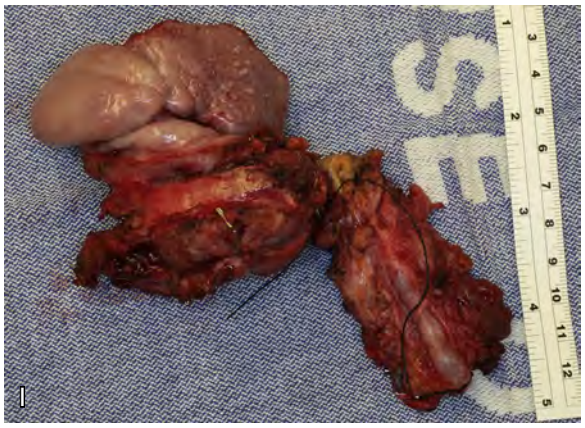
Functional Anatomy

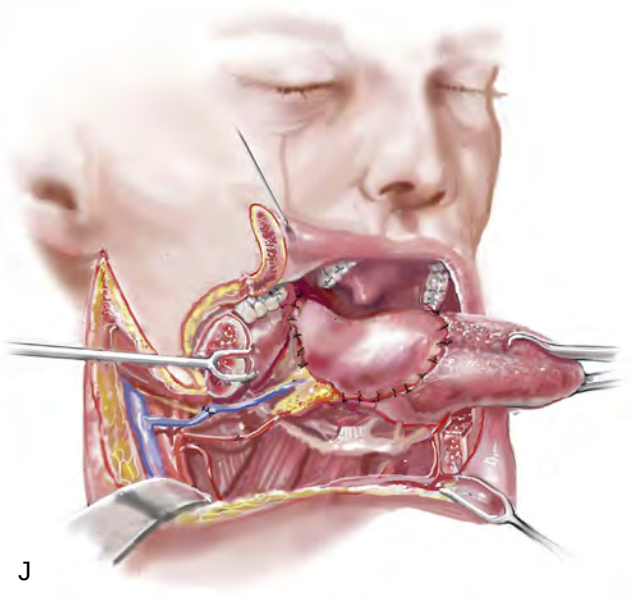
The base of tongue is composed of extrinsic tongue muscles (hyoglossus, genioglossus, styloglossus, and palatoglossus) as well as the intrinsic tongue muscles. It is essential for both the oral and oropharyngeal phases of swallowing. In the oral phase, the base of tongue creates a seal with the soft palate and posterior pharyngeal wall, preventing early passage of the food into the oropharynx and subsequent aspiration. The base of tongue then works to propel the food distally during the oropharyngeal phase.

The lateral pharyngeal walls, which include the tonsillar fossae, is composed of (from superficial to deep) mucosa, pharyngobasilar fascia, superior pharyngeal constrictor muscle, buccopharyngeal fascia, and the parapharyngeal space. The palatoglossus, palatopharyngeus, and stylopharyngeus muscles are intertwined with the superior pharyngeal constrictor muscles. Deep to the parapharyngeal space is the carotid sheath and its contents. The posterior pharyngeal wall, from superficial to deep, is composed of mucosa, pharyngobasilar fascia, superior and middle pharyngeal constrictor muscles, buccopharyngeal fascia, retropharyngeal space, alar fascia, the danger space, prevertebral fascia, and prevertebral muscles. The soft palate is composed of the tensor veli palatini, levator veli palatini, musculus uvulae, palatoglossus, and palatopharyngeus. The lateral pharyngeal walls and posterior pharyngeal wall function to constrict the diameter of the oropharynx. The soft palate muscles elevate and lengthen the palate, pushing posteriorly against the narrowed oropharyngeal lumen, creating velar closure for speech and preventing nasal regurgitation of food during swallowing. The same narrowed oropharynx comes into contact with the elevated base of tongue during the oral and oropharyngeal phases of swallowing.

Defect Analysis

T1/T2 tumors treated with primary TORS rarely require reconstructive surgery because they heal well with secondary intention. Despite healing with scarring that results in less dynamic movement and altered form, the remaining unoperated areas can often compensate, with a notable exception. Even small tumors that extend onto and include the posterior free edge of the soft palate may necessitate some form









• **Fig. 33.19, cont'd** **I,** Resection specimen. **J,** Inset of the radial forearm free flap and microvascular anastomosis. **K,** Intraoperative view before mandibular osteosynthesis with superior and inferior border plates and screws. **L,** Postoperative appearance of patient 6 months after salvage surgery.

of reconstructive surgery to avoid postoperative velopharyngeal insufficiency. In the postradiation salvage setting, defects of the lateral pharyngeal wall should not be left to heal by secondary intention, because the hypocellularity and hypovascularity of the tissue bed are unreliable. Wound infection in this area has the potential for catastrophic carotid artery compromise. Open surgical resection via mandibulotomy approaches or lateral pharyngotomy also generally require free flap reconstruction.

Planning of Reconstructive Surgery

The armamentarium for oropharyngeal reconstruction involves using primary closure when possible, local flaps (pharyngeal flaps), free tissue flaps (radial forearm flaps and anterolateral thigh flaps are the most commonly employed by authors Patel, Cheng, and Bell), regional flaps (pectoralis major flap), or a combination of these. The type of flap depends on the nature of the defect.

Successful reconstruction of base of tongue defects depends on the amount of remaining mobile tongue and the preservation of the lingual and hypoglossal nerves (at least on one side). If half of the base of tongue remains, function is often well preserved. However with near total or total base of tongue resections, restoring function relies on the mobility of the soft palate and pharyngeal walls. To facilitate this, it is necessary to use a flap of sufficient bulk to create a base of tongue mound. This can be done with either an anterolateral thigh flap or a radial forearm flap. A modification of the forearm flap includes a subcutaneous proximal extension (in the shape of a beaver tail) that can be folded under to increase the bulk of the tongue posteriorly.

Surgical Complications

Surgical complications are not uncommon in head and neck oncology, given the complex anatomy, violation of sterile and unsterile body compartments, neurovascular density of the head and neck, and critical functional elements of the affected organs. With improved surgical techniques, antibiotics, and routine use of vascularized flaps, major complications directly related to surgery have decreased substantially. As survivorship improves, particularly in the era of HPV-related oropharyngeal cancer, long-term complications are more evident. The importance of post-treatment quality of life has been studied extensively, and although advances in medicine and surgery have not made a major impact on OS, functional preservation has improved dramatically.

Pharyngocutaneous fistula, dental injury, dehydration, dysphagia, airway edema, malocclusion, nerve injury, and bleeding are associated with surgical approaches to the base of tongue.* Intraoperative hemorrhage and nerve damage are perhaps the two most important complications related to surgical extirpation of base of tongue tumors. The hypoglossal nerve and external carotid system, particularly the lingual artery, are most at risk. Although the overall rates of intraoperative hemorrhage and iatrogenic nerve injury are low, postoperative bleeding is the most common worrisome complication after modern surgery for base of tongue neoplasms, occurring in up to 10% of patients undergoing TORS.[26,50,52] In a recent retrospective single-institution analysis of 224 consecutive patients undergoing TORS, postoperative hemorrhage occurred in 10% of patients ranging from postoperative day 1 to 42. Of patients with postoperative bleeding, 82% required surgical. intervention for hemorrhage control, with a mortality rate of 0.9%.[26]

Many long-term complications are associated with adjuvant therapy, including xerostomia, dental disease, osteoradionecrosis, dysphagia, and radiation-induced fibrosis. Long-term surgical complications of surgery for early-stage base of tongue cancer are primary related to dysphagia and aspiration, although with modern minimally invasive techniques and sophisticated vascularized reconstruction, they are managed well. The rates of permanent gastrostomy tube dependence and tracheostomy dependence are low when compared with patients undergoing primary chemoradiotherapy or patients undergoing therapy for advanced-stage oropharyngeal cancer.[25,28,51,53]

*References: 25, 26, 41, 42, 45, 46, 50, 51.

Post-treatment Surveillance

All head and neck cancer patients require structured surveillance and follow-up because treatment failure and recurrence rates approach 40–50% across all stages. Disease control and cure rates are excellent for early-stage base of tongue cancer, particularly HPV-related disease; salvage in recurrent disease may be better if the recurrence is identified early. Controversy exists among oncologists regarding the optimal surveillance schedule and diagnostic tests. Beyond a 12-week post-treatment PET-CT, the NCCN does not endorse any particular imaging studies. Current NCCN guidelines recommend structured follow-up and examination that decrease in frequency over a 5-year period.

There is scant evidence that imaging surveillance can improve survival outcomes; however, several studies have suggested that more intensive follow regimens do not lead to improved survival in oropharyngeal carcinoma.[54] Two negative PET-CT scans within the first year of treatment may have an implication on prognosis, and PET-CT appears to be the most sensitive imaging study to detect recurrence, but there is a dearth of high-level evidence that endorses the routine use of PET-CT or other imaging studies on a routine basis during a typical 3- to 5-year follow-up period.[54,55] A recent European retrospective analysis of 146 patients with advanced oropharyngeal cancer treated with definitive chemoradiation demonstrated overall sensitivity and specificity of 12-week post-treatment PET-CT of 92% and 85%, respectively; however, the 3-year PFS rates for patients with reassuring PET-CT results were 91.7% for HPV-positive patients and 66.2% for HPV-negative patients.[56] These rates are similar to previously published 3-year disease-free survival rates for these groups of patients, suggesting that negative post-treatment PET-CT scans have little implication for survival.

In 2016, the PET-NECK Trial Management Group published the results of a prospective randomized clinical trial of 564 patients with N2 or greater head and neck cancer undergoing definitive chemoradiotherapy followed by either 12-week post-treatment PET-CT with or without neck dissection or 12-week post-treatment planned neck dissection to assess the non-inferiority of PET-CT. Of the patients enrolled, 84% were treated for oropharyngeal cancer. The data demonstrated that the 2-year OS rate was similar between groups—84.9% in the surveillance group and 81.5% in the planned neck dissection group, with the hazard ratio for death slightly favoring the PET-CT–guided surveillance group. There was no significant difference between the groups with respect to p16 expression (75% of oropharyngeal cancers treated in the study). PET-CT–guided surveillance resulted in savings of approximately $2190 in U.S. dollars per person over the duration of the trial. This established non-inferiority and cost-effectiveness of PET-CT–guided post-treatment surveillance over planned neck dissection.[55]

At our institution, patients are seen every 3 months for the first 2 years after completion of treatment, then every 4 months during the third year, every 6 months for the fourth year, and once in the fifth year. Follow-up examination includes a

comprehensive review of systems and head and neck physical examination. All patients with base of tongue cancer undergo recorded high-definition fiber-optic examination at each visit. Tobacco cessation counseling and risk reduction counseling are provided to appropriate patients, and the warning signs of recurrence are reviewed (new-onset or worsening pain, dysphagia, otalgia, odynophagia, dysphonia, dysarthria, weight loss, malaise).

Speech and Swallowing Therapy

Dysphagia is a common deficit during and after the treatment of base of tongue cancer. It can occur after surgery, chemotherapy, RT, or a combination of any of the three. Dysphagia has an impact on nutrition, hydration, wound healing, and possible aspiration pneumonia.

Surgical resection of base of tongue tumors can modify the structures used to transfer the bolus and protect the airway and nasopharynx. Surgery can reduce velar closure, which may allow foods or liquids to leak into the nasal cavity, and also changes the vocal resonance when speaking. It can reduce the base of tongue–posterior pharyngeal wall contact during swallowing, resulting in post-swallow pharyngeal residue, premature spillage of the bolus, delayed initiation of the swallow, and reduced hyolaryngeal elevation. These can result in aspiration before or after the swallow.

RT, with or without chemotherapy, has acute and long-term effects on swallowing. Acutely, the treatment sequelae have a significant impact on swallowing and speech. These include xerostomia, mucositis, odynophagia, neutropenia, nausea, and malaise. Patients should be monitored closely through radiation for swallowing function, and diet texture tolerance. After completion of radiation, the patient may have long-term dysphagia secondary to radiation fibrotic effects, taste changes, xerostomia, odynophagia, and trismus.

Pretreatment Evaluation

Before treatment of the cancer, an SLP should evaluate the patient's current swallowing and speech abilities. Pretreatment swallowing evaluations allow for assessment of patient's nutritional intake and anatomic and physiologic changes. A thorough oral-motor examination is completed to assess range of motion, strength, and coordination of the oral-pharyngeal system. A clinical swallowing evaluation is used to examine bolus manipulation and control, transfer, weakness, residue, and hyolaryngeal elevation and excursion, and to allow for determination of aspiration risk. Occasionally, an imaging procedure is used to fully visualize the physiology of the swallow. Most often this is done with either a modified barium swallow (MBS) study or a fiber-optic endoscopic evaluation of swallowing (FEES). Counseling before treatment will focus on potential for changes in speech and swallowing after surgery or during and after chemoradiation. If needed, swallowing compensatory strategies may be introduced, and oral supplements or possibly early alternative nutrition may be indicated. This allows for improved nutritional reserves before the beginning of treatment. Patients who have dysphagia before treatment are at higher risk of long-term dysphagia and possibly permanent tube feeding.[57]

Postsurgical Speech and Swallowing Evaluation

After completion of surgery, the patient's dysphagia should be reevaluated. Severity of the patient's dysphagia is related to the size of the surgical resection, type of surgical reconstruction, and decreased sensation postoperatively. Postoperative swelling and pain will also have a significant impact. Surgical resection involving the pharyngeal wall and/or the base of tongue will have increased impact on swallowing. Tonsil resection surgery can affect the bolus transfer into the pharynx, velar closure, and base of tongue contact with the posterior pharyngeal wall. This will often result in delayed oral transit, pharyngeal residue, vallecular pooling, premature spillage of the bolus, and incomplete laryngeal closure. An instrumental swallowing evaluation is often completed to visualize the physiology of the swallow mechanism.

Treatment for swallowing difficulties may include postural changes, diet texture changes, and compensatory strategies. As postoperative swelling reduces, swallowing should improve, although it may continue to be impaired. Introduction of range-of-motion and strengthening exercises has been shown to improve swallow safety.[58]

Speech and Swallowing Evaluation After Chemoradiation Therapy

Swallowing should be monitored before, during, and after chemoradiation therapy. Effects of radiation, with or without chemotherapy, result in changes to the swallowing structures and function, taste, and mucosal lining and the presence of pain. For radiation directed at the base of tongue or tonsil, there can be changes to the motility of the structures including reduced jaw opening, reduced base of tongue retraction, reduced velopharyngeal closure, reduced laryngeal elevation, impaired pharyngeal constriction, and delayed laryngeal vestibule closure. Sequelae related to chemoradiation also affect swallowing, including xerostomia, reduced saliva, and mucositis. Swallowing disorders occur during treatment and can persist long term. There can be continued deterioration of swallowing function years after chemoradiation, secondary to fibrosis.

Treatment strategies during chemoradiation usually involve range-of-motion and strengthening exercises, diet texture changes, and compensatory strategies.

Swallowing Exercises

Swallowing exercises can be beneficial in treating dysphagia secondary to oropharyngeal cancer. These exercises can help to strengthen swallowing structures, improve bolus control, and improve airway protection. For example, the tongue hold swallowing exercise[59] is designed to improve base of tongue and pharyngeal strength. The patient holds the tip of the tongue

gently between the front teeth, and maintains the posture while swallowing. This exercise causes the glossopharyngeal portion of the superior constrictor muscle to use more force in contracting.

The Mendelsohn maneuver[60] can be of benefit to maximize hyolaryngeal elevation. The patient holds the larynx up at the highest point for an extended time, then completes the swallow. The goal is to increase the extent and duration of the laryngeal elevation. The breath hold[58] strategy is used to maximize full closure of the laryngeal vestibule. The patient takes a breath, bears down, and holds the breath for an extended time, then repeats the exercise.

There is significant variability with regard to swallowing deficits for patients with tonsil cancer. Early evaluation of swallowing and introduction of swallowing strategies are beneficial to maintain safe oral intake.

Dental Management

Dental and Oral Considerations

Patients diagnosed with T1/T2 base of tongue SCC present a particular management challenge for the dental and oral oncologist. Because as many as 75% of head and neck cancer patients, with any primary location or stage of disease, have been reported to have foci of dental infection at the time of diagnosis, timely pretreatment dental and oral evaluation is essential.[61] This increase in the likelihood of tooth damage is in theory due to a combination of direct damage to tooth structures and salivary dysfunction.

The entire oral cavity must be considered as a potential focus for local and systemic complications for patients treated with RT and chemotherapy. Short-term risks are increased because these patients are likely to receive concurrent chemotherapy and because chronic dental infections may become acute during therapy, which alters or suppresses the immune response. These foci should be eliminated or treated before initiation of treatment, often at the time of staging laryngoscopy (if patients are being treated with definitive chemoradiation) or at the time of surgical resection before adjuvant therapy. Long-term complications from high doses of radiation to tooth-bearing areas of both the maxilla and mandible place the patient at risk for radiation caries, periodontal disease, dental pathology, and osteoradionecrosis. The larger volume of irradiated oral tissues increases the risk of oral discomfort from mucosal damage, salivary hypofunction and xerostomia, fibrosis of soft tissues, and secondary infections.[62,63] Although there is limited evidence regarding standard radiation doses to tooth-bearing areas, these investigations call attention to the need for a comprehensive examination by a provider with specific training and knowledge in oncologic dentistry and oral care.

Future Directions

The landscape of oropharyngeal cancer has evolved dramatically over the last decade. With the promise of immunotherapy and gene therapy for head and neck cancer, as well as minimally invasive surgery and treatment de-escalation, we may see a paradigm shift toward personalized treatment and improvement in quality of life in the HPV era. The focus of treating patients in a multidisciplinary setting with an expanding library of clinical trials is conducive to comprehensive treatment of cancer patients and advancing the science of head and neck oncology.

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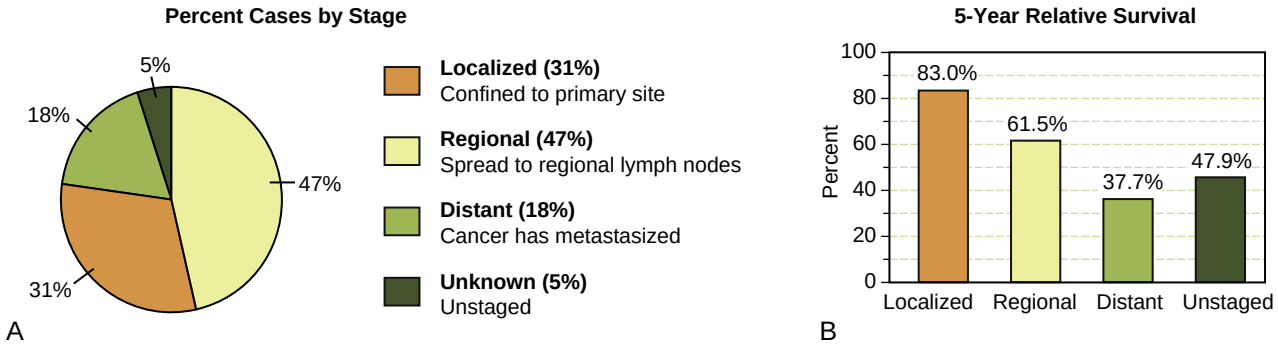
Advanced HPV-Related Oropharynx Cancer

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Clinical Presentation and Pertinent Anatomy

Advanced malignancy of the oropharynx continues to challenge physicians worldwide. Although there are a variety of malignancies that may present in the oropharynx (such as salivary gland tumors, lymphoma, or sarcomas) approximately 90% of these malignancies are squamous cell carcinoma (SCC).[1] The majority of these SCCs are linked to three known risk factors, namely tobacco, alcohol, and human papillomavirus (HPV) viral infection. The synergistic effect of tobacco and alcohol leading to malignancy is well established and was the leading cause of advanced base of tongue malignancy historically.[2] More recently, HPV-related squamous cell carcinoma has become the dominant clinical presentation.[3] These tumors are associated with high-risk HPV serotypes that express the E6 and E7 oncogenes and exhibit a strong correlation with nuclear and cytoplasmic p16 overexpression. The incidence of HPV-related (HPV+) tumors has increased by 225% between 1988 and 2004, whereas the incidence of HPV-negative (HPV–) OPC has decreased by 50%, which is likely related to decreased smoking in the general population.[4] Depending on the population being evaluated, HPV infection has been reported in greater than 80% of oropharyngeal SCC.[5] Fortunately, these malignancies have responded to traditional treatment modalities with favorable survival outcomes when compared to tobacco- and alcohol-related tumors.[6-9] However, many oropharyngeal tumors present at advanced stages with cervical nodal metastasis in the majority of cases.[10] Unfortunately many advanced oropharyngeal tumors continue to have a very poor prognosis, with 20–52% 5-year overall survival[8,11–13] (Fig. 34.1). Because of these data, advanced SCC of the base of tongue and tonsil is generally managed with a multimodality treatment strategy.

The base of tongue (BOT) is defined as the posterior third of the tongue, which is defined anatomically by the circumvallate papilla. In addition to the intrinsic and extrinsic muscles of the tongue, this region is also part of Waldeyer's ring and contains the lymphoid network comprising the lingual tonsillar tissue. Whereas early-stage BOT malignancy is often asymptomatic, patients presenting with advanced BOT malignancy often present with signs and symptoms one would expect from this anatomic subsite. Odynophagia, dysphagia, globus, otalgia, trismus, dysarthria, bleeding from the tongue or throat, and airway obstruction are often observed in these patients. However unexplained cervical nodal mass on initial presentation is also very common (45–78% of cases).[14] Many patients ignore pertinent signs and symptoms prior to presentation, or may have complicating diagnosis such as globus, reflux, or tonsillitis, which may complicate matters. Regarding cervical nodal metastasis, the primary nodal basins at risk for advanced BOT malignancy include bilateral cervical levels II, III, and IV. Other nodal basins may exhibit nodal metastasis in these advanced cases, although less commonly.



• **Fig. 34.1** **A,** Percent of cases, and **B,** 5-year relative survival by stage at diagnosis for oral cavity and pharynx cancer.

In addition to traditional history and physical examination, patients who present with a suspected base of tongue or tonsil malignancy should undergo fiber-optic endoscopy to evaluate the extent of disease. Because of the nature of current imaging modalities, dental artifact, and positional issues related to the tongue base when supine during imaging, fiber-optic evaluation offers the most accurate way to assess the anatomic location of the tumor, and also gives critical information regarding function. An evaluation of swallowing, aspiration, and sensation in the region, as well as determining the feasibility of surgical treatment options is only possible with fiber-optic endoscopy. Imaging studies such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography (PET) are generally standard in the work-up for patients with advanced malignancy of the tongue. The importance of high-quality imaging for staging and treatment planning cannot be overstated. At our institution, we currently employ PET/CT in the majority of these patients, with contrast-enhanced anatomic CT of the tongue base. PET scan is currently used for screening for distant metastasis, which is a significant risk in this population (12–15%).[15] We do not currently obtain routine chest radiographs in this population, and in the event of a positive finding on PET, we often elect to perform dedicated high-resolution CT scanning of the region in question to further evaluate for distant metastasis. We are currently employing MR/PET protocols for patients with significant dental artifact, or in the minority of patients who are considered candidates for surgical resection. MRI provides superior delineation of the extent of disease, especially in tongue base malignancies that exhibit an infiltrative pattern. Tissue diagnosis can be obtained via a variety of modalities including direct laryngoscopy with biopsy, office-based fiber-optic biopsy, or fine-needle aspiration (FNA) biopsy as determined by the treating physician. Excisional biopsy of cervical nodes is generally avoided and in rare situations when FNA is not sufficient we currently employ ultrasound guide core biopsy. At our institution it is currently standard of care to perform p16 staining, and polymerase chain reaction (PCR) HPV viral testing and serotyping on all BOT malignancies. This provides valuable information for the multidisciplinary team and patient in terms of prognosis, treatment options, and clinical trial enrollment.

Staging

After the initial evaluation and imaging studies are performed, the patient is staged according to AJCC staging guidelines and presented at a multidisciplinary tumor board. The current AJCC staging guidelines are noted in Table 34.1.

In conjunction with multidisciplinary tumor board presentation, patients are scheduled for dental evaluation, nutritional assessment, and an evaluation with speech and swallowing (see later section). Many patients with advanced malignancy have a variety of medical comorbidities that require evaluation and management before the treatment plan is formalized. In addition, evaluation by social services is often necessary to coordinate care throughout the treatment and surveillance phase.

Management Principles

The management of advanced oropharyngeal malignancy is generally divided into the primary and salvage settings. Patients with advanced BOT or tonsil malignancy are at high risk for locoregional failure, distant metastasis, and death and therefore require multimodality therapy. In general, non-surgical management with platinum-based concurrent chemoradiation (see later discussion) is the preferred strategy in the primary setting. Alternative strategies may be employed, including surgical resection followed by adjuvant therapy, or induction chemotherapy followed by adjuvant chemoradiation depending on the situation (see later sections). Significant effort must be undertaken to avoid treatment "breaks" or partial treatment plans, which have been shown to be detrimental to survival and increase the risk of treatment failure.[16-18]

At our institution, high priority is placed on enrolling patients with advanced malignancy in clinical trials for which they meet criteria, which often drives the treatment strategy. Current Radiation Therapy Oncology Group (RTOG) data indicate that centers with higher accrual rates to clinical trials improve survival outcomes for patients with head and neck cancer.[19]

It should also be noted that squamous cell carcinoma of the head and neck (SCCHN) is a diverse group of diseases, each with distinct epidemiologic, anatomic, and pathologic features. Although categorized under oropharyngeal carcinoma, SCC of the base of the tongue represents a distinct entity because of its anatomic location, function in speech and swallowing, and tendency to result in late diagnosis and bilateral nodal involvement. There is also a strong causal relationship between HPV-16 and development of SCC of BOT.[20] Despite epidemiologic changes in incidence of HPV-16 related oropharyngeal SCC, including SCC of BOT, HPV status should not be used as a routine consideration in treatment modality selection at this time, unless the patient will participate in a clinical trial that requires the HPV status. It is well established that regardless of treatment modality, patients with HPV-positive cancers have better clinical outcomes, manifested in overall and progression-free survival, when compared with HPV-negative tumors.[21,22] Historically, BOT SCC was treated with surgery followed by adjuvant radiation when indicated, but it was associated with swallowing and speech dysfunction as well as a high rate of local recurrences due to anatomic limitations of wide local excision.[23] Because of the lack of large randomized clinical trials comparing non-surgical organ-sparing versus surgical approaches, data comparing the clinical outcomes of different therapeutic modalities are still scarce. Consequently, conventional surgery followed by post-operative radiotherapy is considered equal in efficacy to concurrent chemotherapy and radiation (CRT), with the exception of organ-preserving attempts in more advanced cases.[24,25] A similar paucity of data is seen in HPV-positive tumors, and there are no universal treatment strategies for this population. Interestingly, even though HPV status should be used as a stratification factor in all clinical trials, HPV testing without specific reason is discouraged by the National Comprehensive Cancer Network (NCCN) panel,

TABLE 34.1 American Joint Committee on Cancer Staging for HPV+ Oropharyngeal Squamous Cell Cancer (8th Edition)

Primary Tumor (T)

T0	No primary identified
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, mandible, or beyond*

Regional Lymph Nodes: Clinical (cN)

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	One or more ipsilateral lymph nodes, none larger than 6 cm
N2	Contralateral or bilateral lymph nodes, none larger than 6 cm
N3	Lymph node(s) larger than 6 cm
N3	Metastasis in a lymph node ≥6 cm in greatest dimension

Regional Lymph Nodes: Pathological (pN)

NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in 4 or fewer lymph nodes
pN2	Metastasis in more than 4 lymph nodes

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is …	And N is …	And M is …	Then the Stage Group is …
T0, T1 or T2	N0 or N1	M0	I
T0, T1 or T2	N2	M0	II
T3	N0, N1 or N2	M0	III
T4	N0, N1, N2 or N3	M0	III
Any T	Any N	M1	IV

Pathologic Stage

When T is …	And N is …	And M is …	Then the Stage Group is …
T0, T1 or T2	N0, N1	M0	I
T0, T1 or T2	N2	M0	II
T3 or T4	N0, N1	M0	II
T3 or T4	N2	M0	III
Any T	Any N	M1	IV

Registry Data Collection Variables

1. Tumor location
2. Lymph nodes
3. Perineural invasion
4. Extranodal extension
5. Smoking history

*Mucosal extension to lingual surface of epiglottis from primary tumors of the base of tongue and vallecula does not constitute invasion of the larynx.

From O'Sullivan B, Lydiatt WM, Haughey BH, et al. HPV-mediated (p16+) oropharyngeal cancer. In Amin MB, et al, eds. *AJCC cancer staging manual*. 8th ed. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

because it may produce additional anxiety and stress for some patients but has no impact on therapeutic recommendations outside of the clinical trial.

Currently, according to NCCN guidelines, only CRT with high-dose cisplatin (with surgery reserved for residual disease) or transoral or open resection of the primary mass and lymph node dissection with adjuvant therapy are defined as preferred regimens. Induction chemotherapy followed by definitive treatment, because of its controversial nature and uncertain benefit over CRT alone, may be considered and offered in more advanced clinical scenarios, but it has a Category 3 recommendation, suggesting that there is a disagreement among the members of the NCCN panel of experts. Because of the lack of clear guidelines on selection of treatment modalities, it is strongly recommended that a multidisciplinary team that includes surgical, medical, and radiation oncologists be involved in the initial evaluation and development of the treatment plan. Also, because of the high risk of chronic post-treatment side effects such as pain, xerostomia, dental complications, speech and swallowing problems, and depression, a nutritionist, speech and swallowing therapist, and dentists, as well as psychosocial experts, should be involved before the initiation of any treatment. Patients should be counseled extensively on smoking cessation, as smoking may jeopardize the treatment efficacy and also adversely affect other health outcomes.[26]

Based on currently published data, either a single agent cisplatin at 100 mg/m^2 given every 3 weeks ×3 cycles or a single agent cetuximab at 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly should be used in patients receiving CRT for definitive therapy.[27,28] If the patient cannot receive the third cycle of cisplatin, an altered radiation fractionation scheme is allowed as per RTOG 0129 results.[29] If alternative chemotherapy combinations are used instead of standard bolus cisplatin, such as carboplatin and 5-fluorouracil, standard radiation fractionation should be employed.[30] Other dosing chemotherapy schedules or altered fractionations have been reported, but consensus has not been reached on the optimal approach. Because of the high toxicity burden with combined therapy, a supportive oncology team should be involved at the very earliest stages of the treatment.

All patients, regardless of treatment modality, should have regular follow-up visits as a part of the oncologic surveillance to assess for possible tumor recurrence as well as for complications of the therapy (see Surveillance). Because the vast majority of recurrences occurred within the first 2 years following diagnosis, the intensity of follow-up visits is higher and includes physical examination, post-treatment baseline imaging of primary as well as neck, speech and swallow evaluation, dental evaluation, and basic blood results (thyroid-stimulating hormone done every 6 to 12 months for patients who underwent neck irradiation). Continuation beyond 5-year surveillance with physical examination should be strongly considered, as the risk of late recurrence or second malignancies may occur, particularly in patients with non-HPV-associated oropharyngeal cancers.

In the salvage setting, the management is generally surgical (see the later discussion of salvage surgery), because most patients have received significant radiation and chemotherapy at that point. Occasionally alternative strategies such as re-irradiation are employed depending on the clinical situation, although this is a relatively rare situation in this population.

Surgical Management of the Primary Tumor

When surgical resection is considered during the management of oropharyngeal malignancy, a variety of techniques and approaches should be assessed. Surgery may be used as part of the multimodality strategy for a variety of reasons, including patient preference, medical contraindications to radiation or chemotherapy, to obtain pathologic information to guide adjuvant therapy, the treating team's preference, or clinical trial participation. Minimally invasive approaches such as transoral laser microsurgery (TLM) and transoral robotic surgery (TORS) may offer similar oncologic outcomes when compared to traditional open approaches, such as transmandibular or transcervical surgery, and have recently been used as a strategy to minimize the functional effects of adjuvant therapy while preserving oncologic outcomes (see Minimally Invasive Approaches, next). Minimally invasive options also allow faster recovery times, shorter operative times, and improved functional and aesthetic outcomes. Recent data indicate that for appropriately selected patients, minimally invasive surgery can offer similar oncologic outcomes with improved functional outcomes when compared with traditional non-surgical strategies, namely concurrent chemoradiation.[31–36]

For patients undergoing tumor resection, the surgical and reconstructive plan should be developed prior to initiation of any treatment. The primary goal of oncologic surgery should be resection of the primary mass if possible with histologic verification of tumor-free margins. Currently there are no clear guidelines for patients with positive surgical margins as to whether they should undergo re-resection or receive adjuvant therapy. The details of resection margins with proper geometric orientation should be included in an operative report. Tumor orientation of additional/supplemental surgical margins if applicable should also be included. Because positive margins increase the risk of local relapse and are an indication for postoperative adjuvant therapy, this information must be available before recommendations regarding adjuvant treatment are made. If lymph node dissection was performed, the type of neck dissection and the anatomic levels of lymph nodes encompassed in the dissection should be included in the final pathology report. Current guidelines, despite increasing incidence of TORS over conventional surgery, consider both techniques equal: There is no definitive randomized evidence that TORS provides equivalent or superior quality of life (QOL) and survival outcomes, although preliminary outcomes have been encouraging.[37,38] Certainly there are contraindications for minimally invasive BOT resection, and open surgery can be considered in these cases if indicated.[39]

Minimally Invasive Approaches

Transoral Laser Microsurgery

Transoral laser microsurgery has been evaluated extensively for a variety of anatomic subsites in the head and neck, including larynx, pharynx, and oropharynx.[40–44] Regarding management

of advanced T3/T4 BOT malignancy, TLM has been evaluated at several centers and has been shown to be an effective surgical strategy with excellent oncologic and functional outcomes in selected patients.[45–49] T3 lesions managed with TLM perform quite well from a functional standpoint; however, patients with T4 lesions have poor swallowing function, and these lesions are associated with a higher conversion to open approach.[50] In addition, as is the case with most surgical approaches, more advanced tumors require multimodality therapy, and therefore case selection for primary surgery in the setting of T3/T4 base of tongue is critical.[49,51] At our institution, we have more experience with TORS and do not routinely employ TLM for advanced BOT cancer, however, the principles are similar despite the differences in technique. Whereas TLM surgery has some advantages in terms of visualization of tumors with more inferior location when compared with current robotic technology, TORS has several advantages over TLM, most notably avoidance of line-of-sight issues and wristed instrumentation.

Transoral Robotic Surgery

Contemporary treatment of oropharyngeal squamous cell carcinoma seeks to improve functional outcomes while preserving oncologic locoregional control and overall survival. Because of the morbidity of traditional open surgery, and the functional effects of concurrent chemoradiation, transoral robotic surgery has been introduced as an alternative. The literature regarding TORS outcomes continues to mature and demonstrates oncologic control comparable to that for concurrent chemotherapy in carefully selected candidates, as well as superior functional outcomes.[31–36,52,53] The application of minimally invasive techniques to access BOT malignancy has been propelled by advances in wristed robotic instrumentation and improved optics via the three-dimensional camera.[33,36] Currently, the primary application of TORS surgery is in early-stage oropharyngeal squamous cell carcinoma, primarily related to oncogenic HPV.[33,34,36] However, experienced centers have used this technology for more advanced tumors of the base of tongue in selected cases. Recent data indicates that there may be a survival advantage to surgical resection of larger tumors followed by adjuvant therapy, when compared to concurrent chemoradiation as stand-alone therapy.[54] At our institution, we continue to favor non-surgical approaches in the majority of advanced BOT tumors because of the high risk of distant metastasis in this population. However, some patients are considered appropriate candidates for TORS surgical therapy prior to adjuvant therapy. Patient preferences for therapy are taken into consideration, as well as anatomic factors related to the tongue malignancy. Certainly, large, deeply invasive BOT squamous cell carcinomas with significant intrinsic/extrinsic tongue muscle involvement are generally not appropriate surgical candidates. In contrast, large obstructive exophytic lesions of the tongue base, which can be safely resected with negative margins, are considered for surgery, if the multidisciplinary team feels that the patient will benefit from an oncologic or functional standpoint. Careful case selection is critical when considering resection for these advanced tumors, and additional imaging, such as an MRI of the tongue base, is often required to optimize treatment planning. At our institution, we do not generally employ TORS resection in the setting of salvage surgery for T3/T4 tongue base malignancy because of issues related to oncologic margin control and access for reconstruction, which is generally required in salvage cases. In addition, the reconstructive algorithm changes in these patients because primary intention is often not appropriate for large defects (see Reconstruction section).

Operating Room Setup

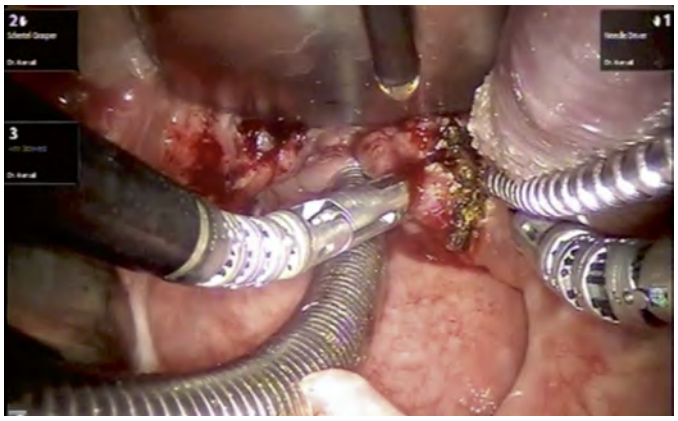
The operating room and robotic system has been described in the literature.[55-57] In general, the base of the da Vinci robotic system (Intuitive Corporation, Sunnyvale, California) is positioned at approximately 30 degrees to the surgical bed to optimize access of the robotic arms for oropharyngeal surgery. Anterior lesions may be amenable to resection with visualization via the 0-degree endoscope; however, we favor the 12-mm 30-degree endoscope for most BOT applications. The 5-mm wristed instruments are used, generally the Maryland forceps and the monopolar cautery. Suction for smoke evacuation is a critical part of the setup and improves efficiency. Suction cautery on a separate suction system is also readily available, as are ligature clips to manage hemostasis. At our institution, we prefer the monopolar cautery attachment for tongue resections, because hemostasis is improved and results are equivalent to those with a CO_2 laser.[38] In addition, when incising through lingual tonsillar tissue, we have observed that the CO_2 laser is less efficient because of the energy-absorbing properties of the lingual tonsillar tissue.

Retractor Placement

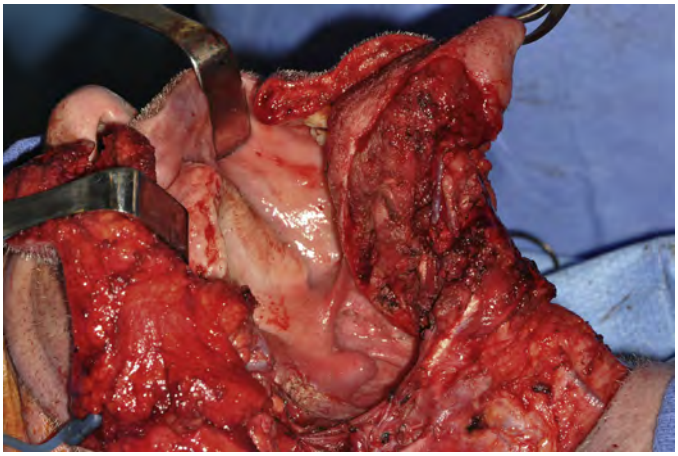
The primary retractor system we use currently at our institution is the FK retractor, although novel retractor systems for TORS are currently under development. To facilitate visualization of the tongue base, a silk retraction suture placed in the anterior tongue helps to position the retractor blade. This portion of the case often requires significant experimentation to determine the optimal position, retractor blade, and visualization prior to initiating the resection.[58] A variety of retractor blades are available with different centers facilitating different approaches.[59–61]

TORS Operative Technique

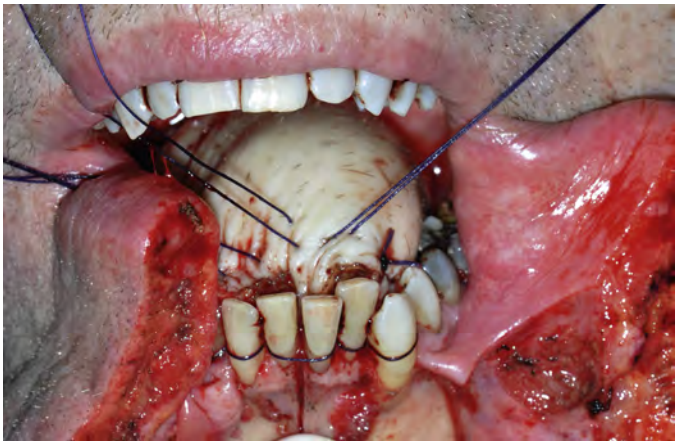
Transoral robotic resection of tongue base malignancy is relatively straightforward. The Maryland forceps is used to grasp the tumor, and the tumor is resected with monopolar cautery. Often it is necessary to make incisions surrounding the tumor and define the oncologic margins with the monopolar cautery to allow an edge to be created to grasp the specimen. Direct grasping of the tumor should be avoided to prevent bleeding and contamination of the operating field. In general, the cautery instrument functions best when on the ipsilateral side of the tumor; however, switching instrumentation can provide improved mechanics in some cases. The maintenance of hemostasis is critical to avoid loss of the surgical margin or disorientation. This is best achieved with slow, steady application of the monopolar cautery when incisions are made, and



• **Fig. 34.2** Transoral robotic surgery tongue base resection.



• **Fig. 34.3** Transmandibular approach to the oropharynx.



• **Fig. 34.4** Transcervical/transpharyngeal approach to the oropharynx.

avoiding unnecessary tumor manipulation (Fig. 34.2). Suction cautery can be employed for smaller areas of bleeding, while larger vessels such as the lingual or ascending pharyngeal branches are controlled with ligature clips. In cases when the lingual artery is very close to the tumor, which is often the case for more advanced tongue malignancies, it is recommended that the neck dissection be completed prior to TORS resection to allow for ligation of external carotid arterial branches (i.e., lingual, ascending pharyngeal), which will allow for a more hemostatic field during TORS and avoid catastrophic bleeding. In some cases when brisk arterial bleeding is encountered during TORS, the bleeding should be controlled by undocking the robotic system and retractor system to allow for direct visualization with a headlight and traditional control of arterial bleeding. This is especially true if the rate of bleeding is impairing visualization during TORS. In all cases of brisk arterial bleeding, branches of the external carotid should be ligated to avoid severe postoperative hemorrhage.

Traditional Surgical Approaches

Transmandibular/Mandibulotomy Approach

Historically, the midline mandibulotomy with a lip-splitting incision was the favored technique to access advanced tumors of the base of tongue. The advent of non-surgical therapy and minimally invasive surgical techniques has dramatically reduced the indications for this relatively invasive surgical approach. Occasionally, and primarily in the salvage setting, traditional transmandibular resection is required for T3/T4 malignancy of the tongue base in the current era. Although these procedures have a long history of application in the field of head and neck oncology with predictable results, significant functional and aesthetic effects are related to this approach.[62-68] The literature regarding the morbidity of midline mandibulotomy combined with the lip-splitting incision has reported complication rates as high as 20–48%,[69,70] although other investigations have not found the functional impact as devastating as previously expected, especially with appropriate reconstruction[71,72] (Fig. 34.3). Nevertheless, these procedures, especially in the salvage setting, provide the optimal access for large BOT malignancies and access for tongue reconstruction. Perhaps the biggest technical advance for this particular procedure is the free tissue transfer. Historically, pedicled flaps (pectoralis major muscle flap) were used in this setting and led to increased functional morbidity due to decreased mobility of the base of tongue and pharynx.[73] Free tissue transfer has dramatically improved these outcomes; however, the functional results remain suboptimal for a variety of reasons, including previous therapy, surgical morbidity of glossectomy, and morbidity related to the transmandibular approach.[62,74,75]

Transcervical/Transpharyngeal Approach

As with the transmandibular approach, the transcervical/transpharyngeal approach is less commonly employed in the current era. In appropriate cases, this approach can provide access to the base of tongue during oncologic surgery and provides excellent visualization while avoiding the sequelae of the transmandibular/lip-splitting approach.[76] Pharyngeal and base of tongue reconstruction are also feasible with this approach (Fig. 34.4). Decreased rates of postoperative fistula, temporomandibular joint disturbance, and aesthetic morbidity have been reported with this approach, when compared to transmandibular surgery.[76] In fact, some authors have questioned the utility of the mandibulotomy approach and cite data indicating that the transcervical/transpharyngeal approach offers

similar oncologic outcomes in terms of margins, but improved functional outcomes with lower complication rates.[77,78] Certainly this approach can be used in cases where surgical resection is indicated and the patient is not a candidate for minimally invasive techniques; however, the procedure is associated with increased morbidity.[62-68]

Reconstruction

The primarily healing modality for surgical resections of the tongue base in the current era is secondary intention. This is primarily due to the fact that many surgical cases are earlier stage disease and oncologic surgery is performed with minimally invasive techniques. When surgical resection of larger T3/T4 malignant lesions is considered, reconstruction is often required. The effects of ablative surgery of the tongue base in terms of speech and swallowing are markedly more pronounced with larger resections. Tongue bulk and movement, velopharyngeal closure, and pharyngeal coordination are critical for swallowing function and are markedly affected after surgery of the base of tongue.[79] The benefits of reconstruction of the base of tongue have been widely reported in the literature and primarily center around the principles of providing adequate tongue bulk, avoidance of tethering of the tongue, and flap reconstruction, which has been reported to have superior outcomes for these extensive defects.[62,74,80,81] Certainly when large resections of the base of tongue are performed via traditional approaches as noted previously, reconstruction will commonly be indicated. Additionally, free tissue transfer is often necessary to partition the oropharynx from the neck if a communication exists, although this is less common in the era of TORS. We currently classify our TORS reconstructive defects as outlined in the literature.[82] Our data indicate that reconstruction for TORS should be considered in the following adverse situations:

1. Moderate to large pharyngocervical communications
2. Carotid artery exposure
3. Extensive palatal defects
4. History of radiation or chemoradiation

In order to classify defects after TORS for reconstructive indications, our institution developed the Classification for Oropharyngeal Robotic Defects (CORD) system.[82] This classification system evaluates a variety of features of the defect and is shown in Table 34.2. Class I and II defects are generally smaller, are not associated with the adverse features noted earlier, and can be left to heal by primary intention. Surgical resections of T3/T4 BOT lesions, especially in the salvage setting, are generally categorized as Class III or IV defects, associated with adverse features, and reconstruction is often indicated in these cases. Large defects of the base of tongue that are allowed to heal without appropriate reconstruction will often result in severe speech and swallowing dysfunction and are associated with high rates of aspiration.

Our institutional data indicated that approximately 85% of TORS defects fall into the Class I/II category, and approximately 15% fall into Class III/IV and may require reconstruction.[82]

Although the technical details of BOT reconstruction are beyond the scope of this chapter, a few points should be reviewed. The goals of tongue base reconstruction include providing adequate bulk, separating the upper aerodigestive tract from the neck and prevent salivary fistula, avoiding tethering of the tongue, optimizing speech and swallowing, and protecting the great vessels if they are exposed. A wide variety of reconstructive techniques are available for reconstruction to achieve these goals when large ablative defects of the base of tongue exist. Pedicle flap reconstruction is still employed (i.e., submental island flap or pectoralis major flap), although less frequently than free tissue transfer.[83,84] Free tissue transfer techniques such as the radial forearm flap or the anterior lateral thigh flap provide excellent bulk and pliability for tongue base reconstruction. Less commonly, lateral arm, rectus abdominis, latissimus dorsi, and medial thigh flaps have been employed at our institution for a variety of indications. Certainly emphasis on watertight closure regardless of the technique employed is critical. Often more inferior defects are closed in the neck with the superior portion of the closure performed transorally. Meticulous technique can help avoid salivary fistula and its associated morbidity. Occasionally, robotic closure of flap reconstruction is performed to provide inferior hypopharyngeal access. This is facilitated by trimming sutures (approximately 10 cm) to avoid tangling with the robotic instrumentation and facilitate knot placement. In addition, urologic needles can facilitate robotic flap inset because of their smaller turning radius, which is beneficial in tighter spaces. Once the flap is inset, the microvascular anastomosis is performed and standard postoperative monitoring protocols are employed.[85]

TABLE 34.2 Classification of Oropharyngeal Robotic Defects

Class I—one subsite of the oropharynx, no adverse features

Class II—involves more than one subsite, no adverse features

Class III—only one subsite, adverse features

Class IV—involves more than one subsite, adverse features

Subsites of the oropharynx: base of tongue, tonsil, soft palate

Adverse features: carotid artery exposure, communication with the neck, >50% soft palate resection

From de Almeida JR, Park RC, Villanueva NL, et al. Reconstructive algorithm and classification system for transoral oropharyngeal defects. *Head Neck*. 36(7):934-941, 2014.

Surgical Management of the Neck

Approximately 15–30% of oropharyngeal squamous cell carcinoma will have cervical nodal metastasis.[86] In the era of HPV-related oropharyngeal cancer, cervical nodal metastasis is often the initial presenting sign of disease. Certainly in the setting of advanced T3/T4 BOT malignancy, the literature is clear that both sides of the neck should be addressed. This may include neck irradiation, neck dissection, or combined modality therapy. If the patient is considered an appropriate candidate for surgical resection in general, bilateral neck dissection is performed including levels II-IV for these advanced lesions.[87-89] Postoperative pathologic results would then guide adjuvant therapy. In cases of surgical salvage, we also

tend to perform bilateral selective neck dissections at the time of resection and reconstruction, primarily due to poor locoregional control and adverse outcomes if surgical salvage fails. Addressing the retropharyngeal node basin dissection may be indicated for lesions of risk with pharyngeal or palate extension, or in salvage situations where salvage radiotherapy is not possible. Occasionally, selective level VI dissection should be considered for advanced disease.[90] Certainly the extent of neck dissection should be determined at a multidisciplinary tumor conference to avoid treatment failures and unnecessary adjuvant treatment, and to ensure that all team members are in agreement with the surgical treatment plan.

When neck dissection is performed in the setting of TORS surgery, the majority of neck dissections are performed simultaneously at our institution. In cases where lingual artery resection is planned or expected, the neck dissection may be performed first in the sequence to allow for control of the vessels prior to TORS resection. In addition, the potential for pharyngocutaneous fistula should be expected for advanced BOT lesions, and the appropriate operative strategy to deal with this issue should be employed. Approximately 30% of TORS resections will have a pharyngocervical communication intraoperatively; however, permanent fistula is rare (<5%).[91] Although some institutions have advocated staged neck dissection, we have not observed adverse outcomes with simultaneous neck dissection. As mentioned previously, in situations of large fistula or post-radiation salvage, free tissue transfer reconstruction should be considered, although the majority of TORS cases in general do not require formal reconstruction.

Complications

Surgical complications are relatively common in this population and include a myriad issues both intraoperatively and postoperatively, given the complex nature of surgery in this area and technical issues related to reconstruction. Certainly the incidence of intraoperative outcomes such as severe bleeding, myocardial infarction, and death has decreased over time; however, postoperative complications including salivary fistula, bleeding, infection, poor speech and swallowing function, airway obstruction requiring tracheostomy, loss of taste, and loss of tongue mobility continue to plague patients and their treating physicians. The counseling of patients undergoing therapy for advanced tongue base malignancy is often as multimodal as the therapy, and frank discussions about expected surgical outcomes and surgical complications, as well as complications related to radiation and chemotherapy, should be held with the patient at several points along the course of treatment.

Postoperative Management

Postoperative management for transoral robotic surgery is relatively routine with administration of IV antibiotics, pain medication, and steroids as indicated. Many patients will require nasogastric feeding tube support during the postoperative recovery for several days, and a gastrostomy tube, although rarely required for early-stage lesions, may be indicated for advanced T3/T4 BOT resection. In addition, it should be noted that aspiration is common in this patient population. Additionally, although prolonged tracheostomy dependence is not usually observed, some patients may require long-term tracheostomy, especially the elderly.[92] It is essential to obtain proper consent from patients for this recovery period.

Outcomes/Salvage

Although outcomes for base of tongue cancer have generally been superior to those for other head and neck subsites (such as oral-cavity or supraglottic squamous cell carcinoma), locoregional recurrence and survival outcomes for advanced lesions continue to challenge physicians.[8,93] This data is difficult to interpret when HPV+ and HPV– data are not evaluated separately, and in fact the improvements in survival associated with oropharyngeal cancer are likely related to the HPV epidemic and changing tobacco abuse rates, rather than any specific treatment advances.[8,94] That being said, advanced T3/T4 cancers, especially those with higher volumes, are associated with poor outcomes, increased distant metastasis, and lower overall survival regardless of etiology.[95,96] Therefore salvage surgery will continue to be needed despite the improved outcomes related to HPV-associated tongue base cancer.

Unfortunately, the data for salvage tongue base surgery indicates poor outcomes, with a survival range of 21–45%.[48,97-99] In addition, these data have some inherent selection bias, as many centers have different criteria for selection of candidates for surgical salvage. Regarding T3/T4 specifically, in order to undergo salvage, many patients will require total glossectomy or subtotal glossectomy and reconstruction. TORS has been used in a small group of these patients with advanced BOT disease; however, these are carefully selected patients, and research in this area continues to determine the role of TORS in the salvage setting for larger BOT tumors.[100,101] At this time no definitive recommendations exist. At our institution, we occasionally salvage T3 BOT malignancies with TORS; however, for larger lesions with planned reconstruction, we frequently employ open approaches as well. Adverse features include nodal disease at the time of local recurrence, close or positive margins, and lymphovascular invasion, which are associated with worse survival outcomes.[102] Compromise of the blood supply of the anterior tongue may require that total glossectomy be performed for advanced tongue base malignancy regardless of oral tongue involvement. Nearly all of these patients will require reconstruction of some type, most commonly free tissue transfer (Fig. 34.5). Certainly, patients who are considered for surgical salvage requiring total glossectomy with or without total laryngectomy must be carefully selected because of poor oncologic outcomes and devastating functional results and QOL impact.[99] That being stated, salvage surgery in this setting can offer significant palliation in terms of pain control, and local control is possible with appropriate technique.[103,104]

In some cases, patients will require salvage neck dissection, after a complete response to the therapy at the primary site. In general, we do not perform bilateral salvage neck dissections



• **Fig. 34.5** Total glossectomy defect, anterior lateral thigh reconstruction.

for salvage of neck disease in the setting of negative imaging on the contralateral side. The extent of the neck dissection is case dependent, based on the level of the disease and risk factors associated with the recurrence (see Surgical Management of the Neck).

Radiation Therapy

General Principles

The surgical resection of locally advanced BOT cancer would leave many patients with potentially unacceptable functional and cosmetic outcomes, and therefore radiation-based therapy is generally the preferred treatment choice. The goal of non-surgical therapy is to provide the maximal control rate while maintaining organ function. Non-surgical organ preservation approaches include a combination of chemotherapy and radiation therapy. Modern planning techniques with intensity-0modulated radiation therapy (IMRT) in addition to the use of daily image guidance for setup have been shown to improve outcomes by reducing treatment-related morbidity.

Dose and Fractionation

The standard treatment approach for patients with locally advanced BOT cancer treated with concurrent chemoradiotherapy is to use once-daily fractionation. Altered-fraction radiation schedules have been investigated in locally advanced oropharyngeal cancer. Accelerated regimens attempt to reduce tumor repopulation, a major cause of treatment failures, by decreasing the total time over which radiation is delivered. This is typically accomplished by the more frequent administration of smaller fraction sizes. By contrast, hyperfractionation attempts to increase the total dose of radiation to improve control by decreasing the size of each fraction. The consequence of potentially increased efficacy with altered fractionation is an increase in acute toxicity; there is less of a concern about increased late toxicity.

The final results of RTOG 9003 demonstrated that at 5 years, hyperfractionation only (81.6 Gy/68 twice daily fractions) improved survival and locoregional control without any concurrent chemotherapy when compared to standard fractionation (70 Gy/35 fractions).[105] The other arms investigated on the trial included two accelerated regimens: 67.2 Gy/42 fractions/6 weeks with a 2-week restart after 38.4 Gy and 72 Gy/42 fractions/6 weeks; however, with longer follow-up, there were no significant advantages with the accelerated regimens. Notably, twice-daily radiation places a significant burden on both the patient and treatment facility, resulting in potential compliance issues.

RTOG 0129 compared standard fraction with concurrent cisplatin with accelerated fractionation, and the two treatment schedules were found to be equivalent to one another.[106] Therefore the most widely adopted regimen is concurrent chemoradiotherapy using standard fraction and concurrent cisplatin. However, if the patient is not a candidate for concurrent systemic therapy because of Karnofsky Performance Status (KPS), age, or comorbidities, definitive radiation using an altered fractionation regimen should be pursued.

Modern IMRT plans allow for the differential delivery of dose to the primary tumor, involved nodes, and at-risk neck. Typically, the primary site and involved nodes are treated to 70 Gy. A node-positive neck is typically treated to 63 Gy, and a node-negative neck to 56 Gy. Alternative regimens include 70 Gy, 59.4 Gy, and 54 Gy in 33 fractions to gross disease, node-positive neck, and node-negative neck, respectively. It should be noted that in the HPV era, there are efforts to reduce the dose of radiation in the definitive setting with a number of ongoing trials attempting to address this question. However, to date there is no prospective evidence that lower doses are equally efficacious.

In the postoperative setting, standard indications for radiation include extracapsular nodal spread, positive margins, pT3 or pT4 primary, N2 or N3 nodal disease, nodal disease in levels IV or V, perineural invasion, or lymphovascular invasion. In this setting, both the primary site and bilateral necks are typically treated to 60 Gy. If a positive margin or extranodal spread is detected, the dose is increased to 66 Gy and typically concurrent chemotherapy is added. Radiation is ideally started within 8 weeks postsurgery.

Treatment Technique

For locally advanced BOT cancers, most centers consider IMRT as the preferred planning technique. The use of IMRT offers many potential benefits. Typically, at least one parotid gland can be spared, minimizing the risk of significant long-term xerostomia. Additionally, the constrictor muscles can be contoured and potentially spared, limiting the risk of dysphagia.[107] Dose to the mandible can also be limited to minimize the risk of osteoradionecrosis. As noted before, IMRT allows for the dose of radiation administered to vary allowing multiple areas within the target volume to different dose levels, thereby providing a simultaneous integrated boost. Although IMRT has many advantages, it is important to note that both treatment time and the amount of normal tissue exposed to radiation increase as compared with 3D CRT.

Treatment Planning

Prior to simulation, patients with oropharyngeal cancer should undergo dental evaluation. Patients should be simulated in the supine position with at least a 5-point face mask for immobilization. Typically a bite block is used to minimize movement of the tongue. Intravenous contrast can be administered during the simulation to improve visualization of the primary tumor and involved lymph nodes. After simulation, any additional imaging such as a PET scan or MRI can be fused with the planning CT scan so that gross disease can be accurately delineated.

Target Volume

The gross tumor volume (GTV) includes all gross disease on physical examination with endoscopy and imaging. All suspicious lymph nodes (necrotic, contrast enhancing, PET avid, >1 cm) should also be contoured as GTV. The clinical target volume (CTV) encompasses all areas of potential microscopic disease and the GTV. For locally advanced BOT cancers, this includes coverage of the adjacent posterior pharyngeal wall, glossotonsillar sulcus, pre-epiglottic space, and a 0.5- to 1-cm margin around the entire base of tongue. In the node-positive neck, the retropharyngeal nodes and levels IB-V are covered. If there is significant extension into the oral tongue, IA should be covered as well. IB can be excluded on the contralateral node-negative neck to reduce dose to the oral cavity. In the postoperative setting, the target volume includes all preoperative disease and the entire postoperative bed. The planning target volume (PTV) is created from the respective CTVs to account for setup uncertainties (Fig. 34.6A and B). Typically expansions vary between 3 and 5 mm, depending on the type of image guidance used, as discussed next.

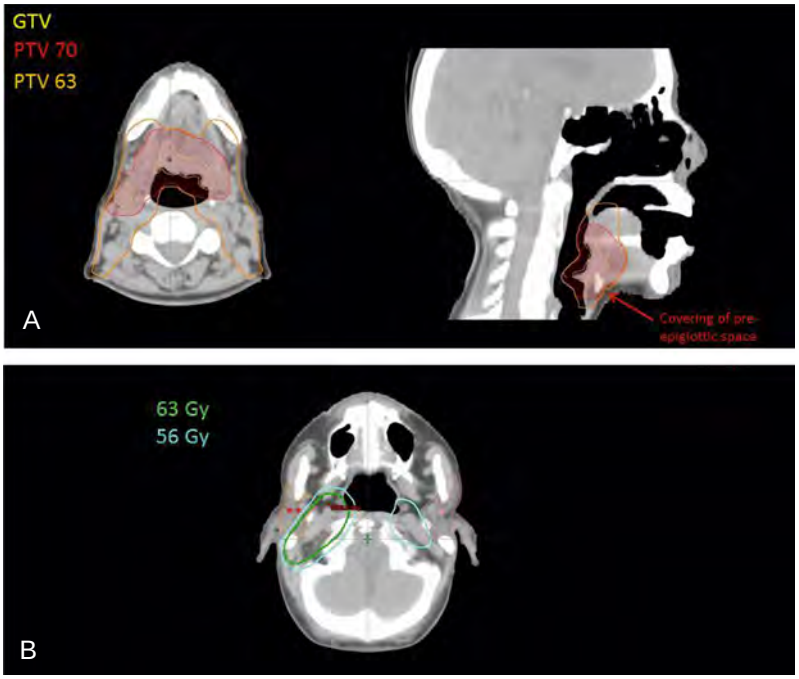
Image Guidance

Daily image guidance of some form is typically used in setup for locally advanced oropharynx cancers treated with IMRT. Uncertainty in patient setup requires extra margins to be added to treatment volumes to ensure that gross disease is adequately covered. The more precise the patient setup, the smaller the margins. This reduction in treatment volume can result in less normal tissue irradiated and therefore an improved toxicity profile.

Image guidance can be obtained either with daily KV images, which are similar to standard x-rays, or daily cone-beam computed tomography (CBCT) images. Daily CBCTs provide an excellent degree of accuracy and precision allowing for very tight margins; however, the time the patient spends on the table is significantly increased. Additionally, the exposure to radiation with daily CTs is increased. Therefore, for most patients, daily KV imaging is sufficient. In the setting of re-irradiation, daily CBCTs may be of use to minimize the amount of normal tissue re-irradiated.

Brachytherapy

Excellent locoregional control can also be obtained using a combination of external beam radiation and a brachytherapy boost. Many institutions have reported their experience with



• **Fig. 34.6** **A**, A patient with locally advanced base of tongue cancer with extension down the vallecula. On axial imaging, the gross tumor volume (GTV) includes disease in the vallecula and adjacent positive node. The planning target volume (PTV 63) for microscopic disease includes bilateral IB-V and retropharyngeal nodes. The PTV 70 includes a margin on the primary tumor. The sagittal section demonstrates that the pre-epiglottic space is covered by 63 Gy. **B**, The dose distribution from the treatment plan generated demonstrates that the left parotid gland *(asterisk)* is spared from high doses in comparison to the right parotid gland *(double asterisk).* The sparing of one gland should result in adequate long-term salivary function.

brachytherapy, with most regional control rates above 80%.[108–111] Complications including soft tissue ulceration and osteoradionecrosis of the mandible are a concern with combination therapy. Overall, with the excellent control rates and favorable toxicity profile of IMRT, the use of brachytherapy in the management of BOT cancer is significantly declining, given the invasiveness of this approach without any clear benefit.

Management of the Neck Following Definitive Radiation With or Without Chemotherapy

The management of the neck in node-positive patients with BOT and tonsil cancer is evolving. Surgical resection of a persistent node should be reserved for clear evidence of residual disease. Fluorodeoxyglucose (FDG) PET is becoming the most commonly used modality in assessing response, along with a diagnostic CT. The negative predictive value of a PET for the neck is over 95%.[112] Therefore, a patient who is PET negative can be closely observed. If there is clinical concern for residual disease, a PET should be performed 10 to 12 weeks posttreatment and any concern for FDG-avid disease should be addressed with a neck dissection.

Toxicity

Even with modern planning techniques, almost all patients undergoing definitive radiation-based treatment for locally advanced BOT will develop some form of acute and late toxicity. The acute side effects typically begin during the second and third week of therapy and include mainly dysgeusia, xerostomia, mucositis, dysphagia, odynophagia, and dermatitis. The acute effects usually resolve within 3 months of treatment. Strategies to minimize these toxicities include daily skin care, intravenous hydration, pain medication, lidocaine-based mouth washes, and oral hygiene. Nutrition supplementation with high-caloric dietary drinks should be encouraged. In cases where patients cannot meet their daily nutritional needs, a percutaneous endoscopic gastrostomy (PEG) tube may be temporarily placed.

Long-term toxicities following definitive radiation-based therapy can adversely affect patients' QOL after their cancer has been successfully treated. Xerostomia is the most common long-term toxicity associated with radiation. The extent of xerostomia is a function of the extent to which the parotid glands can be spared from high doses. Nearly all patients will develop some degree of xerostomia, but most are able to adjust with lifestyle modifications. As a consequence of diminished saliva, BOT cancer patients are at risk for dental caries. Patients should initiate fluoride treatments post-therapy to minimize this risk. Osteoradionecrosis can also develop in areas of the mandible exposed to high doses of radiation. This typically results from damage to the vascular supply to the bone. Extraction of problematic teeth before initiation of radiation is encouraged to minimize the risk of the development of osteoradionecrosis. Hypothyroidism represents another potential toxicity associated with treatment. Radiation induced hypothyroidism typically presents 1 to 2 years following treatment and is related to the dose the gland receives. Patients' levels of thyroid-stimulating hormone (TSH) should be checked every 6 to 12 months following treatment, with hormone replacement as indicated.[113]

Dysphagia is another significant potential toxicity related to radiation. The causes of dysphagia are multifactorial and include tumor location, dose to the constrictors, and concurrent chemotherapy. Patients who rely on a PEG tube for nutrition are also at increased risk secondary to long-term constrictor fibrosis. Although the overall PEG dependence rate is approximately 10%, depending on the institution and series, efforts should be made to minimize dose to the constrictors and encourage nutrition by mouth in patients undergoing definitive radiation.[114,115]

Chemotherapy

Role of Chemotherapy in Management of Base of the Tongue and Tonsil Squamous Cell Carcinoma

With recent epidemiologic changes, such as an increased incidence of HPV, and therapeutic advances, such as changes in radiation techniques and the introduction of chemotherapy, treatment regimens for patients with locally advanced BOT and tonsil cancer has become multimodal and has succeeded in improving locoregional and distant control, organ preservation, and quality of life. Unfortunately, the majority of peer-reviewed publications of randomized clinical trials include all the anatomic sites without taking into account the specific issues inherently related to malignancy of the oropharynx.

Because chemotherapy can be given in various clinical scenarios, we discuss the three most common strategies:

1. Concurrent therapy with chemotherapy or targeted agents given simultaneously with radiation to enhance its effect; also known as combined CRT
2. Induction chemotherapy (IC); also known as neoadjuvant therapy with chemotherapy given before definitive therapy
3. Postsurgical adjuvant therapy that includes concurrent chemoradiation (CRT) or RT alone

Concurrent Chemoradiotherapy

Radiation therapy (RT) plays an important role in the management of patients with SCCHN (see Radiation Therapy section). Because of resistance of tissues to the biologic effects of RT, multiple strategies to improve clinical outcome have been developed, such as altered fractionation and different chemotherapy and radiotherapy schedules.[27,30,116] The most established and well-documented clinical approach in medical literature is concurrent chemoradiotherapy.[27] Significant improvement has been made since Heidelberger pioneered the concept of combined CRT in 1958 to enhance the effect that treatment has on cancer.[117] In early 1960, Adams and colleagues recognized that, in addition to oxygen, electron-affinic compounds can also sensitize cells to radiation, and this idea led

to their discovery of radiosensitizers that enhance the cytotoxic effect of radiation, especially in oxygen-deficient cells.[118,119] Since those scientific breakthroughs, numerous chemical agents have been discovered and used in clinical practice. Chemotherapy and radiotherapy have the same therapeutic aims and share some similarities in principles, but the biology of the two modalities differs significantly. They both destroy cancer cells by damaging genetic material and consequently impairing cancer cell proliferation, but they also have some principal differences. For example, the radiation dose is homogeneously distributed through the whole tumor, whereas chemotherapy is unevenly spread, depending on drug delivery, tumor vascularity, tumor interstitial pressure, and cellular uptake.

Regardless of which mechanism of action is applied, the primary goal of treatment is to eradicate malignant cells and to enhance therapeutic gain, which can be defined as the ratio of the biologic effect of therapy on a tumor compared with its effect on surrounding normal tissue, where the optimum dose of CRT is accompanied with severe, expected side effects. The presence of adverse events should not be considered as a treatment failure as long as it is tolerable by patients. However, the focus should be directed toward greater therapeutic gains, thus lessening the complications of therapy. To improve the therapeutic ratio, combined chemotherapy and radiation was primarily explored with the intent to overcome radioresistance, but also to increase cytotoxic enhancement and to exploit biologic synergy of combined treatment. Based on the results of individual trials and meta-analyses, concurrent administration of chemotherapy and RT has become a standard approach for organ function preservation for resectable disease and for definitive management of unresectable SCCHN.[27,30,120] In an updated and thorough MACH-NC meta-analysis, more than 16,000 patients treated for non-metastatic SCCHN in a total of 87 randomized trials conducted between 1965 and 2000 were enrolled and included. Fifty of 87 studies analyzed the effect of concomitant chemotherapy, and 9615 patients (6560 deaths) were included with updated follow-up for most of the trials; the overall median follow-up was 5.6 years. With a hazard ratio of 0.81 ($P < 0.0001$), the absolute benefit for concomitant CRT was 6.5% at 5 years.[121] Interestingly, in recent trials patients were separated into cancer-related and non-cancer death groups. CRT had no effect on non-cancer deaths (0.96 [0.82-1.12], $P = .62$), and benefit came directly from a drop in cancer-related death (HR 0.78 [0.73-0.84], $P < .0001$). The effect of chemotherapy was significantly higher ($P = .006$) with platinum when compared with other types of mono-chemotherapies, and there was no difference between mono and combination chemotherapy, mainly platinum and fluorouracil. In the updated MACH-NC analysis, a site with 5878 patients having oropharyngeal SCCHN and 82 counterparts reported that the 5-year absolute benefit in overall survival (OS) from CRT was 8.1% (95% CI: 4.8-11.4) with $P < 0.0001$ in this population.[122]

The majority of randomized clinical trials have compared combined treatment to RT alone, providing evidence for platinum-based monotherapy and combination or targeted therapy. In 1987, in RTOG 81-17, Al-Sarraf and colleagues were the first to report a phase I/II study with 124 patients diagnosed with locally advanced inoperable SCCHN, of whom 39% had OPX SCC, who received 66-73.8 Gy of daily radiation with cisplatin 100 mg/m^2 given every 3 weeks. Only 60% of subjects completed planned treatment, with 1-year disease-free survival (DFS) of 51% and OS of 66%. The major toxicities reported were stomatitis (31%), leukopenia (11%), anemia (8%), and nausea and vomiting (6%).[123] Previous forms of chemotherapy, such as cyclophosphamide, vincristine, and bleomycin, resulted in fatal complications and intolerable toxicities (mainly excessive mucositis) and thus led RTOG to use cisplatin in their study.[124] The RTOG 81-17 update in 1990, with reported 4-year locoregional control (LRC) of 43% and an OS of 34%, created a rationale for coordination of a randomized trial comparing cisplatin and radiotherapy versus radiotherapy alone in advanced SCCHN.[125] In 2003 Adelstein and co-workers reported an intergroup phase III study with 295 patients, 160 of whom had oropharyngeal SCC, treated with standard radiation only therapy or two schedules of concurrent chemoradiotherapy, sequential or concurrent. Addition of concurrent high-dose cisplatin to conventional radiation improved 3-year OS with 23% in RT versus 37% in the CRT arm ($P = .014$), establishing bolus cisplatin as a standard chemotherapy used in combination with radiation in SCCHN.[126] Those individual trials, as well as MACH-NC analysis, influenced the NCCN's decision to establish a high-dose bolus cisplatin (100 mg/m^2 on days 1, 22, and 43) as the preferred regimen for treatment of locally advanced SCCHN.

In a multicenter, randomized trial, Calais and colleagues reported a sample size of 226 patients with oropharyngeal SCC, 79 (35%) of whom had BOT SCC. In this study, patients were randomized to a conventional fractionation, 70 Gy in 35 fractions RT-alone arm, or to a combined arm consisting of RT in addition to three cycles of a 4-day regimen containing carboplatin (70 mg/m^2 per day) and 5-fluorouracil (600 mg/m^2 per day) by continuous infusion on days 1, 22, and 43. After a median follow-up of 35 months, the median survival was 15.4 months in the RT-only group and 29.2 months in the CRT group, LRC was 42% (95% CI = 31–56%) and 66% (95% CI = 51–78%) and 3-year OS was 31% (95% CI = 18–49%) and 51% (95% CI = 39–68%) respectively; all were statistically significant, favoring combined CRT. Similar to other studies, combined treatment was more toxic with acute mucositis (71% Grade III and 39% Grade IV) and severe late toxicity (14% Grade III and 9% Grade IV) in the CRT and RT arms, respectively.[30]

In their search for a treatment that is less toxic and equally efficacious to platinum-based concurrent chemoradiation, Bonner and colleagues used compelling data from a phase I study with radiation and cetuximab, an inhibitor of epidermal growth factor receptor (EGFR), to create a multicenter phase III randomized study with cetuximab and radiation versus radiation alone.[28,127] With a total of 424 patients with locoregionally advanced SCCHN, this study showed no adverse changes in QOL but did demonstrate an improvement in the median survival at 3-year and confirmed at 5-year, favoring the cetuximab plus RT arm (Table 34.3). The benefit

TABLE 34.3 Locoregional Control and Overall Survival in Phase III Clinical Trials Using Combined Therapy versus Radiation Alone

Study	Total Number of Patients	Total Number of OPX	Locoregional Control*	Overall Survival*
Bonner et al 3-year[28]	424	253 (59%)	47% vs. 34%	55% vs. 45%
Bonner et al 5-year[28]	424	253 (59%)	Not reported	46% vs. 36%
Adelstein et al 3- year[27]	295	160 (54%)	Not reported	37% vs. 23%
GORTEC 3-year[132]	222	222 (79/222 with BOT)	66% vs. 42%	51% vs. 31%

*Experimental arm versus standard arm respectively.

of cetuximab was more evident in oropharyngeal cancer, in younger patients with good performance status, and when combined with hyperfractionated radiotherapy. Although this study has some limitations due to the lack of data on HPV status and the rate of feeding tube dependence, it still provides a reasonable alternative for patients who cannot tolerate platinum. Disappointing results were seen when using a combination of an EGFR inhibitor with cisplatin during radiation. A large randomized phase III trial (RTOG 0522) with a median follow-up of 3.8 years randomly assigned a total of 940 patients to concurrent cisplatin (100 mg/m^2 on days 1 and 22), given with accelerated radiation (70 Gy in 42 fractions over 6 weeks), with or without concurrent cetuximab. The study showed no difference between the experimental and standard in 3-year PFS (59% vs. 61%) (HR 1.08, 95% CI 0.88-1.32), OS (76% vs. 73%; HR 0.95, 95% CI 0.74-1.21), locoregional failure (26% vs. 20%) and distant metastases (10% vs. 13%), respectively.[128] Similar results were seen in the randomized phase II study with panitumumab and cisplatin given concurrently with RT and in another study where a small-molecule inhibitor of the EGFR, erlotinib, and cisplatin were combined with RT. However, neither study showed any benefit of combination therapy over standard platinum-based concurrent chemoradiation.[129,130]

Two additional important clinical trials established the role of chemotherapy regardless of the type of RT schedule, showing that an acceleration of radiotherapy cannot compensate for the lack of chemotherapy.[131,132] In RTOG 0129, a total of 721 patients were randomly assigned to receive accelerated-fractionation radiotherapy and two intravenous cisplatin doses at 100mg/m^2 on days 1 and 22 or to standard-fractionation radiotherapy and three doses at the same level given on days 1, 22, and 43. The primary end-point was to detect a 25% reduction in the rate of death, but when the accelerated fractionation radiotherapy group was compared to standard fractionation, there was no statistically significant difference between the two arms. With the median follow-up of 4.8 years, the 3-year OS was 70.3% (95% CI, 65.6 to 75.1) versus 64.3% (95% CI, 59.3 to 69.2; P = .18) between the experimental versus standard arm, respectively.[131] Similar results were seen in the GORTEC 99-02 randomized study, which assessed the potential benefit of a combination of different intensification strategies by randomizing 840 patients among three groups: conventional chemoradiotherapy (70 Gy in 7 weeks plus three cycles of 4 days of concomitant carboplatin-fluorouracil), accelerated radiotherapy-chemotherapy (70 Gy in 6 weeks plus two cycles of 5 days' concomitant carboplatin-fluorouracil), or very accelerated radiotherapy alone (64.8 Gy [1.8 Gy twice daily] in 3.5 weeks). No benefit was seen for accelerated RT arms in progression-free survival (PFS) ([HR] 1.02, 95% CI 0.84-1.23; P = .88), OS (1.05, 0.86-1.29; P = .60), locoregional failures (0.97, 0.74-1.26; P = .81), or distant metastases (1.26, 0.90-1.75; P = .18).[132] Some of the limitations of the GORTEC 99-02 study were the lack of information on HPV status, the prohibition of IMRT, and the study design, which allowed the conventional arm to receive more chemotherapy than the accelerated arm. In both studies, the experimental arms added further cost, logistical complexity, and extra toxicity with no improvement in clinical outcome when compared to the standard fractionation arms.

Numerous concurrent modalities provide several therapeutic alternatives for clinicians to choose from depending on the clinical scenario, competing toxicities, and side-effect profiles of individual patients. The past few decades have been rich in the development of a variety of CRT treatments and schedules designed to optimize them. Current areas of interest in SCCHN and BOT tumors include combinations of novel agents and standard chemoradiation, including cytotoxics and biologically targeted agents. These agents may be targeting the microenvironment (e.g., tumor hypoxia and angiogenesis) or the immune system to potentiate the effect of radiation.[133,134]

Induction Chemotherapy

Quantitative results of chemotherapy and radiotherapy when administered sequentially are significantly different when compared with concurrent strategies. Based on current evidence, chemotherapy often leads to a fractional tumor decrease that is not larger than 1 to 2 log. Destruction of the tumor occurs at a constant fraction rather than a constant number of cancer cells, leading to exponential survival curves. Therefore,

chemotherapy alone will rarely lead to complete tumor eradication, and pathologic examination of the tumor site often reveals residual viable tumor cells.[135] These data explain the impressive tumor shrinkage often observed after induction chemotherapy but also highlight the importance of definitive treatment. Definitive radiotherapy is necessary because some surviving tumor cells that are clinically or radiographically undetectable might still be present.[136] Induction chemotherapy, despite its controversial nature, has been gaining gradual acceptance in clinical practice. A MACH-NC meta-analysis on induction chemotherapy trials, which included patients with unresectable disease, showed a small improvement in survival ([HR]: 0.90; 95% CI, 0.82 to 0.99) and distant failures for induction chemotherapy in those trials that used a platinum and 5-fluorouracil (PF) regimen.[120]

Because none of the most recent trials that added taxane to PF IC were included in the MACH-NC meta-analysis, a separate analysis of the MACH-NC Group was published with studies that added the taxanes into PF IC and had completed accrual before January 2007. With median follow-up of 4.9 years in five randomized trials with a total of 1772 patients, absolute benefit at 5 years was 7.4%, from 35–42.4% (HR 0.79 (95% CI, 0.70 to 0.89; $P < .001$) in favor of taxane–PF IC over PF.[137] EORTC 24971/TAX 323, a phase III open-label randomized trial involving 358 adult patients, evaluated the benefit derived from a docetaxel-based chemotherapy regimen (docetaxel, cisplatin, and 5-fluorouracil, TPF) in inoperable locally advanced head and neck cancer.[138] In this study, induction therapy prior to radiation therapy or surgical intervention was assessed in terms of overall survival. Patients treated with TPF prior to surgery or radiation had a significantly longer median OS compared to a standard treatment of PF, with a 28% risk reduction of death, 18.6 versus 14.5 months ($P = .0128$). Patients also had a significantly longer time-to-disease progression of 11.4 months, compared with 8.3 months ($P = .015$) for the patients receiving standard therapy. Posner and colleagues reported the results of a large randomized phase III study (TAX 324) comparing TPF to PF IC.[136] The study showed TPF to be superior to PF for survival, leading to the approval of TPF by the U.S. Food and Drug Administration for the induction treatment of patients with locally advanced head and neck cancer. The combination of the three compounds in the TPF regimen for advanced head and neck cancer in adults has been 75 mg/m^2/75 mg/m^2/750 mg/m^2 (Study TAX323) and 75 mg/m^2/100 mg/m^2/1000 mg/m^2 (Study TAX 324), respectively. Although MACH-NC showed a survival advantage for PF-based ICT over definitive RT alone, it remained unclear whether TPF-based ICT improves OS over definitive CRT alone because neither of the two studies was designed to address this question. Therefore a three-arm phase III trial was conducted by the Spanish Head and Neck Cancer Cooperative Group, where 439 patients with unresectable SCCHN were randomly assigned to CRT with cisplatin at 100 mg/m^2 given on days 1, 22, and 43, or IC either PF+CRT or TPF +CRT. Even though in the intent to treat (ITT) analysis trial no difference was seen between IC followed by CRT versus CRT alone in PFS, a primary end-point of the study, about 78 (45 in TPF-CRT and 33 in PF-CRT) patients did not receive CRT after induction for reasons other than disease progression. Notably, completion of therapy as planned on the two induction arms would involve 525 mg/m^2 or 600 mg/m^2 total cisplatin. Perhaps for this reason, approximately half of patients did not complete radiation and/or concurrent chemotherapy as planned. Also, many patients on induction arm received restricted therapy even though toxicities were manageable.[139] Surprisingly, in contrast to the two previous TAX 323 and 324 trials, a study by Hitt and colleagues did not show an advantage of TPF over PF.[140] Overall, because of the noted limitations, this study still did not provide any strong evidence to help answer this ongoing debate on this controversial topic.

More recently, investigators for the phase III DeCIDE and Paradigm trials presented data assessing ICT plus CRT versus CRT alone (Table 34.4). Both studies accrued slowly without meeting their original enrollment goals, demonstrating the logistical limitations in conducting such trials in SCCHN. In the DeCIDE trial, only 280 of the planned 400 patients were accrued, and in the Paradigm study, 145 of 300. Both studies showed no statistically significant differences in overall survival, the primary end-point of the study, but a difference in distant recurrence without prior locoregional recurrence was found ($P = .043$) favoring sequential therapy in the DeCIDE study, suggesting benefit of a sequential approach in patients with high risk for distant metastases. Although DeCIDE and Paradigm enrolled a majority of patients with oropharyngeal tumors, their study designs did not address the potential impact of HPV positivity on outcome.[141] Presented at the 2014 American Society of Clinical Oncology (ASCO) meeting but only in abstract form, an Italian study by Ghi and colleagues, with a median follow-up of 41 months, showed that treatment with IC followed by CRT significantly improved 3-year OS and PFS compared with CRT alone.[142] In the study, 421 patients with locally advanced (stage III or IV) SCCHN were randomly assigned to IC with three cycles of TPF followed by CRT, or to immediate CRT with follow-up randomization within each arm to cetuximab or cisplatin plus fluorouracil (2 × 2 design). In an unplanned subgroup analysis of 234 oropharyngeal SCCs (56%), 3-year PFS was 43.5% versus 37.1% (HR: 0.81: 95%CI: 0.57-1.15) and 3-year OS was 63.5% versus 52.8% (HR: 0.82; 95% CI 0.55-1.21) with IC followed by CRT versus CRT alone, respectively. Interestingly, the benefit of induction chemotherapy followed by CRT versus CRT alone was higher in non-oropharyngeal cancer, with HR = 0.66 for 3-year PFS and HR = 0.65 for 3-year OS. Also, in the unplanned subgroup analysis, more benefit was seen when induction chemotherapy was used with cetuximab as a radiosensitizer rather than cisplatin plus fluorouracil (HR = 0.57: 95% CI 0.34-0.93 vs. HR = 0.80 95% CI 0.56-1.15, respectively). No HPV data or smoking data were provided in this analysis.[142]

In summary, sequential therapy appears to have an important role in selected clinical situations, especially for patients with high risk for distant metastasis, and the study by Ghi et al revived major interest in this treatment modality.[142] However,

TABLE 34.4 Summary of Modern Randomized Clinical Trials Using Induction Chemotherapy

	Stage	Therapy (Number of Patients)	End-Point	LRC	DC	OS	PFS
Vermorken et al TAX 323[138]	III/IV	TPF (177) PF (181) Followed by XRT alone	3 years			37% 26%	17% 14%
Posner et al TAX 324[136]	III/IV	TPF PF Followed by RCT	3 years	70% 62%		62% 48%	50% 38%
			5 years	*	*	52% 42%	45% 34%
Hitt et al[139]	III/IV	RCT (128) vs. PF (156) vs. TPF (155)	5 years	49.2% 51.3% 52.9%	N/A	37% 37% 32%	25% 30% 32%
Haddad et al Paradigm[140a]	III/IV	RCT (75) vs. TPF (70)	3 years	85% 84%	89% 93%	78% 73%	69% 67%
Cohen et al DeCIDE[141]	IV	RCT (138) vs. ICT (142)	3 years	88% 91%	81% 90%	73% 75%	N/A
Ghi et al[142]	III/IV	RCT (211) vs. ICT (210)	3 years	N/A	N/A	45.7% 57.6%	36.7% 46.8%

DC, Distant control; *IC,* induction chemotherapy; *LRC,* locoregional control; *OS,* overall survival; *PF,* Platinol fluorouracil; *PFS,* progression-free survival; *RCT,* concurrent radiochemotherapy; *TPF,* Taxotere platinum and fluorouracil; *XRT,* radiotherapy.
*No significant difference between treatment groups, but data not shown.

because of differences in design between the IC protocols, a comparative and consistent statement of benefits still has not been definitively obtained.

Adjuvant Chemotherapy and Radiation

Patients who have undergone surgical resection of their primary tumor may be at high risk of recurrent disease, depending on specific adverse prognostic features that include advanced T status, two or more positive lymph nodes, perineural invasion (PNI), lymphovascular invasion (LVI), positive or close resection margins, and extracapsular extension (ECE). The role of chemotherapy in the postoperative management of the patient with adverse prognostic risk factors has been clarified by two separate multicenter randomized trials and a combined analysis of data from those two trials for patients with high-risk cancers of the oral cavity, oropharynx, larynx, or hypopharynx.[143,144] The U.S. Intergroup trial R95-01 demonstrated statistically significant improvement in LRC and disease-free survival but not OS, whereas the European EORTC trial found significant improvement in survival and the other outcome parameters. There were some differences in design, primary end-point, and exclusion criteria between the two trials. To better define risk, a combined analysis of prognostic factors and outcome from the two trials was performed.[145] This analysis demonstrated that patients in both trials with ECE and/or positive resection margins benefited from the addition of cisplatin to postoperative radiotherapy. Chemoradiation is clearly indicated for ECE and/or microscopic positive mucosal margins. There was a trend toward improved survival in favor of chemoradiotherapy in the group of patients who had stage III-IV disease, PNI, vascular embolisms, and/or clinically enlarged level IV-V lymph nodes secondary to tumors arising in the oral cavity or oropharynx, but the differences were not statistically significant. Interpretation of these results is limited by the fact that the data are derived from a post hoc subgroup analysis rather than from a prospective trial in which statistical analysis was adjusted for subgroup comparison. Even though ECE is a well-established prognostic indicator in SCCHN, a recent finding showed no difference in 5-year disease-specific survival (DSS) between the CRT and RT-alone groups in patients with p16/HPV positive oropharyngeal SCC.[146] In another study that used a pathologic grading system for ECE, p16-positive patients with nodal extracapsular extension did not benefit from addition of chemotherapy to radiation because the study showed no proven survival advantage for CRT; only the patients with the highest grade of ECE benefited from the addition of chemotherapy to radiation.[147] This indicates that the presence of ECE may imply a different risk profile when HPV+ and HPV– groups are compared.

To provide some additional evidence for patients at elevated risk for recurrence based on perineural or vascular invasion, two or more involved lymph nodes, or T3 and T4 tumors, defined as intermediate risk, a phase III RTOG 0920 trial is currently comparing RT alone versus RT plus cetuximab (NCT00956007).

In summary, as the role of adjuvant CRT in high-risk patients is well defined, its role in intermediate-risk patients remains to be answered. Also, the definition of positive margins and extracapsular involvement is not standardized and should be better defined and tested in a prospective study, especially in the HPV-positive population.

Role of Human Papillomavirus in Treatment of Base of the Tongue and Tonsil Squamous Cell Carcinoma

The epidemiology of head and neck cancer has changed remarkably, and as reported by Chaturvedi and colleagues, a rapidly expanding subset of head and neck cancers are acquired through HPV infection.[148] Multiple studies have reported favorable clinical outcomes for patients with HPV positivity in OPSCC. The first landmark study on this topic, an organ preservation study with a total of 96 patients with stage III and stage IV, M0 cancer, was reported by Fakhry and co-workers. Patients received paclitaxel/carboplatin IC followed by CRT with weekly paclitaxel at 30 mg/m^2 and standard fractionation radiation. With 38 HPV-positive and 58 HPV-negative patients, those with HPV-positive SCC had a 61% lower risk of death (HR = 0.39, 95% CI = 0.15 to 1.05, P = .06) and a 62% lower risk of progression (HR = 0.38, 95% CI = 0.12 to 1.15, P = .09) versus patients with HPV-negative SCC after adjustments for age, tumor stage, and ECOG performance status.[149]

Similar results were seen in a retrospective report on RTOG 0129 by Ang and associates, with a 3-year OS of 82.4% (95% CI, 77.2 to 87.6) in the HPV-positive SCC subgroup and 57.1% (95% CI, 48.1 to 66.1) in the HPV-negative SCC subgroup, and a 3-year PFS of 73.7% (95% CI, 67.7 to 79.8) and 43.4% (95% CI, 34.4 to 52.4), respectively.[131] Subsequent division of the patients into risk categories based on HPV status, tumor burden, and tobacco use showed tobacco use as an independent bad prognostic factor.

Retrospective analysis of the TAX 324 clinical study reported a favorable OS in patients with HPV-positive tumors, with 5-year OS at 82% for HPV-positive patients compared with 35% of HPV-negative patients and a PFS of 78% versus 28%, respectively, with P < .0001 for both OS and PFS. The improved survival was attributed mainly to significantly better locoregional control in the HPV-positive group (13% in HPV+ vs. 42% in HPV–, P = .0006).[22]

In the previously described studies, patients with locally advanced oropharyngeal SCC were treated in an identical fashion regardless of HPV status. It is well known that for some patients with HPV-positive SCC, such therapy probably represents overtreatment, causing more toxicity than necessary. With recent epidemiologic changes, current research is focused on "de-escalation," aiming to safely reduce toxicity without compromising clinical outcome. The first "de-escalation" trial, the ECOG 1308, was reported at ASCO 2014. It was a randomized phase II trial, in patients with HPV-positive resectable oropharyngeal SCC, of induction chemotherapy with paclitaxel, cisplatin, and cetuximab followed by randomization to low dose versus standard dose of IMRT at 54 Gy in 27 fractions versus a standard radiation arm with 69.3 Gy in 33 fractions with cetuximab used in both arms. The primary endpoint of this study was 2-year PFS after low-dose IMRT. This study showed that low-risk patients (low T stage, low N stage, <10 pack-years smoking) achieved a 95% 2-year OS, favoring de-intensification in this group. This de-escalation study allowed for significant reduction in toxicity while maintaining high OS and PFS in an experimental arm. Smoking history was an independent prognostic factor that affected the clinical outcomes for patients regardless of radiation dose assignment. The ECOG 1308 study provided a promising paradigm for HPV-positive patients, but because de-escalation still remains experimental, HPV-positive patients should be encouraged to participate in clinical trials that are available across the country (Table 34.5).

Future Directions

Currently, there are no treatment modifications based on the anatomic location specifically for BOT SCC, although recent epidemiologic changes in incidence of HPV-positive oropharyngeal SCC may alter this paradigm. Additional molecular studies that will help guide clinicians in how to combine different markers, both clinical and molecular, for prediction of clinical outcome in patients with BOT SCC will be essential. Preventing spread of HPV16 infection by vaccination and de-escalating therapy with the help of additional predictive markers to identify and select HPV-positive patients for those de-escalating trials is the main emphasis of current clinical research. At the present time, patients should be encouraged to participate in clinical studies that offer treatment modifications based on HPV status. It is hoped that results of those studies will help to make changes in our clinical recommendations or guidelines in the future.

Rehabilitation

Patients diagnosed with head and neck cancer will often encounter swallowing difficulties related to the treatment methods used to eradicate their disease. These include one or a combination of modalities including surgical resection, chemotherapy, and/or radiation therapy. Surgery performed to excise the tumor and surrounding margins can interfere with the structures that are vital to bolus formation and transit as well as airway protection.[150] A patient who undergoes BOT resection will likely experience reduced tongue base retraction, resulting in residue in the vallecula after the swallow and reduced strength of the overall swallow.[151] Radiation treatment to the head and neck often causes both acute and chronic side effects, which have a negative impact on swallowing function. In the short term, patients suffer from mucositis, xerostomia, dysgeusia, and odynophagia. Over the long term, reduced blood supply and damage to the nerve endings of the radiated tissues can cause the muscle fibers to become fibrotic. This impairs the range of motion and flexibility of structures necessary for effective swallowing function.[152] Chemotherapy can be given alone or concurrently with radiation therapy. Side effects may include nausea, emesis, neutropenia, mucositis, and lethargy, which can adversely affect swallowing function and nutritional status. In addition, when chemotherapy is combined with radiation therapy, the side effects relating to swallowing function are often amplified.[153]

TABLE 34.5 "De-escalation" Clinical Trials for HPV-Positive Patients

Trial	Primary End-Point of Study	HPV Testing	Inclusion Criteria	Treatment/Chemotherapy/ Radiation Dose
ECOG 1308	2-yr OS	HPV PCR	Stage III, IVA-IVB oropharyngeal SCC	Low-dose IMRT (50 Gy × 27 fractions) + cetuximab vs standard-dose IMRT (60 Gy × 33 fractions)
Quarterback	3-yr PFS	P16 IHC HPV by PCR	Stage III, IVA-IVB oropharyngeal SCC <10 pack-years smoking	IC-TPF followed by randomization to: Weekly carboplatin AUC 1.5/70 Gy × 35 fractions vs Weekly carboplatin AUC 1.5/56 Gy × 28 fractions
NRG 002	2-yr PFS	P16 IHC	Stage III, IV A, B, or C (T1-T2 N1-N2b or T3 N0-N2b); <10 pack-years smoking	IMRT (60 Gy × 30 fractions) ± cisplatin
RTOG 1016	5-year OS	P16 IHC	Stage III-IV Oropharyngeal SCC	IMRT (60 Gy, day 1-4 once daily, day 5 twice daily) and high-dose cisplatin day 1 and 22 vs. weekly cetuximab × 7 weeks
UMCC	Recurrence rate	HPV testing or P16 IHC	Stage III-IV (excluding N3 or T4), <10 pack-years smoking	Standard dose radiotherapy (70 Gy × 35 fractions) + cetuximab
TROG 12.01	Symptom severity	P16 IHC	Stage III (excluding T1-T2N1) or stage IV (excluding T4, N3, and distant metastasis) ≤10 pack years smoking If >10 pack-years, must be N0-N2a	Standard dose radiotherapy (70 Gy × 35 fractions) + weekly cetuximab or cisplatin
De-ESCA-LATE	Severe toxicity	P16 IHC	Stage III-IVa (T3N0-T4N0, and T1N1-T4N3), except N2b, N2c or N3, and >10 pack-years smoking	Standard dose radiotherapy + weekly cetuximab or cisplatin on days 1, 22, 43
ECOG 3311	2-yr PFS	P16 IHC	Stage III-IV A/B (low risk, intermediate risk, and high risk)	A. Low risk: surgery + observation B/C. Intermediate risk: surgery + low dose (50 Gy × 25 fractions) vs. standard dose radiotherapy (60 Gy × 30 fractions) D. High risk: surgery + standard dose radiotherapy (60-70 Gy × 30-35 fractions) + weekly cisplatin or carboplatin
SIRS	3-yr and 5-yr DFS, LR control	P16 IHC HPV PCR	I. Low risk (complete resection, no LVI, no PNI, no ECS, no matted or low nodes) II. Intermediate risk (complete resection, +LVI, +PNI, <3 positive nodes, ≤1 mm ECS) III. High risk (incomplete surgical resection, 3+ nodes, ≤1 mm ECS, matted or supraclavicular nodes)	I. Low risk: observation II. Intermediate risk: radiotherapy III. High risk: concurrent chemotherapy
ADEPT	2-yr DFS, LR control	P16 IHC	T1-T4aN1 +ECS with negative margins after resection	Standard dose radiotherapy (60 Gy x 30 fractions) ± weekly cisplatin
ORATOR	1-yr QOL	P16 IHC	T1-T2N0-N2 with negative margins after resection (TORS)	Standard dose radiotherapy (70 Gy x 35 fractions) ± chemotherapy

AUC, [area under curve]; *DFS,* disease-free survival; *ECS,* [extracapsular spread]; *HPV,* human papillomavirus; *IHC,* immunohistochemistry; *IMRT,* intensity-modulated radiation therapy; *LR,* [local recurrence]; *LVI,* lymphovascular invasion; *OS,* overall survival; *PCR,* polymerase chain reaction; *PFS,* progression-free survival; *PNI,* perineural invasion; *QOL,* quality of life; *SCC,* squamous cell carcinoma; *TORS,* transoral robotic surgery; *TPF,* Taxotere platinum and fluorouracil.

Swallowing Assessment

The management of dysphagia after treatment for BOT cancer, whether that treatment was surgical or organ sparing, begins with an imaging procedure to properly visualize the physiology of the swallow. This is an important first step to assess swallowing where alterations in anatomy and function are prevalent. Typically patients who undergo treatment for T3/T4 tongue base cancer suffer from a reduction of tongue base to posterior wall contact, an important element in achieving adequate bolus propulsion into and through the pharynx, but they can also exhibit increased oral transit times, post-swallow pharyngeal residue, and reduced oropharyngeal efficiency.[154,155]

The modified barium swallow (MBS) is the most useful imagining technique for diagnosing swallowing dysfunction after treatment for tongue base cancer. The MBS is used to identify specific abnormalities to guide therapeutic interventions. During the MBS, patients are administered varying consistencies of radiopaque materials in an effort to simulate what a patient might encounter in a typical meal. The patient's swallow is viewed in the lateral plane, and real-time movements of the swallowing structures, as well as bolus propulsion, are observed and recorded. Based on these observations, interventions to address the specific swallowing deficits and improve swallowing ability are implemented.

Swallowing Treatment

Swallowing treatment may include simple postural changes, which can be used to control the flow of the bolus or reduce the risk of aspiration. For example, the "chin-down posture" is helpful for patients with reduced tongue base retraction, as this action pushes the tongue base and epiglottis closer to the posterior pharyngeal wall. It also helps to widen the vallecular space, resulting in less post-swallow residue.[156] This is a simple technique and easy for most patients to perform correctly. Other postures including head back, head rotation, and lateral head tilt can be attempted during the MBS to determine their effectiveness with each individual patient. Modifications in either bolus size or consistency can also positively affect the swallow. A larger bolus volume may be more effective at eliciting a stronger or timelier pharyngeal swallow by providing greater sensory input.[156] A liquid wash may be helpful in facilitating the bolus transport of a solid consistency.

Patients can also be instructed in specific swallowing maneuvers that attempt to place aspects of the swallow under voluntary control. For example, the super-supraglottic swallow maneuver, which was originally conceived to improve airway protection for patients who have undergone supraglottic laryngectomy, has been shown to improve tongue base motion in patients who have undergone radiation therapy.[157] With this maneuver, patients are instructed to inhale and hold their breath very tightly while bearing down. The patient is then told to swallow while continuing to hold their breath and bear down. After the swallow is completed, the patient is instructed to cough.[158]

Patients with head and neck cancer who have resection of the tongue base or radiation to the oropharynx often experience difficulty achieving complete tongue base to posterior pharyngeal wall contact. The tongue hold maneuver was designed to improve posterior pharyngeal wall movement. With this maneuver, the patient is required to hold the tongue between the central incisors while swallowing. This increases the anterior movement of the posterior pharyngeal wall, facilitating improved contact with the tongue base.

The effortful swallow maneuver is used to increase tongue base retraction and pharyngeal pressure during the swallow in order to improve bolus clearance from the vallecula.[159] With this maneuver, the patient is instructed to squeeze hard with all their muscles as they swallow. This can be performed with a bolus or as a dry swallow for patients who cannot tolerate oral intake. The effortful swallow has been shown to have an impact on other aspects of the oropharyngeal swallow, specifically when there is evidence of reduced tongue strength, reduced pharyngeal contraction, reduced laryngeal elevation, or decreased laryngeal vestibule closure as evidenced by the MBS.[160]

The normal range of motion of the swallowing structures is often disrupted after treatment for cancer of the head and neck, as a result of either surgical resection and reconstruction or fibrosis secondary to radiation therapy. Range-of-motion exercises are designed to increase the movements of a specific structure by extending the movement in the desired direction and holding it in this position until a strong stretch is felt. Post-surgical patients who performed range-of-motion exercises in the first 3 months after surgery have been shown to have significantly better swallowing outcomes than patients who did not perform these exercises.[161] Range-of-motion exercises can be used to improve the movements of the lips, tongue, jaw, and larynx. Trismus, whether radiation induced or from post-surgical scarring, can be reduced with rigorous and consistent jaw range-of-motion exercises.[162]

Although there is considerable evidence regarding the effectiveness of these swallowing interventions for patients suffering from dysphagia related to head and neck cancer treatment, there are still many unanswered questions. Currently, we do not know the relative contributions of these varied treatment approaches, and studies evaluating specific interventions are needed. Additionally, recent studies have shown the benefit of prophylactic swallowing exercise for patients undergoing chemoradiation, but we do not know the optimal strategy in terms of the frequency or intensity of the therapy.[163] Future study to investigate these questions is needed to help in choosing the most effective treatment strategies to rehabilitate dysphagia after treatment for head and neck cancer.

Surveillance

Tumor surveillance for advanced BOT malignancy is performed with two predominant strategies, namely physical examination including fiber-optic evaluation of the tongue and hypopharynx, and imaging studies. Because the vast majority of recurrences occur within the first 2 years following diagnosis, the intensity of follow-up visits is higher and

includes physical examination and post-treatment baseline imaging of the primary, as well as neck, speech, and swallow evaluation, dental evaluation, and basic serum labs (TSH done every 6 to 12 months for patients who underwent neck irradiation). Continued beyond 5-year surveillance with physical examination should be strongly considered because of the risk of late recurrence or second malignancies, particularly in patients with non-HPV-associated oropharyngeal cancers. Although the interval of surveillance visits may vary somewhat depending on the institution, most centers schedule surveillance visits at a 3- to 4-month interval for the first 2 years, and a 4- to 6-month interval for the subsequent 3 years, depending on the risk profile for the individual. Regular fiber-optic evaluation is critical so that providers are familiar with post-therapy anatomy and to monitor for changes. In some cases, surgical resection may alter the anatomy and confuse radiologists during image interpretation (i.e., remaining lingual tonsillar tissue contralateral to the resected tongue base with increased hyperavidity on PET scanning when compared to the treatment side). Regarding imaging modality, a variety of options are used, including contrast-enhanced CT, PET/CT, contrast-enhanced MRI, and PET/MR. At our institution, we commonly employ PET/CT and use MRI or PET/MR in cases with significant artifact, or when symptoms recur and do not match imaging or examination findings. Negative PET/CT after therapy is a good predictor of prognosis after therapy; however, positive PET/CT must be interpreted more cautiously.[15,164] In situations where surgical salvage is considered, contrast-enhanced MRI can be helpful in delineating the extent of disease and offers superior anatomic resolution of the tongue base.

Conclusion

The management of advanced-stage squamous cell carcinoma of the base of tongue continues to challenge physicians. Current standard of care is multimodality therapy with intensive post-therapy rehabilitation. Coordination of high-quality care at institutions with experience in the management of this disease is crucial, given the oncologic outcomes and the often-devastating functional impact of therapy in this population.

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35

Advanced HPV-Unrelated Pharynx Cancer

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PART 1: ADVANCED HPV-NEGATIVE CANCER OF THE OROPHARYNX AND HYPOPHARYNX

Overview

There have recently been significant changes to head and neck cancer staging that are reflected in the 8th edition of the *AJCC Cancer Staging Manual.* These include a separate staging algorithm for human papillomavirus–associated cancer, restructuring of head and neck–specific cutaneous malignancy, and importantly, division of the pharynx into three components: (1) the nasopharynx, (2) human papillomavirus–associated oropharyngeal cancer (OPC), and (3) HPV-negative oropharynx and hypopharynx cancers. Furthermore, major changes have been instituted in regard to staging cervical nodal metastasis, including differentiating between clinical and pathologic N-stage and incorporating extranodal extension (ENE) in characterizing metastatic carcinoma within the lymph nodes. Because of the often overlapping nature of advanced-stage pharyngeal cancer, this chapter will consider these important staging modifications in the context of the three main subsites of the pharynx, with a particular emphasis on tonsillar cancer, which is increasingly the epicenter of upper aerodigestive tract malignancy (advanced base of tongue cancer is detailed in Chapter 33).

Tonsil or tonsillar fossa cancer comprises approximately 50–60% of patients presenting with oropharyngeal squamous cell carcinoma (OSCC), typically involves patients in the fifth through seventh decades of life, and affects men three to five times more often than women.[1-3] Most early T-stage tumors are asymptomatic, and thus the first presenting sign in these cases is generally cervical lymphadenopathy. However, locally advanced cancers of the tonsil or base of tongue (T3/T4, 6th AJCC staging) make up approximately one third of oropharyngeal cancer presentations and can cause odynophagia, dysphagia, or both. The majority of these cases have ipsilateral lymph node involvement, and 30% will have contralateral lymph node involvement, especially if the soft palate is involved.[4,5] Late symptoms include otalgia, bleeding, decreased tongue mobility, and trismus, the last of which is usually due to invasion of the pterygoid musculature.

Tobacco smoking for more than 10 pack-years and alcohol use are major risk factors for OSCC and appear to have a synergistic effect.[1] Recently, human papillomavirus (HPV), especially HPV type 16, has also been shown to be an important independent risk factor for the development of cancer in a rapidly expanding subset of patients with squamous cell cancer (SCC) of the palatine and lingual tonsils.[6] These tumors are associated with high-risk HPV serotypes that express the E6 and E7 oncogenes and exhibit a strong correlation with nuclear and cytoplasmic p16 overexpression. The incidence of HPV-negative cancers in the United States has decreased by approximately 50% during the past three decades, a trend that is attributable to the decreased incidence of smoking.[1] On the other hand, the prevalence of HPV-related OSCC has increased by 225% from 1988 to 2004, according to the Surveillance, Epidemiology, and End Results (SEER) tissue repository data.[7] Depending on the population being evaluated, HPV infection has been reported in greater than 80% of OSCCs. The risk of such infection increases based on the number of sexual partners.[8]

It has become apparent that HPV-positive disease is a distinct clinical and biologic entity and responds much more favorably to conventional treatment than does its HPV-negative counterpart[7] (Table 35.1). Fakhry and colleagues reported the first landmark study that demonstrated significantly better outcomes for HPV-positive patients,[9] in which a total of 96 patients with stage III and stage IV, M0 cancer were treated with induction chemotherapy (IC) followed by chemoradiotherapy (CRT). In this trial, 38 HPV-positive and 58 HPV-negative patients received paclitaxel/

TABLE 35.1 Major Differences Between Head and Neck Squamous Cell Carcinomas (HNSCCs) by Human Papillomavirus (HPV) Status

	HPV-Positive HNSCC	HPV-Negative HNSCC
Risk factors	High-risk sexual practices	Cigarette and alcohol use
Tumor site	Lingual and palatine tonsils	Non-oropharyngeal sites
Histopathology	Basaloid, nonkeratinizing, poorly differentiated	Keratinizing, moderately differentiated
Molecular Genetic Alterations		
P53 pathway disturbances	Degradation of wt p53 by E6	*TP53* mutations, 17p LOH
Rb pathway disturbances	Degradation of wt Rb by E7	*P16^{INK4A}* -promoter hypermethylation, 9p LOH
Relative responsiveness to chemoradiation	Better	Worse
Relative prognosis	Improved	Worse

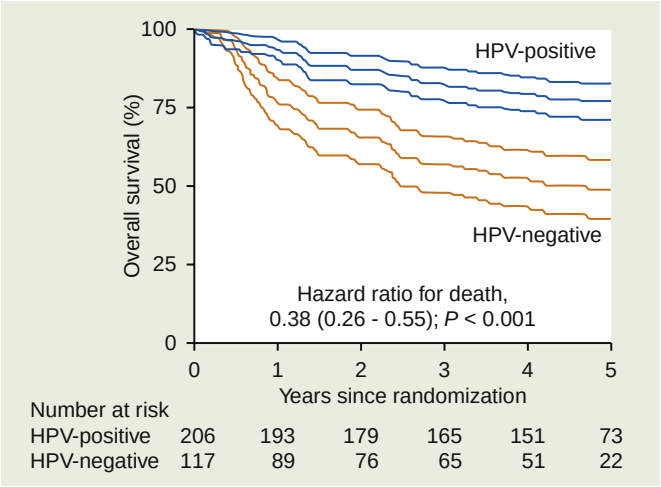
HPV, Human papillomavirus; *LOH,* loss of heterozygosity; *Rb,* retinoblastoma; *wt,* wild type.

carboplatin IC followed by CRT with weekly paclitaxel at 30 mg/m^2 and standard-fractionation radiation. Patients with HPV-positive SCC had a 61% lower risk of death (hazard ratio [HR], 0.39; 95% confidence index [CI], 0.15 to 1.05, P = .06) and a 62% lower risk of progression (HR, 0.38; 95% CI, 0.12 to 1.15, P = .09) than patients with HPV-negative SCC after adjustments for age, tumor stage, and Eastern Cooperative Oncology Group (ECOG) performance status.[9]

Similar results were seen in a retrospective analysis of RTOG 0129 reported by Ang and co-workers,[10] which demonstrated a 3-year overall survival (OS) of 82.4% (95% CI, 77.2 to 87.6) in the HPV-positive SCC subgroup and 57.1% (95% CI, 48.1 to 66.1) in the HPV-negative SCC subgroup, and a 3-year progression-free survival (PFS) of 73.7% (95% CI, 67.7 to 79.8) and 43.4% (95% CI, 34.4 to 52.4), respectively[10] (Fig. 35.1). Subsequent division of the patients into risk categories based on HPV status, tumor burden, and tobacco use showed tobacco use as an independent, negative prognostic factor.

Finally, in a retrospective subset analysis of the TAX 324 clinical trial, favorable OS in patients with HPV-positive tumors was reported, with 5-year OS at 82% for HPV-positive patients compared with 35% of HPV-negative patients and a PFS of 78% versus 28%, respectively (P<.0001). The improved survival was attributed primarily to significantly better locoregional control in the HPV-positive group (13% in HPV-positive vs. 42% in HPV-negative, P = .0006).[11]

Recent investigations suggest that head and neck squamous cell carcinoma (HNSCC) has one of the most complex mutational profiles of all human cancers, exhibiting on average 130 coding mutations per tumor. In 2011, paired studies on genomic mutations in HNSCC using whole exome sequencing were published, which revealed a wide spectrum of unexpected genetic alterations.[12,13] In addition to identifying mutations in previously known HNSCC genes, such as *TP53, CDKN2A,*



• **Fig. 35.1** Overall survival according to tumor human papillomavirus (HPV) status. (From Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010;363:24–35.)

PTEN, PIK3CA, and *HRAS,* these investigators discovered numerous genes not previously associated with HNSCC. The most notable of these mutations were found in genes that regulate squamous differentiation, such as *NOTCH1, IRF6,* and *TP63*.

Both of these studies also suggest important differences in mutation rates in OSCC based on HPV status. Although most of the head and neck tumors examined had mutation rates similar to those for other smoking-related cancers such as small cell lung cancer, the mutation rate of HPV-positive tumors was half that of their HPV-negative counterparts. One important difference is demonstrated by the frequency of *TP53* mutations. Mutations in *TP53* are rarely found in HPV-positive tumors, whereas they are found in the majority of HPV-negative cancers. The viral oncoproteins E6 and E7 cause cell cycle disruption in HPV-positive cancer. E6 binds to p53, which causes the

TABLE 35.2 Oropharynx Risk Stratification

Low risk (3 yr OS = 93.0%):	HPV+
	<10 pack-year smoking history
	N0/N2a nodal disease
Intermediate risk (3 yr OS = 70.8%)	HPV+
	>10 pack-year smoking history
	N2b/N3 disease
	Or
	HPV–
	<10 pack-year smoking history
	N2b or N3 disease
	T2/T3 disease
High risk (3 year OS = 46.2%)	HPV–
	>10 pack-year smoking history
	All T4 disease

HPV, Human papillomavirus; *OS,* overall survival.

loss of a cell cycle checkpoint. E7 acts on the RB protein that normally inhibits cell cycle transcription factors, contributing to cell cycle progression.

Despite technologic advances in surgery and radiation, the defined inclusion of platinum-based chemotherapy into treatment approaches, and the U.S. Food and Drug Administration (FDA) approval of epidermal growth factor receptor (EGFR) inhibitors for use against OSCC, the advanced-stage HPV-negative patient with tonsil or base of tongue cancer continues to have a particularly poor prognosis, with a 5-year survival rate as low as 24%.[14] In contrast to HPV-positive patients, the clinical course of a patient with HPV-negative OSCC is characterized by frequent locoregional recurrences, distant metastases, and second primary tumors, due to a low response rate to current therapeutic strategies. The dichotomy in biologic behavior between these two entities is increasingly driving therapeutic strategies, particularly for patients with small primary tumors. However, for patients with locally advanced disease, the treatment approach may be based on various prognostic features, which have been defined and stratified based on risk of recurrence.

A recursive partitioning analysis of OSCC patients treated with chemoradiation (CRT) has been used to risk stratify patients based on HPV status, smoking history (pack-year smoking history of 10 or more years), tumor stage, and nodal stage as follows[10] (Table 35.2):

1. *Low-risk* patients include those with HPV-positive tumors, a smoking history of 10 or fewer pack-years, and N0 to N2a nodal disease (3-year OS = 93.0%)
2. *Intermediate-risk* patients include those with HPV-positive tumors, a smoking history of more than 10 pack-years, and N2b/N3 disease; or, for those with HPV-negative tumors, a smoking history of 10 or fewer pack-years, N2b or N3 disease, or T2/T3 tumors (3-year OS = 70.8%)
3. *High-risk* patients include those with HPV-negative tumors and a smoking history of more than 10 pack-years; or, for those with HPV-negative tumors, a smoking history of 10 or fewer pack-years, and T4 disease (3-year OS = 46.2%).

Patients with OSCC have an approximately 3–7% risk per year of developing a second primary tumor, the likelihood of which appears to be affected by smoking and HPV status.[15-19] The second primary malignancy rate also appears to be lower for patients with OSCC than for patients with other head and neck sites.[18] Among patients with OSCC, former smokers have a 50% greater risk of second primary malignancy and current smokers had a 100% greater risk than never-smokers.[18]

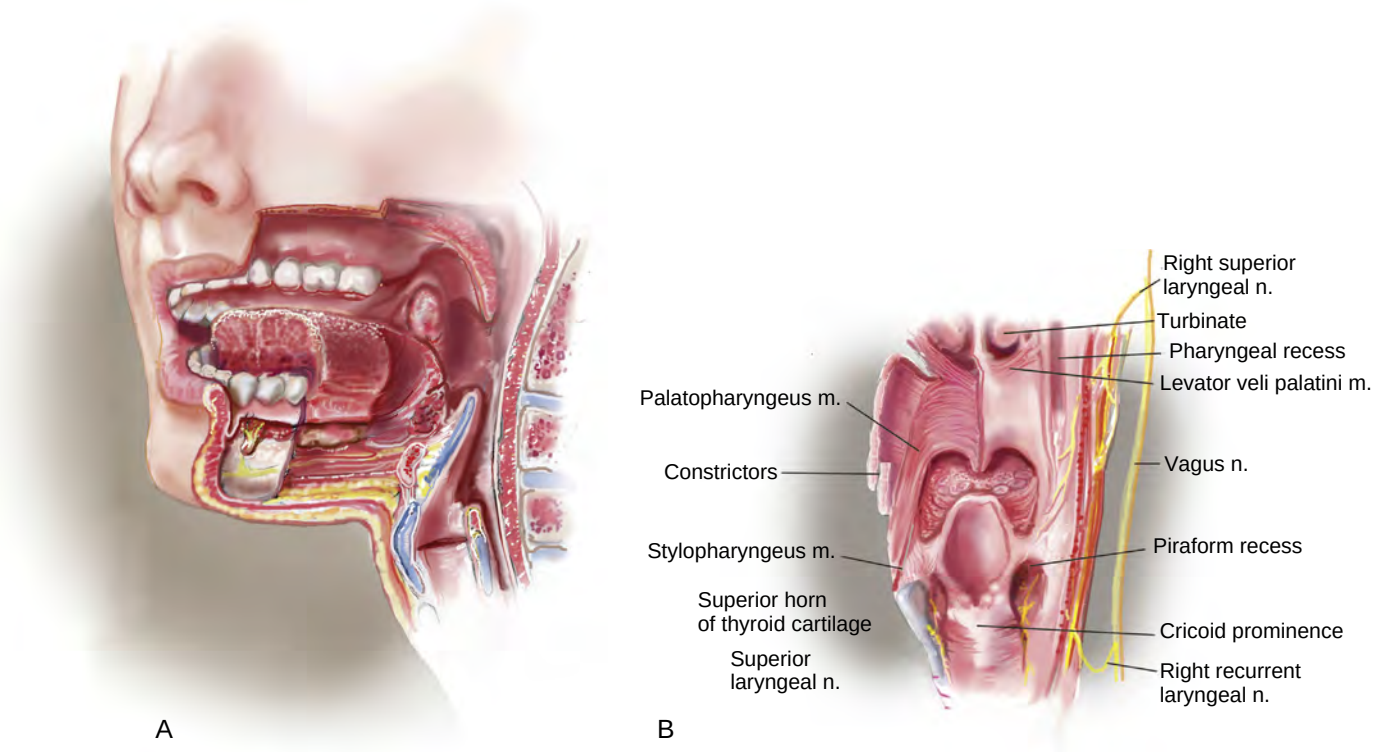
Pertinent Anatomy

The oropharynx is a three-dimensional structure bounded anteriorly by the anterior pillars of the pharyngeal fauces (the palatoglossus muscle), the circumvallate papillae (sulcus terminales), or the junction of the hard and soft palates. Posterior and lateral boundaries are formed by the muscular pharyngeal wall (superior and middle constrictors). The superior extent is the level of the soft palate (some define this as the level of the hard palate). The inferior extent is the level of the base of tongue (level of the hyoid). The oropharynx is further subdivided into five areas. These include lateral pharyngeal walls, tonsillar regions, posterior wall, base of tongue, and soft palate.

The tonsillar pillar anteriorly (the palatoglossal muscle) and posteriorly (the palatopharyngeal muscle) and the glossopalatini sulcus inferiorly form a triangular space that encases the tonsillar lymphoid tissue (Fig. 35.2). Extending from the tonsillar pillars is the soft palate, which demarcates the oral cavity from the oropharynx as well as the oropharynx from the nasopharynx. Innervation is from cranial nerve V.

The glossopharyngeal nerve provides sensory innervation to the oropharynx, tonsils, and tongue base. Referred pain may be present along Jacobson's nerve, which is the tympanic branch of the glossopharyngeal nerve that provides sensation to the medial surface of the tympanic membrane, mucosa of the middle ear, eustachian tube, and mastoid air cells. Pain is described as deep ear pain as opposed to the superficial pain of a trigeminal referred pain.

The lateral pharyngeal walls, which includes the tonsillar fossae, comprise (from superficial to deep) mucosa, pharyngobasilar fascia, superior pharyngeal constrictor muscle, buccopharyngeal fascia, and the parapharyngeal space. The palatoglossus, palatopharyngeus, and stylopharyngeus muscles are intertwined with the superior pharyngeal constrictor muscles. Deep to the parapharyngeal space is the carotid sheath and its contents. The posterior pharyngeal wall, from superficial to deep, is composed of mucosa, pharyngobasilar fascia, superior and middle pharyngeal constrictor muscles, buccopharyngeal fascia, retropharyngeal space, alar fascia, the danger space, prevertebral fascia, and prevertebral muscles. The soft palate comprises the tensor veli palatini, levator veli palatini, musculus uvulae, palatoglossus, and



• **Fig. 35.2** Anatomy of the oral cavity and oropharynx: **(A)** lateral view and **(B)** posterior view of pharynx.

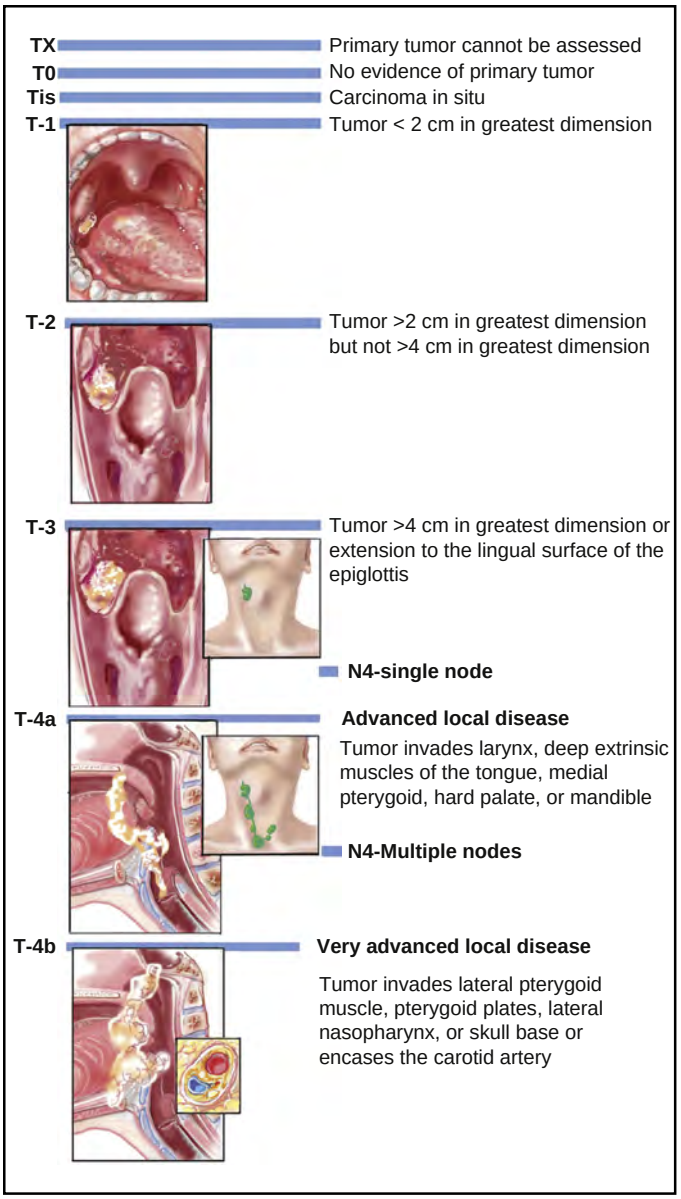
palatopharyngeus. The lateral pharyngeal walls and posterior pharyngeal wall function to constrict the diameter of the oropharynx. The soft palate muscles elevate and lengthen the palate, pushing posteriorly against the narrowed oropharyngeal lumen, creating velar closure for speech and preventing nasal regurgitation of food during swallowing. The same narrowed oropharynx comes into contact with the elevated base of tongue during the oral and oropharyngeal phases of swallowing.

The base of tongue is made up of extrinsic tongue muscles (hyoglossus, genioglossus, styloglossus, and palatoglossus) as well as the intrinsic tongue muscles. It is essential for both the oral and oropharyngeal phases of swallowing. In the oral phase, the base of tongue creates a seal with the soft palate and posterior pharyngeal wall, preventing early passage of the food into the oropharynx and subsequent aspiration. The base of tongue then works to propel the food distally during the oropharyngeal phase of swallowing.

If tonsil cancer spreads locally, it often does so to the tongue, soft palate, or nasopharynx (Fig. 35.3). It can directly invade through the pharyngeal constrictor muscles to the adjacent parapharyngeal space. If the tumor follows the anterior tonsillar pillar and palatoglossus muscle, it can involve the soft and hard palate and/or base of tongue. Posterior tonsillar pillar extension can lead to tumor involving the soft palate, pharyngoepiglottic fold, posterior pharyngeal wall and middle pharyngeal constrictor. Once tumor involves the palate, local extension may affect the tensor and levator palatine muscles and the pterygoid musculature. Extension along the pterygomandibular raphe can lead to oral cavity (retromolar trigone, buccal mucosa) and skull base involvement. Mucosal or submucosal disease spread to the hypopharynx and nasopharynx also occurs. If the tonsil cancer extends superiorly into the nasopharynx, the tumor may spread along the pharyngobasilar fascia.[20] Squamous cell carcinoma of the tonsillar complex is commonly (66–76%) associated with positive lymph nodes at the time of diagnosis, with level II, III, and IV ipsilateral nodes being most commonly affected.[21] Lymphatics from this region drain into the upper jugulodigastric lymph nodes as well as the retropharyngeal lymph nodes.

The hypopharynx is that portion of the pharynx that extends from the superior border of the hyoid bone or vallecula to the lower border of the cricoid cartilage and includes the pyriform sinuses, the lateral and posterior hypopharyngeal walls, and the postcricoid region. The postcricoid region extends from the arytenoid cartilages to the inferior border of the cricoid cartilage, connecting the right and left pyriform sinuses and forming the anterior wall of the hypopharynx. The pyriform extends from the pharyngoepiglottic fold to the upper esophagus. The posterior pharyngeal wall extends from the superior surface of the hyoid bone or vallecula to the inferior border of the cricoid cartilage and the apex of the pyriform sinuses.

The nasopharynx begins at the posterior choana anteriorly and extends to the soft palate. The posterior, superior, and lateral walls include the fossae of Rosenmuller as well as the torus tubaris, forming the eustachian tube orifice. Nasopharyngeal tumors extending to the nasal cavity or oropharynx do not have a worse prognosis in the absence of parapharyngeal space involvement. Involvement of the parapharyngeal space is



• **Fig. 35.3** Locoregional spread of oropharyngeal cancer arranged by stage. Spread is dictated by local anatomy and generally occurs along muscle or fascial planes: superiorly, to the nasopharynx or via the medial pterygoid muscle and pterygoid plate to involve the pterygomaxillary fissure, which lies between the pterygopalatine fossa and infratemporal region; laterally, penetrating the superior constrictor muscle and entering the parapharyngeal space via direct extension, perineural invasion, or lymphatic spread; or inferiorly along the palatopharyngeal muscle to its insertions into the middle pharyngeal constrictor, pharyngoepiglottic fold, and posterior border of the thyroid cartilage.

defined as posterolateral infiltration beyond the buccopharyngeal fascia into the triangular space.

Staging

The staging criteria and staging system for head and neck cancer in general, and oropharyngeal cancer in particular, recently underwent substantive modification as published in the 8th edition of the *AJCC Cancer Staging Manual*, thereby more accurately representing the unique biologic, clinical, and epidemiologic features of HPV-related HNSCC compared to HPV-unrelated disease (Table 35.3). The revised system for HPV-positive OSCC was initially proposed in 2015 based on a cohort of 573 patients with HPV-related OSCC treated with radiation or CRT over a 10-year period and using recursive partition analysis (RPA) and adjusted hazard ratios (AHR) of the current TNM staging criteria to reclassify patients into stage I, II, III, or IV. Two refined staging systems (RPA stage and AHR stage) were proposed based on the current TNM metrics, both of which were superior in prognosticating oncologic outcomes when compared to the current AJCC system.[14]

Following this discovery study, the results of a seven-center study aimed at validating this model were published, with the new HPV OSCC staging system proposed by the International Collaboration on Oropharyngeal Cancer Network for Staging (ICON-S). This was essentially a modified version of the previous AHR system, as the authors felt that smoking and age should be excluded from an anatomically based prognosticating system. In addition, they found no difference in survival between T4a and T4b disease, leading to the consolidation of T4 staging and ICON-S stage IV for patients with metastatic disease.

Immunohistochemistry for p16 overexpression has emerged as an important surrogate biomarker for HPV-mediated disease. p16 is upregulated when HPV16 oncoproteins degrade p53 and pRB, leading to HPV-mediated carcinogenesis. All OSCC should be tested for p16, and those that do not overexpress p16 should be staged using the p16-negative staging system. The cutoff point for determining p16 by IHC is nuclear expression with greater than +2/+3 intensity and >75% distribution, under which tumors should be staged with the p16-positive system.

P16-negative OSCC, OSCC without a p16 immunostain performed, and all cancers of the hypopharynx are now staged separately from p16-positive OSCC (see Table 35.1). Numerous changes to this classification scheme have been included in the updated system, including the following: (1) Separate N category approaches for patients treated without cervical lymph node dissection (clinical N or cN) and patients treated with cervical lymph node dissection (pathologic N or pN); (2) extranodal extension (ENE) is introduced as a descriptor in N categorization for all HPV-negative cancers, and its presence is designated pN2a for a single ipsilateral node <3 cm and pN3B for all other node(s); (3) clinically overt ENE is classified as ENE and is considered ENE (+) for cN; and (54) pathologically detected ENE is classified as either ENE_{mi} (<2 mm) or ENE_{ma} (>2 mm) for data collection purposes only, but both are considered ENE (+) for definition of pN.

The primary tumor stage remains essentially the same in the modified p16-positive staging system as in the traditional p16-negative system, with the exception that the p16-positive classification does not include a Tis category and there is not a T4b subcategory within the T4 group. In addition, the AJCC recommends other prognostic factors be considered and

TABLE 35.3 American Joint Committee on Cancer Staging for Oropharyngeal (p16–) and Hypopharyngeal Squamous Cell Cancer (8th Edition)

Oropharynx (p16–)

Primary tumor (T)

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor >2 cm and ≤4 cm in greatest dimension
T3	Tumor >4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, mandible
T4b	Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
	Mucosal extension to lingual surface of epiglottis from primary tumors of the base of tongue and vallecula does not constitute invasion of the larynx.

Hypopharynx

TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to one subsite of hypopharynx and/or ≤2 cm
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or >2 cm and ≥4 cm without fixation of hemilarynx
T3	Tumor >4 cm or with fixation of the hemilarynx or extension to esophagus
T4	Moderately advanced and very advanced local disease
T4a	Moderately advanced local disease. Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue
T4b	Very advanced local disease. Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
	Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.

Regional Lymph Nodes: Clinical (cN)

Oropharynx (p16–) and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (–)
N2	Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE (–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE (–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE (–)
N2a	Metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE (–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE (–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE (–)
N3	Lymph node(s) larger than 6 cm and ENE (–) or metastasis in any node(s) and clinically overt ENE (+)
N3a	Lymph node(s) larger than 6 cm and ENE (–)
N3b	Metastasis in any node(s) and clinically overt ENE (+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathologic ENE should be recorded as either ENE (–) or ENE (+)

Continued

TABLE 35.3 American Joint Committee on Cancer Staging for Oropharyngeal (p16−) and Hypopharyngeal Squamous Cell Cancer (8th Edition)—cont'd

Regional Lymph Nodes: Pathologic (pN)	Oropharynx (p16–) and Hypopharynx
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (–)
pN2	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE (–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE (–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE (–)
pN2a	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE (+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE (–)
pN2b	Metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE (–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE (–)
pN3	Lymph node(s) larger than 6 cm and ENE (–); or metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE (+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+)
pN3a	Lymph node(s) >6 cm and ENE (–)
pN3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE (+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE (+)

Distant Metastasis (M)	Oropharynx (p16–) and Hypopharynx
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Registry Data Collection Variables

1. ENE clinical: ENE (+) or (–)
2. ENE pathologic: ENE (+) or ENE (–)
3. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
4. Perineural invasion
5. Lymphovascular invasion
6. p16/HPV status
7. Performance status
8. Tobacco use and pack-years
9. Alcohol use
10. Depression diagnosis

TABLE 35.3 American Joint Committee on Cancer Staging for Oropharyngeal (p16−) and Hypopharyngeal Squamous Cell Cancer (8th Edition)—cont'd

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated
G4: Undifferentiated

Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In Amin MB et al, eds. *AJCC cancer staging manual,* 8th ed., New York: Springer, 2017.

recorded along with standard staging information, including ECOG/Zubrod or Karnofsky performance measures, tobacco and alcohol use, tumor location, number and size of nodes, perineural invasion, and ENE. There is no grading system for HPV-mediated oropharyngeal tumors.

History and physical examination are always key components of staging, as no imaging technology is sufficient to replace the clinician's perception and judgment. After tissue confirmation by biopsy of the primary site or a lymph node, computed tomography (CT) and positron emission tomography (PET) scans are recommended for completion of staging. The disadvantages of PET include the decreased spatial resolution offered by this modality (5-mm threshold), the chance of false-negative results with necrosis (particularly in lymph nodes), and the chance of false-positive results in the setting of inflammatory processes, infection, and post-treatment changes. Other causes of false-positive or false-negative findings in PET are regions of normal physiologic uptake that are misinterpreted. Tissues that are normally metabolically active include salivary tissue, lymphoid tissue, and the thyroid gland. The appearance of lymphoid tissue of Waldeyer's ring, in particular, can be confounding. Although FDG uptake in these structures is generally symmetric, focal asymmetry may provide a hint as to the location of a primary tumor for patients with an unknown primary lesion. Obviously, for the patient with a T3/T4 tumor, location of the primary is not an issue. Unfortunately, symmetry of uptake in the lymphoid tissue does not preclude malignancy or inflammation, and asymmetry of uptake does not always indicate malignancy (false positive).[22] Careful clinical evaluation of the site via direct visualization, nasopharyngoscopy, and manual palpation is critical to successful clinical staging.

Magnetic resonance imaging (MRI) may be considered if involvement of the nasopharynx is suspected.[23] PET scans do not distinguish tumor-involved lymph node from reactive lymph node.[24] As noted earlier, HPV-positive cancers seem to have lower incidence of second primary cancers,[25] but unknown primaries are relatively common because of the innocuous nature of many HPV-related primaries. PET scans are useful for suggesting a possible primary site when none can be visualized, and furthermore, they can detect distant metastases as well as synchronous second primary tumors. Upper endoscopy may be considered to rule out synchronous esophageal cancer for patients with risk factors such as chronic alcohol consumption[26]; however, the routine use of "triple endoscopy" (i.e., direct laryngoscopy, bronchoscopy, and esophagoscopy) for all patients is no longer recommended.

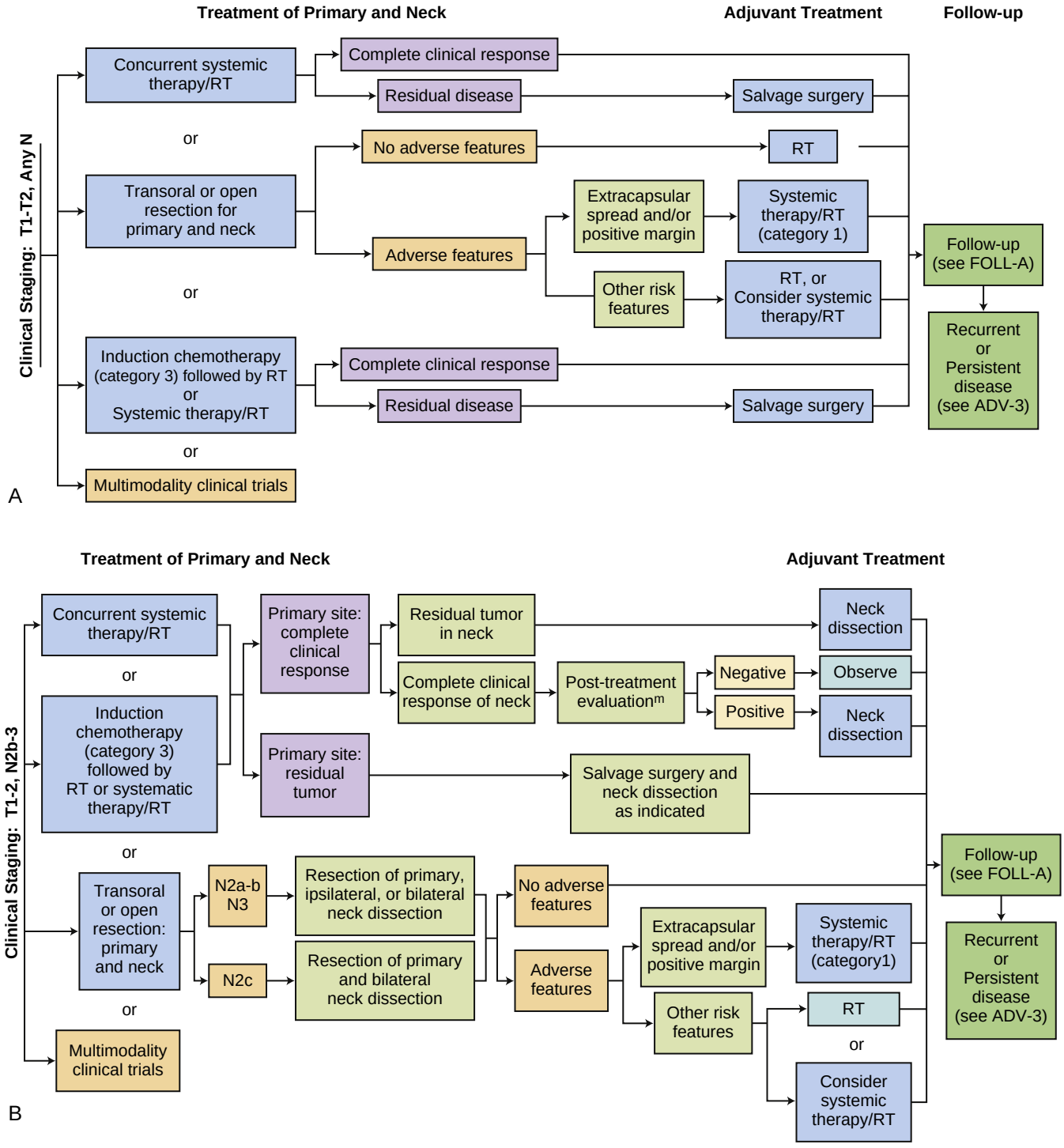
Management

Treatment regimens for patients with locally advanced oropharyngeal or hypopharyngeal cancer are multimodal, and success has been achieved in improving local, regional, and distant control, organ preservation, and quality of life (Fig. 35.4). Although some clinicians question the wisdom of organ preservation for an early tonsil or base of tongue cancer, the removal of which by itself results in little functional deficit, there is little doubt that organ preservation strategies that encompass CRT offer a rational alternative to surgery for bulky tumors that will require radical resection with free flap reconstruction and is preferred to upfront pharyngolaryngectomy in most cases.

Radiation therapy (RT) with concurrent single-agent cisplatin at 100 mg/m^2 given every 3 weeks for three cycles or single-agent cetuximab at 400 mg/m^2 loading dose followed by 250 mg/m^2 weekly is the current standard initial treatment for patients with locoregionally advanced, non-metastatic tonsil cancer who have large primary tumors (T3/T4).[27,28] An altered radiation fractionation scheme is recommended as per RTOG 0129 results if the patient is predicted to be unable to receive the third cycle of cisplatin.[29] Alternatives to cisplatin-based chemotherapy, such as carboplatin and 5-FU, should be based on patient intolerance or protocol and accompanied by standard radiation fractionation.[29]

Early evidence of benefit of adding concurrent CRT to radiation for advanced OSCC was established in that late 1990s by the French GORTEC 9401 study, where patients with stage III/IV disease were randomized to either radiation alone (70 Gy) or radiation combined with three cycles of carboplatin and fluorouracil chemotherapy.[30] Overall survival and locoregional control were both significantly improved with the addition of concurrent chemotherapy. Five-year survival was increased by 6% and locoregional control by 23%. The improvement in survival and locoregional control came at the cost of increased grade 3-4 complications (30% vs. 56%, P = .12). In a meta-analysis of chemotherapy in head and neck cancer (MACH-NC) of 87 randomized studies between 1965 and 2000 encompassing more than 16,000 patients, the 5-year absolute benefit associated with concomitant CRT in OSCC was 8.1%.[31]

Two additional important clinical trials established the role of chemotherapy regardless of the type of RT schedule, showing that



• **Fig. 35.4** Treatment of oropharyngeal carcinoma: **(A)** clinical staging T3/T4a, N0-1; **(B)** clinical staging any T, N2/T3. *RT,* Radiotherapy.

an acceleration of radiotherapy cannot compensate for the lack of chemotherapy.[10,32] In RTOG 0129, a total of 721 patients were randomly assigned to receive accelerated-fractionation radiotherapy and two intravenous cisplatin doses at 100 mg/m^2 on days 1 and 22, or to undergo standard-fractionation radiotherapy and three cisplatin doses at the same level given on days 1, 22, and 43. The primary end-point was to detect a 25% reduction in the rate of death, but there was no statistically significant difference between the two arms. With the median follow-up of 4.8 years, the 3-year OS was 70.3% (95% CI, 65.6 to 75.1) versus 64.3% (95% CI, 59.3 to 69.2; P = .18) between the experimental and standard arms, respectively.[10] Similar results were seen in the GORTEC 99-02 randomized study, which assessed the potential benefit of a combination of different intensification strategies by randomizing 840 patients among three groups: conventional chemoradiotherapy (70 Gy in 7 weeks plus three cycles of 4 days of concomitant

TABLE 35.4 Locoregional Control and Overall Survival in Phase III Clinical Trials Using Combined Therapy Versus Radiation Alone

Study	Total Number of Patients	Total Number of OPX	Locoregional Control*	Overall Survival*
Bonner et al 3-year[28]	424	253 (59%)	47% vs. 34%	55% vs. 45%
Bonner et al 5-year[133]	424	253 (59%)	Not reported	46% vs. 36%
Adelstein et al 3-year[27]	295	160 (54%)	Not reported	37% vs. 23%
GORTEC 3-year[32]	222	222 (79/222 with BOT)	66% vs. 42%	51% vs. 31%

BOT, Base of tongue; *OPX,* oropharynx.
*Experimental arm versus standard arm respectively.

carboplatin-fluorouracil), accelerated radiotherapy-chemotherapy (70 Gy in 6 weeks plus two cycles of 5 days' concomitant carboplatin-fluorouracil), or very accelerated radiotherapy alone (64.8 Gy [1.8 Gy twice daily] in 3.5 weeks). No benefit was seen for accelerated RT arms in PFS ([HR] 1.02, 95% CI 0.84 to 1.23; $P = .88$), OS (1.05, 0.86 to 1.29; $P = .60$), locoregional failures (0.97, 0.74 to 1.26; $P = .81$), or distant metastases (1.26, 0.90 to 1.75; $P = .18$).[32] Some of the limitations of the GORTEC 99-02 study were the lack of information on HPV status, the prohibition of intensity-modulated radiation therapy (IMRT), and the study design, which allowed the conventional arm to receive more chemotherapy than the accelerated arm. In both studies, the experimental arms added an additional cost, logistical complexity, and extra toxicity with no improvement in clinical outcome when compared to the standard-fractionation arms.

As seen in other head and neck cancer sites, IMRT also has had an impact on outcomes in OSCC. Memorial Sloan Kettering reported their experience of 442 patients with advanced OSCC treated between 1998 and 2009.[33] Three-year local control was seen in 94.6% with regional control of 94.4%. IMRT lessened late effects, with grade 2 or higher dysphagia seen in only 11% and xerostomia reported in 29%. MD Anderson, similarly, reported their experience for 776 patients with OSCC treated with IMRT and achieved 5-year OS of 84% and locoregional control of 90% with only 7% of patients recurring at the primary site and neck recurrence in only 3% of patients with controlled primary site.[34] Not surprisingly, the probability of local control depends on tumor volume, with T3/T4 lesions having 80% probability of local control compared to T1/T2 lesions having around 90% probability.[35] This is still improved compared to the historical review prior to IMRT.[36]

The primary management of locally advanced pharyngeal cancer with surgery is often a pyrrhic effort, not only because of the subsequent need for adjuvant radiation plus or minus chemotherapy, but perhaps more importantly, because of the impact on the quality of life. Radical tonsillectomy has traditionally required midline mandibulotomy with flap reconstruction. Patients with poor pulmonary function or those who require significant near circumferential pharyngectomy or subtotal glossectomy often require total laryngectomy to prevent aspiration. Transoral robotic surgery (TORS) and transoral laser microsurgery (TLM) represent minimally invasive surgical techniques that do not require the routine use of access mandibulotomy; however, TORS or TLM is not applicable for most T3/T4 tonsil cancers, even in the salvage setting.

There has not been a randomized study comparing surgery versus radiation for OSCC. To help compare the two outcomes, Parsons et al.[36] published a review of 51 studies reporting on 6400 patients with OSCC treated with surgery with or without radiation therapy (RT) or primary radiation without neck dissection. The majority of these patients underwent open surgical resection with mandibulotomy and radical neck dissection followed by adjuvant RT, or conventional external-beam RT with radical neck dissection after the non-operative therapy. IMRT was not available during the three decades before this review. The results for patients with SCC in the tonsillar region who underwent surgery versus RT were as follows: local control, 70% versus 68% ($P = .2$); locoregional control, 65% versus 69% ($P = .1$); 5-year survival, 47% versus 43% ($P = .2$); 5-year cause specific survival, 57% versus 59% ($P = .3$); severe complications, 23% versus 6% ($P < .001$); and fatal complications, 3.2% versus 0.8% ($P < .001$). The authors concluded that non-operative therapy was preferable to operative therapy for OSCC, regardless of stage.

Because of the better outcomes in HPV-positive cancers, dose de-escalation trials are underway with hopes of reducing the long-term complications from radiation therapy. However, concurrent chemotherapy and radiation to definitive biologically equivalent dose of 70 Gy remains the standard of care for T3/T4 tonsil cancers, regardless of HPV status[37] (Table 35.4).

Radiation Therapy

There are three cardinal rules in radiation therapy. Rule 1: put the tumor in the beam. Rule 2: put organs-at-risk out of the beam. Rule 3: put the tumor in the beam. Identifying the gross tumor volume and its draining lymph nodes is the first and most important step in radiation treatment planning. The technical aspects of radiation therapy are covered in detail in Chapter 13. Tumor target volumes and organs-at-risk (e.g., salivary glands, mandible, spinal cord) are contoured on the CT images taking

into account staging imaging, pathology reports, and physical exam. Target volumes have specific definitions recognized by all radiation departments: The gross tumor volume (GTV) defines the area(s) of known measurable tumor and grossly positive lymph nodes either on imaging or examination, and it receives the highest dose of radiation of 70 Gy. The clinical tumor volume (CTV) is an expansion of the GTV to cover subclinical spread of disease surrounding the GTV. Identifying the various lymph node groups on axial planning CT images is critical, but the CTV volume needs to be adjusted based on clinical judgment.[38] Generally for T3/T4 lesions of the tonsil, bilateral levels I-V plus retropharyngeal lymph node coverage is recommended[39] (Fig. 35.5). The ipsilateral (and contralateral) neck is considered intermediate risk if there is a clinically positive lymph node and is prescribed approximately 60 Gy (see Chapter 13 for details). The contralateral (and ipsilateral) neck, if clinically negative, is considered low risk and prescribed approximately 50 to 54 Gy. In the uncommon case when the ipsilateral neck is clinically negative but the contralateral neck is positive, bilateral necks should be considered intermediate risk because isolated contralateral lymph nodes are rare[40] (Fig. 35.6). Understanding how tumor spreads locally is also regnant in determining the CTVs. For example, for tumors that invade the nasopharynx, the coverage of the pharyngobasilar fascia up to the pterygopalatine fossa is often neglected, which can result in unfortunate recurrences at the base of skull making salvage nearly impossible (Fig. 35.7). CTVs are expanded after they are finalized to create a planning treatment volume (PTV). The PTV expansion accounts for daily variations of patient setup and anatomy and varies between treatment centers based on institutional certainty on the accuracy of the setup procedure, which may be affected by image guidance, immobilization devices, and so on.

The challenge of comparing the outcomes of one institution to another stems from the heterogeneity of the interpretations of what constitutes GTVs and CTVs, and how much to expand the volumes to generate the PTV, even whether or not to add chemotherapy.[41] There are no mandatory guidelines on how one should plan a radiation treatment, so each institution should develop a standard methodology, preferably adhering to a widely accepted published protocol, and make adjustments over time depending on their outcomes. It is also beneficial to have an internal review process of checking the contours among radiation oncologists to help preserve consistency and discover potential mistakes, which should help improve the results of patient care.[42]

No contemporary treatment should use two-dimensional techniques based primarily on x-ray plain film imaging, surface anatomic landmarks, and manual dose calculations. At minimum 3D-conformal radiation therapy (3D-CRT) should be used and preferably IMRT (photon or proton) if available. 3D-CRT and IMRT are discussed in detail elsewhere (Chapter 13). Compared with 3D-CRT, IMRT for head and neck cancer can better reduce treatment-related toxicity, resulting in improved quality of life.[43] A recent meta-analysis of five prospective phase III randomized controlled trials comparing IMRT with two-dimensional radiotherapy or 3D-CRT showed that IMRT reduced the incidence of grades 2 to 4 xerostomia without compromising locoregional control and overall survival.[44]

Image-guided radiation therapy (IGRT) is the process of near real-time imaging during a course of highly conformal radiotherapy, with the ultimate intent of improving target accuracy and precision by correcting for geometric and anatomic deviations. This is also covered in Chapter 13. This technology helps the treating physician to adhere to the three cardinal rules of radiation therapy, because we can "see" the tumor volume at the time of treatment. The temptation arises, however, to make the GTV, CTV, and PTV volumes tighter in order to reduce side effects. Clinical judgment cannot be taught but must come from experience, often compelled by untoward outcomes; therefore a careful follow-up of the patients' outcomes is mandatory in order to develop a keen sense of where not to cut corners.

By default, treatment of T3/T4 oropharyngeal tumors will require a large volume of normal tissue to be exposed to bystander radiation. Any head and neck radiotherapy can cause temporary and/or permanent damage to the parotids, submandibular glands, mandible, and teeth, among other tissues. Studies have shown that parotid gland function is preserved if mean dose to the gland is kept lower than 24 to 26 Gy.[45] This often cannot be achieved without compromising tumor coverage on the ipsilateral side if the patient presents with large level II lymph nodes. In order to adhere to the three cardinal rules, the ipsilateral parotid may have to be sacrificed, which inevitably will lead to compromised quality of life. This underscores the importance of a team approach to radiation therapy.

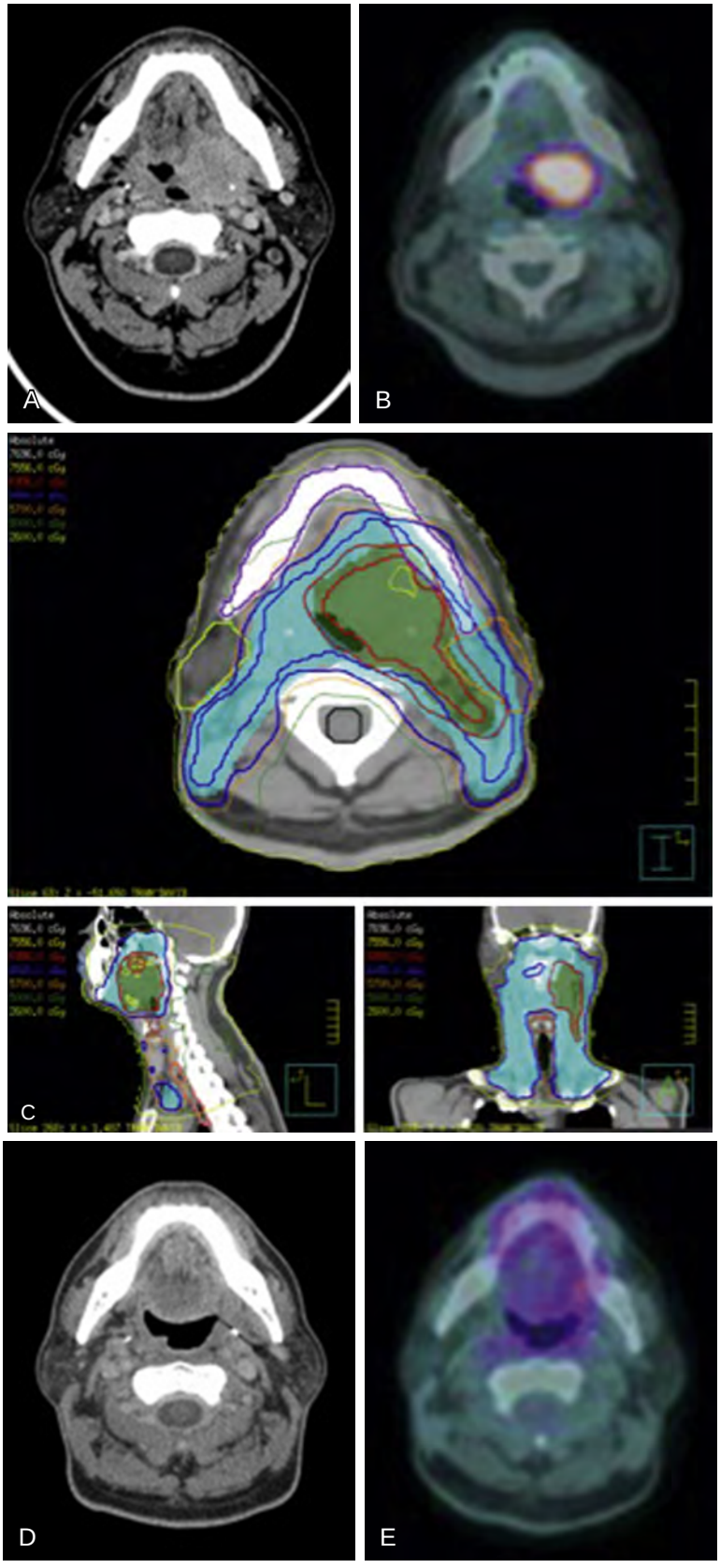
The first step in the management of oral complications of head and neck radiotherapy begins with proper multidisciplinary assessment and dental consultation.[46] Careful examination and imaging is necessary prior to radiotherapy with proper identification of teeth that need to be removed prior to treatment, and particular attention should be drawn to the ipsilateral molars (see Chapter 13 for detailed discussion of oral complications). Radiation therapy for all head and neck cancers should never be viewed as an isolated effort, but must be engaged in as part of a multipronged effort in collaboration with surgeons, medical oncologists, dentists, therapists, nurses, physical therapists, dieticians, and so on. A multidisciplinary approach leads to better adherence to best practice and thus to improved survival.[47,48]

Stereotactic body radiation therapy (SBRT) is an external beam radiation therapy method that very precisely delivers a high dose of radiation to an extracranial target. SBRT is typically a complete course of therapy delivered in one to five sessions (fractions).[49] It usually combines IMRT, IGRT, and stable immobilization to target the gross tumor volume with tight margins in order to deliver high fractional radiation dose. The use of SBRT is emerging for salvage of treatment failures with definitive radiation or chemoradiation,[50,51] but surgical salvage should be considered if possible for recurrent tumors.

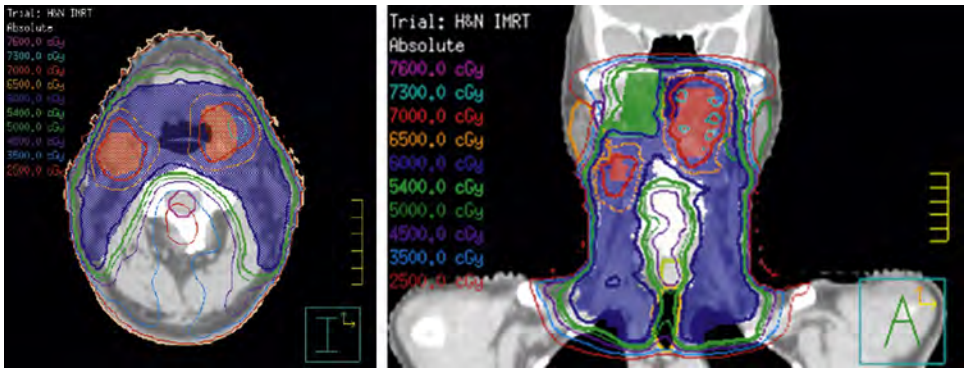
Chemotherapy

Because chemotherapy can be given in various clinical scenarios, the three most common strategies are discussed in this chapter:

1. Concurrent therapy with chemotherapy or targeted agents given simultaneously with radiation to enhance its effect; also known as combined chemoradiation therapy (CRT)



• **Fig. 35.5** A 41-year-old man with cT4N2bM0 squamous cell carcinoma of left tonsil, p16+ diagnosed in July 2013. **A,** Pretreatment CT. **B,** Pretreatment positron emission tomography (PET)/CT. **C,** Isodose lines for planned treatment with concurrent cisplatin and intensity-modulated radiation therapy (IMRT): 70 Gy to gross disease, 60 Gy to bilateral neck due to the primary crossing the midline and having multiple shoddy lymph nodes on the contralateral neck. **D,** CT image 3 years following definitive chemoradiation, clinically with no evidence of disease but with significant dysphagia. **E,** PET/CT 3 years following treatment.



• **Fig. 35.6** Radiation treatment plan for a 70-year-old man with left T3, human papillomavirus (HPV)-positive squamous cell carcinoma (SCC) of the tonsil with an isolated positron emission tomography (PET)-avid contralateral lymph node. The ipsilateral neck, even though clinically N0 and therefore low risk, was treated to 60 Gy (blue isodose line) because of high clinical suspicion of occult lymph node metastases, because isolated contralateral lymph nodes are rare.

2. Induction chemotherapy (IC); also known as neoadjuvant therapy with chemotherapy given before definitive therapy
3. Postsurgical adjuvant therapy that includes concurrent CRT or RT alone

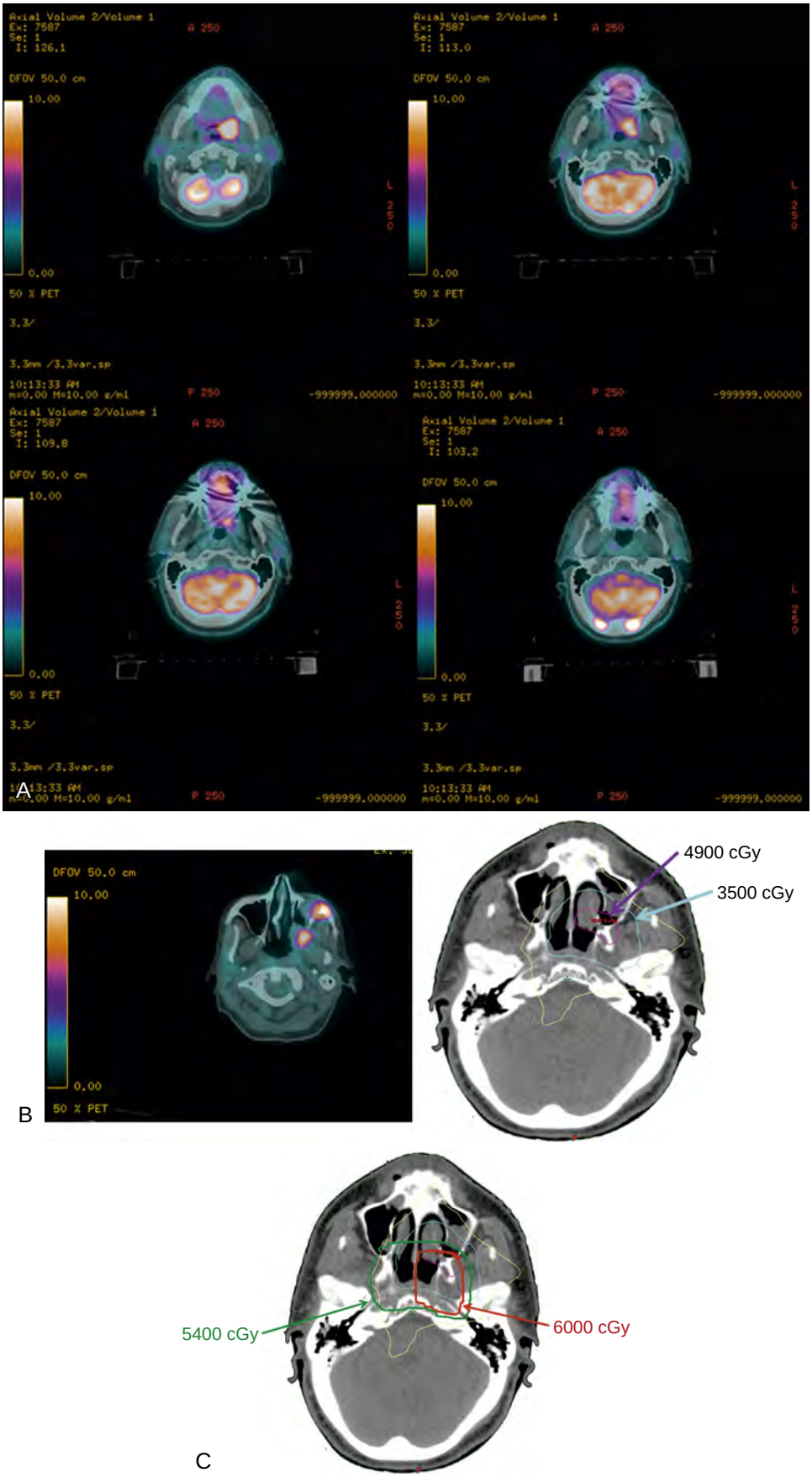
Concurrent Chemoradiotherapy

As noted earlier, based on the results of individual trials and meta-analyses, the addition of concurrent chemotherapy to definitive RT has become the favored approach for organ function preservation for resectable disease and for definitive management of unresectable HNSCC, which results in an OS benefit of 8.1% (95% CI, 4.8 to 11.4, $P < .0001$).[27,30,31,52]

Initial efforts to incorporate chemotherapy into the treatment of HNSCC patients by employing agents such as cyclophosphamide, vincristine, and bleomycin resulted in fatal complications and intolerable toxicities (mainly excessive mucositis) and was thus quickly abandoned in favor of cisplatin.[53] A series of randomized clinical trials have since provided strong evidence for platinum-based monotherapy, combination, or targeted therapy by comparing combined treatment to RT alone (see Table 35.4). In 1987, Al-Sarraf and colleagues reported the results of RTOG 81-17, which was a phase I/II study with 124 patients enrolled with locally advanced inoperable HNSCC, of whom 39% had OSCC, and received 66 to 73.8 Gy of daily radiation with cisplatin 100 mg/m^2 given every 3 weeks. One-year disease-free survival (DFS) was 51% and OS was 66%, but only 60% of subjects completed planned treatment because of major toxicities including stomatitis (31%), leukopenia (11%), anemia (8%), and nausea and vomiting (6%).[54] As data from RTOG 81-17 matured, 4-year locoregional control (LRC) rates of 43% and an OS of 34% were reported in 1990, and a rationale for coordination of a randomized trial comparing cisplatin and radiotherapy versus radiotherapy alone in advanced HNSCC was established.[55] In 2003 Adelstein and colleagues reported an intergroup phase III study with 295 patients, of whom 160 had OSCC, treated with standard radiation only therapy or two schedules of concurrent chemoradiotherapy, sequential or concurrent.[27] Addition of concurrent high-dose cisplatin to conventional radiation improved 3-year OS with 23% in RT versus 37% in CRT arm ($P = .014$), establishing bolus cisplatin as a standard chemotherapy used in combination with radiation in HNSCC.[27] Those individual trials, as well as MACH-NC analysis, influenced the decision of the National Comprehensive Cancer Network (NCCN) to establish a high-dose bolus cisplatin (100 mg/m^2 on days 1, 22, and 43) as the preferred regimen for treatment of locally advanced HNSCC. However, CRT came with the price of significant toxicity and is associated with acute mucositis (71% grade 3 and 39% grade 4) and severe late toxicity (14% grade 3 and 9% grade 4).[30]

In search for treatment that is less toxic and equally efficacious compared with platinum-based concurrent CRT, Bonner and colleagues used compelling data from a phase I study with radiation and cetuximab, an epidermal growth factor inhibitor (EGFR), to create a multicenter phase III randomized study with cetuximab and radiation versus radiation alone.[28,56] The so-called Bonner trial demonstrated an improvement in the median survival at 3 and 5 years, favoring the cetuximab plus RT arm, while showing no adverse changes in quality of life (QOL) in the 424 patients with locoregionally advanced HNSCC who were enrolled.[28] The benefit of cetuximab was more evident in OSCC, in younger patients with good performance status, and when combined with hyperfractionated radiotherapy. Although this study initially had some limitations due to the lack of data on HPV status and the rate of feeding tube dependence, a recent retrospective analysis suggests that the addition of cetuximab to RT improved clinical outcomes regardless of p16 or HPV status versus RT alone.[57] Regardless, cetuximab has provided a reasonable alternative for patients who cannot tolerate platinum and is to date the only systemic agent to be approved by the FDA for use in HNSCC in the past 30 years.

Disappointing results were seen when using a combination of an EGFR inhibitor with cisplatin during radiation. A large randomized phase III trial (RTOG 0522) with a median follow-up of 3.8 years randomly assigned a total of 940 patients to concurrent cisplatin (100 mg/m^2 on days 1 and 22), given with accelerated radiation (70 Gy in 42 fractions over 6 weeks), with or without concurrent cetuximab. The study showed no difference between the experimental and standard treatment in 3-year PFS (59% vs. 61%) (HR, 1.08; 95% CI, 0.88 to 1.32), OS (76% vs. 73%; HR, 0.95; 95% CI, 0.74 to 1.21), locoregional failure (26% vs. 20%), and distant metastases (10% vs. 13%), respectively.[58] Similar negative results were seen in a



• **Fig. 35.7** A 67-year-old man was diagnosed with cT3N2 left tonsil, human papillomavirus (HPV)-positive squamous cell carcinoma (SCC). **A,** Pretreatment positron emission tomography (PET). Note the signal at near the inferior aspect of the left pterygoid plate suggesting involvement of the soft palate and the floor of the nasopharynx. **B,** Four months after completing chemotherapy and radiation, a post-treatment PET *(left)* showed disease near the apex of the pterygoid plates and the maxilla. Review of the isodose lines *(right)* shows that the area of recurrence was inadequately covered prophylactically. **C,** Proposed prophylactic coverage of 60 Gy *(red)* and 54 Gy *(green)*.

TABLE 35.5 Summary of Modern Randomized Clinical Trials Using Induction Chemotherapy

	Stage	Therapy/Number of Patients	End-point	LRC	DC	OS	PFS
Vermorken et al, TAX 323[136]	III/IV	TPF (177) PF (181) Followed by XRT alone	3 yr			37% 26%	17% 14%
Posner et al, TAX 324[134,165]	III/IV	TPF PF Followed by RCT	3 yr 5 yr	70% 62%		62% 48% 52% 42%	50% 38% 45% 34%
Hitt et al[137]	III/IV	RCT (128) vs. PF (156) vs. TPF (155)	5 yr	49.2% 51.3% 52.9%	N/A	37% 37% 32%	25% 30% 32%
Haddad et al, Paradigm[166]	III/IV	RCT (75) vs. TPF (70)	3 yr	85% 84%	89% 93%	78% 73%	69% 67%
Cohen et al, DeCIDE[167]	IV	RCT (138) vs. ICT (142)	3 yr	88% 91%	81% 90%	73% 75%	N/A
Ghi et al[140]	III/IV	RCT (211) vs. ICT (210)	3 yr	N/A	N/A	45.7% 57.6%	36.7% 46.8%

DC, Distant control; *ICT,* induction chemotherapy; *LRC,* locoregional control; *OS,* overall survival; *PF,* Platinol fluorouracil; *PFS,* progression-free survival; *RCT,* concurrent radiochemotherapy; *TPF,* Taxotere platinum and fluorouracil; *XRT,* radiotherapy.

randomized phase II study with another EGFR inhibitor, panitumumab and cisplatin given concurrently with RT, as well as in a trial that tested a small molecule inhibitor of the EGFR, erlotinib with cisplatin, combined with RT. Neither of these studies showed a benefit of combination therapy over standard platinum-based concurrent CRT.[59,60]

Numerous concurrent modalities provide several therapeutic alternatives for clinicians to choose from depending on the clinical scenario, competing toxicities, and side effect profiles of individual patients. The past few decades have witnessed numerous negative clinical trials and only one FDA-approved systemic agent for use in HNSCC. However, combinations of novel agents and standard chemoradiation, including immunotherapies and small molecule inhibitors, are on the horizon.[61,62]

Induction Chemotherapy

Induction chemotherapy has been a controversial but attractive option for managing HNSCC patients in selected clinical situations, especially for patients with high risk of distant metastasis.[63] MACH-NC meta-analysis on IC trials, which included patients with unresectable disease, showed a small improvement in survival (HR, 0.90; 95% CI, 0.82 to 0.99) and distant failures for induction chemotherapy in those trials that used a platinum and 5-fluorouracil (PF) regimen.[52] However, because of differences in design between treatment protocols, a comparative and consistent statement of benefits still remains unknown[64] (Table 35.5).

Quantitative results of sequential chemotherapy and radiotherapy are significantly different when compared to concurrent strategies. Chemotherapy leads destruction of tumor at a constant fraction rather than a constant number of cancer cells and results in a fractional tumor decrease that is not larger than 1-2 log, leading to exponential survival curves. Therefore, chemotherapy alone results in neither complete clinical nor pathologic tumor responses.[65] These data explain the impressive tumor shrinkage often observed after IC but also highlight the importance of definitive treatment.[66]

A separate analysis of the MACH-NC Group was published in 2013 with studies that added taxanes into PF IC. Five randomized trials with median follow-up of 4.9 years and a total of 1772 patients enrolled demonstrated that absolute benefit at 5 years was 7.4%, from 35% to 42.4% (HR, 0.79; 95% CI, 0.70-0.89; $P < .001$) in favor of taxane-PF IC over PF.[67] The efficacy of docetaxel-based chemotherapy regimen (docetaxel, cisplatin, and 5-fluorouracil, TPF) in locally advanced head and neck cancer was evaluated in EORTC 24971, a phase III open-label randomized trial, involving 358 adult patients.[68] Patients in this study treated with TPF prior to surgery or radiation had a significantly longer median OS compared to a standard treatment of PF, with a 28% risk reduction of death, 18.6 versus 14.5 months ($P = .0128$). Patients also had a significantly longer time to disease progression of 11.4 months, compared with 8.3 months ($P = .015$) for patients receiving standard therapy. Posner and coworkers reported the results of a large randomized phase III study (TAX 324) comparing TPF to PF IC.[66] The study showed TPF to be superior to PF for survival, leading to the approval of TPF by the FDA for the induction treatment of patients with locally advanced HNSCC. The combination of the three compounds in the TPF regimen for advanced head and neck cancer in adults has been 75 mg/m^2, 75 mg/m^2, 750 mg/m^2 (Study TAX323) and 75 mg/m^2, 100 mg/m^2, 1000 mg/m^2 (Study TAX 324), respectively. Although MACH-NC showed a survival advantage for PF-based IC over definitive RT alone, it remained unclear

whether TPF-based IC improves OS over definitive CRT alone because neither of these studies was designed to address this question.

To answer this question, a three-arm phase III trial was conducted by the Spanish Head and Neck Cancer Cooperative Group, in which 439 patients with unresectable HNSCC were randomly assigned to CRT with cisplatin at 100 mg/m^2 given on days 1, 22, and 43, or IC with either PF + CRT or TPF + CRT. The intent to treat (ITT) analysis showed no difference between IC followed by CRT versus CRT alone in PFS, which was a primary end-point of the study.[69] Furthermore, in contrast to the two previous TAX 323 and 324 trials, the study failed to show a survival advantage of TPF over PF.[69] More recently, data were published from paired phase III trials (DeCIDE and Paradigm) assessing IC plus CRT versus CRT alone, which again failed to demonstrate a clear advantage to IC (see Table 35.5). Both studies showed no statistically significant differences in overall survival, the primary end-point of the study, but a difference in distant recurrence without prior locoregional recurrence was found (P = .043) favoring sequential therapy in the DeCIDE study and suggesting benefit of sequential approach in patients with high risk for distant metastases.[70]

Adjuvant Chemotherapy and Radiation

Risk-adapted adjuvant radiation therapy for patients who have undergone surgical resection of their primary tumor is dependent on known histopathologic risk factors that include advanced T status, two or more positive lymph nodes, perineural invasion (PNI), lymphovascular invasion (LVI), positive or close resection margins, and extracapsular extension (ECE). The role of chemotherapy in the postoperative management of the patient with adverse prognostic risk factors has been clarified by two separate multicenter randomized trials and a combined analysis of data from those two trials for patients with high-risk cancers of the oral cavity, oropharynx, larynx, or hypopharynx.[71-73] The US Intergroup trial R95-01 demonstrated statistically significant improvement in LRC and disease-free survival but not OS,[71] whereas the European EORTC trial found significant improvement in survival and the other outcome parameters.[72] There were some differences in design, primary end-point, and exclusion criteria between the two trials. To better define risk, a combined analysis of prognostic factors and outcome from the two trials was performed.[73] This analysis of demonstrated that for patients in both trials, only those with ECE and/or positive resection margins benefited from the addition of cisplatin to postoperative radiotherapy. Thus, chemoradiation is clearly indicated for ECE and/or microscopic positive mucosal margins. There was a trend toward improved survival in favor of CRT in the group of patients who had stage III/IV disease, PNI, vascular embolisms, and/or clinically enlarged level IV/V lymph nodes secondary to tumors arising in the oral cavity or oropharynx, but the differences were not statistically significant. Interpretation of these results is limited by the fact that the data are derived from a post hoc subgroup analysis rather than from a prospective trial in which statistical analysis was adjusted for subgroup comparison.

There is evidence to suggest, however, that the usual histopathologic risk factors seen in cancers of the oral cavity, hypopharynx, and larynx are not prognostic for patients with HPV-positive oropharyngeal disease. A recent study demonstrated no difference in 5-year disease specific survival (DSS) between CRT and RT alone in patients with p16/HPV-positive OSCC.[74] Another study that used a pathologic grading system for ECE showed that most p16-positive patients with nodal ECE did not benefit from the addition of chemotherapy to radiation.[75] This indicates that the presence of ECE may imply a different risk profile when HPV-positive and HPV-negative groups are compared.[76,77]

In order to provide some additional evidence for patients at elevated risk for recurrence based on perineural or vascular invasion, two or more involved lymph nodes, or T3 and T4 tumors, defined as intermediate risk, a phase III RTOG 0920 trial is currently comparing RT alone versus RT plus cetuximab (NCT00956007). Another clinical trial that should inform risk stratification for HPV-related HNSCC is ECOG 3311, which is phase II randomized trial of transoral surgical resection followed by low-dose or standard-dose RT for resectable locally advanced OSCC (NCT01898494).

In summary, the role of adjuvant CRT in high-risk, HPV-negative patients is well defined, but its role in intermediate-risk patients remains unclear. Furthermore, the definition of positive margins and extracapsular involvement is not standardized and should be better defined and tested in a prospective study, especially in the HPV-positive population. Ongoing clinical trials may answer these elusive questions.

Role of Human Papillomavirus in Treatment of Squamous Cell Carcinoma of the Tonsil

In the previously described studies, patients with locally advanced OSCC were treated in an identical fashion regardless of HPV status. It is well known that for some patients with HPV-positive SCC, such therapy probably represents overtreatment, causing greater than necessary toxicity. With recent epidemiologic changes, current research is focused on "de-escalation" aiming to safely reduce toxicity without compromising clinical outcome. The first de-escalation trial, ECOG 1308, was reported at ASCO 2014. It was a randomized phase II trial of IC with paclitaxel, cisplatin, and cetuximab followed by randomization to low dose versus standard dose of IMRT at 54 Gy in 27 fractions versus standard radiation arm with 69.3 Gy in 33 fractions with cetuximab used in both arms, in patients with HPV-positive resectable OSCC. The primary end-point of this study was 2-year PFS after low-dose IMRT. This study showed that low-risk patients (low T stage, low N stage, <10 pack-years smoking) achieved a 95% 2-year OS, favoring de-intensification in this group. This de-escalation study allowed for significant reduction in toxicity while maintaining high OS and PFS in an experimental arm. Smoking history was an independent prognostic factor that impacted clinical outcomes for patients regardless of radiation dose assignment. The ECOG 1308 study provided a promising paradigm for HPV-positive patients, but because de-escalation still remains experimental, HPV-positive patients should be encouraged to participate in clinical trials that are available across the country.

TABLE 35.6 American Joint Committee on Cancer Staging for Nasopharyngeal Carcinoma

Primary Tumor (T)

TX Primary tumor cannot be assessed

T0 No tumor identified, but EBV+ cervical node(s) involvement

T1 Tumor confined to nasopharynx, or extension to oropharynx and/or nasal cavity without parapharyngeal involvement

T2 Tumor with extension to parapharyngeal space, and/or adjacent soft tissue involvement (medial pterygoid, lateral pterygoid, prevertebral muscles)

T3 Tumor with infiltration of bony structures at skull base, cervical vertebra, pterygoid structures, and/or paranasal sinuses

T4 Tumor with intracranial extension, involvement of cranial nerves, hypopharynx, orbit, parotid gland, and/or extensive soft tissue infiltration beyond the lateral surface of the lateral pterygoid muscle.

Regional Lymph Nodes (N)

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Unilateral metastasis in cervical lymph node(s) and/or unilateral or bilateral metastasis in retropharyngeal lymph node(s), ≤6 cm, above the caudal border of cricoid cartilage

N2 Bilateral metastasis in cervical lymph node(s), ≤6 cm, above the caudal border of the cricoid cartilage

N3 Unilateral or bilateral metastasis in cervical lymph node(s), >6 cm, and/or extension below the caudal border of cricoid cartilage

Distant Metastasis (M)

M0 No distant metastasis

M1 Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
Tis	N0	M0	Stage 0
T1	N0	M0	Stage I
T1,T0	N1	M0	Stage II
T2	N0	M0	Stage II
T2	N1	M0	Stage II
T1,T0	N2	M0	Stage III
T2	N2	M0	Stage III
T3	N0	M0	Stage III
T3	N0	M0	Stage III
T3	N1	M0	Stage III
T3	N2	M0	Stage III
T4	N0	M0	Stage IVA
T4	N1	M0	Stage IVA
T4	N2	M0	Stage IVA
Any T	N3	M0	Stage IVA
Any T	Any N	M1	Stage IVB

EBV, Epstein-Barr virus.

Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In Amin MB et al, eds. *AJCC cancer staging manual,* 8th ed., New York: Springer, 2017.

Surgical Management

Surgical Management of the Primary Tumor

As stated previously, definitive chemoradiation therapy is the preferred treatment approach for most patients with locally advanced (T3/T4) OSCC. However, surgery may be considered as part of the multimodality strategy in the upfront setting for a variety of reasons, including patient preference, medical contraindications to radiation or chemotherapy, to obtain pathologic information to guide adjuvant therapy, the treating team's preference, or clinical trial participation. Traditionally, surgical resection of tonsil cancer involved a lip-splitting approach with mandibulotomy and swing for access to the oropharynx, which necessitated flap reconstruction. Over the past decade, however, minimally invasive approaches such as transoral robotic surgery (TORS) have been advocated as an alternative to traditional open approaches. TORS was designed to provide transoral surgical access to the oropharynx, hypopharynx, and larynx in order to avoid transmandibular or transcervical access procedures that have been traditionally employed for oncologic pharyngeal resections. Furthermore, TORS may offer similar oncologic outcomes when compared to transmandibular or transcervical approaches and has the added advantage of generally not requiring a reconstructive procedure.[78-83] Although TORS has recently been used as a strategy to minimize the functional effects of adjuvant therapy while preserving oncologic outcomes in T1/T2 oropharynx cancer, its use for treatment of bulkier disease in the oropharynx is more limited, and oncologic outcomes in the salvage setting have not been widely reported.

In the author's (RBB) experience, TORS is safe and efficacious for most T1 and T2 tonsil and base of tongue cancers and for selected T3 tumors. However, because of the proximity of critical structures, the need for reconstruction of larger defects, functional limitations related to soft palate resection, and the limitations of a transoral approach in clearing bulky disease involving the masticator space or extrinsic tongue musculature, it is the author's opinion that there is little or no role for TORS in the management of large T3 or T4 cancer in either the definitive or salvage setting. Furthermore, locoregional control in patients with HPV-related disease treated with primary chemoradiation therapy is in excess of 98% at our institution.[42] Given such success, surgery is best considered as a possible modality to de-escalate therapy and improve functional outcomes for low- or intermediate-risk patients (i.e., most HPV-positive OSCC) or as a method of tailoring or intensifying treatment in patients with high-risk disease (locoregionally advanced, HPV-negative OSCC).

Therefore, our approach is to treat most T3/T4 cancers with definitive chemoradiation, regardless of HPV status (see Fig. 35.4). Local recurrence at the primary site is managed either with TORS (selected T3 tumors only) or, more commonly, via either a transmandibular or transcervical approach. Selected patients with T3 cancers can and do undergo primary surgical resection at our center; however, these patients are often enrolled in IRB-approved clinical trials as a means of providing risk-adapted adjuvant therapy, de-escalating treatment, or incorporating neoadjuvant or adjuvant immunotherapy and concomitant immune/molecular profiling.

Surgical Approaches to the Pharynx

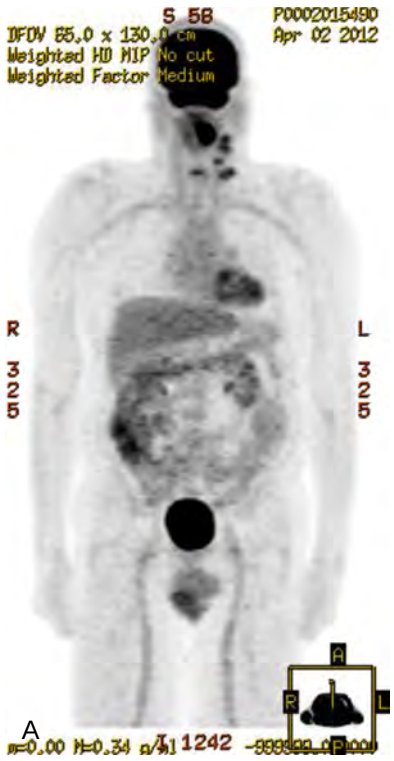
Transoral Robotic Surgery (TORS)

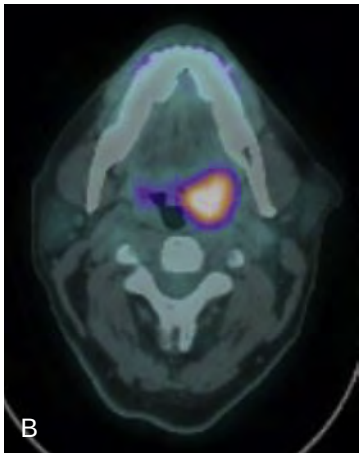
TORS is increasingly used in the surgical management of head and neck malignancies and is presently cleared by the FDA for the treatment of T1 and T2 oropharyngeal tumors. Compared to traditional transoral techniques, such as transoral laser microsurgery (TLM), TORS offers several potential advantages including high-resolution, three-dimensional operative view; improved operative precision; movement scaling; and dynamic multiplanar and true 360-degree rotational motion. Compared to TLM, TORS is not limited by a need for direct line of sight. Exposure is critical to the success of TORS and can be facilitated by employing one of several different oral retractors including the McIvor, Crowe-Davis, Dingman, Feyh-Kastenbauer (FK), or Feyh-Kastenbauer-Weinstein-O'Malley (FK-W0). This decision is based on patient anatomy, tumor size and location, and surgeon preference.

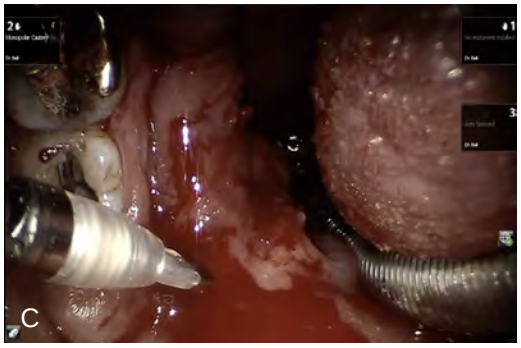
The operation begins with an incision through the palatoglossal sulcus mucosa, extending through the superior constrictor muscle layer. The deep parapharyngeal fat pad is identified, which serves as a landmark for the carotid artery and generally lies posterolaterally to the plane of dissection. Tonsillar branches of the ascending pharyngeal and ascending palatine artery may be visualized here and should generally be ligated with vascular clips. From here the dissection extends into the soft palate and through the posterior pharyngeal mucosa. The posterior pharyngeal dissection is carried down through the pharyngobasilar fascia and the superior or middle constrictor muscles, and to the buccopharyngeal fascia, which usually serves as the deep oncologic margin (Fig. 35.8).

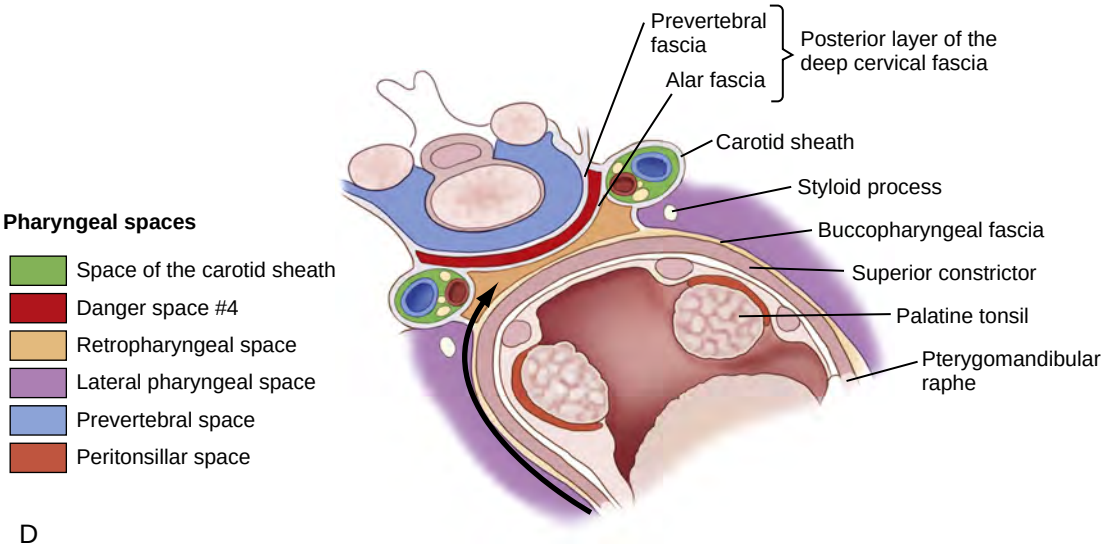
Special care should be taken when operating on bulkier tumors. We suggest performing the neck dissection prior to TORS for T3 tumors in order to obtain vascular access for ligation of the external carotid system or control of hemorrhage if needed. The medial pterygoid muscle should be identified and an assessment of masticator space involvement should be made. In our opinion, significant masticator space involvement or confluence with an enlarged metastatic lymph node is a contraindication to TORS, and if either is encountered, the operation should be converted to an open procedure (if in the salvage setting) or aborted (if in the definitive setting) (Fig. 35.9). Care should also be taken with patients in whom tumor involves the styloglossus or stylopharyngeus muscles, which by definition represents T4 disease, and who are thus poor candidates for TORS.

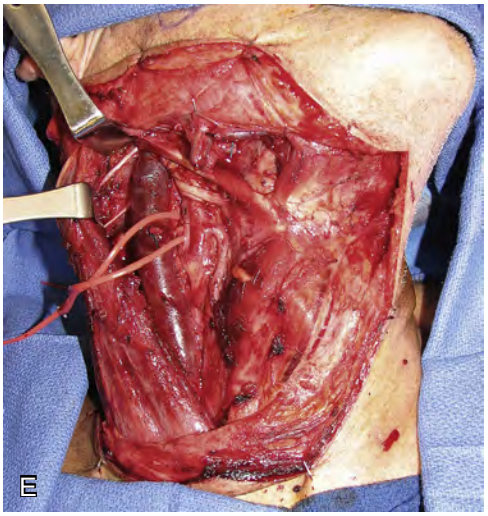
A detailed discussion of the components and operative setup for TORS has been well summarized in a recent review.[84] Unlike TLM, the goal in TORS is to achieve an en bloc resection with 1-cm mucosal margins and a final pathologic margin of 3 to 5 mm. The deep margin is often less than 3 to 5 mm after resection of a tonsillar SCC, given the short distance between the constrictor muscle layer and the parapharyngeal fat. However,



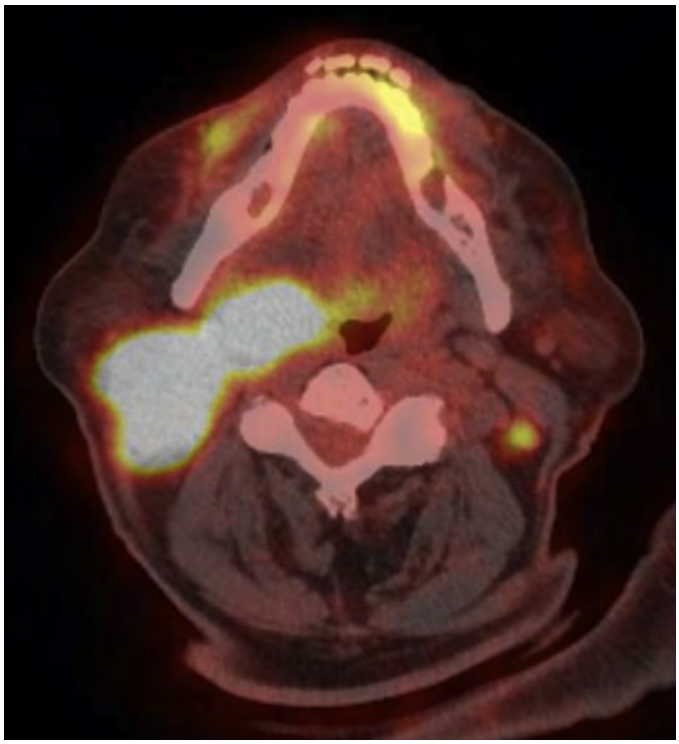








• **Fig. 35.8** A 70-year-old man with cT3N2bM0, squamous cell carcinoma (SCC) of the tonsil. **A,** pretreatment positron emission tomography (PET). Note prominent tumor in the region of the left palatine tonsil with multiple ipsilateral metastatic cervical lymph nodes. **B,** Pretreatment PET/CT demonstrating axial dimension of tonsil tumor. **C,** Clinical view from the robotic console at the time of transoral robotic surgery (TORS). **D,** Illustration *(left)* of the posterior pharyngeal resection, which is carried down through the pharyngobasilar fascia, the superior or middle constrictor muscles, and to the buccopharyngeal fascia, which usually serves as the deep oncologic margin *(right)*. **E,** Modified radical neck dissection performed prior to TORS to facilitate proximal vascular control.



• **Fig. 35.9** Contraindication for transoral robotic surgery (TORS). Large T3-4 disease, masticator space involvement or confluence with an enlarged metastatic lymph node are contraindications to TORS in the absence of clinical trial protocol.

a narrow surgical margin (>1 mm) is oncologically acceptable if the buccopharyngeal fascia is preserved.

The use of TORS plus risk-adapted adjuvant therapy for OSCC during the past decade has resulted in oncologic outcomes similar to those of definitive chemoradiation, but with superior functional outcomes. Postoperative enteral feeding rates and rates of dysphagia at 12 months are significantly reduced after TORS compared to traditional open surgery. In a recent systematic review of more than 400 patients in 12 studies, Hutcheson and colleagues[78] found improved swallowing outcomes and decreased feeding tube use with primary TORS versus historic IMRT cohorts. However, many of these studies are limited by their retrospective nature, potential selection bias, and heterogeneity in regard to HPV status. In the author's experience, selected T3 tumors may be safely managed with TORS, although our bias is to offer this to patients with HPV-negative disease, in whom failure rates with definitive chemoradiation are high and functional outcomes following TORS are acceptable. As mentioned previously, HPV-positive patients with documented T3 disease or those with N2C or N3 neck disease are managed with primary chemoradiation and surgery for salvage.

Transmandibular/Mandibulotomy Approach

Historically, midline mandibulotomy with a lip-splitting incision was the favored technique to access advanced tumors of the tonsil, in either the definitive or the salvage setting. Because organ preservation protocols employing chemoradiation in the definitive setting were popularized in the 1990s, the use of this relatively invasive surgical approach has dramatically declined. Despite this, traditional transmandibular resection is usually required for T3/T4 malignancy of the tonsil. Although salvage surgery is less often necessary in the age of HPV, because of excellent locoregional control with chemoradiation, approximately one third of patients with HPV-negative disease will fail primary treatment (Fig. 35.10).

Transmandibular approaches via a lip-splitting incision offer optimal exposure of the oropharynx, but come at the price of significant dysfunction and esthetic deformity.[85-91] The complication rates of midline mandibulotomy combined with the lip-splitting incision have been reported as high as 20–48%.[92-95] Other investigators have not found that the functional impact is tempered by appropriate reconstruction. Historically, pedicled flaps, such as the pectoralis major muscle flap (Fig. 35.11), were used for reconstruction of oropharyngectomy defects in this setting[96] (Fig. 35.12). Although they still have a role to play, the development of free tissue transfer has dramatically improved the complication rate and functional outcomes[97-99] (Fig. 35.13). Despite this, functional outcomes following salvage oropharyngectomy remain suboptimal for a variety of reasons that are characterized by dysphagia and morbidity related to the transmandibular approach.

Transcervical/Transpharyngeal Approach

The transcervical/transpharyngeal approach is less commonly employed than the mandibulotomy with lip-splitting technique, but it is our preferred approach in many cases of salvage pharyngectomy (Fig. 35.14). This approach provides excellent access for reconstruction of pharyngeal, base of tongue, and soft palate defects using a variety of soft tissue flaps, and the procedure can be performed under robotic assistance to facilitate pharyngectomy (Fig. 35.15). Decreased rates of postoperative fistula, exposed mandibular hardware, non-union of the mandible, and aesthetic morbidity have been reported with the transcervical approach when compared to transmandibular surgery.[100,101]

Composite Resection (Commando Procedure)

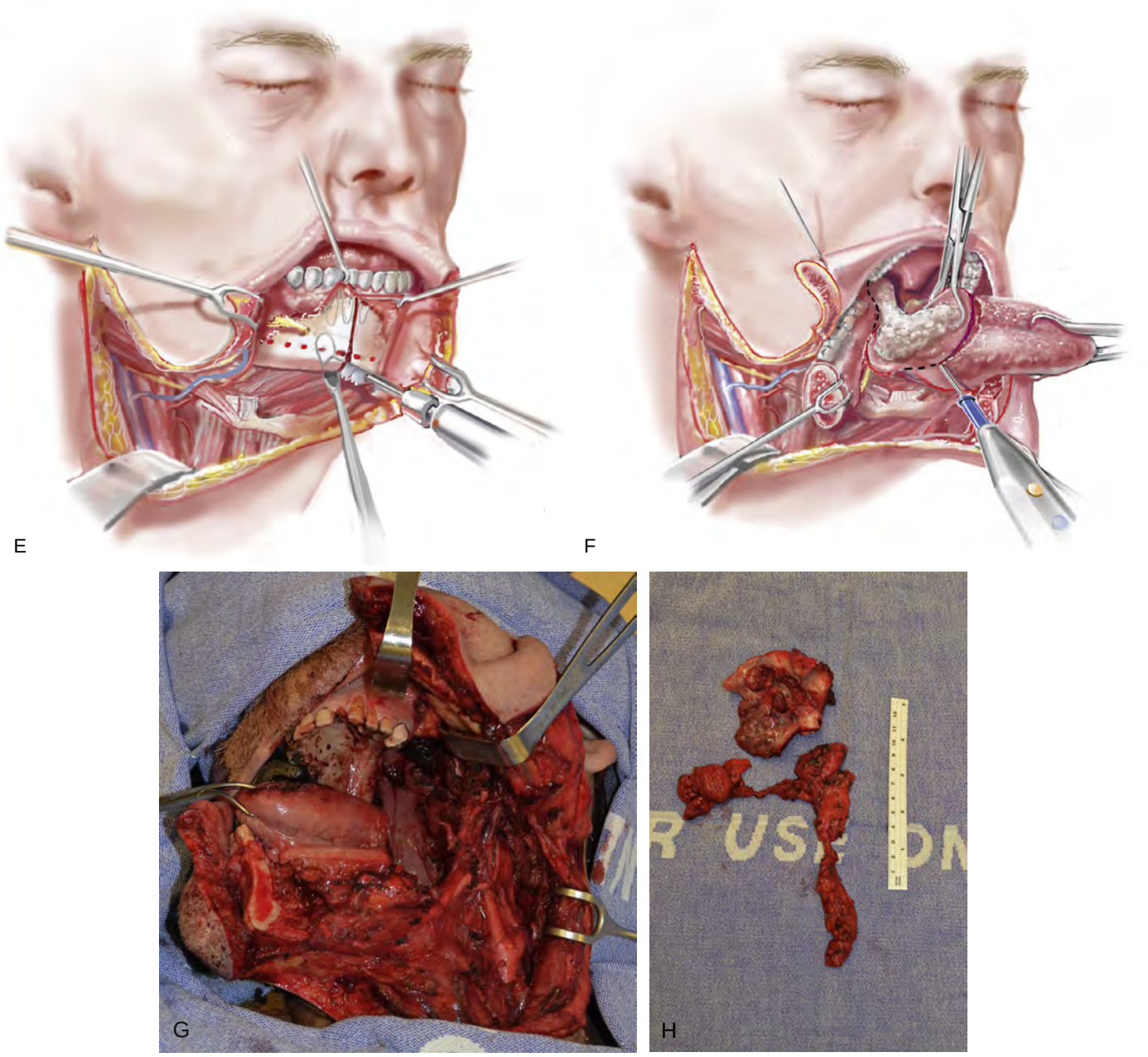
The composite resection, or commando procedure, is a technique used for tumors that invade the mandible and involve the oropharynx. The skin incision may or may not involve a lip-split, although we prefer to avoid it if at all possible. In most instances, access to the lateral mandible will facilitate a proximal mid-body mandibular osteotomy and a mid-ramus, distal osteotomy or even hemi-mandibulectomy, which will facilitate resection of the oral or oropharyngeal tumor.

Skull Base Approaches

Local spread of primary or, more commonly, recurrent oropharyngeal tumors that involve the skull base occasionally occurs. Spread is dictated by local anatomy and generally occurs along muscle or fascial planes: superiorly to the

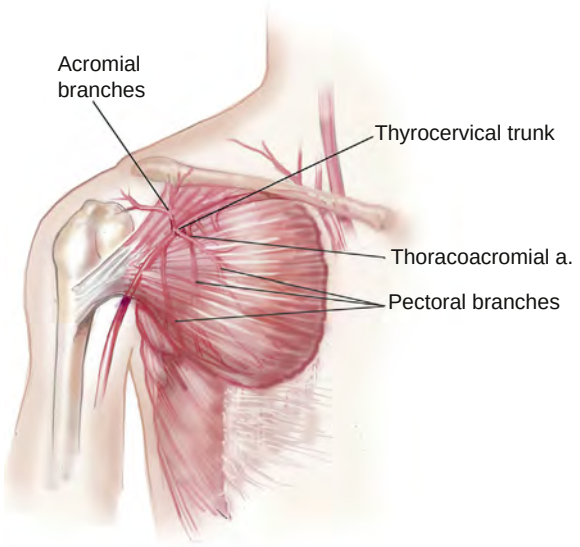


• **Fig. 35.10** A 50-year-old man with recurrent cT3N1M0, human papillomavirus (HPV)-negative squamous cell carcinoma (SCC) of the left tonsil following definitive chemoradiation. **A,** Presurgical salvage positron emission tomography (PET)/CT demonstrating local recurrence in the region of the palatine tonsil. **B,** Presurgical salvage PET/CT demonstrating locoregional recurrence involving a level II cervical lymph node. **C,** Illustration demonstrating lip split incision design. **D,** Incision design at time of surgical resection—note care taken to mark the vermilion border and avoid midline incision chin incision.



• **Fig. 35.10, cont'd** **E,** Illustration depicting midline mandibulotomy, which can be stair-stepped, as shown, or designed as a vertical osteotomy, which is more common in the era of rigid internal fixation. **F,** Midline mandibulotomy with incision through the vestibular mucosa and care to preserve the lingual nerve when possible. **G,** Defect following resection via mandibulotomy and swing prior to reconstruction with radial forearm free flap. **H,** Specimen.

nasopharynx or via the medial pterygoid muscle and pterygoid plate to involve the pterygomaxillary fissure, which lies between the pterygopalatine fossa and infratemporal region; laterally, penetrating the superior constrictor muscle and entering the parapharyngeal space via direct extension, perineural invasion, or lymphatic spread; or inferiorly along the palatopharyngeal muscle to its insertions into the middle pharyngeal constrictor, pharyngoepiglottic fold, and posterior border of the thyroid cartilage (see Fig. 35.3). Not including local or regional recurrence to the cervical lymph nodes in the jugulodigastric chain, isolated recurrence via lymphatic spread to the parapharyngeal space is the most common reason for surgical salvage and may require either midline or ramus mandibulotomy for access (Fig. 35.16). Surgical salvage of recurrent tumors involving the skull base can be a herculean effort, but can be achieved via craniofacial approaches with acceptable functional outcomes (Fig. 35.17).

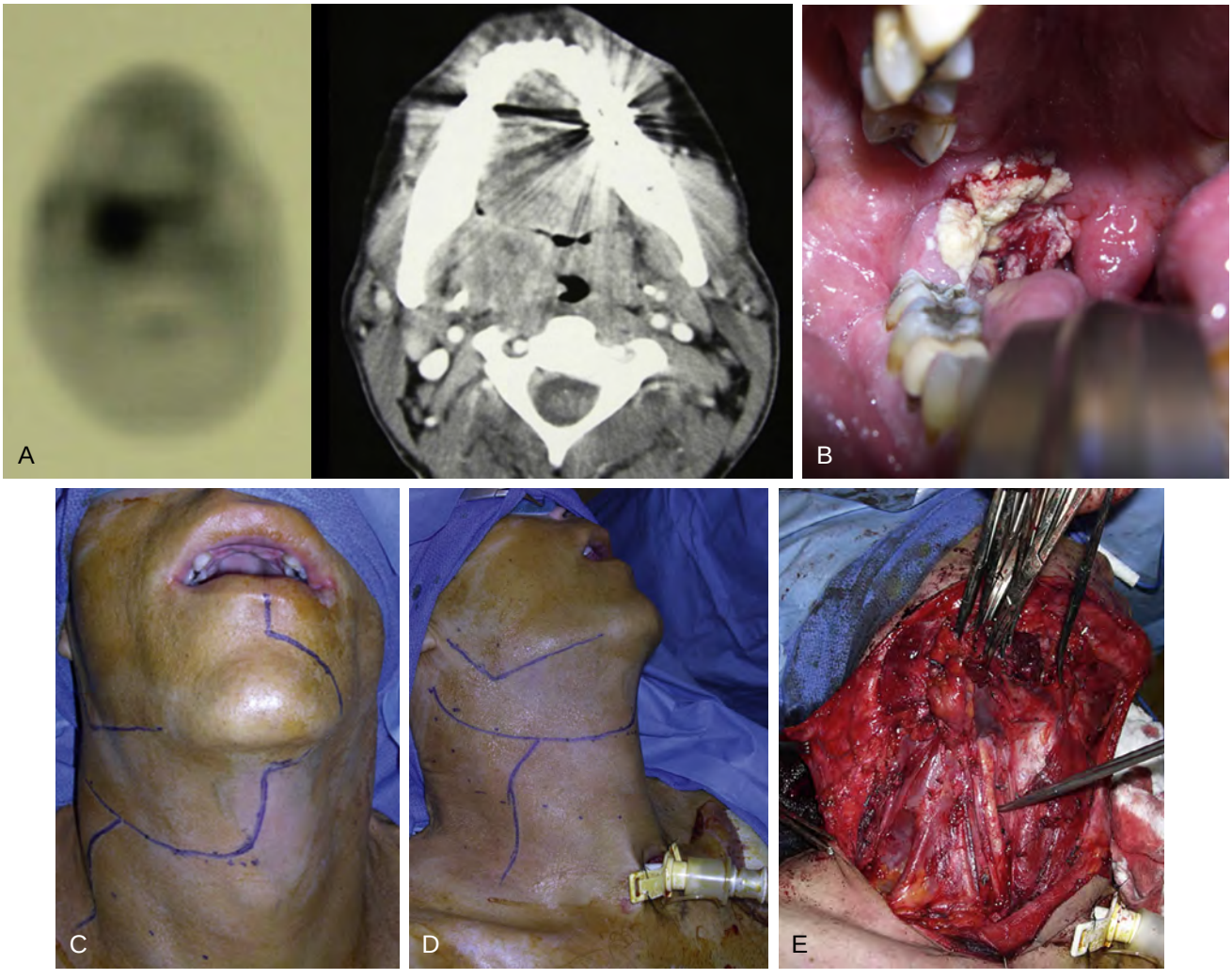


• **Fig. 35.11** Vascular anatomy for the pectoralis major myocutaneous flap.

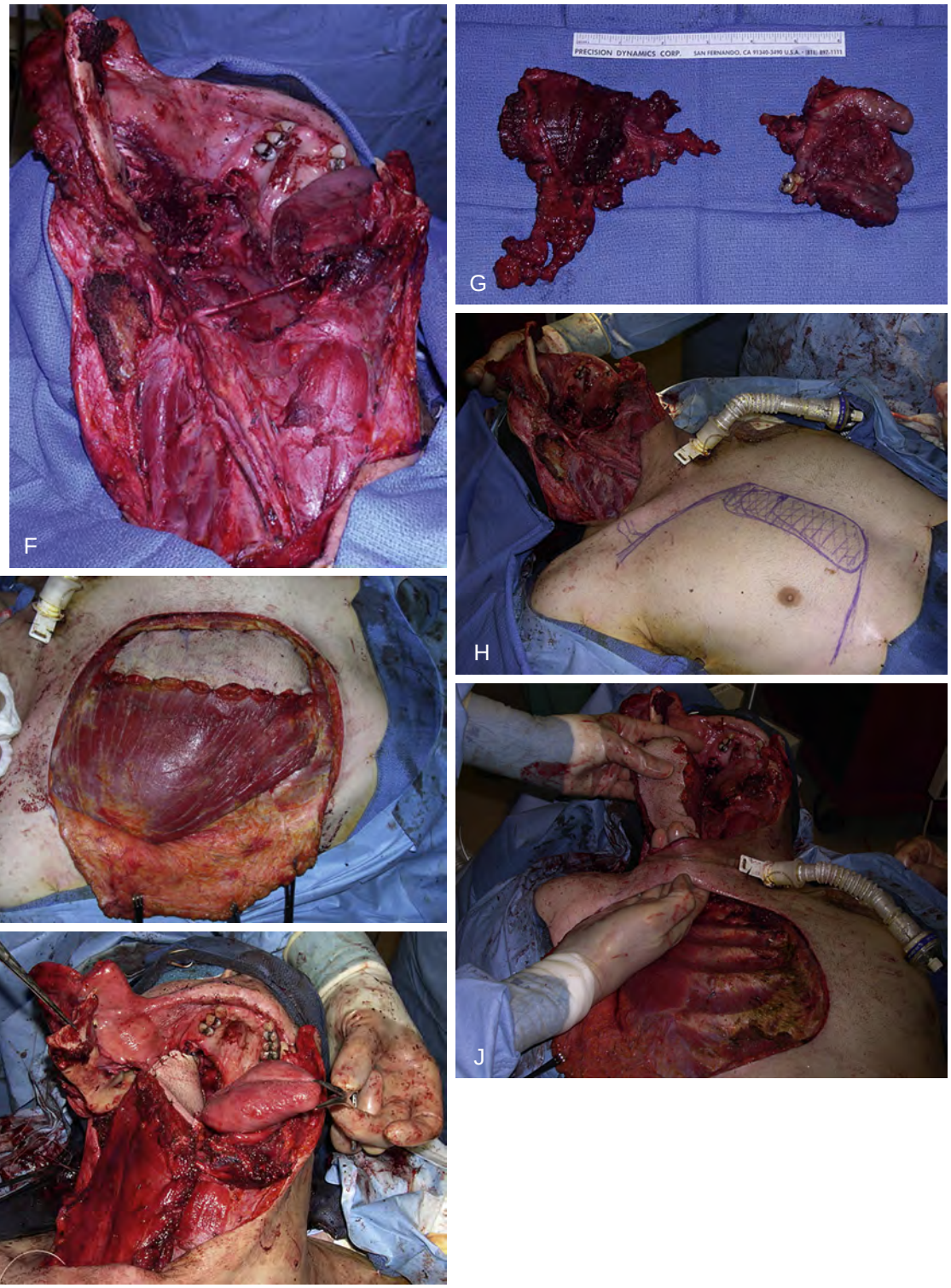
Pharyngolaryngectomy

Oropharyngeal tumors that involve or spread to the hypopharynx or larynx will usually require pharyngolaryngectomy to salvage following definitive chemoradiation therapy (Figs. 35.18 and 35.19). Once the decision has been made to proceed with surgical treatment of primary or recurrent oropharyngeal cancer, there are still multiple factors that must be considered to determine the optimal treatment for the individual patient. These factors include tumor location and extent, patient preference, and surgeon comfort/expertise. Often the first procedure performed is a direct laryngoscopy, which familiarizes the surgeon with the anatomic borders of the tumor and allows precise operative planning.

Laryngopharyngectomy begins with a wide apron incision with superior and inferior skin flaps developed in a subplatysmal plane. The anterior jugular veins are ligated and transected above the hyoid, and the investing layer of cervical fascia is incised along the anterior border of the sternocleidomastoid



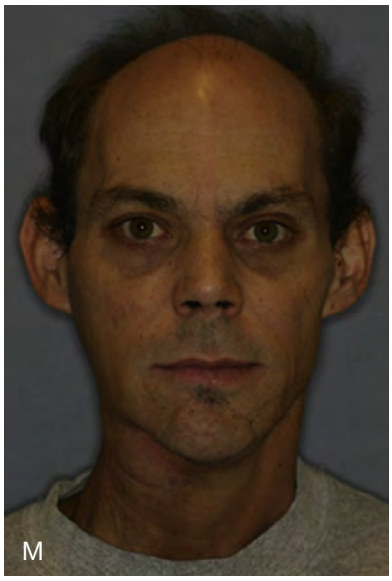
• **Fig. 35.12** A 45-year-old man with recurrent cT3N2bM0, human papillomavirus (HPV)-negative squamous cell carcinoma (SCC) of the right tonsil following definitive chemoradiation. **A,** Presurgical salvage positron emission tomography (PET) *(left)* and CT *(right)* demonstrating local recurrence in the region of the right palatine tonsil. **B,** Clinical appearance of tumor prior to resection. **C,** Incision design. **D,** Incision design.



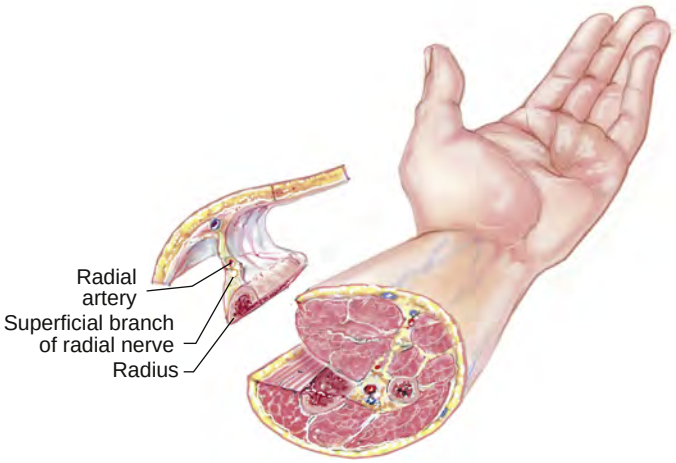
• **Fig. 35.12, cont'd** **E,** Radical neck dissection. **F,** Oropharyngectomy via midline mandibulotomy and swing. **G,** Specimens. **H,** Incision design for pectoralis major myocutaneous flap. **I,** Pectoralis flap harvest. **J,** Pectoralis flap inset via subclavicular tunnel. **K,** Flap inset.

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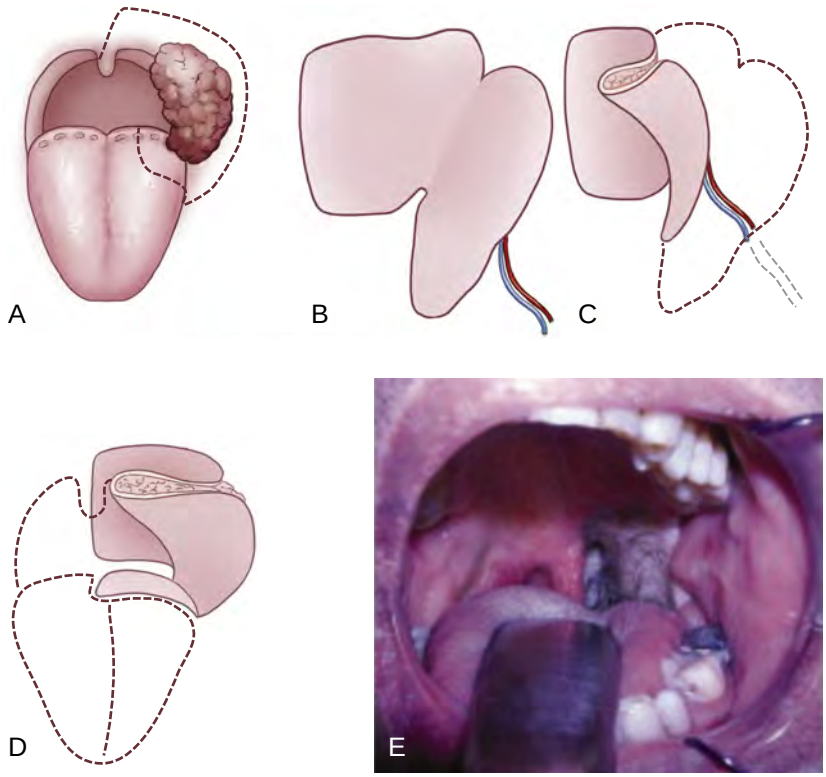
• **Fig. 35.12, cont'd** **L,** Postoperative appearance of oropharynx. **M,** Postoperative appearance 1 year following salvage surgery.



• **Fig. 35.13** Vascular anatomy for the radial forearm. Although this flap can be harvested as an osteocutaneous flap (as depicted) to facilitate bony reconstruction, the primary utility of this flap in oropharyngeal reconstruction is as a fasciocutaneous flap.

muscle. Retracting the sternocleidomastoid muscles laterally, the omohyoid muscle is identified and transected medial to where it crosses the internal jugular vein. The "outer tunnel" is developed by identifying a dissection plane between carotid sheath and larynx and thyroid gland, which is opened to expose the prevertebral fascia. The sternohyoid muscle is divided with electrocautery, and the sternothyroid muscle is identified and divided below larynx. The superior cut end of the sternothyroid is carefully elevated and reflected, and the thyroid isthmus is divided with electrocautery. Beginning on the side opposite of the tumor, the "inner tunnel" is developed by exposing the cervical trachea in the midline, reflecting the thyroid gland, and identifying the tracheoesophageal groove. The larynx is rotated with a finger placed behind the thyroid ala, and the inferior pharyngeal constrictor muscle and thyroid perichondrium are incised with electrocautery at, or just anterior to, the posterior border of the thyroid ala. The lateral wall of the pyriform fossa is stripped off the medial aspect of the thyroid ala in a subperichondrial plane with a swab/sponge held over a fingertip, or with a Freer elevator, only on the side of the pharynx/larynx opposite to the cancer. The surgeon then crosses to the opposite side of the patient and repeats the preceding operative steps. A tracheotomy is then performed at the level that is deemed oncologically sound, and the incision is beveled in a cephalad direction to extend through the posterior membranous trachea and expose the esophagus. An armored endotracheal tube is placed into the distal tracheostoma and secured to the skin. When tumor involves the vallecula, pre-epiglottic space, and/or base of tongue, the pharynx is entered via the opposite pyriform fossa or a retrograde laryngectomy is done, commencing the dissection inferiorly at tracheotomy site.

At this point, the body of the hyoid bone is identified, with care to preserve and protect the hypoglossal nerves and lingual arteries, which lie deep to the greater cornua/horns of the hyoid bone. The suprahyoid muscles are divided with electrocautery along the superior border of the body of the hyoid bone. The digastric tendon and stylohyoid ligament and muscle are released from the lesser cornu of the hyoid, the hyoid is rotated to the contralateral side, and the hyoglossus and middle constrictor muscles are next released from the greater cornu. The superior margin of the body of the hyoid bone is dissected transversely along the superior margin of the pre-epiglottic space. The vallecula mucosa is stripped from the anterior surface of the epiglottis, and the pharynx is entered by incising the mucosa along the superior margin. The epiglottis is retracted anteriorly through the pharyngotomy, and the larynx is inspected for tumor.



• **Fig. 35.14** Transcervical/transpharyngeal approach for lateral oropharyngectomy with reconstruction. **A,** Lateral oropharyngectomy. **B,** Reconstruction with radial forearm free flap. **C,** A template for oropharyngeal reconstruction using a radial forearm flap that incorporates a component for the posterior pharyngeal wall, the soft palate, and the base of tongue. **D,** Filling of the surgical defect with the flap. **E,** Postoperative examination.

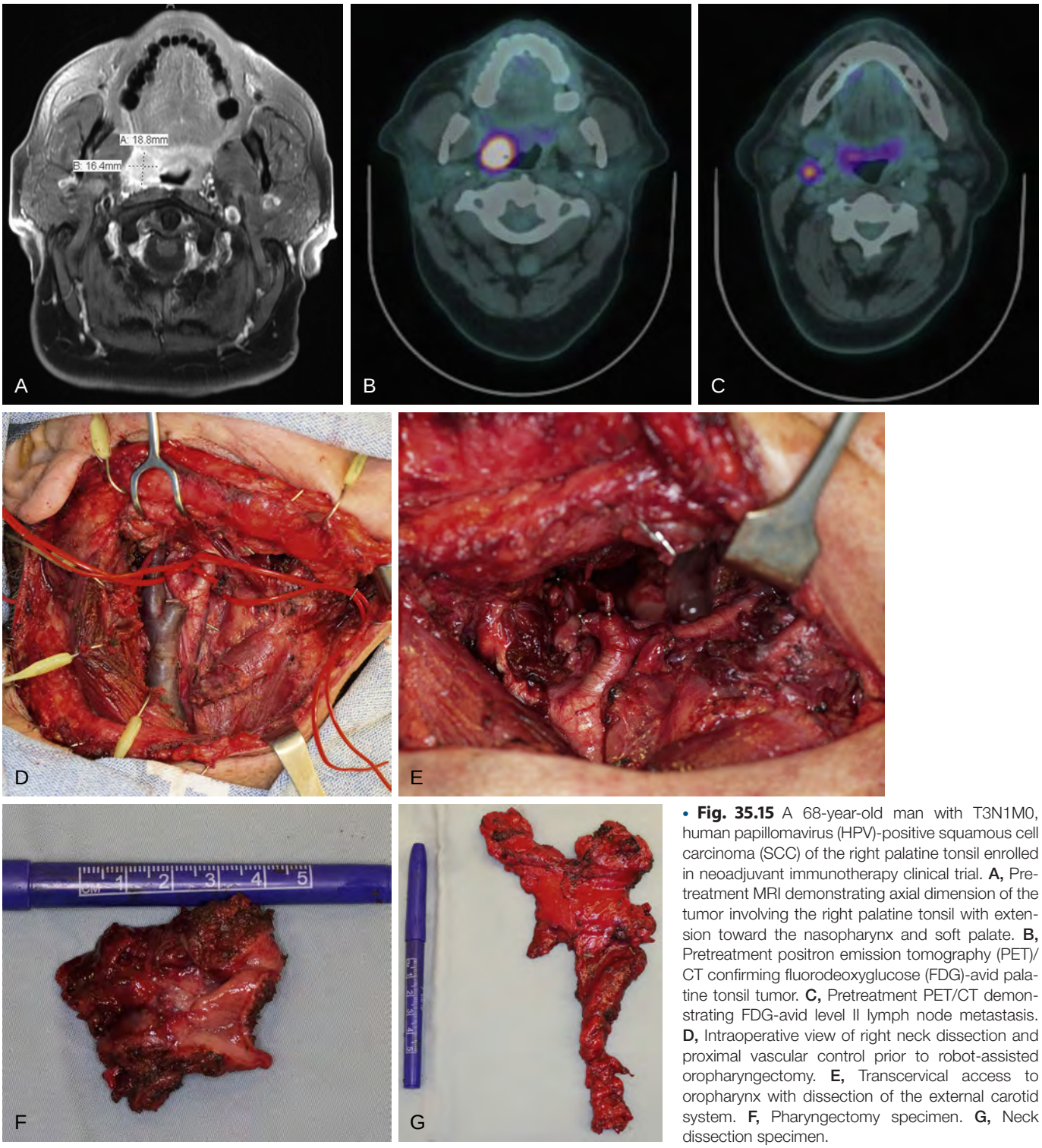
The laryngopharyngeal resection is performed in a prevertebral plane, contralateral to the tumor, using curved scissors with care to obtain at least 1 cm tumor-free margin, without resecting too much pharyngeal mucosa. The posterior wall of the larynx (cricoid, tracheal membrane) is separated from the anterior wall of the esophagus by dissecting along the avascular plane that exists between esophagus and trachea/cricoid. The specimen is delivered en bloc and examined grossly for adequate resection margins. The tracheostoma is spatulated at the membranous posterior wall, plicated to the sternum, and sewn into the superior and inferior skin flaps.

Hypopharynx

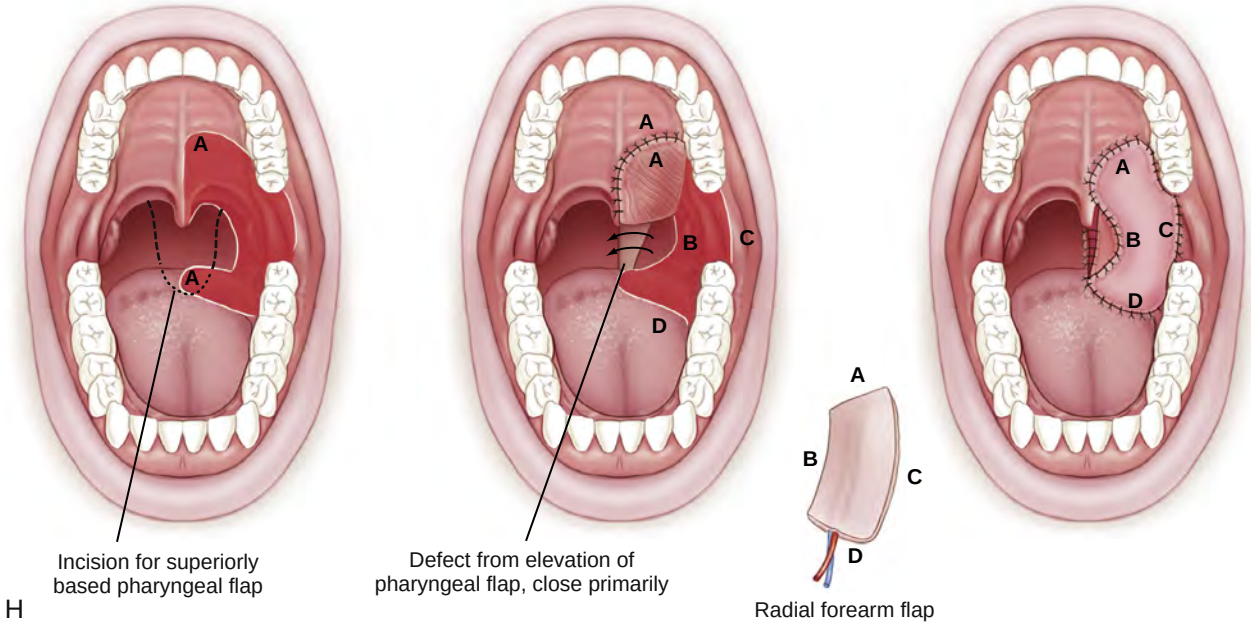
The hypopharynx extends from its juncture with the oropharynx at the tip of the epiglottis (or level of the hyoid bone) superiorly to the inferior border of the cricoid cartilage. It can be divided into three sites: the pyriform sinus, the postcricoid area, and the posterior pharyngeal wall. The hypopharynx functions as a dynamic conduit for food that helps prevent aspiration. As the food bolus is propelled past the epiglottis, contraction of the constrictor muscles propels the food toward the cricopharyngeus. The cricopharyngeus relaxes as the food enters the esophagus, where peristaltic action propels the food to the stomach. Motor innervations of the superior and middle constrictors are by the superior pharyngeal nerve and the pharyngeal branches of the vagus and glossopharyngeal nerves. Innervation of the inferior constrictor is from the external and recurrent branches of the vagus nerve. Sensory innervation of the pyriform sinus is from the internal branch of the superior laryngeal nerve. This complex muscular coordination is disrupted by major surgical reconstruction in this area and may result in severe aspiration even when the laryngeal sphincter is intact.

There are only approximately 4000 cases of hypopharyngeal carcinoma in the United States annually, most of which arise from the pyriform sinus. Regional metastasis at presentation is the norm (70%), and distant metastasis occurs in approximately one third of patients. The hypopharynx can be a difficult area to examine, with early subtle changes in the pyriform sinus often going undetected on fiber-optic examination. The postcricoid area can be difficult to examine in the best of circumstances using the office fiber-optic scope. Unlike oropharynx cancer, these tumors are usually not associated with HPV infection, so we have not seen similar improvements in outcomes.

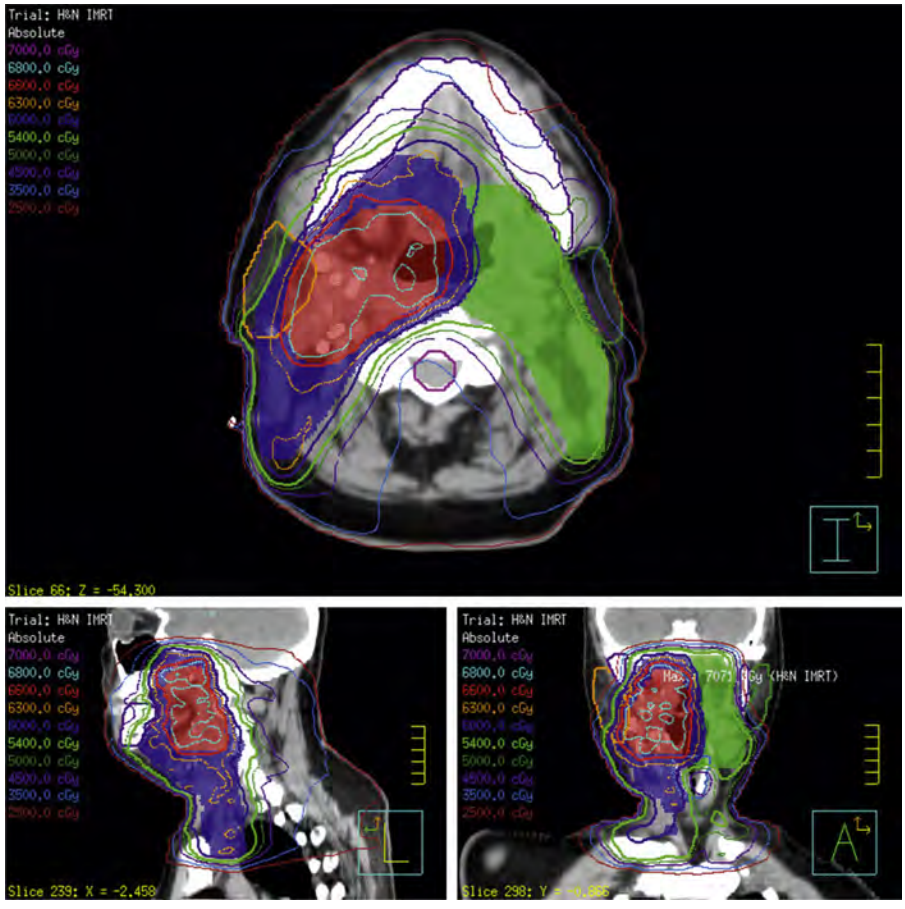
Given the rarity of these tumors, they are often combined with laryngeal malignancies in trials. The standard surgical approach usually includes partial pharyngectomy



• **Fig. 35.15** A 68-year-old man with T3N1M0, human papillomavirus (HPV)-positive squamous cell carcinoma (SCC) of the right palatine tonsil enrolled in neoadjuvant immunotherapy clinical trial. **A,** Pretreatment MRI demonstrating axial dimension of the tumor involving the right palatine tonsil with extension toward the nasopharynx and soft palate. **B,** Pretreatment positron emission tomography (PET)/CT confirming fluorodeoxyglucose (FDG)-avid palatine tonsil tumor. **C,** Pretreatment PET/CT demonstrating FDG-avid level II lymph node metastasis. **D,** Intraoperative view of right neck dissection and proximal vascular control prior to robot-assisted oropharyngectomy. **E,** Transcervical access to oropharynx with dissection of the external carotid system. **F,** Pharyngectomy specimen. **G,** Neck dissection specimen.



H



I

• **Fig. 35.15, cont'd** **H,** Illustration of planned reconstruction, which encompasses radial forearm free flap to reconstruct the posterior pharyngeal wall, soft palate, and base of tongue, combined with a superiorly based pharyngeal flap. Note this cartoon diagram demonstrates the operation on the left side. **I,** Postoperative radiation therapy plan.

Continued



• **Fig. 35.15, cont'd** **J,** External view. **K,** Intraoral view.

combined with total laryngectomy. Most providers therefore attempt chemoradiation as a means to spare the larynx, unless the tumor is associated with extensive cartilage destruction, making this approach less reliable. Survival rates range between 11% and 27% at 5 years. Despite the widespread use of organ preservation, approximately 60% of patients with hypopharyngeal carcinoma will recur following CRT and require salvage total laryngectomy (Figs. 35.20 to 35.22). Many of these patients, particularly those with postcricoid involvement, will also require partial esophagectomy (Fig. 35.23).

Accordingly, organ preservation has been explored in the management of hypopharynx cancer.[102-104] EORTC 24891 evaluated the use of three cycles of induction chemotherapy with cisplatin and fluorouracil to select patients for definitive radiotherapy.[105] Those patients achieving a complete clinical and radiographic response went on to radiotherapy, and patients with less than a complete response underwent surgery followed by radiotherapy. This strategy of induction chemotherapy to select patients for organ preservation did not compromise disease control or overall survival. More than half of the long-term survivors were able to retain their larynx. Unfortunately, 10-year survival was only 13.8% after surgery and 13.1% after induction chemotherapy followed by radiotherapy.

In the United States, most locally advanced hypopharynx patients are treated with concurrent chemoradiation approaches similar to those used for locoregionally advanced larynx cancer as in RTOG 9111. The French included hypopharynx primaries in their recent TREMPLIN study of induction docetaxel, cisplatin, fluorouracil followed by radiation combined with either concurrent cisplatin or cetuximab.[106] Induction chemotherapy remains a reasonable approach for selected patients.

From a radiation treatment planning perspective, it is important to recognize the frequent spread of hypopharynx cancer to regional lymph nodes. It is critical to cover the retropharyngeal nodes when treating hypopharynx carcinomas.

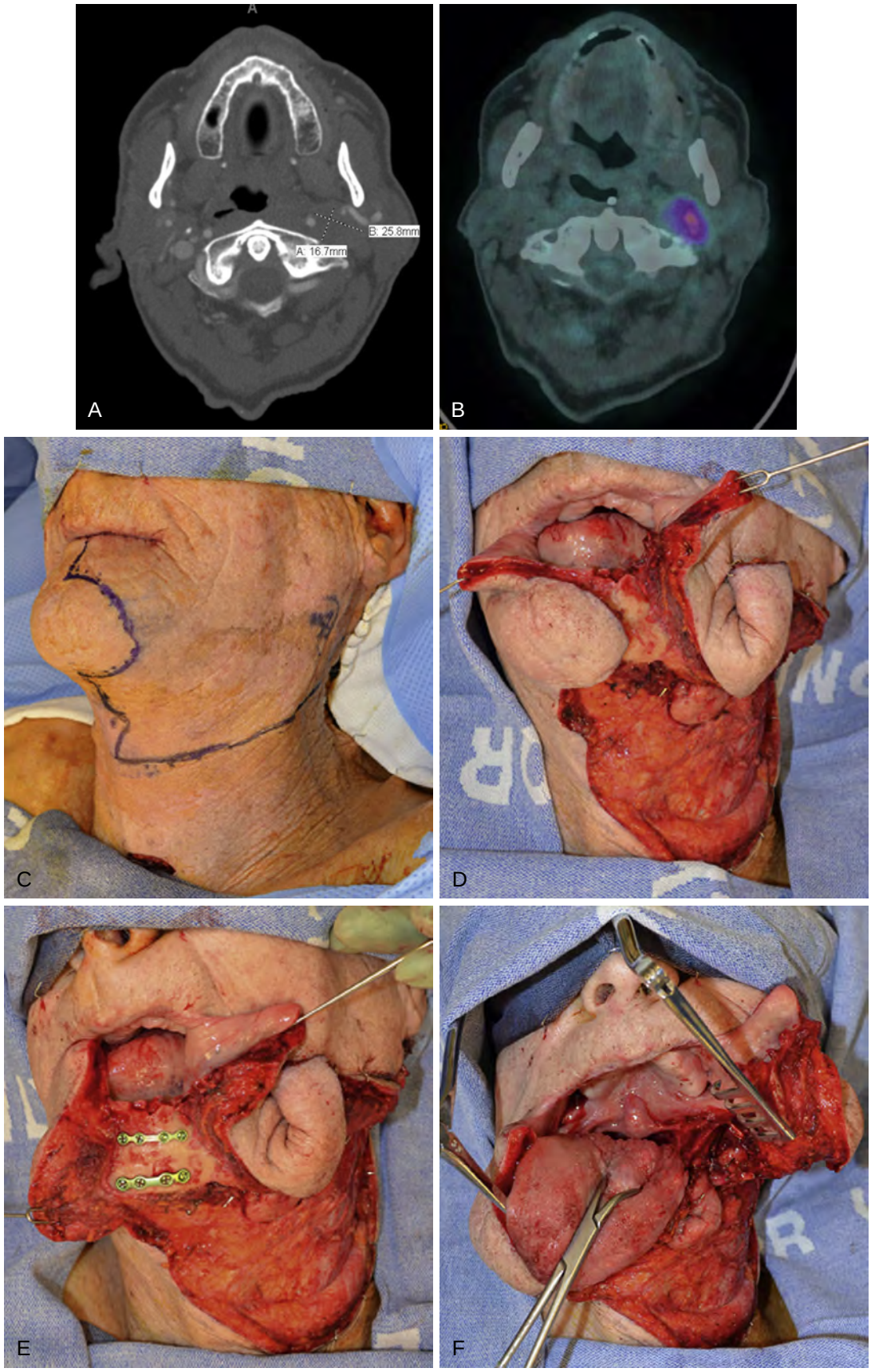
Reconstruction

The primary goal of reconstruction of the oropharynx is to provide coverage and protect vital structures. More specifically, it is to protect the carotid artery and prevent salivary leakage into the danger space (if the tumor requires a resection deeper than the retropharyngeal space). A secondary goal is to preserve function. The muscles of the base of tongue, lateral pharyngeal walls, posterior pharyngeal wall, and soft palate are critically important for both speech and the oral and oropharyngeal phases of swallowing. These two goals create unique challenges. In order to understand these properly, it is helpful to review the anatomy.

Advanced hypopharyngeal and laryngeal cancers that are not amenable to organ-sparing treatment, or have recurred following prior radiation therapy, are managed with pharyngolaryngectomy. Reconstruction of these defects involves surgically separating the airway from the upper digestive tract by creating a neopharynx and tracheal stoma. The primary goals are to safely establish a patent airway that is permanent, create a patent neopharynx for swallowing, and protect the adjacent vital structures from salivary leakage. The last of these poses a significant challenge, especially in the salvage setting after radiation therapy. In previously radiated patients, pharyngocutaneous fistula rates are reported as 30–75%.[107,108] Using soft tissue flaps as part of the reconstruction can reduce these rates to 15–25%.[109]

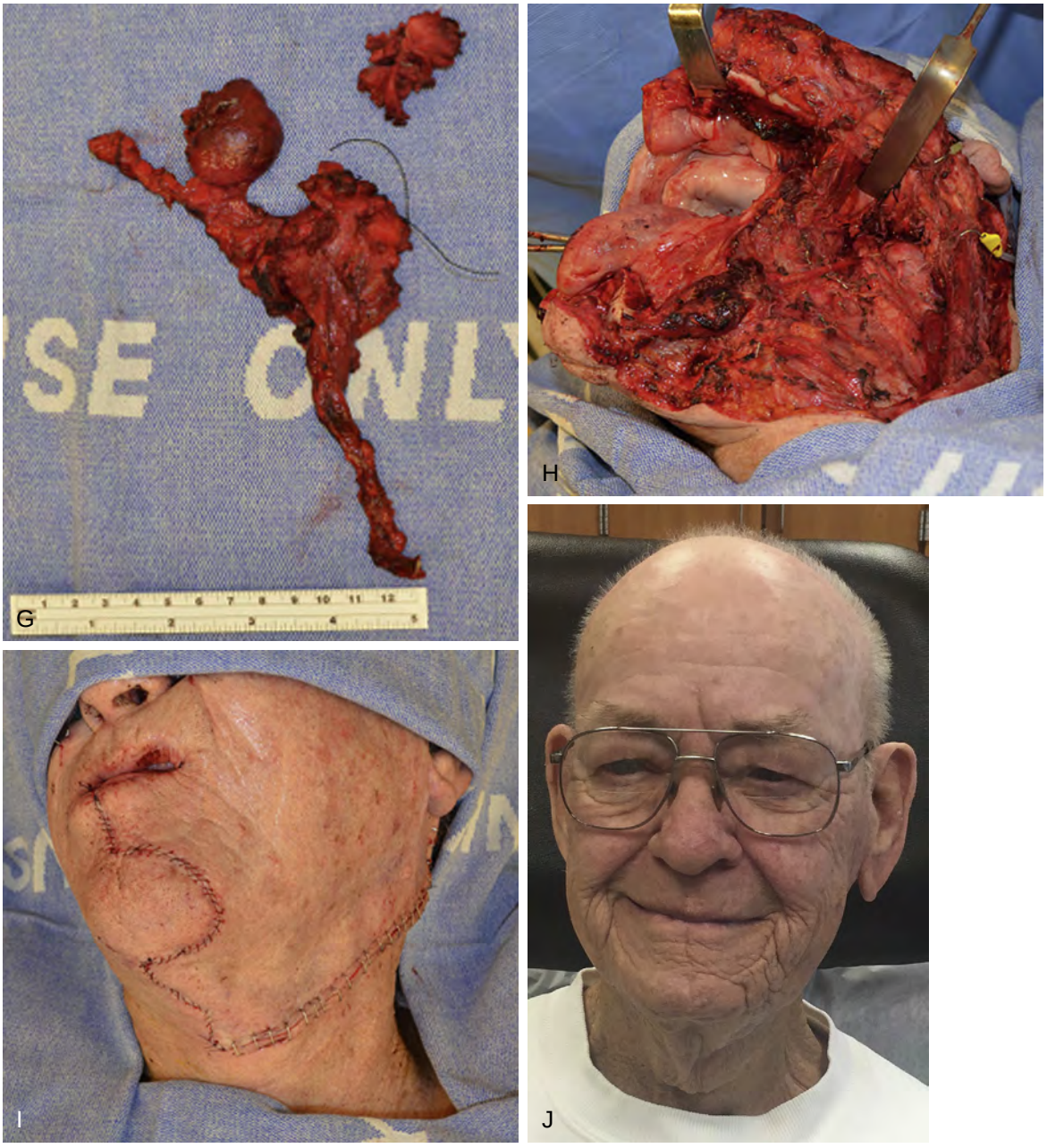
Defect Analysis

T1/T2 oropharyngeal tumors treated with primary surgery rarely require reconstructive surgery, as they heal well with



• **Fig. 35.16** A 77-year-old man with cTxN1M0, human papillomavirus (HPV)-negative squamous cell carcinoma (SCC) with unknown primary metastatic to parapharyngeal space. **A,** Pretreatment CT demonstrating axial dimensions of tumor within the left parapharyngeal space. **B,** Pretreatment positron emission tomography (PET)/CT confirming fluorodeoxyglucose (FDG)-avid tumor in the left parapharyngeal space. **C,** Incision design. **D,** Lip-splitting approach. **E,** Pre-plated paramedian mandibular osteotomy design. **F,** Mandibulotomy and swing to provide access to parapharyngeal space.

Continued



• **Fig. 35.16, cont'd** **G,** Modified radical neck/resection specimen. **H,** Resection defect. **I,** Closure. **J,** Postoperative appearance 3 years following surgery and adjuvant radiation therapy.

secondary intention. Despite healing with scarring that results in less dynamic movement and altered form, the remaining unoperated areas can often compensate, with a notable exception. Even small tumors that extend onto and include the posterior free edge of the soft palate may require some form of reconstructive surgery to avoid postoperative velopharyngeal insufficiency.

However, T3/T4 oropharyngeal tumors are most frequently treated with an organ-sparing approach. For T3 oropharyngeal tumors that are lateralized and confined to the tonsillar fossa and one side of the base of tongue, TORS can be attempted and, when successful, healing by secondary intention yields reasonable results. In the author's experience these patients often complain of food trapping in the adynamic area if the defect crosses the glossotonsillar sulcus. This is mitigated with modified swallowing techniques learned from a speech language pathologist (described in detail later).

Because T3/T4 oropharyngeal tumors are usually treated with organ-sparing therapy, surgery is reserved for the salvage setting. Reconstruction of this anatomically and functionally intricate area after radiation can be an enormously difficult endeavor. The rest of this section focuses on this scenario.

In analyzing the resulting defect from salvage resection of T3/T4 oropharyngeal tumors, the first priority is to provide safe coverage of vital structures. In the post-radiation salvage setting, defects of the lateral pharyngeal wall should not be left to heal by secondary intention, as the hypocellularity and hypovascularity of the tissue bed are unreliable. Wound infection in this area has the potential for catastrophic carotid artery compromise.

The next consideration is functionality. First, determine which anatomic subsites (two lateral pharyngeal walls, posterior pharyngeal wall, soft palate, and base of tongue) will be affected, how much of the subsite is to be removed, and how many subsites remain. It is helpful to think of these subsites as joining to form a muscular ring. When only one of the five subsites is removed, the remaining four walls can often compensate for a hypokinetic area. This becomes more difficult as more of the subsites are removed.

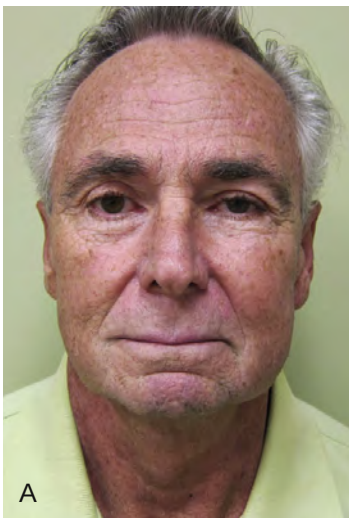
Reconstruction of this "ring" would ideally reestablish muscular continuity. In order to achieve this, restoring form with adynamic tissue is inadequate. It is often better to shrink the size of the oropharynx to improve on the ability of the remaining functioning components to compensate by closing the muscular ring. Achieving normal form is sacrificed for functionality. There are complicated classification schemes for oropharyngeal defects, and although they are helpful for organizing one's thoughts, the author has found them unnecessarily cumbersome. Instead, by understanding the concept of narrowing the oropharynx and restoring the oropharyngeal muscular "ring," the reconstructive surgeon usually can come up with a plan that yields good functional results.

Analyzing the anticipated defect for pharyngolaryngectomy requires careful examination using laryngoscopy techniques. This is done both at the consultation using endoscopes and intraoperatively using palpation and laryngoscopes. Pay careful attention to the location of the tumor, the size, and proximal to distal length. The width and length of the defect, and consequently the amount of remaining pharyngeal mucosa, will determine whether or not primary closure of the pharyngeal mucosa will be possible, whether a patch repair will be necessary, or if a tubed flap for a circumferential pharyngeal defect will be required. Hypopharyngeal defects that involve only the piriform recess on one side can be closed primarily. However, defects involving the posterior cricoid pharynx or both piriform recesses will require importation of tissue to avoid narrowing the neopharyngeal lumen and later pharyngeal stenosis.

Planning of Reconstructive Surgery

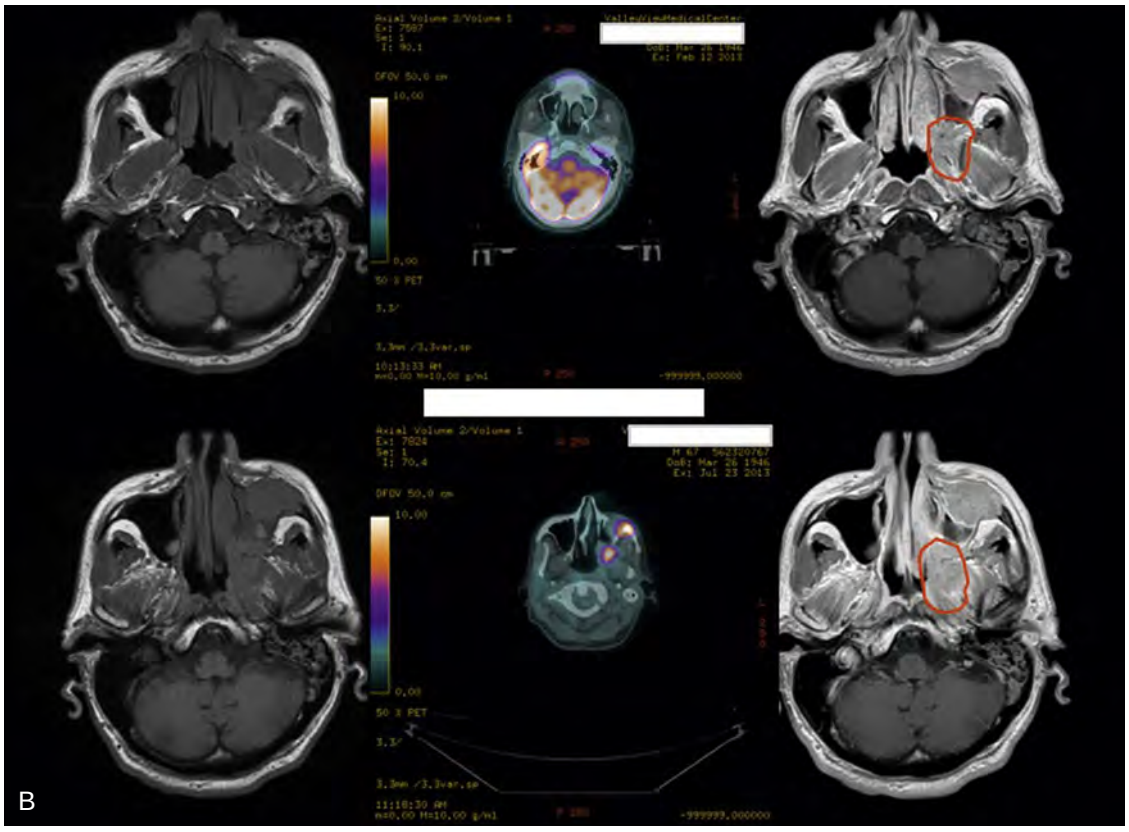
The armamentarium for oropharyngeal reconstruction involves using primary closure when possible, local flaps (pharyngeal flaps), free tissue flaps (radial forearm flaps and anterolateral thigh flaps are the most commonly employed by the author), regional flaps (pectoralis major flap), or a combination of these. The type of flap depends on the nature of the defect.[110-112]

Successful reconstruction of base of tongue defects depends on the amount of remaining mobile tongue, the extent of pharyngeal defect, and the preservation of the lingual and hypoglossal nerves (at least on one side). The radial forearm free flap is the workhorse flap for most pharyngeal defects, as it provides predictable, thin, pliable coverage of pharyngeal defects (see Figs. 35.9 and 35.12). If half of the base of tongue remains, function is often well preserved. However, with near-total or total base of tongue resections, restoring function relies on the mobility of the soft palate and pharyngeal walls. To facilitate this, it is necessary to use a flap of sufficient bulk to create a base of tongue mound. This can be done with either an anterolateral thigh flap or a radial forearm flap. A modification of the forearm flap includes a subcutaneous proximal extension (in



• **Fig. 35.17** A 67-year-old man with recurrent T2N0M0, human papillomavirus (HPV)-positive squamous cell carcinoma (SCC) of the palatine tonsil following definitive chemoradiation therapy (pretreatment images in Fig. 35.7) treated on immunotherapy clinical trial protocol. **A,** Preoperative appearance—note mild left proptosis.

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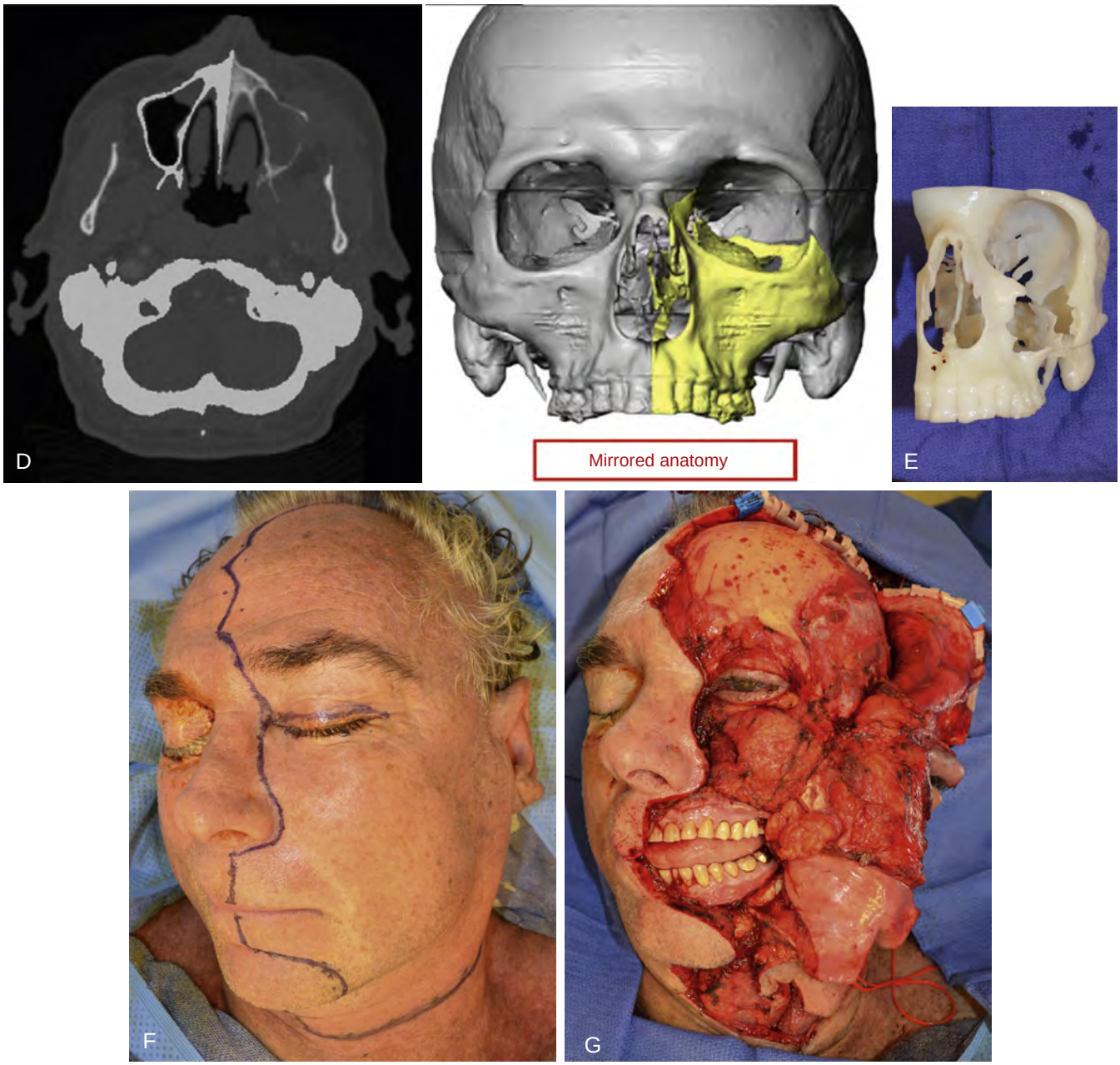




Simulated resected anatomy

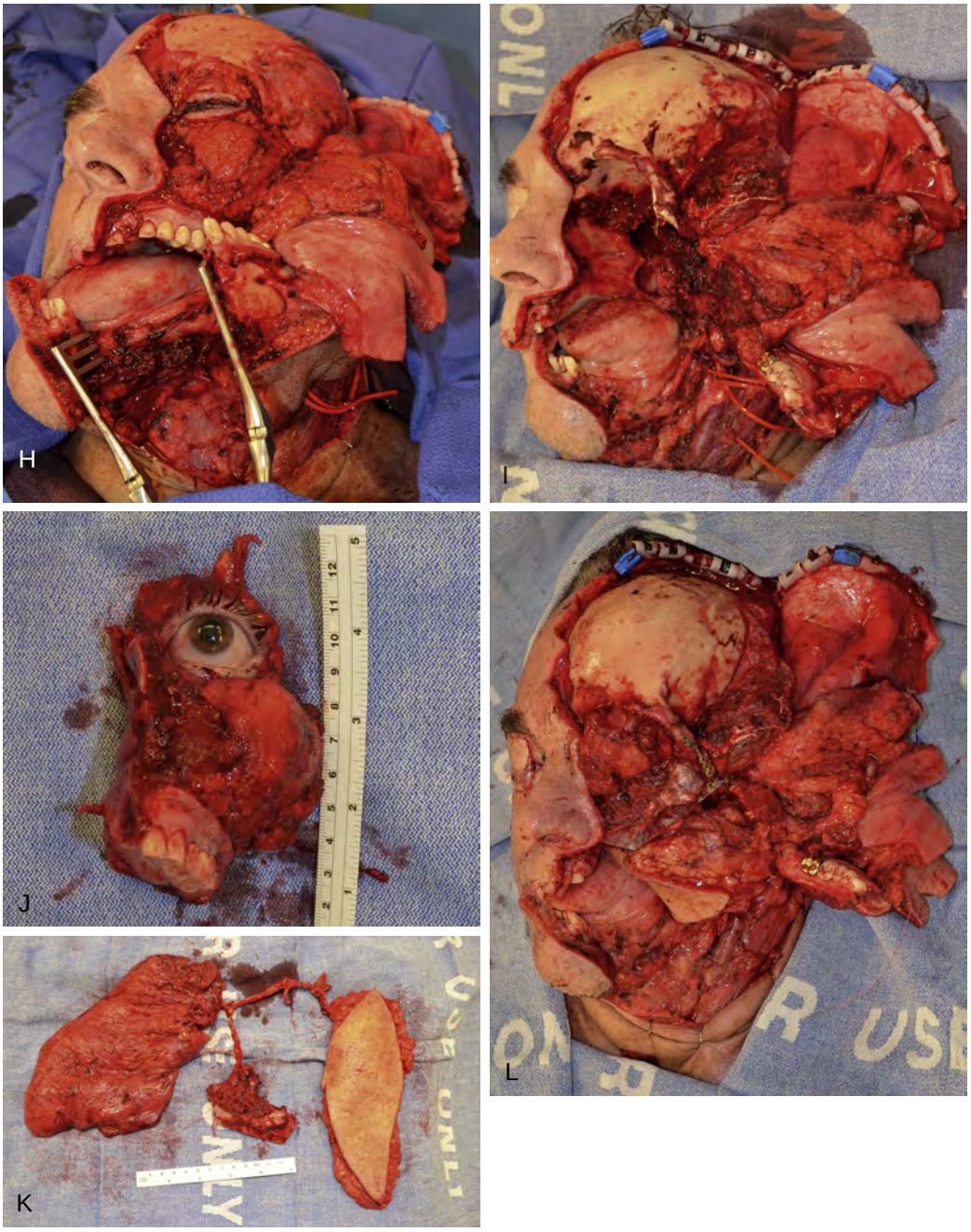


• **Fig. 35.17, cont'd** **B,** Preoperative imaging demonstrating fluorodeoxyglucose (FDG)-avid recurrence in the region of the left pterygomaxillary fissure with encroachment on the infratemporal and parapharyngeal spaces, involvement of the zygomatico-maxillary region with tumor invasion into the orbit and maxillary sinus. **C,** Virtual surgical plan depicting tumor invasion into the maxilla, zygoma, and orbit *(top)* as well as planned resection to be performed under navigation guidance.



• **Fig. 35.17, cont'd** **D,** DICOM data provided for intraoperative navigation *(left)* and mirrored anatomy to serve as a template for reconstruction of the orbit *(right)*. **E,** Stereolithographic model. **F,** Incision design for craniofacial resection with planned mandibulotomy and swing with orbital exenteration. **G,** Coronal, midface, and cheek flaps provide surgical exposure.

Continued



• **Fig. 35.17, cont'd** **H,** Paramedian mandibulotomy to provide access to parapharyngeal space and skull base. **I,** Resection defect. **J,** Specimen. **K,** Subscapular system free flap. **L,** Flap inset.



• **Fig. 35.17, cont'd** **M,** Closure. **N,** 6-month postoperative appearance following gamma knife radiation to skull base margins. **O,** Intraoral appearance. **P,** 1 year following surgery and gamma knife radiation with implant-supported orbital prosthesis in place.

the shape of a beaver tail) that can be folded under to increase the bulk of the tongue posteriorly.

Isolated soft palate defects that include the posterior free edge of the soft palate and leave a break in the continuity of the arch are best reconstructed using pharyngeal flaps. This has two distinct advantages. Using mobile pharyngeal myomucosal flaps restores a continuous muscular oropharyngeal "sphincter." This also will decrease and surgically narrow the oropharyngeal opening, improving on the compensation by unaffected areas. For smaller defects, undermining the lateral pharyngeal wall in a plane deep to the superior pharyngeal constrictor muscles and advancing it medially to primarily close the defect works well. For larger defects (when the superior pharyngeal constrictor cannot be sufficiently undermined for tension-free closure), the author prefers using a superiorly based posterior pharyngeal flap. This should be designed wider and longer than one would think to ensure adequate soft tissue for tension-free closure. The defect in the posterior pharyngeal wall can usually be closed primarily. The distal end of the flap is approximated to the cut edge of the soft palate defect to restore the muscular "ring."

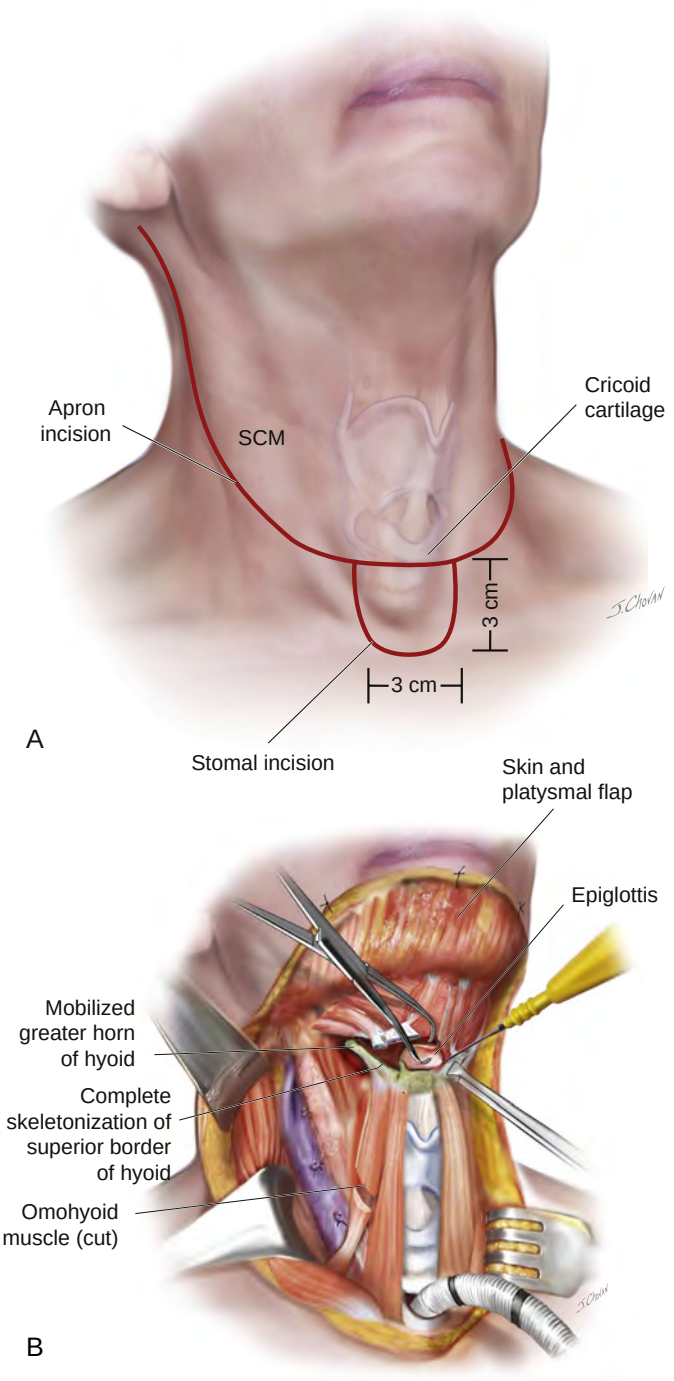
For larger defects of the soft palate, or defects that extend into the lateral pharyngeal wall, the posterior pharyngeal wall, the base of tongue, or all of these areas, a regional or free flap is combined with the local flap.[113]

A commonly seen presentation is a locally advanced tonsillar primary that extends onto the soft palate, leaving a large lateral pharyngeal and soft palate defect that may also extend into the glossotonsillar sulcus and the base of tongue. For this, a superiorly based posterior pharyngeal flap is used to restore muscular continuity and to permanently narrow the oropharynx. The mucosal side of the posterior pharyngeal flap faces the nasal cavity while the raw muscle faces the oropharynx. A radial forearm flap is then used to cover the muscle of the flap as well as the defect in the lateral pharyngeal wall extending onto the base of tongue (see Fig. 35.14). Chepeha and colleagues[114] describe this in detail. Customizing the shape of the skin flap has also been described by this group to facilitate coverage of this complex defect. However, this author has not found it necessary and typically uses a standard rectangular skin paddle that can then be stretched or de-epithelialized as needed.

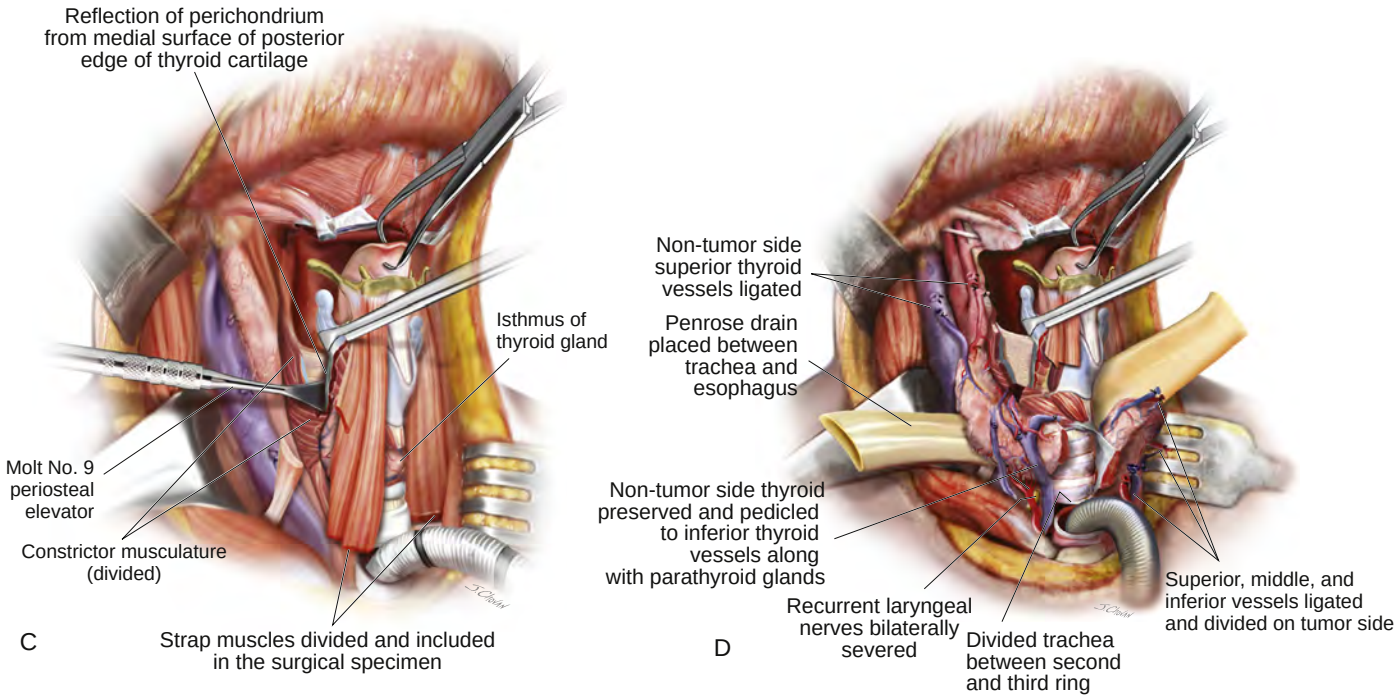
Access for oropharyngeal reconstruction can be a challenge in itself. With a traditional open approach via an access mandibulotomy and lip-split incision, access is widely available. In contrast, when using a completely transoral approach or transoral combined with lateral/suprahyoid pharyngotomy, access is limited. However, with proper instrumentation, this is manageable. Patient factors that limit transoral access include trismus (related to either invasive cancer or prior radiation therapy), presence of teeth, mandibular hypoplasia, a short thyromental distance, and macroglossia. In the absence of these complicating factors, the author has been able to perform pharyngeal reconstructions by using suspension retractors such as a Dingman mouth gag, Crowe-Davis, or the like. Alternatively, the author has also used the da Vinci robot successfully to close difficult-to-reach defects (see Fig. 35.14).

Reconstruction of pharyngolaryngectomy defects varies with the amount of remaining pharyngeal mucosa. As mentioned earlier, loss of the mucosa of the piriform recess on one side will leave enough mucosa for primary closure of the neopharynx. The primary challenge in this scenario is creation of a watertight closure and avoidance of a pharyngocutaneous fistula. This is done with meticulous attention to detail. The mucosa must be handled gently. Connell suturing with 3-0 polyglactin sutures is used to invert the mucosa into the luminal side. The pharyngeal defect is usually closed into a "T." When closing the horizontal limb at the base of tongue, we prefer to thread all of the sutures and tags with hemostats prior to tying them down. The junction of the horizontal and vertical limbs of the "T" creates a point where three corners meet. A Connell stitch that passes through each of these points is used to cinch these together in a purse-string fashion. Once all the sutures are passed, we then tie each of the sutures in order, working from lateral to medial. This avoids the increasing difficulty of suturing as the defect gets progressively smaller.

Even with meticulous closure, rates of pharyngocutaneous fistula remain high in the previously irradiated neck. Fistulas can be very problematic. They often occur adjacent to the stoma, resulting in drainage that is aspirated. Fistulas also result in infections immediately adjacent to the great vessels of the neck, increasing the risk of vascular insult and potentially catastrophic bleeding. For these reasons, every attempt must be made to avoid them. As previously mentioned, the use of flaps when reconstructing the neopharynx has been



• **Fig. 35.18** Laryngopharyngectomy. **A,** Apron incision design. *SCM,* Sternocleidomastoid. **B,** Inner and outer tunnels are defined and the hyoid bone is exposed circumferentially.



• **Fig. 35.18, cont'd** **C,** The perichondrium from the medial edge of the posterior thyroid cartilage is exposed and the larynx rotated. **D,** The trachea and tracheoesophageal groove are exposed and defined.

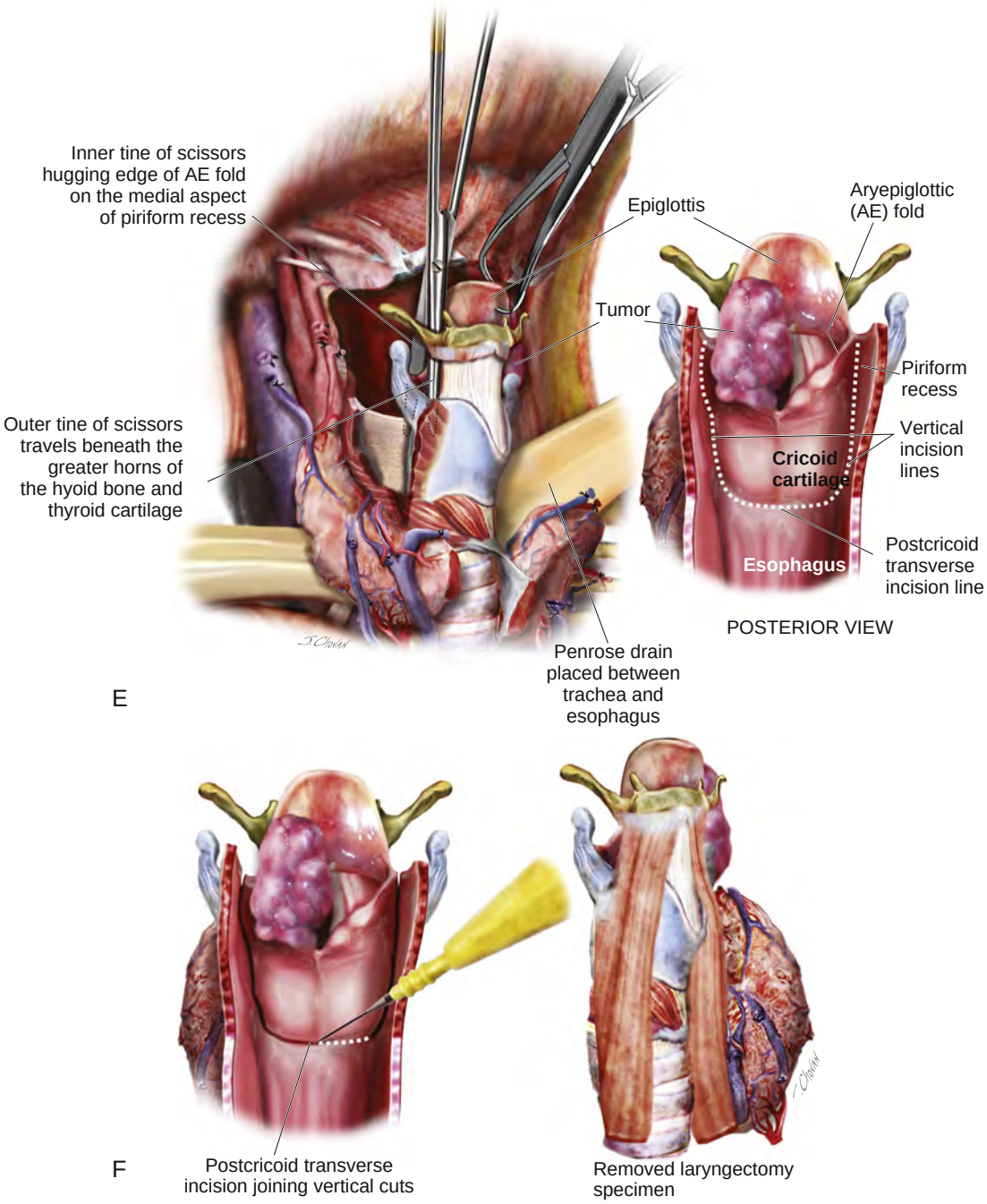
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demonstrated to decrease the rates of fistula formation. In a multicenter retrospective study by Patel and co-workers, the use of the pectoralis major flap, onlaid over the suture line seemed to have the lowest fistula rates (15%).[109] Our practice has been to use a radial forearm adipofascial flap as an onlay over the neopharyngeal suture line. A rectangular adipofascial flap, the width of the volar surface of the forearm and at least several centimeters longer than the suture line, is harvested. To do this, a longitudinal incision is made over the volar forearm, roughly over the palmaris longus, and the skin is sharply elevated off of the underlying subcutaneous fat and fascia in a subcutaneous plane. We found in a series of 13 patients that only one patient developed a fistula. In patients who are not suitable candidates for radial forearm flaps, or who develop fistulas despite the foregoing technique, our backup flap is the pectoralis major flap. Our one patient with wound complications had a complete breakdown of his pharyngeal closure and was secondarily reconstructed successfully with a pectoralis major flap. Another alternative to the radial forearm is the anterolateral thigh flap (ALT). Although effective at buttressing the neopharyngeal reconstruction and reducing the risk of fistulas, we have found that in our population the ALT is a bit too thick, resulting in excessive cervical bulk.

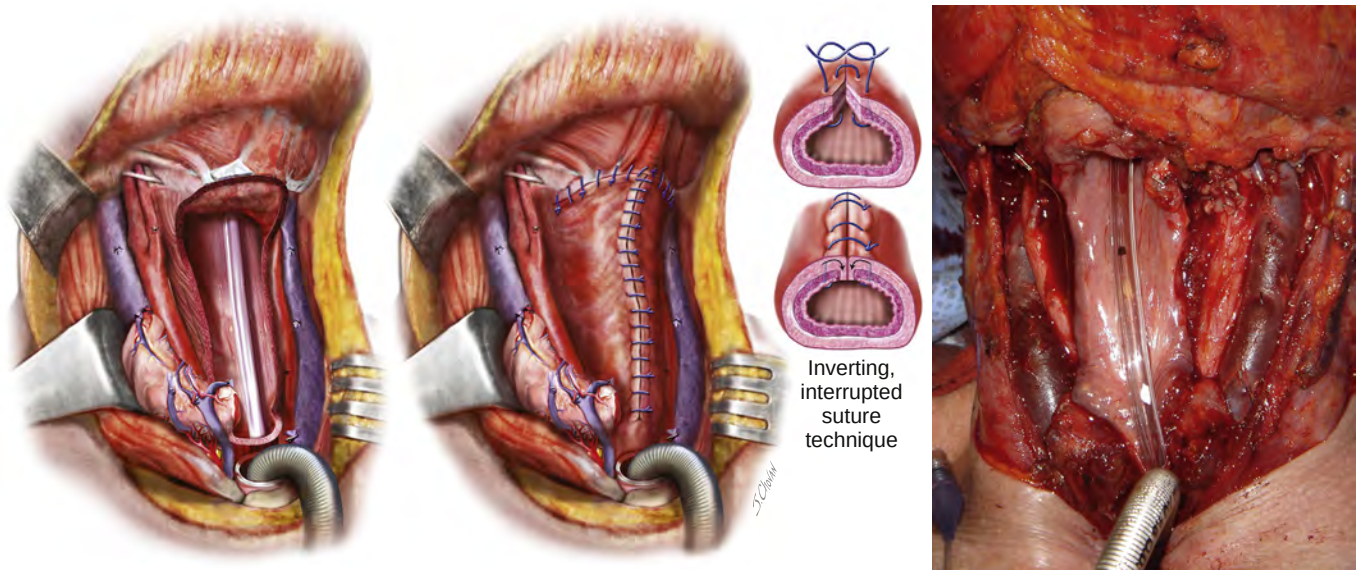
For hypopharyngeal defects that include more than one subsite or extend into the oropharynx, primary closure would result in an unacceptably narrow neopharyngeal lumen. Therefore, an inlay technique with a cutaneous flap is used as a patch reconstruction. Our favored flap, again, is the radial forearm fasciocutaneous flap. When harvesting the flap, we harvest an adipofascial extension of the flap beyond the boundaries of the skin flap. This allows a layer of fascia and fat to buttress the suture line between mucosa and skin. Again, the mucosa and skin are approximated with Connell suturing.

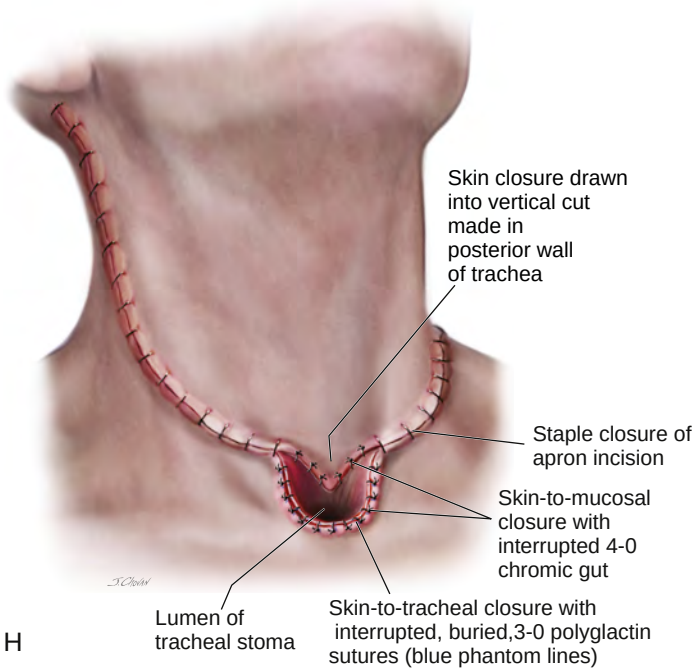
For circumferential pharyngeal defects, a tubed flap is used. Donor site options include the radial forearm, the ALT, and the pectoralis major. We favor the radial forearm, as it is the thinnest and easiest to shape into a tube. Some studies have shown lower fistula rates with the ALT; however, the body habitus of most North Americans results in flap of a thickness that is difficult to tube.[115]

In designing the flap, one must keep in mind that the width of the flap at the donor site is the circumference of the flap after it is tubed. Therefore, the diameter of the pharyngeal lumen is roughly the width of the flap divided by 3.14, or, in other words, a 9-cm–wide flap results in a lumen less than 3 cm in diameter. In order for a lumen of sufficient size to be created, the cutaneous portion of the flap needs to be a minimum of 10 cm at its narrowest portion. Also, the pharynx is not a perfect cylinder. Rather, it is more like a funnel. Therefore, the shape of the flap must resemble a trapezoid. We tend to make the wider portion of the trapezoid the proximal (on the forearm) portion of the flap, as the skin is more abundant in the proximal forearm. When raising the flap, we raise a margin of adipofascial flap beyond the cutaneous flap. This lies over the suture line, providing an additional layer of protection from pharyngeal leak. Last, when approximating the tubed flap to the esophagus, a circular suture line creates an area of likely stricture and stenosis. Hayden, with Nagel, previously described a "key in lock" technique to mitigate this area of stricture by spatulating the esophagus along the posterior wall and harvesting



• **Fig. 35.18, cont'd** **E,** Pharyngeal incision lateral to the aryepiglottic fold. **F,** Postcricoid transverse incision and delivery of the specimen. (From Kademani D, Tiwana P: *Atlas of Oral and Maxillofacial Surgery,* 2015, Elsevier.)

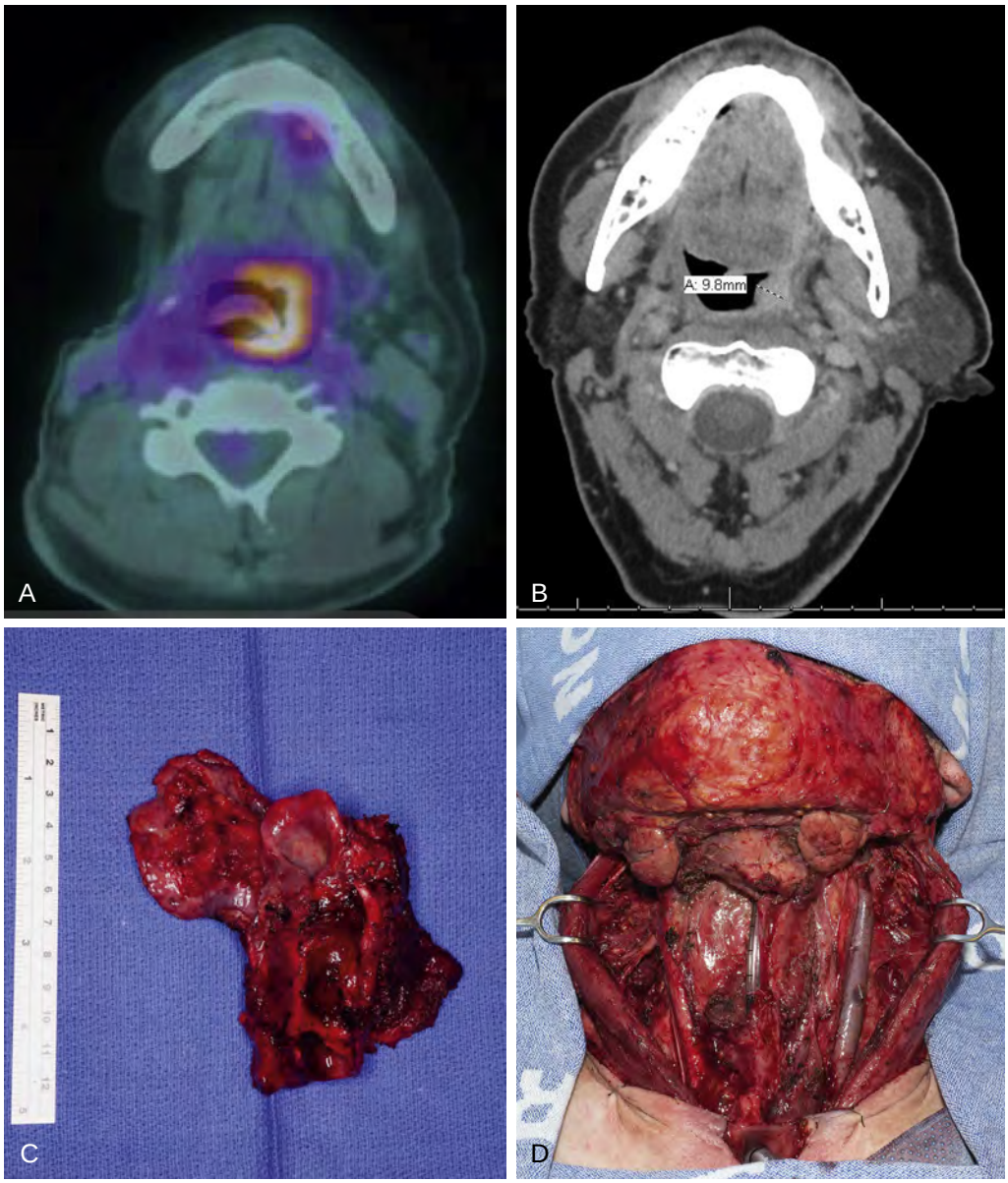




• **Fig. 35.18, cont'd** **G,** Pharyngeal closure (flap inset not shown). **H,** Tracheostoma at closure. (From Kademani D, Tiwana P: *Atlas of Oral and Maxillofacial Surgery,* Chapter 105, St Louis, 2015, Elsevier.)

the forearm flap with a triangular key that fits into the area of spatulation.[115]

After neopharyngeal construction is completed, regardless of the technique, we check that the closure has a watertight seal. This is done as follows. First, we pass an 18 French Salem sump into the stomach. This could be done prior to the pharyngeal closure, to aid in visualization. While placing digital pressure on the esophagus and around the tube, a temporary occlusion of the esophagus distal to the reconstruction is created. Diluted Betadine solution is then used to fill the neopharynx through the mouth until the neopharynx is gently distended. A clean laparotomy sponge is then used to dab around the suture line. Any brown staining on the sponge suggests an area of leakage. Additional horizontal mattresses are used to imbricate the suture line in these areas until the leak is no longer present. After the watertight seal is confirmed, the Salem sump is placed on suction to evacuate the solution. The sump can be kept as a feeding tube or removed if the patient already has a gastric tube. Some surgeons place and leave a Montgomery salivary bypass tube to further reduce leakage, but we have no experience with this technique and have not found rates of fistulas higher than that reported in the literature.



• **Fig. 35.19** A 62-year-old man with recurrent T3N0M0 human papillomavirus (HPV)-negative squamous cell carcinoma of the oropharynx following definitive chemoradiation with hypopharyngeal extension. **A,** Positron emission tomography (PET)/CT demonstrating recurrent tumor in the oropharynx/hypopharynx. **B,** CT image demonstrating recurrent tumor. **C,** Salvage pharyngolaryngectomy specimen. Note tumor extension to the pyriform recess. **D,** Pharyngeal defect prior to radial forearm free flap inset.

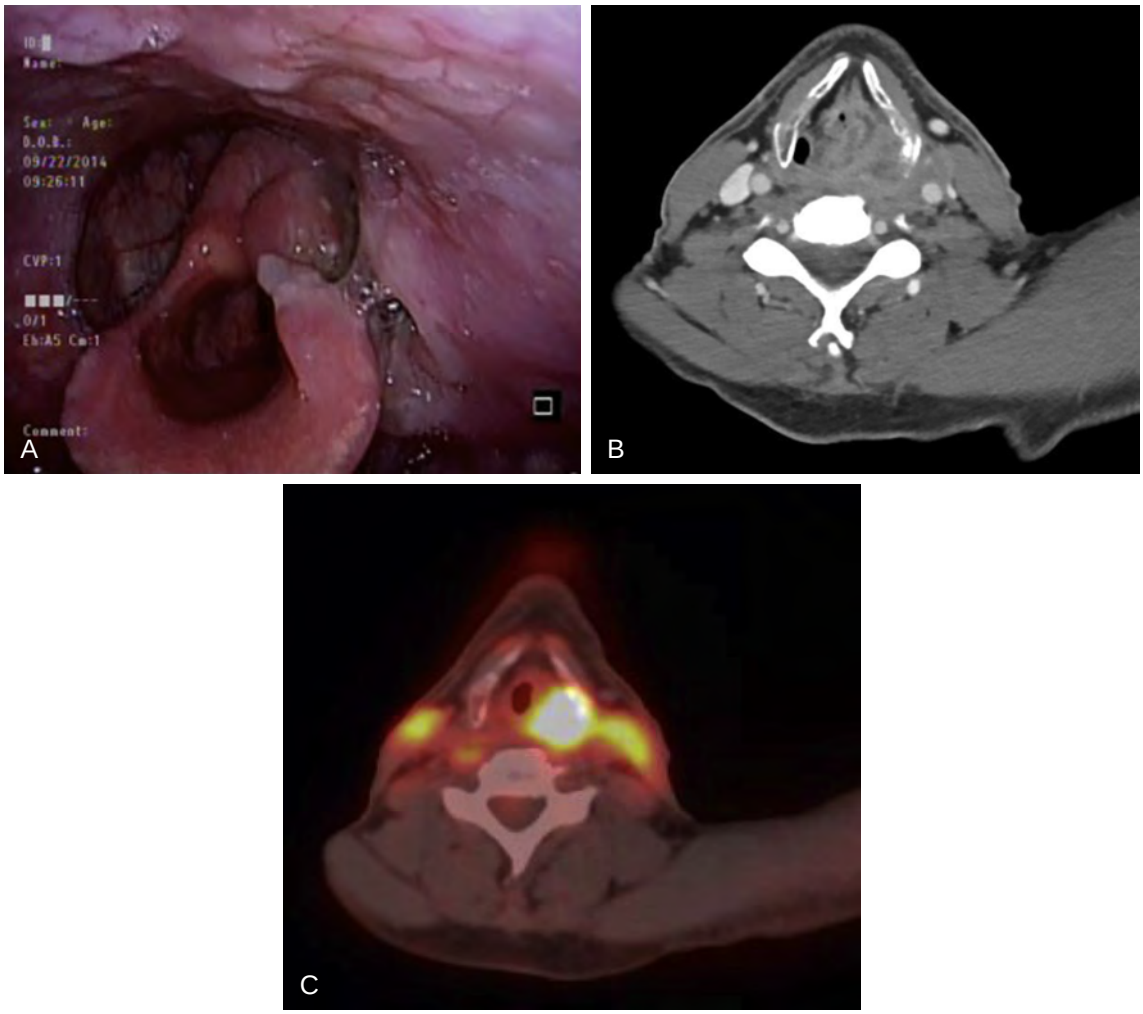
During the postoperative period, the patient is kept NPO and receives nutrition entirely through enteral feeds. At 2 weeks postoperatively, barring the development of an obvious fistula, an esophagram using Gastrografin is obtained at multiple angles to check for leaks. If none are present, the patient is gradually started on a liquid diet with the consultation and expertise of an SLP. If leaks are identified, the patient is kept NPO and an esophagram is obtained again after another interval of time.

Speech and Swallowing Therapy

Dysphagia is a common deficit during and after the treatment of OSCC. It can occur after surgery, chemotherapy, and radiation therapy, or a combination of any of the three. Dysphagia has an impact on nutrition, hydration, wound healing, and possible aspiration pneumonia.

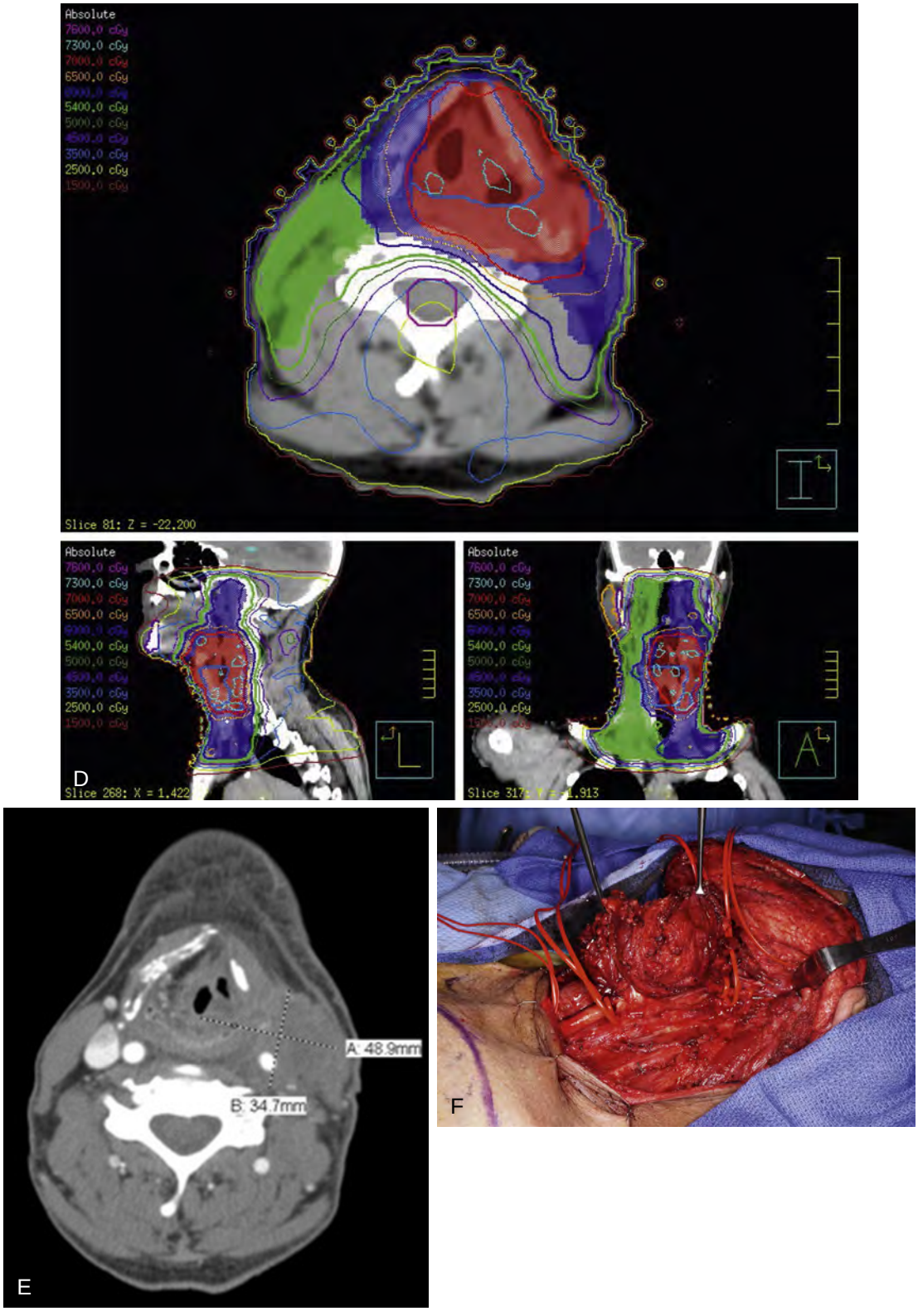
Surgical resection of tonsil tumors can modify the structures that are used to transfer the bolus and protect the airway and nasopharynx. Surgery can reduce velar closure, which may allow foods or liquids to leak into the nasal cavity, and also changes the vocal resonance when speaking. It can reduce the base of tongue/posterior pharyngeal wall contact during swallowing, resulting in post-swallow pharyngeal residue, premature spillage of the bolus, delayed initiation of the swallow, and reduced hyolaryngeal elevation. These can result in aspiration prior to the swallow or post-swallow aspiration.

Radiation therapy, in conjunction with or without chemotherapy, has acute and long-term effects on swallowing. Acutely, the treatment sequelae have a significant impact on swallowing and speech. These include xerostomia, mucositis, odynophagia, neutropenia, nausea, and malaise. Patients should be monitored closely through radiation for swallowing function and diet texture tolerance. After completion of radiation, the patient may have long-term dysphagia secondary to radiation fibrotic effects, taste changes, xerostomia, odynophagia, and trismus.

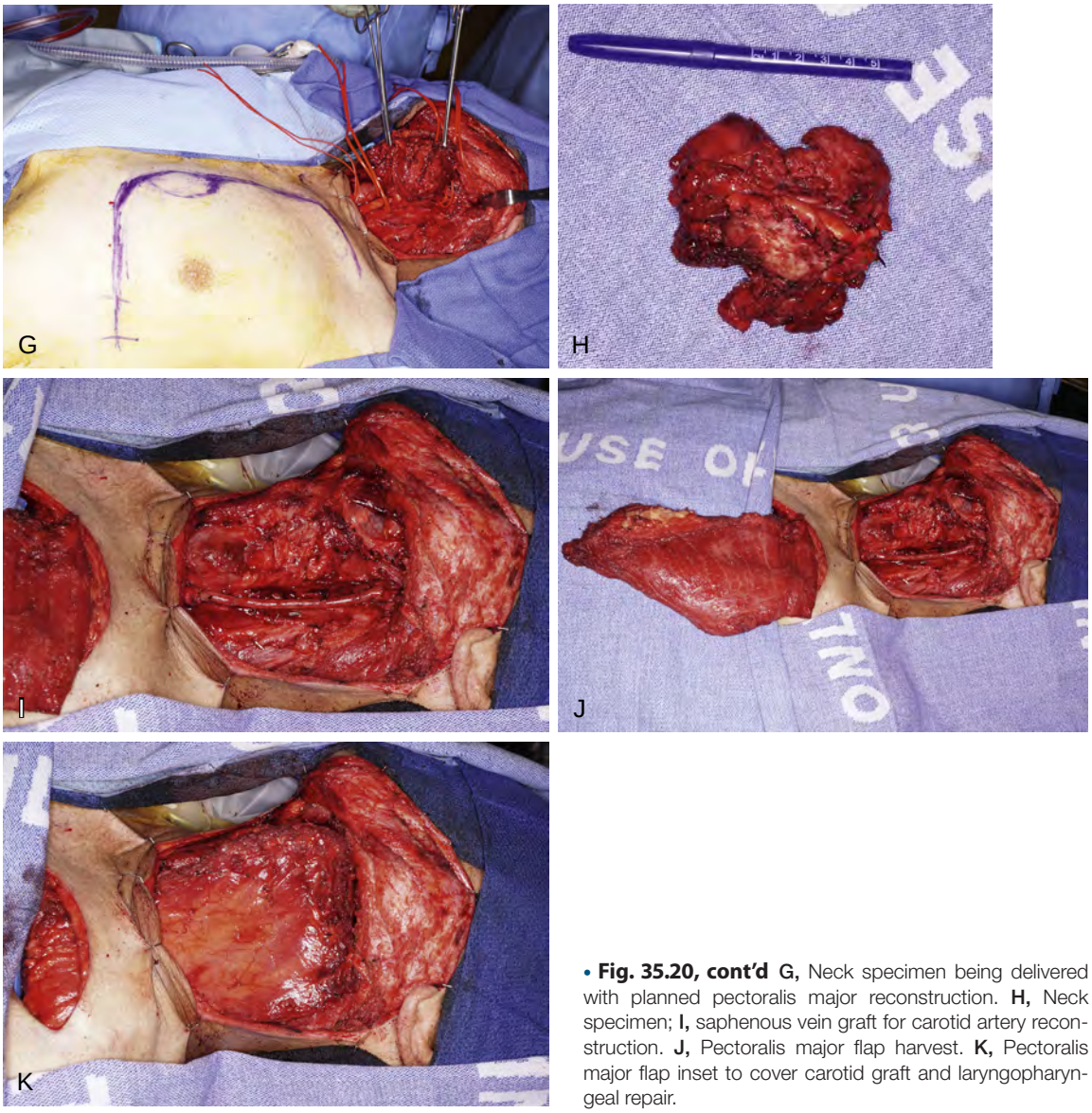


• **Fig. 35.20** A 58- year-old man with T4bN2bM0, stage IVB, human papillomavirus (HPV)-negative squamous cell carcinoma of the hypopharynx with fixation of the hemilarynx. **A,** Endoscopic view of hypopharyngeal tumor with fixation of the hemilarynx. **B,** Axial CT scan demonstrating hypopharyngeal tumor involving the thyroid cartilage, encroaching upon the prevertebral fascia and encasing the carotid artery. **C,** Positron emission tomography (PET)/CT.

Continued



• **Fig. 35.20, cont'd** **D,** Isodosing plan for radiation therapy. **E,** Axial CT image 1 year following completion of chemoradiation, demonstrating locoregional recurrence with carotid artery encasement. **F,** Salvage extended radical neck dissection with partial pharyngolaryngectomy and carotid artery resection.



• **Fig. 35.20, cont'd** **G,** Neck specimen being delivered with planned pectoralis major reconstruction. **H,** Neck specimen; **I,** saphenous vein graft for carotid artery reconstruction. **J,** Pectoralis major flap harvest. **K,** Pectoralis major flap inset to cover carotid graft and laryngopharyngeal repair.

Pretreatment Evaluation

Prior to treatment of the cancer, an SLP should evaluate the patient's current swallowing and speech abilities. Pretreatment swallow evaluations allow for assessment of patient's nutritional intake and anatomic and physiologic changes. A thorough oral-motor exam is completed to assess range of motion, strength, and coordination of the oral-pharyngeal system. A clinical swallow evaluation is used to examine bolus manipulation, control, transfer, weakness, residue, and hyolaryngeal elevation and excursion, and allow for determination of aspiration risk. Occasionally, an imaging procedure is used to fully visualize the physiology of the swallow. Most often this is done with either a modified barium swallow (MBS) study or a fiber-optic endoscopic evaluation of swallowing (FEES). Counseling prior to treatment will focus on potential for changes in speech and swallowing after surgery or during and after CRT. If needed, swallowing compensatory strategies may be introduced, and oral supplements or possibly early alternative nutrition may be indicated. This allows for improved nutritional reserves prior to the beginning of treatment. Patients who have dysphagia prior to treatment are at higher risk of long-term dysphagia and possibly permanent tube feeding.[116]

Postsurgical Speech/Swallowing Evaluation

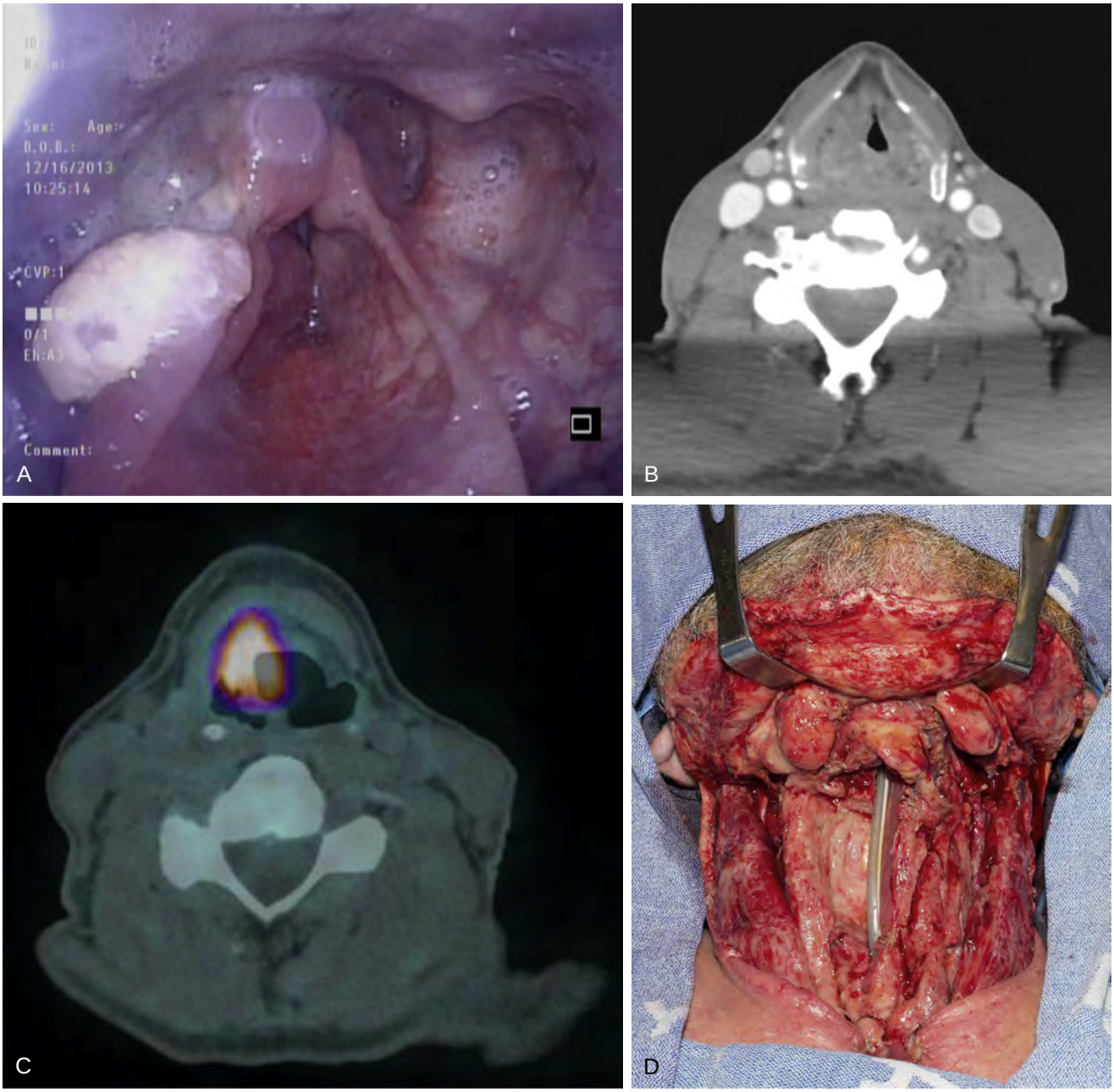
After completion of surgery, the patient's dysphagia should be reevaluated. Severity of the patient's dysphagia is related to the size of the surgical resection, type of surgical reconstruction, and decreased sensation postoperatively. Postoperative swelling and pain will also have a significant impact. Surgical resection involving the pharyngeal wall and/or the base of tongue will have increased impact on swallowing. Tonsil resection surgery can impact the bolus transfer into the pharynx, velar closure, and

base of tongue contact with the posterior pharyngeal wall. This will often result in delayed oral transit, pharyngeal residue, vallecular pooling, premature spillage of the bolus, and incomplete laryngeal closure. An instrumental swallow evaluation is often completed to visualize the physiology of the swallow mechanism.

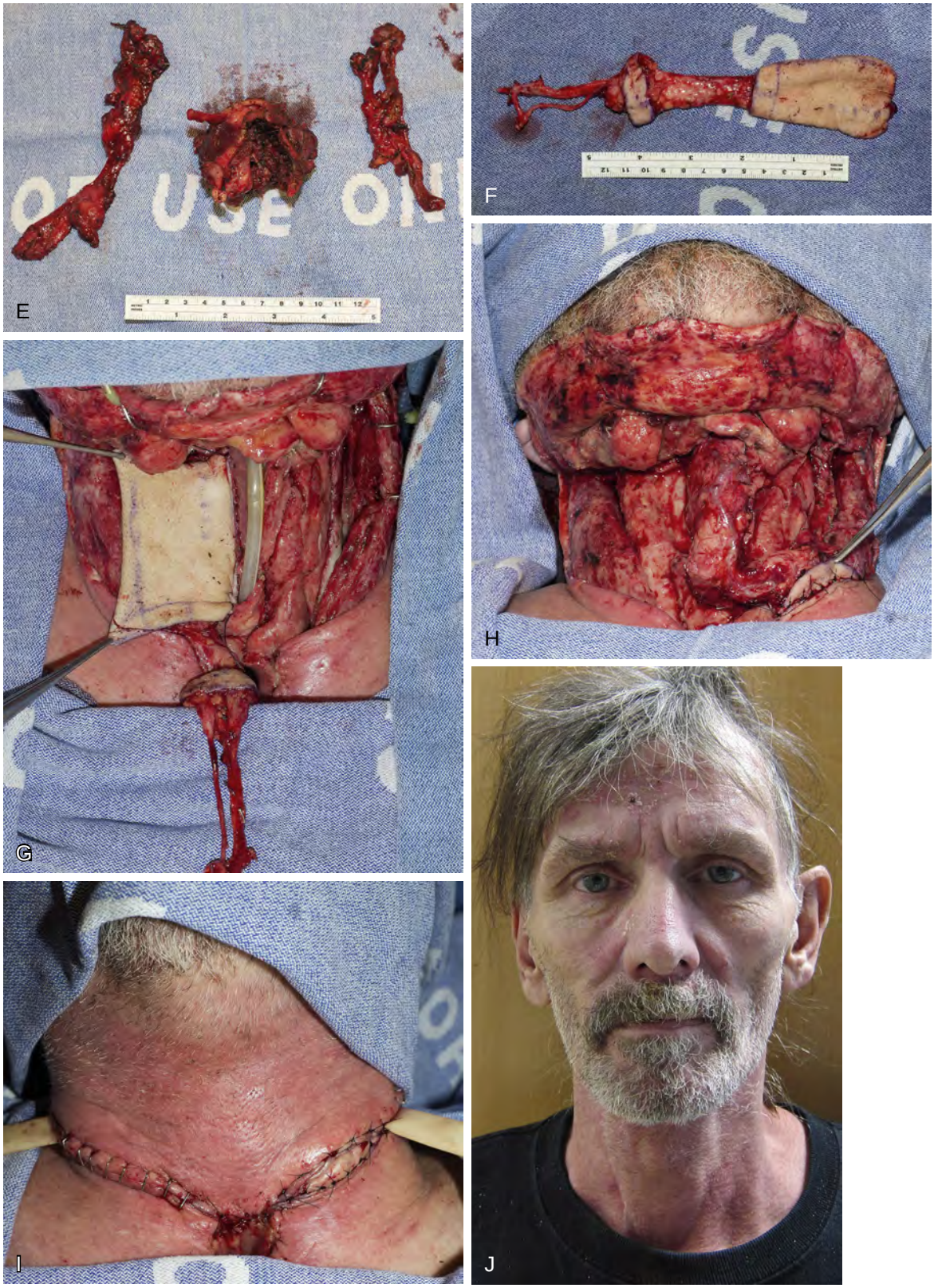
Treatment of swallowing may include postural changes, diet texture changes, and compensatory strategies. As postoperative swelling reduces, swallowing should improve, although it may continue to be impaired. Introduction of range-of-motion and strengthening exercises has been shown to improve swallow safety.[117]

Speech/Swallow Evaluation Following Chemoradiation Therapy

Swallowing should be monitored prior to, during, and after CRT therapy. Effects of radiation, with or without chemo, on swallowing result in changes to the swallowing structures, function, taste, pain, and mucosal lining. For radiation directed at the tonsil, there can be changes to the motility of the structures, including reduced jaw opening, reduced base of tongue retraction, reduced velopharyngeal closure, reduced laryngeal elevation, impaired pharyngeal constriction, and delayed laryngeal

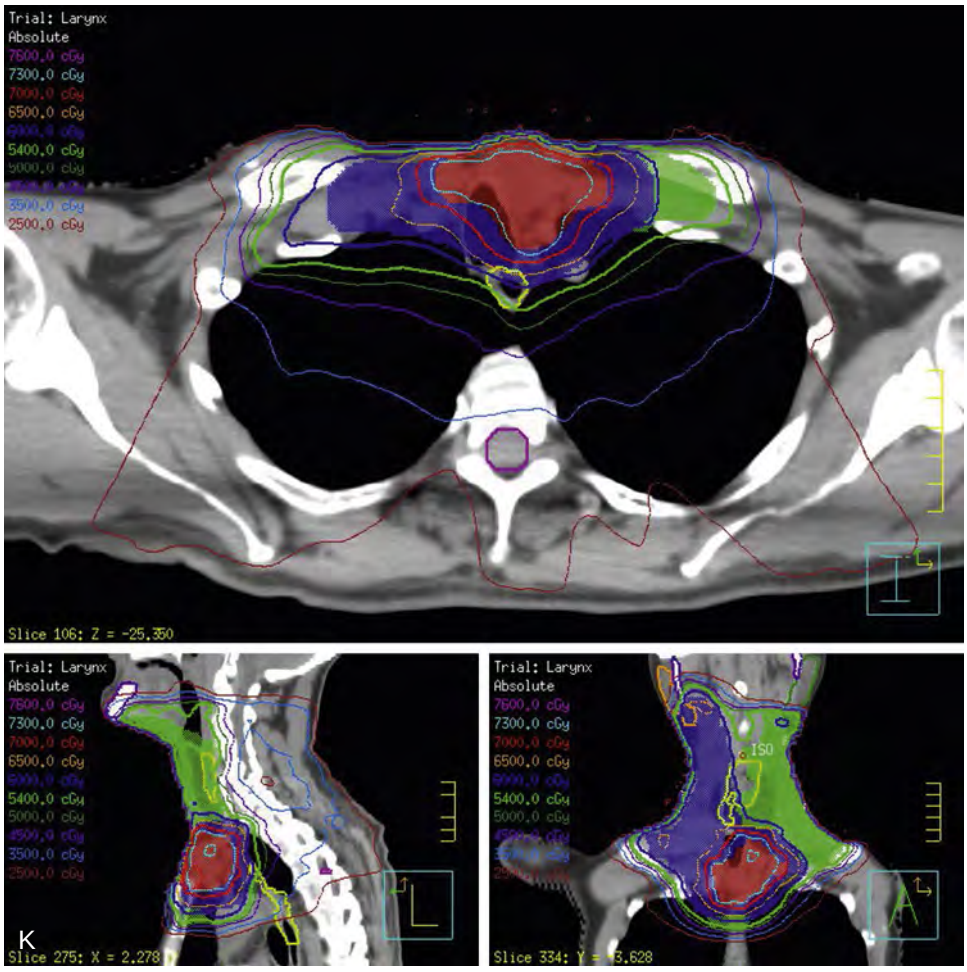


• **Fig. 35.21** A 53-year-old man with recurrent cT2N1M0, stage III squamous cell carcinoma of the pyriform sinus following definitive chemoradiation. **A,** Endoscopic view demonstrating pyriform tumor with extension to aryepiglottic fold and arytenoid. **B,** Axial CT scan. **C,** Positron emission tomography (PET)/CT. **D,** Defect following total laryngopharyngectomy and bilateral II/V selective neck dissections.



• **Fig. 35.21, cont'd** **E,** Surgical specimens. **F,** Radial forearm flap harvest. **G,** Flap inset. **H,** pharyngeal reconstruction prior to closure. **I,** closure; **J,** 2-year postoperative appearance;

Continued



• **Fig. 35.21, cont'd** **K**, Intensity-modulated radiation therapy (IMRT) dose to high-risk areas.

vestibule closure. Sequelae related to CRT also impact swallowing, including xerostomia, reduced saliva, and mucositis. Swallowing disorders occur during treatment and can persist long term. There can be continued deterioration of swallow function years after CRT secondary to fibrosis.

Treatment strategies during CRT usually involve range-of-motion and strengthening exercises, diet texture changes, and compensatory strategies.

Swallowing Exercises

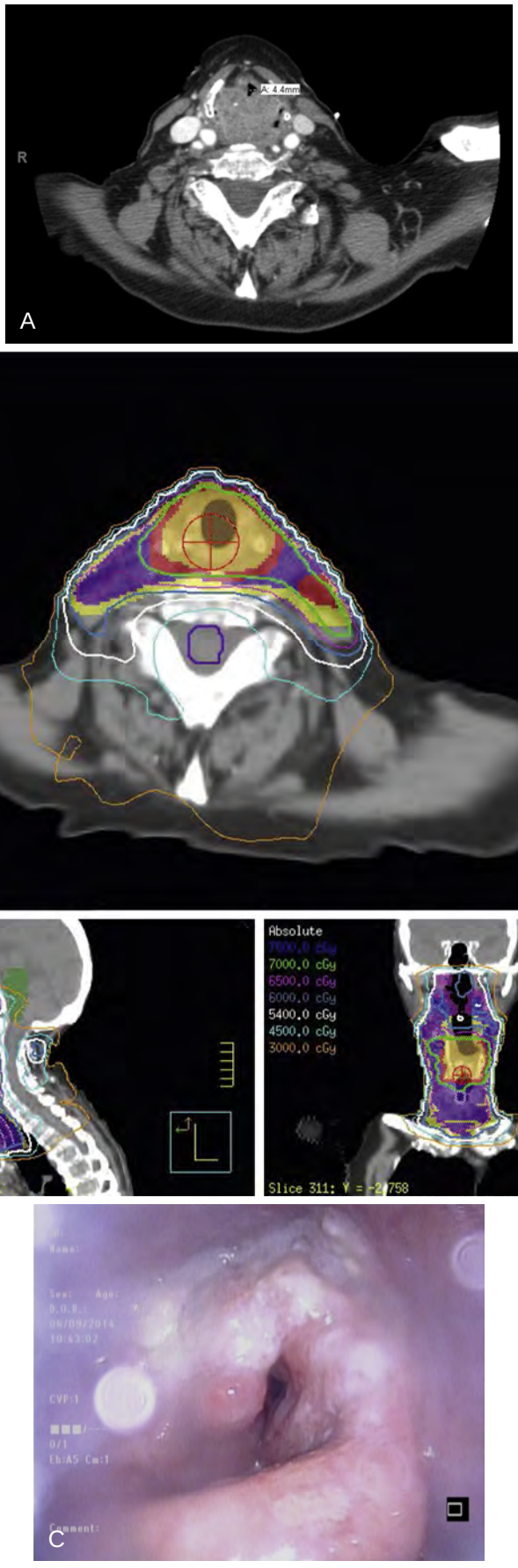
Swallowing exercises can be beneficial in treating dysphagia secondary to tonsil cancer. These exercises can help to strengthen swallowing structures, improve bolus control, and improve airway protection. For example, the tongue-hold swallow exercise[118] is designed to improve base of tongue and pharyngeal strength. The patient holds the tip of the tongue gently between the front teeth and maintains the posture while swallowing. This exercise causes the glossopharyngeal portion of the superior constrictor muscle to use more force in contracting.

The Mendelsohn maneuver[119] can be of benefit to maximize hyolaryngeal elevation. The patient holds the larynx up at the highest point for an extended time, then completes the swallow. The goal is to increase the extent and duration of the laryngeal elevation. The breath hold strategy[108] is used to maximize full closure of the laryngeal vestibule. The patient takes a breath, bears down, and holds the breath. Hold for extended time, and repeat. There is significant variability in swallowing deficits for patients with tonsil cancer. Early evaluation of swallowing and introduction of swallowing strategies is beneficial to maintain safe oral intake.

Dental Management

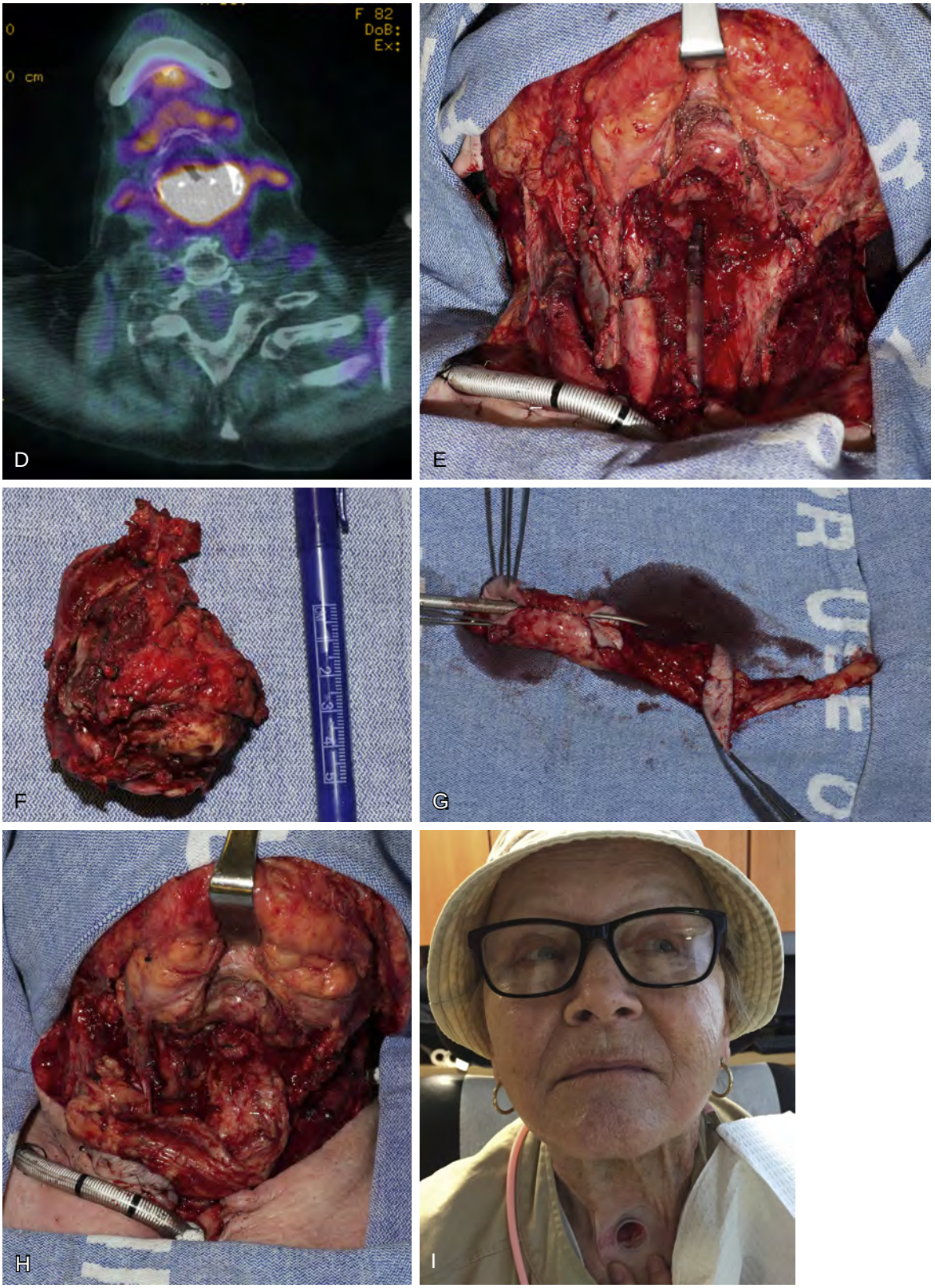
Dental/Oral Considerations

Patients diagnosed with T3/T4 tonsil SCC present a particular management challenge for the dental/oral oncologist. As many patients are treated with definitive CRT, the time from diagnosis to treatment may be extremely short as the period between surgical resection and initiation of CRT is eliminated. Because as many as 75% of head and neck cancer patients, with any primary location or stage, have been reported to have foci of dental infection at the time of diagnosis, timely pretreatment dental/oral evaluation is essential.[1] Increased dental side effects have been reported in doses as low as 30 Gy; however, in sites over 60 Gy there is a 10-fold

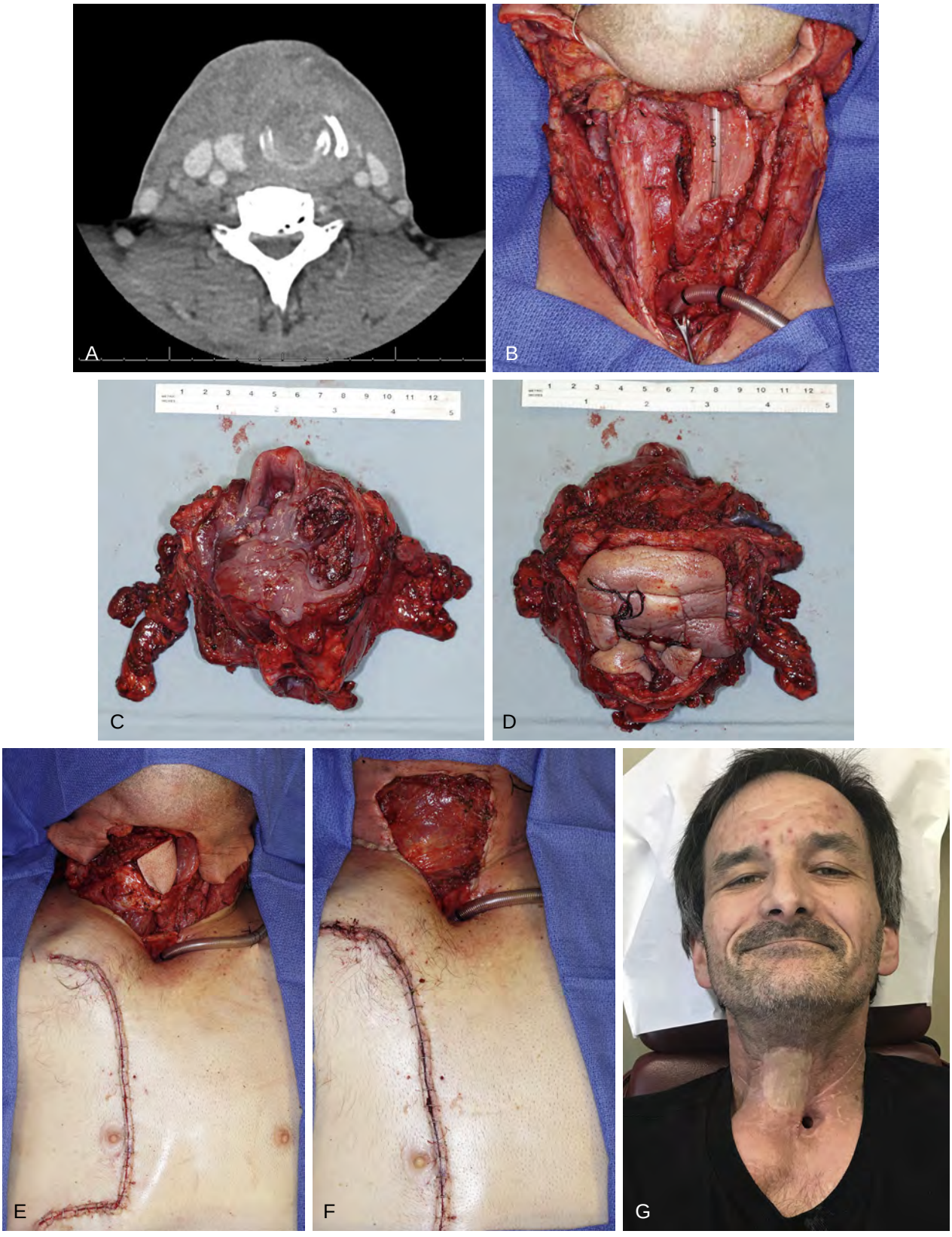


• **Fig. 35.22** A 71-year-old woman with recurrent T3N0M0 squamous cell carcinoma of the hypopharynx with transglottic and esophageal extension, following definitive chemoradiation. **A,** Pretreatment CT. **B,** Intensity-modulated radiation therapy (IMRT) plan, primary site to 70 Gy. **C,** Endoscopic view with recurrent tumor involving the posterior pharyngeal wall, arytenoids, posterior commissure with esophageal extension 3 years following definitive chemoradiation.

Continued



• **Fig. 35.22, cont'd** **D,** Positron emission tomography (PET)/CT demonstrating local recurrence 3 years following definitive chemoradiation. **E,** Pharyngeal defect following salvage pharyngolaryngoesophagectomy with bilateral II-V selective neck dissections. **F,** Surgical specimen. **G,** "Tubed" radial forearm free flap harvest prepared for inset. **H,** Flap inset prior to closure. **I,** 2-year postoperative appearance.



• **Fig. 35.23** A 47-year-old male with cT4AN2cM0, stage IVA squamous cell carcinoma of the hypopharynx with transglottic extension and invasion of the thyroid cartilage, strap muscles and anterior neck skin. **A,** Preoperative axial CT image. **B,** Laryngopharyngeal defect following pharyngolaryngectomy with composite central compartment and skin excision. **C,** Surgical specimen. **D,** Surgical specimen. **E,** Pectoralis major myocutaneous flap inset for pharyngeal reconstruction. **F,** Closure prior to skin graft of the pectoralis muscle. **G,** Postoperative appearance 1 year following surgery.

increase in tooth damage.[120] This increase in the likelihood of tooth damage is in theory due to a combination of direct damage to tooth structures and salivary dysfunction.

Although conventional radiotherapy resulted in increased oral sequelae and morbidity, the location and volume of radiation portals were predictable. For patients treated with IMRT, historic assumptions may not apply, in particular with large oropharynx tumors. Dosimetric evaluation of T3/T4 base of tongue tumors resulted in doses over 60 Gy to all sites of the mandible, including ipsilateral and contralateral molar, premolar, and anterior tooth-bearing regions.[121] In this investigation, mandibular doses were found to be more frequently correlated with tumor size rather than nodal status. Additional studies found that for patients with large oropharynx tumors, the ipsilateral maxillary molars received as high as 89.43% of mean radiation doses.[122]

Patients with large oropharynx tumors are at risk of both short- and long-term oral complications. The entire oral cavity must be considered as a potential focus for local and systemic complications for patients treated with radiotherapy and chemotherapy. Short-term risks are increased, as these patients are likely to receive concurrent chemotherapy and chronic dental infections may become acute during therapy, which alters or suppresses the immune response. These foci should be eliminated or treated prior to initiation of treatment. Long-term complications from high doses of radiation to tooth-bearing areas of both the maxilla and mandible place the patient at risk for radiation caries, periodontal disease, dental pathology, and osteoradionecrosis. The larger volume of irradiated oral tissues increases the risk of oral discomfort from mucosal damage, salivary hypofunction and xerostomia, fibrosis of soft tissues, and secondary infections. Although there is limited evidence on standard radiation doses to tooth-bearing areas, these investigations call attention to the need for a comprehensive examination by a provider with specific training and knowledge in oncologic dentistry and oral care.

PART 2: NASOPHARYNX

Overview

Nasopharyngeal carcinoma (NPC) is a type of squamous carcinoma arising in the nasopharyngeal mucosa. There is a strong association with EBV infection. HPV is a contributing factor in EBV-negative tumors. Other contributing factors include race, genetics, and environmental agents. NPC shows a striking geographic distribution and is common in southern China, Southeast Asia, and northern Africa. The incidence in the non-Asian population in the United States is low. NPC is seen over a wide age range, and there is a 2:1 to 3:1 male predominance. The most common presentation is enlargement of unilateral or bilateral upper cervical lymph node. Half of patients have nasal symptoms including epistaxis, nasal obstruction, and discharge.

NPC is divided into two major categories: keratinizing squamous cell carcinoma and nonkeratinizing carcinoma. The latter is further divided into differentiated and undifferentiated types. Carcinoma with associated lymphoid stroma (lymphoepithelioma) is considered a variant of nonkeratinizing undifferentiated carcinoma. It is not uncommon to see mixed morphologic features, and in such a case, the tumor is classified based on the predominant type. The keratinizing type is similar to conventional SCC of the other head and neck sites and is more likely to be seen in non-Asians. Smoking is a risk factor for this type, and the association with EBV is weak. The keratinizing subtype is more aggressive, less frequently metastatic (30%), and less radiosensitive, and it has a 5-year survival of 40%. The two nonkeratinizing subtypes, differentiated and undifferentiated, have overlapping histologic features, with the subclassification failing to convey significant survival or therapeutic differences. The nonkeratinizing types have a propensity to metastasize, are radiosensitive, and have a 5-year survival of approximately 60%.[123]

Histologically, the keratinizing NPC is morphologically similar to conventional SCC of other sites, demonstrating intercellular bridges and keratinization. The nonkeratinizing differentiated subtype shows distinct cell borders and evidence of maturation within the tumor cords. This subtype mimics the morphologic appearance of transitional cell carcinoma. The nonkeratinizing undifferentiated subtype shows a syncytial growth pattern with indistinct cell borders. The cells are larger with scant cytoplasm, vesicular nuclei, and prominent nucleoli. The nonkeratinizing subtypes evoke no desmoplastic response to tumor invasion. One diagnostic pitfall is that the tumor cells may be rather inconspicuous in the background of lymphoid stroma and sometimes may mimic germinal center cells. Both keratin immunohistochemistry and EBV in situ hybridization can help highlighting these tumor cells.

Staging

The clinical stage is the most important prognostic factor in NPC. Nonkeratinizing NPCs are radiosensitive, and radiotherapy has been the staple of therapy. The keratinized type is less sensitive to radiation and may require surgical resection. Concurrent CRT improves outcome and decreases the incidence of metastasis[124,125].

A number of changes have been incorporated into the 8th edition of the *AJCC Staging Manual* (see Table 35.6): T0 is added for EBV+ unknown primary with cervical lymph node involvement; adjacent muscle involvement, including the medial pterygoid, lateral pterygoid, and prevertebral muscles, is now designated as T2; masticator space and infratemporal fossa are replaced by specific soft tissue descriptors; the previous N3b criterion of supraclavicular fossa is changed in the lower neck; N3a and N3b are merged into a single N3 category; the previous substages IVA and IVB are merged to form IVA; and previous IVC is now upstaged to IVB.

Nasopharyngeal carcinoma is challenging to treat because of its potential patterns of spread. The proximity to the skull base gives potential access for direct extension through foramen rotundum (cranial nerve V2), foramen ovale (cranial nerve V3), and foramen lacerum to the cavernous sinus (cranial nerves III, IV, V1, V2, VI). The parapharyngeal and masticator spaces are potential avenues of spread. It also has high

proclivity to spread both regionally and distantly. It is a disease best treated by radiation, usually combined with chemotherapy. Staging should include MRI to assess local tumor infiltration and PET/CT to evaluate for regional spread and rule out distant metastases. Using these imaging modalities is critical for meticulous radiotherapy planning to ensure all visible and suspected disease is treated appropriately.

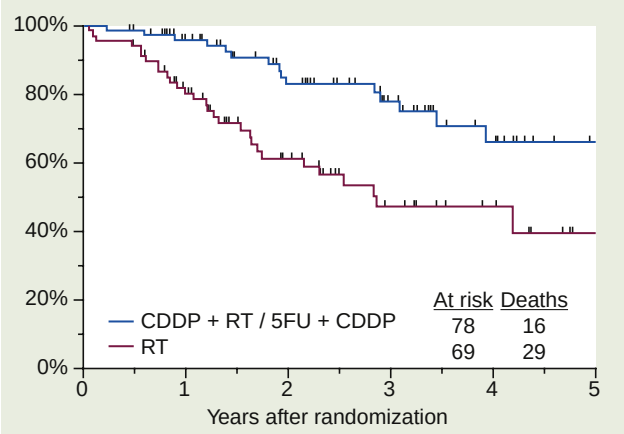
Nasopharyngeal carcinoma is associated with Epstein-Barr virus (EBV) infection. Lin has shown that measuring plasma EBV DNA is prognostic for outcome.[123] Overall survival and recurrence-free survival was shown to be significantly improved in patients with plasma EBV DNA concentrations less than 1500 copies per milliliter. Further, if EBV DNA remains detectable 1 week after completion of radiotherapy, patients had significantly worse overall survival and relapse-free survival.

As most patients with nasopharyngeal carcinoma present with locoregionally advanced disease, concurrent chemoradiation has become the standard of care. Intergroup study 0099 compared radiotherapy alone versus chemoradiation in 193 patients with stage III/IV disease.[124] Patients were randomized to receive 70 Gy alone or with concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 of radiotherapy. Chemoradiotherapy patients also received chemotherapy after the completion of radiation: cisplatin 80 mg/m^2 on day 1 and fluorouracil 1000 mg/m^2 per day on days 1-4, delivered every 4 weeks for three cycles. Combining chemotherapy with radiotherapy increased 3-year survival from 47–78% (P = .005) (Fig. 35.24). This study and subsequent meta-analyses including other randomized trials established chemoradiation as standard of care for the majority of nasopharyngeal cancer patients.[125]

Improvements in radiation planning and delivery, such as IMRT, have also improved locoregional control rates and reduced acute and long-term toxicity. Table 35.7 describes typical radiotherapy dose prescriptions for nasopharynx cancer. IMRT is ideal for nasopharyngeal cancer to spare multiple adjacent normal tissues in close proximity to the tumor target volumes (Figs. 35.25 and 35.26). Lee and colleagues reported the UCSF experience treating 67 patients from 1995 through 2000.[126] Exceptional locoregional control was achieved using IMRT. With median follow-up of 31 months, only one patient suffered local recurrence and one patient failed in the neck, for a 4-year locoregional progression-free survival of 98%. Most patients (75%) received chemotherapy as per the Intergroup 0099 guidelines. Importantly, late toxicity, including xerostomia, was reduced with IMRT compared to historical reports. The ability of IMRT planning to improve the therapeutic ratio for nasopharynx cancers has been confirmed in multiple subsequent retrospective and prospective studies.

Although a majority of patients receive concurrent cisplatin with IMRT, many patients do not receive the post-radiation adjuvant chemotherapy used in Intergroup 0099. Often, the acute toxicities of 7 weeks of concurrent chemoradiation limit the ability to deliver adjuvant chemotherapy. Using post-radiation EBV DNA titer information may help to guide therapy. The NRG-HN001 phase II/III trial is investigating this possibility. For patients with detectable plasma EBV DNA following chemoradiation, adjuvant chemotherapy using gemcitabine/paclitaxel is compared to cisplatin/fluorouracil as used in Intergroup 0099. In contrast, patients having undetectable plasma EBV DNA are randomized to observation or adjuvant cisplatin/fluorouracil.

While outcomes for patients with nasopharyngeal cancer have improved with the addition of chemotherapy and IMRT, locoregional failures still occur. Various approaches have been used to attempt salvage for local recurrence, including re-irradiation with IMRT, stereotactic radiotherapy or radiosurgery, brachytherapy, or proton radiotherapy.[127] Encouraging local control and survival rates have been reported for carefully selected patients, but toxicity can be significant. Stereotactic techniques deliver radiation to small, well-defined targets. Queen Mary Hospital in Hong Kong has used fractionated stereotactic radiotherapy to treat persistent or locally recurrent nasopharynx cancer. Three-year local control is 75%, but late

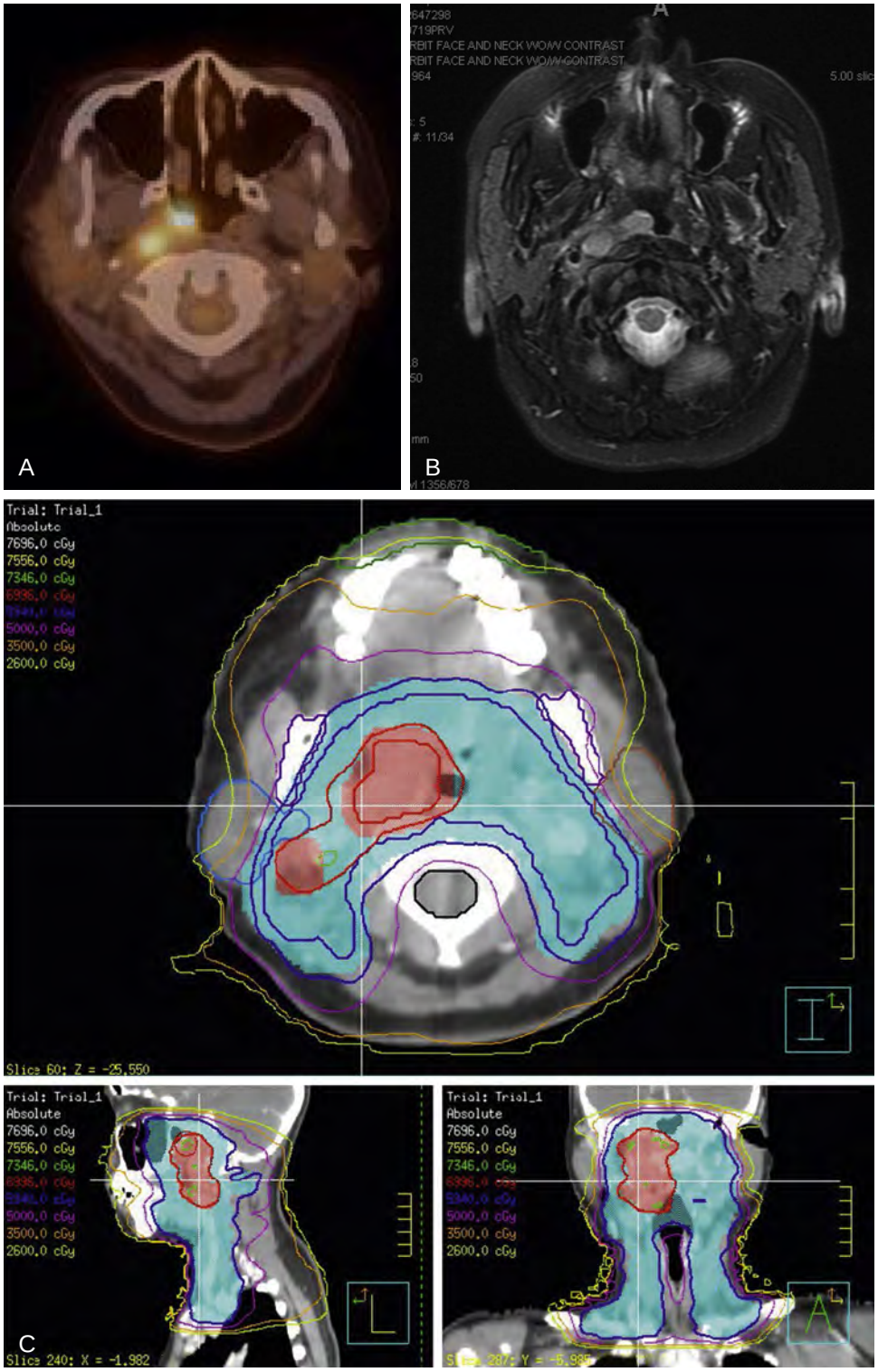


• **Fig. 35.24** Combining chemotherapy with radiotherapy increased 3-year survival from 47% to 78% (P = .005) compared with radiation alone.

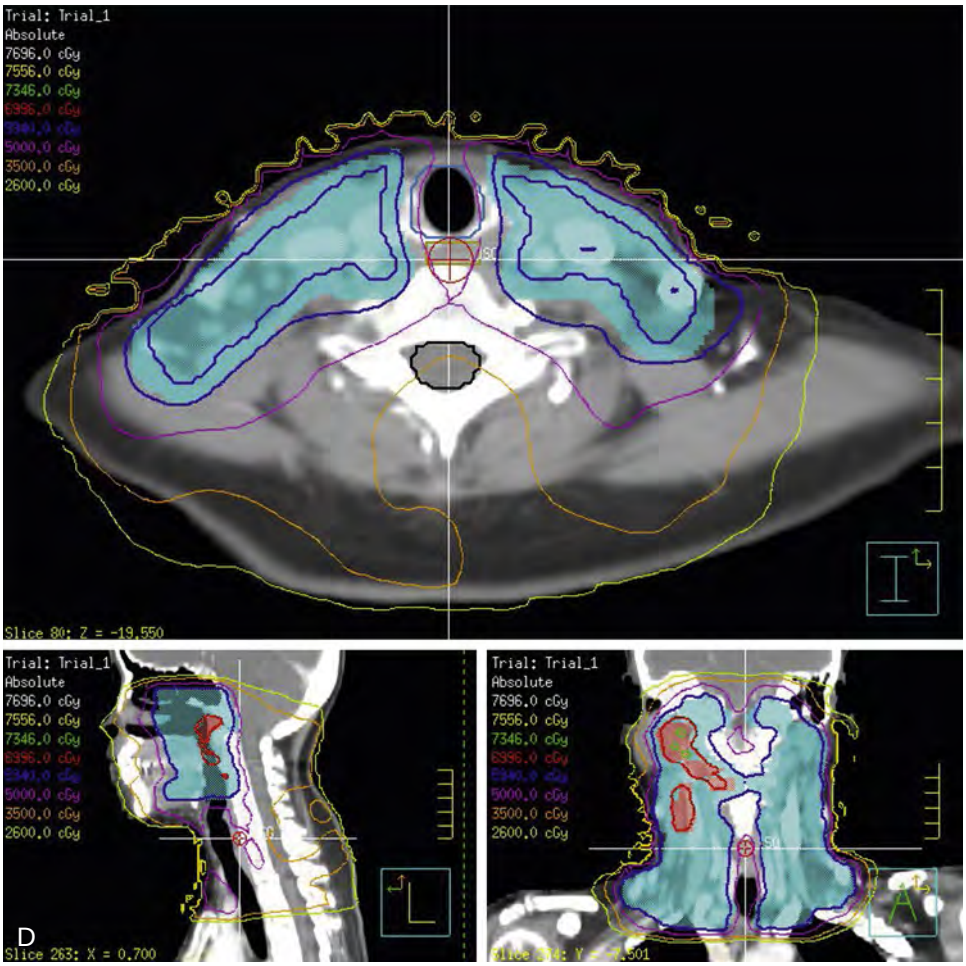
TABLE 35.7 Typical Radiotherapy Prescriptions for Nasopharynx Cancers

Target	Dose
Primary site and involved LN with coverage of possible local and/or LN subclinical extension	70 Gy (2–2.12 Gy/fx)
High-risk areas of suspected subclinical spread. Often this includes entire nasopharynx, sphenoid sinus, cavernous sinus, base of skull, posterior half of nasal cavity, posterior third of maxillary sinuses, posterior ethmoid sinus, pterygoid fossae, lateral and posterior pharyngeal walls to level of mid-tonsillar fossa, bilateral retropharyngeal and cervical nodes	59.4–63 Gy (1.8 Gy/fx)
Low to intermediate-risk areas of suspected subclinical LN spread (e.g., in selected patients low neck or supraclavicular nodes)	54–56 Gy (1.6–1.64 Gy/fx)

fx, Fraction; *LN,* lymph nodes.

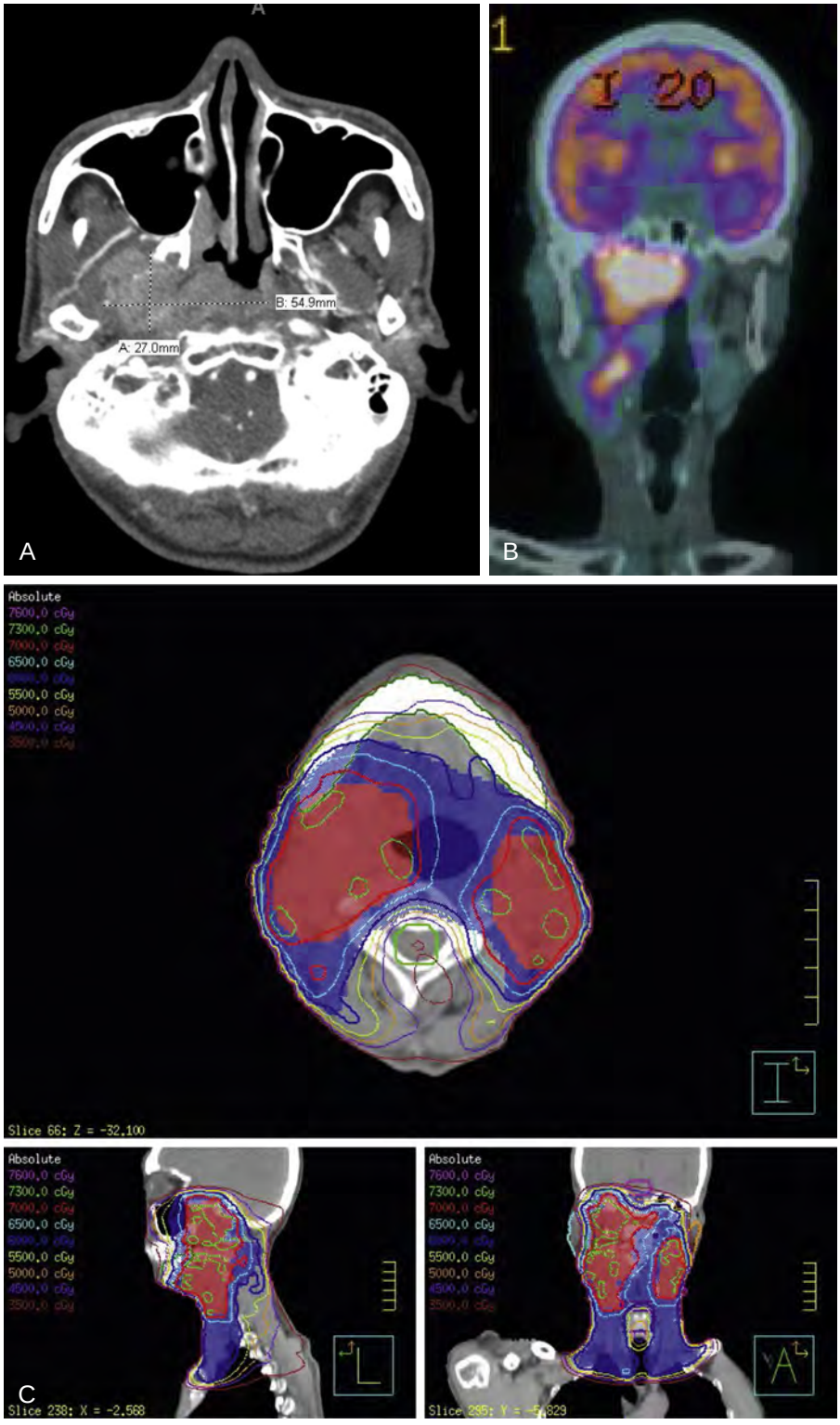


• **Fig. 35.25** A 52-year-old Vietnamese woman with T1N1M0, stage III Epstein-Barr virus positive (EBV+) squamous cell carcinoma of the nasopharynx treated with definitive chemoradiation therapy. **A,** Pretreatment positron emission tomography (PET)/CT. **B,** Pretreatment MRI. **C,** Isodosing for intensity-modulated radiation therapy (IMRT) to primary site and involved lymph nodes treated with 70 Gy.

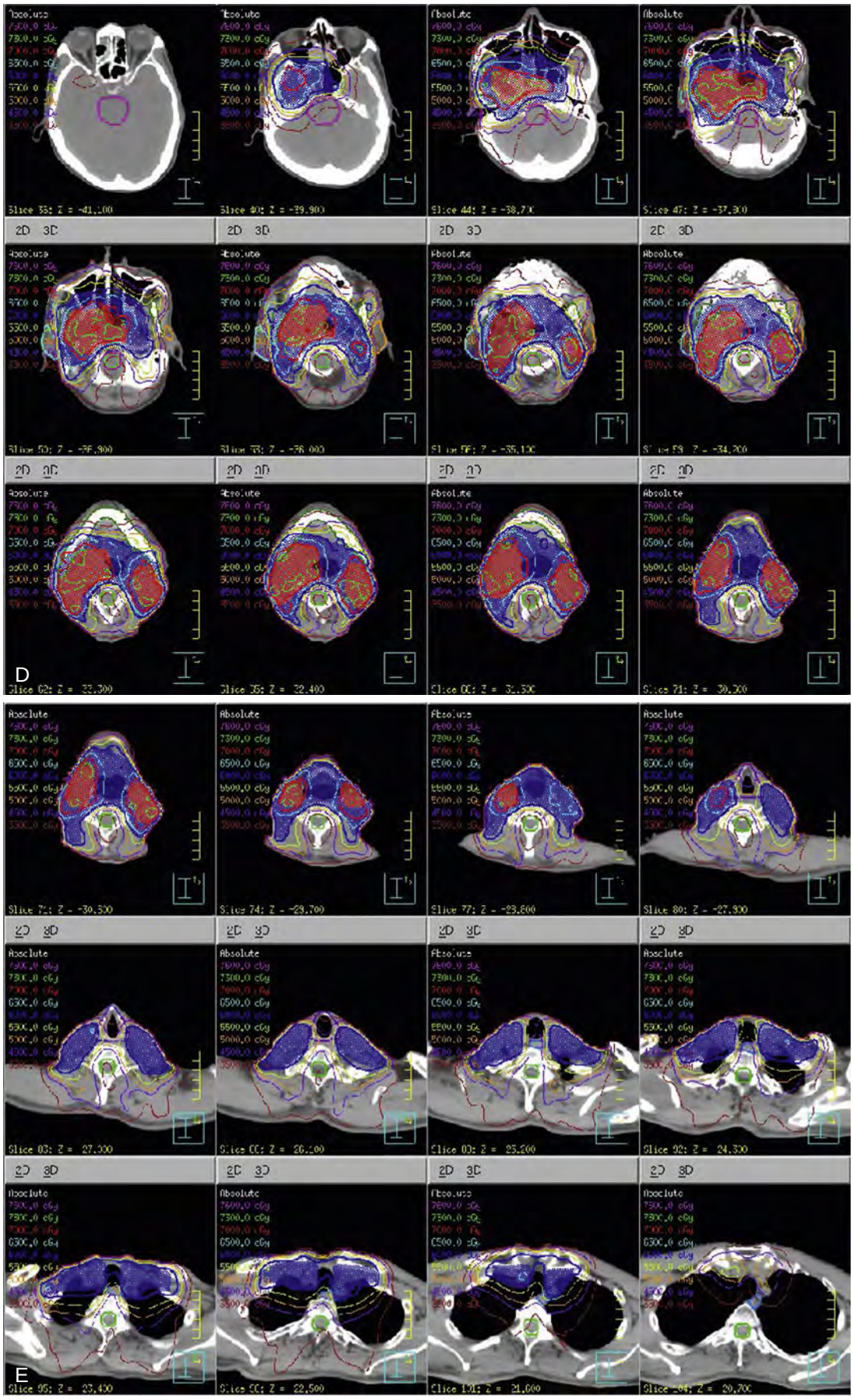


• **Fig. 35.25, cont'd** **D,** High-risk areas of subclinical spread are treated with 60 Gy, and low- to intermediate-risk areas of subclinical lymph node spread are treated to 54 Gy.

complications were seen in 19%, including two patients dying of hemorrhage.[128] Reviewing their experience with locally recurrent nasopharyngeal cancer, Memorial Sloan Kettering found improved results when combining external beam radiation with intracavitary brachytherapy.[129] With this technique, an applicator connected to rubber catheters is positioned into the nasopharynx adjacent to the recurrent disease. Radiation is then delivered via temporary iodine-125 or iridium-192 radioactive sources. Five-year local control was 52% with 60% survival in this series. Importantly, the incidence of late grade 3 or higher complications was lower in those patients treated with combined external beam and brachytherapy (8%) compared with those patients treated entirely with external beam radiotherapy (73%) ($P = .005$). Re-irradiation techniques and results for recurrent head and neck cancers have been summarized nicely in a number of recent reviews.[130-132]



• **Fig. 35.26** A 56-year-old Chinese man with T4N2M0, stage IVA Epstein-Barr virus positive (EBV+) squamous cell carcinoma of the nasopharynx treated with definitive chemoradiation. **A,** Pretreatment CT. **B,** Pretreatment positron emission tomography (PET)/CT. **C,** Intensity-modulated radiation therapy (IMRT) plan for primary site and involved lymph nodes to be treated with 70 Gy.



• **Fig. 35.26, cont'd** **D,** High-risk areas of subclinical spread are treated with 60 Gy. **E,** Given the extent of her disease all nodal groups were deemed high risk and therefore treated to 60 Gy.

Continued



• **Fig. 35.26, cont'd** **F,** 2-year post-treatment PET demonstrating no evidence of disease.

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36

Soft Palate Cancer

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Clinical Presentation and Pertinent Anatomy

Squamous cell carcinoma (SCC) of the soft palate falls under the auspices of oropharyngeal tumors. This anatomic classification includes tumors of the base of tongue, tonsil, and posterior pharyngeal wall. The American Joint Committee on Cancer (AJCC) currently makes no distinction between the four subsites for this disease. The tongue base and tonsil make up 75% of SCCs, and the soft palate and the pharyngeal wall make up the remaining 25%.

According to the Surveillance, Epidemiology, and End Results (SEER) program data from 1999 to 2012, there is an annual percentage change (APC) of 3% ($P < .05$) for cancer of the oropharynx and tonsil in the United States.[1] This represents the greatest increase in incidence of all site-specific tumors of the oral cavity and pharynx. The APC for 1975 to 1999 was 0%. Similarly in the United Kingdom, incidence rates of oropharyngeal carcinoma doubled between 1987 and 2006.[2]

The link between smoking and alcohol consumption and SCC of the soft palate is well documented. This significant increase of oropharyngeal SCC in developed countries appears to be related to increasing numbers of human papillomavirus (HPV)–related carcinomas.[3]

In contrast to other oropharyngeal tumors, SCCs of the soft palate present early in light of their straightforward visualization on clinical examination.[4] This cohort of patients may present with a sore throat, ear pain and odynophagia and/or dysphagia. Tumors of this subsite may also present with changes to the resonance of speech, because the mobility of the soft palate may be impaired by infiltration of tumor.

The soft palate is bounded superiorly by the nasopharynx and inferiorly by the oral cavity. Anteriorly it is continuous with the posterior border of the hard palate, and it demonstrates a free edge posteriorly with the uvula present as a midline structure. At the posterolateral junction, it becomes the superior portion of the palatopharyngeal and palatoglossal folds (Fig. 36.1).

The oral aspect of the soft palate comprises one third of the posterior palate. The mucous membrane is a thin stratified squamous epithelium on both the nasal and oral surfaces. However, near the eustachian tubes, this mucosa becomes stratified and ciliated. The minor salivary glands are present throughout the soft palate and extend into the uvula.[5] In a recent study, the oral aspect of the soft palate was shown to possess a fibro-fatty layer that becomes dense along the midline; the complex musculature is located within this layer[6] (Fig. 36.2).

Five separate muscles form the substructure of the soft palate. The varying insertions and orientation are vital for deglutition and speech resonance, creating velopharyngeal competence. The other main function of the soft palate is to control the patency of the eustachian tube. Delaire, when discussing the soft palate in relation to clefting, distinguished two distinct regions: the anterior portion comprises the tensor veli palatini and the posterior portion contains the levator veli palatini, palatopharyngeus, palatoglossus, and musculus uvulae.[7,8] All the muscles of the soft palate are innervated by the pharyngeal branch of the vagus nerve except the tensor veli palatine, which receives its innervation from the medial pterygoid nerve from the mandibular branch of the trigeminal nerve.

The tensor veli palatine muscle originates from the inferior part of the eustachian tube as well as the scaphoid fossa of the sphenoid bone. It loops under the hamulus and then inserts into the palatine aponeurosis and broadens the soft palate by exerting a lateral force.

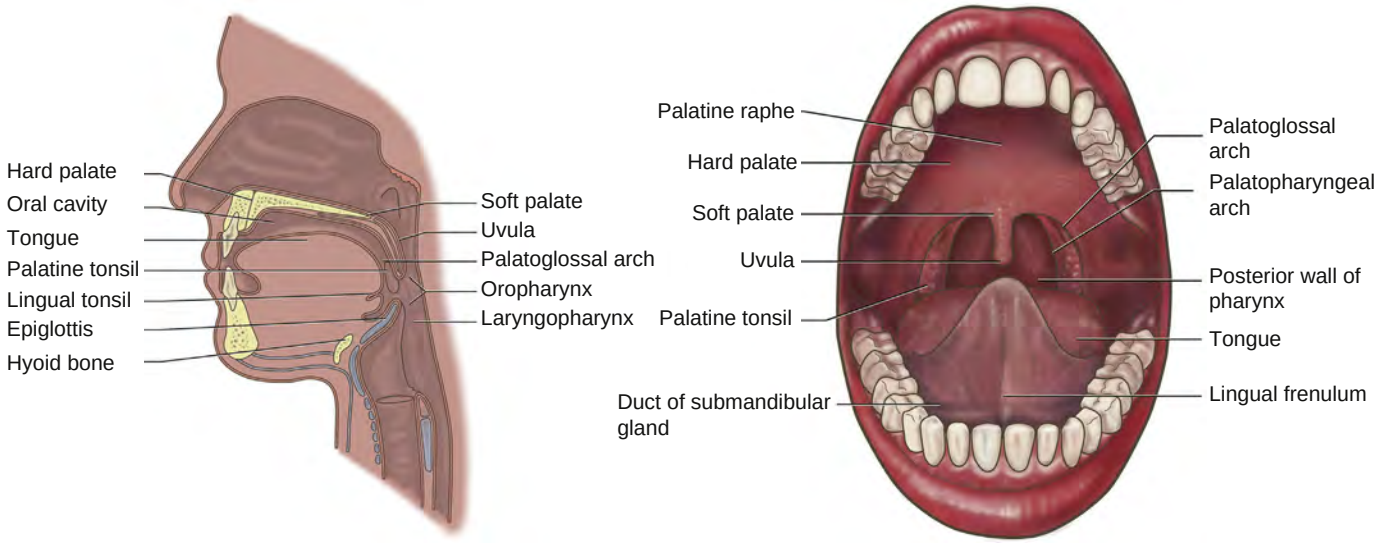
The levator veli palatini also arises from the inferior aspect of the eustachian tube and the petrous part of the temporal bone. Once in the soft palate, it flattens and inserts into the opposing levator veli palatini. This muscle is responsible for motion of the soft palate in a cranio-posterior direction in order to close the nasopharynx during swallowing.

The palatopharyngeus fans into the soft palate from the lateral pharyngeal wall originating at the superior constrictor. It also inserts into the palatine aponeurosis and into the posterior border of the hard palate. Because this muscle also inserts inferiorly into thyroid cartilage, it assists in pulling the pharynx cranially upon swallowing.

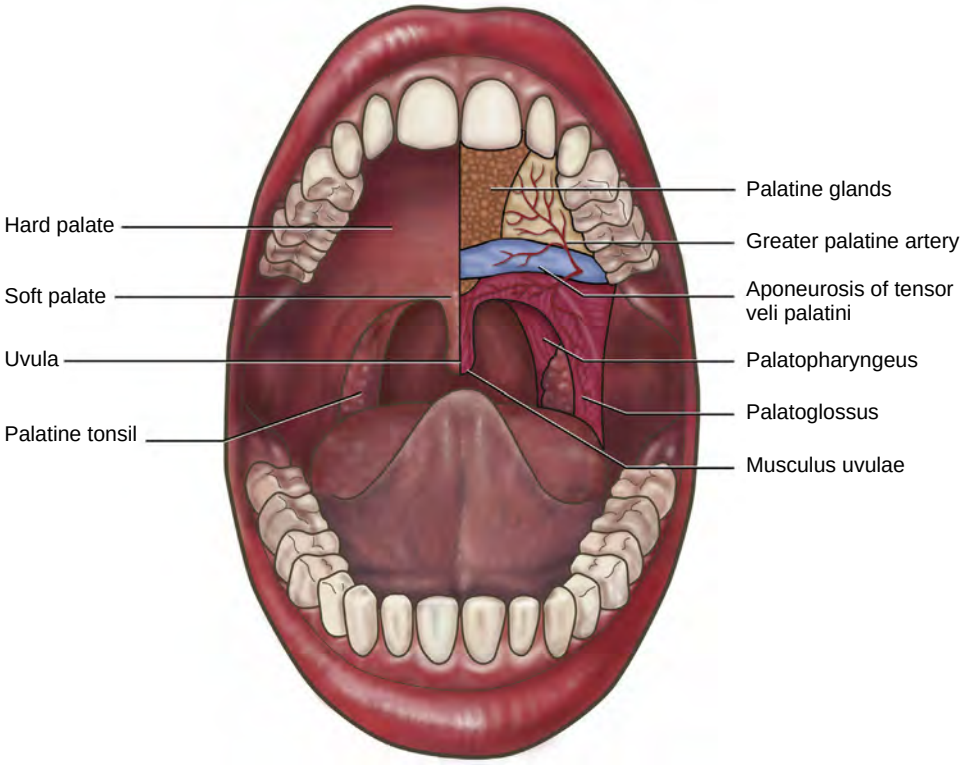
The palatoglossus originates from the palatine aponeurosis and extends into the base of the tongue. It is responsible for elevating the tongue during swallowing.

The musculus uvulae are a pair of muscles that originate from the posterior nasal spine and also the palatal aponeurosis. They essentially broaden and shorten the uvula, which aids in closure of the nasopharyngeal aperture during swallowing.

A sound understanding of this complex anatomic region will allow the multidisciplinary team to reduce the morbidity and achieve optimal quality of life outcomes when treating SCC of the soft palate.



• **Fig. 36.1** Sagittal section (left) and anterior view (right) demonstrating the anatomy of the soft palate.



• **Fig. 36.2** Deep structures of the soft palate.

Staging

As discussed earlier, staging for soft palate SCCs is provided within the National Comprehensive Cancer Network (NCCN) guidelines for oropharyngeal tumors.[9] Work-up of patients in this tumor group should include obtaining a comprehensive history and performing a physical examination. Smoking history in the form of pack-years, alcohol consumption, and betel quid usage should be included in the patient's history. It is important to offer smoking cessation counseling.

Clinical assessment of the primary tumor consists of a thorough head and neck examination including flexible nasendoscopy in the multidisciplinary clinic. The clinician should have a low threshold for performing a full examination of the upper aerodigestive tract under general anesthesia including panendoscopy.

Anatomic magnetic resonance imaging (MRI) with contrast (T1-weighted, T2-weighted, and short tau inversion recovery sequence) incorporating the skull base to the clavicles is carried out before biopsy to prevent upstaging the tumor at the primary site as well as the nodal level. Involvement of the pterygoids

should be noted as should pathologic retropharyngeal nodes. Comuted tomography (CT) with contrast is employed to assess the primary site, neck, and chest for metastatic disease and/or synchronous primary tumors. Thoracic neoplasms are reported in 10% of cases, with half being metastases from the soft palate primary and half from a primary bronchogenic carcinoma.[2]

Tissue sample for diagnosis can be obtained under either local or general anesthesia; however, general anesthesia negates the gag reflex and allows thorough evaluation of the tumor. The specimen is then assessed and reported according to guidelines of the Royal College of Pathologists.[10] At a minimum, the type of carcinoma and the histopathologic grade are needed to determine treatment. In addition, the size of the biopsy area determines whether the pattern and depth of invasion can be assessed. The specimen is also subjected to HPV in situ hybridization and immunohistochemistry for biomarker p16. However, the current NCCN guidelines state that this result should not change management decisions except in the context of a clinical trial.[9] The current literature suggests that p16-positive tumors have a much better prognosis.

All patients should be seen by an experienced restorative dentist to provide preventive oral care and management of active disease. If necessary, any dental extractions should be performed expediently to allow for mucosalization before radiotherapy begins (approximately 10 to 14 days).

Early intervention by speech and language therapists and dietitians can also guide and optimize management before treatment commences.

The extent of the tumor is defined by the T-stage (Table 36.1) and the exact site of the primary, the nodal stage of the neck, and assessment of the chest. Once the TNM classification has been assigned, the disease can be accurately staged.

Each newly presenting head and neck cancer patient's case is discussed at the regional tumor board. This multidisciplinary team comprises head and neck surgeons, radiation and medical oncologists, head and neck radiologists, speech and language therapists, dietitians, restorative dentists, and specialist head and neck nurses. Age, medical history, comorbidity, and social history are a key to the discussion. Ultimately, the best interests of the patient should be placed at the center of this decision-making process.

As part of this multidisciplinary approach, all patients should be considered for entry into an appropriate clinical trial.

Management Principles and Known Outcomes

The aim of treatment is to cure the patient with minimal morbidity, preserving both speech and swallowing function. The treatment options are:

1. No treatment
2. Chemoradiotherapy
3. Surgery

Oropharyngeal tumors as an anatomic subtype have a good response and cure rate when managed by chemoradiotherapy alone. Surgery is reserved for patients who may previously have received radiotherapy or for relatively young patients in whom the tumor can be excised without the need for any adjuvant treatment.

Surgical Management

Surgery is reserved for patients who cannot have radiotherapy (usually because of previous treatment with radiotherapy) or young patients with small tumors in whom a complete resection is possible and the neck nodes are negative. Sound reconstructive decision-making is needed to ensure minimum morbidity and good postoperative speech and swallowing function.

Surgery should not be offered as the primary treatment modality in cases of larger tumors or tumors with positive cervical nodes. The clinical resection margin should be 10 mm to reduce the risk of recurrence. To achieve this clinical resection margin, additional access may be required in the form of a lip split and mandibulotomy or the use of transoral laser or transoral robotic surgery (TORS).

Transoral laser surgery and TORS allow resection of tumors without the need for reconstruction with the outcome that the resected areas will granulate. More extensive resections usually require reconstruction with free tissue transfer. This requires a thorough understanding of the anatomy and the function of the soft palate in speech, swallowing, and mastication. It is impossible to reconstruct the dynamic fibromuscular structure of the soft palate and thus strategies are employed to reduce the caliber of the nasopharynx, ensuring optimum speech and swallowing and reducing nasopharyngeal escape.

Classification of Soft Palate Defects

Urken adopted a classification depending on the size of the defect[11]:

Type I: The defect area of the soft palate is 25% or less.
Type II: The defect area of the soft palate is more than 25%, but 50% or less.
Type III: The defect area of the soft palate is more than 50%, but 75% or less.
Type IV: The defect area of the soft palate is more than 75%, but 100% or less.

Functional outcomes are better when the defect size is less than 50%.[12-14]

Other authors have adopted the classification system of oropharyngeal defects described by Miura and colleagues[15] (Fig. 36.3). Inferior extension of the resection toward the base of tongue is more likely, however, to result in dysphagia. Superior extension of defect toward soft palate is more likely to be associated with hypernasal speech and nasal regurgitation. In fact, many of the soft palate defects extend laterally and inferiorly into the fauces and posterior tongue. Hence, options for reconstruction are listed in Table 36.2 for defects extending inferiorly.

Approach

1. Transoral approach: This technique is limited to smaller lesions that are amenable to resection and primary closure (i.e., T1).
2. Lip split and mandibulotomy: Paramedian lip split mandibulotomy is the author's preferred method of access to soft palate SCC. It allows safer approach for resection and then facilitates insetting of the flap.

TABLE 36.1 **American Joint Committee on Cancer Staging for Oropharyngeal (p16-) and Hypopharyngeal Squamous Cell Cancer (8th Edition)**

Primary Tumor (T)	
TX	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension
T2	Tumor ≥2 cm and ≤4 cm in greatest dimension
T3	Tumor ≥4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, and mandible*
T4b	Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
Regional Lymph Nodes: Clinical (cN)	Oropharynx (p16-) and hypopharynx
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, >6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N3	Lymph node(s) >6 cm and ENE(–) or metastasis in any node(s) and clinically overt ENE(+)
N3a	Lymph node(s) >6 cm and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L).* Similarly, clinical and pathological ENE should be recorded as either ENE(–) or ENE(+)
Regional Lymph Nodes: Pathological (pN)	Oropharynx (p16-) and hypopharynx
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
pN2	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2a	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–)
pN2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN3	Lymph node(s) >6 cm and ENE(–); or metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)
pN3a	Lymph node(s) >6 cm and ENE(–)
pN3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)

TABLE 36.1 American Joint Committee on Cancer Staging for Oropharyngeal (p16-) and Hypopharyngeal Squamous Cell Cancer (8th Edition)—cont'd

Distant Metastasis (M)	Oropharynx (p16-) and hypopharynx
Mx	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M10	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

Registry Data Collection Variables

1. ENE clinical: ENE(+) or (–)
2. ENE pathological: ENE(+) or ENE(–)
3. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
4. Perineural invasion
5. Lymphovascular invasion
6. p16/HPV status
7. Performance status
8. Tobacco use and pack-years
9. Alcohol use
10. Depression diagnosis

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated
G4: Undifferentiated

*Mucosal extension to lingual surface of epiglottis from primary tumors of the base of tongue and vallecula does not constitute invasion of the larynx.
From Lydiatt WM, Ridge JA, Patel SG, Brizel DM, Haughey BH et al. Oropharynx (p16-negative) and hypopharynx. In Amin MB et al., eds. *AJCC cancer staging manual*, 8th edition, New York: Springer; 2017.

Management of Primary

The aim of surgery is to provide sound oncologic ablation and effective functional outcomes. Resection with 10-mm clear clinical margins in all dimensions is the aim.[2,9] In continuity, neck dissection is crucial when the primary tumor extends directly into the neck.[12] En bloc resection of the primary site is desirable when feasible.

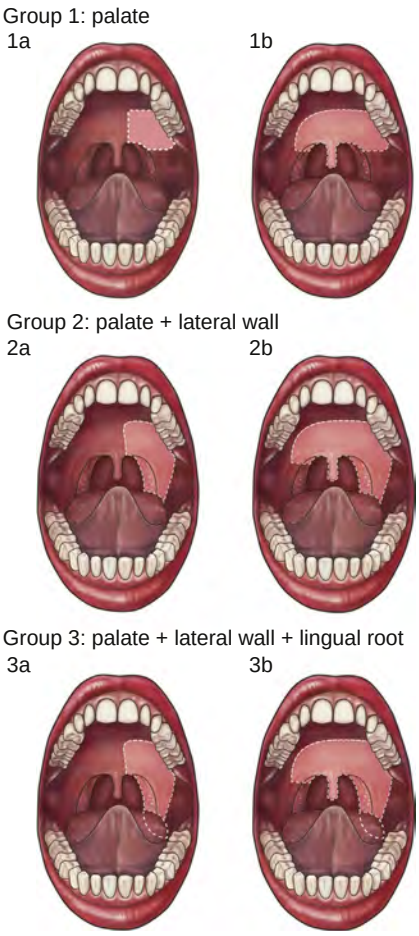
Early Disease: T1-T2, N0

Generally, early-stage oropharyngeal carcinoma can be managed with primary radiotherapy. Five-year disease-specific survival rates of 77–89% were reported based on retrospective case series.[2,16]

When tumor resection involves the free edge of soft palate, which they typically do, reconstruction is a prerequisite to preserve function. This is in contrast to function preserving transoral laser microsurgery and/or TORS, which is advocated for early lesions of all other oropharyngeal sites including base of tongue, pharyngeal walls, and tonsillar sites.[2]

Advanced Disease: T3-T4, N0-N3

Optimum overall survival can be achieved with radical resection in advanced disease followed by radiotherapy/chemoradiotherapy, depending on the resection margin, the presence of extracapsular lymph node involvement, and other adverse pathologic



• **Fig. 36.3** Classification system of oropharyngeal defects. (Redrawn from Miura T, Kishimoto S, Nakatani H, Saitou H: Transition of postoperative function in mesopharyngeal cancer reconstructed with free rectus abdominis myocutaneous flap. *Jpn J Head Neck Cancer* 1998; 24:347–351.

TABLE 36.2 Reconstructive Options for Soft Palate Defects

No reconstruction	Obturation
Local flaps	Superiorly based pharyngeal flap Palatoplasty and lateral pharyngeal flap Palatal island mucoperiosteal flap ± pharyngeal flap Buccinator (facial artery myomucosal) flap, buccal mucosal, or masseter flaps; each of these can be combined with pharyngeal flaps
Pedicled flap	Temporalis flap Galeo-pericranial flap Submental island flaps
Free flaps	Radial forearm flap modifications including: a. Folded flap with palmaris longus tendon b. Radial forearm flap and superiorly based pharyngeal* c. Folded radial and modification of local dermal and pharyngeal flaps. (soft palate insufficiency repair modification)† Anterolateral thigh flap‡ Rectus abdominis musculocutaneous flap§

*Source: Brown JS, Zuydam AC, Jones DC, et al: Functional outcome in soft palate reconstruction using a radial forearm free flap in conjugation with a superiorly based pharyngeal flap. *Head Neck* 19: 524-534, 1997.
†Source: Seikaly H, Reiger J, Zalmanowitz J, et al: Functional soft palate reconstruction: a comprehensive surgical approach. *Head Neck* 30:1615-1623, 2008.
‡Source: Kimata Y, Kiyotaka U, Sakuraba M, et al: Velopharyngeal function after microsurgical reconstruction of lateral and superior pharyngeal defects. *Laryngoscope* 112:1037-1042, 2002.
§Source: Nakatuska in Kimata Y, Kiyotaka U, Sakuraba M, et al: Velopharyngeal function after microsurgical reconstruction of lateral and superior pharyngeal defects. *Laryngoscope* 112:1037-1042, 2002.

features. Radical surgery followed by free flap reconstruction does, however, provide good functional outcome.[2,12-14,17]

Management of Neck

Our current standard of practice is to perform a neck dissection for stage III/IV disease of the soft palate when the primary is being treated with surgery. This is consistent with guidelines from the United Kingdom[2] and NCCN[9] guidelines. However, we approach the neck from three different perspectives:

1. Opportunistic. Access neck surgery to facilitate microvascular anastomosis of the free flap. This applies to early-stage disease (T1-T2, N0), where no formal neck dissection is required but free flap reconstruction mandates neck access.
2. Prophylactic neck dissection. Selective neck dissection I-IV, if the primary is T3 and above, that is, advanced disease (T3-T4, N0-N3), to further stage the disease, looking for adverse pathologic features that will dictate further therapy.[9]
3. Therapeutic neck dissection for node-positive disease. The goal of selective neck dissection I-IV is to preserve all structures of the neck that are not clinically involved. Controversy exists whether to clear levels I-IV or restrict dissection to a supra-omohyoid neck dissection for the N0 neck. However, many clinicians debate where level III ends, considering the variable position of the superior belly of omohyoid.[18] This dissection allows mobilization of the internal jugular vein along its entire length and facilitates venous anastomosis of the flap onto the internal jugular vein.

Reconstruction

The soft palate functions as a valve and helps generate the oral pressure required for normal speech resonance. Speech problems and nasal regurgitation can result from a soft palatal defect. Reconstruction aims more specifically at reducing the size of the velopharyngeal caliber/cross-section to compensate for (1) the lack of mobility in a reconstructed soft palate (all reconstruction ultimately replaces the mobile soft palate with a static structure) and (2) further shrinkage of the flap, particularly when postoperative radiotherapy is required.[12]

Seikaly and colleagues[13] described ideal reconstruction of the soft palate incorporating the following features:

1. Separation of oropharynx and nasopharynx while maintaining nasal patency

2. Restoration of function, in a timely fashion, including:
   a. Intelligibility and resonance of speech
   b. Preservation of safe and efficient swallowing
3. Allowance of cancer surveillance
4. Cost effectiveness

Improved functional outcomes for soft palate reconstruction have been reported over the past 20 years. Yoshida and colleagues in 1993 demonstrated improved function with radial forearm reconstruction when the resection involves the posterior edge of soft palate.[19] Improvised surgical techniques in terms of flap choices and method of inset have been successful in obtaining better functional outcomes.[12,13,20,21]

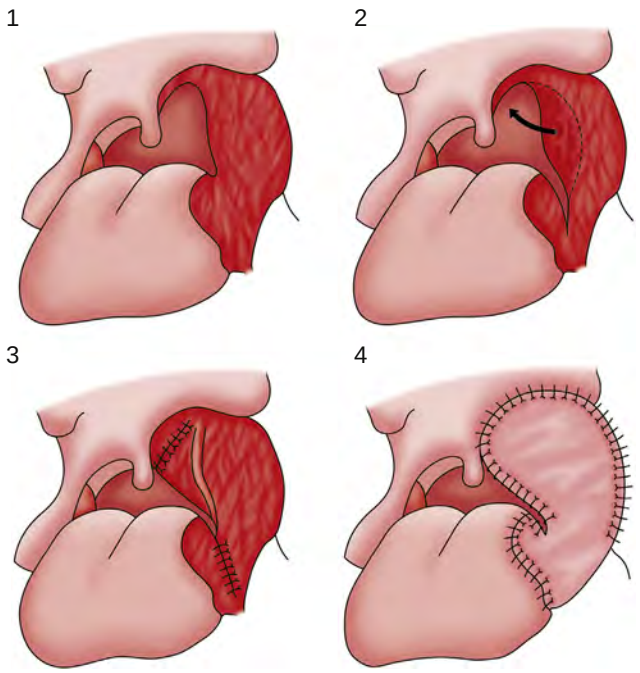
The method and type of reconstruction depend on the size of the defect. Smaller defects may be closed primarily. Defects of less than 50% of the soft palate have been successfully reconstructed with the range of local and regional flaps discussed.[12,14]

For defects involving more than 50% of the soft palate, free tissue transfer is required.[12-15,17,19-23] The goal is to reduce the cross-section of the velopharynx, thus improving functional outcomes. The radial forearm free flap has been used widely to reconstruct defects of more than one third of the soft palate.[12-14,17,19,20] Folding the flap to reconstruct both the oral and nasal aspects of the free edge of the soft palate was first reported by Hatoko and colleagues.[24] This technique aimed to reduce velopharyngeal insufficiency. The palmaris longus tendon sling may be added for suspension of the reconstructed palate in near total/total soft palate reconstruction.[20]

Brown and colleagues[12] suggested that these flaps undergo further cicatricial shrinkage, particularly after radiotherapy, causing velopharyngeal incompetence. They advocated a superiorly based pharyngeal flap along with the forearm free flap. The flap is composed of pharyngeal mucosa and the superior constrictor muscle. Pharyngeal mucosa replaces the nasopharynx and the superior constrictor is sandwiched against the radial forearm flap, producing good speech and swallowing for defects up to 75% of the soft palate.

Seikaly and colleagues[13] described the soft palate insufficiency repair modification of inset. This produced better speech resonance and reduced nasopharyngeal reflex for defects of more than 75% of the soft palate. First, the forearm flap is inset into the defect with the free edge folded to create a neopharyngeal isthmus. Subsequently, an incision extending from the free edge of the folded flap onto lateral pharyngeal wall is performed. The third step is to raise a local subdermal flap on the radial free forearm flap side and mucosal only superiorly based posterior pharyngeal flap. The superior posterior pharyngeal flap is sutured to the posterior free edge of the folded forearm flap. The anterior dermal flap is approximated to the inferior posterior pharyngeal flap, resulting in a two-layer closure of nasopharynx. The patency of nasopharynx is maintained by inserting a nasopharyngeal airway tube. In our practice, we tend to keep these tubes in for 10 days to serve this purpose.

When defects extend laterally toward the fauces and inferiorly into the posterior tongue/tongue base, Inoue and colleagues[20] reported improved long-term outcomes using the Gehanno velopharyngoplasty method of reconstruction. Kimata and colleagues[21] were the first to use this reconstruction technique and to use the term *Gehanno method*. This technique involves an inferiorly based myomucosal pharyngeal flap based on the superior constrictor that will be inset into the soft/hard palate stump. This is followed by suturing the lingual root to the pharyngeal posterior wall stump. The free flap will be inset into the exposed mucosal defect.



• **Fig. 36.4** First, the pharyngeal mucosa is freed from the pharyngeal posterior wall stump over the prevertebral fascia, and the pharyngeal myomucosal flap, which is composed of mucosa and the superior pharyngeal constrictor, is raised. In this step, the mucosa is released to the minimum degree possible. Next, the pharyngeal myomucosal flap is everted in the superomedial direction and sequentially sutured to the residual soft palate stump.

Reconstruction of the lower part of the fauces is narrow and high, thereby preventing postoperative swallowing problems, particularly during the descending phase of the larynx. Moreover, the narrow border between the superior pharynx and the oropharynx does not disturb nasal breathing while restoring the closing function of the nasopharyngeal cavity through the contractility of the pharyngeal myomucosal flap[20,21] (Fig. 36.4).

Complications

Several complications are acknowledged to follow surgical intervention. Based on the functions of the soft palate, they can be divided into three broad subgroups:

1. Speech intelligibility and resonance. Functional outcomes depend on the size of the defect and method of reconstruction.[12-14,22,23,25] Functional speech problems are directly associated with defects approaching half of the soft palate and/or uvula. The radial forearm free flap with or without palmaris longus tendon has been associated with good functional outcomes in defects up to half the size of the soft palate.[6,23,26] Total or subtotal soft palate defects have been reported to be constructed with radial forearm free flap and palmaris longus tendon, with resultant good speech but

moderate hypernasality.[17] This reinforces the findings from the Brown and Seikaly papers, which suggest that the addition of local flaps to the radial forearm flap, with modifications of inset, achieve better functional outcomes.

2. Effective separation of the oropharynx/nasopharynx. Swallowing difficulties are associated with more extensive resection of the soft palate. However, refinement of free tissue transfer techniques has improved these outcomes. Seikaly and colleagues[13] reported that 91% of patients assume an oral diet within the first month postoperatively and only 14% demonstrated mild nasopharyngeal reflux. Barata showed that more than half of swallowing problems were related to solid food.[22]
3. Nasal breathing. In general, the outcomes for nasal breathing are favorable immediately after surgery. The newly formed velopharyngeal port at the border between the superior pharynx and the oropharynx is designed to have a size equivalent to the width of the little finger. According to Brown and colleagues,[12] nasal breathing was not disturbed if a size of at least a quarter of the normal space was ensured.

Radiation Therapy

General Principles

Ionizing radiation remains a key component of treatment protocols for a variety of solid and hematologic malignancies. Radiotherapy is used in a substantial proportion of people who are cured of cancer, and it is widely used for palliation of symptoms of advanced disease.[27] Radiotherapy, in combination with chemotherapy, is the primary curative treatment modality for oropharyngeal squamous cell carcinoma (OPSCC), including those of the soft palate. Technical advances in imaging and in radiation delivery have reduced long-term toxicity but have not significantly improved cure rates, particularly in the case of high-risk locally advanced and HPV-negative disease. However, considerable progress has been made in understanding the biology of the radiation response, opening up the possibility for improved outcomes through rational combinations of ionizing radiation and novel targeted agents.[28]

Ionizing radiation exploits a molecular "Achilles heel" that develops in cancer cells during carcinogenesis. Integral to the molecular hallmarks of cancer is derangement of the DNA damage response (DDR).[29] Cancer cells sustain high levels of genomic instability, in part through loss of critical components of the DDR, such as functional p53 protein, and by activation of compensatory pathways and changes in the tumor microenvironment.[30] In general, this defective DDR means that while tumor cells respond to ionizing radiation-induced double-stranded DNA (dsDNA) breaks by undergoing cell death, normal tissue is able to repair dsDNA damage via the mechanism of homologous recombination, and survive. Radiotherapy dose and fractionation schemes have been evolved over several decades such that they maximize tumor cell death while minimizing collateral damage to normal tissue, in both the short and long term.[31]

Imaging for Treatment Planning and Setup

Patients undergoing radical radiotherapy undergo contrast-enhanced CT following immobilization in the treatment position using a thermoplastic shell. This imaging may be combined with diagnostic MRI, which is ideally performed before biopsy or surgical removal of the primary lesion to mitigate imaging artifact caused by tissue inflammation after the procedure. Positron emission tomography (PET) imaging data and information regarding tumor extent gleaned from clinical examination may also be used to help delineate tumor on the planning CT images.[32]

Volumetric tumor delineation involves use of the aforementioned data to determine a gross tumor volume, which represents clinically and radiologically apparent tumor and involved nodes.[33] The radiotherapy planning software is used to expand this volume geometrically, usually by 1 cm in all directions, to account for subclinical microscopic spread in the immediate vicinity of the gross disease. This volume of tissue is then edited for natural barriers to tumor spread, such as air and bone, and the resulting clinical target volume (CTV) receives the highest dose of radiation, given that sterilization of macroscopic disease requires a higher dose than does microscopic disease. A further CTV, to account for the possibility of tumor dissemination to the remainder of the oropharynx and draining lymph nodes, is then delineated. This receives a lower, "elective" radiation dose. Guidelines for target volume delineation have been issued by the Radiation Therapy and Oncology Group (RTOG) and are widely used.[34] The radiotherapy planning CT is also used to delineate organs at risk (OARs) so that radiation dose to these critical structures can be minimized.

Some centers prefer compartmental volume delineation[35]; in the setting of soft palate cancer, this involves the whole oropharynx and involved lymph node levels receiving the highest radiation dose, while lymph node levels at risk of involvement receive the elective dose. This necessarily increases the amount of normal tissue irradiated to the highest dose.

Imaging for treatment setup depends on the radiotherapy platform used in individual centers. The TomoTherapy system, for example, involves daily megavoltage CT to assess patient position and changes in anatomy during treatment.

Radical Radiotherapy

Intensity modulated radiotherapy (IMRT) is the standard of care for the treatment of soft palate OPSCC.[36] During IMRT, the beam of radiation is shaped by the movement of lead collimators within the treatment machine while the beam is on. Multiple static beams shaped in this way permit the sculpting of radiation dose distribution within tissue to conform to the CTV, reducing the dose to the OARs. A further increase in dose conformality is conferred by arc or helical techniques, in which the treatment machine also moves whilst the beam is on, with the disadvantage being that more normal tissue is irradiated at a lower dose.[37]

Several clinical studies have demonstrated that the dosimetric advantages of IMRT translate to better clinical outcomes in oropharyngeal cancer. The landmark PARSPORT trial, which

randomized patients to either parotid-sparing IMRT or conventional radiotherapy, in which the parotid glands receive the same dose of radiation as the CTV, demonstrated a significant improvement in long-term xerostomia. Patients treated with IMRT reported grade 2 or greater xerostomia rates at 2 years of 29% of the total treated compared with 83% of the total treated for the conventional radiotherapy group.[38] A retrospective analysis[39] of the SEER database examining the outcomes for 3,100 patients with head and neck SCC treated with IMRT between 1999 and 2007 suggested an improvement in cause-specific survival (38.9%) compared with conventional radiotherapy (18.9%, $P < .0001$).

During a 6- to 7-week course of radiotherapy, patients frequently lose weight despite optimal nutritional support. Patient imaging during treatment using CT technology integrated into the linear accelerator allows any significant impact of weight loss on radiation dose distribution to be determined in real time. In general, because of constraints on resources, re-planning based on anatomic alterations is only undertaken in most centers if this process detects a significant underdosing of the CTV or a clinically significant change in radiation dose to an OAR. However, there is evidence that routine re-planning during treatment to account for tumor shrinkage and other anatomic changes is feasible.[40] Identifying which patients benefit most from adaptive radiotherapy is the subject of ongoing study.[41]

Chemotherapy

General Principles and Agents

Platinum-based chemotherapy is widely used in the treatment of oropharyngeal cancer in both the radical and palliative settings. Cisplatin is the agent of choice. When cisplatin is contraindicated because of impaired renal function or concerns about ototoxicity, then carboplatin is the agent of choice. Both are thought by many to be largely interchangeable with regard to efficacy.[42] Both bind to and crosslink DNA, interfering with cell division and leading to cancer cell death. Cisplatin potentiates the cytotoxic effect of ionizing radiation by inhibiting homologous recombination, the main means by which DNA damage due to ionizing radiation is repaired.[43]

The Meta-Analysis of Chemotherapy on Head and Neck Cancer (MACH-NC) examined the addition of chemotherapy to definitive radiotherapy.[44] The most recent update in 2009 pooled data from 16,485 patients across 93 trials and included OPSCC as well as cancer of the oral cavity, hypopharynx, and larynx in the neoadjuvant (induction), concurrent (with definitive radiotherapy), and postoperative settings.

Induction Chemotherapy

The use of induction chemotherapy in OPSCC remains a subject of controversy and debate.[45] There is no doubt that combination chemotherapy regimens that combine a platinum salt with 5-flurouracil (5-FU), with or without the further addition of a taxane compound such as docetaxel, have significant clinical activity in previously untreated OPSCC.[46] There is a two-fold rationale to the use of neoadjuvant chemotherapy: First, downstaging of primary disease in the oropharynx and neck could facilitate definitive chemoradiation, improving local control and reducing toxicity; second, eradication of micro-metastatic disease could reduce distant failure, improving overall survival. This combination of clinical activity and a strong rationale has not, however, translated into definite clinical gains. Three recent trials comparing chemoradiation alone with induction chemotherapy followed by chemoradiation have generated conflicting results. The MACH-NC analysis of 5,311 patients in neoadjuvant studies showed no significant effect on overall survival. Induction chemotherapy is, therefore, generally reserved for patients with a particularly poor prognosis, such as T4 and/or N2c/N3 disease, particularly in cases that are HPV negative. Future studies need to address the role of induction chemotherapy in both HPV-negative and HPV-positive disease, given emerging evidence that a subset of locally advanced virus-driven OPSCC has a worse prognosis.[47] When induction chemotherapy is used, the combination regimen of docetaxel, cisplatin, and 5-FU appears superior to cisplatin with 5-FU alone.[46]

Combination With Radiation-Definitive Setting

In contrast to induction chemotherapy, concurrent chemotherapy confers a clear survival advantage. The MACH-NC analysis of 9,605 patients showed that adding chemotherapy to definitive radiotherapy conferred a 6.5% absolute decrease in mortality at 5 years. This benefit was due to a reduction in cancer death, and there was no significant increase in non-cancer death in the treatment arm. Patients older than age 70 years did not benefit. Concurrent chemotherapy is therefore the standard of care for patients with stage III and IV OPSCC. Cetuximab, an anti-EGFR monoclonal antibody, also acts as a radio-sensitizer and improves overall survival when added to radiotherapy.[48] In practice, concurrent chemotherapy is most commonly used in patients with a contraindication to cisplatin or carboplatin, and is the focus of several trials aimed at reducing treatment toxicity in patients with OPSCC with good prognosis, such as those with early-stage HPV-positive cancer and a minimal smoking history.[49]

Chemotherapy for Distant Metastasis

Patients with OPSCC occasionally present with distant metastasis. More commonly, local and/or distant disease relapse may occur. Although long-term survival is occasionally achieved by salvage surgery of local relapse of aggressive management of oligometastatic disease,[50] for the vast majority treatment is palliative. Combination chemotherapy may be offered to patients with a World Health Organization performance status of 0-2 who are willing to accept the significant toxicity and modest survival advantage of treatment. The most active combination is cisplatin and 5-FU given every

three weeks with cetuximab given weekly; the response rate is 36% and the median overall survival is 10 months.[51] A variety of second-line chemotherapy regimens have been trialed, but efficacy is so modest that there is no consensus on optimal drug usage. Docetaxel, methotrexate, and afatinib all have some activity.[52] Considerable excitement surrounds the development of immunotherapy approaches, with significant response rates being seen in heavily pretreated patients to the PD-1 inhibitor pembrolizumab.[53] Targeting immune checkpoints is likely to have a significant impact on the treatment of OPSCC in both the radical and palliative settings over the coming decade.[54]

Rehabilitation

Dental Rehabilitation/Prosthetic Reconstruction (if Appropriate)

Our unit does not advocate prosthetic rehabilitation for soft palate defects following ablation of malignancy.

Speech and Swallowing Therapy/Voice Rehabilitation

Speech and swallow rehabilitation is provided for people who undergo both surgical and non-surgical treatment of the soft palate, to optimize function and recovery. Both the disease and the oncologic treatment modalities have the potential to compromise speech and swallow, which can impact negatively on quality of life. Research suggests that swallow function is a top priority for patients following treatment for cancer[55]; therefore, timely and effective interventions should be provided from the point of diagnosis and beyond.

Speech

Speech problems following soft palate surgery are diverse and correlate with the size and site of the tumor, as well as the type of reconstruction.[56] Patients may experience hypernasality or hyponasality issues.

Hypernasality is characterized by air passing freely through the velopharyngeal insufficiency. Hypernasality occurs when an inadequate volume of air passes over the articulators, and the reduced intraoral pressure impacts clarity of speech, specifically with plosive sounds.[56] Velar consonants such as /k/ and /g/ may also be problematic,[57] in that correct approximation of the posterior of the tongue against the reconstructed palate can be challenging because of the changes in the anatomy and a lack of sensory feedback in the reconstructed segment.

Hyponasality is caused by reduced airflow into the nasopharynx and through the nasal cavity. Nasal consonants such as /m/ and /n/ may be difficult to articulate, and may be replaced by /b/ or /d/ sounds. Hyponasality may be observed when large defects require reconstruction with bulky flaps such as anterolateral thigh flaps, rather than more discrete radial forearm free flaps; however, there is limited research that explores functional outcomes between the various types of reconstruction.

Patients are advised of the predicted changes to speech after palatal reconstruction and the likely recovery trajectory, in accordance with published guidelines.[58,59] This information can be most effectively tailored to the individual when the speech and language therapist (SLT) undertakes a joint consultation with the surgeon so that detail of the forthcoming surgery may also be described in terms of function and rehabilitation. The preparation phase includes time for the patient and significant others to discuss anxieties and concerns that arise as a result of the complex and challenging psychosocial impact of head and neck cancer.[60,61] Patients may require therapeutic intervention from the SLT or other member of the multidisciplinary team such as the clinical nurse specialist or counselor to manage these issues.[62]

Assessment of speech after soft palate reconstruction is undertaken at the bedside to evaluate the patient's respiratory function for speech and the patient's control and coordination, resonance and phonation, articulation, prosody, and intelligibility.[63] This information forms the basis and rationale for further intervention by the SLT. In the early postoperative phase, edema, tracheostomy, and fatigue are likely to impact speech clarity; the patient is advised that as these variables change, so will speech.

Therapeutic intervention by the SLT may include orientating and educating the patient to the altered anatomy, supporting the patient with anxieties or concerns about communication, providing alternative and augmentative speech aids in the immediate postoperative phase, and suggesting compensatory approaches to improve intelligibility. Compensatory strategies include identification of alternative placements for consonant sounds, such as glottal stops in place of plosives,[57] slowing speech speed, overarticulating consonants, and reducing nasal escape by modifying forced expiratory breathing patterns.

Swallow

Patients may present with swallowing problems at the point of diagnosis, and these can be further compromised by surgery. Aspiration rates of liquid are reported from 12% to 50% following oropharyngeal surgery, and risk of aspiration is exacerbated by adjunctive radiotherapy.[57] McCombe and colleagues[25] explored the effects of soft palate surgery on swallow using videofluoroscopy. Assessment identified the suboptimal resting position of the reconstructed palate, situated some distance from the posterior pharyngeal wall. The group reported that the reconstructed palate appeared "pendulous" and static, not contracting during swallow, bolus was not propelled adequately through the oropharynx, and there was poor swallow efficiency, specifically with residue in the oropharynx. Excessive tongue movement was required to compensate for the changes in intraoral pressures. In our clinical experience, we have observed this typical presentation following palatal surgery, as well as nasal escape of fluid and diet. Although these symptoms impact the effectiveness of swallow and the volume of intake that patients can manage, the psychosocial effects of swallow compromise should also be acknowledged and supported by the SLT.[64]

Therapeutic interventions for swallow compromise are likely to include compensatory strategies, such as postural changes, modifications to diet and fluid, and education on the anatomy and physiology of swallow so the patient can make purposeful adaptations. Interventions should be based on robust, objective assessment of swallow, using bedside observation and/or instrumental tools such as videofluoroscopy or fiber-optic endoscopic evaluation of swallow.[63] Postural changes may be made following individual assessment of swallow, because patients may need to adopt a slight reclining posture to swallow effectively and reduce naso-regurgitation, rather than employing a more traditional chin-down position, which can be effective in many other presentations of dysphagia.[65] Exercise regimens should be carefully considered and used with caution and demonstrable rationale, because exercises such as the Masako maneuver can exacerbate naso-regurgitation following palatal surgery.[66]

Swallow competence changes over time from the immediate postoperative phase, through radiotherapy and beyond. Fibrosis of tissue in the oropharynx following chemotherapy and radiotherapy are well documented in the literature,[67,68] and chronic swallow issues may be experienced by people who receive treatment for soft palate cancer. The SLT should provide responsive and effective therapy that reflects the aims and objectives of the patient, alongside the clinical presentation identified on assessment.

Surveillance

With regard to all head and neck tumors, the U.K. Multidisciplinary Management Guidelines provide a consistent structure to ensure uniformity of review across oncology units.[2] Soft palate SCC requires diligent follow-up in the first 2 years and we would advocate monthly review for the first year and every two months in the second critical year. The frequency of review would then be reduced for the subsequent 3 years with possible discharge at year 5.[69] As supported by grade B evidence, some cases need longer follow-up.

During the follow-up visits, the clinician should broadly address the 12 domains of the University of Washington Quality of Life Questionnaire.[70] Clinical assessment of the cervical lymph nodes and the primary site by means of direct examination and by flexible nasendoscopy allows expedient detection of recurrence or a second primary tumor. There is an incidence of 2–4% for second primary tumors during follow-up periods.[2]

MRI and PET-CT should be used as imaging modalities of choice when recurrence is suspected.[2] However, PET-CT appears to be more accurate and has the advantage over MRI for systemic evaluation.[71]

Finally, during follow-up, this cohort of patients should receive continued support regarding cessation of tobacco consumption and moderation of alcohol intake to reduce the risk of recurrence.

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Early Supraglottic Larynx Cancer

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The most common malignant pathology of the supraglottic larynx is squamous cell carcinoma. Historically, treatment of carcinoma of the supraglottis was managed by open surgical approaches with or without adjuvant therapy. The morbidity of total laryngectomy and some open partial laryngectomies for early cancers led to a reassessment of treatment goals. Most early laryngeal cancers are amendable to larynx-preserving options. Laryngeal conservation treatment can be surgical, namely transoral laser microsurgery, as well as nonsurgical, specifically definitive radiation or chemoradiotherapy. Treatment for T1 and T2 supraglottic carcinoma is based on the clinical setting, patient preference, and institutional bias. This chapter examines early supraglottic cancer and the management options.

Clinical Presentation and Pertinent Anatomy

The supraglottic larynx extends from the epiglottis superiorly to the ventricles inferiorly. Subsites of the supraglottis include the suprahyoid epiglottis, infrahyoid epiglottis, false cords and aryepiglottic folds, and arytenoids. The fat of the preepiglottic space is bounded by the hyoid bone and thyrohyoid membrane anteriorly and merges with the paraglottic fat laterally, where it is bounded by the thyroid cartilage. Local invasion of supraglottic tumors tends to include adjacent subsites in a mucosal or submucosal manner. Locally advanced tumors invade the fat of the preepiglottic and paraglottic spaces and can involve the laryngeal cartilaginous skeleton as well as develop extralaryngeal extension.

Staging

Refer to the American Joint Committee on Cancer (AJCC) TNM staging of supraglottic cancer.[1]

T Classification of Supraglottis Larynx

T1: Tumor limited to one subsite of the supraglottis with normal vocal cord mobility

T2: Tumor invades mucosa of more than one adjacent subsite of the supraglottis or glottis or region outside the supraglottis (e.g., mucosa of the base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx

T3: Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage

T4a: Moderately advanced local disease; tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

T4b: Very advanced local disease; tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Clinical Staging

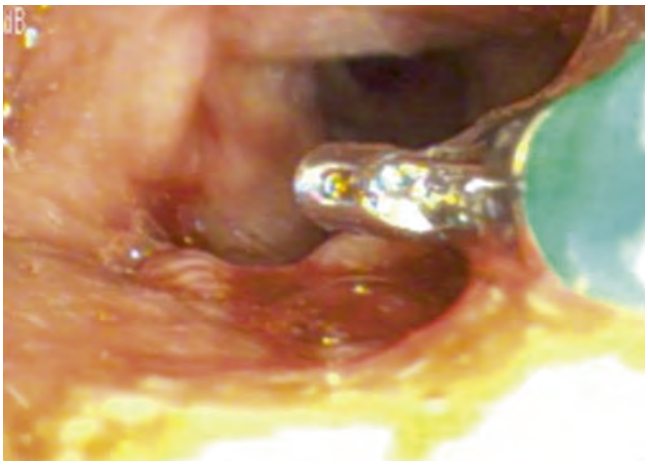
Patients with suspected laryngeal cancer should undergo endoscopy (Fig. 37.1). In-office flexible or rigid endoscopy provides information regarding laryngeal function, namely vocal fold mobility. Direct visualization of the tumor helps to evaluate the tumor site and extent. Examination also evaluates adjacent aerodigestive sites, particularly the base of tongue and hypopharynx—areas that can become involved with more advanced tumors.

Imaging may play a role in evaluating the primary tumor. The most common modalities, magnetic resonance imaging (MRI) and computed tomography (CT) (Fig. 37.2), can help to evaluate submucosal extent of tumor. Tumors may be upstaged with findings of preepiglottic fat invasion or with changes of the thyroid and cricoid cartilage, seen as sclerosis or erosion, suggesting involvement. Several studies have reported that pretreatment CT measurements of tumor volume may help predict local control of supraglottic tumors to treatment with radiotherapy alone.[2–5]

Appropriate distant staging should be performed with an imaging modality: CT, MRI, or positron emission tomography (PET)–CT.

Management Principles

Most stage I and II (T1/T2, N0) cancers of the supraglottic larynx are amendable to larynx-preserving treatment options. Organ-preserving surgical approaches include endoscopic resection with neck dissection or open partial supraglottic



• **Fig. 37.1** Office transnasal laryngoscopy with biopsy. Biopsy forceps are used through a channeled scope to perform biopsy of a tumor on the laryngeal surface of the epiglottis.

laryngectomy with neck dissection. Organ-preserving nonsurgical approaches consist of definitive radiotherapy to the supraglottis and neck. T1 and T2 supraglottic cancers with adverse features (positive margins, perineural invasion, lymphovascular invasion) or pathologic nodal disease with or without extranodal extension may require multimodality treatment. This may include the addition of adjuvant treatment after surgery or the addition of chemotherapy to the definitive radiation regimen.

Surgical Management

Total laryngectomy is first credited to Billroth in 1873. With predictable oncologic and functional results, this became a standard operation for laryngeal cancer. Although total laryngectomy is effective, the separation of the aerodigestive tract into a permanent tracheostoma and a neo-pharynx is a stigma for many patients. Improving quality of life for individuals with the preservation of a functional larynx without sacrificing survival has become an important goal of treating laryngeal cancer. This is particularly pertinent to early T-stage tumors.

In 1958, when referring to carcinoma of the epiglottis, Ogura stated, "The objective of the surgeon should be not only adequate removal of the lesion but also preservation of laryngeal physiology."[6] In a supraglottic laryngectomy (horizontal partial laryngectomy) the supraglottic larynx is resected transcervically in an en bloc fashion, preserving the true vocal cords and cricoarytenoid units. This technique maintains the natural functions of the larynx—respiration, phonation, and deglutition. A tracheotomy and feeding tube are placed at the time of surgery. In previously untreated patients, over 90% decannulation and feeding tube removal can be expected.[7–11] Contraindications to supraglottic laryngectomy are glottic involvement, thyroid or cricoid cartilage invasion, and tongue base involvement, all of which are not consistent with an early supraglottic lesion. For more advanced lesions the supraglottic partial laryngectomy can be extended, most commonly converted to a supracricoid laryngectomy.

Preservation of the cricoarytenoid unit is crucial to swallowing rehabilitation and risk for aspiration. Although results of studies analyzing the risk of aspiration and dysphagia associated with resection of one or more arytenoids are inconsistent, it is generally accepted that loss of one or both units lends to more dysfunction.[7,8,11,12] Caution with regard to arytenoid resection should be taken in patients with poor or marginal preoperative performance status and comorbid lung pathology.[13]

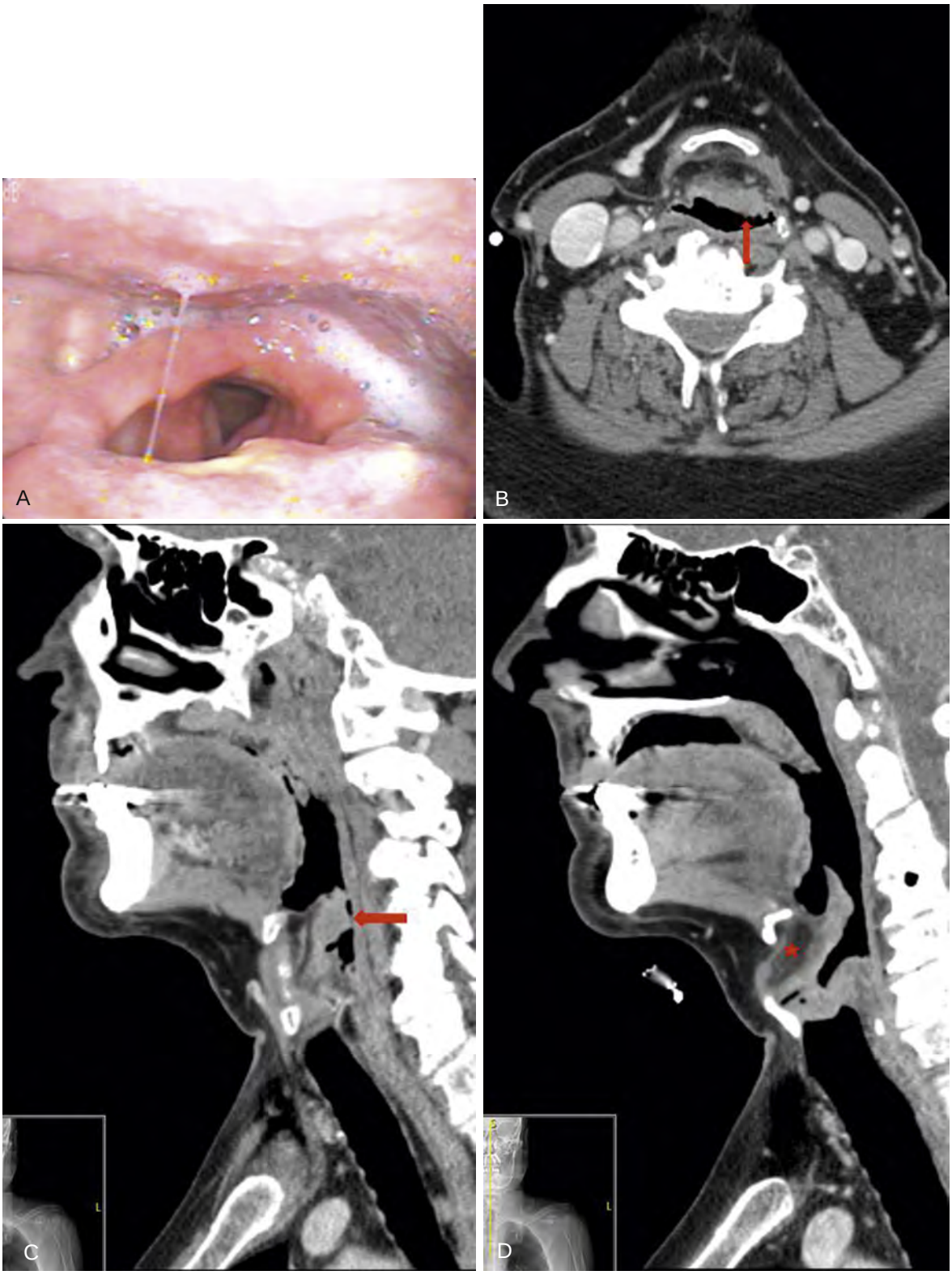
The oncologic outcomes of supraglottic and supracricoid laryngectomy for early supraglottic cancer have been shown to be as effective as total laryngectomy while preserving the function of the larynx. Local control rates for early laryngeal cancer are over 90% for T1 tumors, and over 80% for T2 lesions.[7,9,11,14]

In our practice, open partial laryngectomies have been largely replaced by endoscopic transoral operations. In 2017, the National Comprehensive Cancer Network (NCCN) guidelines on head and neck cancer continued to state, "En bloc resection of the primary tumor should be attempted whenever feasible."[15] Transoral surgery as a proven method of tumor resection is reflected by NCCN guideline comments acknowledging the increasing use of these approaches for cancers in the oral cavity, larynx, and pharynx.

A fundamental surgical principle of endoscopic surgery is piecemeal resection with tumor mapping to attain a gross negative resection. En bloc surgery entails removal of the tumor with a margin of normal tissue without violating the tumor. Although small tumors can be removed en bloc through transoral means, the fundamental difference is the division of tumors into manageable segments, which are separately removed and analyzed. This is a systematic approach to tumor removal that is case and tumor specific.

Small T1 lesions of the supraglottis can be resected in an en bloc fashion. For larger lesions a transtumoral cut is made to assess the tumor depth. For lesions of the epiglottis the cut is extended through the cartilage into the vallecula. Identification and exposure of the hyoid bone laterally from the tumor cut provide orientation and ensure a deep margin, including preepiglottic fat for infrahyoid tumors. The tumor can then be removed in two pieces. For tumors of the false cords and aryepiglottic folds, a transverse cut can be extended inferiorly into the ventricle. The cut is then extended laterally to the inner thyroid perichondrium if paraglottic space invasion is suspected. For a posteriorly based tumor the narrowest margin is likely near the arytenoid. In the majority of cases of early lesions the arytenoid cartilage should be amendable to preservation on initial resection. However, more advanced lesions may require a shave of cartilage or removal.

Visualization of the tumor, normal tissue, and their interface is enhanced by the use of an operative microscope in the setting of transoral laser microsurgery, or camera optics in transoral robotic surgery. The magnification of the operative field and improved visualization helps to differentiate the tumor margins and normal tissue. Strong and Jako revolutionized surgery in the 1960s and 1970s with their work on the carbon dioxide (CO_2) laser.[16,17] The laser power is adjusted to minimize thermal spread in the limited working area of the larynx.



• **Fig. 37.2** Clinical staging of a T2 supraglottic tumor. **A,** Office transnasal laryngoscopy visualizing a tumor that originates on the laryngeal surface of the epiglottis. **B,** Axial image demonstrates the epiglottic tumor *(arrow)* along the laryngeal surface. **C,** Sagittal image demonstrates the exophytic component of the tumor *(arrow).* **D,** Midline sagittal image shows preepiglottic space *(star)* without invasion.



• **Fig. 37.3** Office transnasal laryngoscopy demonstrating postoperative result at 5-year follow-up after transoral laser resection of a T2 squamous cell carcinoma of the epiglottis. This patient underwent surgery and did not require adjuvant radiotherapy.

Low power (3–5 watts) should be used when in the proximity of the glottis, whereas higher power (10–18 watts) may be used in regions such as the epiglottis and when resecting cartilage. The cutting characteristics of the tumor are distinct from the cutting characteristics of normal tissue. Thus when the tumor is divided, the limit of the tumor can be appreciated. Ink is applied to the margins of each segment intraoperatively by the surgeon, and the peripheral and deep margins are then analyzed by a pathologist by frozen sections. If a margin is deemed to be positive, a new margin is created around the area of positivity until the tumor is cleared.

Margin status is considered to be an important prognostic factor for squamous cell carcinoma of the head and neck.[18–20] Experience with transoral technique of tumor resection has led to a reevaluation of margin assessment and the degree of clearance needed to deem a margin "negative."[21,22] A standardized definition of a positive margin is lacking. NCCN guidelines regarding margins defines a clear margin as one that is 5 mm or more; a close margin as one that is less than 5 mm; and a positive margin is one with invasive carcinoma or in situ disease at the resection margin.[15] A survey of American Head and Neck Society members concluded that no uniform criteria exist when defining a clear surgical margin.[23] Yet the referenced number may be an arbitrary acceptance and not necessarily driven by evidence. Even the NCCN guidelines recognize the limitations regarding their definition, suggesting that an adequate margin may be site specific and dependent on technique.[15] The definition of a truly negative margin may be site specific. There are anatomic restraints of the larynx that result in narrower margins, specifically less than 5 mm, relative to other sites within the head and neck.

This technique for tumor resection results in maximal preservation of normal tissue (Fig. 37.3). Similar to open partial laryngectomy, transoral microsurgery attains functional results by maintaining the natural functions of the larynx. But in comparison to open partial laryngectomy, endoscopic laryngectomies can be done with much lower rates of tracheotomies, shorter duration of feeding tube use, and shorter hospital stays.[24–26]

Literature has shown that endoscopic surgical management of supraglottic cancer is oncologically effective. In 1994, Zeitels reported on 45 patients with cancer of the supraglottis and hypopharynx.[27] Twenty-two patients (T1, 16 patients; T2, 6 patients) were carefully selected for small cancer volume and endoscopic accessibility. Of these, 19 had supraglottic tumors. These patients underwent a local en bloc excision of the primary cancer as the sole treatment without local recurrences.

Agrawal and co-workers treated 34 patients with T1–2 (stage I–III) supraglottic cancers with transoral laser microsurgery (TLM) and planned adjuvant radiotherapy to the primary site and necks. Local control was 97%.[28] The single local recurrence was managed with total laryngectomy. The 3-year overall survival (OS) estimate was 88%, and the progression-free survival estimate was 79%. Although four patients required a peri-operative tracheotomy, all were eventually decannulated. Three patients (9%) remained feeding tube dependent.

Grant and colleagues reported on the surgical treatment of 38 patients with supraglottic cancer.[26] All patients underwent treatment of the primary lesion with TLM, 68% had neck dissections, and 34% received adjuvant radiotherapy. All T classifications were represented, with pT1 making up 21% (8 patients) and pT2 making up 37% (14 patients). The 2- and 5-year Kaplan-Meier estimates of overall local control were 97%, with local control in 8 of 8 (100%) T1 cancers and 14 of 14 (100%) T2 cancers. Two- and 5- year Kaplan-Meier locoregional control estimates were 94% and 86%. Estimated survival rates for T1 tumors were 100% and for T2 tumors, 74%.

The largest published patient series originate from Germany. A paper by Iro and colleagues in 1998 retrospectively included 144 patients over a 14-year period.[24] All T classifications were represented in the study, with 65% of patients (T1, 39 patients; T2, 54 patients) having early T-stage lesions. The ability to achieve clear surgical margins was not analyzed relative to T classification, but rather to overall stage. A significant survival difference was found between patients with clear surgical margins compared with those patients with microscopic or macroscopic residual tumor. The overall local recurrence rate was 16.3%, and the regional recurrence rate was 9.9%. The stage-dependent 5-year local control rates were 86.1% for stage I, 74.6% for stage II, 75.4% for stage III, and 78.4% for stage IV.

A second, larger series was published by Canis and colleagues in 2013.[25] From 1980 to 2006, 277 patients with all stages of supraglottic carcinoma were treated with TLM. Twenty-six patients had T1 primary tumors, and 92 patients had T2 primary tumors. A 5-year local control rate of 85% for early (pT1 or pT2) lesions was demonstrated. More specifically, local or locoregional recurrences were noted in 4% (1/26) of T1 tumors and 15% (14/92) of T2 tumors. Organ preservation was achieved in all patients with T1 tumors and in 88 of 92 (96%) patients with T2 tumors. The 5-year recurrence-free and OS rates were 81% and 77%, respectively. This includes a relatively high number of advanced-stage tumors (stage III or IV tumors, 64%).

Non-surgical Management

The use of radiotherapy as a primary treatment modality for head and neck cancer gained momentum in the 1990s. The Department of Veterans Affairs Laryngeal Cancer Study Group in 1991 found no significant difference in survival for patients with stage III and IV laryngeal cancer randomized to induction chemotherapy and radiotherapy compared with patients undergoing total laryngectomy and postoperative radiotherapy.[29] This was followed by the Radiation Therapy Oncology Group (RTOG) 91-11 study, published in 2003, comparing radiotherapy alone versus chemoradiotherapy regimens.[30] The outcome of these studies was an adoption of radiotherapy for early-stage laryngeal cancer and concurrent chemoradiotherapy as a new "standard of care" for laryngeal preservation treatment in advanced laryngeal cancer.

The technology to deliver radiation evolved throughout the early part of this century. CT-based treatment planning allows for three-dimensional conformal radiotherapy and intensity-modulated radiotherapy (IMRT). Conforming radiation doses to the target in three dimensions allows for a reduction in the volume of normal tissues receiving high doses.

The target and normal tissues are contoured on a planning CT scan, thereby generating a profile for designing appropriate beam sizes and arrangements. This creates dose gradients outside the target tissue, resulting in a better sparing of nearby normal tissues—a crucial requisite given that the anatomy of the larynx is spatially complex with many structures in close proximity. Image-guided radiation therapy allows for changes in the tumor over the course of treatment and takes into consideration variability in treatment setup.

Dosimetric parameters are designed around organs at risk for complications when exposed to radiation. Commonly cited organs include the spinal cord, brainstem, cochlea, orbits and optic chiasm, parotid glands, and mandible. A notable late toxicity to radiotherapy for head and neck cancer is dysphagia. The pharyngeal constrictor muscles, cricopharyngeus muscle and tissue at the esophageal inlet, and larynx are areas of particular interest when administering radiotherapy to the supraglottic larynx.[31–34] Several authors have endorsed that a mean dose to the larynx and constrictor musculature above 50 Gy predicts risk for aspiration.[31–33] As tumor stage increases, the addition of chemotherapy to the radiation regimen has proven to yield better outcomes with organ preservation. However, toxicity and late complications increase with the addition of chemotherapy.

Treatment delivery is based on determining gross tumor volume (GTV), clinical target volume (CTV), and planning target volume (PTV). For definitive IMRT, the GTV is often defined as the gross extent of the primary tumor and involved cervical lymph nodes.[2,35,36] The primary tumor limits are determined by physical examination, endoscopic evaluation, and imaging. Pathologic lymph nodes are commonly defined as lymph nodes greater than 1.0 cm in diameter, or those with central necrosis, or those with abnormal fluorodeoxyglucose (FDG) uptake on PET scan.[2,35,36]

CTVs are determined based on microscopic tumor spread and are divided into three categories. CTV1 is defined as GTV with an additional margin, often around 5 mm. For postoperative IMRT, the CTV1 is defined as the surgical bed. CTV2 is defined as high-risk areas for microscopic disease including high-risk local structures around the primary tumor as well as intermediate-risk lymphatic levels of the neck. CTV3 is defined as low- to intermediate-risk lymphatic levels.[2,35,36]

PTV is an expansion of the CTV to account for setup variation and includes an additional several millimeters of treatment. PTV is also grouped into three categories relative to the high-, intermediate-, and low-risk CTV. There are still variations in consensus as to how margins and doses are applied to CTV and PTV. These differences in standards are observed among clinical guidelines, cooperative groups in head and neck cancer clinical trials, and academic institutions.[2,3,4,37-39]

NCCN guidelines for definitive radiotherapy or chemoradiotherapy for cancer of the supraglottic larynx are dependent on the primary tumor and nodal classifications.[15] Because T1 and T2 tumors are, in general, considered low-volume disease, definitive radiotherapy alone is indicated for most T1 or T2 cancers of the supraglottis. For early supraglottic tumors without nodal disease (T1/T2, N0), guidelines recommend conventional fractionation (2.0 Gy/fraction, daily, five times a week) to doses of 66–70 Gy. For select T2 and N0/N1 tumors, high-risk PTV should be treated to a dose of 66–70 Gy (2.0 Gy/fraction, daily, five times a week for 6–7 weeks), including the primary supraglottic tumor and upper and mid-neck jugulodigastric level lymph nodes. Low- to intermediate-risk PTV should be treated to a dose of 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction).

The likelihood of local control after definitive radiotherapy is dependent on the extent of the disease. T classification has traditionally been the primary means of defining the extent of the primary tumor. This includes defining the maximum diameter, involvement of adjacent subsites, preepiglottic space involvement, and vocal cord fixation—parameters that are recognizably defined by AJCC staging criteria. Many have suggested dividing laryngeal tumors into so-called "favorable" and "unfavorable" lesions. "Favorable" lesions are generally considered to be early-stage tumors with low tumor volume. This includes the majority of T1 and T2 lesions. "Unfavorable" lesions are generally considered advanced-stage tumors or those with aggressive features (i.e., vocal cord fixation, preepiglottic space invasion) and/or larger tumor volumes. Accordingly, many T3 and all T4 lesions are classified into degrees of "unfavorability."

Many studies have investigated tumor volume as a parameter to help predict local control of supraglottic tumors with radiotherapy alone.[4,5,40–42] Mancuso and colleagues stratified 63 patients with supraglottic carcinoma treated with radiotherapy alone by pretreatment CT measurements of tumor volume.[3] They found that local control rates were inversely related to tumor volume; local control was 89% in tumors smaller than 6 cm^3 and 54% when volumes were 6 cm^3 or larger (P = .0012). Preservation of laryngeal function with local control was obtained in 89% of patients with volumes less than 6 cm^3 compared with 40% of patients with volumes greater than 6 cm^3 (P = .00004). All T classifications were

represented in the study. The majority of T1 and T2 lesions in this study were smaller than 6 cm^3 (T1, 1 of 1 patient; T2, 19 of 21 patients). On multivariate analysis, local control and laryngeal preservation were dependent on tumor volume, whereas they were not found to be significantly influenced by regional lymph node involvement, preepiglottic space invasion, sex, vocal cord mobility, and T classification. The authors concluded that increasing median tumor volumes were associated with progressively lower likelihood of control at the primary site; and for larger-volume tumors an increase in median tumor volume was associated with an even lower likelihood of preservation of laryngeal function.

Kraas and colleagues reviewed 28 patients who underwent definitive radiotherapy for squamous cell carcinoma of the supraglottis.[4] Patient, tumor, and treatment variables were reviewed along with interpretation of pretreatment CT scans. Two-year local control rates for tumor volumes less than 6 cm^3 and greater than 6 cm^3 were 67% and 43%, respectively (P = .07). Two-year local control rates for tumor volumes less than 8 cm^3 and greater than 8 cm^3 were 70% and 20%, respectively (P = .0077).

Hermans and colleagues reported on CT-derived tumor parameters as predictors of local outcomes of supraglottic tumors.[5] The pretreatment CT scans of 103 patients with supraglottic carcinoma treated from 1985 to 1996 by definitive radiotherapy were reviewed. In the univariate analysis, CT-determined tumor volume was found to be a significant prognostic indicator of local control (P = .0002). In the multivariate analysis, the degree of laryngeal deep tissue involvement was found to be the independent predictor of local outcome rather than the tumor volume.

Johansen and colleagues treated 410 patients, 398 with curative intent, with supraglottic squamous cell carcinoma between 1963 and 1991.[41] Radiation treatment protocols changed over the period of the analysis. Tumors were classified according to the Union for International Cancer Control (UICC) 1982 classification and included 33% stage I, 18% stage II, 23% stage III, and 26% stage IV disease. The frequency of recurrences increased with higher T classification; primary tumor recurrences ranged from 34–38% for T1 and T2 tumors, compared with 51% for T3 tumors and 48% for T4 tumors. On univariate analysis based on T classification, T1a disease-specific survival (DSS) was 72% and OS was 59%; T1b disease DSS was 70% and OS was 52% (standard error ± 6% for each). T2 DSS was 74% and OS was 52% (standard error ± 6%).

Hinerman and colleagues reported on 274 patients who were treated with continuous-course radiotherapy with or without planned neck dissection.[42] Patients were treated from 1964 to 1998, during which time the radiation techniques varied. All T classifications and overall stages were represented in the study. The local control with initial radiation was 100% (18/18) for T1 tumors, 85% (93/109) for T2 tumors, 62% (54/87) for T3 tumors, and 57% (12/21) for T4 tumors. Local control was influenced by T classification, tumor volume, and, for T2 and higher classifications, vocal cord mobility.

Management of the Neck

Regional metastases from aerodigestive tract cancer are dependent on the location and patterns of lymphatic drainage. Rouviére's anatomic dissections and nomenclature of neck lymph nodes along with Lindberg's classic study reviewing the surgical incidence and topographic distribution of metastases have helped to define the at-risk nodal basins for subsites in the head and neck.[43,44]

The lymphatic drainage pathway of the supraglottic larynx is along the jugular chain with bilateral drainage. The highest at-risk nodal basins are levels II, III, and IV of both sides of the neck.[43–45] Owing to the rich lymphatic network of the supraglottis, even early primary tumors are considered at risk for regional cervical metastasis and should be considered for elective treatment. Indeed, even in 1972 Lindberg stated, "The incidence of multiple nodal metastases in lesions of the tonsillar fossa, base of tongue, supraglottic larynx, and hypopharynx is not strongly correlated with the staging of the primary."[43]

Questions continue to be raised as to whether both the ipsilateral and the contralateral sides of the neck should be treated for supraglottic carcinoma and whether this is dependent on laterality of the primary tumor. Clinically node-positive necks should be treated in all cases. As well, supraglottic cancers have a sufficiently high occult regional metastatic rate to warrant elective treatment to the ipsilateral nodal basin.[46-48] The rate of occult regional metastases in the contralateral side of the neck ranges from 4–20%.[47,49,50] Some authors have shown a difference in contralateral disease relative to laterality of the tumor; tumors with clear laterality have a much lower rate of occult disease, suggesting that there may be a role to observation of the contralateral side of the neck.[47,48] Yet other authors have reported no difference in location relative to the midline and promote routine bilateral neck treatment.[49–51]

Lutz and colleagues retrospectively reviewed 202 patients with all stages of supraglottic squamous cell carcinoma treated with surgery alone (102 patients) and combined therapy (100 patients).[50] In 35 of the 39 (90%) patients with a regional recurrence, the recurrent disease developed in the undissected, contralateral side of the neck. Moreover, these authors reported no significant difference in the recurrence rate relative to supraglottic subsite involved. In a follow-up study published 4 years later by Weber and colleagues after a change was made to include routine bilateral neck dissections,[51] it was noted that 7 of the 76 (9%) patients developed a regional recurrence. This reduction in regional recurrences resulted in a conclusion in favor of routine elective bilateral neck dissections for supraglottic carcinoma.

Rehabilitation

Head and neck cancer carries with it great potential to affect quality of life. One's appearance, speech, and swallowing are fundamental to survival as well as intimately tied to social engagement. Functional outcomes are increasingly becoming a priority as the practice of surgical oncology evolves.

Functional outcomes of consequence in cancer of the supraglottis and larynx are primarily deglutition and speech. Rehabilitation begins with initial treatment planning. In our practice, this begins at a weekly multidisciplinary tumor board meeting; a speech and language pathologist is a crucial member of this board. Speech and swallowing therapy begins before initiation of treatment. A baseline preoperative swallow evaluation is performed with a videofluoroscopic swallowing study (VFSS) along with pretreatment counseling and setting of expectations. For patients undergoing surgery, postoperative therapy should begin early and is dictated by the surgical team and surgical healing, usually starting around 10–14 days postoperative. For patients undergoing definitive radiotherapy or chemoradiotherapy, swallowing therapy is initiated and proceeds during the treatment course. The presence of a nasogastric or gastrostomy tube should not preclude swallowing exercises. A combination of fiber-optic endoscopic evaluation of swallowing (FEES) and VFSS is used to monitor and assess progress. For patients undergoing adjuvant radiotherapy, improvement in speech and swallowing during initial healing from surgery may decline during radiation. If there is a pause of therapy during treatment, it is important that therapy resume at the end of treatment.

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38

Advanced Supraglottic Larynx Cancer

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Epidemiology and Clinical Presentation

In the United States, it is estimated that there were 13,560 new cases of laryngeal cancer in 2015, and an estimated 3640 people died of the disease.[1] Geographically, the proportion of laryngeal cancers that originate in the supraglottis varies. In the United States and the United Kingdom, it ranges from 25% to 40%. In Spain, the proportion of supraglottic cancers has changed over time; supraglottic cancers accounted for 62% of all laryngeal cancers in Spain in the 1970s, but this fell to 35% by 2005.[2] In the United Kingdom, data from the 10th National Head and Neck Cancer Audit in 2014 showed that of 1763 newly registered cases of laryngeal cancer, 380 were registered as supraglottic primaries and 970 as glottic primaries.[3] Within the group of 607 advanced laryngeal (T3/T4) cancers, 229 were supraglottic. Of these, 57 of 118 T3 supraglottic cancers (48.3%) and 79 of 111 T4 supraglottic cancers (71.2%) had cervical nodal metastases at presentation.

Whereas glottic cancers tend to manifest earlier with hoarseness and dysphonia, supraglottic cancers typically manifest later with sore throat, odynophagia, referred otalgia, hemoptysis, and, in more advanced disease, enlarged neck nodes, a change in voice, stridor, or airway compromise.

It is well documented that smoking tobacco and its synergistic effect with high alcohol consumption are the main causes of laryngeal cancer. Although human papillomavirus (HPV) plays an important role in the pathogenesis of oropharyngeal squamous cell carcinoma (OPSCC), it appears to have a minor role, if any, in laryngeal cancer, although this may vary depending on the population studied and the methods of HPV detection used.[4] In one study in which a diagnostic algorithm of p16 immunohistochemistry, high-risk HPV in situ hybridization, and quantitative polymerase chain reaction for HPV E6 DNA was used, only 3% of laryngeal cancers were HPV driven, compared with 70% of OPSCCs.[5]

Pertinent Anatomy

The larynx is divided into three anatomic regions:

Supraglottis: includes the epiglottis (lingual and laryngeal aspects), false vocal cords, cranial aspect of the ventricles, and laryngeal aspects of the arytenoid cartilages and aryepiglottic folds

Glottis: includes the true vocal cords and the anterior and posterior commissures

Subglottis: begins 1 cm below the true vocal cords and extends to the lower border of the cricoid cartilage or the upper border of the first tracheal ring

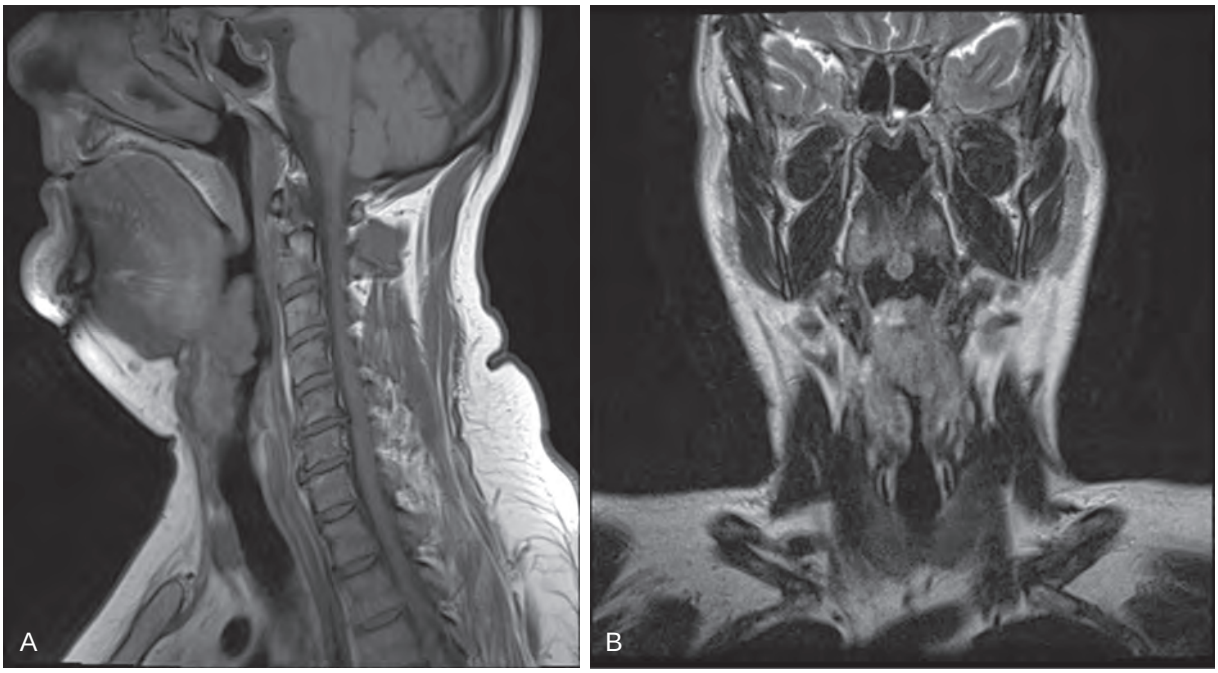
There is no distinct histologic feature or barrier that separates the supraglottis from the glottis. Embryologically, the epiglottis originates from the fourth pharyngeal arch, whereas the arytenoid, cuneiform, and corniculate cartilages originate from the sixth branchial arch.

There is a much richer lymphovascular network draining the supraglottis compared with the glottis. The consequence of this is a higher incidence of ipsilateral, contralateral, and/or bilateral neck node metastasis compared with glottic cancers.[3,6] Of particular note, epiglottic tumors commonly involve the pre-epiglottic space. If this occurs, tumors can then spread inferolaterally through the paraglottic space and/or anteriorly through the thyrohyoid membrane to the strap muscles and soft tissues of the anterior neck and skin.

Staging

In common with other cancers of the head and neck, diagnosis and staging of supraglottic cancers depend on good history taking, clinical and endoscopic examination, cross-sectional imaging, and tissue biopsy. Nodal metastases are commonly encountered in supraglottic cancers and are amenable to ultrasound-guided fine needle aspiration biopsy (FNAB), ideally in a one-stop head and neck clinic in which cytology reporting occurs immediately after needle aspiration. The primary tumor is also, in most cases, readily identified on examination with a fiber-optic laryngoscope in the outpatient department. It is important to note if there is fixation of the vocal cord during fiber-optic examination, because this immediately results in a clinical staging of at least T3 disease. Further features of advanced disease such as invasion of the pre-epiglottic space or paraglottic space and invasion of the laryngeal framework are more readily identified on cross-sectional imaging.

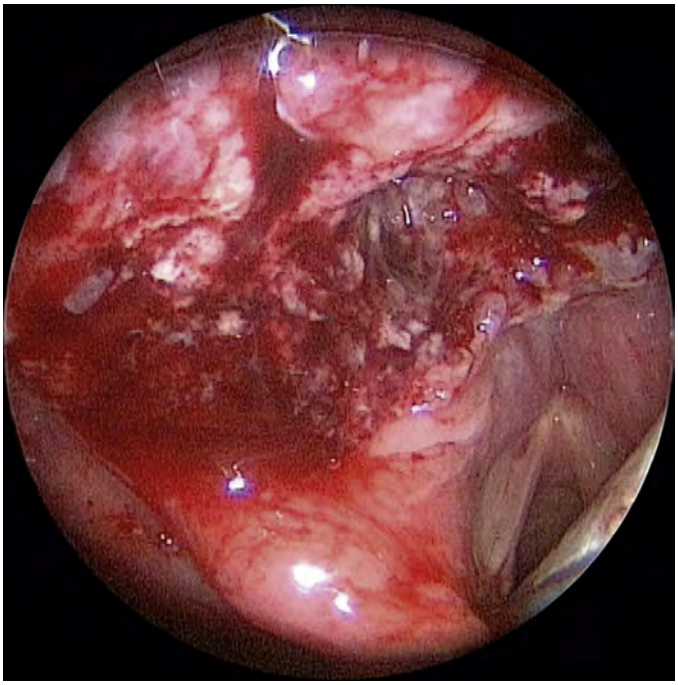
Although variation in imaging protocols is not uncommon and may include ultrasound scanning to stage the extent of lymph node metastasis, most centers perform computed tomography (CT) and/or magnetic resonance imaging (MRI)



• **Fig. 38.1** **A,** Sagittal T1-weighted magnetic resonance image showing a T3 supraglottic squamous cell carcinoma (SCC) with involvement of the pre-epiglottic space. **B,** Coronal T1-weighted magnetic resonance image showing a T3 supraglottic SCC.

of the head and neck, together with a CT scan of the thorax and upper abdomen. CT scans have the benefit of faster acquisition times and thus provide high-resolution images without movement artifacts caused by swallowing and are suited to the assessment of cartilage invasion. In contrast, MRI is better suited to discern spread into the soft tissues of the hypopharynx and/or base of tongue. In addition, as the pre-epiglottic and paraglottic spaces mostly contain fat, T1 and short tau inversion recovery (STIR) sequences of the MRI provide excellent detail in these areas (Fig. 38.1). MRI can also be useful in detecting thyroid cartilage invasion,[7] although some studies cite a significant false-positive rate.[8] Positron emission tomography–computed tomography (PET-CT) scanning is not routinely used in the staging of advanced supraglottic cancer, although it has a role if other imaging modalities suggest a synchronous head and neck primary or distant metastases.

Rigid endoscopic examination and biopsy, usually under a general anesthetic, allows for a better appreciation of the extent of the primary tumor, biopsy, and examination of the rest of the upper aerodigestive tract (Fig. 38.2). There are many benefits of completing cross-sectional imaging before examination and biopsy under general anesthetic. First, it allows for identification of any synchronous primary, which could then be targeted during the endoscopy. Second, it offers valuable information for the anesthetist in planning what could be a difficult intubation. Third, it is possible that the trauma and inflammation following a rigid endoscopy and biopsy could result in upstaging of the primary tumor, particularly if MRI is performed shortly afterward. The examination under anesthesia should routinely involve inspection with rigid straight (0-degree) and angled (30- and 70-degree) endoscopes. In certain cases, the tumor may need to be debulked to provide a safe airway. Debulking may be undertaken using simple avulsion with forceps under direct vision or using a CO_2 laser.



• **Fig. 38.2** An endoscopic view with a 0-degree rigid endoscope of a supraglottic squamous cell carcinoma involving the epiglottis.

Once the information from clinical examination, imaging, and diagnostic endoscopy has been amalgamated, pretreatment staging of the tumor should be carried out according the eighth edition of the American Joint Committee on Cancer staging manual (Table 38.1). From the TNM staging and associated long-term outcome data, prognostic staging groups have been formulated (Table 38.2).

TABLE 38.1 American Joint Committee on Cancer Guidelines for Pretreatment Staging of the Tumor

Primary Tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, pre-epiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Regional Lymph Nodes	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension and ENE(+); *or* >3 cm but ≤6 cm in greatest dimension and ENE([–]); *or* metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE([–]); *or* metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension, ENE([–])
N2a	Metastasis in a single ipsilateral or contralateral lymph node ≤3 cm in greatest dimension and ENE-positive; *or* metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE-negative
N2b	Metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE([–])
N2c	Metastases in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE([–])
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE([–]); *or* metastasis in a single ipsilateral lymph node >3 cm in greatest dimension and ENE(+); *or* metastasis in multiple ipsilateral, contralateral, or bilateral lymph nodes, with any ENE(+)
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE([–])
N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); *or* metastasis in multiple ipsilateral, contralateral, *or* bilateral lymph nodes, with any ENE(+)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

From Amin MB, et al, editors: *AJCC cancer staging manual,* ed 8. New York: Springer; 2017. DOI:10.1007/978-3-319-40618-3_10
Designation of "U" or "L" may be used for any N stage to indicate metastasis above the lower border of the cricoid (U) or below the lower border on the cricoid (L). Similarly, clinical and pathologic ENE should be recorded as ENE-negative or ENE-positive.
ENE, Extranodal extension.

Management Principles and Known Outcomes

In addition to comprehensive clinical and radiological staging, patients with T3 or T4 (advanced) supraglottic cancer should also receive pretreatment nutrition, speech, and swallowing assessment, together with dental evaluation. Smoking cessation advice and support should be given to all current smokers, and all former smokers should be strongly advised to remain abstinent.[9] Patients should be discussed in a multidisciplinary team (MDT) setting and should be considered for participation in a clinical trial, if available. Subsequently, patients should have been seen in a joint clinic by the surgeon and oncologist responsible for their care to have an informed

TABLE 38.2 Prognostic Staging Groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T4b	Any N	M0
	Any T	N3	M0
IVC	Any T	Any N	M1

From Amin MB, et al, editors: *AJCC cancer staging manual,* ed 8., New York: Springer, 2017.

discussion about their diagnosis, proposed management, and clinical trial options.

The management principles of advanced supraglottic cancer are predicated on balancing the likelihood of locoregional control and overall survival (OS) with preservation of laryngeal function and optimization of quality of life. It should be noted that although laryngeal preservation is a goal in the management of supraglottic cancer, laryngeal preservation per se is not necessarily equivalent to preservation of laryngeal function.

Function-sparing surgical options include transoral laser microsurgery (TLM) or transoral robotic surgery (TORS) and open partial surgical procedures

Non-surgical treatment options used with the aim of laryngeal preservation include radical radiotherapy (RT) and concurrent cisplatin-based chemoradiotherapy (CRT), or, in specific indications (metastatic disease, patients unfit for CRT), RT plus epidermal growth factor receptor (EGFR) blockade (e.g., with cetuximab). These are discussed in detail later in the chapter.

A helpful work-up and treatment algorithm for advanced supraglottic cancer has been published by the National Comprehensive Cancer Network (NCCN).[9]

Surgical Management

Management of the Primary

After publication of the RTOG 91-11 study, radical RT with concurrent cisplatin became widely regarded as the standard of care for most patients with advanced laryngeal cancer when laryngeal preservation was a primary aim, with laryngectomy being reserved for salvage surgery.[10] However, a variety of organ- and function-sparing surgical techniques offer the prospect of laryngeal preservation and should be considered for selected patients.

T3 Supraglottic Cancer

Function-sparing surgical options for T3 supraglottic cancers include TLM, TORS, and open partial surgical procedures. Open partial surgical procedures in turn encompass a variety of surgical procedures, including vertical partial laryngectomy (VPL), frontolateral partial laryngectomy (FLPL), supraglottic laryngectomy (SGL), and supracricoid partial laryngectomy with either cricohyoidoepiglottopexy (SCPL–CHEP) or cricohyoidopexy (SCPL–CHP) reconstruction.

Fundamental variables to be assessed when considering organ preservation for T3 supraglottic cancers include tumor size and site, nodal status, performance status, and pretreatment laryngeal and pulmonary function.

Transoral Laser Microsurgery

TLM has an established role in early supraglottic cancer. Pioneering work from Gottingen, Germany by Ambrosch and Steiner demonstrated favorable results with T1/T2 supraglottic cancers.[11] Among a cohort of 48 patients who underwent TLM from 1974 to 1994 for early supraglottic cancer, the 5-year local control rate was 100% for T1 cancers and 89% for T2 cancers. Overall, the 5-year recurrence-free rate and 5-year OS rate in this cohort were 83% and 76%, respectively.

Although there is also a role for TLM in T3 supraglottic cancer, case selection is critical. Published data from case series describing TLM for supraglottic cancer tend to comprise small numbers of T3 cancers.[12–16] A retrospective multicenter study by Hinni and colleagues analyzed data from 117 patients treated by TLM for advanced-stage laryngeal cancer from Mayo Clinic Arizona (Scottsdale), Mayo Clinic Jacksonville (Jacksonville, Florida), Washington University (St. Louis, Missouri), and the University Hospital (Göttingen, Germany).[17] Sixty-five percent of tumors were classified as supraglottic, and of these, 9% were T2, 62% T3, and 28% T4. Ninety patients were alive at the minimum follow-up period of 2 years. The 2-year laryngeal preservation rate was 92% (83/90). The Kaplan-Meier estimate of laryngeal preservation at 5 years was 86%. For the end-point of laryngectomy-free survival, in which either laryngectomy or death from any cause constituted treatment failure, the 2- and 5-year estimates were 70% and 51%, respectively. The 2- and 5-year OS rates were 75% and 55%, respectively. While acknowledging the dangers of making comparisons among different studies, the survival rates reported in this surgical series compare favorably with the 2- and 5-year OS rates of 74% and 54% for CRT and the 75% and 56% rates for RT alone in the RTOG 91-11 study.[18]

One notable study was published by Vilaseca and colleagues.[19] A total of 147 consecutive patients with T3 laryngeal cancer were treated by TLM at the University of Barcelona, Spain. The majority of the cancers (65.3%) were supraglottic; in the vast majority (97.3%), TLM was the initial treatment. The age of patients ranged from 20 to 95 years, and patients were not excluded purely on performance status. With regard to the supraglottic cancers, the pre-epiglottic space was involved in 86.7% of patients, there was focal infiltration of the thyroid cartilage in 24.5% of patients, and

the vocal cord was fixed in 15.6% of patients. Results for the supraglottic subgroup show 5-year OS, 5-year disease-specific survival, and 5-year laryngectomy-free survival rates of 45.8%, 61.8%, and 76.6%, respectively. When glottic and supraglottic subsites were considered, 5-year OS, 5-year disease-specific survival, and 5-year laryngectomy-free survival rates were 53.1%, 70.2%, and 62.3%, respectively. Of note, 25.2% of patients received adjuvant RT. It is interesting to note that these data showed that T3 staging by virtue of involvement of the pre-epiglottic space was the best predictive factor for laryngeal preservation, whereas vocal cord fixation was associated with higher recurrence and worse laryngeal preservation rates. In this group, laryngeal preservation was possible in only one of three patients with pretreatment vocal cord fixation, compared with three of four patients with pre-epiglottic space involvement. The authors comment that this may reflect the fact that complete tumor resection is more difficult to achieve in cases of lateral extension of tumor. More extensive lateral excisions that include the paraglottic space, arytenoids, and parts of the thyroid cartilage also increase the risk of postoperative aspiration. In contrast, when the pre-epiglottic space is involved, good exposure of this area is often possible endoscopically, and a wider excision can be achieved without significant postoperative functional impairment.

Canis and colleagues published the findings from a large series of 226 patients with T3 laryngeal carcinoma treated primarily with TLM at a single center.[20] Of 226 patients, 104 (46%) had supraglottic cancer, and 40 of 226 (18%) received adjuvant RT with or without chemotherapy. Results for the supraglottic subgroup showed 5-year OS, 5-year recurrence-free survival, and 5-year disease-specific survival rates of 66.5%, 67.5%, and 84.2%, respectively. When glottic and supraglottic subsites were considered, 5-year OS, 5-year recurrence-free survival, and 5-year disease-specific survival rates were 64.4%, 63.0%, and 83.3%, respectively. The supraglottic carcinoma subgroup had a laryngeal preservation rate of 92%. Surrogate markers of laryngeal function in this group were very favorable: 1 of 104 had a temporary tracheostomy and 2 of 104 required a permanent tracheostomy; 51 patients (49%) required a temporary nasogastric feeding tube, but only 3 patients required a permanent gastrostomy tube.

Transoral Robotic Surgery

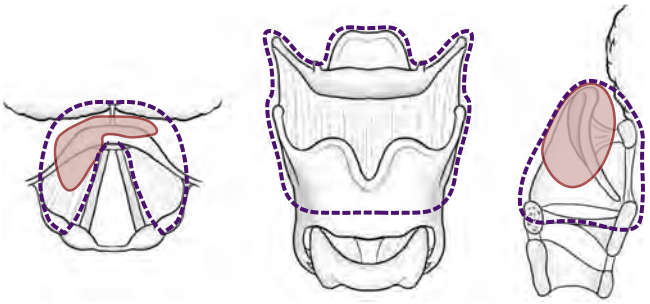
Although there is growing evidence for TORS in OPSCC, its role in laryngeal squamous cell carcinoma (SCC), and in particular advanced supraglottic cancer, is not yet established. An early multicenter study showed TORS to be safe and feasible in head and neck squamous cell carcinoma (HNSCC), although laryngeal SCC comprised only 15% of the cohort.[21] In a large multi-institutional study reporting oncologic outcomes after TORS, supraglottic cancers comprised only 24 of the 410 cases (5.9%), with the oncologic outcomes of this subset of patients not analyzed separately.[22]

The feasibility of TORS SGPL was demonstrated in a pilot study of three patients with supraglottic SCC.[23] However, two of the cases were patients with T2 disease and the remaining patient with T3 disease had positive margins on the main resection specimen. Studies looking specifically at TORS for supraglottic SCC remain few in number. Park and colleagues reported the findings of a series of 16 cases of transoral robotic SGPL.[24] Twelve cases (75%) comprised T1/T2 cancers, with the remaining four cases (25%) being T3. With an average follow-up of 20.8 months, the Kaplan-Meier disease-free survival (DFS) rate at 2 years was 91%. Surrogate markers of function in this group were good. Feeding tubes were all removed before discharge at an average of 8.3 days after surgery, and tracheostomy decannulation was performed after an average of 11.2 days. To date, a cooperative subgroup of Groupe d'Etude des Tumeurs de la Tête et du Cou (GETTEC) has reported the largest series of TORS for supraglottic cancer.[25] This non-randomized retrospective multicenter study identified 84 cases deemed suitable for TORS for supraglottic cancer between 2009 and 2012. Seventy-five T1/T2 cancers comprised the majority of the cases (89%), with the remaining six cases (11%) staged as T3. Large resections were performed in the majority of cases, with 85% of patients undergoing a stage III or stage IV endoscopic SGL.[26] Functional outcomes were comparable to those of TLM SGL. Twenty-four percent of patients had a temporary tracheostomy for an average of 8 days after surgery. One patient (1%) required a permanent tracheostomy. Seventy-seven percent of patients required a nasogastric feeding tube for an average of 7 days; 5% had a gastrostomy lasting 2–42 months, and 2% required a permanent gastrostomy. The short follow-up period (average 14 months) meant that no meaningful oncologic results could be extrapolated.

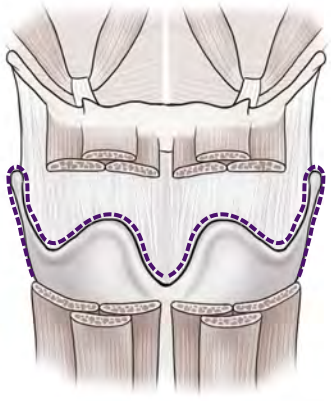
Open Partial Laryngectomy

Partial laryngectomy (PL) procedures were first described by Billroth and others in the late 19th century, primarily for the treatment of small laryngeal tumors.[27] This technique was further developed and refined into VPL by Som in 1951.[28] The term *vertical partial laryngectomy* is used to refer to a spectrum of procedures ranging from laryngofissure with cordectomy to extended hemilaryngectomy. In common with this group of procedures is a vertical transection of the thyroid cartilage together with a glottic resection extending to the paraglottic space. In a classical VPL, two vertical incisions are made through the thyroid cartilage. The anterior incision is made in the midline, and the posterior incision is made just anterior to the posterior edge of the ipsilateral thyroid cartilage. The soft tissue incisions correspond to the cartilaginous incisions and thus include the vocal fold, paraglottic space, part of the subglottis, ventricle, and false cord. Of note, the external perichondrium of the resected thyroid cartilage is preserved. The posterior limit of the VPL is generally the vocal process of the arytenoid. With tumors that involve the anterior commissure, the anterior portion of the contralateral thyroid cartilage is also included and the term *frontolateral partial laryngectomy* is used. Despite the fact that VPL and FLPL have been primarily used for T1 and T2 glottic tumors, they can also be used for selected T3 tumors.[29] Tumors staged as T3 owing to paraglottic extension are still amenable to VPL and FLPL because the paraglottic space and thyroid cartilage are excised. In addition, tumors staged as T3 because of cord fixation from direct invasion of the thyroarytenoid muscle may still be suitable for VPL. However, the presence of radiologic evidence of cartilage invasion, involvement of the posterior commissure, or cord fixation from involvement of the cricoarytenoid joint is considered a contraindication to VPL. SGL was first described in 1947 by Alonso[30] and further developed by Ogura[31] in 1958. SGL

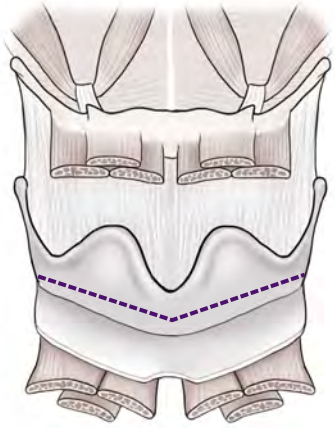
involves resection of the epiglottis, aryepiglottic folds, false cords, and superior portion of the thyroid cartilage with sparing of the vocal folds, arytenoids, and base of tongue. If there is involvement of the vallecula or base of tongue by tumor, the hyoid is also resected. Furthermore, SGL can be extended to include an arytenoid, the pyriform fossa, or a portion of the base of tongue (Figs. 38.3 to 38.7). Impaired vocal cord mobility, involvement of the ventricle, and involvement of the vocal fold are contraindications to SGL.[32] Voice outcomes after SGL are typically excellent because the vocal folds are preserved. However, resection of the supraglottis can have a major detrimental effect on swallowing. As a consequence, a temporary tracheostomy and feeding tube are recommended for all SGL patients. In this context, patient selection and thorough preoperative assessment, taking into account the extent of planned resection and patient comorbidity, are critical. The need for a subsequent laryngectomy owing to aspiration pneumonia and a poorly functioning larynx is increased when there is significant base-of-tongue resection and in patients older than 65 years.[33] Nevertheless, in selected cohorts, 90% of patients achieve oral



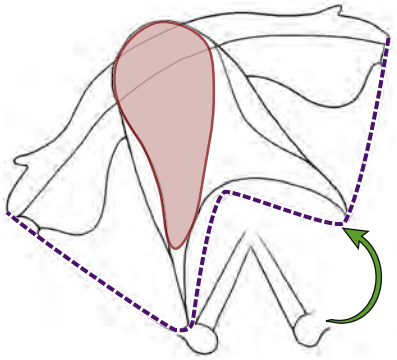
• **Fig. 38.3** Schematic showing the area of resection when performing a supraglottic laryngectomy for a T3 supraglottic tumor involving the preepiglottic space and vallecula.



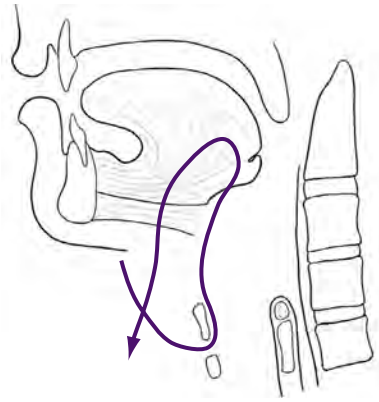
• **Fig. 38.4** After tracheostomy and bilateral neck dissection0s, the infrahyoid strap muscles are divided just below the superior border of the thyroid cartilage. The constrictor muscles are separated from the posterior border of the thyroid cartilage and the suprahyoid muscles are released from the superior border of the hyoid. Care is taken while dissecting the lateral portion of the hyoid to preserve the lingual artery and hypoglossal nerve. The external perichondrium of the thyroid cartilage is incised along the superior and lateral aspects of the thyroid laminae. The perichondrium is then elevated and reflected inferiorly halfway down the thyroid cartilage.



• **Fig. 38.5** The anterior commissure is located at the midpoint of the vertical height of the thyroid cartilage in the midline. A horizontal cut is made 1 mm superior to the anterior commissure using a saw or scalpel, angling postero-superiorly as indicated by the dashed line. The goal is to enter the mucosa of the larynx at the level of the ventricle, starting at the side away from the main tumor bulk.



• **Fig. 38.6** The laryngeal mucosa is incised horizontally, starting at the anterior commissure and heading posteriorly toward the arytenoid. The incision is then curved superiorly to transect the false cord at its attachment to the arytenoid. The resection is continued superiorly, incising mucosa along the aryepiglottic fold. The tumor can be viewed and the resection continued supero-medially with adequate margins including the hyoid and part of the base of tongue as dictated by the tumor.



• **Fig. 38.7** Closure is first performed by suturing the remaining ventricular mucosa to the external perichondrium of the thyroid cartilage. The thyroid cartilage is brought up to the tongue base using a midline suture through the cricothyroid membrane, passing superiorly as it hugs the posterior surface of the thyroid cartilage, then passing submucosally into the base of tongue and then out through the suprahyoid muscles. Two additional sutures are placed 1 cm either side of midline.

intake and decannulation.[34,35] In the past two decades, open SGL has fallen out of favor because patients undergoing transoral laser and transoral robotic SGL have been shown to have shorter feeding tube durations, shorter decannulation times, and shorter hospital stays.[36]

A novel technique of supracricoid partial laryngectomy (SCPL) was initially proposed by Majer and Rieder in 1950 in Vienna.[37] The article was published in French, and several modifications were proposed by Labayle in 1971 and Piquet in 1974.[38,39] Laccourreye amalgamated the various techniques into the modern SCPL with reconstruction as either cricohyoidoepiglottopexy (CHEP) or cricohyoidopexy (CHP).[40] The resection in SCPL includes the aryepiglottic folds, the false cords, the ventricle, the vocal folds, the paraglottic spaces and pre-epiglottic space, the thyroid cartilage, the subglottis up to the upper border of cricoid, and part or all of the epiglottis. The hyoid must be preserved, although one arytenoid may be resected if indicated. Where the suprahyoid epiglottis is preserved, the larynx is reconstructed by bringing the cricoid to the hyoid and epiglottic remnant as a CHEP. In cases where the disease dictates that the epiglottis be completely resected, the larynx is reconstructed by bringing the cricoid to the hyoid and base of tongue as a CHP. The SCPL is a paradigm shift from the traditional focus of preservation of the vocal folds for preservation of laryngeal function. In the SCPL, the mobile cricoarytenoid joints are the foundation of restoration of speech and swallow. Abduction of the cricoarytenoid joints allows for an adequate glottic airway during inspiration. Conversely, adduction of the cricoarytenoid joints, together with impaction of the arytenoids and base of tongue in a CHP, provides airway protection during swallow. With a CHEP, the rotation of the epiglottic remnant provides an additional element of airway protection during swallow. It is crucial that the superior and recurrent laryngeal nerves be preserved in order to have a sensate and mobile neo-larynx for the restoration of swallow. Although speech is restored with SCPL and CHP or CHEP, the quality of the voice postoperatively is substantially different.[41] Videostroboscopy in patients who have undergone SCPL has shown that the mucosal wave is formed at the anterior aspect of the arytenoids.[42] In a series of 124 patients who underwent SCPL–CHP, the average tracheostomy decannulation time was 8 days, with 99.1% of patients being decannulated at 1 year.[43] Restoration of swallow, however, requires intensive rehabilitation and cannot be guaranteed. The average time to removal of nasogastric feeding tube was 22 days, with 91% of patients swallowing without permanent gastrostomy at 1 year.[43] With improved oncologic results and comparable functional outcomes, SCPL has replaced VPL in some units.[44]

Oncologic Results of Open Partial Laryngectomy. Open partial laryngectomy comprises a heterogeneous group of procedures. Before the 1970s, partial laryngectomy primarily consisted of VPL and SGL. As SCPL–CHP and SCPL–CHEP became established in the 1970s and 1980s, data began to emerge showing the improved oncologic results of SCPL over VPL. Laccourreye compared VPL versus SCPL in T2N0 laryngeal cancers. The 10-year local control rate for VPL in 85 patients was 69.3%, compared with 94.6% for SCPL.[44] A systematic review of open conservation partial laryngectomy for primary laryngeal cancer was carried out by Thomas and colleagues.[45] Papers were restricted to those in the English language from 1980 onward from centers reporting more than 10 cases. Outcome measures were pooled but were also reported individually. The pooled local control rate for all the included studies was 89.8% (95% confidence interval [CI], 88.3 to 91.2) with a range of 69.3–100%. Although there are no published results specifically for T3 supraglottic cancer, one case series reported a local control rate of 85% for SCPL–CHEP for T3/T3 glottic cancer.[46] In the studies in which OS was reported, the pooled OS rate was 79.7% (95% CI, 76.5 to 82.8) with a range of 46.2–100%. Similarly, where DFS was reported, the pooled DFS rate was 84.8% (95% CI, 80.6 to 88.7) with a range of 49–100%. The pooled decannulation rate was 96.3% (95% CI, 94.9 to 97.6), pooled laryngectomy rate for function 1.7% (95% CI, 1.2 to 2.2), pooled laryngectomy rate for salvage 6.0% (95% CI, 4.6 to 7.6), and pooled larynx preservation rate 90.9%. The pooled operative mortality rate was 0.7%. The heterogeneous results reflect different operations with follow-up periods ranging from 24 to 120 months. Data for SCPL were also separately analyzed, showing a pooled local control rate of 93.5% and a DFS rate of 80.5%.

T4 Supraglottic Cancer

Total laryngectomy remains the mainstay of surgical treatment for advanced T4 supraglottic cancer. With regard to non-surgical treatment, the Veterans Affairs Laryngeal Cancer Study Group (VALCSG) study showed reduced tumor response to induction chemotherapy (ICT) and significantly higher rates of salvage laryngectomy for T4 tumors of 56% versus 29% for T3 tumors.[18] Furthermore, patients with large-volume T4 tumors (defined as extension of tumor through cartilage or tumor extension >1 cm into the base of tongue) were excluded from RTOG 91-11 because they were considered non-curable with surgery and postoperative RT.[10] Indeed, although RT, CRT, transoral surgery, partial laryngectomy, and total laryngectomy are all suggested potential treatment options for T3 supraglottic cancer in the current NCCN guidelines (version 1.2015), only total laryngectomy is suggested for T4aN0/N+ supraglottic cancer, with non-surgical treatment reserved for patients who decline TL.[9]

Management of the Neck

In the absence of clinical or radiologic evidence of nodal disease (cN0), elective treatment (RT or surgery with or without postoperative RT) is recommended to lymph node levels II, III, and IVa bilaterally. In addition, in node-positive disease, lymph node levels II–V should be treated on the involved side.

It is usual that if surgery is employed for the primary tumor and the neck is N+, then the neck is also treated surgically, followed by adjuvant treatment (RT with or without chemotherapy) as dictated by the pathologic N stage and the presence or absence of extracapsular spread. Surgery to the neck will typically involve a selective neck dissection, involving dissection

of the lymph node levels outlined earlier. (However, if there is no radiologic evidence of involved lymph nodes in level V, it is common practice to dissect levels II, III, and IV, relying on adjuvant RT to treat level V.) Should lymph node disease extend to involve local structures in the neck, a more extensive neck dissection—modified radical, radical, or extended radical—may be performed.

Non-surgical Management of T3 and T4 Supraglottic Cancer

T3 Supraglottic Carcinoma

Most patients with T3 supraglottic cancers are suitable for radiation-based laryngeal preservation therapy. T3 supraglottic cancers have a significantly higher risk of nodal disease (occult and clinical) than glottic tumors, and even in the absence of clinical or radiologic evidence of nodal disease, elective irradiation is recommended to at least lymph node levels II, III, and IVa bilaterally.

The potential of RT and chemotherapy for larynx preservation was established by the landmark VALCSG study,[18] a randomized controlled trial of 332 patients. ICT plus RT yielded similar OS (68% at 2 years) to laryngectomy followed by adjuvant RT for stage III/IV laryngeal cancer with high rates of larynx preservation (64% at 2 years). Of recruited patients, 63% had supraglottic cancers. There was no significant difference in OS between patients with glottic and supraglottic cancers, but salvage laryngectomy was required less often in patients with supraglottic cancers (31%) than in those with glottic cancers (43%), although this difference was not statistically significant. Of patients in the VALCSG study, 65% had T3 cancers; most of the remainder had T4 cancers. Salvage laryngectomy rates were significantly lower for T3 than for T4 disease (29% vs. 56%, $P = .001$).

A subsequent randomized controlled trial of 547 patients, RTOG 91-11,[10] demonstrated that concurrent CRT was superior to sequential ICT followed by RT and to RT alone in terms of laryngeal preservation (88% vs. 75% vs. 70% laryngeal preservation rate, respectively, at 3 years), although OS in each treatment arm was similar. Sixty-nine percent of patients had supraglottic cancers, and the majority of these (79%) were T3 tumors. It is interesting to note that an updated analysis of RTOG 91-11 confirmed the superiority of concurrent CRT, but a significant, unexplained, increase in non-cancer deaths in the concurrent CRT group was reported.[47] The exact reason for this has not yet been established. The use of concurrent CRT for locally advanced head and neck cancers, including laryngeal cancers, is also supported by meta-analysis data.[48]

Despite the laryngeal preservation and survival rates conferred by non-surgical strategies, robust data relating to laryngeal function after CRT are lacking. Although most patients appear to achieve satisfactory swallowing function eventually, a small percentage of patients will require a total laryngectomy for functional reasons. Although TLM or partial open surgical procedures may be considered as an alternative to non-surgical treatment for selected cases in appropriate centers, laryngectomy may be preferred for patients with significant preexisting laryngeal destruction by tumor and/or a pretreatment tracheostomy; however, reports of whether a pretreatment tracheostomy negatively affects outcome after RT are conflicting, and concurrent CRT remains an option for these patients (25% of patients in the VALCSG study had a baseline tracheostomy and they were not excluded from RTOG 91-11). Vocal cord fixation is not a contraindication to larynx preservation (for either surgical or non-surgical modalities), although there was a non-significant increase in salvage laryngectomy rates in patients with fixed vocal cords (41%) compared with those with mobile vocal cords (29%) in the VALCSG study ($P = .103$).

T4 Supraglottic Carcinoma

Larynx preservation with CRT can also be considered for T4 tumors, unless there is tumor invasion through cartilage into the soft tissues of the neck, when total laryngectomy yields better outcomes. The VALCSG study[18] showed reduced tumor response to chemotherapy and higher rates of salvage laryngectomy for T4 tumors (56% for T4 vs. 29% for T3 tumors; $P = .001$). Furthermore, two recent retrospective studies from the Netherlands and Canada[49,50] suggested that total laryngectomy (with or without adjuvant RT) yields better OS outcomes for T4 disease compared with CRT. Nevertheless, laryngectomy-free survival can be achieved in carefully selected patients with T4 disease, and patients with low-volume T4 disease with minimal cartilage involvement appear to be best suited to RT or CRT.[49] Patients with large-volume T4 tumors—defined as extension of tumor through the thyroid cartilage or tumor extension more than 1 cm into the base of tongue—were excluded from RTOG 91-11, because they are poor candidates for organ preservation.[10] Patients with significant preexisting laryngeal destruction by tumor and/or a pretreatment tracheostomy may also be better suited to a total laryngectomy. Total laryngectomy may confer a better quality of life than a preserved but poorly functioning larynx.

Patients with large-volume T4 tumors who are unsuitable for surgery either because of inoperable (T4b) disease or medical comorbidities have been treated with combined-modality organ preservation therapy with significant rates of disease control (71% at 4 years) and OS (56% at 4 years) in retrospective studies.[51] ICT may be used to treat large-volume, symptomatic disease before commencement of concurrent CRT.

T4 supraglottic tumors have a high risk of nodal disease (occult and clinical) and, as for T3 tumors, even in the absence of clinical or radiologic evidence of nodal disease, elective irradiation is recommended to at least lymph node levels II, III, and IVa bilaterally.

Systemic Therapy for T3/T4 Supraglottic Cancers

Standard concurrent chemotherapy regimens include cisplatin (100 mg/m^2) on days 1, 22, and 43 of RT and carboplatin/fluorouracil (5-FU) on weeks 1 and 5 of RT. Concurrent CRT is, however, associated with a significant increase in acute and late toxicity compared with RT alone. The long-term side effects of CRT are well documented: 43% of patients develop severe (grade III or IV) late toxicity, including a reduction in speech and swallowing function, which

can lead to lifelong dependence on a feeding tube (13% of patients 2 years after treatment) and have a profound effect on quality of life.[52] Older age, advanced T stage, larynx or hypopharynx primary site, and neck dissection after CRT all increase the risk of severe late toxicity after CRT, and the additional benefit of chemotherapy must be balanced against the risks for individual patients. The benefit of chemotherapy decreases with age and is non-significant above 70 years of age; thus its use may be less appropriate in older patients. Other systemic therapies that may be given concurrently with RT include cetuximab, a monoclonal antibody that competitively inhibits the cell-surface EGFR. Cetuximab was shown to improve locoregional control (3-year LRC 47% vs. 34%, $P < .01$) and OS (by 10%—3-year OS 55% vs. 45%) over RT alone in a study of patients with locally advanced (stage III or IV) head and neck cancer (27% of whom had laryngeal cancer),[53] and the benefit is maintained on longer follow-up (5-year OS 46% vs. 36%).[54] Toxicities of cetuximab include an acneiform rash and hypersensitivity reactions, but it does not increase the rate of severe radiation-related mucositis; it is an alternative to concurrent CRT for patients with laryngeal cancer who cannot receive concurrent CRT.

ICT with cisplatin and 5-FU (PF) before RT may also improve survival,[55] but the benefit of ICT before standard concurrent CRT schedules is currently unproven. If ICT is used, docetaxel in combination with cisplatin and 5-FU (TPF) has a higher overall response rate and larynx preservation rate compared with PF in patients with stage III or IV laryngeal cancer and may improve OS.[56,57]

Radiotherapy Principles and Treatment of the Neck

RT may be used as a single modality when comorbidity precludes the use of concurrent chemotherapy, cetuximab, or surgery. Conventional RT alone may be suboptimal for the treatment of advanced laryngeal cancer. Altered fractionation regimens (including acceleration and hyperfractionation) improve locoregional control and OS compared with standard fractionated RT for head and neck cancer patients (albeit at the cost of higher mucosal toxicity) who elect or are selected to receive RT alone.[58] However, altered fractionation regimens do not appear to improve outcome compared with or when combined with concurrent CRT, which should be regarded as the standard of care for the non-surgical management of advanced laryngeal cancer. Accelerated fractionation with hypoxia modification using either nimorazole or carbogen/nicotinamide holds some promise and is currently being tested in a randomized study in the United Kingdom (NIMRAD, NCT01950689).

RT for T3-T3 supraglottic cancers is typically delivered in 30–35 fractions over 6–7 weeks to a total dose equivalent of 65–70 Gy. Intensity-modulated radiotherapy (IMRT) or volumetric rotational arc therapy (VMAT) or tomotherapy is recommended for treatment planning and delivery in order to produce conformal dose distributions and allow delivery of differential doses of radiation to the primary site and different nodal groups simultaneously. Recommended dose levels for IMRT are 65–70 Gy (definitive) and 54–56 Gy (elective) in 30 fractions when two dose levels are used and 66–70 Gy (definitive), 60 Gy (intermediate for areas at high-risk microscopic disease), and 54–56 Gy (elective) in 30 fractions or equivalent when three dose levels are used.

The supraglottis has a rich lymphatic supply and, as a consequence, the risk of nodal disease is high. In the absence of clinical or radiologic evidence of nodal disease (cN0), elective nodal irradiation is recommended to at least lymph node levels II, III, and IVa bilaterally. This volume should extend from the caudal edge of the lateral process of the C1 vertebral body to 2 cm cranial to the sternal manubrium as defined in the DAHANCA, EORTC, HKNPCSG, NCI CCTG, NCRI, RTOG, TROG consensus guidelines (2013).[59] In node-positive (N+) disease, it is recommended that lymph node levels II, III, IVa, and Va-b be irradiated bilaterally. If level II nodes are involved, the treatment volumes may be extended to include ipsilateral level Ib nodes and level VIIb (retrostyloid) nodes; they may also be extended to include levels IVb and Vc nodes in the supraclavicular fossa (SCF) if there is nodal disease in level IVa or Vb.

Traditionally, there has been general agreement that CRT is sufficient to treat early nodal disease (N1, single lymph node <3 cm) in patients with head and neck cancers, including supraglottic cancers. The management of N2 (multiple lymph nodes and/or >3–6 cm) or N3 (>6 cm) nodal disease has been recently informed by the publication of the randomized controlled PET-Neck clinical trial.[60] The data confirm that PET-CT surveillance obviates the need for an elective neck dissection in patients with a complete response on PET-CT scanning after CRT.

Postoperative Radiotherapy and Chemoradiotherapy

RT, delivered postoperatively to the primary site and/or neck, in patients at high risk of locoregional recurrence can improve locoregional control and survival. Postoperative RT is recommended for pT4 laryngeal cancers of any nodal stage, for pT1/T2/T3 tumors with N2 or N3 nodal stage, and for all patients with positive or close primary tumor resection margins and/or extracapsular spread of nodal disease. Other unfavorable pathologic factors, including perineural and vascular invasion, are relative indications for postoperative RT. Administration of concurrent cisplatin chemotherapy with postoperative RT improves locoregional control and DFS compared with postoperative RT alone for locally advanced tumors,[61,62] albeit at the expense of increased mucosal and hematologic toxicity and possibly increased deaths. It improves OS in selected patients, particularly with extracapsular spread and/or positive margins,[61] and should be used selectively for patients at highest risk of relapse.

Rehabilitation

Swallowing is an integrated and finely tuned process involving the coordination of over 25 pairs of muscles, under both voluntary and involuntary neural control. Swallowing needs to be executed safely to avoid the spillage of material into the airway and beyond. This is achieved through several airway protective

mechanisms including vocal fold closure, braced arytenoids moving superiorly and anteriorly toward the base of the epiglottis, epiglottic inversion, hyolaryngeal elevation, and a brisk cough reflex to expel any penetrated material.

The following section gives an overview of recommended swallowing rehabilitation for patients with T3 or T4 supraglottic cancer, treated with CRT or RT and/or laryngeal conservation surgery. At the outset, it is essential to appreciate that individual patient selection and a pretreatment assessment are critical components for successful swallowing outcomes.

Pretreatment Swallowing Assessment

The purpose of a pretreatment swallowing assessment is to record baseline functioning, assess for dysphagia, and intervene where necessary.[63] Moreover, this information provides prognostic information for likely swallowing outcome to identify patients who may be at risk of severe and/or protracted dysphagia, taking into account comorbidities that may reduce tolerance to aspiration (e.g., chronic obstructive pulmonary disease [COPD]). This also informs feeding tube selection. Accurate information about the likely outcome of the treatment in relation to acute and chronic swallowing difficulties can then be offered to patients and their families.[63–66] Additional patient and medical factors are important for treatment selection. For example, rehabilitation after laryngeal conservation surgery frequently requires intensive therapy, involving intricate swallowing instructions. This type of procedure may not be suitable for someone with severe depression or cognitive or memory difficulties.

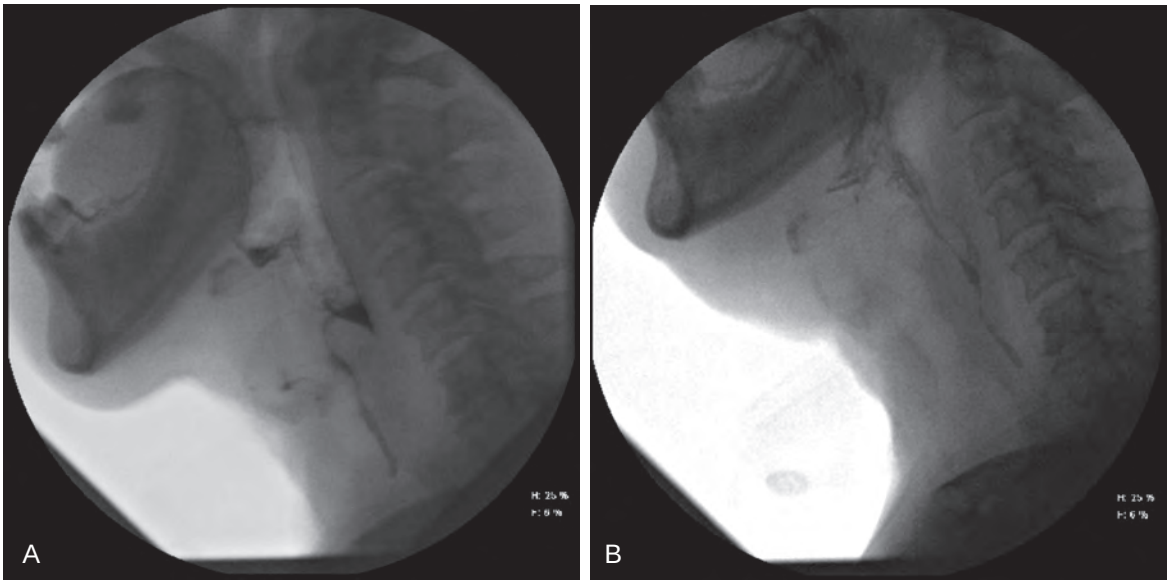
Swallowing Assessment

A clinical swallowing evaluation usually involves gathering pertinent information on patient demographics and medical issues relating to dysphagia. An oromotor and physical examination and a swallowing test are performed to observe for any signs of dysfunction. However, given that head and neck cancer patients often have major anatomic changes, complex pathophysiology, and comorbidities, a full picture cannot be determined by clinical assessment alone. Instrumental swallowing evaluations including fiber-optic endoscopic evaluation of swallowing (FEES) and videofluoroscopic swallowing study (VFSS) provide more comprehensive, objective evaluation of swallowing safety and pathophysiology and are critical to a tailored swallowing rehabilitation program. Either test can be used for assessing laryngeal penetration, aspiration, pharyngeal residue, and the response to therapeutic interventions.

A VFSS is conducted using food and liquid boluses mixed with radiopaque contrast, tracking the swallowing process from the oral cavity to the upper esophagus (Fig. 38.8). A standardized protocol for performing a VFSS for laryngeal conservation clinical trials has been outlined by an international consensus panel.[67] FEES allows the direct visualization of both the pharynx and the larynx and their non-deglutitive function. The endoscopic view allows an assessment of secretion management, especially pertinent for tracheostomy weaning. Real-time visual feedback during FEES can facilitate patients' learning of airway protection swallowing maneuvers.[68]

Radiotherapy With or Without Chemotherapy

Acute side effects during RT are well recognized and include xerostomia, dysgeusia, nausea, and painful mucositis.[69] Between 60% and 100% of patients require tube feeding.[70] Patients are often encouraged to maintain oral feeding as much as possible, to keep the swallowing system mobile.[71] Neuropathic pain control can improve patients' ability to maintain eating and drinking functioning during treatment.[72] In the



• **Fig. 38.8** **A,** Videofluoroscopic swallowing study (VFSS) in a patient 2 years after chemoradiotherapy for supraglottic cancer. Note that there is aspiration of contrast into the trachea. **B,** VFSS of the same patient, this time performing a swallow with a breath-holding technique. Contrast now flows into the esophagus without laryngeal penetration or aspiration.

long term, radiation can cause fibrosis of soft tissues leading to stiffness of the swallowing musculature.[73] Muscle atrophy and chronic edema of the laryngopharynx also affect the range, strength, and coordination of movement necessary for deglutition. Xerostomia is often chronic, making it difficult to prepare solid foods for swallowing. Common features of post-CRT or post-RT dysphagia include reduced pharyngeal contractile peristalsis; abnormal upper esophageal opening, reduced posterior base of tongue retraction, incomplete or delayed laryngeal closure, reduced laryngeal elevation, and impaired epiglottic inversion. Approximately one third of patients have chronic aspiration after CRT,[74] with severe dysphagia being an independent predictor of survival.[75] For some, swallowing deteriorates further, beyond 1 year, and a small percentage may be left with a non-functioning larynx.[76] Strategies to reduce dysphagia include radiation dose restriction to the swallowing structures, pre-CRT swallowing exercises, and post-treatment swallowing therapy.[77]

Laryngeal Conservation Surgery

The incidence and severity of dysphagia after laryngeal conservation surgery depend on the nature and extent of the resection, as well as other more patient-specific factors. Although the oral stage of swallowing is usually left intact, multiple breakdowns are possible at the laryngopharyngeal stage of swallowing. Airway protection is a major issue, with aspiration being possible before, during, and after the swallow. Aspiration has been reported in up to a third of patients after cordectomy,[78] which may be transient until healing is complete. For more extended resections, reports of aspiration range from a third to up to 94%.[79–81] Some papers report better swallowing outcomes with CHEP than with CHP,[82,83] whereas others have found no difference.[79,84] Although some postsurgical patients can tolerate a degree of aspiration without pulmonary complications, others may develop respiratory complications in the long term.[85]

Swallowing rehabilitation requires a clear understanding of which structures are left intact and an assessment of which structures may be used to compensate for the surgical defect. Therapy commonly consists of a combination of swallowing postures (e.g., head turn to one side), diet texture modification, and airway protection techniques. For example, in the absence of the epiglottis, aspiration may be prevented by the arytenoids contacting the base of tongue during the swallow. High success rates (up to 81% for SCPL) for return to oral feeding have been reported.[79,86] Factors that may influence swallowing outcomes include age, degree of arytenoid resection, and preoperative or postoperative RT.[87]

Post-treatment Surveillance

Regular follow-up of patients after completion of treatment is a fundamental part of their care. It allows for the evaluation of response to treatment, identification of treatment-related morbidity and complications, early identification of recurrence, and detection of new primary tumors. In patients treated with transoral laser surgery or TORS, it may be advisable to perform second-look microendoscopic laryngoscopy to detect any residual tumor, particularly if there is any concern about completeness of resection once histopathology of the resection becomes available. There is good evidence that patients with an SCC of the upper aerodigestive tract have an increased risk of developing a second malignancy, with one study of 1845 patients showing an incidence of 4% per year.[88]

Tumor surveillance involves both a complete head and neck examination and fiber-optic examination. Radiologic investigations such as MRI and PET-CT have been shown to be superior at detecting both recurrent tumors as well as second primaries, particularly in the context of patients with advanced head and neck SCC.[89]

ENT guidelines from the United Kingdom recommend a minimum 5-year follow-up period, with a higher frequency of follow-up in the first 2 years, when the risk of locoregional recurrence is highest. The follow-up in the first 2 years should be between 4 and 8 weeks and then 3–6 months thereafter.[90]

Summary

Although the management of advanced supraglottic cancer continues to offer challenges, the principles of balancing the likelihood of locoregional control and OS with preservation of laryngeal function and optimization of quality of life have led to the development of a variety of surgical and non-surgical options.

Function-sparing surgical options include TLM or TORS and open partial surgical procedures. The evidence for TORS in advanced supraglottic cancer is currently not robust but should emerge in the near future. Total laryngectomy remains a good option for T4 disease.

RT has evolved with IMRT and VMAT, along with altered fractionation regimens, which have shown improved locoregional control. However, CRT should still be regarded as the standard of care for the non-surgical management of advanced laryngeal cancer.

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Early Glottic Larynx Cancer

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The management of early glottic cancer can be challenging. Health care providers should attempt to ensure the highest degree of treatment success while minimizing side effects, which can greatly affect voice, swallowing, and airway outcomes. Although a multidisciplinary approach is often necessary to treat late glottic cancer, single-modality treatment with either surgery or radiation is typically sufficient for early glottic cancer. Understanding the complex laryngeal anatomy and discovering the extent of disease are imperative for determining the appropriate treatment course. The information provided in this chapter will help guide providers caring for patients with early glottic cancer from diagnosis to work-up to treatment and follow-up.

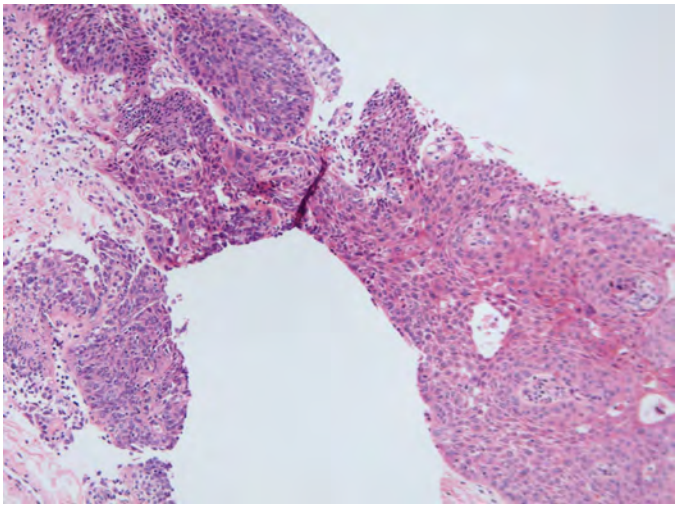
Clinical Presentation

Laryngeal cancers can manifest in many different ways. Patients with supraglottic tumors may complain of hoarseness, muffled voice, or "hot potato" voice, and subglottic tumors may not be noted until patients begin to notice dyspnea or neck masses; glottic tumors most commonly manifest with hoarseness. Because very small tumors may significantly disturb the mucosal waveform, resulting in perceptible voice change, these cancers may be found much earlier than tumors elsewhere in the airway or upper aerodigestive tract. Only when quite advanced do glottic cancers produce dysphagia, throat pain, stridor, hemoptysis, otalgia, or neck mass. This early presentation typically allows a greater breadth of treatment options with improved overall survival. That said, radical treatment of laryngeal cancers can be particularly devastating to communication and social interaction, necessitating early detection to optimize function.

The single greatest risk factor for laryngeal carcinoma is tobacco use. Alcohol use appears to have a synergistic effect, exponentially increasing the risk of laryngeal carcinoma when coupled with tobacco usage. As tobacco use in the United States has decreased in recent years, so too has the overall incidence of laryngeal carcinoma. However, additional risk factors have also been identified. Moderate to severe gastroesophageal reflux disease (GERD) has been theorized to contribute to the development of carcinoma because of its chronic irritative effect on the larynx. In 1988, Ward and Hanson retrospectively reviewed the charts and video recordings of direct laryngoscopy of 138 patients who were followed for chronic laryngitis, pharyngitis, leukoplakia, or contact granulomas that developed into carcinoma of the larynx.[1] Of these patients, 16 were identified who had never used tobacco or alcohol. Three additional patients included in the study had been very light drinkers but had never used tobacco products. The degree of the patients' GERD was then retrospectively graded (on a scale of 0 to 4+) by inspection of indirect laryngoscopy recordings. Eighteen (95%) of the patients had GERD rated as 3+ or 4+. Although this study did not prove a cause-and-effect relationship between GERD and laryngeal carcinoma, it suggested correlation between the chronic irritative effect of GERD and the development of carcinoma.[2] Stronger evidence of this connection has not been made beyond the suggestion that laryngopharyngeal reflux may be a cofactor in the development of premalignant and malignant lesions.

Oncogenic human papillomaviruses (HPVs) have also been shown to be associated with head and neck malignancy, most commonly with oropharyngeal tumors. However, recent data suggest that HPV is also a risk factor for laryngeal carcinoma. A prospective case-control study by Mork and colleagues evaluated the rate of seropositivity of HPV subtypes in patients who eventually developed head and neck cancers (at an average of 9.4 years after enrollment).[3] HPV-16 was found to be most highly correlated with the incidence of head and neck malignancy. Of nearly 900,000 participants, 76 developed squamous cell carcinoma of the larynx. Of these, 12% (9/76) were seropositive for HPV-16 compared with only 5% (20/411) of matched controls. This led the authors to calculate an adjusted odds ratio of 2.4 for HPV-16 seropositivity in the development of laryngeal cancer.

Leukoplakia has been identified as a potential precursor lesion to invasive squamous cell carcinoma. In a meta-analysis by Isenberg and colleagues, a pooled group of 2188 biopsies for leukoplakia were retrospectively analyzed.[4] Initial histopathologic analysis revealed no dysplasia in 53.6% of biopsies, mild-moderate dysplasia in 33.5%, and severe dysplasia or carcinoma in situ (CIS) in 15.2%. After these patients were followed for 3 years, invasive carcinoma developed in 3.7% of patients without dysplasia, 10.1% of patients with mild-moderate dysplasia, and 18.1% of patients with severe dysplasia or CIS. It is important to note that this was a treatment study and those with more advanced lesions had more comprehensive excisions than



• **Fig. 39.1** Hematoxylin and eosin stain histopathology demonstrating sheets of exophytic carcinoma in situ with focal invasive squamous cell carcinoma.

those with earlier lesions. Simply sampling lesions along the vibratory surface of the vocal folds can have remarkably deleterious effects on vocal quality, and indiscriminate resection is to be avoided. It is generally accepted that hyperkeratosis, parakeratosis, and mild-moderate dysplasia may be observed carefully with judicious biopsy or very conservative resection when necessary, whereas severe dysplasia and CIS are treated more aggressively as early glottic cancers (Fig. 39.1).

Pertinent Anatomy

A thorough and comprehensive understanding of the surgical anatomy of the larynx is imperative for any surgeon managing laryngeal cancer. It is important to fully understand the complex, intricate nature of the larynx, in particular how each structure contributes to the airway, voice, and swallowing functions of the larynx. This knowledge is key in order to navigate the nuanced indications and techniques of laryngeal preservation strategies. Furthermore, understanding of the lymphatic pathways and nodal anatomy is crucial when considering management options of regional metastases.

Laryngeal Anatomy

The larynx is a complex structure composed of numerous bones, muscles, cartilages, ligaments, nerves, and vessels that function together to provide airway, swallowing, and phonatory function. It is situated in the midline of the neck deep to the paired infrahyoid or "strap" muscles (sternohyoid, sternothyroid, thyrohyoid, and omohyoid). Additional extrinsic muscles that provide mobility to the larynx include the mylohyoid, geniohyoid, and digastric muscles (attached to the superior border of the body and greater cornua and lesser cornua of the hyoid bone, respectively). Palpable external landmarks include the hyoid bone, thyroid cartilage notch or prominence, and cricoid cartilage. The isthmus of the thyroid gland may also be palpable as it crosses inferior and superficial to the cricoid cartilage, corresponding with the location of the upper tracheal rings.

The thyroid cartilage is shield shaped and opens posteriorly. The cricoid cartilage is ring shaped and considerably taller along the posterior aspect. The cricoid serves as the base for the entire larynx. The arytenoid cartilages articulate with the posterior cricoid lamina and function to abduct and adduct the vocal folds via attachments to the vocal processes of the arytenoids. Intrinsic laryngeal muscles (lateral and posterior cricoarytenoid) arise from the cricoid and insert onto the arytenoid cartilages, causing them to rotate. The cricoarytenoid unit is the functional unit of the larynx, a principle on which the use of laryngeal preservation surgery is based. Paired corniculate and cuneiform cartilages are present within the aryepiglottic folds at the tips of the arytenoids. These cartilages may provide some support to the true vocal fold and tend to thicken the aryepiglottic folds, sometimes necessitating their removal during the reconstruction portion of laryngeal preservation surgery to prevent overly redundant mucosa and glottic obstruction. The epiglottis is a fibrous cartilage situated behind the angle of the thyroid cartilage. The petiole, or base, is attached to the midline of the thyroid cartilage by the thyroepiglottic ligament. The epiglottis is divided into a suprahyoid portion (consisting of lingual and laryngeal surfaces) and an infrahyoid portion, which has only a laryngeal surface.

The larynx has a superior and an inferior neurovascular bundle. The superior bundle consists of the superior laryngeal artery, vena comitans from the common facial vein, and the internal branch of the superior laryngeal nerve. It emanates from the vagus nerve high in the neck near the skull base, entering the thyrohyoid membrane laterally to provide sensory innervation to the larynx. The external branch of the superior laryngeal nerve innervates the cricothyroid muscles, which act to alter vocal pitch by lengthening the glottis and increasing vocal fold tension during phonation. The inferior neurovascular bundle contains the recurrent laryngeal nerves and branches of the inferior thyroid arteries. The recurrent laryngeal nerves branch into anterior and posterior branches and provide motor innervation to the intrinsic muscles of the larynx and inferior constrictors, as well as sensory innervation to the larynx, esophagus, and trachea. The inferior neurovascular bundle follows the trachea superiorly, posterior to the thyroid gland, and enters the larynx just above and behind the cricothyroid joints.

The pyriform sinus mucosa is reflected posteriorly over the thyroid and cricoid cartilages. The pyriform sinus may be approached surgically by incising the inferior constrictor over the posterior border of the thyroid cartilage. The mucosa may be reflected posteriorly, revealing the cricoid and arytenoid cartilages. This permits preservation of the mucosa to be used during partial or total laryngectomy.

The laryngeal cartilaginous framework is bound together by intrinsic ligaments, which consist of broad bands of fibrous tissue. The conus elasticus, or lateral cricothyroid ligament, extends from the anterior commissure, vocal ligaments, and vocal processes of the arytenoids to the superior border of the cricoid cartilage. The quadrangular membrane is less developed than the conus elasticus and extends from the anterior lateral surface of the epiglottis posteriorly to the arytenoid cartilages and inferiorly to become continuous with the

ventricular ligaments. Although cartilage provides a relatively strong defense against malignant invasion, certain areas where ligamentous attachments or fenestrations for neurovascular bundles are located are more susceptible to tumor invasion. The fibroelastic ligaments and membranes are felt to provide a lesser degree of protection but can still prevent some spread of malignancy; however, more aggressive or advanced tumors frequently invade through these fibrous attachments.

The laryngeal cartilages, ligaments, and membranes form the boundaries of the spaces or compartments of the larynx. In general, early or less invasive lesions will remain bound within these spaces until they develop invasive features or grow to a large enough size. The Reinke space consists of the submucosal space along the free edge of the true vocal fold. The supraglottic space is the submucosal space superficial to the quadrangular membrane. Likewise, the subglottic space is the submucosal space that is superficial to the conus elasticus and extends from the inferior edge of the true vocal fold to the cricoid cartilage. The cricoid space is the inferior extension of the subglottic space down to the trachea, medial to the internal perichondrium of the cricoid cartilage. The preepiglottic space is formed by the boundaries of the hyoepiglottic ligament superiorly, the thyrohyoid membrane and thyroid cartilage anteriorly, and the epiglottic cartilage and thyroepiglottic ligament posteriorly. The space is filled with fat and areolar tissue and contains the saccule. Laterally, the preepiglottic space is continuous with the paraglottic space deep to the quadrangular membrane, although this has not been found to be a common route for tumor spread. Carcinoma on the laryngeal surface of the epiglottis can easily spread into the preepiglottic space. The paraglottic space is bound by the conus elasticus inferiorly, the thyroid cartilage laterally, the quadrangular membrane superiorly, and the pyriform sinus posteriorly. The paraglottic space is continuous with the submucosa of the ventricle and is paramount in the spread of carcinoma within the larynx. Tumors arising in the ventricle, vocal fold, lateral supraglottis, or pyriform sinus can spread to the remainder of the glottis via the paraglottic space. Invasion of the paraglottic space can be signified preoperatively by impairment or fixation of the true vocal fold.

The larynx is divided into three anatomic subsections: the supraglottis, glottis, and subglottis. The glottis contains the true vocal folds, anterior commissure, and posterior commissure. The triangular opening between the true vocal folds is named the rima glottidis. The anterior two thirds of the true vocal folds is called the *membranous portion* and consists of vocal ligaments covered in mucosa. The anterior commissure is the point at which the true vocal folds insert into the thyroid cartilage in the midline, approximately halfway between the most inferior aspect of the thyroid notch and the inferior border of the thyroid cartilage. The tendon of the anterior commissure is referred to the *Broyles ligament* and contains lymph and blood vessels, which may account for frequent invasion of the thyroid cartilage when the vocal ligament or paraglottic space is involved with carcinoma. The posterior one third of the true vocal folds consists of the vocal processes of the arytenoid cartilage covered in mucosa. This portion of the vocal folds as well as the interarytenoid mucosa is called the *posterior commissure.*

The supraglottis, or vestibule, consists of the ventricles, false vocal folds, laryngeal surface of the epiglottis, and aryepiglottic folds, as well as the mucosa covering the arytenoids. The subglottis begins at the level of the conus elasticus (about 5 mm below the inferior edges of the true vocal folds) and extends to the inferior border of the cricoid cartilage. The upper half of the subglottis is formed by the mucosa over the conus elasticus, which covers the thyroarytenoid muscle. The lower half is formed by the region of the cricoid cartilage and is lined by mucosa. The mucosa of the supraglottis and glottis consists of stratified squamous epithelium, whereas the mucosa of the subglottis is pseudostratified ciliated epithelium. The presence of numerous submucosal mucous or minor salivary glands characterizes the supraglottis and subglottis. Aside from the ventricles, the glottis does not contain minor salivary glands.

The division between the glottis and the supraglottis, as defined by the American Joint Committee on Cancer (AJCC), is at the level of the horizontal plane through the apex of the ventricle.[5] The division between the subglottis is parallel and 1 cm inferior to this horizontal plane. It was previously widely believed that the boundary between the glottis and the supraglottis represented a strong barrier to supraglottic cancers, and that supraglottic lesions only rarely entered the glottis. In a study by Weinstein and colleagues, 37 surgical specimens from patients undergoing total laryngectomy for supraglottic carcinoma were evaluated retrospectively.[6] Of these specimens, it was discovered that 20 of 37 (54%) exhibited extension from the supraglottic to the glottic level. In patients with abnormal (fixed or impaired) vocal fold mobility, the risk of extension to the glottis was much higher (75%) than in those with no glottic extension (6%) (P = .0002). In the two patients with normal fold mobility despite glottic extension of the tumor, it was discovered that there was no paraglottic space invasion and extension occurred anteriorly at the anterior commissure mucosa or tendon. In 19 of 20 (95%) of patients with glottic extension, involvement of the quadrangular membrane was identified, which is one potential connective tissue barrier along which carcinoma can spread. Because of potential selection bias, the authors theorized that the actual rate of glottic level invasion from the supraglottis is somewhere between 20% and 54%.

Although invasion of the thyroid cartilage in advanced tumors is common and subglottic extension with involvement of the cricoid cartilage is not rare, pathology studies have shown that the hyoid bone is typically uninvolved even in advanced laryngeal cancer. One study by Timon and colleagues evaluated 755 whole-organ laryngeal specimens and found an incidence of 1.46% (11/755) of hyoid bone involvement with squamous cell carcinoma.[7] Of these 11 patients, 10 (91%) had involvement secondary to direct tumor spread, and all 11 patients had advanced (stage IV) disease. Of the 11 cases with hyoid bone involvement, 4 (36%) were due to supraglottic laryngeal carcinoma, 1 (9%) was due to transglottic laryngeal carcinoma, and 1 (9%) was due to isolated glottic carcinoma. Because the hyoid bone is typically free of disease, an oncologic margin of resection can include the periosteum of the hyoid but preserve the hyoid bone itself, allowing its use in reconstructive techniques in partial laryngectomy such as cricohyoidoepiglottopexy (CHEP) or cricohyoidopexy (CHP).

Lymphatic Anatomy

The lymphatic drainage of the larynx involves a superficial (intramucosal) and deep (submucosal) network of lymphatics.[8] Lymph flow for the supraglottic and glottic larynx differ based on the separate embryologic development of the supraglottis and the glottis. The major dividing boundary between the lymphatic drainage of the supraglottis and glottis is the level of the false vocal fold. The superior larynx lymphatic drainage travels through the thyrohyoid membrane, whereas the inferior lymphatics travel through the cricothyroid membrane. Dye studies have been undertaken that show that submucosal injection of dye in the supraglottis remains limited to the tissues above the ventricle[9]; however infusion with massive amounts of dyes results in some spread to the glottic level, likely via spread from the lateral preepiglottic to the paraglottic space.[10] This shows that although there are connective tissue barriers that may initially impede the spread of carcinoma from the supraglottis to the glottis, carcinoma has the potential to spread as it progresses. Injections into the free margin of the vocal fold (Reinke space) remain confined to that space. In contrast, dye injection into the ventricle spreads deeply and widely among the soft tissue of the paraglottic space along lymphatic channels, in addition to direct extension to disseminate both within and beyond the larynx.

Characteristic lymphatic drainage patterns also exist within the neck. Fisch and Sigel[11] published a report of 100 cases in which lymphography was performed in healthy patients with use of patent blue dye injected into a deep retroauricular lymphatic vessel. This resulted in the observation that the normal pattern of cervical lymph flow occurred from retroauricular nodes (level IIb) to level IIa, then proceeding to level III and level IV. Some lymph also flowed from level II to level Va or Vb. This lymph then proceeded either to level III or to level IV; however, contralateral or retrograde flow (e.g., level III to level II or level IV to level V) was not observed. Furthermore, the prelaryngeal, paratracheal, and mediastinal nodes were not involved in this lymphatic pathway. The prelaryngeal (level VI) lymph nodes are supplied by the endolarynx alone.[12] The supraglottic larynx does not normally achieve lymphatic drainage via the prelaryngeal nodes. Prelaryngeal nodes are typically removed en bloc in all total and most partial laryngectomies.

Lindberg performed a retrospective review of 2044 patients with previously untreated squamous cell carcinoma of seven major subsites of the head and neck, including the supraglottic larynx and hypopharynx.[13] This study evaluated the presence of clinically positive (>1 cm, firm) nodal metastases in different nodal groups within the neck. Of 267 patients with squamous cell carcinoma of the supraglottic larynx, 147 (55%) had clinically positive nodes; 98 (67%) of these patients with nodal metastases had clinically positive lymph nodes in level IIa, 70 (48%) had positive nodes in level III, and 22 (15%) had positive nodes in level IV. Relatively few patients had nodal metastases in levels Ia (1, or <1%), Ib (2, or 1%), Va (8, or 5%), or Vb (5, or 3.4%). Of 267 patients with squamous cell carcinoma of the hypopharynx, 202 (76%) had clinically positive nodes; 148 (73%) of these patients with nodal metastases had clinically positive lymph nodes in level IIa, 112 (55%) had positive nodes in level III, and 43 (21%) had positive nodes in level IV. Again, relatively few patients had nodal metastases in levels Ia (1, or <1%), Ib (2, or 1%), Va (23, or 11%), or Vb (6, or 3%).

Another study, by Shah, retrospectively evaluated 1081 patients who underwent traditional radical neck dissection for squamous cell carcinoma of the upper aerodigestive tract.[14] Of 1081, 343 patients (32%) underwent elective neck dissection in the N0 neck, 620 patients (57%) underwent neck dissection with clinically positive disease at presentation, and 156 patients (14%) developed nodal neck disease during a period of observation and subsequently underwent neck dissection. Any patients who had undergone prior radiation or a modified radical neck dissection were excluded from the study. The study found that nodal metastasis was pathologically present in 82% of patients undergoing therapeutic neck dissection and in 33% of patients undergoing prophylactic neck dissection. In 262 patients undergoing neck dissection for laryngeal cancer, nodal metastases were identified in 183 samples (70%). Nodal disease was confirmed in 84% of therapeutic (N1–N3) neck dissection samples and discovered in 37% of prophylactic (N0) neck dissections. Levels II, III, and IV were most frequently involved in those with nodal disease present (66%, 68%, and 33%, respectively), with levels I and V less frequently involved (16% and 10%, respectively). Of note, these studies were undertaken before routine use of computed tomography (CT) or positron emission tomography (PET) to radiographically identify nodal metastasis before treatment planning.

Evaluation and Staging

Accurate staging of laryngeal carcinoma is rooted in performing a comprehensive evaluation of the patient, including complete head and neck physical examination, endoscopy, and radiographic imaging techniques. The National Comprehensive Cancer Network (NCCN) has published clinical practice guidelines, which have been widely accepted for the work-up and management of laryngeal carcinoma. The minimum work-up of laryngeal carcinoma as recommended by the NCCN guidelines for cancer of the glottic larynx[15] includes the following: history and complete physical examination; laryngeal examination by mirror or fiber-optic laryngoscopy; biopsy of primary lesion or fine needle aspiration of a neck metastasis; chest imaging to rule out metastasis; thin-cut computed tomography (CT) with contrast of the larynx and/or magnetic resonance imaging (MRI) of the larynx and neck; endoscopic examination under anesthesia; preanesthesia studies; dental evaluation; nutrition evaluation; and speech and swallowing evaluation and therapy. Positron-emission tomography (PET)–CT scanning should be considered in patients suspected of having advanced (stages III/IV) disease. Pulmonary function

studies should be obtained in selected patients, particularly those who may be candidates for conservation laryngeal surgery. Video stroboscopy and multidisciplinary consultation may also be obtained in selected patients. Accurate staging at the time of diagnosis can have significant consequences on the treatment recommendations that are developed. It also plays a large role in prognostic considerations, as prognosis worsens with increasing stage. The mere presence of lymph node metastasis to the neck drops cure rates by nearly half.[14]

Imaging techniques have evolved to the point where they are essential in evaluating abnormalities of the head and neck and can help distinguish malignancy from other pathologic entities. Cross-sectional imaging of the larynx should be performed using thin slices (2 mm), and the entire head and neck should be evaluated with slightly thicker slices (5 mm). Contrast should be used to help distinguish pathology from vascular structures. CT, magnetic resonance imaging (MRI), and PET are different modalities that are commonly used in laryngeal cancer. Each has its own advantages and disadvantages, and the modalities may be complementary. MRI has the advantage of clearly distinguishing between malignancy and normal soft tissue structures and evaluating cartilage invasion. However, the specificity of MRI is not as reliable as that of other modalities, and positive predictive value range is only 68–71%.[16] MRI is more time-consuming, expensive, and less well tolerated. MRI studies also have varying degrees of quality, and a poor-quality MRI can be almost useless. CT is usually the first imaging modality performed in a patient with suspected laryngeal malignancy. CT is less expensive, faster, less susceptible to motion artifact, and appropriate for patients with implantable electrical devices. It also offers improved discrimination of fat and bone. However, disadvantages include decreased sensitivity of cartilaginous invasion and the necessity for intravenous contrast. PET with administration of fludeoxyglucose (^{18}F) (FDG) can be fused with CT imaging to show a body map of increased activity with a higher risk of malignancy. It can be helpful in identifying regional or distant metastases. However, the resolution is poorer than that of CT or MRI, and specificity for malignancy is low. Furthermore, PET can be cost-prohibitive. Imaging modalities have improved diagnostic ability with respect to accurate staging. In a study by Zbaren and colleagues, the accuracy of staging with clinical examination and laryngoscopy alone was 57.5%. The addition of CT increased accuracy to 80%, and MRI increased accuracy to 87.5%.[17] However, a tendency was noted for CT to understage and MRI to overstage patients.

The staging of laryngeal carcinoma has been developed and studied by the AJCC. Staging for tumors has been divided into the primary laryngeal subsites of the supraglottis, glottis, and subglottis. Staging is described by the tumor-node-metastasis (TNM) naming convention, providing a separate stage for the primary tumor (T), regional lymph nodes (N), and distant metastasis (M). Staging for laryngeal carcinoma[5] has been provided in Tables 39.1 and 39.2. The staging of tumors of the supraglottis and subglottis is also included in the tables; however, these anatomic considerations will not be discussed further in this chapter. For purposes of staging, the anatomic subsites of the supraglottic larynx include the suprahyoid epiglottis, infrahyoid epiglottis, aryepiglottic folds (laryngeal aspect), arytenoid cartilages, and ventricular bands (false vocal folds). Anatomic subsites of the glottic larynx include the true vocal folds, anterior commissure, and posterior commissure.

Staging of glottic tumors is related to the depth of invasion. In a study by Kirchner, 200 pathologic specimens from patients with laryngeal cancer were studied by serial section to determine patterns of growth and spread of each lesion.[18] In T1 tumors in which both vocal folds retain full mobility, lesions are typically found superficial to the conus elasticus, which may represent a relatively tough barrier and safe surgical margin. T1 tumors are either confined to a single vocal fold (T1a) or cross the midline at the anterior commissure (T1b) (Fig. 39.2). In T2 tumors in which there is limitation (but not fixation) of one or more vocal folds, motion impairment may be caused by the weight of a bulky tumor, moderate invasion of the thyroarytenoid muscle, paraglottic space invasion, or growth along the superior surface of the vocal fold. In more advanced tumors (T3 or T4), vocal fold fixation was found to be related to complete replacement of the thyroarytenoid muscle by direct tumor invasion (most frequently); spread of cancer along the superior surface of the vocal fold, fixating it to the thyroid cartilage; extension of the tumor to the subglottis (at least 1 cm anteriorly or in the midportion, or at least 5 mm posteriorly); extensive paraglottic space invasion; or radiation fibrosis with residual tumor. In locally advanced (T4) tumors that invaded through the thyroid ala, the majority of tumors also showed extension superiorly (high into the ventricle) or inferiorly (to the subglottis).

The accuracy of purely clinical staging with regard to the primary site has been called into question. Accurate staging is imperative because a slight change in staging may have significant impact on treatment recommendations and, in particular, whether conservation laryngeal surgery is possible. A study by Nakayama and Brandenburg retrospectively evaluated the histopathologic specimens of 57 patients who had undergone total laryngectomy for T3 or T4 laryngeal cancer.[19] In this study, 72% (41/57) of patients were clinically staged as T3 and 28% (16/57) of patients were clinically staged as T4. They found that 49% (20/41) of those clinically staged as T3 had cartilage involvement that upstaged them pathologically to a T4. None of the T3 or T4 specimens had been overstaged. As part of the study, the authors identified five objective indicators that point to thyroid cartilage invasion: transglottic lesion (risk of cartilage involvement, 74%), extensive cartilage ossification (73%), extensive anterior commissure involvement (67%), tumor length greater than vocal fold length or 2 cm (66%), and vocal fold fixation (54%).

TABLE 39.1 American Joint Committee on Cancer Staging for Laryngeal Cancer (8th Edition)

Primary Tumor (T)

Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ

Supraglottis

T1	Tumor limited to one subsite of supraglottis with normal vocal fold mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal fold fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease; tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease; tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Glottis

T1	Tumor limited to the vocal fold(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal fold
T1b	Tumor involves both vocal folds
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal fold mobility
T3	Tumor limited to the larynx with vocal fold fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease; tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, thyroid or esophagus)
T4b	Very advanced local disease; tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Subglottis

T1	Tumor limited to the subglottis
T2	Tumor extends to vocal fold(s) with normal or impaired mobility
T3	Tumor limited to the larynx with vocal fold fixation
T4a	Moderately advanced local disease; tumor invades cricoid or thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease; tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Regional Lymph Nodes: Clinical (cN)*

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none larger than 6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral lymph node ≥3 cm but ≤6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes ≤6 cm in greatest dimension and ENE(–)
N3	Lymph node(s) larger than 6 cm and ENE(–) or metastasis in any node(s) and clinically overt ENE(+)
N3a	Lymph node(s) >6 cm and ENE(–)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L)*. Similarly, clinical and pathological ENE should be recorded as either ENE(–) or ENE(+)

TABLE 39.1 American Joint Committee on Cancer Staging for Laryngeal Cancer (8th Edition)—cont'd

Regional Lymph Nodes: Pathological (pN)

NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(–)
pN2	Metastasis to a single ipsilateral lymph node ≤3 cm in greatest dimension and ENE(+) or metastasis in a single ipsilateral lymph node >3 cm but ≤6 cm in greatest dimension and ENE(–); or metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–); or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN2b	Metastases in multiple ipsilateral lymph nodes none >6 cm in greatest dimension and ENE(–)
pN2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
pN3	Lymph node(s) >6 cm and ENE(–); or metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)
pN3a	Lymph node(s) >6 cm and ENE(–)
pN3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or with multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

From Patel SG, Lydiatt WM, Glastonbury CM, et al. Larynx. In Amin et al (eds). *AJCC cancer staging manual*. 8th ed. New York: Springer; 2017.
*Metastases at level VII are considered regional lymph node metastases.

TABLE 39.2 Prognostic Group Staging According to the American Joint Committee on Cancer (AJCC)

When T is…	And N is…	And M is…	Then the Stage Group is…
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

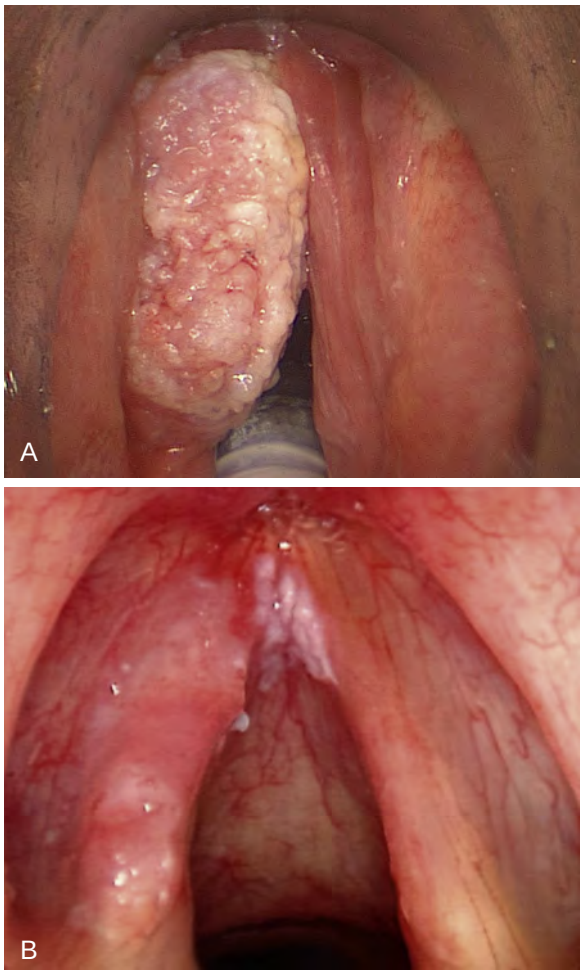
Registry Data Collection Variables

1. ENE clinical: ENE(+) or (–)
2. ENE pathological: ENE(+) or ENE(–)
3. Extent of microscopic ENE (distance of extension from the native lymph node capsule to the farthest point of invasion in the extranodal tissue)
4. Perineural invasion
5. Lymphovascular invasion
6. Performance status
7. Tobacco use and pack-years
8. Alcohol use
9. Depression diagnosis

Histologic Grade (G)

GX: Grade cannot be assessed
G1: Well differentiated
G2: Moderately differentiated
G3: Poorly differentiated

From Patel SG, Lydiatt WM, Glastonbury CM, et al. Larynx. In Amin MB et al, eds. *AJCC cancer staging manual*. 8th ed. New York: Springer, 2017.



• **Fig. 39.2** **A,** A T1a left vocal fold squamous cell carcinoma that is large, but spares the ventricle, subglottis, and anterior commissure. **B,** A much less bulky T1b cancer that involves the left as well as the right vocal fold across the anterior commissure.

The accuracy of clinical staging of the neck has also been challenged. However, as evaluation of the neck has evolved from purely physical examination to more sensitive imaging such as CT or PET, the accuracy of staging of nodal disease has improved with time. In one study by DeSanto, 1048 neck dissection samples in patients with squamous cell carcinoma of the upper aerodigestive tract were retrospectively evaluated.[20] Preoperative clinical stage was compared with postoperative histopathologic stage to determine the accuracy of nodal staging based on purely clinical criteria. The study found that nodal staging was accurate clinically only 65% of the time. An understaging error occurred 27.6% of the time, and overstaging occurred 7.8% of the time.

Because a higher stage is assigned to tumors with increased tumor burden and spread, prognosis worsens as the stage increases. AJCC data show that 5-year relative survival rates for carcinoma of the glottic larynx are 89.8%, 74.0%, 55.7%, and 44.4% for stage I, stage II, stage III, and stage IV disease, respectively.[5] The mere presence of nodal metastasis decreases 5-year survival rates by 50%, and extracapsular spread decreases survival even more.[21]

Management Principles and Known Outcomes

In advanced laryngeal cancer, the paradigm shift from surgical management with total laryngectomy to "organ preservation" with primary chemoradiation occurred in 1991 with the publication of the randomized controlled trial of the Department of Veterans Affairs Laryngeal Cancer Study Group.[22] However, no such landmark randomized controlled trial has been performed to date in patients with early laryngeal cancer. Because stage I and stage II disease is more localized, outcomes in prospective and retrospective studies have been similar among patients treated surgically and those treated with radiation with or without chemotherapy. A 2006 clinical practice guideline published by the American Society of Clinical Oncology recommends treatment of all Tis, T1, or T2 lesions with either organ preservation surgery or definitive radiation, with similar survival outcomes.[23] Therefore the choice of primary treatment modality can sometimes become quite complex. Often, patient factors such as medical comorbidities, compliance with treatments, and socioeconomic status dictate each patient's treatment recommendation. It is therefore necessary to consider all viable treatment options for the patient, ideally discussing options and treatment alternatives at a meeting of a multidisciplinary tumor board consisting of a surgeon, radiation oncologist, and medical oncologist, as well as providers of ancillary services such as speech-language pathology, nutrition, social work, and palliative care.

After the publication of the Department of Veterans Affairs Laryngeal Cancer study, advanced chemotherapy and radiation protocols were developed and routinely used with increased frequency. However, local long-term effects of these treatments have resulted in some patients losing physiologic function of the larynx despite retaining the anatomic structure. Studies have also shown no overall improvement in survival. Overall survival in laryngeal cancer patients also decreased during that time, although, as described by Hoffman and colleagues, "it is not possible to conclude definitively if these treatment factors are causally related or merely associated in the database. Confounding factors may be masking the effects of the different treatments on survival."[24] In one study, overall rates of laryngeal preservation at 3 years for patients with T2, T3, or T4a laryngeal carcinoma was 67% in those who underwent radiotherapy alone, 72% in those who underwent induction chemotherapy followed by radiotherapy, and 82% in those who underwent concurrent chemotherapy and radiation.[25] Five-year laryngectomy-free survival rates in these groups were 38%, 43%, and 45%, respectively. In selected patients, certain laryngeal preservation surgeries may be an option, in which certain tissues of the larynx are surgically removed and reconstruction is performed with the goal of providing a physiologically functional and tumor-free neo-larynx. Patients who are candidates for these procedures must have lesions with specific characteristics as described later in this chapter, but also must have strong cardiopulmonary reserve. Laryngeal preservation surgeries can be time-consuming, and many patients will experience postoperative aspiration for a short period of time after surgery. Thorough preoperative work-up for patients with tumors appropriate for laryngeal preservation surgery is imperative and should include routine preanesthesia work-up, chest x-ray examination, pulmonary function tests, and evaluation by a speech-language pathologist.

The most important factor in the management of laryngeal cancer is local control. Overall survival is significantly decreased whenever a local recurrence occurs after the primary treatment modality. For early lesions, primary management should involve either surgery alone, radiation alone, or chemoradiation (for advanced T2 lesions only). CIS lesions may successfully be managed with judicious but complete excisional biopsy maintaining approximately 2-mm margins. Surgery with postoperative radiation is not indicated in early-stage laryngeal cancer; instead, radiation should be reserved for salvage in patients whose disease recurs after they have undergone primary surgical management.[23]

Surgical Management

Indicating patients for laryngeal preservation surgery is more of an art than science. Many complex factors play into the surgical recommendation, including patient compliance and overall health, tumor characteristics, surgeon experience, and local treatment patterns. Throughout this section of the chapter, the different considerations for laryngeal preservation surgery for early glottic carcinoma are discussed. A detailed discussion of total laryngectomy is undertaken in Chapter 40.

Approach

One of the principles of surgical management of early glottic carcinoma is understanding the key anatomic structures that have been involved with tumor. Selecting a laryngeal

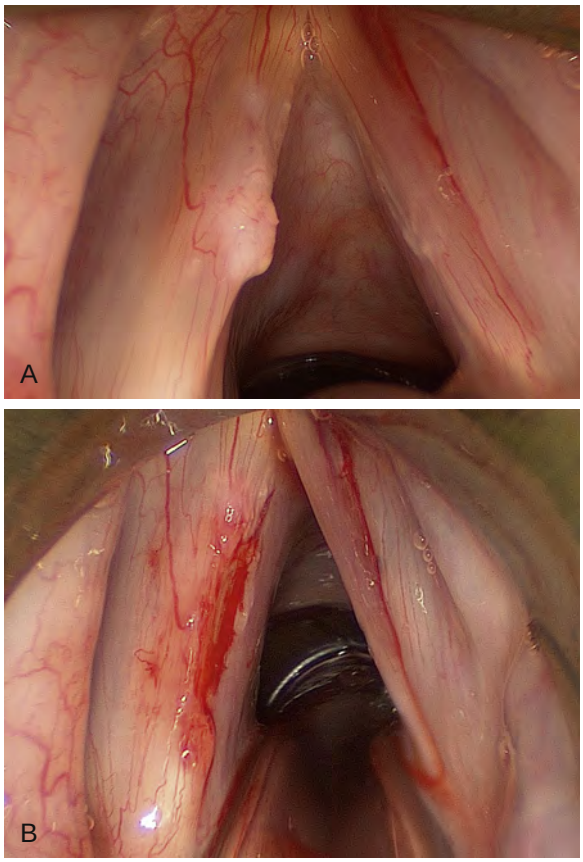
preservation surgery is predicated on knowledge of the tumor itself. Therefore a thorough head and neck evaluation is essential. Laryngoscopy must be performed with a mirror, flexible laryngoscope, rigid Hopkins rod telescope, or videostroboscope. Laryngovideostroboscopy can be invaluable in evaluating mucosal wave abnormalities in early glottic lesions. Unlike in the other subsites of the larynx that do not vibrate, the presence and extent of vibratory mucosal epithelium can indicate depth of invasion. Accordingly, premalignant lesions and early cancers confined to the vibratory epithelium may be distinguished and treated with strong correlation between preoperative and intraoperative assessment of disease extent. In short, laryngovideostroboscopy greatly enhances the surgeon's ability to assess the disease and make the best decision regarding the type of treatment and expected functional result. Arytenoid mobility must be accurately assessed, and the cause of vocal fold fixation (paraglottic space invasion versus cricoarytenoid joint involvement) must be determined. Having the patient cough gently while being evaluated with a flexible laryngoscope can assist in this determination. Pretreatment endoscopy under anesthesia with direct microlaryngoscopy and bimanual palpation must be performed in every patient, regardless of the treatment modality.[26] Examination with 0-, 30-, and 70-degree endoscopes is the only way to fully evaluate the subglottis and ventricle.

Laryngeal preservation surgery offers significant quality-of-life benefits over total laryngectomy with tracheoesophageal puncture. Weinstein and colleagues reported on a series of 31 patients who underwent either supracricoid partial laryngectomy (16 patients) or total laryngectomy with primary or delayed tracheoesophageal puncture.[27] The authors found statistically significant ($P < .05$) higher quality-of-life scores in the patients undergoing supracricoid partial laryngectomy in the University of Michigan head and neck quality-of-life and voice-related quality-of-life assessments in the following domains: eating, pain, and physical function of voice. Supracricoid partial laryngectomy patients also scored statistically higher in 7 of 10 SF-36 general health status measure domains; there were no statistically significant differences among groups in the remaining 3 domains.

Management of the Primary Lesion

Endoscopic Partial Cordectomy and Transoral Laser Microsurgery

Early (Tis or T1) lesions can frequently be excised endoscopically with excisional biopsy or partial cordectomy. This may be performed with or without CO_2 laser. Transoral laser microsurgery (TLM) has also been used on selected supraglottic and hypopharyngeal lesions with good rates of disease control, laryngeal preservation, and survival.[28] Small lesions that are completely visible through the laryngoscope are appropriate for resection by this method. Vocal fold margins are adequate at 1–3 mm, and larger margins (5–10 mm) are adequate in the supraglottis or hypopharynx[29] (Fig. 39.3). No reconstruction is typically performed, and the wound is left to heal by secondary intention with granulation tissue formation, contraction, and remucosalization. A literature review by Mendenhall and



• **Fig. 39.3** **A,** T1a squamous cell carcinoma of the left vocal fold. **B,** Same larynx immediately after endoscopic resection of the lesion.

colleagues found that local control rates after transoral endoscopic excision ranged from 80% to 90% for T1 lesions and 70% to 95% for T2 lesions.[30] In recent years, transoral microsurgery has been performed in even locally advanced laryngeal tumors. One downside to this is that many patients will need to undergo re-resection, either for positive or uncertain margins on histopathologic examination or for clinically apparent recurrence. These patients must be followed very closely. In a study by Jäckel and colleagues, a retrospective review of 1467 patients undergoing TLM for laryngeal carcinoma of all T stages was undertaken.[31] Twenty-five percent of patients also underwent postoperative radiotherapy, and an additional 9% underwent concurrent chemotherapy. This study showed that 71% of patients had negative margins at the initial surgical procedure. The remaining 29% had positive or uncertain margins. In patients who underwent re-resection, 82% were found to have no residual tumor in their surgical specimen. The overall rate of locoregional control in this group was 73%, with the majority of these recurrences occurring locally (62% of patients whose disease recurred). The study showed that although patients with positive or uncertain margins at initial surgery require re-resection, this does not negatively affect their overall outcomes. Although these patients require close follow-up, one benefit of these procedures is that the laryngeal framework is left intact, and only soft tissue of the glottic larynx is excised, leading to excellent functional outcomes. The larynx preserves its sensation and ability to elevate, allowing low rates

of postoperative aspiration. Voice outcomes after TLM have shown a mild to moderate degree of voice impairment on perceptual analysis that is slightly worse when compared with outcomes after primary radiotherapy,[32] although objective voice outcome measures, such as the Voice Handicap Index (VHI), have shown to improve in the long term when compared with preoperative voice.[33] However, TLM may be repeated as necessary for recurrence, and voice impairment after surgical salvage for radiation failures tends to be more severe.

Complications after endoscopic partial cordectomy and TLM are relatively frequent. In one study published by Vilaseca-Gonzalez and colleagues, the overall complication rate in 257 patients undergoing TLM for laryngeal cancer was 18.9% of patients[34]; 9.8% of complications were defined as major complications and the remaining 9.1% were defined as minor. Complications included postoperative bleeding (8%), dysphagia or aspiration pneumonia (6.1%), dyspnea from edema or stenosis (1.8%), subcutaneous emphysema (1%), local infection (0.8%), and cutaneous fistula (0.4%). Although rare, airway ignition is also a risk and occurred in 1 of 257 patients (0.4%) in this study. Such ignitions are expected to be fatal, and this fact underscores the necessity that all surgeons who look to treat early glottic cancers with TLM must be highly experienced in safe laser use in confined spaces immediately adjacent to oxygen-containing endotracheal tubes.

Open Cordectomy

Open cordectomy via a thyrotomy or laryngofissure approach is not routinely used with current advances in endoscopic laryngeal surgery and laryngeal preservation surgery. It is indicated for tumors with carcinoma limited to the middle third of the true vocal fold when there is no fixation (T1/T2 tumors) and is more of historical interest than modern practice because radiation therapy is more commonly performed for tumors of this size that cannot be exposed transorally. Radiation failures almost always have more extensive disease than could be managed by open cordectomy, and open partial laryngectomy should be considered in these cases.

Vertical Partial Laryngectomy (Hemilaryngectomy)

A vertical partial laryngectomy (VPL) or hemilaryngectomy excises the entire true vocal fold along with the anterior commissure and several millimeters of the contralateral vocal fold, a portion of the ipsilateral thyroid cartilage, and the paraglottic space on the tumor-bearing side. It provides a wider surgical margin than cordectomy alone and is indicated for carcinoma of the true vocal fold that extends anteriorly or posteriorly onto the membranous vocal fold. Because the paraglottic space is only partially resected on the affected side, VPL should not be performed if there is paraglottic invasion. Contraindications for a standard VPL include true vocal fold fixation, invasion of the anterior aspect of the arytenoid cartilage, transglottic tumor, anterior subglottic extension, and invasion of more than one third of the contralateral true vocal fold. Modifications of the procedure may widen the surgical margin, resulting in an "extended" VPL. This may be an option when there is some limitation or fixation of the true vocal fold or extension of the carcinoma beyond the confines of the true vocal fold. In these instances, however, the surgeon should remain cautious for more locally advanced tumors because involvement of the paraglottic space or thyroid cartilage will increase the risk of local recurrence after an extended VPL. The advent of supracricoid VPL in recent years has decreased the use of VPL for advanced T2, T3, or T4 lesions.

The technique for a VPL has been well-documented.[8] A tracheostomy is typically performed at the start of the procedure. After an apron flap is raised in a subplatysmal plane, the strap muscles are separated in the midline. A vertical thyrotomy through the thyroid ala slightly toward the non–tumor-bearing side is made to enter the laryngeal lumen. Accordingly, entry into the larynx is "blind" and the surgeon is provided with a narrow field of exposure, which is one of the major disadvantages to this technique. The surgeon can then visualize the endolarynx. The ipsilateral thyroid ala is skeletonized superficial to the perichondrium. An additional vertical thyrotomy is performed approximately two thirds of the distance posteriorly. The posterior one third of the thyroid cartilage will be used for reconstruction and is left attached to the inferior constrictor muscle. The internal and external perichondrium should be preserved to assist with preservation of the blood supply. The pyriform sinus mucosa can be visualized deep to this portion of the thyroid cartilage. The inferior cornu of the thyroid is disarticulated from the cricoid, allowing lateral retraction. Under direct visualization, the mucosal incision is planned and made with scissors—the inferior extent passes through the cricothyroid membrane, the aryepiglottic fold superiorly, and the thyroid membrane anteriorly. A larger segment of the opposite true vocal fold can be resected if the anterior commissure is involved. The interarytenoid mucosa is incised to define the posterior extent of the resection. It is crucial not to accidentally transect the mucosa of the anterior hypopharynx, which is deep to the interarytenoideus. A finger is placed into the pyriform sinus, and the cricoarytenoid joint is separated with scissors. The arytenoid is separated from the anterior aspect of the pyriform sinus, freeing the specimen. A cartilage flap consisting of the middle one third of the posterior thyroid ala on the tumor-bearing side is prepared, modeling the size and shape of the resected arytenoid. Holes are drilled into the cartilage flap and the cricoid cartilage, and the cartilage flap is sutured to the cricoid. The pyriform sinus mucosa is sutured to the cut edge of the laryngeal mucosa to cover the cartilage flap. The sternohyoid is sutured to the anterior edge of the hypopharynx mucosa. Wound closure proceeds with reapproximation of the strap muscles, platysma, and skin.

A modification known as the anterior commissure, or anterior frontal, VPL can be performed in a similar manner. This is used primarily for T1 or T2 tumors that are limited to the anterior commissure and do not extend to the posterior membranous vocal fold. This procedure is performed in a similar way as the standard VPL with some modifications. The thyrotomies are performed 0.5–1.0 cm to either side of midline based on involvement to each side. The larynx is entered via a cricothyrotomy. The bilateral true vocal folds are incised so that only a small band of mucosa remains over the arytenoid.

A silastic keel is placed so that it separates each side of the vocal fold stump from the other to avoid webbing. The keel is sewn to the remaining sides of the thyroid cartilage and left in place for 6 to 8 weeks.

One study performed by Laccourreye found that local control and laryngeal preservation rates were lower in VPL for early glottic carcinoma involving the anterior commissure (T1/T2N0) when compared with supracricoid partial laryngectomy with CHEP.[35] Local recurrence rates for VPL ranged from 16% to 29% for T1N0 tumors and 25% to 41% for T2N0 tumors on literature review, compared with 1.6% (1/62) in Laccourreye's group undergoing supracricoid partial laryngectomy. This patient was successfully salvaged with radiotherapy, leading to an overall local control and laryngeal preservation rate of 100%.

Supracricoid Partial Laryngectomy With Cricohyoidoepiglottopexy

Supracricoid partial laryngectomy with CHEP is an option for carcinoma of the glottic larynx with limited involvement of the paraglottic space or thyroid cartilage. It is not an option when the tumor has extended beyond the paraglottic space to the supraglottis superiorly. The procedure involves removal of the complete paraglottic space and thyroid cartilage. Mobile arytenoids (one or both) are preserved, as well as the cricoid cartilage and the superior two thirds of the epiglottis.

Indications include unilateral T1 glottic carcinoma with extension to the anterior commissure, bilateral T1 glottic carcinomas (with or without involvement of the anterior commissure), T1 glottic carcinomas with dysplasia or hyperplasia in the paraglottic space or thyroid cartilage, T2 glottic carcinomas with or without impaired mobility of the vocal fold, and early T3 glottic carcinoma with intact ipsilateral arytenoid mobility. Because this procedure preserves a majority of the preepiglottic space, lesions with known or suspected invasion of the preepiglottic space should not be resected with this procedure. Other relative contraindications include lesions originating in the ventricle or anterior commissure (which have a high propensity for invading the pre-epiglottic space), ipsilateral arytenoid cartilage fixation (with invasion of the cricoarytenoid joint, posterior cricoarytenoid muscle, or posterior aspect of the cricoid cartilage), and subglottic extension of more than 1 cm anteriorly or 0.5 cm posteriorly.

The procedure has been well described by Laccourreye.[36,37] The procedure is approached in the typical manner, with skin incision being performed via an extended Kocher or U-shaped incision, depending on the need for concurrent neck dissection. Subplatysmal flaps are elevated to at least 1 cm above the level of the hyoid. Sternohyoid, thyrohyoid, and sternothyroid muscles are divided along the superior border of the thyroid cartilage. The inferior pharyngeal constrictor and thyroid perichondrium are transected along the posterior border of the thyroid cartilage lamina. The pyriform sinuses are released with a Freer elevator. The cricothyroid joints are carefully disarticulated and the thyroid isthmus is transected. Blunt dissection along the anterior wall of the trachea is performed to assist with substernal release and superior mobility of the trachea. The larynx is entered via an incision through the epiglottis along the superior border of the thyroid cartilage. A horizontal cricothyroidotomy along the superior aspect of the cricoid cartilage is also performed. A guarded oroendotracheal tube is inserted into the cricothyroidotomy. The larynx is retracted inferiorly and anteriorly, which allows the surgeon direct visualization of the tumor location and extension. On the non–tumor-bearing side, a prearytenoid incision is made extending from the aryepiglottic fold to the superior border of the cricoid. This cut, which is made with scissors, allows the entire paraglottic space to be resected in conjunction with the specimen, while sparing the pyriform sinus (posterior and lateral to the plane of dissection). The cricothyroid muscle is transected, which connects the vertical prearytenoid incision with the cricothyrotomy on the non–tumor-bearing side. The thyroid cartilage is fractured along the midline, allowing complete visualization of the tumor-bearing side. Excision of the tumor can proceed with similar incisions while ensuring an adequate margin of grossly normal-appearing tissue. The arytenoid cartilage on the affected side may be partially or completely removed as needed. The remaining arytenoid cartilage(s) can be sutured to the cricoid with a Vicryl suture to prevent posterior displacement. The hyoid bone is affixed to the cricoid cartilage using 1 Vicryl or 0 Prolene sutures placed in the midline and exactly 1 cm to each side of the midline, looping around the body of the hyoid bone, passing through the remaining epiglottic cartilage and around the cricoid. Care must be taken to ensure that these sutures are secure and that there is no gap between the hyoid and cricoid. A tracheotomy is performed through the initial skin incision. Closure of the neck proceeds in layers with reapproximation of strap muscles, platysma, and skin.

The initial outcomes study by Laccourreye's group evaluated 36 patients with glottic laryngeal carcinoma who underwent supracricoid partial laryngectomy with CHEP.[36] The majority of patients were staged as T2 (26/36, or 72%), with the remainder staged as T1a (3%), T1b (22%), and T4 (3%). Eight of 36 (22%) had impaired mobility of the ipsilateral true vocal fold and 1 of 36 (3%) had impaired mobility of the ipsilateral arytenoid. Patients with vocal fold fixation were excluded. In this study, 26 of 36 patients (72%) received preoperative chemotherapy with cisplatin and 5-fluorouracil (5-FU). Dysplasia or hyperplasia of surrounding laryngeal mucosa was identified in 50% (18/36). Ipsilateral selective neck dissection was performed in 50% of cases (18/36), and postoperative radiation was not performed in any patient. Minimum follow-up was 18 months. The 3-year survival rate was 86.5%, local recurrence rate was 6% (2/36), and nodal recurrence rate was 8% (3/36). Preoperative chemotherapy was not shown to significantly affect rates of recurrence. All patients were decannulated at an average of 7 days postoperatively. Nasogastric feeding tubes were left in place for an average of 15 days, and 35 of 36 (97%) were able to resume swallowing and resume physiologic voicing within the first postoperative month. There was a 0% incidence of infectious complications, and 1 patient (3%) experienced progressive hyoid necrosis and was managed conservatively. Subsequent studies have resulted in similar findings.[30]

Physiologic function of phonation and deglutition can occur because the superior laryngeal and recurrent laryngeal nerves are preserved, maintaining the sensation and mobility of remaining structures. The sphincteric function of the larynx is achieved by contact between the preserved arytenoid(s) and the preserved portion of the epiglottis. Phonation is possible through the formation of a transverse neo-glottic chink replacing the normal rima glottidis.

Supraglottic Laryngectomy and Supraglottic Horizontal Partial Laryngectomy

Supraglottic laryngectomy, also termed a *supraglottic horizontal partial laryngectomy,* is a procedure appropriate for isolated supraglottic tumors without extension to the glottic larynx. Please refer to Chapter 40 for a detailed discussion of this procedure.

Supracricoid Partial Laryngectomy With Cricohyoidopexy

Supracricoid partial laryngectomy with CHP is an option for certain glottic carcinomas with extension to the supraglottis (i.e., "transglottic" tumors). A standard horizontal supraglottic laryngectomy for supraglottic tumors is contraindicated if there is extension to the supraglottis via the anterior commissure or ventricle, invasion of the paraglottic space with limitation or fixation of a true vocal fold, or thyroid cartilage invasion. However, transglottic tumors with these characteristics may be amenable to a type of partial horizontal laryngectomy known as the *supracricoid partial laryngectomy with CHEP.* This procedure involves complete removal of bilateral true and false vocal folds, both the preepiglottic and paraglottic spaces, as well as the associated epiglottic and thyroid cartilages. The cricoid cartilage is maintained and affixed to the hyoid bone. One or both arytenoid cartilages, if mobile, are also preserved to assist with voice and swallowing function. Although long-term aspiration is a risk for these patients, the majority are able to achieve normal swallowing function long term. Intensive speech therapy and preservation of both arytenoids have been shown to improve long-term deglutition.[38,39] Vocalization can be achieved by vibrations of the arytenoid mucosa against the base of the tongue, resulting in a deep voice with a fundamental frequency of around 80 Hz and intensity between 60 and 70 dB.[39] Because the cricoid cartilage is maintained in its entirety, physiologic airway preservation is possible without a long-term tracheostomy.

Indications and contraindications have been outlined by numerous studies.[38,39] A supracricoid partial laryngectomy with CHP reconstruction is indicated for the following lesions: T1/T2 supraglottic lesions with extension to the ventricle, infrahyoid epiglottis, or posterior third of the false vocal fold; T1/T2 supraglottic lesions with extension to the glottis or anterior commissure with or without vocal fold impairment; T3 transglottic lesions with limitation or fixation of the true vocal fold; and selected T4 supraglottic or transglottic lesions invading the thyroid cartilage. Absolute contraindications include the following: subglottic extension of more than 1 cm anteriorly or 0.5 cm posteriorly; arytenoid cartilage fixation (indicating invasion of the posterior intrinsic laryngeal muscles, cricoarytenoid joint, or arytenoid cartilage); massive preepiglottic space invasion; or lesions with extension to the pharyngeal wall, vallecula, base of tongue, suprahyoid epiglottis, cricoid cartilage, postcricoid region, or interarytenoid region.

The procedure has been well described by Laccourreye.[38] The procedure proceeds much in the same way as a supracricoid partial laryngectomy with CHEP as described earlier. Notable differences are as follows.

The exposure is performed in the same manner. Once the hyoid is exposed, the periosteum of the hyoid bone is incised laterally and anteriorly, and a Freer instrument is used to release the preepiglottic space from the posterior surface of the hyoid bone. Rather than entering the larynx through the epiglottis, entrance occurs via the vallecula with a horizontal pharyngotomy. Excision of the tumor proceeds in a similar fashion, with the entire epiglottis removed en bloc with the tumor specimen. Again, the arytenoid cartilage on the affected side can be preserved or removed partially or completely as dictated by the extent of the tumor. After resection of the tumor, the hyoid bone is affixed to the cricoid cartilage using 0 Prolene sutures placed in the midline and 1 cm to each side, looping around the body of the hyoid bone and cricoid cartilage. A tracheotomy is performed through the initial skin incision. Closure of the neck proceeds in the usual fashion.

In the initial outcomes study of the procedure by Laccourreye, and colleagues, 68 patients undergoing this procedure were studied.[38] The majority of patients in this study received preoperative chemotherapy (60/68). All patients with clinically negative necks underwent concurrent bilateral modified radical neck dissection, and patients with palpable lymphadenopathy greater than 2 cm underwent radical neck dissections. Twenty-five percent (17/68) of patients underwent postoperative radiation therapy to the neck if extracapsular extension was identified on pathologic examination of the neck specimen. Twenty-two percent (15/68) of patients retained both complete arytenoid cartilages, and the remaining 78% (53/68) of patients had one arytenoid partially or completely removed. In this study, 3-year survival was 71% (the majority of deaths were related to second primaries), local recurrence rate was 0%, recurrence in the neck was 5.8%, and distant metastasis rate was 8.8%. All patients were eventually decannulated at an average time of 7 days, and the nasogastric feeding tube was removed after an average of 15 days. Twenty-five percent of patients required endoscopic gastrostomy placement for weight loss or aspiration pneumonia within the first month after surgery, and gastrostomy was in place for an average of 5 months. Physiologic voicing was attained by all patients within 2 months postoperatively.

Another study by Chevalier evaluated 61 patients who underwent supracricoid partial laryngectomy with CHP for supraglottic carcinoma, with similar results.[39] In this study, 3-year survival was 83% and 5-year survival was 79%, with death most commonly caused by second primary cancer. Local recurrence rate was 3% (2/61), and rate of recurrence in the neck was 3% (2/61).

Subtotal Laryngectomy With Tracheohyoidopexy

Supracricoid partial laryngectomy is typically contraindicated if there is extension of tumor to the subglottis or cricoarytenoid joint. However, a subtotal laryngectomy in which a portion of the cricoid is removed may be an alternative to total laryngectomy in certain cases. This is indicated when there is subglottic extension of laryngeal tumors, when one cricoarytenoid joint is involved, or if there is anterior extension through the thyroid cartilage. Contraindications include tumors that reach both the arytenoid and posterior commissure, or those that extend to the base of the tongue, hypopharynx, or trachea. This procedure proceeds much in the same way as a supracricoid partial laryngectomy with CHP; however, a large portion of the cricoid is removed, and only the portion of the cricoid at the uninvolved cricoarytenoid joint(s) is preserved. This procedure has not been studied in significant detail, and its use is not widely accepted. Rizzotto and colleagues have described the procedure, dubbing it the "supratracheal partial laryngectomy," and reported outcomes of 70 patients who underwent this procedure.[40,41] In their series, 5-year overall and disease-free survival were 80% and 72.9%, respectively, with 2-year laryngeal preservation rates of 80%. Because it requires additional investigation into long-term outcomes, this procedure should be considered experimental at this time.

Transoral Robotic Surgery

Robotic surgical systems have been used with increased frequency over the past 15–20 years. Although they have revolutionized cardiac, urologic, and gynecologic surgery, their application in otolaryngology remains limited. Transoral robotic surgery (TORS) has been used most frequently for base of tongue lesions. The benefit of robotic surgery is that the "line of sight" limitation that accompanies the use of a laryngoscope is eliminated. Thus TORS may be an option when the tumor location precludes the use of traditional transoral surgical instrumentation. Feasibility of performing resection of supraglottic, hypopharyngeal, and glottic tumors has been demonstrated in the literature in small case series[42,43]; however, long-term outcomes have not been studied in large groups. The use of robotic surgery for management of these lesions may be an appropriate option in the future, but additional research must be undertaken before it achieves widespread use.

Surgical Salvage With Laryngeal Preservation Surgery

For patients who have undergone primary radiation or chemoradiation, local recurrence has traditionally been managed surgically with total laryngectomy. However, over the past 30 years, laryngeal preservation procedures have been used in very specific clinical scenarios. Contraindications to supracricoid partial laryngectomy for surgical salvage include subglottic spread of the lesion, fixation of the ipsilateral arytenoid cartilage, cricoid cartilage invasion, and extralaryngeal spread of tumor. Rates of local control in selected patients undergoing surgical salvage with postradiation laryngeal preservation surgery have been shown to be similar to those of patients undergoing postradiation total laryngectomy.[44]

In a study by Laccourreye and colleagues, retrospective review was undertaken of 12 patients with recurrent squamous cell carcinoma of the larynx after failed primary radiotherapy.[45] In this study, 9 of 12 patients (75%) had laryngeal carcinoma of the glottis, and 3 of 12 (25%) had supraglottic tumors. Total dosage of initial radiation ranged from 65 to 75 Gy. None of the patients exhibited nodal recurrence, and distant metastasis was suspected in 1 patient. All patients underwent a supracricoid partial laryngectomy. Six patients underwent CHEP for reconstruction, 4 underwent CHP, and 2 underwent a tracheocricohyoidoepiglottopexy (TCHEP). Total resection of arytenoid cartilage occurred in 5 patients, partial resection in 3 patients, and preservation of both arytenoid cartilages in 4 patients. The 3-year survival rate was 83.3%, and local recurrence occurred in 17%. Local recurrence was treated with total laryngectomy, resulting in an overall local control rate of 100% and a laryngeal preservation rate of 75%. Complications included perichondritis (17%), anterior neck abscess (17%), persistent arytenoid edema (42%), and aspiration pneumonia (8%). All 10 patients who underwent CHP or CHEP were decannulated within 1 month, whereas the 2 patients who underwent TCHEP were unable to be decannulated. Compared with non-irradiated patients, the patients in the study experienced increased duration of tracheostomy, significant postoperative edema, and increased incidence of arytenoid edema and neck abscess.

In a meta-analysis by Motamed and colleagues, similar rates of local control were noted in patients salvaged by vertical or supracricoid partial laryngectomy.[46] Their study evaluated a pooled total of 407 cases, and the local control rate was 56–100% with a weighted average of 77%. Subsequent total laryngectomy was performed in 15% of cases. The group also evaluated outcomes when TLM was used for surgical salvage, which occurred in 145 cases in the pooled literature. Up to 40% of cases required repeat laser surgery, and local control rates ranged from 51–87%, with a weighted average of 65%. This technique of repeated endolaryngeal surgery for laryngeal carcinoma has been pioneered by Steiner[47] but remains relatively controversial. Although local control rates in patients undergoing surgical salvage will be lower in those who undergo TLM or supracricoid partial laryngectomy when compared with a total laryngectomy, satisfactory rates of local control and laryngeal preservation can still be obtained.

Management of the Neck

A traditional radical neck dissection involves en bloc removal of the lymphatic nodes and vessels of the lateral neck, as well as the internal jugular vein, sternocleidomastoid muscle, spinal accessory nerve, and (usually) submandibular gland. A modified radical neck dissection involves removal of all of the lymphatic metastasis, along with none or some of the aforementioned additional structures; it does not affect metastases affecting muscle, fascia, or vascular adventitia. Recurrence rates have not differed in patients undergoing a radical neck dissection as opposed to a modified radical neck dissection.[20] In contrast, a selective neck dissection removes only a portion of the lymphatic tissue and may or may not remove the additional structures in the lateral neck.

The type of neck dissection that is appropriate to be performed for any patient with laryngeal cancer will certainly be directed by the clinical and radiographic stage of the primary tumor as well as the neck. In general, the nodal level above and below any apparent involved level should be included in the neck dissection. Skip lesions are highly uncommon. For example, in a patient with a single pathologic lymph node in level III, neck dissection should include removal of at least levels II, III, and IV. In a patient in whom levels II, III, and IV are pathologically involved, a complete modified radical neck dissection should be performed. In patients with no evidence of neck disease, a prophylactic selective neck dissection involving levels II, III, and IV will likely be adequate because these are the nodal levels most at risk.

Postoperative Management

Postoperative management of patients undergoing conservation laryngeal surgery involves inpatient admission postoperatively. The patient's pulmonary status should be monitored with continuous pulse oximetry. A nasogastric feeding tube is placed at the time of surgery and used for primary nutritional support and oral medications. A speech-language pathologist should begin working with the patient and perform a clinical assessment of swallowing function as early as the first postoperative day. Trials of thickened liquids should be initiated when the patient is tolerating secretions, and the diet advanced as clinically indicated. The feeding tube should be removed when the patient is able to maintain nutritional intake by physiologic swallowing alone. If a patient continues to have severe dysphagia that is expected to last for at least 1 month, a percutaneous endoscopic gastrostomy (PEG) tube should be placed. Many institutions place gastrostomy tubes during most if not all organ preservation procedures. There is no consensus among the literature regarding the need and duration for postoperative antibiotics. In general, intravenous antibiotics covering oral and respiratory flora should be continued for at least 48 hours postoperatively and longer as clinically indicated. Because transient postoperative aspiration is a common occurrence, it is safer to continue antibiotics longer than typical in other procedures. In the event that a CHEP or CHP was performed, we also recommend keeping the patient in gentle neck flexion for 1 week postoperatively. This may be undertaken with the placement of a "Grillo stitch," which keeps the neck in a flexed position by securing a stitch from the chin to the manubrium. However, patients often find this uncomfortable, and gentle neck flexion may also be obtained by use of an external Minerva brace, which is fitted for us by the occupational therapist. A circumferential compression dressing around the neck may also be placed in the event of bilateral neck dissection to prevent hematoma. The cuff on the tracheotomy tube may be deflated as tolerated as early as postoperative day 1 and transitioned to a cuffless tracheotomy tube. This may assist with improvement in physiologic deglutition, because a tracheotomy cuff can compress the pharynx. Furthermore, early decannulation provides an opportunity for physiologic function of the larynx to return more quickly and may help improve mobility of the arytenoid.

Radiation Therapy

General Principles

Radiation therapy can be a highly effective treatment modality in patients with early laryngeal cancer. Conventional radiotherapy in the definitive setting is typically given at 1.8 to 2.0 Gy per fraction, one fraction per day, 5 days per week in a continuous course with total dose ranging from 60 to 66 Gy. In general, early glottic cancers should be treated with a single modality of therapy, either radiation or surgery. When radiation is used in the adjuvant setting after TLM or partial laryngectomy for positive margins, the total dose can be reduced to 55.8 Gy with 1.8 Gy fractions owing to an increased risk of complications.[48] Patients are typically treated with 4- to 6-mV x-rays. The primary site and upper neck are conventionally irradiated with parallel opposed fields, and the low neck is irradiated with an en face anterior field. This type of conventional radiotherapy has been named *three-dimensional conformal radiotherapy* (3DCRT). In recent years, intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) have been introduced in the management of laryngeal cancer to decrease the radiation dose to surrounding normal tissues. During treatment planning for radiotherapy, patient factors such as compliance, social support, and ability to be treated in a radiation center must be ascertained. Patients should be counseled on the time commitment required for successful completion of a radiotherapy program (daily fractions for up to 6–7 weeks), as well as potential complications that may arise from radiotherapy.

Radiation to the Primary Site

The target area for radiotherapy to the glottic larynx should be limited by the upper border of the thyroid cartilage and the caudal border of the cricoid cartilage. Five-year local control rates after radiotherapy have been shown to be adequate, particularly for T1 tumors (85–94%). A study by Franchin and colleagues evaluated 410 patients with early glottic carcinoma of the larynx (stage I and II) and treated them primarily with radiation therapy.[49] Patients with prior head or neck irradiation were excluded. Sixty-five percent (267/410) were staged as T1a, 14% (56/410) as stage T1b, 17% as stage T2a (70/410), and 4% (17/410) as T2b. Stage I patients underwent treatment using four alternating isocentric field techniques (two latero-lateral fields with 30-degree wedge filters and two anterior oblique fields with 45-degree wedge filters), with total doses ranging from 63 to 68.4 Gy in 33 to 39 fractions (1.8–2.25 Gy per fraction over 38–56 days). Patients with stage II disease were uniformly treated using latero-lateral fields and 45-degree wedge filters. Follow-up ranged from 8 to 193 months (median 63 months). Five- and 10-year survival rates were 83% and 63.5%, respectively. Thirty-three patients (8%) developed local recurrence, and only 2 patients (0.5%) developed nodal recurrence. Second primary tumors developed in 91 patients (22%), with a 10-year survival rate of 32%. Local control rates were improved in stage I disease (91%) compared with stage II disease (80%). In a preliminary study by the same group evaluating 276 of the

aforementioned patients, tumor size greater than 1 cm and an infiltrative lesion were associated with increased risk of local recurrence.[50] Patients receiving 1.8-Gy fractions had a statistically lower rate of control (80%) compared with patients receiving 2.25-Gy fractions (90%).

Recent advances in the knowledge of cell growth mechanics have led to several changes in the dose and schedule of radiotherapy. Modified fractionation schedules have been studied extensively, and hyperfractionation (increases in the total radiation dose with lower doses per fraction) and acceleration (reductions in overall treatment time) have been used with increasing frequency in recent years. Many different dose schedules including hyperfractionation, acceleration, or both have been devised and studied. In his description of experience at Massachusetts General Hospital, Wang describes results achieved after definitive radiotherapy for supraglottic and glottic laryngeal cancer using hyperfractionated (two fractions per day) dosing.[51] Fractions were delivered at 1.6 Gy per fraction twice daily for a total goal dose of 70.4 Gy in 6 weeks. For supraglottic carcinoma, 5-year local control rates were 83%, 71%, and 84% in 126 T2, 136 T3, and 18 T4 lesions, respectively. These results were compared against patients receiving conventionally scheduled radiotherapy, and local control rates were significantly improved in the hyperfractionation group. Similar findings were noted in patients undergoing radiotherapy for glottic carcinoma as well. In this group, patients undergoing hyperfractionated radiotherapy had 5-year local control rates of 83%, 72%, and 67% in 76 T2a, 61 T2b, and 41 T3 lesions, respectively. Again, these rates of local control were improved over the conventional radiotherapy schedule group. Because radiation is given more frequently, acute mucosal toxicity is increased in these patients. Because of acute toxicity effects, many patients will need to take a midtreatment break. In another report by Wang and colleagues, the rate of local control was evaluated in patients with T3 glottic carcinoma when undergoing accelerated hyperfractionation radiotherapy with a midtreatment gap.[52] In this study, 162 patients were reviewed. Local control rates were found to be unchanged if a short midtreatment break was taken after 38 to 48 Gy with certain restrictions. Local control rates were statistically lower, however, if the midtreatment break lasted longer than 14 days, total treatment course was longer than 45 days, or total dose was less than 67 Gy. In cases where patients required a longer midtreatment break, the authors recommend increasing the final total dose to 72 to 75 Gy or increasing the fraction sizes after the break to 1.8 to 2.0 Gy twice daily. Accelerated radiotherapy dose schedules have also been shown to significantly improve local control rates. In the Danish Head and Neck Cancer Group 6 study, 649 patients with squamous cell carcinoma of the glottic larynx were randomized to receive either conventional radiotherapy (2-Gy fractions daily, five doses per week) or accelerated radiotherapy (2-Gy fractions, six doses per week).[53] In most cases, patients in the experimental arm received the extra dose on the same day as another dose, with at least 6 hours separating administration of the two fractions. Randomization was stratified by T stage (T1/T2 or T3/T4) and gender. Minimum follow-up in the study was 5 years. Statistically significant improvements in local control rates were noted in both T-stage groups in patients receiving accelerated radiotherapy. In the patients receiving six fractions weekly, 5-year local failure rates were 17.9%, 11.0%, and 60.8% for overall, T1/T2, and T3/T4 groups, respectively, compared with failure rates of 26.0%, 19.4%, and 64.0% in the control group. Acute morbidity was increased in the accelerated group, with a significant increase in mucositis; however, 98% of both treatment groups were able to complete the planned radiotherapy treatment, and all acute morbidity resolved within 3 months. There was no statistical difference between treatment groups in terms of moderate- or late-term morbidity with the exception of taste (relative risk 1.4 for the experimental group). Additional studies have confirmed that hyperfractionation and accelerated fractionation with a concomitant boost provide benefit to local control rates; however, these studies have shown no change or just a modest improvement (0–3%) in overall survival rates in patients undergoing alternative fraction radiotherapy.[54–56] Short- and long-term functional results have not been well described for radiation or chemoradiation therapy protocols. Although many patients may keep their larynxes, voice, airway, and swallowing may be compromised years after initial treatment. Surgical salvage is also substantially more complicated and yields poorer functional results as compared with primary surgical approaches.

Radiation to the Neck

In prior years there was significant debate over whether prophylactic radiation to a clinically negative neck was indicated. However, in recent years, with significantly more sensitive imaging modalities, the support for prophylactic neck irradiation has decreased. In the setting of a clinically or radiographically positive neck, the recommendation is generally to consider adjunctive radiation. Recurrence rates after neck dissection without radiotherapy range from 26.5–36.5%,[20] which prompts multidisciplinary teams to consider irradiating the neck to eradicate microscopic metastatic disease in patients with proven nodal disease. Radiation is particularly advantageous if there is extracapsular spread of the tumor on histopathologic dissection.[21] However, because early-stage (stage I or II) laryngeal cancer is N0 by definition, routine radiation to the neck is not indicated in these cases.

Imaging for Treatment Preparation and Setup

Accurate pretreatment imaging is essential to developing a successful radiotherapy treatment plan. Patients undergoing conventional radiotherapy typically undergo CT as part of simulation. However, PET and PET/CT scans are superior owing to their increased sensitivity in delineating tumor extension compared with CT. Furthermore, post-treatment evaluation is improved with PET and PET/CT, as tumor recurrence can be differentiated from laryngeal edema or fibrosis, conditions that are common after radiotherapy. Thus, current practice trends have shifted to the performance of fused PET-CT before radiotherapy.

Intensity-Modulated, Image-Guided, and Adaptive Radiotherapy

The traditional radiotherapy techniques described previously have been dubbed *three-dimensional conformal radiotherapy* (3D-CRT). With this conventional technique, two lateral fields have been matched with an anterior supraclavicular field. However, this technique does not allow normal tissues to be spared high doses of radiotherapy, which may damage normal, uninvolved tissue sites. Patients undergoing 3DCRT may experience radiation-related damage of salivary glands leading to xerostomia, osteoradionecrosis of the mandible, and hearing loss from cochlear damage. Therefore, intensity-modulated and image-guided techniques have been introduced into the management of laryngeal cancer because of their rapid dose fall-off away from the target, minimizing tissue damage to surrounding structures.

IMRT involves using pretreatment imaging and computer applications to tailor the dose of radiation delivered to each tissue site. With this technique, high doses of radiation can be delivered to the target tissue, and minimal radiation doses are delivered to normal tissue types. IGRT involves the use of frequent imaging throughout the course of radiotherapy for the purpose of improving accuracy and precision of radiation delivery. Other methods of IGRT include placing surface or implanted radiolucent markers within the patient's body. IMRT and IGRT can be used in conjunction with each other to improve high-dose delivery of radiotherapy to the target tissue while minimizing normal tissue damage. Although IMRT and IGRT have been widely accepted in other tissue sites, their use in laryngeal carcinoma is still relatively novel. The use of IMRT and IGRT has been pioneered by Nguyen and colleagues, and their early studies have shown that treatment toxicity is significantly improved with IMRT and IGRT without worsening of locoregional control rates.[57–59] In another study by Nguyen and colleagues, 27 patients undergoing IMRT or IGRT for laryngeal cancer were studied.[60] The mean total radiation dose to the larynx was 72.5 Gy; mean total radiation doses to surrounding tissues were 37.9 Gy to the mandible, 11.3 Gy to the temporomandibular joints, 30.0 Gy to the parotid glands, and 9.2 Gy to the cochlea. In this study, however, rates of grade 3–4 mucositis and late toxicity (dysphagia, aspiration pneumonia) remained high despite the use of IMRT, with 4 of 27 (15%) of patients relying on a long-term feeding tube.

Complications

Complications of radiotherapy have been well-documented. Side effects may be acute and short term, or may be permanent. Short-term complications include mucositis and pain. Long-term complications include pain, numbness, dysphagia, xerostomia, taste alteration, hair loss, edema, skin changes, mucosal atrophy, fibrosis, perichondritis, osteonecrosis, dental caries, and tracheostomy dependence.[53]

Chemotherapy

General Principles and Agents

In general, chemotherapy may be recommended as an adjunctive treatment modality in the treatment of laryngeal cancer. Chemotherapy is commonly used in patients with more advanced disease locoregionally or with distant metastases. Because early-stage laryngeal cancers are locally contained, many can be treated with a single modality. However, because chemotherapy alone is traditionally considered insufficient to treat laryngeal cancer, the focus has been on its use as an adjunctive therapy. Therefore chemotherapy is not routinely a part of the recommended primary treatment algorithm for early-stage laryngeal cancer. Chemotherapy may be indicated in patients with early-stage laryngeal cancer whose disease recurs after treatment with surgical or radiation modalities. Chemoradiation as an adjunct to surgery is not used in early-stage laryngeal cancer, and distant metastases are not present in early-stage laryngeal cancer. Because these treatment modalities are not routinely used for early laryngeal cancer, please refer to Chapter 40 for further discussion of these topics.

Induction Chemotherapy

Induction chemotherapy has been shown to have a positive benefit by inducing a clinically noticeable response in some patients. Tumors that are chemosensitive also tend to be radiosensitive.[61] Most medical oncologists advocate a platinum-based chemotherapeutic agent, and the most common regimen includes cisplatinum.[62] 5-FU and cetuximab may also be used. In one study by Richard and colleagues, 68 patients with T3 laryngeal cancer were randomized to receive either total laryngectomy or three cycles of cisplatinum and fluorouracil followed by radiotherapy (if a clinical response was seen) or total laryngectomy (if no response was seen).[63] Two-year survival was significantly higher in the group allocated to total laryngectomy (84–69% in the chemotherapy group), but 42% (15/36) of the chemotherapy group avoided laryngectomy. Similar results are seen in a meta-analysis of other similar studies in which pooled results showed a 6% increase in 5-year survival in the surgery group, although 58% of those in the chemotherapy group preserved their larynx at 5 years.[64] Alternative chemotherapy regimens have been proposed. In a study by Holsinger and colleagues, 30 patients with stages II/IV laryngeal cancer were treated with an alternative chemotherapy regimen (three to four cycles of paclitaxel, ifosfamide, and cisplatin).[65] If a complete response was noted, then patients were treated with an additional three cycles of the chemotherapy regimen without adjunctive treatment. Patients with partial response underwent partial laryngectomy. In patients treated with chemotherapy alone (11/30 patients, or 37%), 10 of 11 (91%) did not have local or regional recurrence at 5 years. Although the majority of the patients enrolled were T2 (71%), this study shows promise for potential chemotherapeutic regimens as a primary modality. However, no large or long-term studies have been undertaken to evaluate the effect of chemotherapy alone, and these regimens are largely experimental at this point.

In a study by Laccourreye and colleagues evaluating 20 patients with T3 glottic squamous cell carcinoma and a fixed true vocal fold, neoadjuvant chemotherapy was performed, followed by supracricoid partial laryngectomy with CHEP.[66] Neoadjuvant chemotherapy was administered to each patient before surgical resection (18 patients with cisplatin/fluorouracil and 2 patients with vincristine sulfate/methotrexate/bleomycin). Response to chemotherapy was assessed before laryngeal preservation surgery. A single patient staged as T3N2M0 underwent postoperative radiation of the neck. In this study, 17 of 20 (85%) patients exhibited some response and 6 of 20 (30%) exhibited complete clinical response to neoadjuvant chemotherapy. Four of 20 (20%) patients exhibited no tumor in pathologic specimen, indicating complete histologic response. Three-year survival was 75%. Local recurrence occurred in 2 of 20 (10%) and nodal recurrence occurred in 1 of 20 (5%). Second primary tumors occurred in 2 of 20 (10%) patients. Taken with Holsinger's results, these results suggest that neoadjuvant chemotherapy may have a role in the management of laryngeal cancer with organ preservation surgery.

Combination With Radiation in the Definitive Setting

Although rates of local control and laryngeal preservation are improved in concurrent chemoradiation therapy compared with induction chemotherapy or radiotherapy alone, no significant differences in overall survival have been observed. One study by Forastiere and colleagues, mentioned earlier in the chapter (RTOG 91-11), evaluated definitive chemoradiation in advanced laryngeal cancer (T2/T4a).[25] The group evaluated 547 patients with advanced laryngeal cancer. Patients were randomized to chemotherapy followed by radiotherapy in responders, concurrent chemotherapy, or definitive radiotherapy alone. Patients were followed for a mean of 3.8 years. Patients who did not respond or whose disease recurred underwent total laryngectomy. Two-year laryngeal preservation rates were 84% in the concurrent chemotherapy group, 71% in the induction chemotherapy group, and 66% in the radiotherapy-alone group. However, rates of 5-year overall survival were similar (around 55% for all three groups). Rates of acute effects of radiotherapy (e.g., mucositis) were nearly twice as high in the concurrent group; however, there were no differences in long-term treatment effects among groups.

Rehabilitation

Rehabilitation in patients with early glottic carcinoma will depend on treatment modalities performed. Early involvement of a speech-language pathologist with specific training in laryngeal carcinoma is highly recommended. If possible, pretreatment consultation is ideal. The speech-language pathologist can assist with pretreatment counseling and begin initiating education on exercises that can help improve phonatory and swallowing functions after treatment. Intensive speech and swallowing therapy is initiated as soon as possible after treatment.

Surveillance

Primary

Early detection of local recurrences is imperative but may be difficult in post-treatment patients. The topography of the larynx is altered after medical or surgical treatments, and adequate evaluation of the larynx may not be possible in the clinic. Patients with symptoms such as increasing pain, otalgia, or dysphagia should undergo repeat imaging (CT, MRI, or PET) and endoscopic evaluation with biopsy if warranted. NCCN guidelines discuss timing for clinical surveillance, and recommend history and physical examination with laryngoscopy every 1 to 3 months for the first post-treatment year, every 2 to 6 months in the second year, every 4 to 8 months in the third to fifth years, and every 12 months more than 5 years after treatment.[15] Post-treatment baseline imaging (CT, MRI, or PET-CT) may be obtained within 6 months of treatment, although indirect laryngeal examination is more sensitive than imaging at detecting persistent disease at the primary site. Thyroid-stimulating hormone (TSH) levels should be checked at least annually if the patient has undergone irradiation of the neck or total laryngectomy.

Metastatic Disease

Studies have shown that most recurrences in the neck occur within 24 months after initial surgery, and nearly all within 5 years.[20] Any worrisome symptoms (neck mass, worsening pain, otalgia) should be evaluated with complete physical examination and imaging studies. Routine surveillance for distant metastasis should include at least an annual chest x-ray study or chest CT, with consideration of PET-CT for any concerning findings.

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Advanced Larynx Cancer

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Approximately 13,560 new cases of laryngeal squamous cell carcinoma (SCC) were projected to have occurred in 2015, leading to an estimated 3640 deaths. The primary risk factor for the development of laryngeal carcinoma is tobacco use; when coupled with alcohol abuse, a synergistic increase in cancer risk occurs. Because of the declining rate of tobacco use in most Western countries, the overall rate of laryngeal carcinoma has also been decreasing over the past two decades. However, laryngeal cancer remains a problem in populations with higher rates of tobacco use, and is a common disease faced by head and neck surgeons and oncologists.

Most glottic carcinomas become symptomatic at a relatively early stage because even a small lesion may significantly disrupt the voice and lead to hoarseness. At an early stage, glottic carcinoma is often cured through either surgery or radiation treatment. However, owing to a variety of factors such as patient neglect, delays in diagnosis, or tumor physiology, approximately 40% of laryngeal carcinomas are at advanced stages on presentation for treatment. The larynx plays a critical role in several vital functions, including respiration, deglutition, and voicing. Advanced tumors of the larynx may significantly impair one or more of these functions; common presenting signs and symptoms include dysphonia, dyspnea, dysphagia, odynophagia, otalgia, neck mass, and hemoptysis. Unfortunately, treatment of advanced laryngeal cancer also has significant adverse effects on these critical laryngeal functions. Treatment planning for patients with advanced laryngeal carcinoma hinges on the selection of the treatment strategy that will deliver good oncologic control while leaving the patient with the best respiratory, voicing, and swallowing function possible.

Laryngeal Anatomy

A thorough knowledge of laryngeal anatomy is critical to understanding both the pathophysiology of laryngeal carcinoma and proper treatment of this disease. Although a detailed discussion of laryngeal anatomy is beyond the scope of this chapter, certain key features of the larynx are critical to understand tumor spread and decision points regarding oncologic treatment.

The larynx is divided into three regions: the supraglottis, glottis, and subglottis. The supraglottis is composed of the epiglottis, aryepiglottic folds, false vocal folds, and arytenoids. The supraglottis extends inferiorly to the lateral apex of the ventricle; in this region the respiratory epithelium of the supraglottis transitions to stratified squamous epithelium of the glottis, but this transition point is somewhat variable. The glottis is composed of the true vocal folds and extends from the lateral extent of the ventricle superiorly down to a point approximately 1 cm inferior to the true vocal folds. The vocal fold itself is composed of stratified squamous epithelium, underlying lamina propria, and the vocalis muscle. The subglottis extends from the inferior border of the glottis to the inferior border of the cricoid cartilage. It is rarely the primary site of cancer but is often involved by tumors extending inferiorly from the glottis.

Tumor growth within the larynx tends to follow the path of least resistance along certain key potential spaces and is constrained by other anatomic barriers. The preepiglottic space is bordered by the hyoepiglottic ligament superiorly, the thyrohyoid membrane and thyroid cartilage anteriorly, and the thyroepiglottic ligament inferiorly. The thyroepiglottic ligament does not provide a substantial barrier to tumor spread, making this the typical route for tumors to reach this space. Laterally and posteriorly, the preepiglottic space communicates with the paraglottic space. This space is bordered by the quadrangular membrane and conus elasticus medially, the thyroid cartilage and cricothyroid membrane laterally, and the piriform sinus posteriorly. Tumors extending into the paraglottic space typically impair vocal fold movement, and this space provides a route for the transglottic spread of tumor.

The laryngeal cartilages, in particular the thyroid and cricoid, form a relatively resistant barrier to tumor spread. The perichondrium itself is quite a strong barrier; however, several weak points within the cartilaginous framework exist where tumor extension is more likely. These typically occur at areas of muscular insertion where the perichondrium is naturally deficient, such as at the Broyles ligament and the anterior commissure. Cartilage invasion is much more likely in this area, and close attention should be paid to tumors in this region to determine the extent of cartilaginous involvement. Full-thickness penetration of the thyroid cartilage (rather than just erosion of the inner cortex) upstages a tumor to T4a status, and as discussed later, may significantly alter treatment planning owing to the relative inferiority of chemoradiation in this situation.

Other fibrous structures within the larynx, such as the hyoepiglottic ligament, conus elasticus, and quadrangular membrane, also form relatively strong barriers to tumor spread, and obvious tumor invasion through any of these structures indicates an aggressive malignancy.

The lymphatic drainage of the larynx is fairly predictable and has been mapped out in detail.[1] Lymphatic drainage is dictated by the embryologic origins of the larynx. The supraglottis is derived from a midline structure and contains abundant lymphatic channels; thus, bilateral nodal metastases are frequently seen with supraglottic tumors. In contrast, the glottis and subglottis are derived from laterally based furrows and have unilateral drainage along with relatively sparse lymphatic supply. Thus, lymph node metastases are less common in tumors of the glottis and subglottis, and tend to occur ipsilateral to the primary tumor. However, advanced-stage glottic tumors often cross embryologic boundaries into the supraglottis, making bilateral nodal metastases more common with any advanced laryngeal cancer.

Evaluation and Staging

According to National Comprehensive Cancer Network (NCCN) guidelines, the minimum required work-up of a patient with glottic carcinoma consists of a complete head and neck examination including mirror or fiber-optic laryngeal examination, neck computed tomography (CT) or magnetic resonance imaging (MRI), chest imaging, and a tissue biopsy. This tissue may be obtained via directed biopsies of the primary tumor or through fine-needle aspiration of suspected nodal metastasis. This is the bare minimum needed to diagnose the disease, assess the extent of the primary lesion, and evaluate for metastatic disease of the cervical lymph nodes or lungs. However, a more detailed evaluation may provide additional information regarding the disease stage and help to determine the optimal treatment course.

Imaging of the primary tumor should ideally be done with dedicated thin-cut sections through the level of the larynx. CT or MRI with thin sections can provide extensive detail needed to properly stage advanced laryngeal carcinoma, such as paraglottic and preepiglottic space involvement, thyroid and/or cricoid cartilage erosion, and extension beyond the larynx into the tongue base, hypopharynx, or lateral neck. The information gained from thin-cut CT scan of the larynx complements direct inspection of the tumor with flexible or rigid laryngoscopy to fully evaluate the extent of the primary tumor.

Fludeoxyglucose F 18–positron emission tomography (^{18}FDG-PET) imaging is also quite useful in the evaluation of advanced stage glottic cancer and is suggested by current NCCN guidelines. One prospective, multicenter trial showed that performing ^{18}FDG-PET improved patient staging and altered treatment decisions in nearly 14% of head and neck cancer patients,[2] and subsequent studies[3,4] demonstrated the usefulness of PET scans during the initial evaluation of patients with laryngeal carcinoma. PET scans are frequently employed to assess treatment response after chemoradiation; thus it is also quite beneficial to acquire a pretreatment scan as a benchmark to assess the efficacy of treatment. For these reasons a PET scan is often used in lieu of chest CT or x-ray examination to complete the imaging work-up of advanced laryngeal carcinoma.

Panendoscopy, including direct laryngoscopy, is a well-established and extremely useful means of assessing the anatomic extent of the primary tumor and obtaining a tissue biopsy. Traditional panendoscopy includes a thorough oral inspection, direct laryngoscopy, esophagoscopy, and possibly bronchoscopy. Historically, this complete evaluation of the upper aerodigestive tract was necessary to assess for the presence of second primary malignancies. However, multiple studies have shown that bronchoscopy and esophagoscopy have a low rate of second primary detection in laryngeal cancer and do carry some procedural risk.[5,6] Furthermore, modern imaging techniques such as PET scans are as good as or better than direct inspection for the detection of possible second primary malignancies.[7,8] Direct laryngoscopy, however, is indispensable in the assessment of the primary tumor for treatment planning, particularly when surgical resection is planned. Before total laryngectomy, direct laryngoscopy provides important information on the involvement of nearby areas such as the piriform sinuses and the vallecula to determine the full extent of resection. This assessment is often performed immediately before the surgical resection. However, when conservation partial laryngectomy procedures such as supraglottic or supracricoid laryngectomy are planned, a separate panendoscopy procedure is useful to determine if the planned conservation surgery is feasible and to properly counsel the patient before surgery. Information gained from a separate panendoscopy procedure may thus significantly alter clinical decision making and should be considered in nearly all patients with advanced glottic cancer, aside from those with obvious indications for total laryngectomy such as gross thyroid or cricoid cartilage invasion.

Laryngeal cancer is currently staged using the seventh edition of the American Joint Committee on Cancer (AJCC) system of tumor-node-metastasis (TNM) staging. This anatomically based staging system incorporates the extent of the primary tumor; presence, number, and location of cervical nodal metastases; and presence of distant metastases to stratify patients (Table 40.1). This system does not incorporate pathologic findings such as extracapsular spread, perineural invasion, or tumor differentiation, or other molecular or biochemical biomarkers of prognosis.

Management Principles

Although early-stage glottic cancer can frequently be treated with a single modality, late-stage glottic cancer will typically require a multimodality treatment approach. The goal of treatment for laryngeal cancer is to obtain the best oncologic outcome while preserving functional voice, swallowing, and quality of life. Since the 1980s, several studies have compared the ability of different treatment modalities to achieve that goal.

Perhaps the most influential study regarding the treatment of laryngeal carcinoma is that of the Veterans Affairs Laryngeal Cancer Study Group, published in 1991.[9] This

TABLE 40.1 American Joint Committee on Cancer (AJCC) TNM Staging System for Laryngeal Cancer

T Stage—Supraglottis	
T1	Tumor limited to one subsite with normal vocal cord mobility
T2	Tumor invades mucosa of more than one subsite of supraglottis or glottis or region outside supraglottis without fixation of larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx: trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, esophagus
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinum
T Stage—Glottis	
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to larynx with vocal cord fixation and/or invades preepiglottic space and/or inner cortex of thyroid cartilage
T4a	Tumor invades through the thyroid cartilage and/or invades tissues beyond the larynx: trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, esophagus
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinum
T Stage—Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to the vocal cords with normal or impaired mobility
T3	Tumor limited to the larynx with vocal cord fixation
T4a	Tumor invades the cricoid or thyroid cartilage and/or invades tissues beyond the larynx: trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, esophagus
T4b	Tumor invades prevertebral space, encases carotid artery, or invades mediastinum
N Stage	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph nodes metastasis
N1	Metastasis in a single ipsilateral regional lymph node measuring less than 3 cm in diameter
N2a	Metastasis in a single ipsilateral regional lymph node more than 3 cm and less than 6 cm in diameter
N2b	Metastasis in multiple ipsilateral lymph nodes, none greater than 6 cm in diameter
N2c	Metastasis in bilateral or contralateral lymph nodes, none greater than 6 cm in diameter
M Stage	
M0	No distant metastasis
M1	Distant metastasis
Prognostic Groups	
Stage 0	Tis N0 M0
Stage I	T1 N0 M0
Stage II	T2 N0 M0
Stage III	T3 N0 M0, T1–3 N1 M0
Stage IVA	T4a N0–1 M0, T1–T4a N2 M0
Stage IVB	T4b Any N M0, Any T N3 M0
Stage IVC	Any T Any N M1

From Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual*. 8th ed. New York: Springer; 2017.

was a multi-institutional randomized clinical trial designed to determine whether induction chemotherapy and radiation, with laryngectomy reserved for salvage, was a better primary treatment than primary surgery with adjuvant radiotherapy in patients with advanced laryngeal cancer. Patients received either the standard therapy of surgery followed by adjuvant radiation or the experimental arm of induction chemotherapy with two cycles of cisplatin and 5-fluorouracil (5-FU). Those in the experimental arm were reassessed after two cycles, and if there was at least a partial response, they received a third cycle followed by definitive radiotherapy. If there was no response after two cycles they received salvage surgery. The majority of patients included in the trial had advanced T-stage disease, with 65% T3 and 25.6% T4. The tumor subsite was glottic in 37.3% of patients and supraglottic in 62.6% of patients. The study found that both treatment arms had similar overall survival at 2 years (68%) and that survival rates were similar for the patients who responded to chemotherapy and those who did not (P = .98). However, a majority of patients in the chemoradiation arm were able to avoid total laryngectomy and its functional consequences. This approach, aimed at organ preservation, was later extrapolated to many other subsites for SCC within the upper aerodigestive tract, and was further refined by the RTOG 91-11 trial,[10] which established concurrent chemoradiation as the modality of choice over induction chemotherapy followed by radiation.

However, a published review of the Surveillance, Epidemiology, and End Results (SEER) database showed a decrease in 5-year relative survival from 68.1% (1980–1982) to 64.7% (1992–1999) for laryngeal SCC.[11] Hoffman and colleagues[12] reviewed the larger National Cancer Database (NCDB), which also confirmed the decrease in survival. Five-year relative survival for laryngeal SCC recorded in the NCDB ranged from a high of 68.1% in 1985 to a low of 62.8% in 1993. Because the timing of the decrease in survival noted among patients with laryngeal SCC correlated with the publication of the Veterans Affairs study, some hypothesized that practice changes resulting from the Veterans Affairs study were responsible. Hoffman's analysis found that there was an increase in non-surgical management of laryngeal cancer with an increase in irradiation alone and combined with chemoradiation. The NCDB data favored initial treatment with surgery and irradiation (5-year relative survival 65.2%) compared with chemoradiation (5-year relative survival 59.2%) [= .067] for T3N0M0 laryngeal SCC of all subsites. However, when looking specifically at T3N0M0 glottic SCC, survival after treatment with chemoradiation was similar to that of surgery combined with irradiation.

A study by Grover and colleagues also reviewed the NCDB but looked more specifically at T4aN0 SCC.[13] It was noted that the two large randomized trials included only a minority of patients with T4a disease, 26% in the Veterans Affairs study and 10% on RTOG 91-11 (which also excluded patients with tumor penetrating through the thyroid cartilage or more than 1 cm into the base of tongue). The study analyzed both practice patterns and survival and found that 64% of patients were treated with laryngeal-preserving chemoradiotherapy and 36% received total laryngectomy. Median survival for patients treated with total laryngectomy was 61 months versus 39 months for chemoradiotherapy (P < .001). The pattern seen in this review of the database, in which the majority of T4a patients are being treated with chemoradiotherapy, is not in concordance with the clinical practice guidelines established by the NCCN.[14] The guidelines suggest that laryngeal tumors that have invaded through cartilage and into the extralaryngeal soft tissue of the neck or adjacent structures (thyroid, esophagus, and base of tongue) are better treated with primary surgery. Total laryngectomy as a salvage procedure is indicated for patients in whom treatment with chemoradiation, radiation, or partial laryngectomy has failed. Although salvage surgery is most often performed for locoregional recurrence, sometimes salvage is required when the larynx is left non-functional from prior treatment, resulting in either intractable aspiration or chondroradionecrosis. In the RTOG 91-11 study, 16% of patients who received concurrent chemotherapy and radiation required salvage, and 31% of those who received radiation alone required it (P = .002).[15]

Surgical Management

Once the decision has been made to proceed with surgical treatment of advanced laryngeal cancer, there are still multiple factors that must be considered to determine the optimal treatment for the individual patient. These factors include tumor location and extent, patient preference, and surgeon comfort and expertise. As mentioned previously, often the first procedure performed is direct laryngoscopy, which familiarizes the surgeon with the anatomic borders of the tumor and allows precise operative planning.

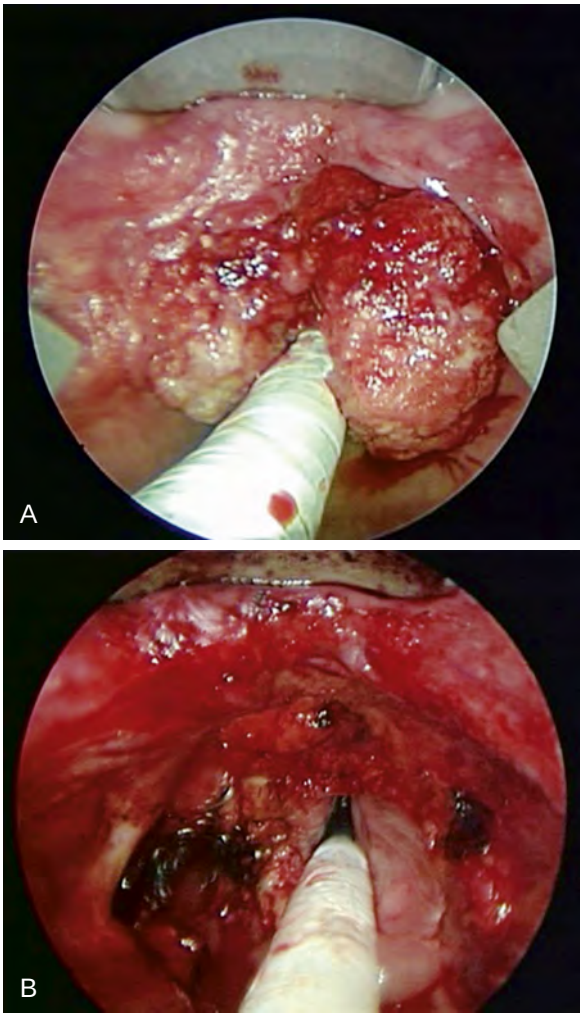
Transoral Laser Microsurgery

Although transoral laser microsurgery (TLM) is primarily used for early-stage laryngeal cancers, some surgeons perform endoscopic partial laryngectomy for the treatment of locally advanced glottic and supraglottic tumors. This type of surgery uses a microscope and CO_2 laser and removes a portion of the endolarynx while leaving the cartilaginous support structure intact (Fig. 40.1). Frequently the patient can be spared a tracheotomy after the procedure, and the swallowing rehabilitation can ideally be shorter than with similar open procedures. Removal of a large tumor requires excising the tumor in a piecewise fashion, although it does not appear to affect locoregional control rates. A retrospective review of TLM for advanced laryngeal cancer was performed by Hinni and colleagues; this review included 117 patients with stage III or IV SCC of the glottic or supraglottic larynx treated with TLM at multiple institutions.[16] The researchers examined laryngeal preservation, overall survival, disease-free survival, locoregional control, and distant metastases. The percentage of patients with an intact larynx 2 years after treatment was 92%. The 5-year Kaplan-Meier estimates were local control, 74%; locoregional control, 68%; disease-free survival, 58%; overall survival, 55%; and distant metastases, 14%. The conclusion of Hinni and

colleagues was that in the right patients, TLM offers acceptable rates of organ preservation and locoregional control with low morbidity.

Supraglottic Laryngectomy

Supraglottic tumors that are confined above the vocal folds may be amenable to supraglottic conservation surgery. A supraglottic laryngectomy involves removal of the epiglottis, the hyoid bone, and the upper half of the thyroid cartilage above a plane through the ventricles. This approach will not remove tumors that have invaded the paraglottic space but can be used for those with limited involvement of the preepiglottic space. Supraglottic tumors extending onto the lingual surface of the epiglottis or base of the tongue or those involving thyroid cartilage are not candidates for this procedure.[17] Both vocal folds should be mobile and the patient must have good pulmonary reserve because some aspiration after this procedure is guaranteed. A tracheotomy is placed for pulmonary toilet in the postoperative setting.

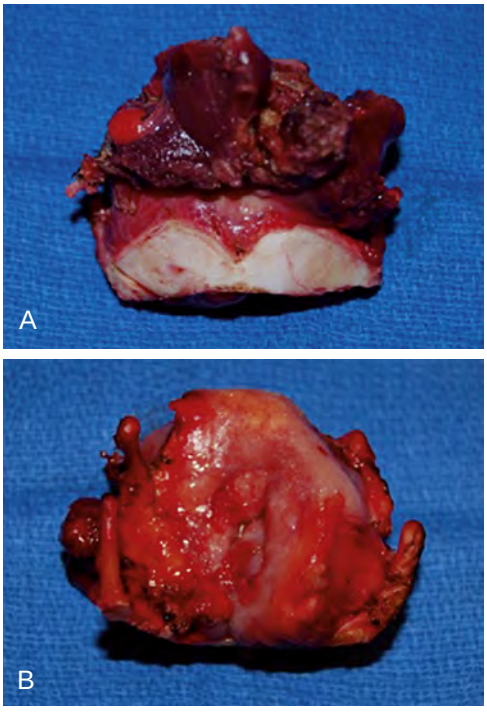


• **Fig 40.1** Laser assisted endoscopic supraglottic laryngectomy. Intraoperative view from **A,** before and **B,** immediately after the resection. Although a significant portion of the supraglottis can be removed endoscopically, resection of the thyroid cartilage is not typically performed during this procedure. (Courtesy Joshua Schindler.)

The surface of the thyroid cartilage is exposed, perichondrium is elevated off, and a transverse incision is made in the superior one third of the cartilage. The hypopharynx is entered through the pyriform sinus and the cut is extended into the vallecula. The line of resection transects the aryepiglottic fold just anterior to the arytenoid on the uninvolved side and extends through the ventricle (Fig. 40.2). The mucosal cuts can then be made with direct visualization of the tumor. The anterior spine of the thyroid cartilage can be split to improve the view of the involved side.[18] Once the supraglottic larynx has been removed, the perichondrium can be sutured to the base of tongue to close the defect.

Weinstein and colleagues first described the feasibility of supraglottic partial laryngectomy (SPL) using transoral robotic surgery (TORS).[19] Since then, multiple studies have shown that it is a safe and sound oncologic approach in select patients.[20,21] Park and colleagues performed a prospective case study of 16 patients with supraglottic SCC who were treated with TORS supraglottic laryngectomy. Seven patients had T1 tumors, five had T2, and four had T3. These researchers described superior visualization and the improved ability to remove supraglottic tumors and preepiglottic fat as advantages over TLM. Negative margins were obtained in 88% of patients, and disease-free survival was 91% at 1 year.[21]

Chun and colleagues compared the efficacy of different treatment modalities for supraglottic cancer.[22] They retrospectively examined 48 patients who were treated with SPL and 20 who were treated with radiotherapy. Patients with N+ disease who received SPL also were treated with neck dissection(s). In stage III and IV disease, 5-year disease-free survival rates were



• **Fig 40.2** Supraglottic laryngectomy. **A,** Antero-inferior and **B,** postero-superior views of the specimen from open supraglottic laryngectomy. Note that the thyroid cartilage has been transected above the level of the glottis. (Courtesy Joshua Schindler.)

estimated at 85% in SPL and 52% in the radiation treatment group (P = .338), and 5-year overall survival rates were 83% and 61% for SPL and radiation treatment groups, respectively (P = .058). Functional outcomes of swallowing and phonation measured by fiber-optic endoscopic evaluation of swallowing (FEES) and videostroboscopy were also measured, and no significant differences were noted between groups.

Supracricoid Laryngectomy

Supracricoid partial laryngectomy combines the supraglottic laryngectomy with removal of one or both vocal folds and thyroid cartilage. The operation is based on the concept that the cricoarytenoid unit is the functional anatomic unit of the larynx. As long as one cricoarytenoid unit and the cricoid cartilage are left intact and functional, the operation can be a success. It allows for clearing of the entire preepiglottic and paraglottic spaces. Because the vocal folds are removed, this procedure can be performed on immobile cords. Contraindications include fixation of the cricoarytenoid joint, invasion of cricoid cartilage, subglottic extension, posterior commissure involvement, and tumor extension through outer perichondrium of thyroid cartilage.[17] Again, this procedure requires a patient with good cardiopulmonary reserve because postoperative aspiration will occur. A temporary tracheotomy is performed for postoperative pulmonary toilet.

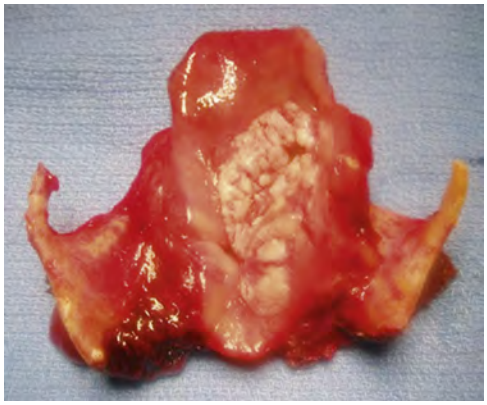
The type of reconstruction needed will depend on the extent of the tumor. If the tumor is confined to the glottis, a cricohyoidoepiglottopexy (CHEP) can be performed, leaving an epiglottic remnant. If the tumor is transglottic and extends into the supraglottis, then a cricohyoidopexy (CHP) will be necessary. The cricothyroid membrane is incised as the inferior extent of the resection, and the superior incision will be just above thyroid cartilage for a CHEP and just below the hyoid for a CHP. The procedure is begun on the less involved side just anterior to the arytenoid cartilage, connecting with the cricothyrotomy[17] (Fig. 40.3).

Naudo and colleagues performed a retrospective review of 124 patients who underwent supracricoid partial laryngectomy with CHP for laryngeal SCC.[23] The postoperative mortality was 1.6% with a mean duration of follow-up of 7 years. All but 1 patient were decannulated. Completion total laryngectomy and permanent gastrostomy were required in 2.5% and 2.5% of patients, respectively. This study and others highlight the critical importance of a speech-language pathologist to maximize functional outcome.

Supracricoid partial laryngectomy also has a role for salvage surgery after radiation failure in well-selected patients treated initially for T1 and T2 disease. Holsinger and colleagues reviewed 32 patients who underwent supracricoid partial laryngectomy for salvage and found that the rates of locoregional recurrence and disease-free interval were similar to those after total laryngectomy.[24] Marioni and colleagues performed a meta-analysis of 103 cases of radiation failure treated with salvage supracricoid partial laryngectomy and found a locoregional recurrence rate of 15.5%, with 66% of those failures later salvaged with total laryngectomy.[25]

Total Laryngectomy

The first total laryngectomy for cancer was performed by Billroth on December 31, 1873.[26] The surgical technique has since been revised but remains the gold standard for treatment of cancer of the larynx. A total laryngectomy refers to en bloc resection of the entire larynx including the hyoid, thyroid, and cricoid cartilages, down to the tracheal rings (Fig. 40.4). In cases at high risk for thyroid invasion, such as subglottic tumors or subglottic extension of glottic tumors, the thyroid isthmus is divided and the ipsilateral thyroid gland and paratracheal nodes are taken with the specimen.[27] The pharynx and/or base of the tongue can also be taken if involved with tumor. After removal, the proximal trachea then is sutured to the skin to create a permanent tracheostoma.[28]



• **Fig 40.3** Supracricoid laryngectomy. View of resected specimen from a patient with a T3 tumor involving the preepiglottic space. The entire thyroid cartilage is removed during this procedure. The epiglottis may or may not be removed; removal of the epiglottis allows for the entire preepiglottic space to be resected with this procedure. The cricoid cartilage is left in situ with either one or both arytenoids and the associated innervated musculature. (Courtesy Joshua Schindler.)



• **Fig 40.4** Total laryngectomy. View of resected specimen from a patient with a submucosal tumor of the cricoid region. Total laryngectomy includes resection of the hyoid, thyroid, and cricoid cartilages. (Courtesy Joshua Schindler.)

The pharyngotomy can be made through either the vallecula or the contralateral pyriform sinus, depending on the location of the tumor as assessed by direct laryngoscopy. Care must be taken to ensure clear margins around the tumor while still trying to preserve the maximum amount of pharyngeal mucosa. A complete cricopharyngeal myotomy is performed by sharply incising the muscle to improve postoperative deglutition and alaryngeal voicing. If a nasogastric tube is to be placed, it can be done at this time before closing the pharynx. If planned, a tracheoesophageal prosthesis can be placed at this time through the posterior tracheal wall. The clavicular heads of the sternocleidomastoid are sectioned so the stoma sits more superficially, permitting easier finger occlusion and stoma management. Options for closure of the pharynx include primary closure, primary closure with overlay of vascularized flap, or interposition of vascularized flap. Primary closure uses a running inverted suture to close the pharyngeal mucosa and can be done in a vertical, horizontal, or T fashion. Vascularized flaps for interposition or overlay can be either a pectoralis major rotational flap or a free tissue transfer with radial forearm.

Neck Dissection

As mentioned previously, the lymphatic spread of each laryngeal subsite must be considered to determine the necessity of treating the neck. The glottic larynx has poor lymphatic supply and therefore cervical metastases from isolated glottic tumors are unlikely. In contrast, the supraglottic larynx has a rich lymphatic supply and has a tendency to spread to bilateral cervical lymph nodes. However, once glottic tumors grow into the supraglottis, bilateral lymphatic spread can occur. Shah showed that the nodal basins at greatest risk of involvement from laryngeal SCC are levels II–IV and level VI.[29] The risk of occult metastases from advanced laryngeal SCC is 30%.[30] Therefore an N0 or N1 neck should be treated with either radiation or neck dissection, depending on and staying consistent with the treatment of the primary tumor. If a patient is treated with chemoradiation, however, a neck dissection should be performed for incomplete clinical response. Multimodality treatment with both surgery and radiotherapy should be used for N2 or N3 disease.[31] For salvage surgery, the risk of occult metastases is low and neck dissection should be dictated by clinical findings.

Complications

Complications seen in the early postoperative period after laryngectomy include bleeding, hematoma, wound breakdown, infection, and pharyngocutaneous fistula. Hematoma requires opening the wound and addressing the source of bleeding. Infection is treated with antibiotics and possible opening and packing of the wound. Pharyngocutaneous fistula is a troublesome complication resulting from breakdown of the pharyngeal closure whereby pharyngeal contents leak out the skin of the neck. Published results on incidence of fistula vary greatly, from 3–65%. A meta-analysis performed by Paydarfar and colleagues[32] found that preoperative radiotherapy was associated with an increased rate of fistula formation. Because of the increased risk of fistula in salvage laryngectomy, Patel and colleagues[33] compared pharyngeal closure technique in a multi-institutional retrospective review and found that the incidence of fistula was significantly decreased with pectoralis major onlay over the pharyngeal suture line (15% incidence) and interposed free tissue transfer (25% incidence) compared with primary closure (34% incidence). A fistula is treated conservatively initially with antibiotics, nothing by mouth (NPO) status, and wound packing. If conservative management fails to heal the wound, then surgical reconstruction is required, often with the use of a vascularized tissue flap.

In the late postoperative period, complications include pharyngeal stricture, stomal stricture, and hypothyroidism. Performing a cricopharyngeal myotomy at the time of surgery improves postoperative deglutition but a stricture may still develop, leading to dysphagia and difficulty with tracheoesophageal speech. Patients may require periodic dilations of esophageal strictures in the late postoperative course. Stomal stenosis can often be avoided with proper surgical technique during creation of the tracheostoma, taking care to create a large stoma and obtain wound edge eversion. Hypothyroidism can result from radiation or thyroidectomy, and therefore thyroid hormone levels should be monitored regularly in the postoperative setting.

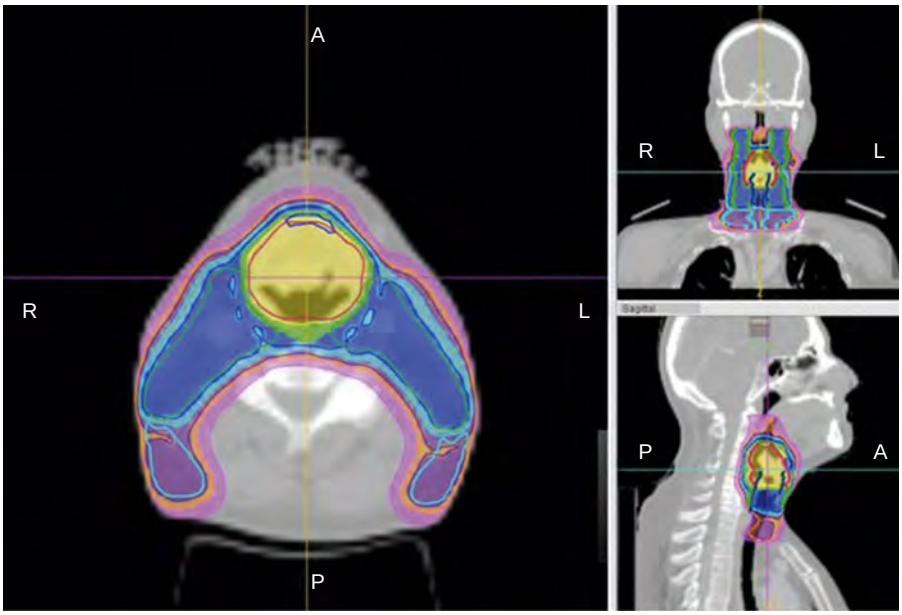
Radiation

Radiotherapy Planning and Techniques

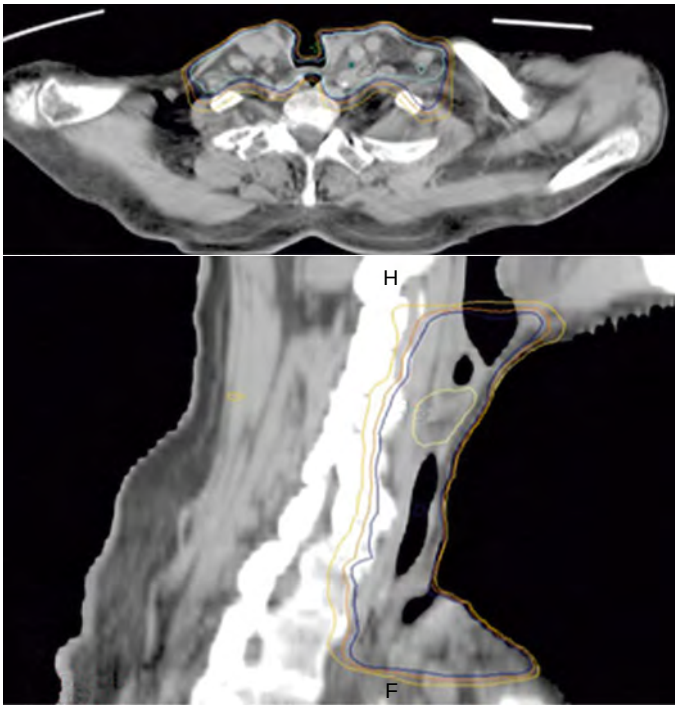
The logistics of radiotherapy planning and treatment are quite detailed. Please refer to Chapter 39 for a detailed flow diagram that outlines the general logistics and treatment planning and delivery paradigm.

Although intensity-modulated radiotherapy (IMRT) has reduced long-term toxicity in oropharyngeal, nasopharyngeal, and paranasal sinus cancers, the use in advanced laryngeal cancer can still be debated and is used under the direction of the treating physician. IMRT has been shown to reduce the dose to the salivary glands, temporal lobes, cochlea, and optic apparatus[34] and therefore is considered the optimal technique when radiation treatment volumes abut these structures. Fig 40.5 shows an IMRT plan for a patient with a cT3N0 glottic SCC with treatment of the primary tumor to 70 Gy in 35 fractions, also with coverage of elective nodal volumes. It can be seen on the coronal view in Fig 40.5 that the inferior portion of the parotid glands will abut the treatment field and could benefit from the use of IMRT. Also, a recent meta-analysis of five prospective phase III randomized controlled trials comparing IMRT with two-dimensional radiotherapy or three-dimensional conformal radiotherapy (3D-CRT) showed that IMRT use reduced the incidence of grade 2–4 xerostomia without compromising locoregional control or overall survival.[35]

In the postoperative setting, peristomal tissues require special attention. Salvage of stomal recurrence is challenging owing to the adjacent vessels and airway. The key to therapy is to prevent recurrence by adequate coverage of the peristomal tissues.[36] Patients requiring emergent tracheostomy, tumors with greater than 5 mm subglottic extension, tumors with significant invasion of soft tissues of the neck, extranodal extension in level VI, or tumors resected with



• **Fig 40.5** Treatment plan of a man with cT3N0 squamous cell carcinoma of the glottic larynx treated with definitive chemoradiotherapy to 70 Gy in 35 fractions. The primary volume treated to 70 Gy is in yellow, the high-risk nodes in blue, and the low-risk nodes in pink. The entire treatment was delivered over 35 fractions, with the yellow, blue, and pink volumes treated at 2, 1.8, and 1.6 Gy per day, respectively.



• **Fig 40.6** Treatment plan of a patient with pT4N1 squamous cell carcinoma of the larynx. The sagittal cut is provided for further clarification of the dose distribution around the peristomal tissue.

close or positive margins are thought to be at high risk for stromal recurrence. Fig 40.6 shows a postoperative radiotherapy plan.

Patient Setup

As part of the radiotherapy planning session, patients initially undergo simulation consisting of head and neck immobilization and imaging, usually with CT. A typical treatment setup for advanced laryngeal cancer would include immobilization with a thermoplastic face mask (see Fig. 13.6) and shoulder retractors (a device to immobilize the shoulders and push them inferiorly to minimize shoulder obstruction in the treatment of the low neck). After the face mask is constructed, a contrast-enhanced CT scan is obtained. The simulation CT images may be fused with scans obtained with other imaging modalities, such as MRI or PET, to better aid in delineation of target and/or organ at risk.

Image-Guided Radiation Therapy

Image-guided radiation therapy (IGRT) is the process of performing imaging before daily radiotherapy, with the intent of improving target accuracy and precision by correcting for geometric and anatomic deviations. IGRT techniques consist of planar or volumetric imaging, which allows for tighter treatment margins. This improved precision leads to more accurate radiotherapy to tumors and less morbidity by sparing more normal tissue. A valuable and frequently used pretreatment imaging modality used in head and neck radiotherapy is cone-beam computed tomography (CBCT). CBCT is a type of volumetric imaging that has been integrated into treatment linear accelerators, which allow final adjustments to be made to patient position before treatment, ensuring accurate and precise radiation targeting.[37]

Adaptive Radiotherapy

Adaptive radiotherapy (ART) for head and neck cancer is an emerging tool to counter morphologic changes in patient and tumor anatomy during a course of radiotherapy by creating new radiation plans during the course of treatment. ART for head and neck cancer has been shown to decrease the dose to

the mandible and the mean dose to the parotid glands and larynx in all head and neck cancer patients.[38] The two most common causes of anatomic change prompting ART are excessive weight loss secondary to treatment side effects and tumor shrinkage from response to therapy.[39,40] When treating advanced laryngeal cancer, significant weight loss or dramatic shrinkage of malignant adenopathy may lead one to consider ART.

Morbidity

Acute side effects include hoarseness, skin irritation or burns, mucositis with dysphagia or odynophagia, dysgeusia, and xerostomia. Long-term risks include laryngeal edema, dysphagia and chronic aspiration, and hypothyroidism Patients may require feeding tubes before, during, and after completion of chemoradiotherapy, as well as the occasional temporary tracheostomy before or during treatment to manage symptoms from the tumor and radiotherapy. Feeding tubes and tracheostomy can be required long term after chemoradiation. In fact, the term *laryngoesophageal dysfunction–free survival* (LODFS) has been developed to describe patients who have no evidence of cancer but also do not need a tracheostomy or feeding tube long term.

As with other head and neck cancer sites, patients with advanced-stage laryngeal cancer receiving radiotherapy require diligent nursing and provider care during and shortly after the course of treatment to provide symptom management and support. Chronic changes in the neck muscles causing fibrosis, limited range of neck motion, and muscle spasms can also be seen long term.[41] The mandible and hyoid may also receive significant radiation dose when upper neck lymph nodes are involved, increasing the risk of osteoradionecrosis; however, this is rarely seen in radiation doses of less than 50 Gy.[42–44]

Chemotherapy

As introduced previously, the Veterans Affairs laryngeal study first evaluated induction chemotherapy as a means to select patients with advanced laryngeal cancer who could be treated successfully with larynx-preserving radiation.[9] This study examined 332 patients with stage III/IV laryngeal cancer stratified by response to two cycles of induction cisplatin (100 mg/m^2 on day 1) and fluorouracil (1000 mg/m^2 on days 1–5) chemotherapy. Patients with at least a partial response received one more cycle of chemotherapy followed by definitive radiation. Non-responders after two cycles of induction chemotherapy received laryngectomy followed by postoperative radiation. Most of the patients in this study (85%) had a response to chemotherapy (31% complete, 54% partial) and received the third cycle of chemotherapy followed by radiation. The larynx was preserved in 64% of the enrolled patients. At 2 years, there was no difference in the overall survival in the patients who had received radiation or laryngectomy—68% in each arm.

The Veterans Affairs larynx trial was followed by a phase III randomized trial, RTOG 91-11, to address induction versus concurrent chemotherapy with radiotherapy for organ preservation. Patients with advanced larynx cancer were randomized to one of three arms: induction cisplatin and fluorouracil as per the Veterans Affairs larynx trial; concurrent radiation and cisplatin 100 mg/m^2 on days 1, 22, and 43; or radiation alone.[10] Patients with T4 disease (penetrating through the cartilage or with more than 1 cm base of tongue invasion) were excluded. With a median follow-up of 3.8 years, laryngeal preservation rates for the concurrent, induction, and radiation-alone arms were 84%, 72%, and 67% respectively. At 5 years, the overall survival was not significantly better in any of the arms: 54–56%. Long-term results at 10 years confirmed that concurrent cisplatin and radiation continues to provide the highest locoregional control and laryngeal preservation rates.[45]

The European TREMPLIN study (Radiotherapy With Cisplatin Versus Radiotherapy With Cetuximab After Induction Chemotherapy for Larynx Preservation) used a different induction strategy for laryngeal preservation, with three cycles of docetaxel and cisplatin (75 mg/m^2 each on day 1) and fluorouracil (750 mg/m^2 on day 1–5). As with the Veterans Affairs trial, patients not achieving at least a partial response underwent laryngectomy. Responders were then randomized to radiation with concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 or concurrent cetuximab 400 mg/m^2 loading dose followed by 250 mg/m^2 per week during radiotherapy.[46] This study showed no significant difference in laryngeal preservation or overall survival. There were fewer overall local failures in the cisplatin arm, but salvage surgery was possible only in the cetuximab arm owing to increased cervical fibrosis seen with concurrent radiation and cisplatin.

Two phase III randomized clinical trials were run simultaneously to evaluate the effect of chemotherapy in the adjuvant setting. Both studies compared the addition of high-dose cisplatin to radiotherapy versus radiotherapy alone after surgery in patients with HNSCC. In the U.S. study RTOG 95-01, 231 patients were randomized to receive radiotherapy alone (60–66 Gy) as adjuvant therapy after surgery for curative intent, and 228 patients were randomized to receive the same therapy plus concurrent cisplatin (100 mg/m^2 on days 1, 22, and 43). After a median follow-up period of 45.9 months, local and regional control was significantly higher in the concomitant chemoradiotherapy group than in the radiation-alone group ($P = .01$).[47] The European study EORTC 22931 (European Organisation for Research and Treatment of Cancer) randomized 167 patients to radiotherapy alone after resection of all visible disease and 167 patients to the same radiotherapy plus concurrent cisplatin. After a median follow-up period of 60 months, the rate of progression-free survival was significantly higher in the combined-therapy group ($P = .04$).[48] Both trials were designed similarly yet had different primary end-points and definitions of "high risk." Therefore a comparative analysis was performed using pooled data from these two trials to determine precisely which patients were most suitable for such intense treatment. The analysis found that the two risk factors for which chemotherapy-enhanced radiation therapy significantly improved outcomes were extracapsular extension and microscopically involved surgical margins.[49]

Patients with recurrent or metastatic head and neck cancer may require chemotherapy as a first-line therapy when surgery

is no longer a viable treatment option. The EXTREME trial (Erbitux in First-Line Treatment of Recurrent or Metastatic Head and Neck Cancer) included 442 patients who were randomized to receive either chemotherapy alone (cisplatin 100 mg/m^2 or carboplatin 5 mg/mL per minute on day 1 followed by 5-FU 1000 mg/m^2 per day for 4 days) or the same chemotherapy regimen combined with weekly cetuximab (loading dose 400 mg/m^2 followed by weekly doses of 250 mg/m^2).[50] Cycles were repeated every 3 weeks for a maximum of six cycles. Patients in the combined arm with stable disease then continued to receive cetuximab until the occurrence of disease progression or unacceptable toxic effects, whichever occurred first. Patients who received a combination of cetuximab with platinum/5-FU benefitted from a significantly increased median overall survival of 10.1 months compared with 7.4 months for the chemotherapy alone group ($P = .04$). The median progression-free survival was also significantly extended from 3.3 to 5.6 months ($P < .001$), and response rate increased from 20% to 36% (P .001). The added benefit was seen in the patients treated with cisplatin/5-FU with cetuximab as well as carboplatin/5-FU with cetuximab. The most common adverse events were anemia, neutropenia, and thrombocytopenia, which were seen in both arms of the study, although sepsis occurred in nine patients in the combined cetuximab group and one patient in the chemotherapy-alone group.

Rehabilitation

Because the larynx is a critical structure in the functions of voice, swallowing, and breathing, patients who are treated for advanced laryngeal cancer will experience a change in some or all of these abilities. Changes in voice will be most dramatic for those who undergo total laryngectomy. Three options for postlaryngectomy voice restoration include an artificial or mechanical larynx, esophageal speech, and tracheoesophageal puncture (TEP) speech. An artificial larynx is a handheld device that is pressed against the neck and creates vibrations that make sound while the patient moves his or her mouth to create speech. It is a skill that can be rapidly learned by most users and allows loud speech, but the device can be expensive, relies on batteries, and requires use of hands. Esophageal speech involves ingesting air into the esophagus and then expelling it into the pharyngoesophageal segment, which will vibrate to produce sound. Although this method allows hands-free communication, the sound produced has an unusual low pitch and guttural quality, phrases must be short, and it is a difficult technique to master.

TEP speech has become the standard for postlaryngectomy speech. A tracheoesophageal prosthesis is a one-way valve that is placed in a surgically created tracheoesophageal fistula. The fistula can be safely created either at the time of initial surgery or as a secondary procedure weeks later.[51] TEP speech is performed by exhaling tracheal air into the pharynx via the prosthesis, which causes the pharynx to vibrate and produce sound. Once the airflow stops, the valve closes to prevent leakage through the TEP and potential aspiration. TEP speech permits natural phrasing and a more acoustically normal sound, as well as the potential for hands-free speech with certain adaptors. Complications include leaking prostheses, aspiration, formation of granulation tissue, and inability to achieve successful speech. Leakage can occur as a result of incorrect sizing, enlargement of the fistula, or failure of the prosthesis. The device is prone to *Candida* colonization, which can lead to premature failure if not treated with oral antifungals when diagnosed. Patients must have a correctly sized stoma and adequate manual dexterity to use effectively and should work with a speech pathologist to maximize communication outcomes.[52]

Dysphagia after treatment of laryngeal cancer is common and multifactorial, with reports of postoperative dysphagia after total laryngectomy as high as 72%.[53] If the patient is undergoing surgery, a feeding tube is placed through the nose, a tracheoesophageal fistula, or the abdomen at the time of surgery. Initiation of an oral diet is usually delayed for 7 days because of concern for development of pharyngocutaneous fistula, sometimes longer for salvage surgery, depending on surgeon preference. Long-term changes in dietary habits are reported in 25–50% of patients undergoing laryngectomy. Dysphagia that persists once the primary healing from the surgery is complete should be investigated with a modified barium swallow study (MBSS). Anatomic abnormalities such as strictures can be seen on MBSS and treated appropriately with dilation. In partial laryngectomy techniques such as supraglottic and supracricoid procedures, aspiration can be frequent, with a reported incidence as high as 94%.[54] Involvement of a speech pathologist who is familiar with laryngectomy is paramount to optimize dysphagia rehabilitation. With total laryngectomy, aspiration is uncommon unless leakage occurs around or through a tracheoesophageal fistula.

Surveillance

Surveillance for advanced laryngeal cancer is similar to that for cancer of other head and neck sites. NCCN guidelines recommend a complete history and physical examination every 1–3 months for the first year, every 2–6 months during the second year, every 4–8 months during years 3–5, and annually after 5 years.[14] Recurrence after total laryngectomy is often discovered during these follow-up examinations. In a retrospective study of 259 patients who underwent total laryngectomy, 80 patients (30.9%) developed a recurrence of their cancer. Locoregional and stomal recurrence occurred in nearly 60%, and distant metastases were seen in 25%. The mean interval between surgery and the diagnosis of recurrence was 11.6 months, and 90% of recurrences were discovered within 2 years. No difference was found in the disease-free interval between those undergoing salvage surgery and the patients with primary laryngectomy.[55] Other studies have reported the 5-year overall survival rates for T3N0M0 glottic SCC treated with total laryngectomy as 54%[56] and 39% for stage IV disease. The overall recurrence rate for stage IV disease was 39%, with locoregional recurrence in 36%.[57]

Patients with a history of laryngeal cancer surgery and radiation are at significant risk for hypothyroidism and should have their serum thyroid-stimulating hormone (TSH) checked at 6-month intervals for the first 5 years, then annually after.[58]

Chest imaging, looking for either distant metastases or metachronous primary, has traditionally been performed with annual chest radiography. However, the usefulness of post-treatment screening with chest x-ray examination is questionable because it does not seem to improve survival in patients who develop lung cancer.[59] Studies have shown that chest CT is a more sensitive test than chest radiography for detecting pulmonary disease, and therefore some authors recommend surveillance chest CT instead of x-ray studies, although again, no survival benefits have been shown.[60]

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Subglottic Larynx Cancer

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Although the subglottis is frequently involved by direct extension of supraglottic and glottis carcinomas, true subglottic carcinoma is a relatively rare entity. In contemporary series, it represents only 0.2–1.8% of all laryngeal malignancies.[1–5] As with cancers of other laryngeal subsites, it typically is seen in older male patients, in the seventh decade of life. Tobacco and alcohol use are the major risk factors for development of subglottic carcinomas.[6] Patients with early-stage disease tend to have hoarseness, whereas airway obstruction is the most common presenting sign in patients with late-stage disease. Symptoms may also include voice changes, shortness of breath, hemoptysis, or cough.[6] Squamous cell carcinoma is the most common pathology, followed by adenoid cystic carcinoma and chondrosarcoma. Neuroendocrine carcinomas, lymphoma, and undifferentiated carcinoma may also occur in this location. As a result of its rarity and location, subglottic carcinoma presents unique diagnostic and therapeutic challenges.

Pertinent Anatomy

The subglottis is the often-neglected inferior subdivision of the larynx, important in a number of conditions including iatrogenic injury, congenital malformations, idiopathic stenosis, laryngeal trauma, and malignant neoplasms.

The most current American Joint Committee on Cancer (AJCC) staging guidelines describe the superior border of the subglottis as 1 cm below the apex of the laryngeal ventricle.[7] This location approximates the histologic transition from stratified squamous epithelium of the glottis to respiratory epithelium of the distal respiratory tract. The location of this transition varies from 5 to 10 mm inferior to the free edge of the vocal fold and may be reduced to 1 mm at the anterior commissure. In the subglottis, folded layers of respiratory epithelium overlie a submucosal loose connective tissue layer. The submucosa contains collagen fibers that fuse with the conus elasticus caudally, and radiate cranially through excretory ducts toward the stratified squamous epithelium.[8] Laterally, the subglottis is bounded by the fibroelastic conus elasticus cranially, and the cricoid cartilage caudally. The anterior border is composed of the inferior rim of the thyroid cartilage cranially, the anterior arch of the cricoid cartilage caudally, and the cricothyroid membrane in the central portion. The cricoid lamina bounds the subglottis posteriorly, and the inferior border of the subglottis is located at the inferior rim of the cricoid cartilage.

The development of squamous cell carcinoma isolated to the subglottis has been proposed to occur after squamous metaplasia of the pseudostratified epithelium, or arise from the stratified squamous epithelium found in the excretory ducts of the submucosal glands. When tumors occur at the transition zone of the glottis and subglottis, lesions are designated as subglottic if more than 50% of the tumor is situated inferior to this line.

Subglottic carcinomas spread most commonly via direct extension, and infrequently through vascular or perineural spread. Submucosal spread is a common feature, as is circumferential intraluminal spread.[9] Cartilaginous involvement has been noted in up to 50% of studies of resected subglottic carcinomas.[10,11] This finding has been corroborated by radiographic findings in the series of Saleh and colleagues.[12] The conus elasticus, cricothyroid, cricotracheal, and intratracheal membranes resist the spread of cancer in only the earliest stage lesions. Networks of blood vessels traverse these membranes, connecting the subglottic submucosa to the pre-laryngotracheal space. Once a cancer reaches the adipose tissue anterior to the subglottis, it faces an unobstructed pathway for direct spread into the thyroid gland and the paraglottic and preepiglottic spaces. Impaired movement of the vocal cord indicates deep invasion through the conus elasticus and into the intrinsic muscles of the larynx.

The lymphatic drainage of the subglottis is to the pretracheal, paratracheal, and inferior jugular nodes through the cricothyroid and cricotracheal membranes, as well as the upper mediastinal lymph nodes as described in Welsh's 1964 radioisotope studies.[13] An anterior lymphatic pedicle penetrates the cricothyroid membrane, draining to the prelaryngeal and delphian nodes. Two posterior-lateral pedicles penetrate the cricothyroid membrane, ultimately draining to the paratracheal and superior mediastinal nodes.[13]

Staging

Accurate staging of subglottic carcinoma requires a thorough description of the size and extent of the primary tumor, assessment of cervical lymph node involvement, and determination

of the presence or absence of distant metastasis. Local extent is first assessed through physical examination. Direct palpation of the larynx and lower neck may help to determine cartilaginous involvement or destruction by the tumor, as well as more advanced local spread. In-office fiber-optic examination is the mainstay of the physical examination and may be facilitated by anesthetization of the vocal cords with topical lidocaine to allow for closer inspection of the subglottis and proximal trachea. However, limitations of in-office examination may result in underestimation of the size and extent of subglottic lesions. Direct endoscopic examination under anesthesia in the operating room facilitates a more thorough and accurate assessment, as well as the procurement of tissue for pathologic diagnosis.

The second major contributor to staging involves imaging studies. Computed tomography (CT) with contrast and thin cuts through the larynx is recommended for assessment of the inferior extent of the disease, cartilage invasion, paraglottic space or prelaryngeal soft tissue involvement, and involvement of the paratracheal, jugular chain, and mediastinal lymph nodes. Magnetic resonance imaging (MRI) may be complementary to CT scan or used in place of CT to assess cartilage invasion, extralaryngeal soft tissue spread, or involvement of the carotid or prevertebral space. Chest imaging is also required to assess for distant metastases. Current National Comprehensive Cancer Network (NCCN) guidelines state that the minimum necessary imaging is a chest radiograph, which may be sufficient for limited early-stage cancers. However, most practitioners use at least a chest CT scan to determine the presence of pulmonary metastasis. Alternatively, positron emission tomography–computed tomography (PET-CT) can be considered in stage III–IV disease to further evaluate for distant metastatic spread.

Clinical staging is determined on the basis of physical examination and radiographic findings, and is designated by the TNM classification. Information from the eighth edition of the AJCC Cancer Staging Manual[7] is shown in Fig. 41.1 and Table 41.1.

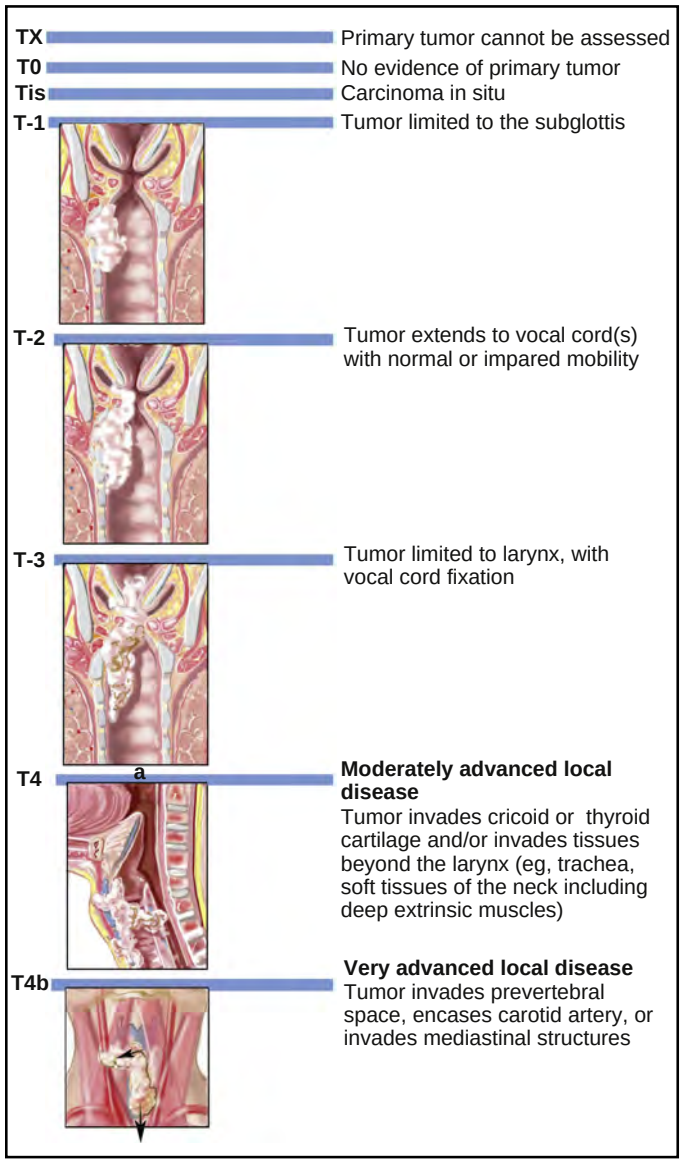
The most common stage at presentation varies by report. Given that early-stage lesions are often asymptomatic, in the past most patients with subglottic carcinoma have had late-stage disease at presentation. Of 212 patients included in nine contemporary series of subglottic carcinoma,[1–6,14–16] 45% presented at an early stage (I or II), whereas 55% presented at a late stage (III or IV) (Table 41.2).

The propensity for nodal metastasis is also a matter of debate. The incidence has been reported to be between 0% and 33% (see Table 41.2). Of the 163 patients in whom data regarding nodal staging were available in modern series, 13% had reported nodal involvement.[1–6,14–16] The incidence of occult paratracheal and mediastinal nodal involvement also remains unresolved.

Historically, cancers of the subglottis were considered to carry a poor prognosis relative to other laryngeal subsites. Overall survival is reportedly 44–77%,[2,14] and disease-free survival 46.2–68.6% at 5 years[1,4] (Table 41.3). Distant metastatic disease at the time of presentation is uncommon in all but one series.[5] The eventual development of metastatic disease is reported to occur in 15.4–32% of cases.[1,17] In patients who developed distant metastatic disease, the average time from initial presentation to discovery of metastases was 16 months.[15] Lung, bone, and mediastinum are the most common locations for metastases. Recurrence is most often local, seen in 33.3–38.5% of patients, and can occur in patients with both early- and late-stage disease.

Management Principles

In principle, treatment for subglottic carcinoma is tailored to the stage of the disease, with a focus on maximizing local control while maximizing quality of life. In practice, management remains controversial and varies by institution; no large-scale studies comparing treatments have been conducted. Conflicting case series have demonstrated the superiority of a primary surgical approach, whereas others espouse the efficacy of radiotherapy alone, with surgery reserved for salvage treatment.



• **Fig. 41.1** Staging guide for subglottic cancer.

Given the poor overall rate of survival and the propensity for subglottic tumors to recur locally, treatment of subglottic carcinomas is often more aggressive when compared with treatment of similarly staged cancers of other locations in the larynx.[1–6,9,12,14–21]

Treatment for early-stage disease typically involves either definitive radiotherapy or concurrent chemoradiation. Radiation therapy alone is often preferred as it may allow for preservation of normal voice and swallowing function, though rates of long term tracheostomy or feeding tube dependence are not reported in published series[1–6,9,12,14–21]

Advanced-stage disease can be treated either with concurrent radiation and chemotherapy or with surgery followed by postoperative radiation without or without chemotherapy. Surgery is preferred for advanced-stage, large-volume disease; patients who cannot be easily assessed for radiation therapy; or patients who have persistent or recurrent disease after primary radiation.

TABLE 41.1 American Joint Committee on Cancer (AJCC) Staging of Subglottic Carcinoma

Tx	Primary tumor cannot be assessed
Tis	Carcinoma in situ
T1	Tumor limited to the subglottis
T2	Tumor extends to the vocal cord(s) with normal or impaired mobility
T3	Tumor limited to the larynx with vocal cord fixation
T4a	Moderately advanced disease Tumor invades cricoid or thyroid cartilage and/or invades beyond the larynx (e.g., tracheal, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

From Amin MB, et al, eds. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

Surgical Management

Management of the airway is a key component of treatment of subglottic carcinoma. Tracheotomy is indicated for airway obstruction and should proceed as a planned procedure if airway compromise is noted at the time of initial evaluation. Awake fiber-optic intubation or awake tracheostomy is frequently necessary to secure the airway in such patients.

In general, surgical treatment of primary subglottic carcinoma is aggressive and must take into consideration the likelihood for extralaryngeal spread and the unique pattern of lymphatic drainage. Historically, lesions were excised by a total laryngectomy, total thyroidectomy (with or without autotransplantation of the parathyroid glands), and ipsilateral or bilateral neck, paratracheal, and superior mediastinal lymph node dissection.[19] Those who believed that likelihood of cervical lymph node metastasis was low did not recommend elective dissection of first-echelon lymph nodes in the absence of clinically evident lymphadenopathy. Contemporary management guidelines consistently call for treatment of the neck when clinically or radiographically evident lymph node involvement is present.

Management of the Primary

Transoral resection has gained popularity for early-stage lesions of the supraglottic and glottic larynx. However, this approach is typically not recommended for subglottic lesions. The subglottic larynx is much more difficult to expose transorally for adequate surgical access, and early-stage lesions are generally quite infrequent. In addition, open partial laryngectomy procedures, which are also used in supraglottic and glottic carcinomas, are not a viable option in cancers of the subglottis. These

TABLE 41.2 Series of Subglottic Carcinoma

Study	Patients	Mean Age (Range)	Incidence % (n)	Early Stage	Late Stage	Nodal
Dahm[1]	28	62.9	1.8% (39/2201)	67.9% (19/28)	32% (9/28)	21.4% (6/28)
Smee[3]	10	(55–89)	1% (10/969)	60% (6/10)	40% (4/10)	0% (0/10)
Santoro[16]	49	NR	NR	35% (17/49)	65%	NR
Strome[6]	10	NR	NR	(5/9)*	(4/9)*	10% (1/10)
Haylock[4]	23	67 (50–79)	8.7% (23/263)	57% (13/23)	43% (10/23)	4% (1/23)
Paisley[15]	43	NR	1.9% (55/2908)	53.5% (23/43)	46.5% (20/43)	2.3% (1/43)
Shaha[2]	16	60 (33–77)	1% (22/2108)	19% (3/16)	81% (13/16)	25% (4/16)
Garas[5]	15	(22–79)	1.4% (15/1098)	20% (3/15)	80% (12/15)	33% (5/15)
Cassidy[14]	18	NR	NR	33.3% (6/18)	66.7% (12/18)	16.7% (3/18)

*Numbers discordant with series N because staging information missing for one or more patients.
NR, not reported

TABLE 41.3 **Treatment and Outcome Summary of Subglottic Carcinoma Series**

Series	N	Treatment Modality	N	Treatment- Specific Local Control	Treatment-Specific DFS	Treatment-Specific OS	RT dose (Gy)/ Fractions	Overall Survival			Disease-Free Survival		
								2 yr	3 yr	5 yr	2 yr	3 yr	5 yr
Smee[3]	10	RT	4	90% (9/10)	—	—	56.25	NR	NR	NR	NR	NR	NR
		Surgery	1		—	—	—						
		Surgery + adj	5		—	—	55						
Dahm[1]	28	RT	10	4/10	22.2%, 5 yr	—	—	NR	NR	57.70%	NR	NR	46.20%
		Surgery	13	5/13	41.7%, 5 yr	—	—						
		Surgery + adj	5	—	100%, 5 yr	—	—						
Cassidy[14]	18	RT	12	—	—	—	74	NR	NR	44%	NR	NR	66%
		Surgery	*Early stage:* 5	100% (5/5)	—	—							
		Surgery + RT	*Late stage:* 7	71% (5/7)	—	—							
			—	—			—						
			6	—			58.3						
			Early stage: 1	100% (1/1)									
			Late stage: 5	80% (4/5)									
Paisley[15]	43	RT	30	*T1:* 63.6% (7/11)	—	—	50–52	NR	NR	50.30%	NR	NR	66.90%
		RT + salvage	13	*T2:* 66.7% (8/12)	—	—	—						
		Surgery	—	*T3:* 50% (4/8)	—	—	—						
		Surgery + adj	—	*T4:* 41.7% (5/12)	—	—	—						
				81%									
				—									
				—									
Shaha[2]	16	RT	—	—	—	—	—	NR	NR	77%	NR	NR	NR
		Surgery	16	11/15	—	—	—						
		Surgery + adj			—	—	—						
Haylock[4]	23	RT	21	16/23	69%, 2 yr	—	66 (2 Gy/day)	69%	NR	57.70%	68.60%	NR	68.60%
		RT + salvage	2	—	—	—	—						
		Surgery	—	—	—	—	—						
		Surgery + adj	—		—	—	—						
Garas[5]	15	RT	4	—	—	20%, 3 yr	—	NR	25%	NR	NR	NR	NR
		RT + salvage	2	—	—	0%, 3 yr	—						
		Surgery	3	—	—	33%, 3 yr	—						
		Surgery + adj	6	—	—	40%, 3 yr	—						
Santoro[16]	49	RT	6	—	0/6, 5 yr	0%, 5 yr	—	NR	NR	56%	NR	NR	NR
		Surgery	17	—	8/17, 5 yr	47%, 5 yr	—						
		Surgery + adj	18	—	15/18, 5 yr	83%, 5 yr	—						

NR, not reported; *RT,* radiotherapy; adj, adjuvant therapy (ie, radiation or chemoradiation)

procedures require the preservation of the cricoid cartilage in order to preserve laryngeal function. Resection of the cricoid cartilage, which would be required in most subglottic carcinomas, would render the larynx nonfunctional, thereby negating the usefulness of these procedures. Therefore, total laryngectomy remains the mainstay of surgical treatment.

Total laryngectomy for subglottic carcinoma is not infrequently a more extensive procedure than that performed for supraglottic and glottic carcinomas. Harrison noted that local failures are often the result of inadequate resection along the inferior extent of the tumor and advocated for the resection of additional rings of the trachea at the time of laryngectomy to increase local control.[19] Prior tracheostomy has also been reported to increase the likelihood of inadequate resection. Given the concern for adequate clearance of the inferior margin, a 2-cm inferior margin is often recommended. This may often entail resection of a significant portion of the cervical trachea, increasing the difficulty of cervical stoma creation. Additional maneuvers such as mediastinal release of the trachea or resection of the manubrium may be required to create a relatively tension-free tracheostoma.[20] Rates of thyroid involvement vary in the literature.[9,10,19] Given the propensity for extralaryngeal spread, recommendations range from isthmusectomy with or without ipsilateral hemithyroidectomy to total thyroidectomy. Authors do agree that the thyroid needs to be addressed if cartilage invasion or prelaryngeal spread is evident, which includes most T3 and T4 tumors. Gross involvement of the thyroid gland necessitates total thyroidectomy.

Management of the Neck

Bilateral paratracheal and prelaryngeal lymph node dissection is indicated in any patient treated by a primary surgical approach. Because elective neck dissection for an N0 neck has not been shown to improve survival, dissection of the jugular chain lymph nodes can be reserved for those patients with clinically positive lymph nodes. However, many surgeons elect to perform lateral neck dissection in the clinically N0 patient owing to the pathologic staging information this provides that may alter adjuvant therapy, as well as the relatively low morbidity involved when coupling a neck dissection with total laryngectomy. Neck dissection at the time of total laryngectomy is also a controversial topic, with some authors advocating for this while other studies concluding that it is unnecessary.[1–3,5,6] However, nearly all data pertaining to neck dissection at the time of total laryngectomy relate to supraglottic and glottic carcinoma; given the rarity of subglottic carcinoma in general, it is unlikely that this question will be answered in the near future. Thus, elective neck dissection at the time of salvage laryngectomy for subglottic carcinoma remains up to the discretion of the individual surgeon.

Reconstruction

Surgical treatment of subglottic carcinoma results in a range of laryngopharyngectomy defects that require closure to restore pharyngeal continuity and a mature stomal airway. Tension-free primary pharyngeal closure is preferred method of reconstruction for those patients with sufficient residual pharynx and no prior history of radiation. Pedicled or free tissue transfer or gastric pull-up may be necessary if sufficient pharynx is not present or in cases of total laryngopharyngectomy. The most common flaps employed are the pedicled pectoralis major, or supraclavicular island flap, and the anterolateral thigh and the radial forearm free flap, because they offer thin pliable paddles versatile as a patch or tubed conduit. Jejunal free flaps may also be used if a total laryngopharyngectomy defect is present. In patients undergoing salvage laryngectomy after radiation, reconstruction with tissue transfer has been demonstrated to decrease the incidence of postoperative pharyngocutaneous fistula,[21] and may decrease the rate of stenosis.

Considerations of voice rehabilitation in laryngectomized patients are similar to those for patients with supraglottic or glottic primaries, and are extensively covered in Chapter 17.

Outcomes

Overall survival and disease-free survival rates vary by series, and are summarized in Table 41.3. Surgery in combination with postoperative radiation appears to achieve higher rates of local control, disease-free survival, and overall survival than surgery alone.[1–3,5,16]

Radiation Therapy

General Principles

As with other locations in the head and neck, radiation is the mainstay of organ-sparing treatment for locally advanced carcinoma. The general principles, technique, and biology of radiotherapy are covered in Chapter 13.

When radiotherapy is used in the definitive setting for subglottic carcinoma, early-stage disease is treated much like early-stage glottis cancer to a dose of 63–65.25 Gy (2.25 Gy per fraction). Alternative plans have been proposed, such as a median dose of 56 Gy in 25 fractions over 40 days, designed to include the primary site and adjacent lymph node basin. Extending radiation fields to include the mediastinal lymph nodes has not been demonstrated to improve locoregional control and remains an area of controversy. Late-stage T3–T4 disease less than 3.5 cm^3 is treated with concomitant chemotherapy (weekly cisplatin 30 mg/m^2) and radiation to either 66–70 Gy (2–2.2 Gy per fraction daily), 72 Gy (1.8 Gy per fraction with 1.5 Gy per fraction boost for the last 12 treatments), or 81.6 Gy (1.2 Gy twice per day).[22,23] Although RTOG 91-11 included only stage III and IV glottic and supraglottic tumors, many radiation oncologists extrapolate and use concurrent chemoradiation in an attempt at organ preservation[23] for appropriate locoregionally advanced subglottic cancers. At our institution, patients receive 35 fractions of 2 Gy to 70 Gy with concurrent cisplatin 100 mg/m^2 on days 1, 22, and 43 of radiation. As in the treatment for glottic or supraglottic laryngeal cancer, T4 tumors with penetration through cartilage are less likely to benefit from organ preservation techniques,

and primary surgical alternatives should be considered, such as laryngectomy followed by radiation or chemoradiation, based on pathologic findings.

In 2002 Paisley published the findings from a series of 43 patients treated with definitive radiotherapy at Princess Margaret Hospital.[15] The most frequent regimen was 50–52 Gy in 20 fractions over 4 weeks. Fields were designed in a lateral oblique approach, angled caudally. Treatment fields were designed to include the primary tumor and the first echelon nodes. The median field size was 96 cm^3 extended from above the hyoid superiorly, posteriorly to the vertebral body, anteriorly to the skin, and inferiorly below the known disease with an additional margin.

The contemporary series by Cassidy and colleagues in 2012 delivered an average dose of 74 Gy in the definitive setting; those treated with adjuvant radiotherapy received 58.3 Gy.[14] Patients with early-stage disease were treated with fields directed to the primary with a 2-cm margin. Those with advanced-stage disease or evidence of lymph node involvement underwent irradiation to the primary and the neck bilaterally.

Although definitive radiation remains a viable option for many subglottic tumors, surgery is preferred for large-volume tumors with evidence of cartilage destruction or extralaryngeal spread. Such tumors are typically treated postoperatively with adjuvant radiation to 60 Gy for negative margins, to 66 Gy if microscopically positive margins are present, and to 70 Gy for gross residual disease. Indications for postoperative radiation include pT4, pN2–N3, close or positive margins, perineural invasion, spread to multiple regional nodes, and extracapsular nodal spread. Concurrent adjuvant chemotherapy is indicated for positive margins, extracapsular extension, or other adverse pathologic features. Given the propensity for peristomal recurrence, the tracheostoma should be irradiated in patients requiring emergent tracheostomy, tumors with subglottic extension greater than 5 mm, tumors with significant invasion of soft tissues of the neck, extranodal extension in level VI, or close or positive margins.

Imaging for Treatment Planning and Setup

In 1991 Guedea and colleagues published the findings from a series of six patients treated with definitive radiotherapy.[18] To target low-lying disease, these researchers advocated use of two lateral portals and separate anterior low-neck portals encompassing both the primary site and regional lymphatics. Four-field box technique was used as an alternate.

Paisley and colleagues[15] noted that the delivery of radiation to the subglottic region is complicated by the anatomy of the shoulders. The angled-down wedge pair technique has been advocated to adequately target the tumor volume. This technique is not necessary in patients with a long neck who can adequately depress their shoulders. However, in modern practice, intensity-modulated radiotherapy (IMRT) is typically employed. Static field or arc treatment plans can adequately cover the subglottic larynx, minimizing concerns for shoulder clearance. Use of IMRT can also allow good coverage of the low neck and upper mediastinum while sparing critical adjacent organs including the spinal cord. When IMRT is used for planning and delivery, it is necessary to use volumetric image guidance such as cone-beam CT to ensure precise radiation treatment. The details of this treatment and complications of radiation therapy to the larynx are covered extensively in Chapter 13.

Outcomes

Rates of local control, overall survival, and disease-free survival vary by series, and are summarized in Table 41.3. Single-modality radiotherapy local control rates range from 63.6% to 100% for early-stage disease,[14,15] but these rates drop as the stage of the disease progresses. In the largest radiation series,[14,15] 5 years' overall survival ranged from 50.30% to 57.5%, and disease-free survival from 66.9% to 68.6%.

Chemotherapy

General Principles and Agents

The use of chemotherapy in the treatment of subglottic carcinoma fits within contemporary organ preservation treatment protocols for stage III and IV disease. The principle agent remains cisplatin, as detailed extensively in Chapters 16, 37 to 40. Because this topic has been extensively covered in these previous chapters, it will not be recapitulated here.

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Major Salivary Gland Cancer

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Overview

Malignant tumors of salivary glands represent around 6% of all head and neck neoplasms, with an incidence rate of around 12 per million of the population per annum.[1] There is no observable gender bias.[2] The median age of presentation varies between 50 years of age for acinic cell carcinoma and 70 years for squamous, small cell, and large cell carcinomas.[2]

Whereas most head and neck carcinomas tend to be of the squamous type, major salivary gland carcinoma extends across a much wider spectrum with at least 20 histologic subtypes being described.[2] Among the primary malignant tumors, the most common are mucoepidermoid carcinoma (MEC), adenoid cystic carcinoma (ACC), and acinic cell carcinoma. Secondary metastases from cutaneous squamous carcinoma or melanoma account for up to 44% of cases in some series.[3]

As a general rule, as the size of the major salivary gland decreases, the chances of a tumor being malignant rather than benign increases; rates are 25%, 50%, and 75% for the parotid, submandibular, and sublingual glands, respectively.[4,5] Despite this, the majority of malignancies occur within the parotid gland (around 65–80%) with the exception of ACC, which affects the parotid and submandibular glands equally.[6,7] Excluding metastatic lesions, the most common salivary gland malignancies in men are MEC (incidence rate [IR] 3.23) and adenocarcinoma–not otherwise specified (NOS) (IR 1.71); MEC (IR 2.67), acinic cell carcinoma (IR 1.57), and ACC (IR 1.40) predominate in women.[8]

In terms of risk factors, no strong correlation appears to exist in relation to environmental conditions. Although there seems to be some correlation with family history, no overt evidence of any genetic correlation has been demonstrated. Ionizing radiation has been established in the development of MEC, but little role in the pathogenesis of other pathologic subtypes.[9,10] There is no clear evidence of occupational risks, although some studies have linked malignancies of major salivary glands to chronic exposure to wood dust, silica dust, rubber processing, or nickel compounds.[11]

Clinical Presentation and Pertinent Anatomy

There are three paired major salivary structures—the parotid, submandibular, and sublingual glands. The parotid gland is predominantly serous secreting and is located lateral and posterior to the mandibular ramus and the masseter muscle covered by fascia. Inferiorly, it is in continuity with level II of the neck; posteriorly it rests on the upper third of sternocleidomastoid muscle and anterior cartilage of the auditory canal. The main trunk of the facial nerve enters the parenchyma of the gland from its posterior aspect before dividing into the five main branches within it. All the lobules and ducts eventually drain into the Stensen duct, which passes through buccal mucosa at the level of the upper premolar teeth.

Although the submandibular gland is a mixture of serous and mucinous elements, the former predominates. It is located in level Ib of the neck, inferior and medial to the mandibular body, within a triangle defined by anterior and posterior bellies of the digastric muscle. The mylohyoid muscle superiorly and medially separates it from the oral cavity. Lobules and ducts eventually drain into the floor of the mouth via the Wharton duct.

The sublingual gland has a predominance of mucus-secreting cells. It lies underneath the ventral aspect of the tongue on top of the superior aspect of mylohyoid muscle. It drains through several ducts, the largest being the Bartholin duct.

Because all the major salivary glands are either subcutaneous or submucosal, they remain easily accessible to clinical examination, and therefore changes in size, shape, or consistency are readily appreciated. Most major salivary gland tumors tend to be asymptomatic at presentation. Parotid tumors can occasionally affect facial nerve function secondary to infiltration and lead to presentation varying from partial facial weakness to complete palsy. Concurrent cervical metastases are rare.

Classification

Malignant tumors of the salivary gland have been classified by histological type as detailed in the WHO classification below (Table 42.1). The major group represents epithelial neoplasms, with hematolymphoid neoplasms being less common. Separate

TABLE 42.1 World Health Organization (WHO) Histologic Classification of Malignant Tumors of the Salivary Glands

Malignant Epithelial Tumors
Acinic cell carcinoma
Mucoepidermoid carcinoma
Adenoid cystic carcinoma
Polymorphous low-grade adenocarcinoma
Epithelial-myoepithelial carcinoma
Clear cell carcinoma, not otherwise specified
Basal cell adenocarcinoma
Sebaceous carcinoma
Sebaceous lymphadenocarcinoma
Cystadenocarcinoma
Low-grade cribriform cystadenocarcinoma
Mucinous adenocarcinoma
Oncocytic carcinoma
Salivary duct carcinoma
Adenocarcinoma–not otherwise specified
Myoepithelial carcinoma
Carcinoma ex pleomorphic adenoma
Carcinosarcoma
Metastasizing pleomorphic adenoma
Squamous cell carcinoma
Small cell carcinoma
Large cell carcinoma
Lymphoepithelial carcinoma
Sialoblastoma
Hematolymphoid Tumors
Hodgkin lymphoma
Diffuse large B-cell lymphoma
Extranodal marginal zone B-cell lymphoma
Secondary Tumors

Adapted from Barnes LB, Eveson JW, Reichart P, Sidransky D, eds. *Pathology and genetics of head and neck tumors.* Lyon: IARC Press; 2005.

groups include secondary tumors that metastasize to the glands from primaries either within the head and neck or further afield.

Staging

Once a histopathologic or cytologic diagnosis has been obtained, disease is further characterized according to the TNM classification (Table 42.2). T describes the primary tumor mass with size criteria, N defines the locoregional lymph nodal status, and M acknowledges the presence or absence of distant metastases. A combination of different T, N, and M then defines the staging of the disease, which ranges from 0 to IV (A, B, C). TNM staging is key to addressing an individual patient's treatment plan as well as facilitating data transfer across centers with a simple and effective language that is accepted worldwide.

Peri-operative Diagnosis—Fine Needle Aspiration Cytology, Fine Needle Biopsy, and Intraoperative Frozen Section

Given the variety of different malignant lesions that may affect the major salivary glands, accurate diagnosis is crucial to defining a patient's treatment plan. In so doing it is important to gather enough information to be able to differentiate among various and sometimes controversial histopathologic subtypes. Given that a definitive and unequivocal pathologic diagnosis on occasions only occurs postoperatively, the preoperative setting often relies on only partial sampling.

Diagnostic tools have greatly improved in the last few decades, becoming more accurate and less morbid. As minimally invasive and consistently reliable procedures, fine needle aspiration cytology (FNAC) and fine needle aspiration biopsy (FNAB) are both largely in use in the salivary gland setting, with or without ultrasound guidance.

FNAC has been widely in use since the 1980s. It is simple, safe, fast, cost-effective, minimally invasive, and reliable in experienced hands.[12] The technique only becomes controversial in situations in which suboptimal sampling occurs and as a result nondiagnostic or false-negative results ensue. The diagnostic performance of FNAC can be improved with ultrasound guidance or with a cytologist-led service that permits immediate assessment of samples. Nevertheless, even when optimized, cytology of salivary malignancies can still be difficult to interpret because by their very nature, cellular interaction with the surrounding tissues cannot be appreciated.

FNAB has been performed with good effect since the late 1990s and uses an 18-gauge needle instead of the traditional 23-gauge needle used for FNAC.[13] FNAB results tend to reveal consistently higher sensitivity and levels of accuracy when compared with FNAC. Likewise, nondiagnostic rates tend to be lower—around 4% in FNAB compared with 6.4–18% in FNAC.[14-16] However, the procedure of FNAB can be more morbid and has the theoretical potential to seed tumor and risk injury to the facial nerve. Although pathologic processing takes longer than cytology, it permits better characterization of tumor subtypes.

Despite the potential for increased morbidity, FNAB is well tolerated under local anesthesia. The potential for tumor seeding is still hotly debated, with some authors going so far as to suggest surgical removal of the biopsy tract at the time of surgery.[17] An extensive review of the literature published between 1970 and 2014 found only seven reports of

TABLE 42.2 American Joint Committee on Cancer Staging for Salivary Gland Cancer (8th Edition)

Primary Tumor (T)

TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor ≤2 cm in greatest dimension without extraparenchymal extension (clinical or macroscopic evidence of invasion of the soft tissues, not microscopic evidence)
T2	Tumor >2 cm but not >4 cm in greatest dimension without extraparenchymal extension
T3	Tumor >4 cm and/or tumor has extraparenchymal extension
T4a	Moderately advanced disease. Tumor invades the skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease. Tumor invades skull base and/or pterygoid plates and/or encases carotid artery

Regional Lymph Nodes (N)

NX	Regional nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, ≤3 cm in greatest dimension
N2	Metastasis in a single ipsilateral lymph node >3 cm but not >6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node >3 cm but not >6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension
N3	Metastasis in a lymph node >6 cm in greatest dimension

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Clinical Stage

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
II	T2	N0	M0
III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
IVB	T any	N3	M0
	T4b	N any	M0
IVC	T any	N any	M1

From Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE 42.3 Diagnostic Accuracy of Fine Needle Aspiration Cytology (FNAC), Fine Needle Aspiration Biopsy (FNAB), and Frozen Section (FS) in Malignant Tumors of the Salivary Glands

	FNAC	FNAB	FS
Sensitivity	64–90%	92–94%	75–98.5%
Specificity	86–100%	99–100%	98–100%
Accuracy	93.2–97.2%	96%	96.8–99.2%
Positive predictive value	61–83.3%	100%	92–100%
Negative predictive value	90–96.77%	90%	87–99%

seeding—five after FNAC and two after FNAB. The real incidence rates of seeding are notoriously difficult to calculate but have been estimated to be 0.00012% and 0.0011% after FNAC and FNAB, respectively.[18] Other reviews have suggested no evidence to support tumor cell seeding after either technique.[19]

The role of intraoperative frozen section (FS) remains controversial. Although the technique is routinely performed in a small number of centers, most authors consider three main indications—namely, when FNAC and/or FNAB has been repeatedly nondiagnostic; when there is a need to check operative margins when dealing with extensive and infiltrative disease; and when one needs to ascertain nerve involvement and so facilitate intraoperative decision making regarding potential nerve resection and reconstruction. Although an accurate and reliable diagnostic tool, FS obviously increases operating time, adds costs estimated at $1500 per case, and may additionally burden pathology departments.[20,21]

FNAC, FNAB, and FS vary in their diagnostic accuracies[14,15,20,22–32] (Table 42.3). The lower sensitivity of FNAC can probably be attributed to the challenge of diagnosing low-grade carcinomas by cellular morphology alone. Low-grade subtypes may include ACC, acinic cell carcinoma, MEC, epithelial-myoepithelial carcinoma, and adenocarcinoma–NOS, all of which may appear as false negatives.[29,32] Nevertheless, FNAC is used as a first-line diagnostic tool in centers because it not only is easy to perform but is well tolerated by patients and in most cases provides the relevant information from which to formulate an appropriate treatment plan. Ultrasound-guided FNAB is usually reserved for cases in which a nondiagnostic FNAC has been obtained or for more complex cases in which the histologic subtype characterization proves more challenging. Because a combination of FNAC or FNAB, imaging, and clinical judgment can usually consistently lead to accurate diagnosis, FS is rarely part of routine practice.

Imaging

Imaging is instrumental in the diagnosis, staging, treatment planning, and follow-up of major salivary gland cancer. Multimodality assessment with ultrasound, computed tomography (CT), and multiparametric magnetic resonance imaging (mp-MRI) is standard practice. With these techniques much vital information not clinically apparent can be gleaned. It should be possible by imaging to distinguish an intrinsic salivary gland mass from adjacent adenopathy, floor-of-mouth tumors, or obstructive sialadenitis, all of which may be difficult to separate clinically. Although significant overlap exists in the imaging appearances of benign and malignant salivary gland tumors, cross-sectional imaging is often helpful in this distinction.

The modality of first choice for assessment of a salivary gland mass is determined in general by the degree of clinical suspicion of malignancy. Magnetic resonance imaging (MRI) is the preferred modality for assessing major salivary gland masses when malignancy is suspected, such as with facial nerve palsy, infiltration of the skin, or regional adenopathy.[33]

Anatomic information essential for surgical planning can be obtained, including tumor extent, involvement of adjacent compartments, perineural invasion, and bony infiltration. Vital for the surgeon is the likelihood of involvement of the facial nerve and skull base.

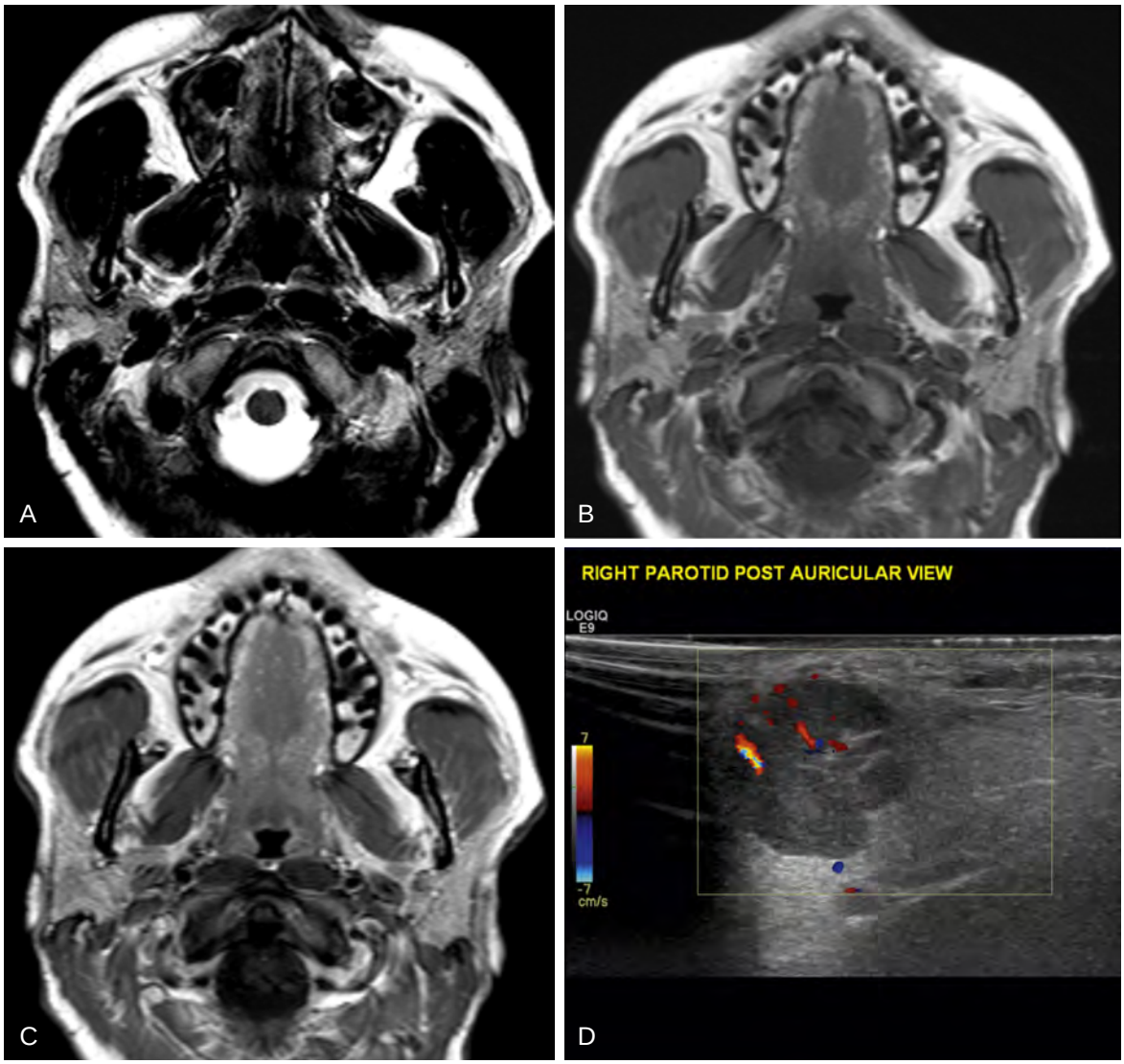
Ultrasound-guided FNA allows cytologic confirmation of the tumor's cell type. Once malignancy has been confirmed, cross-sectional imaging is required to establish nodal and metastatic status and for follow-up.

Ultrasound

Ultrasound is a simple method of assessing superficial parotid, submandibular, and sublingual masses, without the use of ionizing radiation. It is reliable at distinguishing intraglandular from extraglandular masses.[33]

Ultrasound features suggestive of malignancy include poorly defined boundaries, heterogeneity, central cystic or necrotic changes, and infiltration of local structures or skin (Fig. 42.1). Malignant salivary gland tumors tend to be hypervascular, with elevated resistive indices (RI >0.8).[34] Involvement of deep structures, perineural spread, and bony or skull base and facial nerve involvement are not assessable sonographically.[35]

In the assessment of salivary gland tumors the main role of ultrasound is in image-guided FNA of the mass and/or regional nodes for cytologic analysis. The accuracy of ultrasound-guided FNA is operator dependent, but is high when experienced operators and cytopathologists are available. Owing to the heterogeneity of some tumors (e.g., pleomorphic adenomas) ultrasound-guided FNA may be inconclusive and



• **Fig. 42.1** Acinic cell carcinoma of the right parotid gland. **A,** Axial T2-weighted image showing a small, lobulated, and partly cystic lesion in the right superficial parotid gland. **B,** Precontrast and **C,** postcontrast axial T1-weighted images demonstrating low-grade enhancement. **D,** Doppler ultrasound image of the right superficial parotid gland. The lesion is best illustrated in this case by Doppler ultrasound because of its superficial position. The solid elements and vascularity are clearly depicted.

may be technically difficult or impossible for tumors of the deep parotid lobe.[36] It should also be borne in mind though that inflammatory masses can mimic malignant salivary gland tumors on cytology.[37] Quoted sensitivities of ultrasound-guided FNA range from 80% to 100%, with an inconclusive rate of up to 10%, but a more consistently high specificity of 95–100%.[38,39,40]

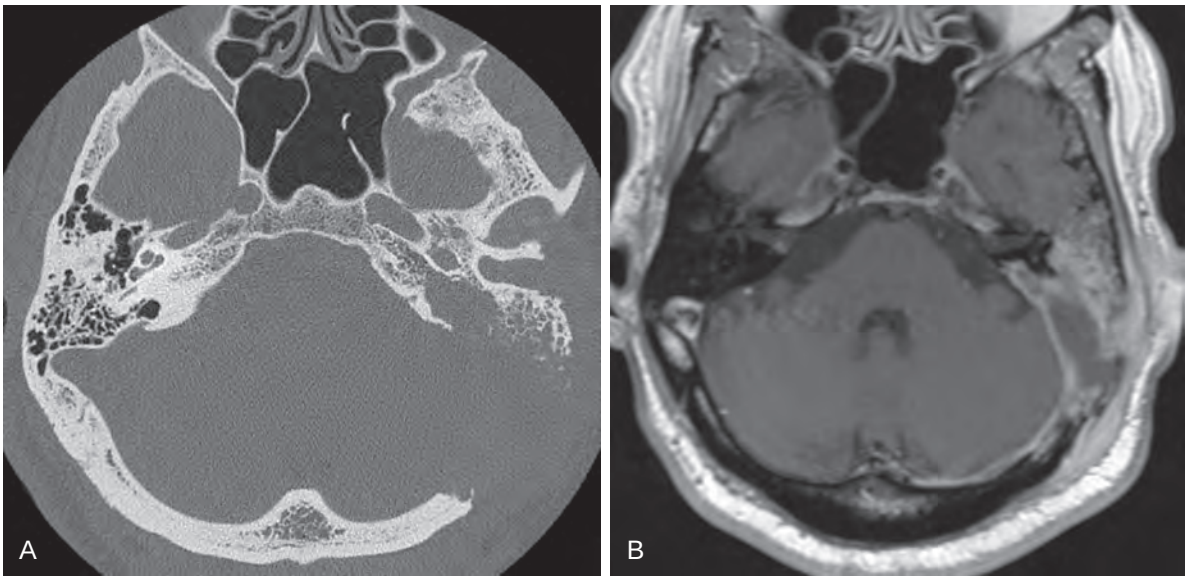
Computed Tomography

CT is most helpful at identifying features of inflammatory processes, such as calculi and ductal dilatation. Where an inflammatory "pseudo-mass" associated with sialadenitis is a strong possibility, CT should be the modality of first choice, as small calculi may not be resolvable on MRI, in which case the abnormality may mimic malignancy.

Although CT performed with and without contrast will demonstrate genuine enhancement, local invasion, and occasionally gross perineural spread of disease, the density and enhancement of benign and malignant tumors on CT overlap significantly. Compared with MRI, CT is less accurate at predicting malignancy (60–70%). It has the associated risks of ionizing radiation and iodinated contrast injection. However, CT is considered superior in the assessment of cortical bone invasion[33] (Fig. 42.2). CT is also routinely used for completion of staging.

Magnetic Resonance Imaging

Because of its superior contrast resolution, MRI offers the most detailed illustration of tumor extent and other characterizing features. It also does not rely on ionizing radiation. MRI is,



• **Fig. 42.2** Recurrent acinic cell carcinoma of the left parotid gland. **A,** Axial computed tomography (CT) image through the skull base using a bone algorithm, on which the bone destruction of the left mastoid is best appreciated. **B,** Axial gadolinium-enhanced T1-weighted image at the same level; the enhancing soft tissue elements at the site of bone destruction are more apparent.

however, more expensive and time-consuming, is prone to artifacts (from movement and dental work), and may not depict cortical bone destruction as well as CT.

Conventional Magnetic Resonance Imaging

Although superior to ultrasound and CT, MRI also cannot reliably distinguish benign from malignant salivary gland tumors, with a reported sensitivity on the order of 71%.[41] Malignant lesions have a greater predilection for involvement of the deep lobe or both lobes, although Warthin tumors and schwannomas may also arise in the deep lobe. Tumor size and patient age and gender are not reliable predictors. Nor is cystic or necrotic change, which may occur in Warthin tumors and pleomorphic adenomas.[42]

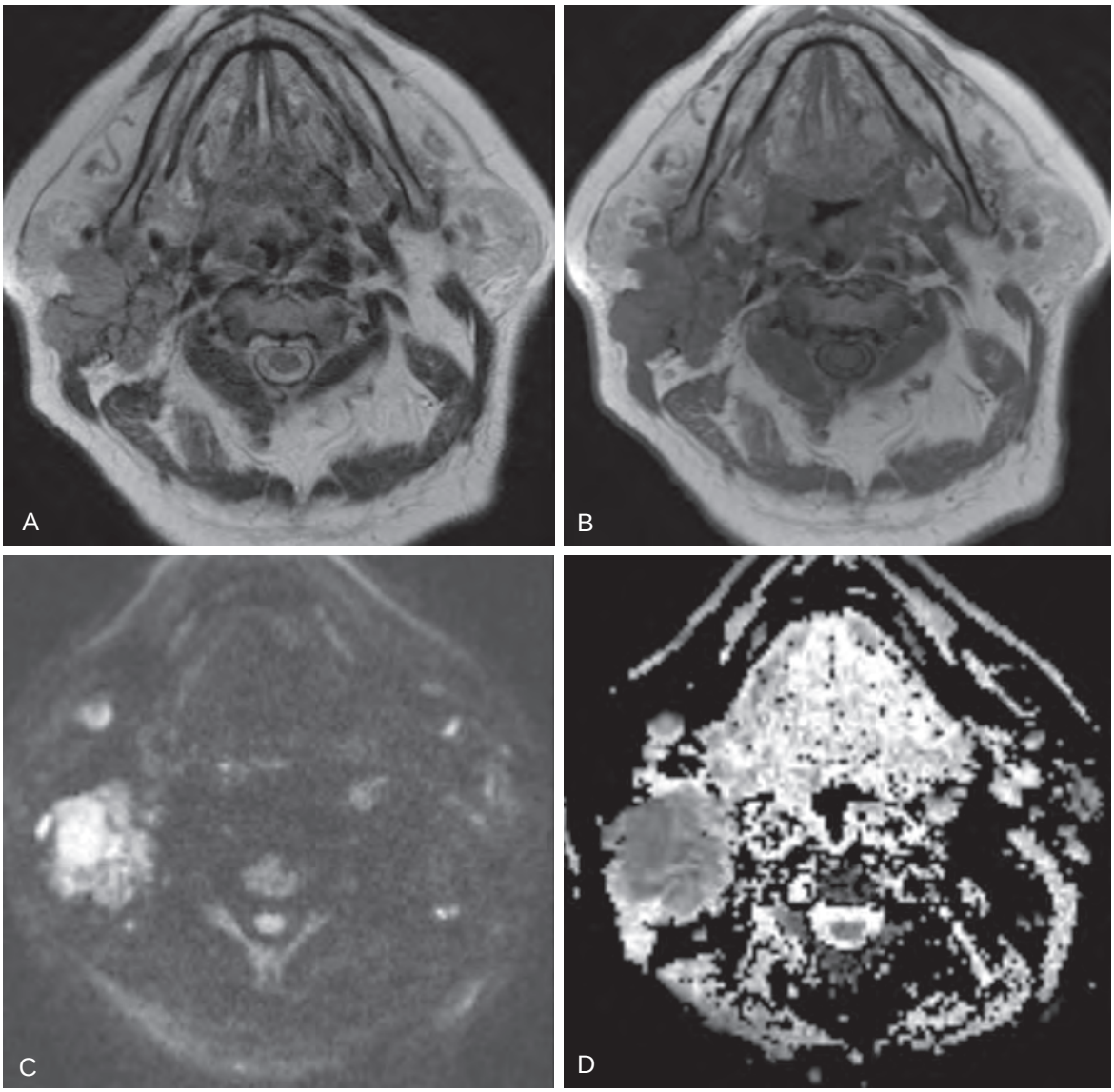
Certain features on conventional MRI sequences are, however, strongly indicative of malignancy. Christe and colleagues found that the best morphologic indicator of malignancy was ill-defined margins, followed by T2 hypointensity.[42] Poorly defined margins on postcontrast imaging were found in 59% of malignant tumors and 21% of benign masses ($P = .001$). The signal intensity of a salivary gland mass should be assessed relative to that of normal background glandular tissue. Although T2 hyperintensity suggests benign disease (e.g., pleomorphic adenoma), T2 hypointensity was found in 26% of malignant and 9% of benign tumors ($P = .001$).[43] High-grade malignancies, in particular, are likely to be T2 hypointense; however, low-grade cancers can be T2 hyperintense. Warthin tumors (the second most common benign tumor of the parotid gland) can also be T2 isointense, hypointense, or heterogeneous.[33] The presence of either T2 hypointensity or ill-defined margins predicts malignancy with a sensitivity and specificity of 70% and 73%, respectively (Fig. 42.3). Occasionally, infection or inflammation (e.g., granulomatous diseases) can also produce ill-defined borders, mimicking malignancy, but is more likely to be T2 hyperintense. Subcutaneous involvement (Fig. 42.4), invasion of other local structures or compartments (Fig. 42.5), perineural extension, and bone invasion are also highly specific for malignancy.

Perineural invasion is best appreciated on postcontrast fat-suppressed T1-weighted sequences, appearing as thickening, nodularity, and/or abnormal enhancement of the nerve, or effacement of the perineural fat at the skull base neuroforamina. Discontinuous perineural spread ("skip lesions") may also occur. Perineural involvement of the mandibular division of the trigeminal nerve (V3) may occur with tumors of the deep parotid and is associated with hemifacial sensory disturbance. When there is a history of a hoarse voice, dysphagia, shoulder weakness, or hemiglossal atrophy, involvement of the glossopharyngeal nerve (cranial nerve [CN] IX), vagus nerve (CN X), accessory nerve (CN XI) or hypoglossal nerve should be sought. The phenomenon may be visible extending into the skull base neuroforamina. As a late manifestation, neuroforaminal expansion may be appreciable on CT.[44]

Bone invasion appears as osseous hypointensity on precontrast T1-weighted imaging, adjacent to enhancing soft tissue disease.[45] Superficial lobe location, together with T2 hyperintensity and well-marginated edges, strongly favors benign disease.

Dynamic Contrast-Enhanced Magnetic Resonance Imaging

Contrast-enhanced MRI is a means of assessing the relative vascularity of a structure. The technique employs the intravenous injection of a paramagnetic contrast agent (gadolinium). In highly vascular structures, the contrast agent is released from the intravascular space into the extravascular space, where it induces shortening of T1 relaxation times in the hydrogen atoms contained in that tissue. On



• **Fig. 42.3** Mucoepidermoid carcinoma of the right parotid gland. **A,** Axial T2-weighted image and **B,** non-contrast T1-weighted image showing an irregular mass involving the superficial and deep parotid gland, with invasion of the sternocleidomastoid muscle posteriorly and areas of T2 hypointensity, indicating malignancy. **C,** Diffusion-weighted image (b1000) and **D,** apparent diffusion coefficient (ADC) map showing high and low signal, respectively, in keeping with restricted diffusion and again favoring a finding of malignancy.

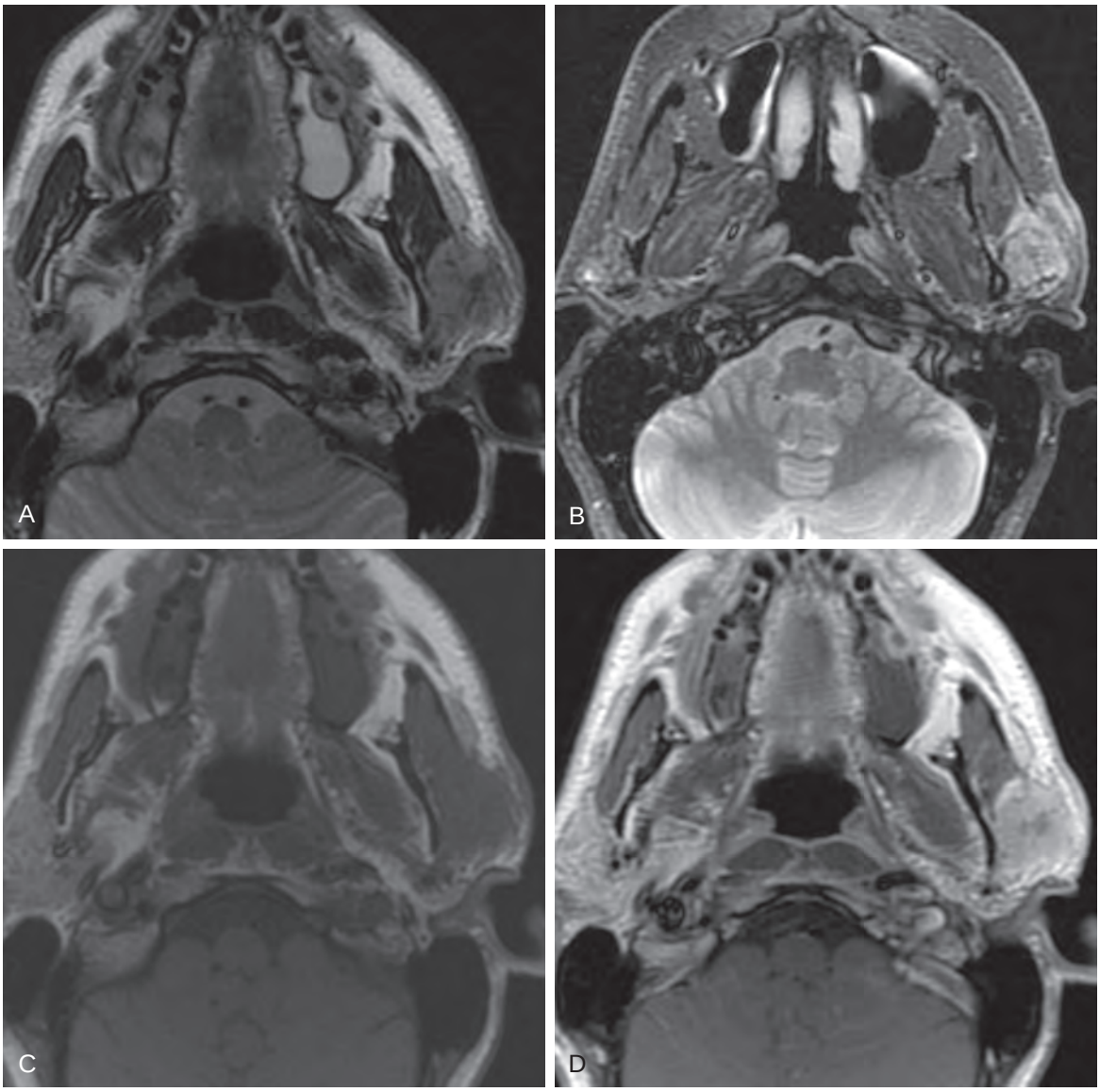
MRI, this process is depicted as high signal on postcontrast T1-weighted sequences relative to the precontrast T1-weighted sequence. That tissue is thus said to be enhancing and therefore vascular.

In most organs, hyperenhancement is generally a feature of malignant disease; however, benign and malignant salivary gland tumors are difficult to discriminate on this basis, because they are both usually T1 hypointense and exhibit at least some enhancement.

Although absolute tumor enhancement is not a reliable discriminator of tumor types, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is able to further characterize the type of enhancement by pharmacokinetic analysis of the rate of passage of contrast between the intravascular and extravascular spaces, depicted through time-intensity curves.[46]

Close correlation has been shown between time to peak enhancement (T_{peak}) and angiogenesis and between "washout ratio" (WR) and cellularity.[47] Because of neovascularization, malignant salivary gland tumors are expected to be relatively vascular masses and therefore rapidly enhancing and with short T_{peak}. In comparison, benign tumors, owing to their predominant stromal content, tend to exhibit gradual enhancement and delayed washout.[48,49]

DCE-MRI assessment of salivary gland tumors is an ongoing area of research, with no universally agreed parameters. Applying different thresholds for T_{peak} and WR, a number of authors have attempted to more reliably differentiate benign



• **Fig. 42.4** Adenoid cystic carcinoma of the left parotid gland. **A,** Axial T2-weighted image showing a solid heterogeneous mass in the left parotid, including areas of T2 hypointensity (a feature of malignancy) and invasion of the left masseter. **B,** Axial short tau inversion recovery (STIR) image on which invasion of the overlying skin is best appreciated. **C,** Precontrast and **D,** postcontrast axial T1-weighted images showing solid enhancement.

and malignant salivary gland tumors, with varying results. For most reliable prediction the morphologic sequences should first be examined for best selection of regions of interest (ROIs). Salivary gland tumors are histologically heterogeneous, containing cellular (proliferating) tumoral areas, as well as myxoid, lymphoid, necrotic, and cystic areas. If these areas are included together in the same ROI analysis, accurate characterization may be compromised.[50] Another significant confounder in several studies is the overlapping enhancement patterns between malignant tumors and Warthin tumors. Warthin tumors also have rich microvasculature and, like malignant tumors, are often rapidly enhancing. It is generally observed, though, that Warthin tumors tend to wash out more rapidly than malignant tumors.[51] A more recent, larger study by Lam and colleagues using a higher temporal resolution (at 5-second intervals), found the optimal peak enhancement time threshold to be 150 seconds. This was said to reliably distinguish pleomorphic adenomas from other tumors. Of the remaining tumor types, a WR at 5 minutes of 30% most reliably distinguished malignant from benign tumors—in particular, malignant from Warthin tumors.[52]

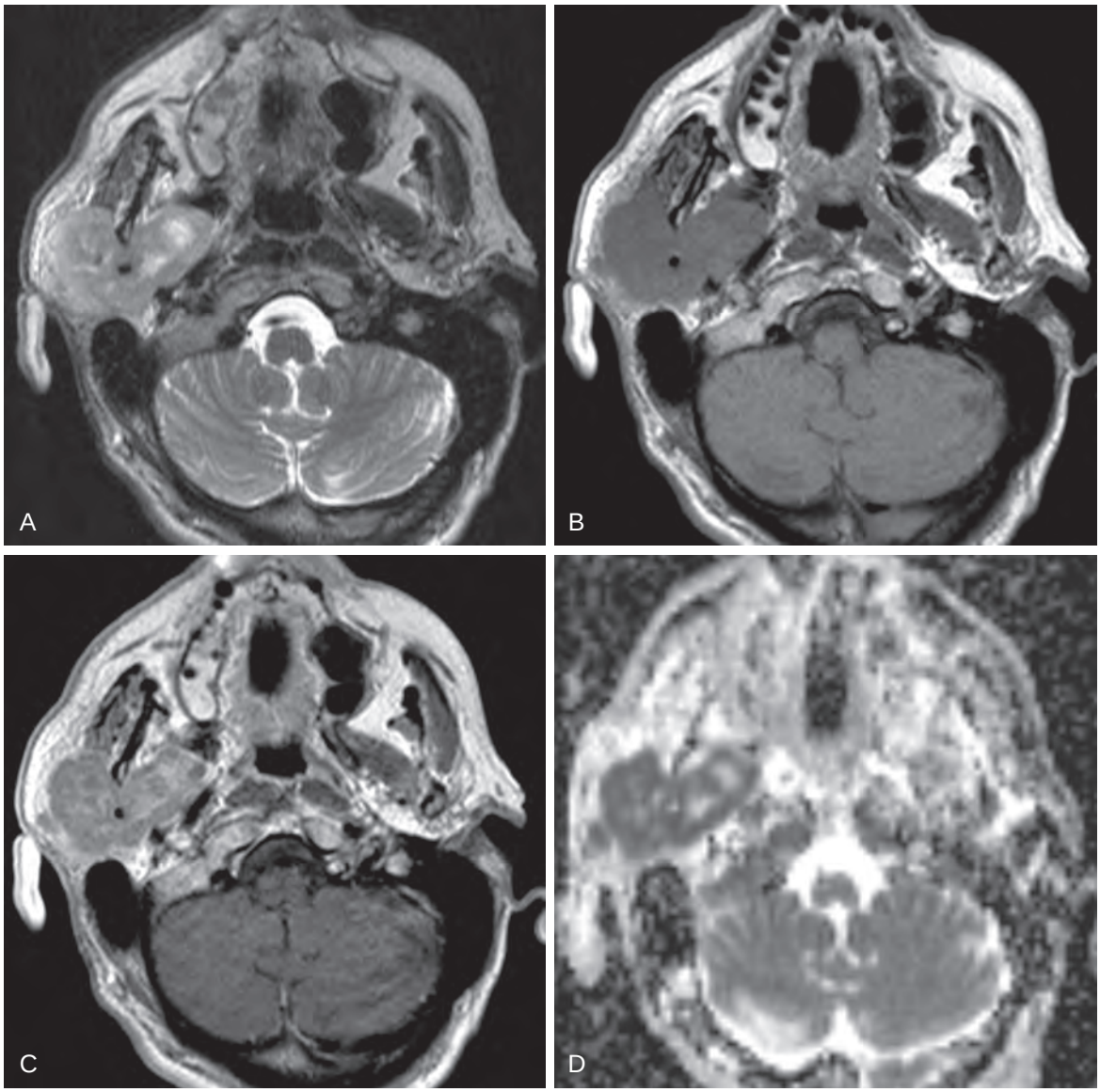
Time–signal intensity curves may thus be categorized as follows: type A, with delayed enhancement (T_{max} ≥150 s); type B, with early enhancement and early washout (T_{max} ≤150 s and WR ≥30%); type C, with early enhancement and delayed washout (T_{max} ≤150 s and WR ≤30%); and type D, with a flat curve (no enhancement).[52] A type A curve is strongly suggestive of a pleomorphic adenoma. Warthin tumors exhibit either

a type B or a type D curve (Fig. 42.6). According to Lam and colleagues, a type C curve predicted malignancy with a sensitivity of 79%, specificity of 95%, and accuracy of 91%. Of their five false negatives, three were cases of parotid gland lymphoma and produced a type B curve. This presumably reflects the high cellularity of lymphoma. For this reason, distinguishing Warthin tumors from lymphoma of the salivary glands with DCE-MRI is likely to be especially challenging.[52]

Diffusion-Weighted Imaging

Diffusion-weighted magnetic resonance imaging (DW-MRI) is a means of assessing the relative cellular density of a tissue or tumor. Water molecules move (diffuse) within a tissue by a process of Brownian motion. The diffusion of water molecules is restricted within highly cellular tissues owing to the limited space among the densely packed cells. On DW-MRI, this is depicted as high signal on B-value sequences and low signal on the apparent diffusion coefficient (ADC) map. Where a tissue has low cellular density, it will demonstrate high signal on both B-value imaging and on the ADC map and is said to demonstrate free diffusion.[53]

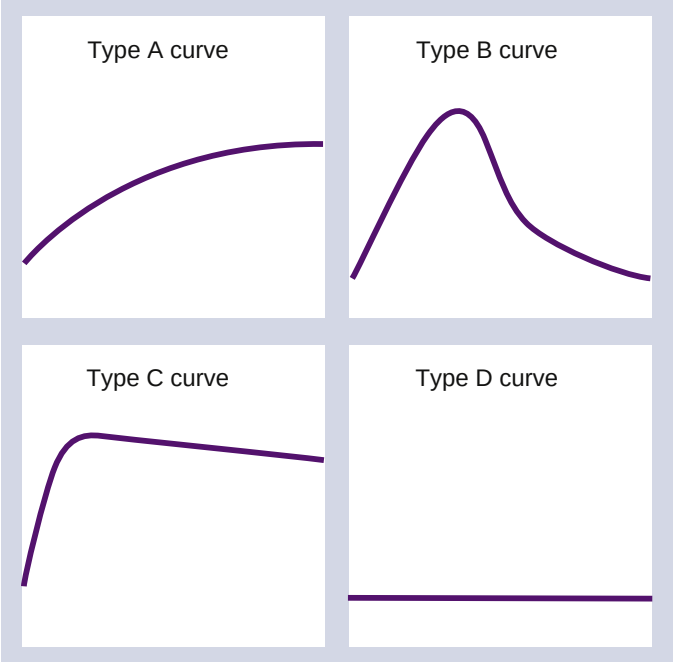
In general, malignant masses exhibit lower ADC values than benign lesions. Using an ADC value threshold of 1.22×10^{-3} mm^2/s or less, the sensitivity, specificity, and accuracy for detection of malignancy are 84%, 91%, and 86%, respectively[54] (see Fig. 42.3). However, although this technique is able to reliably discriminate benign pleomorphic adenomas from nonpleomorphic adenomas, Warthin tumors are again confounding, because they too may exhibit low ADC values, with a mean of 0.83.[55]



• **Fig. 42.5** Adenocarcinoma of the right parotid gland. **A,** Axial T2-weighted image showing tumoral replacement of the gland, with central necrosis, vascular encasement, and invasion of the right pterygoid muscles and masseter. **B,** Precontrast and **C,** postcontrast axial T1-weighted images showing fairly heterogeneous enhancement. **D,** Apparent diffusion coefficient (ADC) map showing low signal, indicating restricted diffusion, suggestive of malignancy.

Using an algorithmic approach to combining ADC with time-intensity curve analysis, Eida and colleagues achieved a sensitivity, specificity, and accuracy of malignancy detection in salivary gland tumors of 86%, 100%, and 97%, respectively.[50]

Although it is not yet possible to reliably distinguish benign from malignant salivary gland tumors with mp-MRI in the absence of fine needle aspiration (FNA) or core biopsy, the additional information may still be contributory in cases in which parotid tumors are inaccessible to ultrasound-guided FNA. Distinguishing malignant masses from Warthin tumors on cytology can also be difficult; hence mp-MRI could assist in identifying suspected sampling error in cases in which imaging characteristics are discordant.[52]



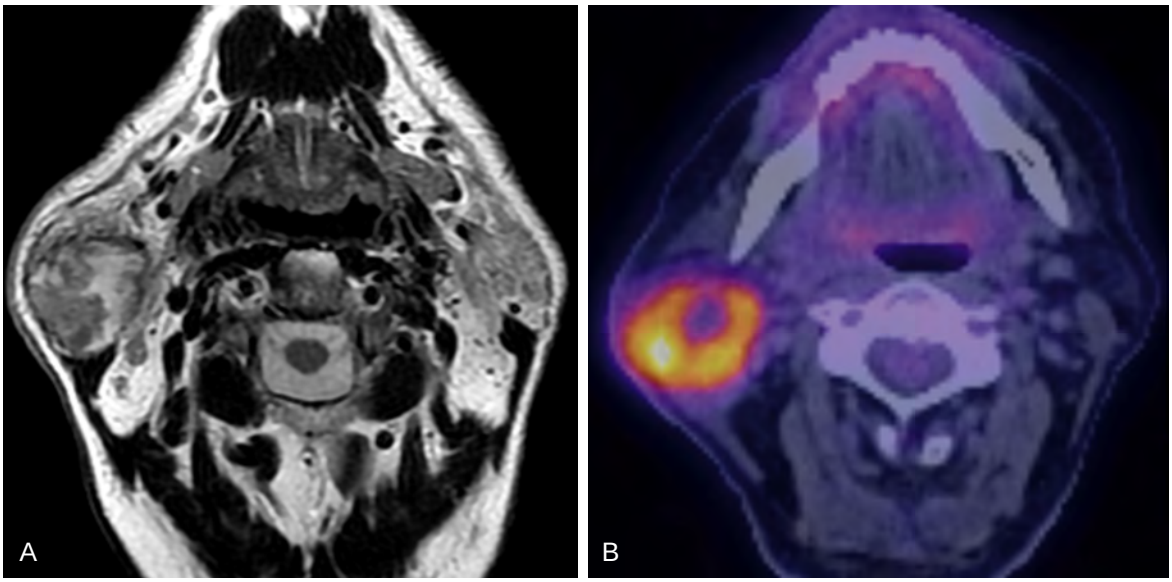
• **Fig. 42.6** Time–signal intensity curves. The type A curve is characterized by a delayed time to peak intensity (e.g., ≥150 seconds). The type B curve has an early time to peak intensity and relatively high washout ratio (e.g., <150 seconds and >30%, respectively). The type C curve has an early time to peak intensity and relatively low washout ratio (e.g., <150 seconds and <30%, respectively). The type D curve is flat (no or minimal enhancement).

Proton Magnetic Resonance Spectroscopy

Using in vivo proton magnetic resonance spectroscopy, it is possible to determine the structure of a tissue's constituent compounds by analyzing their carbon-hydrogen framework. Choline, a marker of membrane turnover, is detectable in malignant and benign salivary gland tumors, but not in the normal gland. King and colleagues found statistically significant differences in the choline/creatinine ratio of benign and malignant salivary gland tumors. Ratios were highest in Warthin tumors, followed by pleomorphic adenomas, and lowest in malignant tumors. They found that a ratio greater than 2.4 was 100% sensitive and specific in predicting a benign salivary gland tumor. However, the analysis was possible only on masses greater than a centimeter in size, and even then a choline/creatinine ratio could be detected in fewer than half. The authors concluded that the technique could be helpful when availability of ultrasound-guided FNA is limited but required further study.[56]

Nuclear Medicine

Positron emission tomography (PET) using 2-deoxy-2-(^{18}F) fluoro-D-glucose (FDG) has a role in the assessment of salivary gland tumors. Compared with MRI, it has a relatively low accuracy of 69% in classifying salivary gland tumors[57] (Fig. 42.7). Although malignant tumors are variably FDG



• **Fig. 42.7** Squamous cell carcinoma of the right parotid gland. **A,** T2-weighted image showing a heterogeneous mass, with central necrosis and invasion of sternocleidomastoid. **B,** Fused positron emission tomography–computed tomography (PET-CT) image, in this case demonstrating avid fludeoxyglucose (FDG) F 18 uptake.

avid, certain benign processes, including Warthin tumors and inflammatory conditions, typically accumulate FDG; hence the technique is prone to false negatives and false positives. Its main role is therefore in the nodal and metastatic staging and follow-up of confirmed cases of malignancy.

To overcome the overlap in low ADC values between Warthin tumors and malignant salivary gland tumors, Miyake and colleagues combined DWI-MRI with ^{99m}Tc pertechnetate scintigraphy. ^{99m}Tc pertechnetate scintigraphy after lemon juice stimulation had a sensitivity for diagnosing Warthin tumor of 94–100% and specificity of 94%. Using a diagnostic algorithm combining ADC_{mean}, sex, and age (men 40 years old and older, who account for 93% of Warthin tumors) and in applicable cases ^{99m}Tc pertechnetate scintigraphy, a sensitivity and specificity for diagnosing Warthin tumors of 92% and 95%, respectively, were achieved. These authors suggested that pleomorphic adenoma can be diagnosed reliably by ADC values, and Warthin tumors, when ADC is low, by ^{99m}Tc pertechnetate scintigraphy.[58]

Tumor Types

Malignant salivary gland tumors are a diverse group, and accordingly it is not possible to reliably distinguish cell type on imaging, but certain features may be suggestive. Because pleomorphic adenoma and Warthin tumors are the most common parotid masses, it is also worth describing the typical imaging features of these important benign differentials.

Common Benign Salivary Gland Tumors

Pleomorphic adenomas (the most common benign parotid tumor) are typically well defined or multilobulated masses. Because 90% of pleomorphic adenomas occur in the superficial parotid, they are usually assessable with ultrasound, typically showing a hypoechoic mass, often with through-transmission and hypervascularity. They are normally hyperdense on CT relative to the parotid gland, but may be isointense and therefore difficult to appreciate.[59] On MRI, an appearance of T1 hypointensity and T2 hyperintensity (because of the fibromyxoid stroma) with avid, homogeneous enhancement is considered strongly indicative of pleomorphic adenoma. There may, however, be heterogeneity in the presence of cystic change, hemorrhage, or dystrophic calcification, and these tumors may not be distinguishable from malignant tumors. Long-standing lesions are at risk of malignant transformation.

Warthin tumors (the second most common benign parotid tumor) are more frequently found in men and with increasing age. They tend to occur in the tail of the parotid and are multiple or bilateral in 15% of cases. Although the appearances may mimic pleomorphic adenoma, typically they are well-defined, septated, cystic masses, moderately T2 hyperintense, with either homogeneous or heterogeneous enhancement.

Malignant Salivary Gland Tumor Types

MEC is the most common malignant salivary gland tumor, mostly occurring in the parotid gland and minor salivary glands (50% and 45%, respectively) (see Fig. 42.3). Imaging appearances vary with tumor grade; appearance of low-grade lesions overlaps with benignity, tending to be better circumscribed, and high-grade lesions more irregular and infiltrative. Mucoepidermoid carcinomas may exhibit low to intermediate signal on both T1- and T2-weighted imaging. They may also exhibit perineural invasion and metastatic disease to local lymph nodes, lungs, and bones.[60]

ACC is the second most common major salivary gland malignancy and most common in the submandibular and sublingual glands (see Fig. 42.4). Appearances of low-grade tumors may overlap with benign masses. High-grade tumors are typically infiltrative and especially prone to perineural invasion (present in 50–60%), occasionally manifesting with apparent perineural "skip lesions."[33] Due vigilance should be paid to the possibility of late recurrence in these tumors.

Acinic cell carcinoma is the second most common parotid tumor and second most common pediatric malignant salivary gland tumor in children (see Fig. 42.1). They may be multifocal or bilateral. Their imaging features are often non-specific and not reliably distinguishable radiologically from benign lesions such as Warthin tumors or pleomorphic adenoma. They may be solid or partly cystic and may be partly encapsulated. They have a somewhat lower metastatic potential.[61]

Salivary duct carcinomas (SDCs) are rare, aggressive tumors, prone to nodal spread (present in 70%) and perineural invasion. They may exhibit low to mildly high signal on T2-weighted imaging. Intrinsic T1 hyperintensity may be observed, resulting from internal hemorrhage. The tumor may exhibit an irregular periphery and functional parameters indicative of malignancy, including low ADC values, early enhancement, and rapid washout.[62]

Adenocarcinoma–NOS of the major salivary glands may vary in presentation and appearance, from indolent painless masses to aggressive painful tumors, and may be well or ill defined (see Fig. 42.5). Although more commonly found in the oral cavity, polymorphous low-grade adenocarcinoma (PLGA) may occur in the parotid gland. A slow-growing, infiltrative, and perineural pattern of spread is typical.

Primary squamous cell carcinoma (SCC) of the major salivary glands is far less common than metastatic SCC at these sites but may occur owing to metaplasia resulting from chronic inflammation and typically affects men in their 50s or 60s (see Fig. 42.7). These are usually rapidly growing tumors, prone to invasion of adjacent structures and skin. A necrotic center is characteristic.

Untreated pleomorphic adenoma carries a 25% risk of malignant transformation. Carcinoma ex pleomorphic adenoma is a malignant tumor arising from a transformed benign mixed tumor or in a patient who has undergone previous resection of a pleomorphic adenoma. They have high metastatic potential (reportedly 25–76%) and may exhibit areas of low T2 signal.[44]

Metastatic disease to the major salivary glands most commonly arises from skin malignancies such as melanoma or SCC but is also associated with other tumor types, including renal, gastrointestinal, lung, and breast tumors. Owing to the presence of lymph nodes within it, draining the face, scalp, and

internal auditory meatus, the parotid gland is most vulnerable. Multiplicity is typical, but appearances are otherwise variable. There may or may not be a known primary to raise suspicion, but FNA is needed for confirmation.

The major salivary glands may be involved in 1–8% of cases of systemic lymphoma. Primary lymphoma of the major salivary glands, mucosa-associated lymphoid tissue (MALT) lymphoma, is far less common than secondary involvement of the salivary glands and is diagnosable on the exclusion of nodal involvement elsewhere. Patients with autoimmune disorders, such as Sjögren disease and rheumatoid arthritis, are at a higher risk, as are immunosuppressed patients. Imaging may reveal multiple well-defined masses or an infiltrative pattern.[44]

Nodal and Metastatic Status

The presence of nodal disease has a bearing on the patient's prognosis, reducing the 10-year survival from 63% to 33%. Overall nodal metastases occur in up to 53% of malignant salivary gland tumors, although likelihood varies according to histological subtype. The parotid and submandibular glands drain to the deep cervical nodal stations, whereas sublingual glands drain to the submental and submandibular nodes. An enlarged node (short-axis dimension >10 mm) at the site of drainage of a salivary gland tumor should be regarded with suspicion. Other imaging features of nodal involvement include internal hemorrhage, necrosis, and extracapsular spread. Additional suspicious ultrasound features include a rounded shape, loss of central fatty hilum, and hypervascularity. Suspicious nodes identified on ultrasound may be sampled with FNA. MRI is helpful in identifying abnormal signal in regional lymph nodes. A high index of suspicion should be had for nodal metastatic disease where there is evidence of facial nerve involvement or a known high-grade tumor, which are strong predictors of nodal spread. Mucoepidermoid parotid cancers are most prone to nodal spread.[63] Imaging evidence of metastatic disease is a further unfavorable predictor of prognosis and is most common in ACC.

Metastasis to the Major Salivary Glands

Secondary metastatic lesions, particularly to the parotid gland, are surprisingly common and in one series accounted for 44% of malignant parotid gland lesions.[64] Most such lesions target intraparenchymal lymph nodes rather than salivary gland tissue itself. Metastases to the parotid gland most frequently originate from cutaneous SCC or melanomas of the head and neck, particularly when the index tumor involves the scalp, external ear, or upper third of the face.[65] More rarely, metastases to the parotid gland can originate from basal cell carcinomas, Merkel cell tumors, pleomorphic sarcoma (previously called *malignant fibrous histiocytoma*), nasopharyngeal carcinoma, and sebaceous carcinoma of the eyelid.

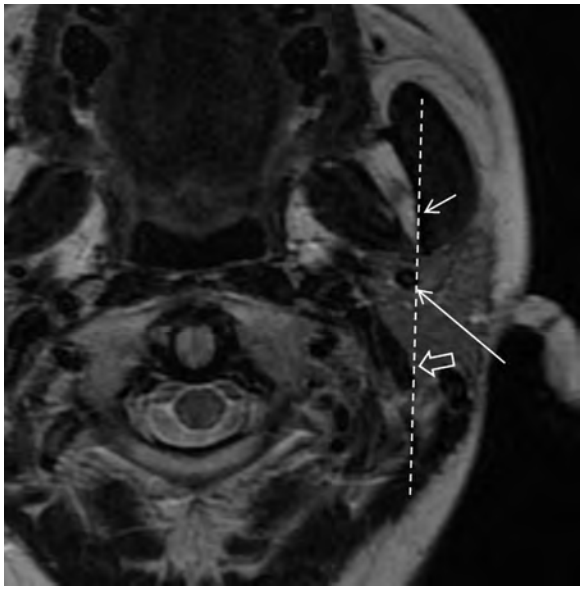
In addition to metastases from head and neck primaries, as many as 10–20% of metastatic salivary gland lesions originate from primaries below the clavicle, such as hepatocellular carcinoma, breast cancer, and, most frequently, renal cell carcinoma.[66]

As with most primary salivary gland malignancies, many metastases are asymptomatic, with the index tumor being clinically undetectable. In particular, the presence of an oncocytic or clear cell neoplasm in the salivary glands should raise the suspicion that it is a metastasis.[67]

Radiologically Assisted Surgical Planning

Benign tumors of the parotid gland require only local excision or extirpation or partial parotidectomy, whereas malignant masses necessitate total parotidectomy, with the associated risk of facial nerve sacrifice.[68] Injury to the lingual nerve in sublingual gland surgery or of the hypoglossal nerve in submandibular gland surgery is in part debilitating but arguably does not produce the major cosmetic and functional consequences of facial nerve injury. Facial nerve involvement is therefore of particular surgical and prognostic importance in parotid gland tumors. It confers a poor prognosis, with a risk of nodal metastases of 66–77% and 5-year survival of 9–14%.[69]

The facial nerve represents an arbitrary boundary between the superficial and deep lobes of the parotid gland. The nerve cannot usually be resolved by conventional imaging. Instead, anatomic landmarks are used, by drawing an imaginary line from the junction of the retromandibular vein and lateral border of the posterior belly of the digastric muscle to the most lateral aspect of the mandible[70] (Fig. 42.8). The retromandibular vein itself may also be used as a surrogate boundary between the superficial and deep lobes.[71] Although not in routine practice, tractography, a three-dimensional depiction of neural tracts by way of MRI diffusion tensor imaging, has the potential to optimize presurgical assessment of the facial nerve. A study by Attyé and colleagues demonstrated the feasibility of intraparotid depiction of the facial nerve, in which



• **Fig. 42.8** Left facial nerve landmarks. The position of the facial nerve and boundary of the deep and superficial parotid gland are inferred by aligning the lateral edge of the posterior belly of the digastric muscle, the retromandibular vein, and the lateral edge of the mandibular ramus.

surgeons were able to identify the facial nerve and its contact with parotid tumors.[72]

When tumor invasion of the parapharyngeal space is suspected on imaging, the surgeon may consider a cervical approach to resection, potentially with a mandibulotomy. Transmastoid surgery may be considered when imaging indicates invasion of the stylomastoid foramen. Skull base neuroforaminal invasion may warrant resection of the cartilaginous auditory canal, mastoidectomy, and/or resection of the ascending mandibular ramus and the associated risks of skull base surgery.

Surgical Management of the Primary Tumor

In general, surgery is the primary modality of treatment.[73,74] Malignant salivary gland disease is relatively resistant to radiotherapy (RT), and systemic anti-cancer treatments are mainly used in the palliative setting.

The concept of surgical excision with clear margins is sought in general, although tumor-specific factors should influence this objective—the primary site of disease, stage, histologic type and grade, invasive border, and, in the case of parotid malignancy, function of the facial nerve. There is a general consensus that RT has a role in treating microscopic disease such as may occur after total conservative parotidectomy sparing the facial nerve.[74]

Advanced-stage parotid cancer does not respect the boundaries of traditional surgical disciplines in the head and neck. Multispecialty input for vascular, neurosurgical, and free tissue reconstruction may be required.

Parotid malignancy may involve branches of the carotid artery, prevertebral muscles, retropharyngeal region, and infratemporal space including mastoid, middle ear, skull base, temporomandibular joint, and ramus of mandible. Local extension of parotid malignancy to the temporal bone requires respective surgery aiming to clear disease. Lateral temporal bone resection can include mastoidectomy, removal of bone at the epitympanum with progression to de-roof the facial nerve canal medially along with exposure of the jugular bulb and carotid artery. The external auditory meatus and tympanic membrane can be excised with the specimen. If the facial nerve is clinically clear, FSs of the proximal nerve can formally demonstrate clearance, skip lesions aside. The facial nerve can be grafted immediately. Bone removal of the mastoid sinus can facilitate facial nerve resection.

Involvement of the medial auditory meatus require a subtotal temporal bone resection, the medial extent of which is the internal carotid artery. If the tumor extends beyond the limits of a subtotal temporal bone resection, a total bone resection is indicated. These procedures are rarely performed and risk significant morbidity.

Surgical treatment of parotid gland malignancy is frequently complicated by a desire to preserve the facial nerve.[75,76] Of parotid malignancies, 25% involve the facial nerve at presentation. Complete paresis in some or all branches is an indication for partial or complete sacrifice.[77,78] Difficulty arises when the parotid lesion is suspected to be malignant on clinical or histocytopathologic grounds without facial nerve compromise. Macroscopic involvement observed during surgery, through which a plane cannot be found, justifies segmental resection of that branch to avoid tumor spillage.[79–84]

Management of the sacrifice of the facial nerve is covered later. Briefly, options to mitigate against the ensuing morbidity can broadly be considered as immediate or delayed; direct or grafted; and static, dynamic, or spontaneous dynamic.

Advanced lesions with skin fixity or ulceration necessitate skin excision, which, if not amenable to primary closure, may require local rotation and/or free tissue transfer. The latter option affords a means of filling the volume defect left after traditional forms of parotidectomy. Options for volume restoration include sternocleidomastoid flap, fat graft using either the Coleman needle technique or a periumbilical fat graft, or a free tissue transfer; further discussion is outside the scope of the chapter.

Submandibular gland malignancy is managed according to clinical stage. Low T-stage (T1) malignancy of the submandibular gland by definition has not breached the capsule of the submandibular gland and may, depending on histologic subtype, require gland excision alone.[85] A breach in the capsule, radiologic evidence of regional spread, or an unfavorable histologic subtype are indications for selective neck dissection of associated levels.

Sublingual gland tumors account for about 1% of major salivary gland neoplasms, and the vast majority are malignant.[86] The most common malignancies of the sublingual gland are MEC and ACC.

Surgical Anatomy and Access to the Parotid Gland

The parotid occupies the retromandibular region of the upper neck. The surface anatomy of the superficial component (lobe) includes the zygomatic arch superiorly; the posterior border of the mandibular ramus anteriorly, although the parotid often rests superficially over (an inconsistent part of) the masseter; and the upper third of the sternocleidomastoid muscle inferoposteriorly, the latter meaning that the tail of the parotid occupies the neck. At the anterior limit of the parotid, 1 cm below and parallel to the zygomatic arch, is the origin of the parotid duct, which passes across the masseter muscle before plunging through the buccinator muscle to open at the papilla consistently opposite the upper second molar tooth in the upper vestibule. The duct itself can be surrounded by a small separate aggregation of parotid tissue termed the *accessory lobe* and is closely associated with the buccal branch of the facial nerve. The deep component of the parotid, which is defined as deep to the plane of the facial nerve, has the posterior border of mandibular ramus and medial pterygoid anteriorly, the inferior surface of the petrous temporal bone superiorly, the styloid process and associated muscles (styloglossus, stylopharyngeus, and stylohyoid) medially, and the posterior belly of the digastric muscle inferoposteriorly. The deep lobe sits adjacent to the prestyloid parapharyngeal space. The retrostyloid space, defined

anteriorly by the tensor veli palatini fascia and the internal surfaces of the styloid muscles laterally, has as its medial limit the pharyngobasilar fascia overlying the superior constrictor muscle and posteriorly the prevertebral fascia. The retropharyngeal space contains the internal carotid artery, internal jugular vein, lower CNs (IX–XII), and sympathetic chain.

The digastric and styloid muscles separate the gland from the internal jugular vein, the internal carotid artery (the terminal branches of the external carotid pass through the deep lobe), and the lower CNs (IX, X, XI, and XII). The deep lobe accounts for 20% volume of the parotid. The parotid is surrounded by fascia; the superficial portion contains scant strands of muscle fibers in the direction of the platysma muscle with which it has a continuation. The deep layer is attached to the mandible and temporal bone at the tympanic plate, styloid, and mastoid processes.

The parotid contains 15 to 12 lymph nodes, the majority in the superficial lobe. The lymph channels lie in the superficial system of the head and neck. A rich network of lymph channels connects these intraglandular nodes. The parotid drains to the upper group of nodes in the deep cervical chain. The parotid lymph nodes are frequently the first-echelon nodes to the skin of the ear, cheek, temple, forehead, and anterior scalp.

A well-defined lesion of the superficial parotid mass can be approached either via a lazy-S preauricular cervicofacial (modified Blair) or a rhytidectomy incision. The rhytidectomy incision can be considered for patients concerned with optimal esthetics who have a small (<2 cm) mobile superficial mass in the mid to lower pole of the parotid.

The preauricular cervicofacial incision is marked in the pretragal groove (some advocate taking the incision onto or behind the tragus for improved cosmesis) and around the lobule of the ear, preserving 1 to 2 mm of facial skin. The incision passes posterior to the lobule over the attachment of the sternocleidomastoid muscle to the mastoid and then curves down and forward into an upper neck crease two fingerbreadths below the angle and lower border of mandible into the submandibular region. Hemostasis of the subdermal fat allows further careful dissection through platysma inferiorly. At this stage the greater auricular nerve (parallel to the external jugular vein) is encountered, and if possible the posterior branches are preserved. Subplatysmal dissection up to the tail of the parotid creates an inferior pocket. The preauricular incision is undermined either in the supra-superficial muscle aponeurotic system (SMAS) plane (with a face-lift technique through subcutaneous fat) or directly onto the parotid capsule to the anterior limit of the gland. Caution is required anteriorly to not damage branches of the facial nerve emerging in this zone. The upper pocket and lower pocket are joined by incision through fascia as it condenses in the lower anterior edge of parotid gland over the lower border of the mandible, and the skin flap is reflected with stay sutures. The preauricular incision is deepened by blunt dissection to spread tissues off the tragal cartilage in an avascular plane until the tragal pointer is encountered. The fascia overlying the upper third of the sternocleidomastoid muscle is raised and followed onto the muscle's medial surface, where the posterior belly of the digastric is exposed. This marks a depth plane for the emergence of the facial nerve. With the wide preparation above and below the stylomastoid region, careful dissection, with magnification and good illumination, in the direction of the facial nerve proceeds. There is usually perineural fat and a single overlying vessel encountered just before the facial nerve. A nerve stimulator is often useful at this stage. Once identified, the trunk is closely followed until it branches (at the pes anserinus). The upper and lower divisions are traced, and the parotid tissue cauterized with bipolar diathermy before division between the nerve branches.

Masses of the deep lobe can grow unnoticed until they manifest either as a retromandibular or a parapharyngeal mass. In one report, 20% were found incidentally.[87] A well-defined lesion of the deep parotid can be approached intraorally with an incision onto the anterior paratonsillar fold. This approach has the advantage of reduced morbidity and improved esthetics when compared with transcutaneous access but has the disadvantage that there is no option for control of the internal carotid proximally and limited access risks tumor capsule rupture and/or spillage. Larger or infiltrative lesions requiring wide margins may require adjunctive access procedures such as formal transcervical incisions and mandibulotomy.

Extracapsular dissection is advocated for benign parotid disease because there is growing consensus that it represents an oncologically safe procedure with lower risks of transient nerve weakness and reduced rates of Frey syndrome. Permanent facial nerve injury rates are similar. Advocates argue that there is little difference oncologically between accepting a close margin when the facial nerve is intimate and accepting a close circumferential margin when using the extracapsular techniques. There is no consensus about its role in low-grade malignancy, with most authors continuing to advocate as an absolute minimum a partial parotidectomy for any form of malignancy, which by definition will include associated intraglandular lymph nodes, which represent sentinel nodes for the purpose of staging.

Facial Nerve Monitoring

Facial nerve monitoring aims to highlight to the surgeon unexpected stimulation of the nerve intraoperatively to avoid irreversible injury. It also allows evaluation and prognosis of nerve function at the end of the surgical procedure.[88,89] Neuromuscular block should be avoided during parotidectomy. Needle electrodes are inserted into four regions of the face at the SMAS level, representing myotomes of the facial nerve main branches (excluding cervical). The learning curve for those unfamiliar with the use of a facial nerve monitor is steep. Trainees learn to interpret audible alarms by their character and volume and to identify false-positive sounds and learn that occasionally the equipment fails to identify what clinically appears to be facial nerve. A recent meta-analysis suggests that with routine use of the facial nerve monitor, temporary paralysis rates can be reduced but permanent paralysis rates are unchanged, although this review dealt with mostly benign disease (90%) and excluded studies that included salvage operations.[90] Advocates for routine use of facial nerve monitoring state that it is simple, relatively cheap, and safe. Most surgeons recognize its

usefulness in difficult parotid surgery—namely, salvage cases and/or advanced disease.

Surgical Anatomy and Access to the Submandibular Gland

The submandibular gland is situated under the lower border of mandible bilaterally. It is intimately associated anteriorly with the mylohyoid muscle, which forms a cleft in the anterior surface of the gland, producing a superficial and deep component. The superficial component is bordered by the digastric muscle antero-inferiorly and the stylohyoid muscle postero-inferiorly. The anterior facial vein and facial artery take a tortuous course in the fascia surrounding the posterior portion of the gland. The marginal mandibular branch usually runs superficial to the anterior facial vein, and in 20% of people runs below the palpable lower border of the mandible.[91] The deep lobe of the gland wraps around the free edge of the mylohyoid muscle and abuts the hyoglossus. Unlike the parotid gland, the submandibular gland does not contain lymph nodes. The submandibular duct exits the medial aspect of the superficial lobe and takes a submucosal course to the papillae just lateral to the lingual frenum in the floor of the mouth. The submandibular duct is surrounded by sublingual gland salivary units. The lingual nerve initially lies lateral to the submandibular duct but passes under and medially close to the gland hilum before penetrating the substance of the tongue. The hypoglossal nerve runs inferiorly to the submandibular duct on the hyoglossus muscle.

Excision of the submandibular gland is undertaken in the supine position with neck extension and some contralateral lateral flexion. A cervical incision is made no less than two fingerbreadths below the lower border of mandible. Incision of the platysma at the lower level of the submandibular gland demonstrates the investing layer of deep cervical fascia. Incision through this onto the gland permits identification of the anterior facial vein, which is ligated and retracted superiorly. This establishes a plane of dissection that protects the marginal mandibular nerve. The gland is freed inferiorly from the tendon of the digastric muscle and anteriorly from the fibrofatty tissue of level Ib, which is usually rich in small vessels that need careful cauterization. The facial artery is identified embedded in the posterior portion of the gland and can be ligated if required. The mylohyoid muscle is identified on the medial surface of the superficial gland and retracted anteriorly. The gland is bluntly dissected off the lower border of the mandible and is retracted in an inferior direction to demonstrate the lingual nerve and submandibular ganglion. Bipolar cautery through the ganglion allows the lingual nerve to be retracted to safety. The duct is traced before ligation, being separated from surrounding fibrofatty tissue rich with venous vessels.

Surgical Anatomy and Access to the Sublingual Gland

The sublingual gland is the smallest of the major salivary glands. It consists of a head anteriorly, known as the *lesser sublingual gland,* and a smaller tapered tail posteriorly, known as the *greater sublingual gland.* Functionally it is less a major gland than an aggregation of minor salivary gland units (there is no capsule), each with an individual duct that drains either into the main duct (tail portion) or directly into the floor of the mouth via ducts of Ranvier (head portion). The head of the gland lies lateral to the genioglossus muscle and medial to the inner table of the mandible. It lies on the mylohyoid muscle immediately under the mucosa of the floor of the mouth. The submandibular duct and lingual nerve run medially.

The sublingual gland is accessed via an intraoral incision medial to the palpated course of the submandibular duct. Submucosal dissection is started to identify the duct. This allows countertraction, which protects the duct during medial dissection of the gland off the genioglossus and hyoglossus muscle. Anterior release allows the deep and lateral surfaces of the gland to be freed from the mylohyoid muscle, with preemptive hemostasis of the rich venous channels transgressing the muscle. Proximal dissection of the gland off the duct will reveal the lingual nerve looping from lateral to medial under the duct. This is carefully isolated, and the posterior component of the gland is identified near the leading edge of the deep lobe of the submandibular gland.

Early-stage disease may be amenable to gland excision alone. Surgical excision with margins leaves a substantial defect in the floor of mouth. If this coexists with neck dissection, a low threshold exists for local flap or free tissue transfer to reconstruct the floor of the mouth to prevent neck contamination with saliva and preserve tongue movement.

Surgical Management of the Neck in Primary Parotid Malignancy

Clinical presentation of cervical lymphadenopathy is currently the key to planning management of the neck for salivary gland malignancy. At presentation, 15–29% of patients have neck disease.[79] When present, levels II, III, and IV are most commonly involved.[74]

Factors associated with nodal involvement include histologic type, grade, gender, preoperative course, facial paralysis, advanced T stage, and major nerve, soft tissue, lymphatic, vascular, perineural, or extracapsular invasion.[92] In one study, age over 54, increasing tumor size to 4 cm, perilymphatic spread, and extracapsular extension were associated with a 95% chance of neck metastases.[93]

In the absence of systemic metastasis, patients with a clinically positive neck should be offered an ipsilateral neck dissection, which should aim to preserve uninvolved structures. Procedures involving the clinically and radiologically node-negative neck are more difficult to plan. If the risk of cervical metastasis is greater than 15–20%, many would advocate elective treatment of the neck, with observation offered to those who do not meet this threshold. Currently no randomized controlled trials are available to aid in decision making for this clinical scenario. RT to an unoperated ipsilateral neck is an option after surgery to the primary site on the basis that it currently has a role in treating residual

TABLE 42.4 Risk Classification of Nodal Metastases in Primary Parotid Malignancy

	Tumor Histology	Comments
Low risk	Acinic cell carcinoma Low-grade polymorphous adenocarcinoma Low-grade mucoepidermoid carcinoma Oncocytic carcinoma Carcinoma ex pleomorphic adenoma Clear cell carcinoma Low-grade adenocarcinoma	Acinic cell carcinoma can transform into high-grade disease.
High risk	High-grade mucoepidermoid carcinoma Carcinoma ex pleomorphic adenoma (widely invasive or high grade) Adenoid cystic carcinoma High-grade adenocarcinoma Salivary duct carcinoma Metastatic squamous cell carcinoma Large cell carcinoma Small cell carcinoma Carcinosarcoma	

microscopic disease postoperatively.[74] Alternatively, a staging selective neck dissection, removing at a minimum levels Ib, II, III, and Va, is a consideration. A further option, although one infrequently adopted, is to perform FS analysis of lymph nodes within the digastric triangle; if positive, this becomes a prelude to a concurrent neck dissection. Zbaren and colleagues demonstrated concordance between FS and final histology with regard to correct histopathologic subtype and grade in only 43.4% and 44.6% of cases, respectively.[94] When the primary site is the parotid, intraglandular lymph node metastasis has been shown to independently predict occult metastasis to the neck, although how this finding will be implemented into an intraoperative management strategy is unclear.[95] Future research is likely to define the role of sentinel node biopsy in this setting.

To a degree, histologic subtype can inform management of the node-negative neck. Ductal carcinoma, adenocarcinoma, SCC, high-grade MEC, and undifferentiated carcinoma are associated with an average 68% probability of occult neck disease and are considered high risk.[96] Human epithelial growth factor receptor 2 (HER2) and deletion of tumor suppressor gene phosphatase and tensin homologue *(PTEN)* suggest high metastatic potential.[97] The grade of differentiation within each subtype is prognostically significant.[98,99] Table 42.4 suggests a risk classification based on the two factors of tumor subtype and grade.

In summary, patients with high-risk parotid tumors and a clinically and radiologically negative neck should be considered for elective treatment of the ipsilateral neck, be it a surgery or RT. It has been suggested that all patients with malignant submandibular tumors except T1 should have elective treatment to the neck.[85]

TABLE 42.5 Staging of Parotid and Neck Metastasis From Cutaneous Malignancy

P1	Single parotid lymph node <3 cm in diameter
P2	Parotid node >3 cm and <6 cm in diameter
P3	Parotid node >6 cm or facial nerve and/or skull base involvement
N0	Neck disease absent
N1	Single cervical node <3 cm in diameter
N2	Cervical node >3 cm or multiple nodes

Surgical Management of the Parotid and Neck for Metastatic Cutaneous Malignancy

The parotid lymph nodes are frequently the first-echelon nodes to the skin of the ear, cheek, temple, forehead, and anterior scalp. Cutaneous malignancy of these areas can manifest with parotid lymph node metastasis, often with features of aggressiveness such as fixity, skin ulceration, facial nerve weakness, and concurrent cervical metastases. SCC, malignant melanoma, and Merkel cell tumors are the most common skin malignancies that affect the parotid. Metastatic basal cell carcinomas are exceedingly rare and arise from neglected giant basal cell carcinomas (BCC) or the basosquamous subtype.[100]

Overall 5% of cutaneous SCCs will metastasize, but the rate increases to over 20% for those involving the scalp, external ear, temple, and periocular region.[101,102] SCCs are considered high risk when they are greater than 2 cm in maximum diameter (three times more likely to metastasize), are greater than 4 mm thick, involve the subdermal fat, are poorly differentiated or of histologic desmoplastic subtype, or show perineural and/or lymphovascular invasion, or when the patient is receiving immunosuppressant therapy.[103,104] It is suggested that given the thin skin of the face, SCCs at this anatomic site merit the lower thickness threshold of 2 mm.[103] The seventh edition of the staging classification by the American Joint Committee on Cancer (AJCC) incorporates these additional risk factors in the T-staging of cutaneous SCC, including the 2-mm cutoff.[105] Positive margins and local recurrence are also risk factors.

O'Brien suggested a staging system for metastatic cutaneous SCCs based on involvement of the parotid.[106] Patients with involved parotid nodes have a high incidence of clinical (26%) or occult (35%) neck metastases, which correlates with 5-year survival.[107] Disease staged as P1N0 (Table 42.5) have an overall 5-year survival rate of 65–70%, reducing to 30% with N2 disease.

The confirmation of metastatic cutaneous SCC in the parotid or neck is usually initially by needle aspiration cytology, preferably ultrasound guided, which has a specificity of 98%.[108] A nondiagnostic result should prompt repeat testing, which, if a cytologist is present in the clinic, incurs no delay. If the result is still nondiagnostic, a lymph node biopsy within an access incision, placed with mindfulness of the possibility of later surgery, is indicated.

Parotid metastases not involving the facial nerve should be treated with a therapeutic superficial or total parotidectomy depending on the clinical and radiographic evidence of involvement of the deep lobe. If facial paresis is present, then the nerve should be resected in the course of a radical parotidectomy with consideration of FS control of the proximal facial nerve stump. If the rate of occult metastases to the neck is greater than the 20% threshold suggested by Weiss, elective neck dissection may be indicated.[109] Parotidectomy and elective RT to the N0 neck is an option, with equivalent control shown to surgery and RT.[110] Elective neck dissection of the cN0 can be selective based on the primary tumor site. O'Brien investigated neck metastases in a series of 242 patients with P+N0 disease. Levels II and III most frequently had pathologic evidence of micrometastases (33% and 14%) but when clear, levels IV and V were rarely involved (6.7%). When the primary site was the external ear, level IV was involved infrequently (2.7%), and level V was not involved if levels II and III were clear. If the primary site was the posterior scalp, involvement of levels IV or V was 15.8% without involvement of levels II and III.[107] When the primary site was the anterior face and levels II and III were uninvolved, level I nodes could still be positive (10.5%) but level IV or V nodes were not involved. These authors concluded that for anterior face primaries with parotid metastases (cP+N0), levels I–III should be electively treated, and for posterior primaries levels II–V should be treated.[107] When nodal disease is clinically evident, a comprehensive neck dissection is indicated. The NIS3 staging system devised by Forrest and colleagues, which incorporates parotid involvement, has been externally validated and has strong prognostic value in the Australian population.[111]

The role of the sentinel node in the management of cutaneous SCC is still being clarified. It appears to be feasible, with sentinel nodes being found in 90% of cases and a sensitivity of 94%.[112] A prospective trial in Australia suggested that definitive evidence for survival benefit would require a prospective randomized controlled trial of over 1000 patients.[112]

Cutaneous melanoma of the head and neck accounts for 15% of all cutaneous melanoma. Malignant melanoma of the upper face and anterior scalp or mid-scalp spreads via the superficial lymphatics to the parotid gland and cervical nodes, although the pattern of spread can be unpredictable. In a subgroup analysis of 45 patients with regional node-positive head and neck melanomas, 33 of 45 cases (73.3%) were in the anticipated area, 2 of 45 were contralateral, and 6 of 45 relapsed in the contralateral neck.[113] Clinically evident parotid deposits justify parotidectomy with ipsilateral comprehensive neck dissection because occult neck disease is found in 40%. Posterior scalp and postauricular primaries merit a level V neck dissection, which includes superficial nuchal lymphatic tissue. Elective neck dissection has been superseded by sentinel node biopsy if the primary is stage Ib (or >1 mm in depth) or greater. If the sentinel node is positive, patients usually proceed to a comprehensive neck dissection, which, if the primary is on the upper face or mid-face, anterior scalp, vertex, or ears, should be undertaken alongside a parotidectomy. Whether survival benefit is conferred to patients managed with sentinel node biopsy remains the focus of intense debate.

Merkel cell carcinoma is an aggressive cutaneous tumor of neuroendocrine origin with a metastatic potential of 45–65%. Its mortality rate exceeds that of melanoma. For primary Merkel cell carcinomas of the head and neck, a low threshold should be set for investigating the parotid and neck. The role of sentinel node biopsy is being explored for this purpose and mirrors the role in cutaneous melanoma. A positive intraparotid node merits parotidectomy and comprehensive neck dissection. The limitations of sentinel node procedures—namely the false-negative rate resulting from the aberrant superficial lymphatic drainage of the head and neck, in-transit metastases, or extreme proximity to the primary site, and the increased morbidity of subsequent completion neck dissection—are no different from when the technique is used for melanoma.

Complications of Surgery for Salivary Gland Malignancy

Complications of parotid surgery for malignant disease can be divided into immediate, early, or late categories. Immediate complications are mainly related to hemostasis and injury to the facial nerve. Early complications are usually wound related and include infection, breakdown, and salivary collections or fistula. Late complications include Frey syndrome.

The facial nerve is the most important structure to identify during the procedure, and immediate damage to the trunk or major branches will produce facial paresis that carries significant functional and psychosocial morbidity for the patient. Facial nerve–sparing operations have a temporary paresis rate of 15–25% for superficial parotidectomy and 20–50% for total parotidectomy.[114–117] Permanent paresis rates of 1–2% for superficial parotidectomy and 4–6% for total parotidectomy are commonly quoted.[114–117]

The greater auricular nerve supplies sensation to the lower third of the anterior and posterior skin of the external ear. Although its loss does not have a profound effect on quality of life, preservation of the posterior branch, advocated by some, reduces the risk of permanent sensory loss from up to 60% to 20%.[118]

Wound breakdown can occur because of skin edge ischemic necrosis, particularly if a cervicomastoid (modified Blair) incision is excessively high in the mastoid or postauricular region. Hematoma rates should be less than 1%, and a drain in the wound bed is required in most circumstances. Where parotid gland tissue remains, salivary fistula and sialocele are possible; if the duct is not damaged, management includes a pressure dressing, which normally suffices. If persistent, saliva flow can be reduced by transcutaneous or retrograde (Stenson duct) injection of botulinum toxin or, less commonly, the use of systemic anticholinergic therapy with hyoscine bromide, scopolamine patches, or alternatives.

Frey syndrome, or gustatory sweating, is reported to occur in 70–80% of patients after parotidectomy.[119,120] Surgical interventions used intraoperatively to limit the frequency of Frey syndrome include interposing SMAS flaps, sternocleidomastoid muscle, or a de-epithelialized fat-dermal flap. If Frey

syndrome occurs postoperatively and is distressing, the favored management is to use the Minor starch-iodine test to delineate the affected zone, followed by intradermal infiltration of botulinum toxin. This method has a mean therapeutic window of 11 months.[120]

Complications of submandibular gland surgery are related to the superficial and deep relationships to neurovascular structures. The anterior facial vein toward the posterior aspect of the gland is usually just below the marginal mandibular branch of the facial nerve. The nerve is vulnerable to a traction injury, or, if the wrong plane is entered, it may be inadvertently transected. The deep and cephalic aspect of the gland lies close to the lingual (CN V3 anterior division) and hypoglossal nerve (CN XII), both of which may be damaged. Excessive tension or zealous cautery across the parasympathetic ganglion (between the lingual nerve and the gland) risks nerve injury. The submental branch of the facial artery or the facial artery itself can bleed if not ligated effectively, causing an expanding neck hematoma. The duct is ligated as near to the floor of the mouth as possible. Occasionally, retained duct stones become symptomatic.

Complications of the sublingual gland are usually related to the associated neurovascular structures. The lingual nerve is at risk as it passes from lateral to medial under the proximal third of the submandibular duct. Venous connections transgressing the mylohyoid muscle can be difficult to control. The duct may be damaged by excessive handling, or it may be cut or ligatured inadvertently, risking an obstructive episode of submandibular gland swelling.

Management of the Facial Nerve

If part or all of the facial nerve is dysfunctional before surgery for parotid malignancy, partial or complete nerve resection is usually indicated. Current opinion recommends that every effort be made to preserve functional branches by dissecting through the interface between tumor and nerve, although this usually assumes that postoperative RT is available to the patient.

In addition to the adverse effects to the periocular and perioral regions, a significant psychosocial morbidity also ensues after facial nerve sacrifice. Planned procedures to mitigate against the cosmetic and functional sequelae of facial nerve injury can be categorized broadly by site (periocular and perioral), timing (immediate/delayed and temporary/permanent), and static, dynamic, or spontaneous dynamic subgroup. Ophthalmic consultation peri-operatively is useful if facial nerve sacrifice is planned. Periorbital swelling in the early postoperative phase may mask high risk for development of lagophthalmus and exposure keratitis. Ophthalmic considerations include prevention of corneal exposure, correction of lower lid ectropion, and management of brow ptosis. Periocular temporary measures to protect from xerophthalmia include temporary punctal occlusion, lateral tarsorrhaphy, and adhesive gold weight for the upper lid. Definitive oculoplastic procedures include formal lateral tarsorrhaphy (which is easily reversible), medial canthoplasty, upper lid retractor recession, lower lid lateral strip, and canthopexy with or without wedge excision and gold or platinum upper lid implants, which sit in the pretarsal plane.[121] The sub–orbicularis oculi fat (SOOF) can be lifted via a lower eyelid transconjunctival incision combined with lateral canthotomy and inferior cantholysis. The SOOF and periosteum are dissected off the anterior maxillary wall inferiorly, released with transverse incisions, and reattached to the arcus marginalis and superficial temporal fascia. A mid–face-lift carried out in the subperiosteal plane can address more lateralized effects of gravity. Brow ptosis can be managed by direct brow lift, endoscopic brow lift, or upper third face-lift.

Asymmetry at the oral commissure can be ameliorated with immediate or delayed hitch stitching using non-resorbable monofilament sutures or grafting with tensor fasciae latae or palmaris longus tendon. Botulinum toxin injected into the contralateral depressor anguli oris can mitigate the asymmetry seen in the lower lip during smiling.

Direct nerve repair is indicated if the nerve segment loss is under 1 cm and nerve ends are proven free of tumor, usually by intraoperative FS control. The best recovery rates are seen if this is feasible without excessive tension at the neural anastomosis. Electromyography (EMG) monitoring is recommended by some, although many think it offers little. Certainly there is little point in encouraging the patient to practice facial movements before repolarization potentials are established (around 4 months) and objective movements start to appear (6 months).[121] One benefit to using EMG is reexploration of the anastomosis, which maybe indicated if repolarization potentials are not appearing after 6 months. If the nerve gap is greater than 1 cm, immediate nerve graft is possible when proximal and distal portions of the facial nerve remain. The facial nerve is a monofascicular nerve requiring an epineural repair. Non-resorbable monofilament 10/0–12/0 grade is used to oppose the epineurium. Sources of nerve graft include the greater auricular nerve, which is usually readily available on the ipsilateral side, or the sural nerve. Rerouting techniques that involve mastoid drilling to retrieve the intracanalicular portion of the facial nerve maybe indicated to mobilize a sufficient distance of proximal facial nerve to allow microsuturing.[122] Nerve grafting can achieve an improvement in tone and activity in 60% of patients.[123] Time to recovery is unaffected by age, indication, length of graft, number or type of grafts, and RT. A case-control study of 52 patients receiving nerve grafts showed no significant difference in recovery to House-Brackman (HB) score 3/4 between the non-irradiated group and the irradiated group.[124] A jump graft from the contralateral facial nerve (termed a *cross-facial nerve graft*) can achieve similar levels of dynamic recovery of facial movement (HB score <4) that is "spontaneous" (not in a temporal sense, but an emotive sense), meaning no new learned behaviors are required to effect a motor stimulus.

When the proximal facial nerve is absent or insufficient for grafting or there is a delay of over 6 months from loss of nerve function, nerve jump anastomosis is indicated. The hypoglossal nerve and the nerve to the masseter muscle have been described as sources of motor innervation when the proximal facial nerve is absent. Nerve anastomosis may be possible

directly or indirectly, using a jump graft. To animate the lower lip, a direct neurorrhaphy of the proximal marginal mandibular branch of the facial nerve to a portion of the hypoglossal nerve (usually <30%) may be possible. To animate the buccal and zygomatic muscles, a direct neurorrhaphy of the nerve to the masseter muscle may likewise be possible. This has the advantage of limiting the potential for synkinetic movements developing between the upper and lower face. Rehabilitation necessarily requires learning to activate the tongue or ipsilateral masseter to effect facial movement. This can lead to substantial gain in tone and some improvement in psychosocial functioning, but the learned movement is never "spontaneous" and therefore the patient may request another repair technique. There is a clarification of the role of these techniques to maintain muscle tone while alternative strategies are entertained. Malik compared outcomes in 25 cable grafts from the contralateral facial nerve and 28 hypoglossal-facial transpositions and found superior outcomes with cable grafts using the HB scale for assessment.[125]

When direct nerve repair is not possible and a graft or transposition is entertained, one option, if a substantial defect requires cosmetic or functional reconstruction, is muscle free tissue transfer harvested with the associated nerve (for jump grafting). Examples include harvesting of vastus lateralis with its motor nerve or latissimus dorsi with the thoracodorsal nerve. Some consider the vascularized nerve to offer a more reliable source of jump graft, but this has been argued as ignoring the known pathophysiologic changes of a severed peripheral nerve.[125] Further (simpler) muscle transfer procedures should be chosen for immediate results if life expectancy (or expected tumor-free interval) is unlikely to exceed 1 year because the alternative nerve regeneration techniques progress over a period of 18 months before the final result is obtained.

For the paralyzed face that has no prospect of recovery and requires dynamic function, muscle transplantation remains an alternative. Regional muscle transposition of temporalis muscle and masseter muscle are options that when used together can contribute to improved position of the ptotic nasolabial fold and degree of animation at the modiolus. Alternatively, free tissue transfer using microvascular techniques can contribute muscle and nerves to the ablative region. Gracilis muscle or pectoralis minor muscles transferred with their respective motor nerves 6 months after cross-face grafting are used for this purpose.

Non-surgical Therapy for Salivary Gland Tumors

The recurrence rate for salivary gland tumors after initial surgical management remains less than optimal, with rates of 20% in T1 and T2 tumors rising to 47% in larger T3 and T4 tumors at 10 years.[126] RT has historically been used in the adjuvant setting to reduce this relapse rate and to improve locoregional control (LRC). Prospective randomized trial evidence is lacking, but a review of retrospective series showed that the addition of RT to surgery improved LRC from 66–84% to 73–96%.[127] RT seems to be beneficial only with advanced disease (stages III and IV), node-positive disease, the presence of close or positive resection margins, bone or perineural invasion, or high-grade tumors. In these situations, adjuvant RT improves 5-year LCR from 17% to 51%.[128–130]

Salivary gland tumors are not very radiosensitive. The dose required is 60 Gy for microscopic disease, increasing to 70 Gy for macroscopic residual disease in 30 fractions or equivalent. The delivery of radiation can be difficult owing to the proximity of the surgical bed to critical structures, with dose tolerances lower than required to sterilize the malignant cells. The propensity for perineural spread of salivary gland tumors, particularly ACC, requires the radiation oncologist to have knowledge of and to include the pathways of the local nerves from the tumor bed to the skull base. This adds to the complexity of radiation target volumes and the challenges of delivering a cytotoxic dose. Intensity-modulated radiotherapy (IMRT) techniques have improved the dose gradients that can be achieved in these circumstances, enabling a steep fall-off of dose from the target to adjacent critical structures. There is still a role for conventional conformal techniques using a wedged pair beam approach for more simple volumes such as the parotid bed, where the volume of low-dose radiation to normal tissues can be minimized compared with that of IMRT.

Particle RT—for example, proton beam therapy—has the potential to overcome some of the problems encountered with standard photon beam RT, such as reducing the dose to critical organs at risk and minimizing low dose to normal tissues, thereby reducing risk of second malignancy.[131] Radiobiologically, particle therapy may also provide an advantage over photons owing to the low radiosensitivity and indolent nature of these tumors.[132]

Dosimetric studies in SCC of the head and neck suggest benefits in terms of target volume coverage and dose to organs at risk when the target volume lies close to critical structures, but data in salivary gland tumors, particularly in the postoperative setting, are lacking. In cases of inoperable macroscopic disease or reirradiation, particle therapy may provide a benefit over standard photon therapy for the radiobiologic reasons and normal tissue–sparing effects outlined earlier.

The radiation target volume delineation depends on initial disease extent and pathologic findings after surgery. The whole surgical bed should be included in the high-dose volume. In parotid tumors this will include the parapharyngeal space and infratemporal fossa, together with the local nerve pathways back to the skull base (particularly in ACC, which has a high propensity for perineural spread). Ipsilateral neck node levels I–V should be included in the case of pathologically positive nodes. It is recommended to electively treat ipsilateral node levels I–III because of a 20–30% risk of subclinical nodal disease in clinically node-negative cases. If tumors lie close to or across the midline, then contralateral levels I–III should also be treated. In case of perineural invasion, CN pathways up to the base of the skull must be included in the target volume.[129]

RT also has a role in the palliative situation. Inoperable recurrent disease may be suitable for reirradiation if localized and of small volume. This may be appropriate even if distant

metastases are present—for example, in ACC, in which the progression of distant disease can be quite indolent, with patients living for many years with systemic metastases. In this situation, focused RT using stereotactic or IMRT techniques can provide symptomatic relief from local relapse with minimal toxicity. Palliative RT for distant metastases within bone or soft tissues may also provide a benefit and should be considered if surgical resection is not possible.

Chemotherapy has a limited role in palliation but remains investigational in the adjuvant setting. Chemotherapy for inoperable recurrent or metastatic disease has not been proven to improve overall survival. Multiple agents and regimens have been studied, with cisplatin, cyclophosphamide, doxorubicin, and 5-fluorouracil being the most active agents, but still with disappointing response rates of only around 20%.[133]

An increased understanding of the pathogenesis of these salivary gland tumors provides the potential for predictive and prognostic molecular biomarkers. A, *MYB–NFIB* gene fusion derived from the t(6;9) translocation has been identified in ACC; however, this has yet to be shown to provide any prognostic or predictive information.[134-137] The tyrosine kinase receptor KIT is overexpressed in ACC, and it was hoped that this might provide a therapeutic target. Unfortunately, results with the tyrosine kinase inhibitor imatinib proved disappointing.[138,139] Disruption of a NOTCH signaling pathway because of a translocation t(11,19) involving the *MALM2* and *CRTC1* genes has been described in MEC and appears to correlate with a less aggressive phenotype with improved survival.[140,141] No successful targets have been found in MEC that are suitable for drug therapy. The molecular alteration ETV6–NTRK3 has led to the definition of a new salivary gland tumor entity, the mammary analog secretory carcinoma. The IGF1R/insulin receptor (INSR) signaling axis is necessary for oncogenic transformation induced by ETV6–NTRK3, and inhibition of this pathway is being investigated as a potential disease-modifying approach. Carcinoma ex pleomorphic adenoma and SDCs may have *HER2* amplification and may benefit from treatment with an anti-HER2 agent such as trastuzumab with improved disease-free and overall survival.[142] Around 75% of SDC expresses high levels of androgen receptors (ARs), and androgen blockade has been shown to be useful therapeutically in AR-positive tumors.[143]

Future therapeutic benefits of this understanding of the molecular basis of these tumors are eagerly awaited in the absence of useful therapies for most advanced disease at this time.

Factors Influencing Survival

Survival analysis after diagnosis of salivary carcinoma is problematic. Data derived from single-center longitudinal reports have their limitations. Because salivary gland carcinoma is a rare disease, such reports span decades, during which time treatment has undoubtedly developed, making interpretation of aggregate survival rates difficult. Many centers have considered revisiting past published cohorts in light of the updated histologic classification. Different inclusion criteria have meant that some cohorts have not excluded surgically managed disease with palliative intent.

Longitudinal studies of salivary gland malignancies have shown that independent predictors predicting outcome known preoperatively are age, gender, site, histologic type, histologic grade (differentiation), size of tumor at presentation, pain, and cervical metastasis and, if reporting only parotid malignancies, facial nerve involvement and skin involvement (Table 42.6) Postoperative poor prognostic factors include pathologic findings of peri-neural infiltration, positive margins, and multiple neck node metastases.

Because of the perceived shortcomings of established staging systems (AJCC, 3rd edition), there are proponents for analyses that enumerate the risk based on multivariate statistics that effectively model survival.

Historically, management of salivary gland malignancy has been based on a crude distinction between malignant and benign tumors. There are recent large high-quality additions to the literature of salivary gland malignancy that address histologic subtypes of salivary gland malignancy and should improve treatment strategies designed for the patient. Studying each histologic subtype is extremely difficult without adequate recording and reporting systems in place with a high level of consistency across geographical areas and time periods because of the relative rarity of the diseases.

One such study is a population multicenter report of 2400 cases investigating MEC, the most common salivary gland malignancy. MEC accounts for around 40% of salivary gland malignancies.[144] MEC is believed to be a tumor of large duct (striated or excretory) origin. MEC has traditionally been divided into low, intermediate, and high grades. Tumor grade can be considered high risk or non–high risk in relation to risk of metastases and disease-specific survival. Level I–III nodal metastasis rates were 3–8% for low and intermediate grades and 36% for high grade; level IV–V nodal metastasis rates were 0.4–0.6% for low and intermediate grades and 9% for high grade. A 9% skip metastasis rate was seen in high-grade MEC that was not observed in low and intermediate grades. Disease-specific survival at 5 years was 98–97% for low and intermediate grades (non-significant difference) and 67% for high grade. A recently discovered genetic translocation, specifically an oncogene fusion point, CRTCI-MAML2, is found in around 30–55% of cases of low and intermediate grades of MEC[145]; p27 was found in 70% of low- and intermediate-grade MEC. Both markers are independently correlated with lower incidence of metastasis and better outcome.

ACC is the second most common salivary carcinoma. It occurs more commonly in women than in men (60:40) and affects people commonly in the fifth and sixth decades. ACC is important because it is a low-grade carcinoma that causes significant mortality, and 40% of patients develop metastatic disease. It characteristically grows slowly and metastases late (after 10 years). Perineural spread causing skull base extension is a frequent occurrence. The pulmonary system and liver are common sites of distant metastasis, but often with an indolent course. Surgical resection with clear margins provides the best chance of cure, but margins are difficult to delineate clinically

TABLE 42.6 Table of Published Cohorts Including Multivariate Analyses for Factors Predicting Survival

Study	Institution	N	Site	T	Nodes	Fixity	VII Nerve	Grade	Age	Male Sex
O'Brien (1986)	Alabama	113	P, SM, M	+++*				++	++	
Theriault and Fitzpatrick (1986)	Toronto	271	P only	+++	+++				+	
Spiro (1989)	SKIV CC	463	P, SM	+++*				+++	++	
North (1990)	John Hopkins	87	P, SM			+	++	+		+
Frankenthaleret (1991)	MD Anderson	178	P only	++	++		++	++		
Kane (1991)	Mayo Clinic	194	P only	+*				+	+	+
Leverstein (1998)	VJ Amsterdam	65	P only	+	+					
Calearo (1998)	Ferrara	167	P only	++						
Van de Poorten (1989)	NCL Amsterdam	151	P only	+	++†	+			+	
Reneham (1996)	Manchester	103	P only	++	++			++		
Kirkbride (2001)	Toronto	184	P only	+++					+++	
Terhaard (2004)	Amsterdam	565	P, SM, M	++	++	+			++	+
Lima (2005)	Brazil	150	P	+						
Kalkarala (2010)	United States	639	M	+	++				++	++
Cheung (2011)	United Kingdom	1573	P, SM, M	+++*				++	++	++
Biorndal (2012)	Denmark	871	P, SM, M	+++	+++			+++	+++	
Chang (2014)	Korea	98	P	+	++		++			
Lee (2015)	United States	2626	SM	++				++	++	++
Jagadeesh et al (2015)	United States	112	P, SM, M	+			++			++

*American Joint Committee on Cancer (3rd) staging.
†Included histologically positive nodes.
M, minor salivary gland; *P,* Parotid gland, *SM,* submandibular gland; +, <0.05; ++, <0.001; +++,<0.0001.

because of the absence of a desmoplastic response at the advancing front of tumor, which is characteristically widely infiltrative. Cervical node metastases are rare, and a neck dissection is not indicated for staging. A recent report suggested no survival benefit after elective neck treatment for major and minor salivary gland ACC.[146] A retrospective review of 616 adenoid cystic salivary gland carcinomas estimated the frequency of cervical metastases as 10%, but up to 19% when the primary site was the lingual tonsil–lateral tongue–floor of mouth complex—specifically involving the "tunnel-style" metastasis, which implies direct spread.[146] ACCs are graded based on pattern, with solid areas correlating with a worse prognosis. Single metastases or multiple metastases located in a single lobe of the lung or liver may be amenable to mastectomy in surgically selected patients. There is some evidence that *MYB–NFIB* gene fusion and subsequent overexpression of *MYB* RNA oncogene can be used as a diagnostic aid, because it is expressed in over 86% of ACCs, but it remains unclear whether it holds prognostic or therapeutic significance.[147]

PLGAs mainly involve minor salivary glands of the palate, buccal mucosa, and upper lip. PLGA is rare in major glands, unlike ACC, which it can mimic histologically. PLGAs account for 40% of malignant minor salivary gland tumors. As the name suggests, PLGA is regarded as a low-grade neoplasm, but behavior is unpredictable and similar or worse than that of MEC. Fifteen percent of cases are associated with cervical metastases, 7.5% with distant metastases, with 12.5% of patients dying from their disease. The diagnostic difficulties arise in needle or incisional biopsies, in which the periphery of the tumor is not available to determine whether infiltrative growth is present or absent.

Acinic cell carcinoma is a low-grade malignant salivary neoplasm that represents 6–7% of primary salivary gland malignancies. A slowly growing mass in the parotid gland (90%) is the most common mode of presentation. Acinic cell carcinoma has a significant tendency to recur and to produce metastases (cervical lymph nodes and lungs) and may undergo evolution to a high-grade variant wherein the facial nerve is more frequently involved (70%) and pain can be reported (25%). The presence of immunohistopathologic markers (cyclin-D1, p53, and Ki-67) are predictors of high grade and should prompt aggressive management with a lower threshold for facial nerve sacrifice.[148] Mortality from acinic cell carcinoma is reported as less than 10%, the highest survival rate among the histologic subtypes of salivary carcinoma.

AR is usually expressed in SDC, otherwise known as *mammary analog salivary gland tumors.* Histologically, it appears as a subgroup of acinic cell carcinomas, although deplete of basophils. Immunohistochemistry, however, differentiates the two pathologies in showing S100, mammaglobin, vimentin, and MUC4.[5] Fluorescence in situ hybridization (FISH) analysis shows the fusion oncogene *ETV6–NTRK3* in 100% of patients. Those positive for this receptor should be offered hormone suppression treatment. Mammary analog salivary gland tumors have a high metastatic potential, which merits elective treatment of the clinically normal neck. Survival is worse than with acinic cell carcinoma, with a reported mean disease-free survival of 92 months—hence the need to treat as a high-risk salivary malignancy.

Cervical metastases have a negative prognostic effect. In a large series of 288 cases, Spiro and colleagues reported from Memorial Sloan Kettering Cancer Centre that overall 5-year survival in salivary cancer was 75% in the cN0 neck, reducing to 10% in patients with cN+ neck at presentation.[149] Furthermore, when cervical nodal metastases developed after primary treatment, survival was only 17% at 5 years.

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43 Melanoma

MARK B. FARIES, BRENDAN D. CURTI

Cutaneous Melanoma

Melanoma has one of the most rapidly increasing incidences of any solid tumor. Over the last 5 decades, it has increased fivefold. The disease often strikes individuals in the prime of life, with peak age of onset in the sixth decade, and it is responsible for one of the highest losses of productive years of life of any tumor type.[1] Fortunately, there have been improvements in the care of the disease that have made therapy more successful and less morbid. It appears this pace of improvement will continue in the near future. Advances include improved screening with earlier diagnosis, improved surgical therapy using less morbid techniques, and recent rapid discovery in systemic therapies powered by improved understanding of tumor biology and tumor immunology.

Melanoma of the head and neck shares many of the characteristics of melanomas that arise in other anatomic locations, but there are several specific considerations in this region. These include differences in the demographics of the patient population, the likely etiology and mutational makeup of tumors, patterns of spread and prognosis, and anatomically derived differences in treatment difficulty.

Demographics and Etiology

Melanomas of the head and neck tend to occur in older patient populations than melanomas at other anatomic sites.[2] It is also a more male predominant disease, particularly for lesions on the scalp and ears. Differences in hairstyles and hair loss between men and women are the likely source of this difference. Anecdotally, scalp melanomas in women seem to occur close to parts in the hair, making that area of particular interest during skin surveillance. Table 43.1 contrasts the features of melanomas of the head and neck to those of other sites. The features of these melanomas may be the result of the chronic sun exposure of this area of the body and cumulative ultraviolet radiation damage. This also seems to result in a different genetic profile with regard to mutations found in these tumors. The causative nature of ultraviolet radiation for these patients has been confirmed by analysis of mutations that occur. These mutations in melanoma in general, and particularly in chronically sun-damaged skin of the head and neck, demonstrate cysteine to thymidine change, which is characteristic of ultraviolet damage.

Other patterns of damage are distinct for the chronic sun damage of the head and neck. Early genomic evaluation demonstrated a different pattern of alterations across the genome compared with melanomas at intermittently sun-damaged areas or acral or mucosal melanomas.[3] More recent evaluation of specific mutations has demonstrated a greater tendency of melanomas in the head and neck to harbor *NRAS* or *c-kit* mutations rather than *BRAF,* which is the most common mutation in most other body sites. This pattern is also true for older patients, who more typically have head and neck primary melanomas. These genomic differences have implications for the therapies most likely to be beneficial.

Diagnosis

In general, because melanoma is a tumor that most frequently begins on the surface, early diagnosis should be possible in most patients. Increased awareness and emphasis on screening seem to have yielded benefits related to earlier diagnosis and improved prognosis. Features of skin lesions that generally suggest a risk for melanoma classically are remembered with the "ABCD(E)" mnemonic, with *a*symmetry, *b*order irregularity, *c*olor variegation, increased *d*iameter, and *e*volution of the lesion as warning signs.[4] Another rule of thumb highlights "ugly duckling" lesions, which are lesions that are dissimilar in appearance to the patient's other nevi or pigmented lesions. Such "odd" lesions warrant particularly close examination and possibly biopsy. Finally, lesions that the *patient* is concerned about demand more attention. The patient is often the individual with the greatest expertise regarding his or her own skin, so the patient's concern about a particular skin lesion demands special consideration.

Melanomas in the head and neck may be more difficult to diagnose than melanomas on other parts of the body owing either to location on the top of the head (above the examiner's view or hidden by hair) or to being hidden in a broader field of sun-damaged skin. It is often useful to have the patient sit in a lower chair, not on an examination table, to facilitate examination of the scalp. Taking the time to examine the skin beneath the hair can also be an important addition to the examination and frequently does not take much additional time. The best

TABLE 43.1 Comparison of Head and Neck Versus General Melanoma

Feature	Head and Neck	General Melanoma
Median age	60s	50s
Gender	Strong male predominance*	Minimal to moderate male predominance
Histology	Increased desmoplastic and lentigo maligna†	Predominant superficial spreading
Predominant metastasis route	Less commonly nodal	Principally nodal
Mutational status	Wild type, NRAS†	BRAF

*Source: Monroe MM, Pattisapu P, Myers JN, Kupferman ME. Sentinel lymph node biopsy provides prognostic value in thick head and neck melanoma. *Otolaryngol Head Neck Surg* 2015;153:372–8.

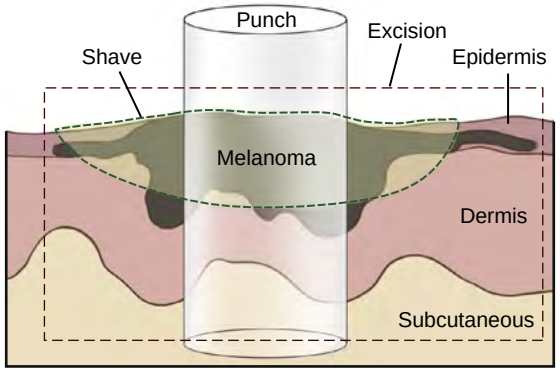
†Source: Helsing P, Robsahm TE, Vos L, Rizvi SM, Akslen LA, Veierod MB. Cutaneous head and neck melanoma (CHNM): a population-based study of the prognostic impact of tumor location. *J Am Acad Dermatol* 2016;75(5):975-982.e2.

opportunity to examine the scalp is probably while someone is washing or cutting the patient's hair, and the patient's barber or hairdresser can be an ally in surveillance.

The second challenge in diagnosis is the unusual appearance of many melanomas in the head and neck. The prevalence of lentigo maligna melanoma, desmoplastic melanoma, and amelanotic melanoma in the head and neck leads to tumors without typical features. This calls for a relatively high index of suspicion, particularly for patients at higher risk for melanoma and a low threshold for biopsy. Dermoscopy may be of some help. The dermatoscopic features typical at other sites of the body can also be applied to head and neck cutaneous lesions, but there are distinct features that may be present specifically in head and neck melanomas.[5] These include low frequencies of irregular dots, two or fewer colors in lesions, the presence of pseudonetworks, increased density of vascular networks, and red rhomboidal structures.

Biopsy

Lesions that are suspicious for melanoma, nonmelanoma skin cancer, or atypical melanocytic tumors should undergo biopsy and pathologic evaluation (Fig. 43.1). Several biopsy techniques can be applied as long as the specimen retrieved is adequate to render an accurate diagnosis. The most thorough technique from a pathologic standpoint is excisional biopsy. This eliminates the risk for understaging of the lesion as a result of inadequate sampling. Any excisional biopsy should be performed with the thought of eventual wide excision kept in mind. This means the orientation of the biopsy and closure should be able to be incorporated into the final excision without compromise of options for reconstruction.



• **Fig. 43.1** Biopsy techniques. Multiple techniques can be used to evaluate skin lesions suspicious for melanoma. Excisional biopsy provides the most complete assessment. Care must be taken with punch or shave biopsies to minimize the risk of understaging tumors because of sampling errors.

Such anticipation of the final closure technique can be difficult in the head and neck area. Also, the limited space of this body region and its cosmetic sensitivity may limit the ability to perform excisional biopsy of many lesions. Shave biopsy is the most commonly employed biopsy technique in the much of the head and neck. An inadequately performed shave biopsy can compromise the histopathologic staging of the tumor and make treatment decisions more difficult. The most significant problem is a biopsy that is too shallow, leaving a positive deep margin. The depth of a melanoma is a principal determinant of both the width of the final excision margin and the need for regional lymph node staging, and underestimation of the depth of a melanoma can result in undertreatment. Particularly with relatively thin melanomas, an insufficient initial biopsy can make it extremely difficult or impossible to accurately determine the depth, even if one were to re-perform the biopsy at that site, because deeper portions of the tumor may be lost owing to cautery or inflammation resulting from the initial biopsy. Finally, in broad lesions, complete biopsy, whether excisional or shave, may be impossible, particularly when close to important structures such as the eyelid or lip. Incisional or punch biopsies may, therefore, be necessary. These too may understage the tumor, although in that case, the eventual final staging at complete excision would be accurate. Multiple incisional or punch biopsies in large lesions may help decrease the risk of inadequate initial evaluation.

Prognosis and Staging

Cutaneous melanoma is staged based on the features of the primary tumor, the status of regional lymph nodes, and the presence of any distant sites of metastasis.[6] Clinical staging is based on physical examination and the pathologic findings of the primary biopsy. The work-up required for pathologic staging varies based on the risk of the primary tumor.

Primary tumor staging is principally determined by the depth, with greater depth corresponding to worse prognosis. In the past, this depth was measured in two different ways: by Breslow thickness measured in millimeters of invasion from the granular layer of the epidermis to the deepest penetration

of tumor cells,[7] or by Clark's levels of invasion,[8] based on the anatomic layers of the skin though which the tumor had penetrated. It appears that the micrometer measures are more reproducible and are now almost exclusively used in staging. In the eighth edition of the American Joint Committee on Cancer (AJCC) staging classification,[6] tumors less than 1 mm in thickness are T1, tumors 1 to 2 mm are T2, tumors 2 to 4 mm are T3, and tumors larger than 4 mm are T4. The presence of ulceration increases the stage—for example from T2a to T2b—and for thin lesions, thickness of >0.8 mm also increases the stage from T1a to T1b. As melanomas increase in thickness, the risk of regional and distant metastases increases, as does consideration for surgical staging of regional lymph nodes and possibly radiographic imaging of the remainder of the body. Through use of these staging characteristics, patients can be given information regarding their risk of metastasis, and these estimates can facilitate selection of appropriate treatment. Several prognostic risk calculators are now available online.

Prognosis of melanomas of the head and neck appears to be worse than that of melanomas in other sites. This is, in part, due to the increased frequency of high-risk features in these melanomas and to the increased difficulty in accurately staging them. There also appears to be an increased risk of metastasis and melanoma-death from head and neck melanomas that is independent of features such as tumor depth.[2] The worse prognosis appears to be particularly related to melanomas of the scalp and ear and may be genetically determined with higher frequencies of adverse mutations such as in *NRAS*.[9]

Treatment

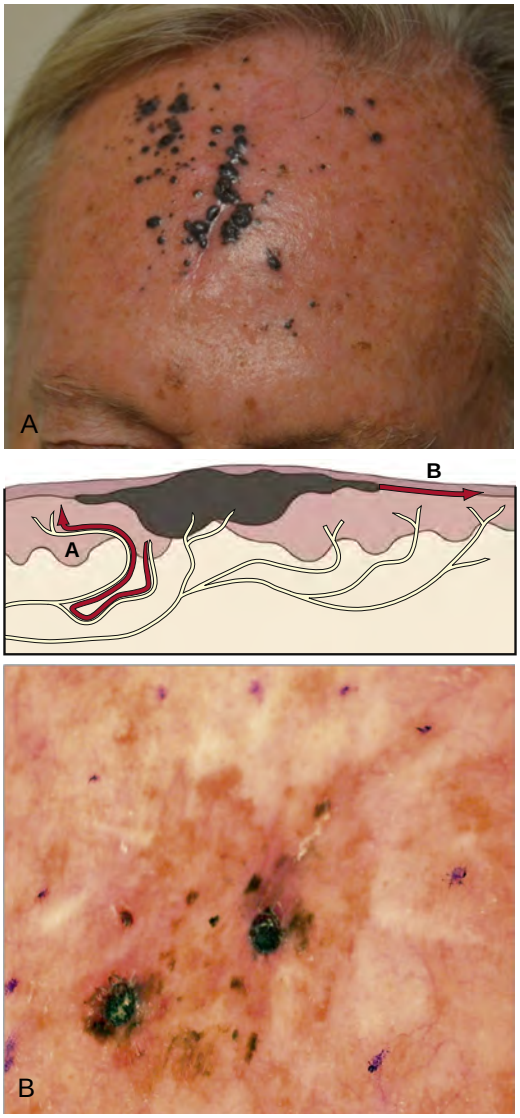
Appropriate treatment of melanoma is dependent on the stage of disease. The vast majority of melanomas appear as clinically localized primary tumors. Occasionally melanomas appear with nodal or hematogenous metastases on presentation, which markedly changes initial therapy. However, for primary melanomas without clinical evidence of metastases, treatment is undertaken with the goals of providing adequate excision of the primary tumor and complete staging information to determine if metastasis has occurred. This is accomplished by wide excision with or without sentinel lymph node (SLN) biopsy.

Treatment of primary melanoma is by wide excision. This is accomplished by removal of the entire clinically apparent lesion with a rim of normal-appearing skin of a measured width. The propensity of melanoma to spread radially or through local lymphatic channels leads to this approach, rather than that of simply obtaining negative margins, which is the goal for lower-risk tumors such as squamous or basal cell carcinomas.

Historically, margins for melanoma excisions were quite wide. Autopsy studies in the 19th century by W. Sampson Handley identified rests of tumor distributed throughout the soft tissue surrounding a primary melanoma.[10] More modern pathology studies also found increased frequencies of melanocytes in the skin adjacent to some melanomas.[11] These findings led to the use of quite wide margins for many years. Initially, the most commonly recommended margins for wide excisions were 5 cm. However, such wide margins were associated with considerable morbidity, and a series of randomized trials was performed to determine if narrower margins were safe. In general, these trials supported the safety of narrower margins, and recommendations have narrowed over the last several decades. Initially, relatively lower-risk melanomas with thicknesses less than 2 mm were evaluated in these trials. Margins of 2 cm were compared with 5 cm in the first trials, and then margins of 1 cm were compared with 3 cm.[12–14] None of the trials showed significant decreases in disease-free or overall survival, and margin recommendations were narrowed for those tumors. The Intergroup study, conducted primarily in North America, examined melanomas 1 to 4 mm in thickness and compared 2-cm and 4-cm margins.[15] Again, the narrower margin was found to be safe and has been adopted as a standard recommendation. For higher-risk melanomas, greater than 2 mm in thickness, a trial performed in the United Kingdom compared 1-cm margins and 3-cm margins.[16] This trial found an increase in locoregional recurrence with the narrower margin, suggesting that it is possible to narrow margins too much. However, this trial precluded the use of lymphatic staging by SLN biopsy, and much of the observed difference in recurrence was in regional nodes, leading to some uncertainty in the interpretation. A similar study conducted in Sweden, also enrolling patients with melanomas greater than 2 mm in thickness, compared 2-cm margins and 4-cm margins.[17] This trial demonstrated the safety of 2-cm margins, and this has become the standard recommendation for tumors of this thickness throughout most of the world.

Head and neck melanomas, though, present particular challenges with regard to wide excision and margins for two reasons. First, primary melanomas of this region may have indistinct boundaries, making initial determination of the extent of the lesion difficult. Second, there is limited space in many parts of the head and neck to obtain wide margins without unacceptable morbidity in terms of function or cosmesis. Many of the randomized margin trials excluded patients with head and neck primary tumors for these reasons, and most guideline margin recommendations allow for consideration of narrowing margins to avoid unacceptable functional compromise that might result from standard measures. Unfortunately, head and neck melanomas have an increased risk of local recurrence, which may be in the epidermis, owing to radial spread of abnormal cells, or at a deeper site owing to spread along nerves or through local lymphatic channels (Fig. 43.2).

Radial spread of abnormal cells along the skin surface is characteristic of heavily sun-damaged areas, including the head and neck. This spread can be difficult or impossible to see by clinical inspection preoperatively, leading to positive margins at the time of wide excision and the need for re-operation or increasing the risk of local recurrence. There have been attempts to address this issue of margin assessment. The Mohs technique with complete intraoperative margin assessment may be problematic in this disease for two main reasons. First, the subtle nature of the pathologic findings in these cases makes intraoperative frozen section assessment difficult. Use of rapid immunohistochemical staining has been explored as a means of overcoming this problem, but has not been widely adopted.[18]

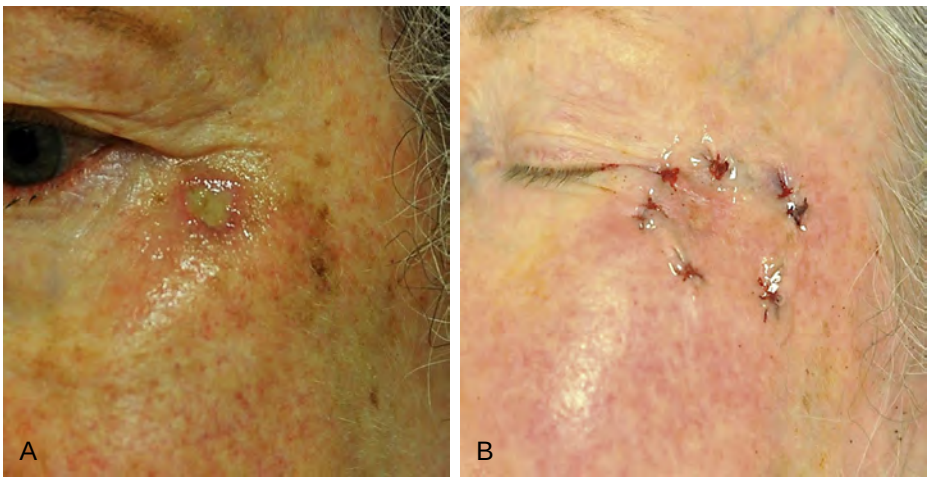


• **Fig. 43.2** Local recurrences in melanoma may be spread through lymphatic channels to satellite or in-transit skin sites **(A)** or by direct radial spread along the dermoepidermal junction **(B).** The type of metastatic spread shown in **A** is illustrated schematically in the *A arrow* in the drawing, and the type of metastatic spread in **B** is shown by the *B arrow* in the drawing.

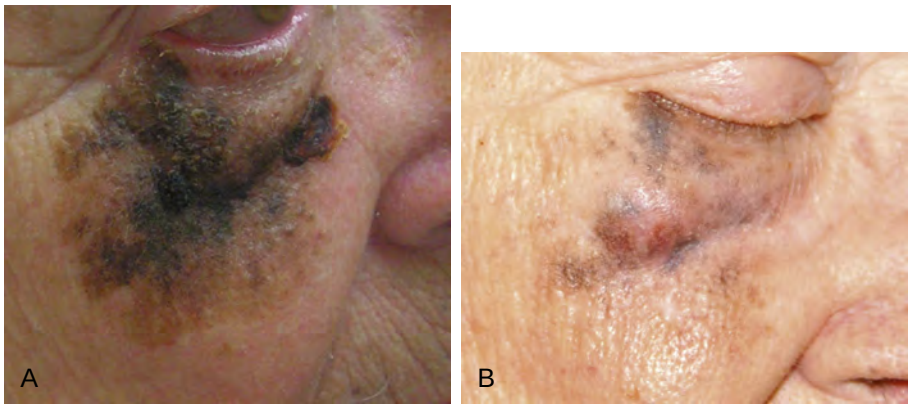
Use of the Mohs approach, but with standard pathologic processing and staining, has also been proposed. This "slow Mohs" procedure does allow for optimal pathologic assessment of margins, but requires additional time, leaving the patient with an open wound for longer periods of time. In addition, as with a standard Mohs approach, it assumes that an acceptable margin for the lesion will eventually be obtained. However, in the head and neck, such a final clear margin may require a resection that is more extensive than is acceptable from a morbidity standpoint.

An alternative is preoperative assessment of a proposed margin through margin-mapping biopsies (Fig. 43.3). This may be done through multiple punch biopsies sampling a proposed margin, or by excision of a strip of skin including the entire proposed margin but leaving the central tumor undisturbed. If the margin-mapping biopsy specimens are clear, the final wide excision can be undertaken with greater confidence that the final excision margins will be clear. If the margin mapping shows disease, additional biopsies can help determine the full extent of the lesion and a more deliberate determination of reconstruction plans. If it appears that a definitively clear margin will not be feasible without undue toxicity, non-surgical treatments might also be considered.

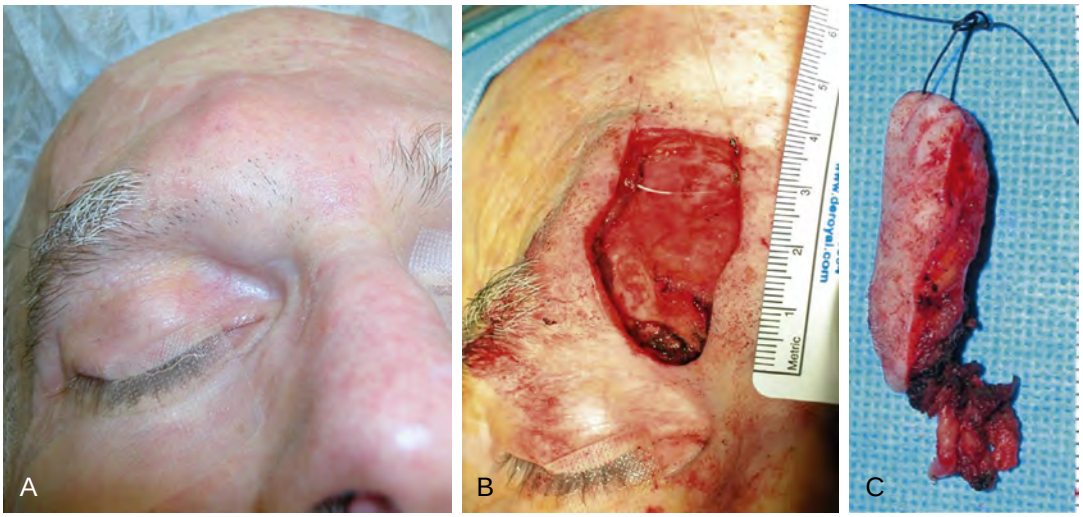
Surgical resection is the gold standard treatment for primary melanomas, but non-surgical approaches have also been used when resection is not feasible or if the patient is not a candidate for surgery. Non-surgical treatments include radiation, laser ablation, and topical application of imiquimod[19] (Fig. 43.4). Read and colleagues conducted a review of these non-surgical approaches in the setting of lentigo maligna. Radiation demonstrated mean recurrence rates of 11.5%, and rates as high as 31% in some studies. Imiquimod recurrence rates were up to 50% with a mean of 24.5%. With laser treatment, mean recurrence rates were 34.4%, with rates up to 100% reported. However, the studies in this review were statistically heterogeneous, so no formal meta-analysis was performed. Given those results, these alternatives should be reserved for patients in whom adequate surgical resection is not possible.



• **Fig. 43.3** Margin-mapping biopsies performed to help determine the pathologic extent of a melanoma of the face preoperatively. Biopsy at the 9-o'clock margin showed additional melanoma in situ, leading to a wider margin at that site and negative margins at the final wide excision. **A,** Appearance of primary melanoma site after diagnostic biopsy. **B,** Appearance of site after margin mapping punch biopsies.



• **Fig. 43.4** Nonoperative treatment with imiquimod. A broad, biopsy-proven melanoma of the face in a patient with extensive comorbid conditions **(A)** was treated topically with imiquimod. Post-treatment biopsies of the area demonstrated absence of abnormality in the previous tumor area **(B).** However, the patient developed melanoma recurrence in the underlying dermis 1-year later.



• **Fig. 43.5** Desmoplastic neurotropic melanoma. A patient with a prior forehead desmoplastic melanoma developed a palpable recurrence at the superior orbital rim **(A).** Resection of the recurrence traced enlarged supraorbital and supratrochlear nerves to the orbit **(B).** Nerve margins **(C)** were involved, even several centimeters from the main tumor mass. A subsequent resection of the nerves to the posterior margin of the orbit enabled clear nerve margins.

Another new modality that may become helpful in some cases is the use of in vivo confocal microscopy. This technique may allow evaluation of the histologic details of tissue in the area of the melanoma while it is still intact. Again, the subtle nature of these lesions histologically may make such assessments challenging.

The other challenge with primary tumor treatment in the head and neck is the propensity of these lesions to be more aggressive in the local tissues through invasion of either peripheral nerves or lymphatic channels. The former is a frequent feature of desmoplastic melanomas, which more commonly occur in the head and neck[20] (Fig. 43.5). Careful assessment of nerves contained within the specimen is advisable in these cases. Tumor cells may spread along nerves for a considerable distance and may track both distally and proximally. Involvement of sensory nerves, which reach the skin, is more common than involvement of motor nerves. Occasionally, nerve involvement may be so extensive as to preclude complete excision, even when the nerves are tracked as close to their origin as possible. Radiation may be used as an adjunctive treatment in those cases.[21]

Melanoma commonly metastasizes through lymphatic channels. Although this most often results in nodal metastases, at times melanoma cells may travel distally within lymphatics, leading to recurrences in or below the dermis of the skin within the region of the primary tumor. This phenomenon is more common with primary melanomas of the lower extremity and the head and neck.[22] These are metastases, rather than true local recurrences, and generally portend a worse prognosis and are staged as stage IIIb or IIIc depending on the status of regional lymph nodes. These metastases may be surgically excised if they are few. However, frequently the number of lesions is too great to allow easy excision, and recurrence rates are high even if resection is possible. In the extremity, these lesions may be treated with regional perfusion with high-dose chemotherapy, but this is obviously not possible in the head and neck. An

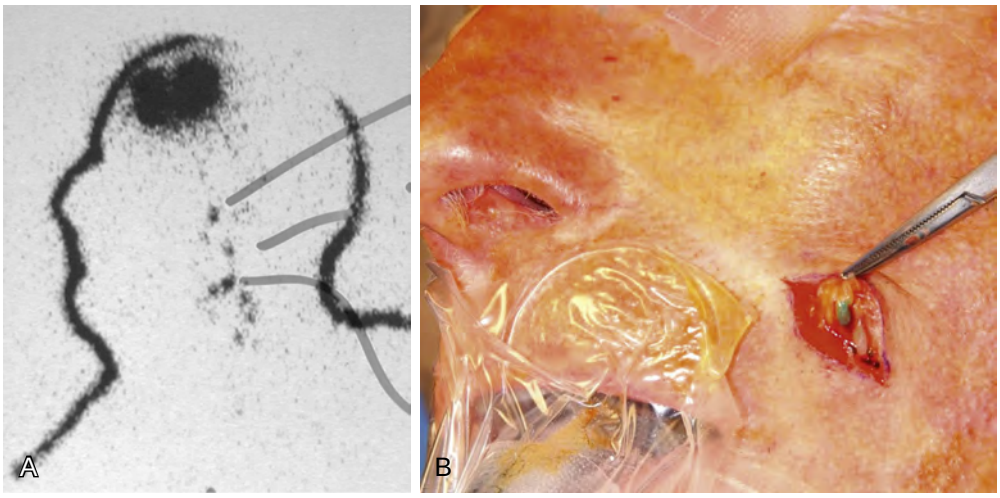


• **Fig. 43.6** Local immunotherapy for in-transit metastases. This 74-year-old woman developed multiple in-transit metastases despite multiple prior surgeries and scalp radiation **(A)**. These were treated with initial bacillus Calmette-Guérin (BCG) injections, inducing moderate inflammation at the injected sites **(B),** and subsequent topical imiquimod **(C).** She has had a complete and durable response in all metastases **(D).**

alternative strategy is intralesional immunotherapy, which uses various agents to induce a local immune response at the tumor site. This frequently results in regression of the directly treated lesion and may also induce regression of other lesions, presumably through immune mechanisms.

Agents used for such intralesional approaches include bacillus Calmette-Guérin (BCG), dinitrochlorobenzene, and imiquimod.[23,24] BCG has demonstrated regression in approximately 80% of injected lesions and in approximately 15% of non-injected lesions.[25] In early reports, BCG also was reported to cause severe or even fatal inflammatory reactions, but more recent reports with lower dose regimens did not indicate similar problems. Imiquimod has been evaluated in small series and demonstrated sustained responses as well. The combination of BCG and imiquimod has also been reported with high response rates in small series[26] (Fig. 43.6).

More recently, oncolytic viruses have been actively evaluated in this situation. Viruses that have been evaluated include Coxsackie A and modified herpes simplex virus type I.[27] The latter has been evaluated in a randomized phase III trial in patients with unresectable, accessible metastatic melanoma, with subcutaneous granulocyte-macrophage colony-stimulating factor (GM-CSF) as a control treatment. The trial demonstrated a significant benefit in durable response rate, which was the primary end-point of the trial. There was a marginally significant ($P = .051$) benefit in overall survival, which was highly significant in the subgroup of patients with stage IIIB or IIIC disease. The drug is now approved for this treatment by the U.S. Food and Drug Administration.



• **Fig. 43.7** Complexity of lymphatic mapping in the head and neck. The region is characterized by a greater number of draining lymph nodes and complex drainage patters, seen on this lymphoscintigram **(A).** Nodes may also lie outside of the boundaries included in typical regional dissections **(B).**

The other component of initial treatment is evaluation for metastatic disease. Because the initial mode of metastasis is nodal in most cases, for patients with a reasonable risk of metastasis based on their primary tumor characteristics, lymph node assessment is performed. In the past, options for that assessment were largely limited to either clinical examination or complete dissection of the entire nodal basin. The development of lymphatic mapping and SLN biopsy created a new and superior option, which is now a standard for appropriately selected patients.

Nodal Staging and Treatment

Regional lymph nodes have long been a source of controversy in melanoma. The propensity of melanoma to spread to regional lymph nodes was recognized early, and at the end of the 19th century, Herbert Snow, a London cancer surgeon, proposed *anticipatory gland excision,* or as it subsequently came to be known, *elective lymph node dissection.*[28] Snow and many others believed that early excision of lymph nodes in the region, before they had developed clinically apparent metastases, would catch early metastases and eliminate them before they had a chance to spread to more distant sites. However, most patients with clinically localized melanoma do not have nodal disease, and lymph node dissections are attended by a moderate risk of morbidity. Therefore, there was significant controversy regarding the value of elective lymph node dissection. Multiple randomized clinical trials were performed over a number of decades, with some variation in trial designs.[29–31] In most of these trials, patients with head and neck primary lesions were not eligible. The trials demonstrated fairly congruent results with superior survival in the early dissection arm, by a non-significant amount. In two studies the patients with intermediate-thickness melanomas enjoyed a significant benefit, but because these were subgroups, this evidence was not considered definitive.

As this controversy continued, development of a new technique, the SLN biopsy, occurred and led to a change in the standard of care that made the elective lymph node dissection controversy moot. The concept of a "sentinel lymph node"—a node that specifically receives lymphatic drainage from a given anatomic location—has existed for many years, dating back as far as Rudolf Virchow. In parotid tumors and penile cancer, Gould and Cabanas, respectively, described sentinel nodes serving this function in specific anatomic locations.[32] However, the current understanding of a sentinel node and the technical procedure used to identify it were not developed until the 1980s and grew out of attempts to improve elective lymph node dissection. For melanomas located on the trunk, the direction of lymphatic drainage, and therefore the most appropriate basin for dissection, was often unclear. In an effort to rationalize the process, lymphoscintigrams, initially using colloidal gold, were used to identify the draining basin.[33] As radiotracers and imaging capabilities improved, it became evident that drainage was generally to an individual or small number of nodes, rather than the entire nodal basin. Use of blue dye in the operating room enabled identification of that first draining node or SLN, and clinical trials confirmed that that node was representative of the pathologic status of the basin.[34–36] This meant that nodal staging could be accomplished by using a minimally invasive operation with markedly decreased morbidity relative to full dissection. The technique has been improved by the addition of intraoperative detection of the injected radioactive lymphoscintigraphy tracer and is now a standard procedure for appropriately selected patients with melanoma.

Sentinel node biopsy in the head and neck region is more difficult than it is in other sites, but it provides powerful prognostic information here as it does in the remainder of the body.[37] Studies of head and neck sentinel node biopsy have demonstrated marked effects on disease-free and overall survival based on SLN status. SLN identification rates may be slightly lower in the head and neck region, with an average identification rate in one review of 94.7%.[38]

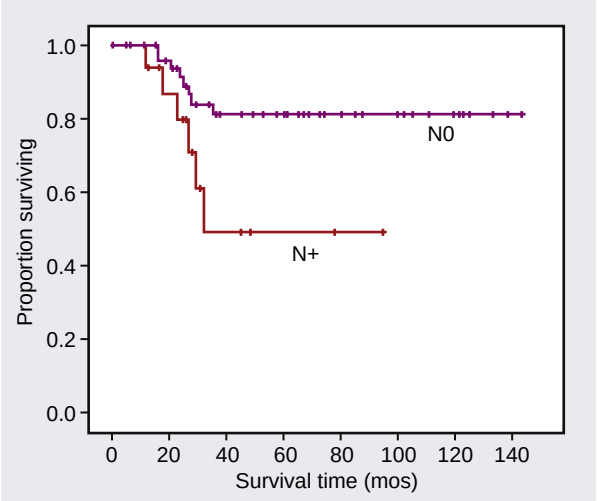
This difficulty results from a combination of factors including the frequent close proximity of nodes to the primary tumor site. Significant residual radioactivity at the injection site can obscure the location of sentinel nodes in those cases. In addition, the drainage patterns of lymphatics in the head and neck are more complex, and there are frequently more and smaller draining nodes (Fig. 43.7A). Lymph nodes draining melanomas may

also be in unusual locations, outside of the normal boundaries of regional node dissections (Fig. 43.7B). This has led to a higher false-negative rate for sentinel node biopsies in the head and neck. A retrospective study at three German centers found that the rate of false-negative SLN biopsy was higher for head and neck melanoma than for other primary tumor sites.[38,39] False-negative recurrence was associated with significantly worse survival than true-positive disease undergoing immediate dissection.

Efforts to improve the accuracy of mapping in the head and neck include the use of single-photon emission computed tomography (SPECT)–CT as the preoperative imaging modality for the lymphoscintigram, which can provide more detailed evaluation of the location and number of draining nodes.[40] A retrospective study of 22 consecutive patients with head and neck melanoma treated between 2010 and 2013 was conducted.[41] Lymphoscintigrams using technetium 99m (^{99m}Tc) nanocolloid were imaged with planar and SPECT-CT imaging. SLNs were detected in 91% of planar images and 95.4% of SPECT-CT images. SPECT-CT was felt to be more accurate in the majority of cases. Similarly, Chapman and colleagues examined 176 patients with head and neck melanomas, of whom 85 underwent SPECT-CT imaging.[41a] Use of SPECT-CT improved detection of melanoma SLN metastases on multivariate analysis.

Not all melanoma patients require regional nodal staging. The most important factor for appropriate selection of patients is the features of their primary melanoma, particularly the thickness of the lesion. In general, patients who are surgical candidates with intermediate-thickness melanomas should be recommended to undergo SLN biopsy. Patients who have thicker, higher-risk melanomas are more likely to have concomitant distant metastases, which might decrease the significance of any findings in their regional nodes. These patients therefore have not been included in most trials of elective lymph node dissection. However, many studies have now documented the importance of SLN status for determining prognosis for melanomas in general. In the head and neck specifically, Monroe and colleagues studied 77 patients with melanomas greater than 4 mm in thickness.[42] The identification rate in the study was 91%, and 24% of patients had nodal metastases. A positive SLN portended significantly shorter disease-free (74 vs. 36 months, P = .026) and melanoma-specific (121 vs. 59, P = .035) survival rates (Fig. 43.8). On multivariable analysis, SLN status was the most important prognostic variable for disease-free survival (hazard ratio [HR], 4.2; 95% confidence interval [CI], 1.5–11.6; P = .006), although not melanoma specific survival (MSS).

At the other end of the thickness spectrum, patients with thin melanomas have a relatively low risk for nodal metastasis, and for many the risk is too low to justify the added procedure. However, because the number of patients with thin melanomas is very large, the absolute number of nodal metastases in this group is significant. The challenge is in determining which patients with thin melanoma have sufficient risk, and consensus on final criteria has not been reached. The National Comprehensive Cancer Network guideline recommendation for SLN biopsy with thin melanomas is largely based on thickness.[43] For primary melanomas less than 0.75 mm in thickness,



• **Fig. 43.8** Impact on survival of sentinel lymph node status in thick melanomas. (From Monroe MM, Pattisapu P, Myers JN, Kupferman ME. Sentinel lymph node biopsy provides prognostic value in thick head and neck melanoma. *Otolaryngol Head Neck Surg.* 2015;153:372–378.)

biopsy is generally not recommended. For primary melanomas between 0.75 mm and 1 mm without an adverse, high-risk feature, it is recommended that biopsy be discussed; and for those with such features, biopsy should be offered. There is significant disagreement, however, regarding what features should be considered "high risk." Ulceration and a high mitotic rate are uncommon in thin melanomas. Other clinical features such as age (younger patients having higher risk of nodal metastasis) and gender (men have a higher risk of nodal recurrence) have been suggested, as have other pathologic features including vertical growth phase, regression, and Clark level.

The SLN procedure itself is simple in concept, but can be more difficult in implementation. It requires expertise of three disciplines: nuclear medicine, surgery, and pathology. The challenges in nuclear medicine are discussed earlier in this chapter; these may be ameliorated with improving technology. Surgical challenges include the complex drainage patterns, numerous nodes, and small nodal size that characterize the region. In addition, nodes must be handled with care to avoid compromising the subsequent pathology evaluation. Pathologists must use both hematoxylin-eosin stain and immunohistochemical stains to ensure accurate and complete detection of metastases. Care must also be taken to distinguish true SLN metastases from benign nodal nevi.

Lymphoscintigraphy is usually performed on the same day, or in the afternoon before the surgical procedure. Nodes are identified by use of both dynamic early imaging and more delayed images. SLN locations are confirmed at the time with a hand-held gamma counter and marked on the skin. When the patient arrives at the operating room, the location of the SLN is again confirmed in the operative position by use of the gamma counter, and blue dye is injected intradermally at the primary tumor site. Vital dyes used around the world for this purpose vary and include Lymphazurin and Patent V. Methylene blue has also been used, although there is a concern for skin necrosis if the injected area is not resected at the same time.

In general, risks of the procedure are low. One risk that is more of a concern in the head and neck region is nerve injury.

SLNs are frequently located adjacent to nerves; proximity to the spinal accessory nerve and marginal mandibular branch of the facial nerve is particularly common. The greater auricular nerve may also be at risk, and for SLNs located in the parotid, the remainder of the branches of the facial nerve are frequently close. The danger to these nerves may be mitigated by meticulous dissection. Avoiding paralysis and relaxation as a component of the patient's anesthesia can facilitate identification of the nerves, and in some cases a nerve stimulator may be helpful. It is also important to realize that it is frequently possible to perform a sentinel node biopsy with transection of few adjacent structures. Often, blunt dissection and gentle retraction are often sufficient to perform most of the dissection in reaching the SLN.

In the past, there was concern that SLN biopsy of parotid lymph nodes entailed more risk than a superficial parotidectomy. However, with experience and care, the rate of facial nerve injury during biopsy of parotid SLNs should be extremely low, even without full dissection of the nerve.[44]

Complete lymph node dissection (CLND) may be indicated in the setting of clinically evident nodal metastases or after a positive SLN biopsy. The location of second-echelon nodal drainage cannot be accurately predicted, so selective dissection of fewer stations is generally not possible. For inferior or posterior primary sites and limited nodal tumor burden, the submandibular and submental nodes may be spared. Parotidectomy may also be avoided in patients who are unlikely to have parotid disease. This would include those with primary lesions posterior to the coronal suture or with lymphoscintigraphy showing drainage channels behind the ear. Drainage to the parotid appears to be primarily from the anterior scalp and forehead.

Whether to perform a completion lymph node dissection in the setting of a positive SLN has remained an uncertain area. Most patients with SLN metastases do not have involvement of non-SLN metastases found at the time of complete node dissection.[45] In addition, those patients who do have non-SLN metastases have quite a poor prognosis, and many cannot benefit from additional early or prophylactic nodal surgery. Accordingly, patients may consider the option of observation of the nodal basin. Dissection of the cervical basin should be less likely to result in long-term morbidity such as lymphedema, compared with dissection of the axilla or groin. Therefore, the threshold for proceeding with a completion dissection may be lower for this region. For melanoma in general, retrospective studies have produced conflicting data regarding any survival impact from CLND.[46,47] For the head and neck specifically, Fritsche and colleagues performed a retrospective analysis of patients with positive SLN who either underwent immediate CLND or were observed.[48] Patients younger than 60 years with thin (<1 mm) melanomas had significantly improved melanoma-specific survival with immediate dissection. Patients 60 years or older had worse outcomes with immediate dissection. Unexpectedly, the groups that were most likely to have involved non-sentinel nodes were not more likely to have improved survival with immediate CLND. In addition, Kretschmer and colleagues found that the rate of nodal recurrence in a dissected nodal basin after a positive SLN finding was higher in the neck than in other basins (neck, 44.1%; axilla, 17.2%; groin, 15.5%).[39]

A single prospective study has been reported to date, but this trial excluded patients with head and neck cancer and was not adequately powered to rule out a significant benefit to early CLND.[49] The second Multicenter Selective Lymphadenectomy Trial randomized nearly 2000 patients with SLN metastases to either immediate dissection or observation with nodal ultrasound. This trial includes patients with head and neck primary melanomas and will have sufficient statistical power to provide guidance on CLND.

Radiation

Traditionally, melanoma has been considered a radioresistant tumor. Melanocytes are relatively tolerant to radiation, and higher doses or dose-fraction treatment regimens have often been used as a result. Radiation has been used for treatment of primary melanomas and in-transit metastases, adjuvant therapy to regional nodal basins, stereotactic treatment of individual lesions, particularly brain metastases, and palliation.

In general, primary melanoma radiation has been reserved for patients who are unable to undergo surgery. It has been more commonly employed at European centers, with several series of more than 100 patients reported.[50] However, patient populations in these studies were heterogeneous, and follow-up was often short. With mean reported recurrence rates of over 10%, the therapy has not become a commonly used option when alternatives are available. Similarly, radiation has been used as primary treatment for in-transit metastases, but it rarely proves curative in such situations.

Radiation is more effective in microscopic disease in melanoma, as is true in other malignancies. Primarily it has been used in the adjuvant setting for regional nodal or in-transit spread, or after resection of brain metastases. The highest-level evidence is available for adjuvant regional nodal radiation: a prospective international randomized trial among 250 patients who had undergone lymph node dissection for metastatic melanoma.[51] The trial was open to patients with palpable metastases or with three inguinal, two axillary or cervical, or one parotid nodal metastasis. The treatment regimen was 28 Gy in 20 fractions over 4 weeks. The trial clearly demonstrated a reduction in the risk of in-basin nodal recurrence (HR, 0.52; P = .023), but no indication of distant disease-free or overall survival benefit. There was an increase in amount of edema and regional symptoms related to therapy for the radiation group.

Radiation is also considered as adjuvant therapy at the primary tumor site for certain high-risk lesions.[52] These include desmoplastic melanomas, particularly in the head and neck region where wide margins are frequently not possible. Neurotropism and the presence of satellites both predict a high rate of local failure. No prospective data are available to evaluate radiation in these settings, but retrospective studies support its use in selected patients.

Finally, radiation may be used in the treatment of certain metastases. This may have palliative intent, as with certain bone

metastases, or therapeutic intent, as with stereotactic radiation to brain metastases. The precision of stereotactic techniques has increased with improving technology, and early detection of brain metastases through MRI allows for effective treatment of many brain metastases.[53]

Systemic Treatment

Melanoma has also proven to be resistant to most forms of systemic therapy that have been applied for many years. This has been true in both the adjuvant and the metastatic setting. However, in the last few years, tremendous strides have been made in treatment, which has made melanoma the model for other cancer types. Much of the progress has fallen into two types of therapies: targeted therapy and immunotherapy.

The earlier era of systemic therapy was characterized by few approved therapies and little evidence of improvement in most clinical trials. The approved agents were limited to cytotoxic chemotherapy with dacarbazine or cytokines including interleukin-2 and interferon alfa-2b. None of those agents had demonstrated a survival benefit; dacarbazine was given as a palliative measure, and interleukin-2 was approved based on its ability to produce long-term durable remissions in a small fraction of patients. Clinical trials were not much more encouraging. A meta-analysis of the phase II trials conducted by cooperative groups between 1975 and 2005 found that no trial was likely to have found a beneficial effect on survival of patients.[54] In the adjuvant setting, interferon alfa-2b was approved in 1997.[55] It has demonstrated consistent benefit in terms of disease-free survival, but inconsistent and limited effects in overall survival. Pegylated interferon was more recently approved based on similar benefit to the earlier formulation of the drug, but in a regimen that was possibly slightly better tolerated.[56] Retrospective evaluation of pegylated interferon suggested that it may be particularly useful in the subgroup of patients with ulcerated primary melanoma with micrometastatic nodal disease, but that finding has not yet been prospectively validated.

Targeted therapy in melanoma uses the presence of specific driver mutations in tumor cells that can be inhibited by small-molecule drugs. The most common such mutation is in *BRAF,* which is present in approximately half of metastatic melanomas. The frequency of this mutation in head and neck melanoma is somewhat less than at other sites, because it is less frequently found in chronically sun-damaged skin, typified by the head and neck.[9] BRAF inhibition using vemurafenib or dabrafenib will produce rapid clinical responses and palliation in patients, even with advanced metastatic disease if their tumor harbors the mutation.[57] However, most such patients develop resistance to the drug, on average in 5 to 7 months. The period of therapeutic effect can be extended by adding inhibition of the next step in the driving molecular pathway, MEK.[58] Two MEK inhibitors, trametinib and cobimetinib, are now approved and are used in combination with BRAF inhibitors for BRAF-mutant melanoma. The next most common driver mutation in melanoma is in *NRAS.* This also signals through the same molecular pathway, and MEK inhibitors have demonstrated some efficacy in such patients, although not to the same degree as the benefit seen in BRAF-mutant melanomas. Again, resistance and eventual progression are the rule.

Immunotherapy had previously demonstrated hints of effectiveness in melanoma.

As noted earlier, with in-transit melanoma, injections of BCG have been known to produce regression of melanoma both at injected sites and in non-injected sites. Although the cytokine therapies of interleukin-2 and interferon alfa-2b did not help most patients who received them, there were tantalizing, though infrequent, durable remissions in patients with metastatic disease, suggesting the possibility of curing patients with metastatic solid tumors.[59] That kind of response has almost never been seen in any other disease.

This hope regarding immunotherapy has now been realized in the development and approval of checkpoint inhibition drugs targeting either cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) or programmed cell death protein 1 (PD-1). These target regulatory mechanisms that normally dampen immune responses. Blocking those mechanisms allows for more immune recognition and destruction of malignant cells. The first of these agents to be approved was ipilimumab, which was the first drug to demonstrate significant survival benefit in metastatic melanoma.[60] Although the benefit is limited to about one patient in four, it may be durable over many years.[61] The drug does have the potential for serious or even fatal autoimmune toxicities and must be given with care and with close monitoring of patients.[62] Fortunately, it appears that treatment of toxic side effects of the drug does not impair ongoing responses to therapy.

The second immune checkpoint to be targeted is PD-1, expressed on activated lymphocytes, and programmed death-ligand 1 (PD-L1), expressed on tumor cells and immune cells within the tumor microenvironment.[63–65] Two therapeutic antibodies have been approved: nivolumab and pembrolizumab. Clinical data regarding these drugs available to date are similar. The response rates to PD-1 blockade are higher than those to CTLA-4 blockade, and toxicity is less. In clinical studies, adverse events requiring cessation of therapy were rare. Long-term follow-up data for PD-1 blockade are not yet available, but it is hoped that durable responses will be seen with this strategy as they were with ipilimumab.

Combination of CTLA-4 and PD-1 blockade has also been evaluated.[66] This approach is both more therapeutic and more toxic than either approach alone. Expression of PD-L1 in tumor tissue is being explored as a possible biomarker to determine the need for the combination. It appears that patients with high PD-L1 expression do equally well with anti–PD-1 monotherapy. Other combinations, using radiation, injected oncolytic viruses, and systemic immunomodulators, are now in clinical trials.

Summary

Overall, cutaneous melanoma of the head and neck remains a difficult problem. The nature of these tumors, their

predominant patient population, and the particular challenges of the head and neck region make optimal treatment harder than is the case for melanomas in general. Progress in recent years has made melanoma therapy more accurate, more effective, and less toxic. There is great promise for additional improvements in the near future.

Mucosal Melanoma

Mucosal melanoma is markedly different in incidence and presentation compared with cutaneous melanoma. In the United States, mucosal melanoma makes up only 1.3% of all melanomas.[67] It does represent a larger fraction of cases in demographic groups in which melanoma is less common. For example, mucosal primary sites may account for over 10% of melanoma among African Americans, and 30–40% of cases in China.[68] It appears that, even though the proportion of mucosal primaries is higher, the absolute incidence of mucosal melanoma does not vary markedly among different populations and is approximately 0.15 per 100,000.[69] This incidence has not increased in recent years, as has been the case for cutaneous melanoma.

The adverse clinical behavior of mucosal melanoma has been attributed to late diagnosis, which may be related to the relatively hidden anatomic sites of these tumors, or to the rich network of blood and lymphatic vessels that invest their mucosal locations. It is now apparent that there are also genetic or mutational differences in mucosal melanomas, which may not only explain some of the differences in biologic behavior, but may also open new avenues for treatment.

Presentation and Prognosis

First described by Weber in 1859, head and neck mucosa melanoma is the most common mucosal subtype, making up more than half of the cases (55.4%).[67,70] The age of diagnosis of mucosal melanomas is approximately 10 years older than that of cutaneous melanoma, with peak age in the seventh decade. A population-based evaluation of these tumors found the most common primary site to be the nasal cavity (49.1%), followed by the paranasal sinuses (23.1%), the oral cavity (18.8%), the nasopharynx (5.5%), and the oropharynx (3.2%).[71] There may be regional variation in the epidemiology of head and neck mucosal melanoma; a relatively large series from Shanghai found a significantly greater male predominance and much younger age of onset (54.1 years) than other series.

The presentation of head and neck mucosal melanoma is largely dependent on location. For lesions in the nasal cavity, the most common symptoms are epistaxis (72%) and unilateral nasal obstruction (53.5%), but pain, facial deformity, or blindness may occur with more advanced lesions.[72] Oral melanomas are frequently discovered owing to a pigmented lesion (62%), ill-fitting dentures (25%), or bleeding (13%).[70] Oral melanosis, a generally benign proliferation of melanocytes in the mucosa, may precede melanoma in up to one third of cases. Most lesions manifest while still clinically localized (60–88%), with a minority having evident nodal (10–30%) or distant (<15%) metastases.[73–75]

Unfortunately, the prognosis for mucosal melanoma remains poor. Formerly, the most frequently used staging system had been proposed by Ballantyne in 1970[76] and included three stages: I, localized; II, regional metastases; and III, distant metastases. In the most recent AJCC staging manual (seventh edition), head and neck mucosal melanoma was given its own classification.[77] This system is interesting in that the lowest tumor stage is T3, which is considered stage III disease. T4a tumors represent more advanced disease involving deep soft tissue, cartilage, bone, or overlying skin. Any nodal involvement is categorized as stage IVA. T4b tumors are "very advanced" and involve brain, dura, skull base, lower cranial nerves, masticator space, carotid artery, prevertebral space, or mediastinum.

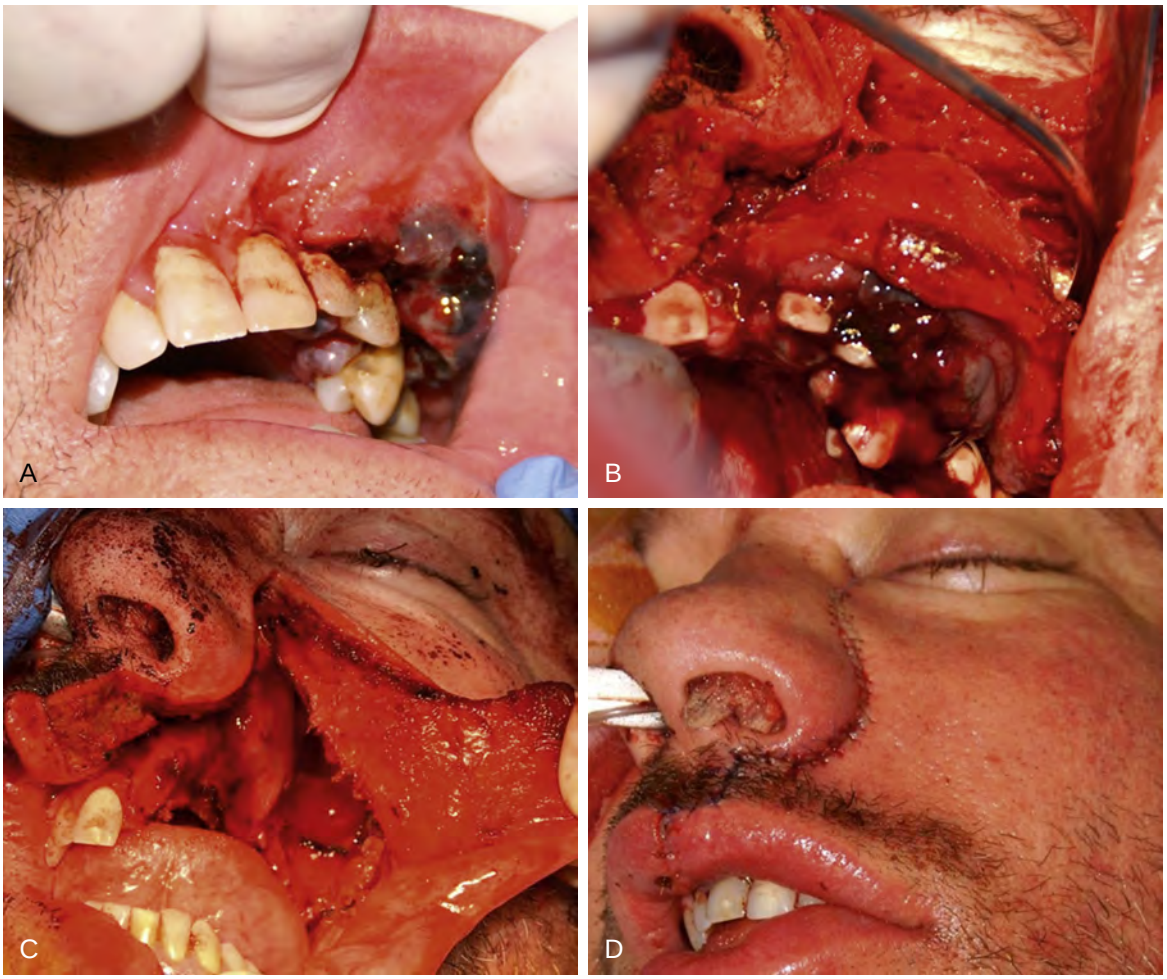
Other prognostic factors have been examined. Tumor size,[71] thickness,[78] and depth of invasion[79] have been found by some to be prognostic, but not by others.[80] Increased age,[74] increased mitoses, increased Ki-67, absence of p53, margin-positive resection, and vascular invasion are also potential prognostic variables. Nasal lesions seem to have the best prognosis (5-year survival, 15–30%) followed by oral lesions (5-year survival, 12%) and sinus lesions (5-year survival, 0–5%).[70]

Etiology and Genetic Basis

Unlike cutaneous melanoma, mucosal melanoma does not appear to be related to ultraviolet radiation exposure. Various alternate etiologies, including viral causes such as herpesvirus type VIII and human papillomavirus type XVI, have been examined, but no evidence for these as causative agents has been found.[81] There has also been speculation that environmental factors, related to the potential role of melanocytes in detoxifying polycyclic hydrocarbons, including those in tobacco, may play a role in mucosal melanoma.[78] Other environmental factors, including exposure to formaldehyde, have been suspected as well.

Curtin and colleagues examined genetic changes found in melanomas from various body sites including melanomas from chronically sun-damaged skin, intermittently exposed skin, and acral skin and from mucosal sites.[3] Specimens derived from mucosal or acral sites demonstrated a much greater degree of chromosomal aberrations than those from chronically or intermittently sun-exposed skin. In particular, amplifications were much more frequent (85%) in mucosal melanoma than in the chronic or intermittent sun-exposed sites. Whereas mutations in specific components of the mitogen-activated protein kinase (MAPK) pathway were common in intermittently sun-exposed areas (BRAF, 59%; NRAS, 22%), they were very uncommon in mucosal sites (BRAF, 11%; NRAS, 5%).

One gene of particular interest for mucosal melanoma is *KIT*.[82] Paradoxically, although CD117 is commonly expressed in normal melanocytes and benign nevi, expression is frequently lost in dysplastic nevi and is not commonly seen in nodular melanomas or superficial spreading melanomas.[83] Screens by



• **Fig. 43.9** Gingival melanoma. The lesion was locally advanced, which is not unusual for mucosal melanomas **(A).** It was resected by en bloc technique **(B** and **C)** and reconstructed with prosthetics and local tissues **(C** and **D),** with a good cosmetic result.

immunohistochemistry of some melanoma subtypes demonstrated expression of the protein, and follow-up genetic studies found mutation or amplification of the gene to be present in some patients. Mutations in *KIT* in melanoma have been identified in exons 11, 13, 17, and 18. Curtin and colleagues reported a frequency of 21% (8/38) of *KIT* mutations and 26% (10/38) of amplifications in mucosal melanoma. Very similar mutation frequencies (15–38%) and amplification frequencies (20–33%) have been reported in several subsequent series.[84–88] Identification of *KIT* mutations in melanoma may require sequencing, because immunohistochemical staining for CD117 does not appear to be a satisfactory screening test.[89]

Treatment

Mucosal melanomas of the head and neck are very difficult to treat. The modalities available include surgery, radiotherapy, and medical therapy. However, none appears sufficient in itself. Surgical resection remains the main treatment modality, but the possibility of radical resection is limited owing to the frequently advanced nature of the primary lesion and the close proximity of vital structures. In addition, the microscopic extent of the tumor frequently exceeds the visible area of involvement. This characteristic makes clear margins even more difficult to achieve, and local recurrence is a frequent problem.

When the lesion is relatively small, surgical resection may be considered as monotherapy as long as negative margins are obtained. Negative margins have been associated with better overall survival and may be achieved in a repeated resection with outcomes similar to those of single-stage resections.[74] An en bloc resection has been associated with improved prognosis, but it is not clear from the retrospective data available whether this association was due to the surgical technique or to the size and location of tumors that could be successfully excised in this fashion.[90] In recent series, several authors have recommended consideration of endoscopic resection. This generally precludes the possibility of an en bloc resection, but a complete resection may be possible. One endoscopic series reported that 70% of endoscopic resections were complete.[91] It should be noted, however, that a functional and cosmetically acceptable result can be obtained in many radical, open resections through the use of prosthodontic obturators, which play an important role in preserving quality of life for these patients[92] (Fig. 43.9).

Regional lymph nodes are a frequent site of early metastasis. However, elective CLND is not indicated because it is unlikely to improve outcomes. Lymphatic mapping and SLN biopsy in selected patients with no clinically involved regional lymph nodes have been used with success.[70] It may be particularly good for patients with oral or nasal primary lesions.

Because the anatomic location and pathologic nature of head and neck mucosal melanoma are associated with high local recurrence rates (>50%) even with radical approaches, strong consideration should be given to adjuvant therapies. A review of 160 patients at several institutions in France demonstrated that there was a substantial improvement (55.6% vs. 29.9%, $P < .01$) in local recurrence when radiotherapy was used as a postsurgical adjuvant. The multivariate HR for local recurrence was 0.31 (95% CI, 0.15–0.61; $P < .01$) in favor of radiation.[93] Other reports noted similar findings.[91] Radiotherapy has also been used as a definitive therapy without surgery in a few small series, although with mixed results.[94] In a meta-analysis of radiotherapy in the setting of mucosal melanoma, no impact was found on overall survival (HR, 1.07; 95% CI, 0.8–1.36; $P = .903$).[95] Surgery with radiation reduced the risk of local recurrence (HR, 0.51; 95% CI, 0.35–0.76; $P = .155$). The risk of distant metastasis was not improved (HR, 2.26; 95% CI, 1.01–5.05; $P = .006$).

Systemic therapy for mucosal melanomas is also difficult, and improved options are needed. Cytotoxic chemotherapy has been frequently used, in part because of lack of alternatives. Postsurgical adjuvant therapy regimens with dacarbazine and cisplatin have been reported to achieve favorable outcomes in those patients compared with those who did not receive chemotherapy.[96] A series of 15 patients receiving biochemotherapy demonstrated a remarkably high rate of objective response (47%) and complete response (27%.)[73] Several of those responses were durable up to 49 months.

Patients with KIT abnormalities may benefit from targeted therapy with tyrosine kinase inhibitors such as imatinib, dasatinib, or sorafenib. These inhibitors have demonstrated dramatic effectiveness in gastrointestinal stromal tumors (GIST). However, initial clinical results have been somewhat disappointing. In several trials of unselected melanoma patients, the agents led to no detectible benefit.[97–100] More recent efforts have focused on patients with confirmed KIT abnormalities. Several striking case reports documented remarkable responses in a handful of patients who harbored KIT aberrations.[101–103]

A clinical trial of imatinib in patients with KIT mutation or amplification reported a response rate of 29% among 25 patients with mucosal, acral, or chronic sun-damage melanomas. All responses were seen in KIT-mutant tumors, and none with KIT amplification.[60] Another trial screened 295 patients for KIT mutation or amplification.[104] Among 51 patients with genetic aberrations, 28 were treated with imatinib at 400 mg twice daily. The overall durable response rate was 16%, and median overall survival was 46.3 weeks. Responses tended to occur in patients with mutations at certain hot spots (e.g., Exon 11 L576P, Exon 13 K642E) and in tumors with a high mutant–to–wild type allele ratio. Buchbinder and colleagues reported a trial of 52 patients with mucosal or acral melanoma using sunitinib. This showed activity in the patient population that was not depended on KIT mutation status.[105]

Non-KIT mutations that might allow treatment with other targeted therapies are not typical of mucosal melanomas. For example, Lyu and colleagues found BRAF mutations in only 3.5% of mucosal melanomas, none of which were the V600E mutation that leads to sensitivity to available BRAF inhibitors. None of their 57 patients had NRAS mutations, and none had GNAQ or GNA11 mutations typically found in uveal melanomas.[106]

Finally, little information is available on the efficacy of checkpoint inhibition drugs in mucosal melanoma. Theirauf and colleagues examined 23 head and neck mucosal melanomas and found that 13% had PD-L1 staining.[106a] This is a lower rate than in cutaneous melanoma. However, clinical evaluation of anti–PD-1 in acral and mucosal melanomas suggests that efficacy may be similar to that seen in cutaneous melanoma.[107]

Summary

Overall, there has been tremendous progress in the treatment of patients with melanomas. Improved understanding of melanoma tumor biology and tumor immunology and extensive clinical trial evaluations have enabled better, more effective treatments to be available with substantially decreased morbidity. Improved staging techniques and tumor evaluations have made accurate selection of patients for therapies increasingly possible, and a growing foundation of knowledge promises to continue to improve care of these patients into the future.

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44

Aggressive Non-melanoma Skin Cancer

DIMITRIOS NIKOLARAKOS, ALEXANDER M. BOBINSKAS, JAMES E. JACKSON, SANDEEP BHUTA, MARCO MATOS

Nonmelanoma skin cancer (NMSC) is the most common malignancy worldwide. NMSC represents a diverse group of tumors including cutaneous squamous cell carcinoma (cSCC), basal cell carcinoma (BCC), Merkel cell carcinoma (MCC), dermatofibrosarcoma protuberans, sebaceous carcinoma, malignant fibrous histiocytoma, and any other cancer of the skin excluding melanoma.[1] Although NMSC includes numerous pathologies, the term *non-melanoma skin cancer* is frequently used to describe BCC and cSCC.[2] To avoid ambiguity, it has been suggested that when jointly referring to only cSCC and BCC the term *keratinocyte carcinoma* (KC) should be used because this does not encompass the other pathologies that may technically fall under the term *non-melanoma skin cancer.*[1,3] KC is the most common malignancy in the United States; estimates have indicated that 3.5 million cases of KC managed in 2006,[4] with this figure increasing to 5.4 million cases in 2012.[5] BCC is considered to be more common than cSCC, with cSCC accounting for approximately 20–30% of KC.[2] The incidence of cSCC and BCC varies throughout the world. In the United States the incidence of BCC varies substantially; incidences of 170–936 per 100,000 person-years have been reported, with higher incidences reported at lower latitudes.[6] The incidence of BCC in England is estimated to be 76 per 100,000 person-years,[6] and Australia has the highest incidence of BCC in the world with more than 1000 per 100,000 person-years reported.[6]

Etiology

Ultraviolet (UV) radiation (UV) exposure, in particular chronic sun exposure, is considered the predominant risk factor contributing to the development of KC.[7] UV B radiation is considered more contributory to the development of KC than UV A because of its ability to cause direct damage to cellular DNA and RNA.[8,9] A variety of other risk factors for the development of KC have been identified, including skin type, predisposing skin lesions, genetic syndromes, immunosuppression, and chronic inflammation.[2,10]

Clinical Presentation

The head and neck area is a commonly sun-exposed region of the body and thus is a common site of occurrence for KC, accounting for up to 80–90% of KC lesions.[11] KC typically occurs in patients older than 60 years[12,13] and is more common in males than in females.[10]

BCC has six histologic subtypes; the most common—nodular BCC—classically manifests as a nonpigmented raised lesion with pearly edges, superficial telangiectasia, and ulceration.[10] Although clinical presentations of various the histologic subtypes have been describe, presentation may be variable because between 10–40% of BCCs have mixed histologic subtypes.[14,15] Diagnosis of KC based on clinical appearance of the lesion has been found to be accurate in approximately 66–84% of cases, with clinical diagnosis of BCC typically being more accurate than cSCC[16,17] and with the experience of the practitioner influencing the accuracy of clinical diagnosis.[18,19] Clinical diagnosis is considered appropriate for diagnosis of BCC; however, when there is doubt as to the nature of the lesion, incisional biopsy is recommended to confirm the diagnosis before definitive treatment.[20] Metastatic spread is rare in BCC, with a recent review identifying 234 cases in the literature between 1981 and 2011.[21]

cSCC may arise from precursor lesions such as actinic keratoses or de novo.[10] Lesions typically occur as indurated scaly plaques or nonhealing ulcers.[2] Clinically suspected cSCC should be confirmed histologically[22] and referred to an appropriately trained specialist for management. The parotid nodes are the most common site of nodal involvement[23]; they drain the forehead, temporal region, and anterior scalp and may also receive drainage from the face and ear.[23] Lesions involving the posterior pinna and posterior scalp may drain directly to the occipital nodes.[23] Regional metastases have been identified in approximately 4% of patients with cSCC.[24,25] However, in patients with evidence of metastases to the parotid, occult involvement of cervical nodes has been found in 15–35%.[26,27]

Staging

NMSC of the head and neck should be staged according to the American Joint Committee on Cancer (AJCC) TNM classification for cutaneous squamous cell carcinoma and other cutaneous carcinomas.[28] It should be noted that this staging system is not applicable to MCC or NMSC of the

eyelid, which have separate staging systems. Although the AJCC TNM staging system forms the basis for NMSC staging, it has been suggested that it does not fully consider factors that may influence the prognosis of KC, in particular cSCC. Some advocate that in addition to TNM staging, clinicians evaluate a number of other factors that have been shown to confer increased risk of treatment failure, locoregional recurrence, and poor prognosis[11]. These high-risk features include high-risk histologic subtype of cSCC, lymphovascular invasion, poorly defined border of primary lesion, tumor arising within an area of chronic inflammation or scarring, immunocompromise, and previous radiotherapy.[11]

Imaging

Multimodality cross-sectional imaging plays a critical role in staging of aggressive skin-based NMSCs. Goals of cross-sectional imaging in aggressive skin-based primary cancers are as follows:

1. Evaluation of primary site of skin malignancy for local invasion, TNM staging. and preoperative planning
2. Assessment of large nerve perineural spread (LNPNS) of the tumor
3. Detection of distant metastatic disease
4. Planning of image-guided interventions and biopsy
5. Evaluation of postoperative or post-treatment neck to assess recurrent and residual disease, especially at clinically occult sites (e.g., free flaps)
6. Long-term imaging follow-up to monitor treatment response and disease recurrence or progression

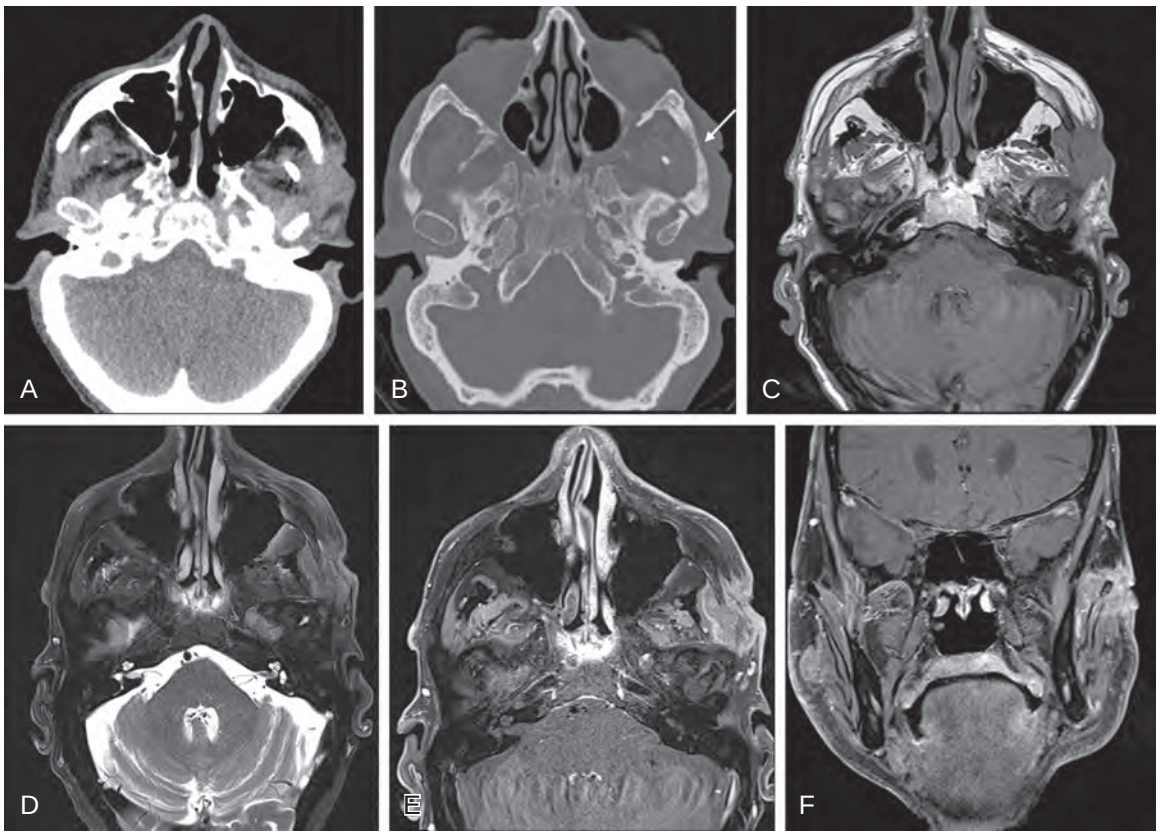
Imaging Modalities

Plain Film or Computed Radiograph

In modern days of head and neck cancer staging, there is hardly any role for plain x-ray studies and computed radiographs. Plain films are an interesting historical footnote but currently play no significant role in the work-up of aggressive cutaneous malignancies, except perhaps for screening chest radiographs for metastatic disease and baseline orthopantomogram (OPG).[29]

Computed Tomography

Computed tomography (CT) scan of the head and neck is a baseline examination for local staging of the primary and nodal involvement. For optimum results, dual-phase contrast-enhanced imaging of the neck is performed after intravenous injection of iodinated contrast. Images are reconstructed in all three planes, and bone windows help to identify any periosteal invasion or bony erosion that significantly changes the T-staging of the tumor and surgical approach (Figs. 44.1 and 44.2). Imaging-based nodal



• **Fig 44.1** An 87-year-old man with left temporal region squamous cell carcinoma. Computed tomography demonstrates ulcerated and infiltrative mass with deep extension to the left zygoma. **A** and **B,** Permeative bony destruction of left zygoma (*arrow,* **B**). T1-weighted axial **(C)** and T2 fat-saturated axial images **(D)** show deep infiltration in the masticator space with marked enhancement **(E** and **F)**.

classification is used from levels I–VII.[30] Contrast-enhanced computed tomography (CECT) is ideal for demonstrating the enhancing and necrotic skin-based primary, the extent of skin infiltration, depth of invasion, and extension to the adjacent fat, underlying bone, and muscles is well identified, although magnetic resonance imaging (MRI) is far superior in this aspect because of better contrast resolution (Figs. 44.1 to 44.3). Dual-phase neck CECT is ideal for demonstrating metastatic nodes.

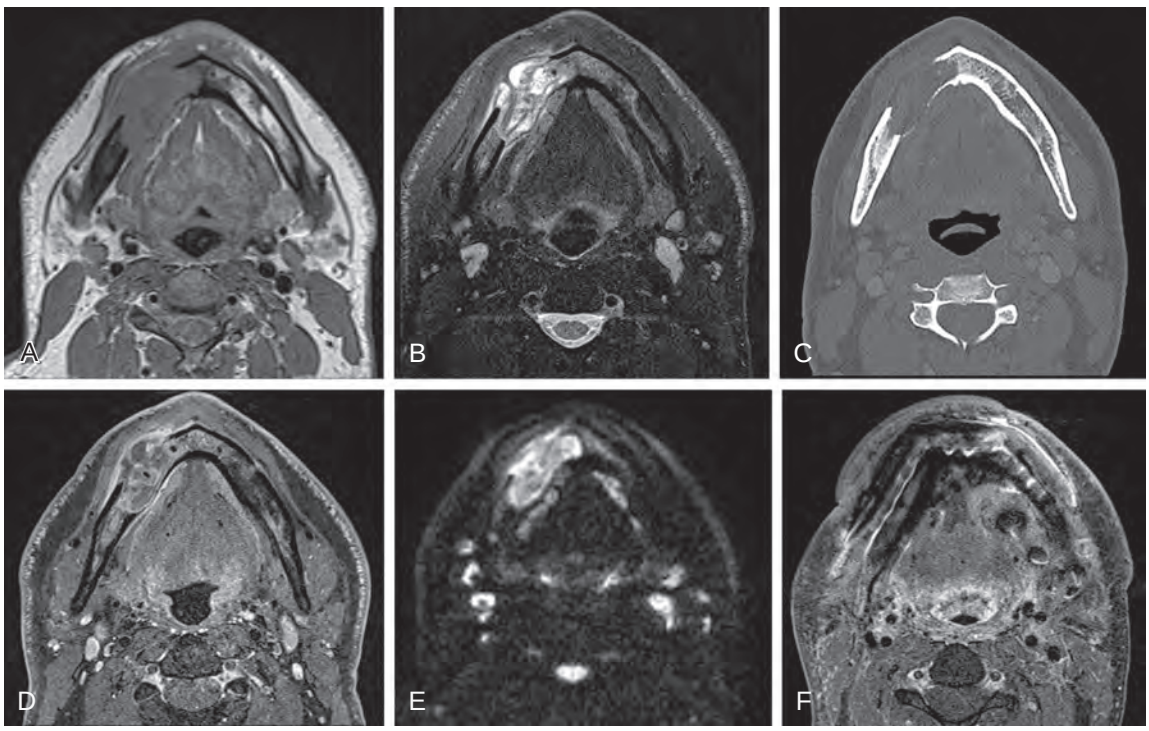
Nodal stations, extent of necrosis, and extracapsular spread are all vital parameters influencing the prognosis of patients with aggressive SCC and BCC (Fig. 44.4). Various literature reports reveal that imaging can identify 7.5–19% of clinically silent metastatic nodes.[31–34] CT is inferior to MRI in showing the extracapsular nodal spread, perineural spread, and involvement of the central skull base (see Fig. 44.4). It may show loss of cortical bone margins and widening of the neural foramina, which are usually seen in late stages of perineural spread. CT scan of the neck is also valuable as a baseline study in assessing disease recurrence in postoperative and/or radiotherapy-treated necks. PET-CT has been proven to be equally effective in serial follow-up after treatment.

The main advantages of CT include speed, intermediate cost, easy accessibility at most institutions, and, in particular, bone detail permitting assessment for subtle sclerotic or bony erosion.

Magnetic Resonance Imaging

MRI is the preferred imaging method for the evaluation of skin SCC and BCCs as well as metastatic disease within the neck because of its superior tissue contrast and multiplanar capabilities and hence forms the mainstay in accurate staging of the disease. The extent of skin involvement and adjacent subcutaneous fat and tissues are best evaluated with T1-weighted images, T2-weighted fat-saturated images and postcontrast T1-weighted fat-saturated images (see Figs. 44.3 and 44.4). Most researchers believe that the prognosis is not related to the histologic grade; however, the depth of invasion and the amount of surface area between the tumor and stroma may be related to the incidence of metastasis. Once squamous cell carcinoma of the skin has metastasized, the prognosis is poor, with 57.3% of patients dying of their disease within 5 years.[33,34]

MRI is particularly useful to detect early perineural spread and early signs such as muscle denervation, which is well identified as high signal within the muscles because of increased water content—edema on T2-weighted fat-saturated images. The explanation for T2 prolongation noted in muscles undergoing denervation relates to the size of the extracellular fluid space (extracellular water), which has a much longer T2 prolongation than intracellular water.[35] Precontrast T1-weighted images are helpful in detecting obliteration of fat along the nerves or in the juxtaforaminal fat. Fat is your friend![36] MRI

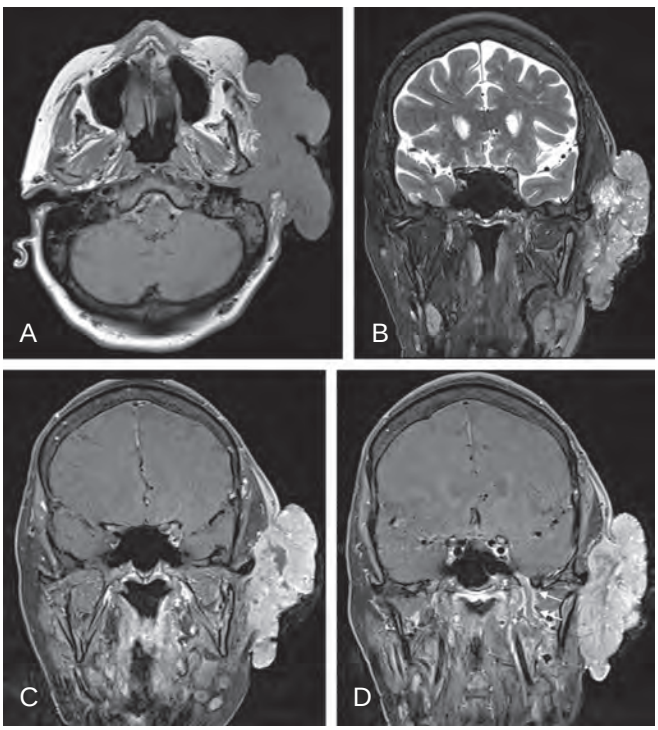


• **Fig 44.2** A 37-year-old man with recurrent right chin and lip squamous cell carcinoma (SCC) (clinical photographs, Fig. 44.13A–F). T1-weighted axial and T2 fat-saturated axial (**A** and **B**) images show deep tumor recurrence subdermal in location and involving the right hemimandible with erosion of both lingual and buccal cortex of the mandible **(C).** Note marked enhancement and diffuse soft tissue infiltration by recurrent SCC on postcontrast T1-weighted fat-saturated axial image **(D).** Tumor is hypercellular and aggressive, as seen by restricted diffusion on diffusion-weighted imaging sequence **(E).** Postoperative magnetic resonance image with marked artifact from metal hardware is suboptimal but shows no evidence of residual tumor **(F).**

can identify perineural spread along the large nerves at an earlier stage and hence is a preferred modality in local staging of skin-based primary SCC and BCC (Figs. 44.5 to 44.7). Postgadolinium images are excellent in identifying primary ulcerative skin-based masses as well as necrotic nodes with extracapsular spread and perineural spread (see Fig. 44.4).

Perineural spread of carcinoma can also be insidious, because patients may be asymptomatic for years before the symptoms of perineural spread manifest clinically.[37] Perineural spread needs thin-slice 1- to 2-mm high-resolution images with optimum fat saturation to detect subtle thickening and enhancement along the course of the large cranial nerve branches (e.g., trigeminal nerve [V_1, V_2, and V_3] and facial nerve). Perineural extension seen on imaging can be divided into three zones: zone 1, peripheral; zone 2, central and skull base; and zone 3, cisternal (Table 44.1), this classification has management implications and prognostic significance.[38,39] Perineural invasion (PNI) is observed in a minority (4.9–14%) of patients with cSCC and BCC, and advanced perineural spread has been associated with a uniformly poor prognosis.[36,40] Certain patients with perineural spread of squamous and basal cell skin cancer are curable by radiotherapy and/or surgery if the perineural disease is recognized early and appropriately treated (see Fig. 44.5).

Postoperative neck can pose some challenges to MRI as a result of metal implants, surgical clips, and so on; but with modern imaging techniques, metallic susceptibility artifacts can be minimized and diagnostic-quality imaging can be obtained.



• **Fig 44.3** A 50-year-old woman with large basal cell carcinoma along the left temple and preauricular region. Note deep extension of tumor into masticator space, left temporomandibular joint, pinna, external auditory canal, and mastoid on T1-weighted axial and T2 FS coronal images **(A** and **B)**. On postcontrast fat-saturated T1-weighted coronal images, the enhancement of the mass is seen beyond the skin attachment margins **(C** and **D)**. Arrows point to perineural spread along left V_3 at the level of foramen ovale **(D).**

Ultrasonography

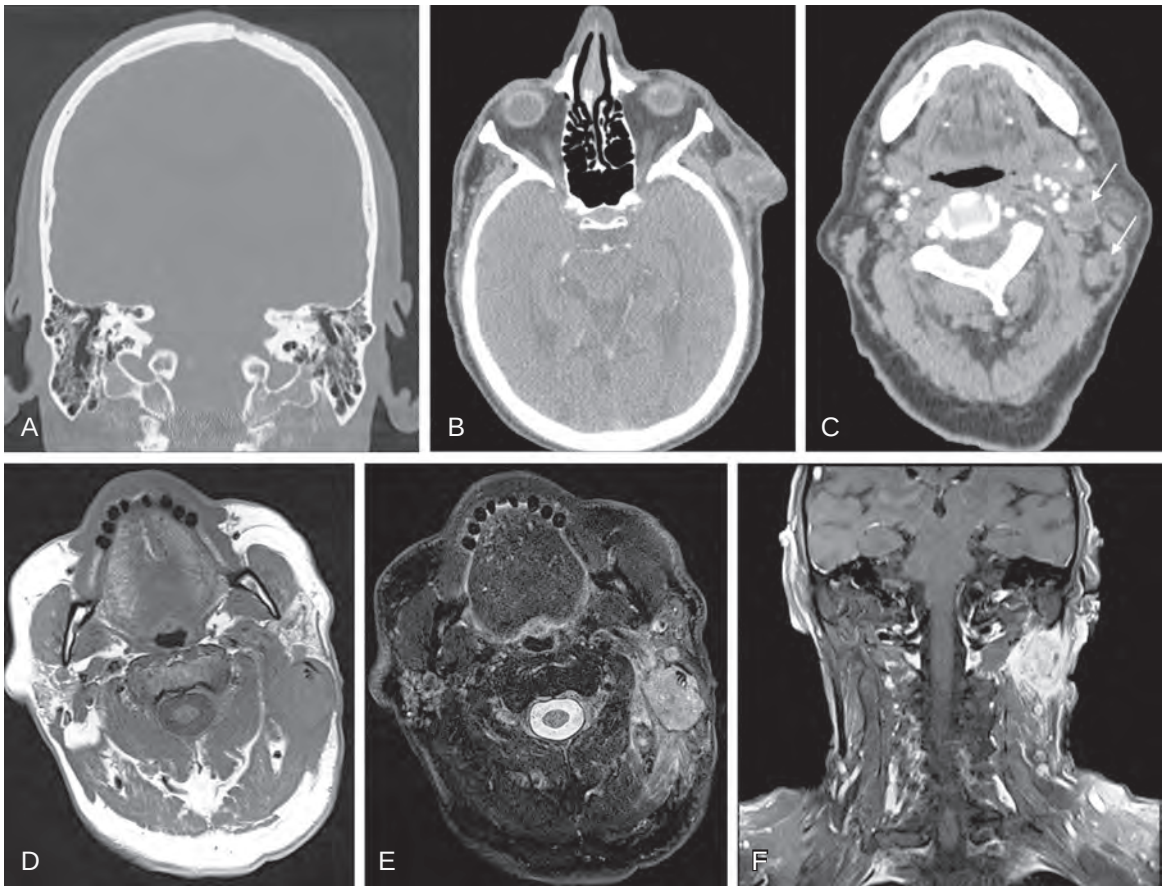
The neck is examined with a high-frequency linear array transducer ranging from 7.5 to 14 MHz. Blood flow can be studied using color Doppler imaging.[34] Levels I to V of both sides of the neck should be examined for the presence of enlarged nodes, particularly in patients with a known skin primary.[34] Particular attention should be paid in assessing intraparotid nodes because they are often enlarged in SCC and can demonstrate unilateral nodal disease long after the primary skin malignancy has been resected. All nodes that are visible on ultrasound are measured in the axial plane. Quick nodal assessment can be performed with ultrasonography before fine-needle aspiration cytology (FNAC). Ultrasound features such as the shape of the node, fatty hilum, echotexture and necrosis within the node, and central versus peripheral flow can assist in selecting the appropriate node for FNAC or core biopsy.

The lack of ionizing radiation; real-time image reconstruction; small size of the transducer; and suitability for use with ancillary equipment, such as needle guides and cryogenic probes, make ultrasound a key modality for intraprocedural imaging and, in particular, image-guided procedures.

Positron Emission Tomography–Computed Tomography

Positron emission tomography (PET) imaging uses fluorodeoxyglucose F 18 (PET-FDG) to identify tissues with high metabolic activity. In particular, tumors with high glycolytic activity will accumulate fludeoxyglucose F 18, as the initial glycolytic metabolite becomes trapped within the cell after initial phosphorylation.[29] PET-CT has many applications in head and neck cancer imaging, but it is particularly useful in detection of nodal and distant metastasis and is superior to CT alone, especially in Merkel cell carcinoma (Fig. 44.8). Integrated PET-CT in the evaluation of cervical lymph nodes found PET-CT superior to PET or CT alone. Lesion localization is also improved when using PET-CT rather than when using PET or CT alone.[41] The most powerful application of PET-CT is in detection of residual or recurrent primary neoplasm, with a high sensitivity (95%) but not as high a specificity (60%).[41] PET-CT also has prognostic value. Pretreatment standardized uptake value (SUV) mean is suggested to be a useful prognostic parameter for patients who will be undergoing radiation therapy (RT). PET-CT is probably useful for the staging of head and neck cancer, as long as there is no N0 disease. PET has an exceptionally high negative predictive value (NPV) and can be considered highly suggestive for the absence of viable disease. Scans performed 12 or more weeks after the completion of definitive therapy have a moderately higher diagnostic accuracy.[42]

New techniques such as PET-MRI have only recently become available and offer further promise in evaluation of skin cancers and follow-up imaging. Early work is underway on hybrid PET-MRI scanners that would reduce the total ionizing radiation to patients and also benefit from the improved soft tissue resolution obtainable with MRI.



• **Fig 44.4** Two different patients: a 65-year-old male **(A–C)** and a 54-year-old male **(D–F)** with history of multiple skin squamous cell carcinomas (SCCs) excised in the past. Recurrent scalp SCC is causing bony erosion of the left frontal bone on computed tomography **(A)** with extensive left facial **(B)** and left level II necrotic lymphadenopathy **(C).** Note significant soft tissue infiltration on magnetic resonance imaging **(D)** with frank extracapsular spread well identified on T2-weighted fat-saturated axial and postcontrast T1-weighted fat-saturated coronal images **(E** and **F)**. Note extension to adjacent perivertebral musculature.

Treatment

Management of advanced NMSC depends on a variety of factors including the patient's preferences and fitness for treatment, the location and extent of disease, previous therapies, and available resources.

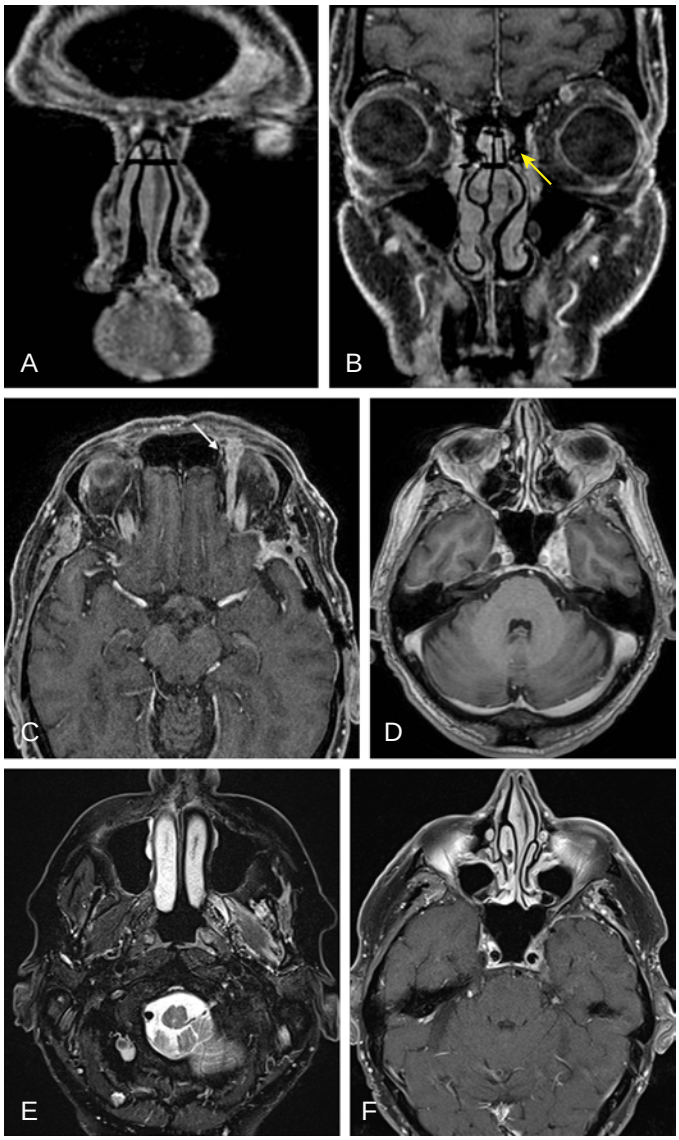
Management of advanced NMSC (i.e., stage II, III, or IV disease) involves multimodality treatment in a multidisciplinary team (MDT) setting, and thus such patients should be urgently referred for specialist care.

Surgical Therapy

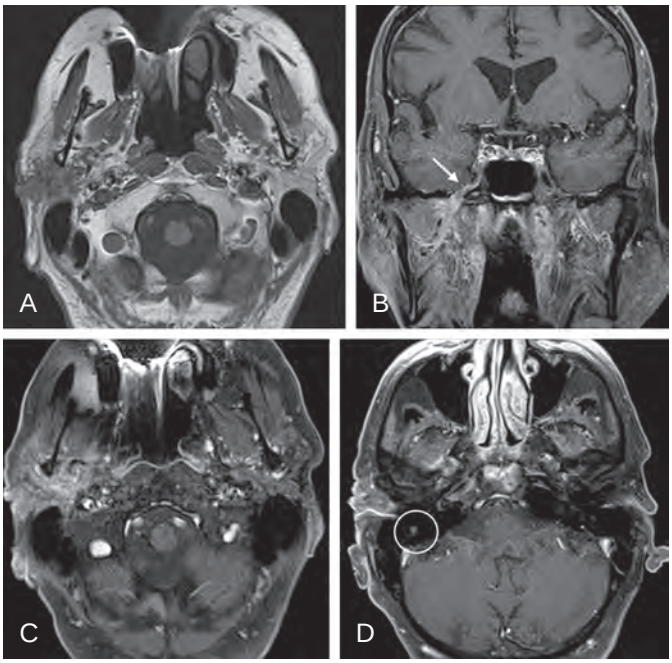
Treatment of locally advanced NMSC will depend on the site and extent of disease. Optimal treatment will typically involve surgical resection of the tumor and invaded structures to obtain histologically clear margins, followed by reconstruction of the resultant defect.

When surgical excision is recommended, resection margins for BCC vary by size and histologic subtype. For small (<2 cm) well-defined primary lesions, 3-mm margins will result in tumor clearance in 85% of cases. When 4- to 5-mm margins are used, a clearance rate of 95% is expected.[20] Morphoeic BCC notoriously has indistinct margins and is associated with extensive microscopic invasion; thus margins of 13–15 mm have been advocated in order to obtain a clearance rate of greater than 95%.[20,43] No clear guidelines or consensus exists for planned surgical margins in tumors larger than 2 cm. Patients with stage II disease or above should be managed by an appropriate MDT,[44-46] which will determine the appropriate treatment for each patient. When surgery is indicated, the aim of surgical resection should be to obtain clear surgical margins while minimizing morbidity to the patient. In high-risk lesions, tumors with poorly defined margins, and those involving the central face, eyelids, nose, lips, and ears, Mohs micrographic surgery should be considered when possible to facilitate satisfactory tumor clearance and preservation of uninvolved tissue.[20,45]

For treatment of cSCC, surgical excision is the treatment of choice.[22] In primary tumors less than 2 cm in greatest diameter without high-risk features, a 4-mm excision margin is appropriate and would be expected to achieve complete removal of the tumor in 95% of cases.[47] For tumors larger than 2 cm or those with high-risk features, margins of at least 6 mm or removal via Mohs micrographic surgery has been recommended[45]; however, 10-mm margins for tumors larger than 2 cm or with high-risk features have recently been advocated.[11,22]



• **Fig 44.5** A 55-year-old man with left sixth nerve palsy and history of multiple skin cancers—squamous cell carcinoma. T1-weighted fat-saturated postcontrast coronal image **(A)** demonstrates skin-based primary with perineural spread (**B;** *arrow*, **C**) along left V_1. Note marked thickening and enhancement of left cavernous sinus and Meckel cave **(D),** explaining left sixth nerve palsy. Follow-up magnetic resonance image 1 year after radiotherapy shows marked improvement. Denervation in left pterygoid muscles is seen, but cavernous sinus disease is almost resolved **(E** and **F)**.



• **Fig 44.6** A 64-year-old man who had undergone right superficial parotidectomy 6 months previously developed right facial palsy. T1-weighted axial image **(A)** confirms tumor recurrence at operative site with infiltration into deep lobe of parotid. Postcontrast T1-weighted axial images **(C** and **D)** show marked enhancement of left facial nerve *(circle)* in mastoid segment; also visible is enhancement along left V_3 at foramen ovale (*arrow,* **B**) suggestive of perineural spread.

The basic principles of removal of adequate tissue margins or one anatomic boundary beyond the tumor holds true for most cutaneous malignancies. Advanced disease often necessitates the removal of extensive facial tissue that may include skin, cartilage, muscles involved in mastication and facial animation, the parotid gland, the facial nerve, and parts of the facial skeleton.

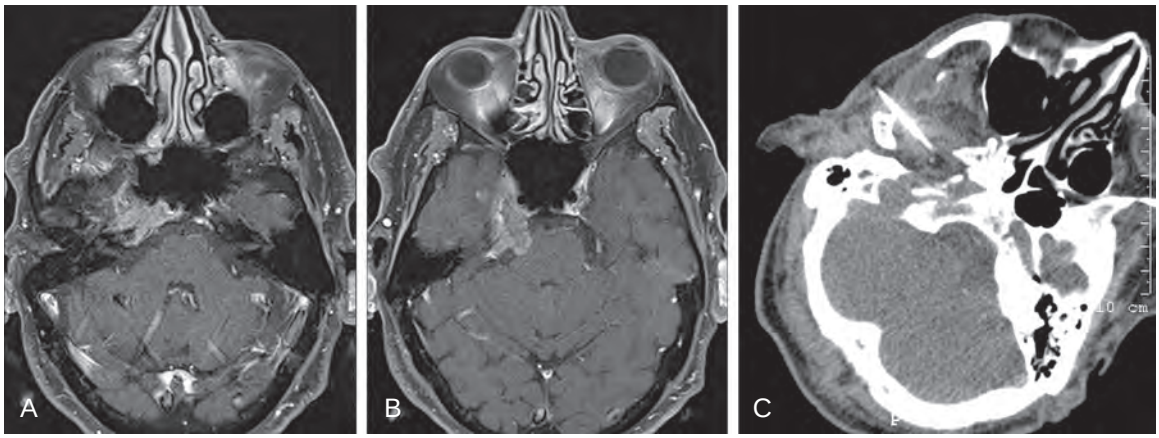
Tumors that frankly invade the orbit or necessitate the sacrifice of intraocular muscles may warrant orbital exenteration to obtain adequate margins or to avoid the complications of permanent untreatable ophthalmoplegia and diplopia. Cases requiring adjuvant radiotherapy near the orbit and globe may also benefit from evisceration or exenteration to avoid some of the debilitating eye complications of radiotherapy such as intractable pain.

Large nerve PNI such as that involving the facial, auriculotemporal, or infraorbital nerve will benefit from dissection of these nerves as far as is surgically practical. This PNI can extend well beyond the visible margins of the body of the tumor and represent sites of potential recurrence if inadequately treated. This type of recurrence is often in sites that are not amenable to further treatment, such as the cavernous sinus or the middle cranial fossa. The trunk of the facial nerve can be effectively traced back through a lateral temporal bone dissection; the infraorbital nerve can be followed back to the inferior orbital fissure in the orbit.

Cases of advanced malignancy involving the calvaria should be evaluated and treated in conjunction with neurosurgical colleagues. Preoperative imaging will help assess for the involvement of dura, frank invasion of the brain parenchyma, and the involvement of the venous sinuses. The morbidity associated with resecting some of these structures may sometimes outweigh the probability of cure.

In patients with no evidence of parotid or cervical lymph node involvement, elective neck dissection (END) is not recommended in BCC or SCC owing to the low probability of metastases.[22] Sentinel lymph node biopsy (SLNB) has been trialed with promising results; however, the routine use of SLNB is not yet established.[11,23]

When regional nodal metastases are suspected, fine-needle aspiration biopsy is recommended. If parotid nodal



• **Fig 44.7** A 50-year-old man with history of cryotherapy to squamous cell carcinoma (SCC) on chin. Postcontrast T1-weighted axial images illustrate marked tumor infiltration in right foramen oval and Meckel cave with perineural spread to cisternal segment of right trigeminal nerve up to pons **(A** and **B)**. Computed tomography–guided biopsy confirmed SCC at foramen ovale **(C)**.

TABLE 44.1 Zonal Classification of Perineural Invasion in Head and Neck Malignancies

Zone 1	V_1 (ophthalmic nerve) to the superior orbital fissure; V_2 (infraorbital nerve) to the external aperture of the foramen rotundum; V_3 (mandibular nerve) to the external aperture of the foramen ovale; VII (facial nerve) to the external aperture of the stylomastoid foramen
Zone 2	V_1, V_2, V_3: from zone 1 to the gasserian ganglion cistern; VII: from zone 1 up to the lateral end of the internal auditory canal, including the geniculate ganglion and the labyrinthine segment
Zone 3	All nerves: proximal to the ganglion, into the cisterns, or into the brainstem

involvement (P+) or cervical node involvement (N+) disease is confirmed, radiologic investigation is indicated to evaluate the extent of regional disease.[23] In P+ disease without cervical node involvement (P+/N0), therapeutic parotidectomy and END are indicated, with the extent of END determined by the site of the primary tumor.[23] Primary lesions of the anterior face and neck should undergo END of levels I–III (including the facial node); in lesions of the posterior face, ear, and anterior scalp, END should encompass levels II–III; and when the primary site is the posterior scalp and neck, END of levels II–V should be performed.[23] In N+ disease, therapeutic neck dissection of levels I–V is advised. When there is also parotid involvement (P+/N+), therapeutic parotidectomy should also be undertaken; and in situations without obvious parotid involvement (P0/N+), superficial parotidectomy should be considered unless the primary tumor is situated in the anterior face or neck.[23] Structures such as the facial nerve, internal jugular vein, accessory nerve, and sternocleidomastoid muscle should be sacrificed only if invaded by tumor.[4]

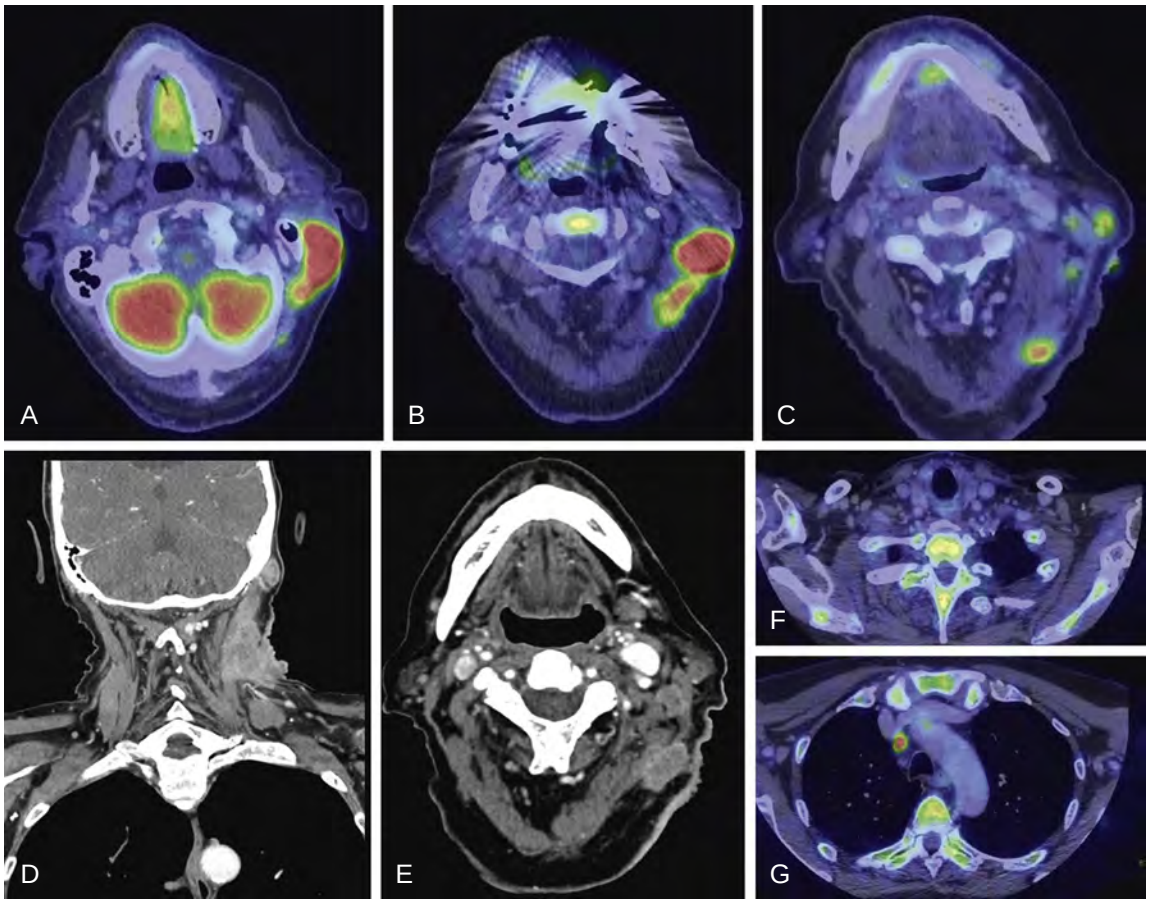
Reconstruction

Management of defects created by ablative surgery for cutaneous malignancies pose unique challenges for the reconstructive surgeon. No other head and neck defects have such significant esthetic demands that must be considered as highly as functional ones. In addition, the involvement of critical structures involved in the senses, facial function, and mastication adds another layer of complexity. These revolve around the orbital tissues, facial nerve, ears, nose, lips, and temporomandibular joint.

The decision-making process is as fundamental to success as is the execution of the reconstructive techniques. The surgeon must be prepared to balance conflicting reconstructive requirements with techniques that all have advantages and limitations. The patient's global medical and functional status must be considered when deciding which reconstructive techniques to apply, along with the likely need for postoperative radiotherapy, because these factors will dictate fitness for surgery and the time available for reconstruction and complete healing.

The principles involved in choosing the appropriate reconstructive technique do not differ from those for other head and neck sites. The reconstructive ladder reminds us to use the simplest technique possible to achieve the desired goals. This is particularly true in cutaneous defects because locally available tissues are often the closest match for those that need replacing. Replacing tissue like for like will often result in superior functional and esthetic results. This may necessitate composite tissue techniques to replace the bony and cartilaginous foundations, tissue volume, and cutaneous or mucosal surfaces. Such procedures can be supplemented by facial nerve reconstruction and primary or secondary reanimation techniques to restore lost facial muscle movement.

It is not possible to present a comprehensive guide to reconstructing defects after ablation of advanced head and neck cutaneous malignancies in this chapter. We will instead review the general principles of the management of the most common defects and provide some examples.



• **Fig 44.8** A 60-year-old male with metastatic Meckel cell carcinoma. Positron emission tomography–computed tomography scans confirm extensive disease along left mastoid and postauricular region **(D** and **E)** with multiple areas of uptake in left suprahyoid neck suggestive of metastatic disease **(A** to **C)**. Also note bony metastasis to vertebral bodies **(F)** and mediastinal nodes **(G).**

The requirements for the reconstruction of tissue of the face and scalp are as follows:

1. Match the native skin color, thickness, and texture, including special skin-covering areas such as the eyelids.
2. Follow facial contours and place scars at the boundaries of facial esthetic units if possible.
3. Replace the volume of tissue lost with dimensionally stable tissue.
4. Reestablish the cartilaginous and bony skeleton of the face.
5. Provide flexibility for facial animation.
6. Contribute to reanimation through static tone or active movement.

Skin grafts can be very effective in replacing some esthetic units of the face and scalp, especially if the donor tissue can match skin color, texture, and thickness. Common donor sites for smaller defects include the neck and preauricular and postauricular regions. Larger defects may require skin from the abdomen or limbs, with split-thickness skin best for large areas requiring coverage. When skin grafts are used, it is ideal to replace entire esthetic subunits of the face to maximize the esthetic outcome. Special skin of the eyelids and periorbital regions is best replaced by grafts harvested from the contralateral eyelids or very thin full-thickness grafts from nearby sites. Skin grafts can line very large scalp defects. These can even be placed directly onto calvarial bone that has been burred to expose the medulla.

Small to medium-sized defects can be adequately reconstructed with local flaps. A wide range of techniques including rotation, advancement, and transposition can be used to help hide scars at the boundaries of facial esthetic units and minimize the distortion of adjacent tissues.

Larger defects may require the mobilization of regional tissue. Many regional flaps have been described in the head and neck with varying advantages and limitations. One of the most reliable techniques for repairing facial defects is the cervicofacial rotation flap. This flap of widely mobilized skin adjacent to the defect is created through dissection in the safe superficial musculoaponeurotic system (SMAS) plane of the face and subplatysmal plane in the neck. Blood supply is maintained through a broad base and by maintaining an adequately thick subdermal layer to protect the vascular network of the subdermal plexus. Once mobilized, the tissue can be rotated and advanced into position using V-Y closure or Z-plasties. By placing the edges of the flap in natural crease lines and at the junction of esthetic subunits, this flap can provide highly esthetic results. Occasionally, deeper defects may require volume replacement. This can be achieved with alloplastic materials or autologous tissue grafting such as bone or fat (Fig. 44.9A, B). Larger defects can be managed by extending the flap onto the chest as a cervicopectoral flap. Care



• **Fig 44.9** **A,** A large cheek defect after re-excision of residual cutaneous squamous cell carcinoma with deep margin taken to periosteum of zygoma. Cervicofacial flap marked, along with further skin excision and Z-plasty to manage "dog-ears." **B,** Flap raised and malar polyethylene implant secured to replace lost soft tissue volume overlying the zygoma. **C,** Result at 3 months after surgery without revision.

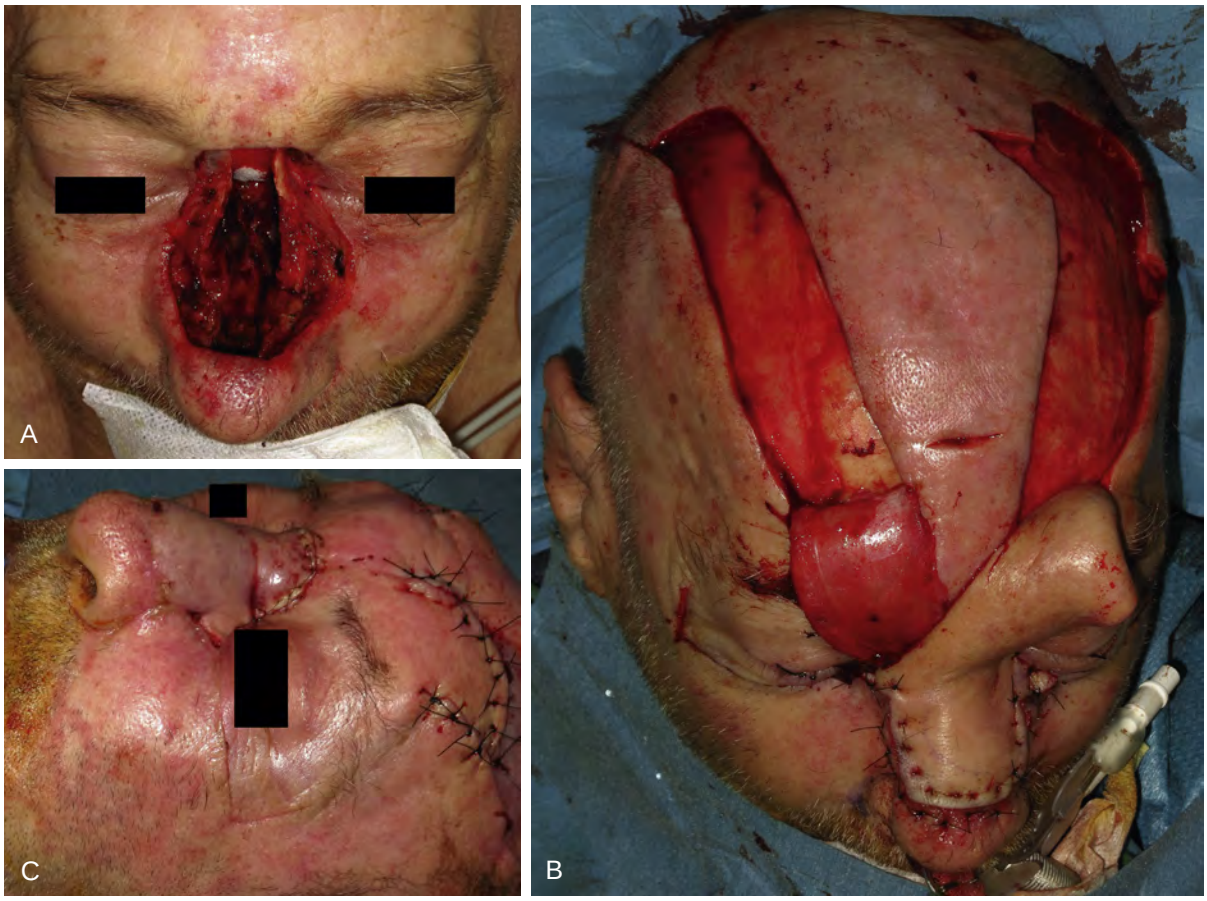
must be taken to preserve the ipsilateral perforating branches of the internal mammary artery to maintain the vascularity of such a large area of skin (Fig. 44.10A, B).

The paramedian forehead flap is a workhorse flap for midface repair. Its robust blood supply and reasonable skin match make it one of the most commonly used regional flaps for nasal reconstruction. For management of subtotal or total nasal reconstruction, two forehead flaps can be combined to form internal and external lining along with a bone strut to provide support for the nasal bridge and cartilage to support the nasal tip and alae. Although these flaps require a multistage approach to repair, they do arguably provide esthetic results that are superior to those of free flaps (Fig. 44.11A–C). Total nasal prosthesis made a resurgence in recent years with the introduction of implant retention and may produce some outstanding esthetic results for these most difficult of cases. Prostheses also allow for more precise sculptured individualization and different skin tones to match the facial skin changes that occur with the seasons.

Other regional flaps that can provide facial skin replacement include the pectoralis major flap, the latissimus dorsi flap, and the supraclavicular flap. These are limited to repair of the lower face up to approximately the level of the tragus of the ear due to their pedicle length. They do offer large volumes of tissue with robust blood supply that can cover reconstruction plates and bone. They can also provide intraoral lining in through and through defects of the cheek. The large muscular flaps do suffer from poor cosmesis owing to their bulky volume over the clavicle and in the neck as well as the subsequent contracture of that tissue within the neck. The temporoparietal galeal flap can be rotated from its superior position of harvest but requires the addition of a split skin graft for rapid and reliable healing.



• **Fig 44.10** **A,** Very large cheek squamous cell carcinoma and second primary on right shoulder; planned repair with cervicopectoral flap. **B,** Result 6 months after surgery without revision.



• **Fig 44.11** **A,** Subtotal nasal defect after resection of extensive nasal squamous cell carcinoma involving septum and ethmoid sinuses. **B,** Bilateral paramedian forehead flaps for internal and external lining supported by calvarial bone strut wrapped in pericranium. **C,** Second-stage inset of flaps.



• **Fig 44.12** **A,** Large recurrent cutaneous squamous cell carcinoma of the scalp marked for resection. **B,** Postresection defect. **C,** Result of antero-lateral thigh (ALT) free flap repair at 2 months without revision.

Free flaps have afforded the reconstructive surgeon with the ability to manage very large and complex defects. These flaps can be soft tissue only, such as the radial forearm and anterolateral thigh flaps, or composite such as the fibula and scapula free flaps.

Soft tissue flaps provide substantial surface area and volume replacement. They can be combined with fascial slings to create the appearance of facial tone, cable nerve grafts to repair facial nerve defects, or a dynamic muscle flap to provide facial animation. Soft tissue flaps can have variable dimensional stability. They often atrophy in unpredictable ways, compromising esthetic outcomes.

Broad soft tissue free flaps such as the anterolateral thigh flap, latissimus dorsi muscle–only flap, and omental flaps are the gold standard for replacing total or subtotal scalp defects. Split skin graft coverage of these flaps aid in healing (Fig. 44.12). These free flaps can be used in combination with alloplastic vault implants to repair bony defects but can suffer from exposure of the underlying implant through a dehiscence in the flap, especially after adjuvant radiotherapy.

Composite flaps allow the surgeon to replace the lost skeletal supports of the face. Even limited bony resections of the malar prominence and orbital rim can leave unsatisfactory contour defects if repaired with soft tissue alone. All the bone-containing flaps have a role in repairing the facial skeleton. The shape and volume of bone to be replaced and the required pedicle length will determine the choice of flap type.

Condylar resection for management of preauricular skin cancers often does not necessitate replacement of the condylar head. Control of the occlusion during the postoperative healing along with intensive physiotherapy is enough to encourage a pseudo-arthrosis with reasonable mouth opening and

function. Persistent trismus can be the result of inadequate obturation of the infratemporal and masseteric spaces leading to hematoma and scar formation with contracture within these deep spaces, causing mechanical confinement of the mandible.

Occasionally defects may require multiple independent elements, which can be managed with a single subscapular system flap or multiple individual flaps. This is especially true with malignancy involving the lower lip. In advanced cases bony invasion and perineural spread can necessitate mandibular resection, total cheek and lip resection, and removal of the inferior alveolar nerve up to its junction with the lingual nerve. The requirements for this defect are many and varied. Skin is required for the face and lip, lining of the buccal mucosa must be reestablished along with continuity of the mandible, and adequate bone stock is required for dental implantation. Finally, the muscle tone and animation of the face may require addressing. The subscapular system flap can incorporate a bony element for the mandible, skin paddles, and a muscle paddle for repair of the face and oral cavity. These can be oriented somewhat independently of each other but require only one harvest and one set of anastomoses. The alternative is to use two flaps such as the fibula and radial forearm flaps to achieve the same goals (Fig. 44.13).

Radiation Therapy

RT plays an important role in the treatment of advanced NMSC and needs to be integrated into the plan of management before therapy is begun. In the vast majority of advanced NMSC of the head and neck, RT is used as an adjuvant treatment after surgical resection. Definitive RT is an acceptable radical therapy when surgery is contraindicated or impractical or will have an unacceptable impact on cosmesis and function.[48] RT is an effective means of palliation for incurable lesions that are bleeding, fungating, or malodorous owing to secondary infection.

Ultimately, around 5% of patients with NMSC will have clinicopathologic risk factors for an increased risk of recurrence.[49] Because of the lack of high-level evidence on the management of advanced NMSC, including the benefit of adjuvant RT, retrospective series and low-level systematic reviews form the basis of many treatment guidelines.[48] The National Comprehensive Cancer Network (NCCN) consensus guidelines recommend that patient with complex cases seek consultation with a multidisciplinary tumor board so that diagnostic test results can be evaluated and multidisciplinary care can be planned in a coordinated fashion with input from all members of the team.[50]

High-Risk Primary Lesions

Risk stratification of patients with locally advanced primary tumors is often based on the size of the lesion as well as other risk factors for recurrence. The AJCC published a revised skin cancer TNM staging classification on 2010.[51] In larger tumors, this system reflects local invasion into surrounding structures and PNI of the skull base. The AJCC further defines T stage by the presence of high-risk features. Conversely, the Union for International Cancer Control (UICC) published revised guidelines in 2009 that define early-stage tumors solely based on size.[52] This may limit the ability of this system to predict poor outcomes in small tumors with high-risk features.[53] A recently published review article by Porceddu and colleagues[48] has summarized risk stratification based on prognostic factors, as displayed in Table 44.2.

Regional Lymph Nodes

Elective treatment of regional lymph nodes is based on the presence of high-risk features of the primary tumor. Elective therapy is often considered if the perceived risk of occult nodal disease exceeds 15–20%.[48] Regional nodes may be treated electively either by END or by elective nodal irradiation, both of which are highly effective. If RT is being delivered to the primary site, elective nodal RT can be added; this is advantageous in elderly patients in whom the increased operating time for neck dissection may involve extra risk. Clinically or pathologically node-positive patients should be offered adjuvant RT in the presence of high-risk nodal features,[48] as summarized in Box 44.1.

Perineural Invasion and Large Nerve Perineural Spread

PNI is malignant infiltration of the potential space between nerve sheath and axon and occurs in 2–6% of cSCC and BCC.[54] PNI detected incidentally at histopathology is an identified risk factor for recurrence.[51] This risk may increase with increasing nerve diameter,[55] the number of nerves affected, and how far the PNI extends away from the primary tumor. The presence of clinical symptoms related to the involved nerves (formication, motor loss) and the presence of radiologically detectable disease[54–57] indicate more advanced PNI disease.

LNPNS is the spread of malignant cells along large nerves both distally, toward the dermis, and proximally, toward the nerve origin in the skull base.[58] This most commonly affects branches of the trigeminal and facial nerves. If the patient is medically able to undergo surgery and the disease is potentially resectable, excision with clear margins should be attempted, and this should be followed by adjuvant RT.

The aim of RT is to prevent disease recurrence or progression in the extra and intracranial skull base, as well as cutaneous recurrence. Areas of gross disease and/or the paths of resected nerves should be included in the gross and clinical target volumes, respectively. Zonal anatomy of the cranial nerves is described earlier in this chapter (see Table 44.1). As a general principle, one zone proximal to the detectable or resected disease should be irradiated electively (i.e., zone 2 should be irradiated for resected zone 1 disease, zone 3 should be irradiated for resected zone 2 disease).[59] In curative-attempt therapy for LNPNS, bolus should be placed over the cutaneous distribution of the involved nerves to prevent cutaneous relapse.[58] Omission of bolus may be considered in palliative cases, to reduce acute toxicity. Crossover between named nerves may occur in the dermis. Extending dermal coverage across dermatomes, across the distribution of known neural conduits (e.g., the auriculotemporal nerve), and even across midline should be considered in at-risk patients.[59] As for other NMSCs, elective treatment of at-risk nodal regions should be considered if the perceived risk of involvement exceeds 15–20%.



• **Fig 44.13** **A,** Preoperative photo of patient with recurrence of cutaneous squamous cell carcinoma of lower lip that has invaded the right side of the mandible with inferior alveolar nerve perineural spread beyond the lingula of the mandible. **B,** Planned resection margins. **C,** Resection specimen including skin, lower lip, segmental mandible, and inferior alveolar nerve to its take-off in the base of skull. **D,** Mandible fixated with reconstruction plate in preparation for fibula free flap inset replacing mandible bone and oral mucosa. **E,** Radial forearm free flap inset to repair cutaneous defect. **F,** Result 2 weeks after surgery.

TABLE 44.2 Risk Factors for Non-melanoma Skin Cancers of the Head and Neck

Risk Factor	Low Risk	High Risk
T stage	T1–2	T3–4
Tumor size	≤20 mm	>20 mm
Tumor thickness (SCC)	<2 mm	≥2 mm or Clarke level 4 or higher
Site		Lip or mask areas of face
Differentiation	Good	Poor
Subtype (SCC)		Basosquamous, desmoplastic, or adenosquamous
Perineural invasion	Absent	Present
Rapid growth	Absent	Present
Lymphovascular invasion	Absent	Present
Borders	Well defined	Infiltrative or in transit
Resection margin	Not involved	Involved
Immune suppressed	Absent	Present
Scars or chronic Inflammation	Absent	Present
Previous radiation therapy	No	Yes

SCC, squamous cell carcinoma.

• Box 44.1 Indications for Radiation Therapy After Lymphadenectomy

- Any node ≥30 mm in maximal dimension
- Two or more involved lymph nodes
- Extracapsular extension
- Involved surgical margin
- Dermal or in-transit metastases
- Invasion into surrounding structures

For medically inoperable cases, RT may be used alone as definitive treatment and may provide durable control of disease in approximately 50% of cases.[56,60]

Merkel Cell Carcinoma

MCC is much less common than BCC or SCC, with approximately 400 cases diagnosed per year in Australia.[61]

MCC is the most aggressive of all skin cancers and has the propensity for dermal lymphatic invasion and nodal and distant spread. Locoregional control and survival are improved with the addition of RT.[62]

Wide local excision, with a 1- to 2-cm minimum margin, is recommended for lesions smaller than 2 cm. Wide surgical margins are not critical if adjuvant RT to the primary site is to be used, and excellent local control to the primary site is achievable with close or positive margins.[63] Adjuvant RT is often used to reduce the risk of local recurrence but is sometimes omitted for primary lesions smaller than 1 cm in diameter with no high-risk features and margins greater than 1 cm.[62,64] Margin-negative surgery combined with adjuvant RT provides excellent local control without the need for wide margins, which are often difficult to achieve in the head and neck.[65] Definitive RT can achieve 75–85% field control rates.[63]

Regional lymph node involvement is common in MCC, and a 15–20% risk is seen even with small lesions.[66] Elective nodal irradiation for stage I MCC has been shown to reduce the risk of regional relapse from 16.7% to 0%.[67] Elective nodal RT should be considered in all stage I and II MCC patients, with the possible exception of those with a negative sentinel node biopsy. Sentinel lymph node imaging may assist in identifying the nodes at risk, especially for midline lesions. Staging with PET may also have an impact on patient management, upstaging 17% of patients in a study by Siva and colleagues.[68]

Patients undergoing therapeutic lymphadenectomy for MCC will often require adjuvant RT owing to high-risk nodal features. RT to the primary site and nodal basin is an alternative to neck dissection with a high rate of in-field control, while sparing the toxicity associated with combined modality treatment.[48]

Radiation Therapy Planning

RT planning occurs 2–4 weeks postoperatively when the wounds are healed and postoperative swelling has settled. Patients are required to lie supine for up to 30 minutes for the planning process to occur. Custom upper body supports and a thermoplastic shell are recommended to ensure optimal patient immobilization, stability, and reproducibility of setup. Surgical scars and biopsy and drain sites should be marked with radiopaque material to assist in target delineation. Using clinical photographs, taken both preoperatively and at simulation markup, is desirable. A planning CT scan with a maximum slice thickness of 2–3 mm should be acquired at simulation for all patients to be treated with megavoltage photons, and is recommended in electron therapy to assess tissue depth for energy selection. When available, preoperative imaging including PET-CT and MRI scans should be co-registered with the planning CT to serve as an aid to volume delineation and quality assurance.

Because some skin sparing will occur with megavoltage photons and electrons, bolus must be applied to areas where the dermis is considered at risk (surgical scars or areas at risk for dermal seeding). The thickness of the bolus will depend on the physical characteristic of the beam. Bolus is a material of tissue density that is placed on a patient surface to increase dose deposition in the skin. It is indicated in the treatment of advanced primary lesions, including MCC, where spread within dermal lymphatics is common. The use of bolus to prevent cutaneous recurrence in cases of LNPNS has been discussed previously.

The use of bolus for treating advanced nodal disease or for operative beds covered by flaps or grafts is less defined. Common indicators for bolus placement include positive superficial margin, dermal metastases, extracapsular spread (ECS), lymphovascular invasion (LVI), and PNI.

Treatment volumes and organs at risk (OARs) are delineated by the radiation oncologist. Once this has been completed, radiation therapists and physicists will develop and quality assure the treatment plan in conjunction with the radiation oncologist.

Radiation Therapy Dose

RT treatment usually extends over a 5- to 6-week period and is given on a daily basis Monday to Friday. The treatment will take approximately 15–20 minutes depending on complexity and technique. Dose and fractionation recommendations for NMSC[48,50] are outlined in Table 44.3. Doses for MCC tend to be lower owing to radiosensitivity of this disease. When a simultaneous integrated boost (SIB) technique is used, absolute doses will need to be adjusted in accordance with the time in which they are delivered to maintain biologic equivalence.

Modality

Adjuvant therapy for high-risk primary tumors can often be performed using electron, megavoltage photon, or either electronic or sealed source brachytherapy.[69,70] Megavoltage photon therapy is indicated for larger operative beds, large reconstructions, LNPNS, and advanced nodal disease, to provide adequate irradiation to at-risk target tissues.

Three-dimensional conformal RT can often achieve adequate radiation coverage in the aforementioned cases; however, intensity-modulated radiotherapy (IMRT), including helical IMRT, is emerging as the preferred technique to minimize unintentional irradiation of normal structures. IMRT is used to maximize dose to target volumes while minimizing dose to structures such as optical apparatus, optic chiasm, cochlea, salivary glands, oral cavity, and pharyngeal tissues. Minimizing dose to these structures can reduce the incidence and severity of acute and late toxicities and positively affect long-term quality of life.[71]

Image-guided RT is essential for megavoltage photon therapy, especially IMRT, in which steep dose gradients between target volumes and OARs exist. Optimally, daily imaging is performed immediately before irradiation to ensure that the patient is accurately set up according to the treatment plan. This is ideally performed via cone-beam CT, but orthogonal kilovoltage portal images are acceptable in its absence. The displacement between the pretreatment and simulation images is compared in three planes. If this displacement exceeds the departmental threshold for action, usually 1–3 mm, the treatment couch can be shifted, in three planes, to correct this displacement. Correcting rotational discrepancies is feasible with many modern RT couches, and the value of this correction is apparent in stereotactic RT.[72] Image guidance improves clinician confidence that a target volume is being treated and that organs at risk (OARs) are not. Effective and reproducible immobilization and accurate image guidance can lead to a decreased margin of uncertainty around target volumes and consequently lower volumes of normal tissues being intentionally irradiated.[73] Margins for internal organ movement and uncertainty, the planning target volume (PTV) margin, vary among institutions and are largely based on experience and quantification of observed random and systematic errors.[74]

TABLE 44.3 Recommended Radiation Therapy Dose and Fractionation Schedules

Setting	Dose (Gy)	Number of Fractions	Fractions per Week
Squamous and Basal Cell Carcinoma			
Primary Definitive			
≤20 mm	24	4	1
	35	5	3–5
	45	10–15	5
	50	20	5
>20 mm	50–55	20	5
	64–70	32–35	5
Primary Postoperative			
Positive margins	55	20	5
	64–70	32–35	5
Negative margins	50	20	5
	60	30	5
Regional nodes			
Unresected	66–70	33–35	5
Resected	60	30	5
Extracapsular extension	60–66	30–33	5
Elective	50	25	5
Merkel Cell Carcinoma			
Primary Definitive			
	60–66	30–33	5
Regional Nodes			
Unresected	60–66	30–33	5
Positive margins	56–60	28–30	5
Negative margins	50–56	25–28	5
Elective	46–50	23–25	5
Simultaneous Integrated Boost (Common With IMRT Technique)			
Equivalent to 66 Gy	66	33	5
	63–64	30	5
Equivalent to 60 Gy	60	30	5
	63	35	5
Equivalent to 50 Gy	50	25	5
	56	35	5
	54	30	5

IMRT, intensity-modulated radiotherapy.

Adaptive Radiotherapy

Through a course of RT, a patient's body contour may change and this may affect the dosimetry. This may be detected clinically or via guidance imaging. Patients often lose weight, or gross disease may regress through therapy. If a contour change exceeds a departmental threshold, further imaging and dose calculation should be undertaken to ensure that dose-to-target volumes are sufficient and not excessive and that dose to OARs remains acceptable. If not, a new RT plan will need to be designed. Likewise, if gross disease progresses or new disease develops during therapy, re-imaging and re-planning may be necessary. In the latter case, clinical work-up and multidisciplinary input are often warranted.

Toxicity

RT toxicities reflect dose deposited in normal structures surrounding the RT field. The degree of toxicity will be affected by the dose, volume, overall time of treatment, dose per fraction, general condition of the patient, and addition of chemotherapy.

Acute toxicities occur in rapidly proliferating tissues such as skin and mucosa, occur during and in the months after therapy, and usually include skin erythema and desquamation. Treatment for nodal disease can often cause acute xerostomia, dysgeusia, and odynophagia owing to radiation deposited in the salivary glands, oral cavity, and pharynx. Late toxicity occurs in more slowly proliferating tissues such as vasculature, connective tissue, and nerves and typically occurs more than 6 months after RT completion. This may include hypopigmentation, telangiectasia, alopecia, and, rarely, skin necrosis. Fibrosis and fat necrosis commonly occur in the months to years after adjuvant RT to large resected and/or reconstructed sites.[71,75] Surgery will increase the amount of fibrosis that occurs from radiation treatment.[76]

Treatment for LNPNS, especially for V_1 and V_2, can cause acute eye toxicities such as keratoconjunctivitis, epiphora, and acute glaucoma. Late ocular toxicities may include xerophthalmia, glaucoma, and monocular blindness related to optic nerve or retinal damage. Bilateral blindness is a rare and dreaded late sequela of excessive irradiation to the optic chiasm.[71,75] An ophthalmologic assessment before commencement of RT is recommended in these cases.

Structures such as brainstem, cochlea, medial temporal lobes, and hypothalamus and pituitary must be considered; normal tissue tolerances are described in Quantitative Analysis of Normal Tissue Effects in the Clinic (QUANTEC).[71] If a normal structure is at high risk of infiltration and destruction by untreated tumor, a relatively higher risk of late RT toxicity to this structure may be acceptable to the patient and clinician.

RT has an effect on normal cells as well as tumor cells. The therapeutic ratio is enhanced with good RT technique that includes dose fractionation schedules and conformal radiation techniques with relative sparing of the normal tissues.

Systemic Therapy

Medical oncologists are less often involved in the management of early stages of skin malignancies. There is no strong evidence that systemic therapy would prevent recurrence after primary or secondary resection except for the use of retinoids in post-transplant patients. There is also no evidence to support its use in combination with RT as adjuvant therapy.

The need for more research using newer systemic therapeutic options (chemotherapy, targeted therapy, and immunotherapy) is emphasized in every report on the management of NMSCs.

Squamous Cell Carcinoma

Localized disease is treated surgically. Some patients considered at high risk receive adjuvant RT. High risk for recurrence is defined by the size of the lesion (>2 cm, T3–4), lymph nodal involvement, aggressive subtype, presence of perineural or lymphovascular invasion, positive resection margins, and immunocompromised state.

The rate of recurrence of non-melanoma skin cancers is around 8%, but it could be as high as 25% in those patients considered at high risk.

There has been only one phase III randomized trial in the adjuvant setting. Sixty-six patients considered at high risk for recurrence (>2 cm, lymph node involvement, PNI, and deep invasion) were randomized to 6 months of 13-*cis*-retinoic acid and interferon alfa. Almost 30% of patients needed dose reduction owing to grade 3–4 toxicity. There was no risk reduction over placebo.

The TROG 05.01 (Trans Tasman Radiation Oncology Group) randomized trial (ClinicalTrials.gov identifier NCT00193895) trial is looking at adding weekly platinum chemotherapy to 6 weeks of RT (60–66 Gy) over 6 weeks. The results are not available yet.

In the advanced setting, for inoperable recurrent or metastatic disease, patients receive platinums, fluorouracil, taxanes, methotrexate, or, less often, bleomycin. The data supporting the use of these drugs are limited.

A small Australian prospective trial treated 14 patients with unresectable disease with concurrent chemoradiation therapy with weekly cisplatin or carboplatin and 70 Gy of radiation over 7 weeks. Complete response rate was 57%. Three-year survival was reported as 54%.

There is only one "nonrigorous" randomized phase III trial comparing bleomycin with physician's choice of chemotherapy, in 70 patients with advanced SCC (but only 6 had skin SCC). Both arms reported a response rate of around 39%.

A summary of phase II trials of immunotherapy, chemotherapy, and epidermal growth factor receptor (EGFR) inhibitors for NMSC is shown in Table 44.4.

EGFR inhibition is an attractive option considering the high frequency of EGFR expression and very uncommon presence of RAS mutations in NMSC.

A number of immunotherapeutic approaches are under research, including T-cell vaccines, cytokines, and monoclonal antibodies.

Basal Cell Carcinomas

Non-operable BCCs or metastatic BCCs are rare events. These patients are traditionally treated with platinum, 5-fluorouracil (5-FU), and taxane chemotherapy. A retrospective review of 53 patients treated with platinum-based chemotherapy reported

TABLE 44.4 Summary of Phase II Trials of Immunotherapy, Chemotherapy, and Epidermal Growth Factor Receptor (EGFR) Inhibitors for Non-melanoma Skin Cancer

	No. of Patients	RR %	DCR %	Two-Year Survival Rate
Cisplatin, interferon, and retinoic acid Shin	39	34	68	58
Cetuximab Maubec	36	26	69	52
Panitumumab Foote	16	31	68	
Gefitinib Glisson	18	13	27	

DCR, disease control rate; *RR,* response rate.

Sources: Shin DM, Glisson BS, Khuri FR, et al. Phase II and biologic study of interferon alfa, retinoic acid, and cisplatin in advanced squamous skin cancer. *J Clin Oncol*. 2002;20:364-370; Maubec E, Petrow P, Duvillard P, et al. Cetuximab as first-line monotherapy in patients with skin unresectable squamous cell carcinoma: final results of a phase II multicenter study [abstract]. *J Clin Oncol*. 2010;28:8510; Foote MC, McGrath M, Guminski A, et al. Phase II study of single-agent panitumumab in patients with incurable cutaneous squamous cell carcinoma. *Ann Oncol*. 2014;25:2047-2052; Glisson B, Kim S, Kies M, et al. Phase II study of gefitinib in patients with metastatic/recurrent squamous cell carcinoma of the skin. *J Clin Oncol*. 2006;24(18 suppl):5331.

an overall response rate of 83%, with 45% complete response in patients with metastatic disease and 30% in those with locally advanced disease.

It was recently discovered that approximately 90% of the sporadic BCCs have an identifiable mutation in at least one allele of the patched gene *PTCH1* (loss-of-function mutation) and about 10% have activating mutations in the smoothened *SMO* gene (gain-of-function mutation) causing dysregulation of the Hedgehog pathway, which plays a critical role in the pathogenesis and development of BCCs.

Vismodegib, an oral small molecule hedgehog inhibitor, showed activity in the phase II trial ERIVANCE, which enrolled 104 patients in Europe and Australia; half of the patients with locally advanced disease responded, and one third of the patients with metastatic disease responded, with a median duration of response of 7.6 months.[77]

Another hedgehog inhibitor, sonidegib, showed impressive disease control rates of over 80%.

Merkel Cell Carcinoma

MCC is a rare but usually aggressive cancer of cutaneous neuroendocrine cells when presentation is in the late stages.

A recent increase in the incidence of MCC in immunocompromised populations (transplant and AIDS patients) led to the discovery of a polyomavirus, Merkel cell polyomavirus (MCV), phylogenetically linked to the murine polyomaviruses, opening the opportunity for research on other therapeutic options (immunotherapy).

Surgery is the primary treatment for localized disease. In general, adjuvant radiotherapy is recommended for lesions with lymphatic or margin involvement despite the limited available data. There are no strong data to support adjuvant chemotherapy, including the survival data from 6908 cases in the National Cancer Database in the United States.

Systemic treatment is reserved for metastatic or recurrent disease. The preferred regimen is a platinum and etoposide, with an initial good response rate of 60–70%; unfortunately, most patients relapse within 4–6 months.

Currently, the focus has shifted toward immunotherapy. Reports suggest improved disease survival in patients with MCV-positive disease. Antiviral drugs to large and small T viral antigens and vaccine development are attractive areas of research.

Immunotherapy trials with checkpoint inhibitors programmed cell death protein (PD-1) and programmed death receptor ligand 1 (PD-L1) and anti–cytotoxic T-lymphocyte–associated protein 4 (Anti–CTLA-4) antibodies are ongoing. The increased mutational rates of MCC, increased infiltrating T cells, and the high expression of immune response mediators suggest a promising outcome.

Summary

NMSC is the world's most common cancer. Advanced disease in the head and neck presents a diagnostic and treatment challenge owing to the many critical structures that may be involved. Cases should be discussed in an MDT meeting so that the treatment can be coordinated and allied health teams can support the patient.

Clinical evaluation is the mainstay of staging; however, when regional or distant metastases are suspected, radiologic assessment is indicated. This may involve CT, MRI, or PET scanning, depending on patient factors and institutional preferences.

Cross-sectional imaging of skin cancers is accurate and offers critical information about locoregional disease extent and metastasis. Early detection of perineural spread on high-resolution MRI is a vital piece of information. All of these factors influence the TNM staging, which in turn helps the surgeon to predict the type and extent of surgery required. Tumor recurrence can be identified with a high degree of accuracy, and imaging provides a good indication of prognosis and outcome.

Surgery is the main treatment modality for most cutaneous malignancies. It can address the primary site as well as regional metastasis. Advanced disease requires generous tissue margins and may require extensive composite resection of skin, cartilage, muscle, bone, and nerves. PNI necessitates dissection of these nerves well beyond the primary site. Careful consideration must be given to the involvement of vital organs such as the eyes, as well as the side effects of treatments on these structures.

Reconstruction after surgery is challenging and requires the addressing of both the lost tissues and the lost functions. Simple local and regional flaps continue to provide excellent and predictable outcomes. Free tissue transfer has improved the

surgeon's ability to manage large-volume tissue loss and composite replacement of the facial skeleton and soft tissues. Nerve grafting and facial reanimation techniques can further improve quality of life by ameliorating the effects of the loss of facial tone and movement required for function and social interaction.

RT plays an important role in securing locoregional control in advanced NMSC. RT is most commonly given as an adjuvant after resection of gross disease but may be used as definitive treatment for medically or surgically inoperable cases. It is highly effective as an elective treatment for nodes at risk.

Systemic treatment has been limited to those patients with unresectable disease or with disease not amenable to other local interventions (e.g., RT). Systemic therapy is often guided by the physician's personal experience and the patient's comorbidities and tolerance. Immune therapy trials have shown some promise and will be a topic of further investigation going forward.

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45 Osteoradionecrosis

ANDREW J. LYONS

Osteoradionecrosis (ORN) is a condition that afflicts between 2% and 22% of patients who have radiotherapy to the head and neck.[1] It is often defined as an area of exposed bone that persists for 3 months or longer when all other diagnoses have been excluded (Fig. 45.1A). However, this is not correct, in that ORN has a characteristic appearance that can be seen radiographically without any breach of the oral mucosa or cervicofacial skin (Fig. 45.1B). This variant was included in a classification by Støre and Boysen.[1] Hence a better definition is "a portion of bone exhibiting characteristic radiolucency that may cause breakdown of the overlying tissue, when all other diagnoses have been excluded."

The severity of the condition and its effect on the patient may vary from cases that are entirely asymptomatic to those that cause severe pain, disfigurement, and functional impairment of the jaws, with significant impairment of the patient's quality of life. This variation in severity determines the therapeutic management of the condition.

Previous Classifications

A number of classifications have been developed to aid management of the condition. Until recently Marx's classification was probably the most widely used worldwide. This classification was unsurprisingly intimately related to Marx's theory of the development of ORN. In 1983 Marx[2] described ORN as emanating from a triad of hypoxia, hypocellularity, and hypovascularity. As a logical solution to this etiology, he developed specific treatments that involved the use of hyperbaric oxygen (HBO), which could be used as the sole treatment or as an adjunct depending on the presenting features of the condition or the patient's response to it. He then developed and published a classification essentially based on the patient's response to HBO.[3] Although he based the guidelines for management on the response to HBO rather than on the clinical signs and symptoms, clinicians must have found it useful, because it is still used fairly widely 3 decades later. Epstein and colleagues published a classification in 1987,[4] which is also widely used. Both classifications undoubtedly have merits but both involve the use of HBO, which as a single treatment has been proved to be ineffective.[5] Although a recent Cochrane review[6] concluded that HBO might be marginally helpful as an adjunctive treatment, the results of studies into its efficacy have been variable.[6] Notani and colleagues[7] graded ORN according to its anatomic extent, which has important implications for management, as shown by the series of patients who were treated to formulate it. However, it does not mention symptoms, which are crucial in the management of the condition.

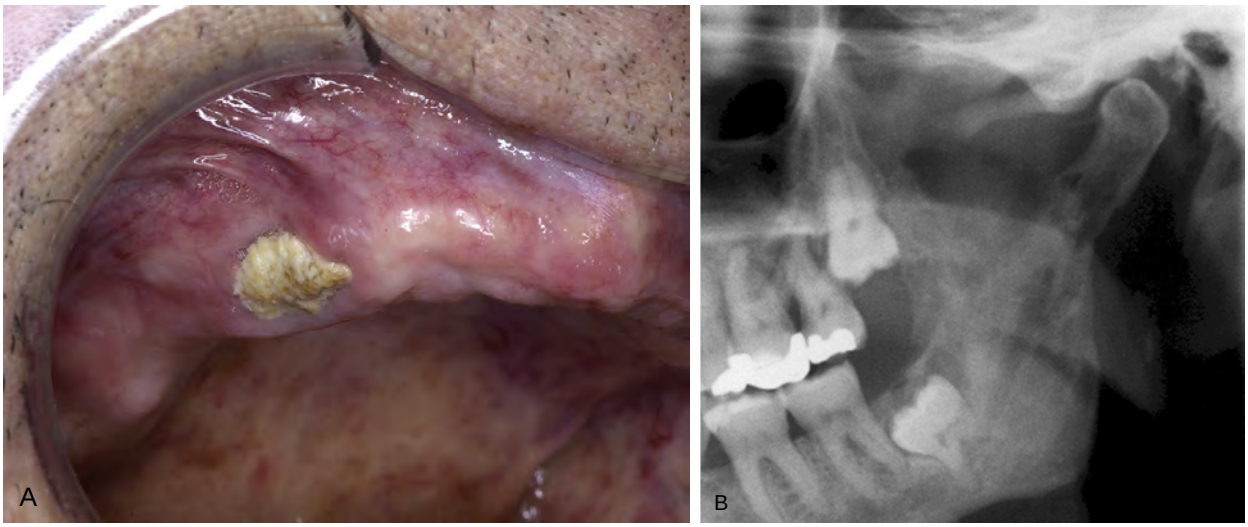
Pathophysiology of Osteoradionecrosis

Since Marx described the pathophysiology of ORN, no other explanations were offered until Delanian and colleagues[8] published the fibroatrophic theory in 1993. They described three distinct phases. The first is a prefibrotic phase in which changes in endothelial cells predominate with an acute inflammatory response. The second is a constitutive, organized phase in which abnormal fibroblastic activity predominates, and the extracellular matrix becomes disorganized. Finally, in the late fibroatrophic phase, attempted tissue remodeling forms fragile healed tissues, which have a serious inherent risk for late reactivated inflammation in the event of local injury and which may result in necrosis in bone. The fibroatrophic theory supposes that the changes in bone that cause this process are very similar to those that occur when physical injuries affect other tissues in the body, such as the lungs and liver.[9] Apart from undermining the treatment of ORN by HBO—and by inference the classifications by Marx and Epstein and colleagues—this etiology infers alternative treatments to HBO.

Antifibrotic Therapy of Osteoradionecrosis

Pentoxifylline is a vasodilator that has antifibrotic effects. Several publications describe its success alone or in combination with clodronate and vitamin E as an antioxidant to treat fibrosis after radiotherapy and after chemical damage to a number of organs, although the precise mode of action in ameliorating radiation fibrosis is unclear.[10,11] A prospective randomized trial has also confirmed the benefit of pentoxifylline for cirrhosis of the liver.[12]

Although the combination of pentoxifylline, clodronate, and vitamin E has not been studied in a prospective randomized controlled trial, the combination has been used to great effect in treating small areas of ORN with visual and symptomatic



• **Fig. 45.1** **A,** Extensive ORN associated with the second molar, but with no mucosal or cutaneous bone exposure or sinus. **B,** Radiograph showing extensive ORN with a fracture of the condyle, but with no mucosal or cutaneous bone exposure.

TABLE 45.1 Osteoradionecrosis Classification

Stage 1	<2.5 cm length (damaged or exposed bone), asymptomatic, medical treatment only
Stage 2	>2.5 cm length asymptomatic including pathological fracture and or ID nerve involvement, medical treatment only, unless dental sepsis or obviously loose necrotic bone
Stage 3	>2.5 cm length symptomatic but with no other features despite medical treatment, consider debridment of loose or necrotic bone and local pedicle flap
Stage 4	>2.5 cm length, and/or with pathological fracture, and/or ID nerve or orocutaneous fistula

From Lyons A, Osher J, Warner E, et al. Osteoradionecrosis—a review of current concepts in defining the extent of the disease and a new classification proposal. *Br J Oral Maxillofac Surg*. 2014;52(5):392–395.

resolution of the condition.[13-16] In a paper published in 2005, Delanian and Lefaix[9] showed that areas of ORN less than 2.5 cm in area could be treated effectively with these drugs. Larger areas may be stabilized but do not resolve with this treatment.[15]

Unfortunately, debridement of inflamed and fragile fibroatrophic bone, coupled with the inability of irradiated soft tissues to adequately cover exposed bone, may worsen the condition and convert relatively stable ORN into a progressive type. Indeed, although some consider incisional biopsy to exclude another diagnosis, in cases such as in Fig. 45.1A and B, where there is no external or intra oral bone exposure.

A New Classification of Osteoradionecrosis

A classification was thus developed that takes into account the use of pentoxifylline and vitamin E[17] (Table 45.1). Although it offers guidelines, it is not intended to be dogmatic. Easing

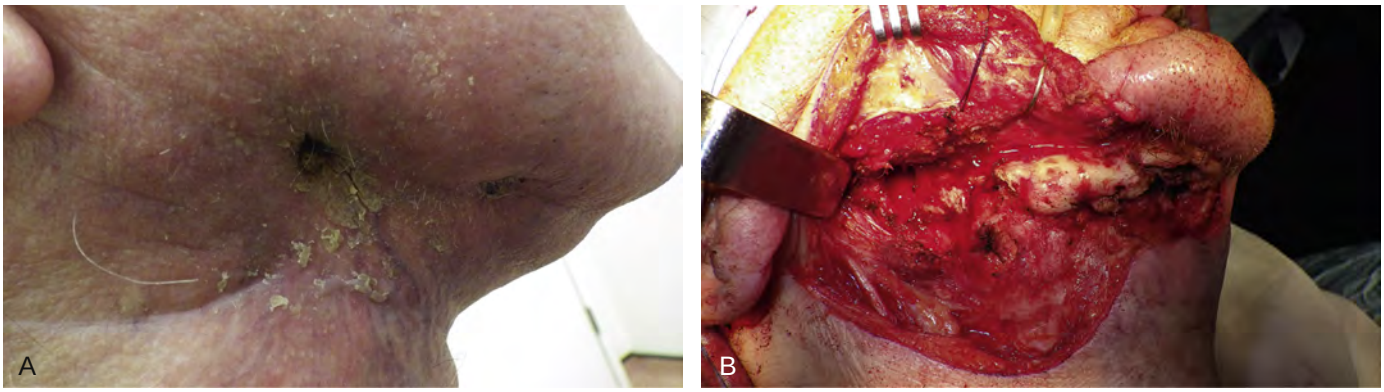


• **Fig. 45.2** Radiograph showing a displaced pathologic fracture, but the patient is and has remained asymptomatic.

sequestrated bone out in groups 1 to 3 without any further treatment is usually helpful.

Otherwise, those in stages 1 and 2 should receive medical treatment only. As the classification points out, this even applies to asymptomatic patients with jaw fractures (Fig. 45.2). ORN is a difficult condition to treat surgically (discussed later).

Where there are symptoms refractory to medical treatment and the ORN is fairly localized without fistula or fracture, a conservative surgical approach should be adopted. Although "conservative surgical approach" is an oxymoron, the aim of carrying out limited surgery is to control symptoms while reducing the probability of the ORN progressing. Limited surgery means removing a small amount of necrotic bone until viable bone is reached, although small areas of nonviable bone



• **Fig. 45.3** **A,** Obvious cervical fistula or sinus. **B,** Case in Fig. 45.4 at time of surgery showing comminuted pathologic fracture.

TABLE 45.2 Patients Grouped According to Described Classification

Stage	No. of Patients	Resolved	Improved	Stable	Progressed
1	28	17	5	6	0
2	7	2	1	2	2
3	12	2*	1	2	7
4	38	35†	33	2	1

*With local flap.
†Free flap, 33; pectoralis major, 1; excision and primary closure, 1.

can be left. The area should be covered by a local flap, such as a facial artery mucosa muscle (FAMM) or nasolabial flap, which can still be used despite the flap areas having been irradiated.[18]

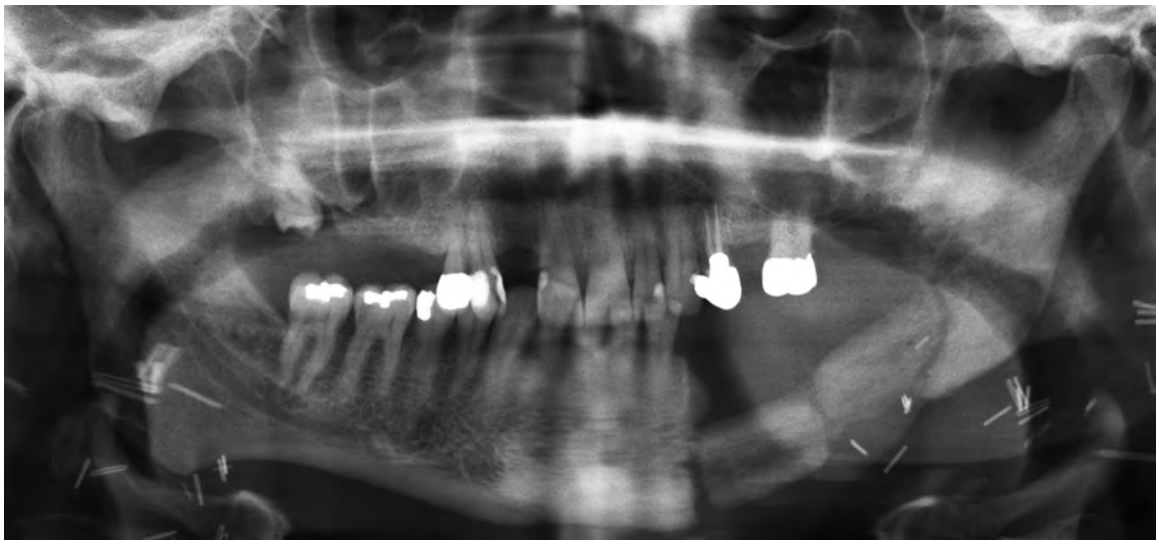
When serious symptoms such as pathologic fracture or fistula occur (Fig. 45.3), resection of the necrotic bone and other tissues is often the only option. Ideally, reconstruction should be carried out with composite free tissue transfer[19], although this may be precluded by the patient's performance status.

One of the most interesting points of the new classification is the number of cases in the early stage that do not progress. Outcomes in Table 45.2 show that ORN was stable in patients with early stage disease and did not progress to higher stages during follow-up periods of at least 3 months. We cannot state categorically that early-stage disease will not progress during a patient's lifetime, but the proportion may be very small. The same is not true of stage 3 disease, which in a few patients progressed to stage 4. Most of those with stage 4 disease required and consented to complex surgical management.

It is difficult to say whether the medication stopped the condition progressing in the earlier stages. ORN may heal, regress, and stabilize spontaneously, but few patients in other series have required reconstructive surgery for disease that has progressed. In the series reported by Epstein and colleagues,[4] 57% of cases that resolved with conservative treatment were stable (15% complete resolution and 42% stable). Other authors report similar figures, although in some cases, conservative treatment involved sequestrectomy and other minor operations. However, in the Epstein series, pathologic fractures developed in 23% of patients during the study period and 19% of cases were progressive. Only 2 of our 36 patients in stage 1 or 2 progressed to higher stages.[17] If our new classification is applied to the series reported by Delanian and colleagues,[14] ORN reduced or completely resolved in all 54 patients with grade 1 or 2 disease who were prescribed pentoxifylline and vitamin E. Delanian may well have achieved these impressive figures by adding clodronate to the other two drugs. Maxillofacial surgeons are averse to this medication in that it can rarely cause osteonecrosis. However, this drug has an antifibrotic[20] effect that acts synergistically with pentoxifylline and vitamin E, and this triple combination has been shown, again by Delanian and colleagues, to be effective in ORN refractory to other medical treatments.[21] A small series reported by McLeod and colleagues[15] found that only one of 12 patients progressed to a higher Epstein grade. Other reports of the successful use of pentoxifylline and vitamin E for small areas of ORN are now quite numerous.[14,15]

Surgical Treatment of Osteoradionecrosis

Several authors have alluded to the high rate of morbidity, which can be up to 55%,[22-31] when undertaking reconstruction for advanced ORN of the jaws. Ninety-five percent survival of flaps is considered the standard acceptable outcome in reconstructions with free vascularized flaps and no previous radiotherapy, but a rate of 85% has been reported in a series of 53 patients who had reconstruction for ORN.[30]

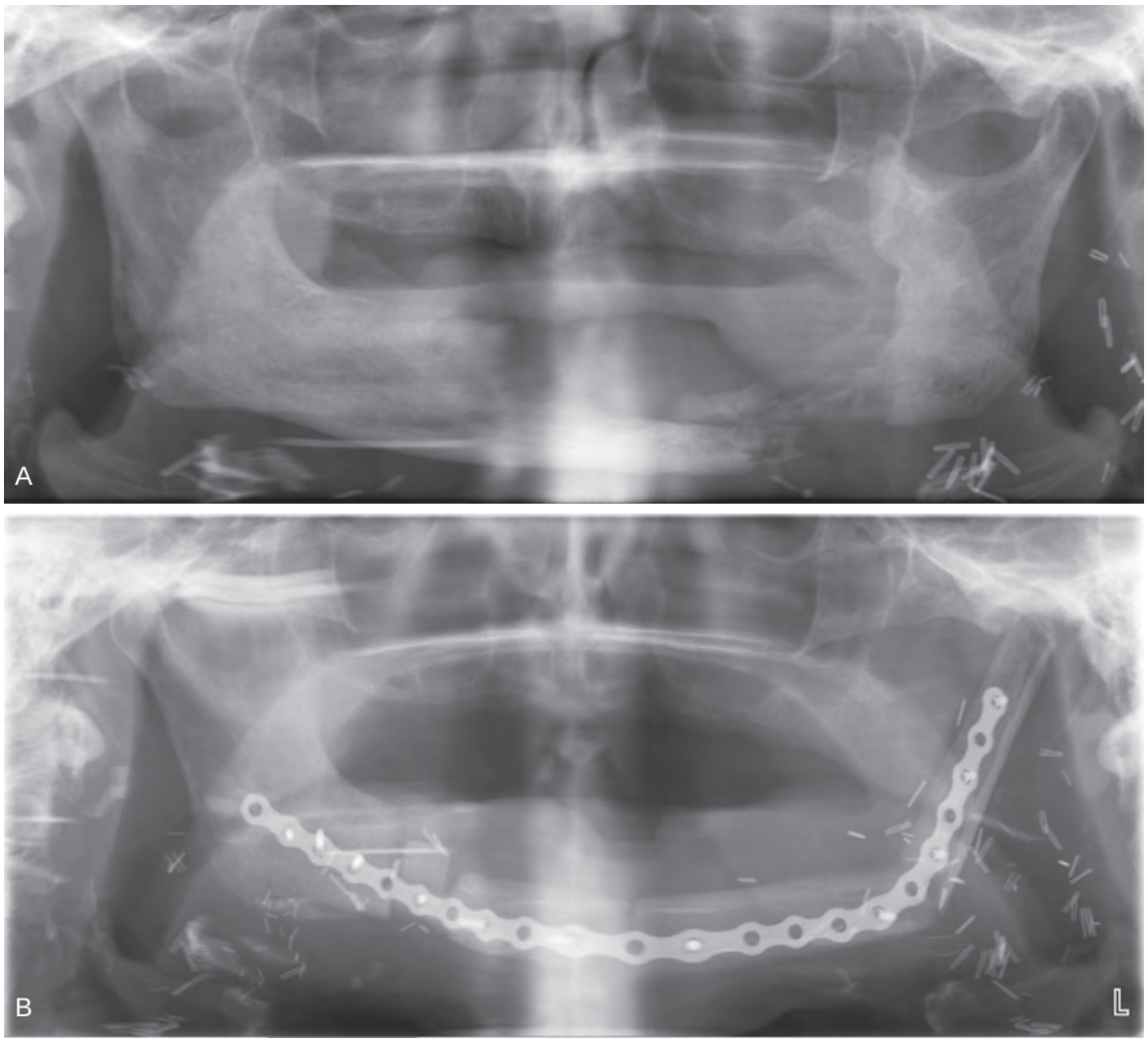


• **Fig. 45.4** The osteoradionecrosis in the left body was successfully reconstructed; however, despite being unaffected at the time of reconstruction, the left condyle became osteoradionecrotic.

Although these patients are at risk for wound healing complications that may be fatal, many have an uncomplicated operation and recover at least as well as those who have similar operations but do not have ORN. A recent study put the average duration of in-patient stay as 19 days.[32] Recognized coexisting conditions such as poor nutrition, diabetes, and alcohol misuse may increase the risk of problems with healing. One study found that smoking reduced the risk of ORN recurrence.[30] Another study found that the longer the onset of severe ORN from the date of radiotherapy, the greater the likelihood of complications.[25] However, if treatment with hyperbaric oxygen (HBO) fails, then patients with ORN have a higher risk for complications after free tissue transfer than those not previously exposed to HBO.[26,27] Other than this, it is difficult to predict which patients will have complications after reconstruction for ORN. A recent Cochrane review mentioned earlier has indicated that it may be of marginal benefit in these cases.[6] No particular method of reconstruction seems to cause fewer or more complications.

Nearly always there is a composite defect, and bringing in a vascularized rather than a pedicle flap is likely to produce a superior functional and esthetic result, together with better healing due to the new blood supply. However, the choice of free or pedicled flap is to some extent determined by the patient's performance status. Given that most ORN occurs within 2 years of treatment and these patients have undergone radical radiotherapy and often radical surgery, this is unlikely to be an issue. Ideally, because in most instances only one side of the neck is affected severely by radiotherapy and often surgery, the opposite side of the neck should be used for anastomosis of the pedicle. There is often a paucity of donor vessels in the neck where the radiotherapy damage is, and both the vein and artery can be incredibly fragile and tear either during careful exposure or suturing. The deep cervical vessels lower in the neck are often spared of radiotherapy damage and are a reasonable size. If venous drainage is a problem, the cephalic vein can be cut just above the elbow and transposed superiorly into the neck. Use of a cephalic vein loop between the great vessels in the neck is a possibility, but these are often too damaged to be viable. Therefore, a loop between the axillary vein and artery may be a solution. Lastly, the internal mammary vessels may also be harvested halfway down the sternum and transposed into the neck. Although the artery is almost always adequate in terms of diameter and flow, the venae comitantes are less constant. However, there is no reason why this cannot be supplemented by a cephalic vein transposition. The next stage is to determine which composite flap to use.

When in the preoperative assessment it is decided to use a free vascular composite flap, then first the bony requirement must be determined. Clearly, the ORN must be resected to bleeding bone and this can usually be assessed fairly accurately with plain imaging. Second, it needs to be determined which bone may become osteoradionecrotic after surgery. There is always a temptation not to resect the condyle and possibly the coronoid, leaving variable quantities of ramus, because this part of the mandible is non–tooth-bearing and hence infrequently affected by ORN. This will make the reconstruction easier to execute, and better mandibular function can be expected if the natural condyle is used for articulation. However, perhaps because the blood supply is compromised during surgery, no matter how large or small this proximal fragment, there is always the high risk that this will necrose following the surgery (Fig. 45.4), the condyle should therefore be replaced and reconstructed (Fig. 45.5). The chance of the remaining mandible becoming osteoradionecrotic is not likely in the body, but once the angle is approached, the remaining proximal mandible is at risk of osteoradionecrosis in the future and so should be excised. In determining the likelihood of further bone loss due to ORN after surgery, the presence of teeth likely to require extraction or cause sepsis is of concern, particularly in the mandible area. If these teeth abut the area to be resected, then the problem can be resolved by extending the area of bone to be resected. During osteocutaneous reconstruction, where

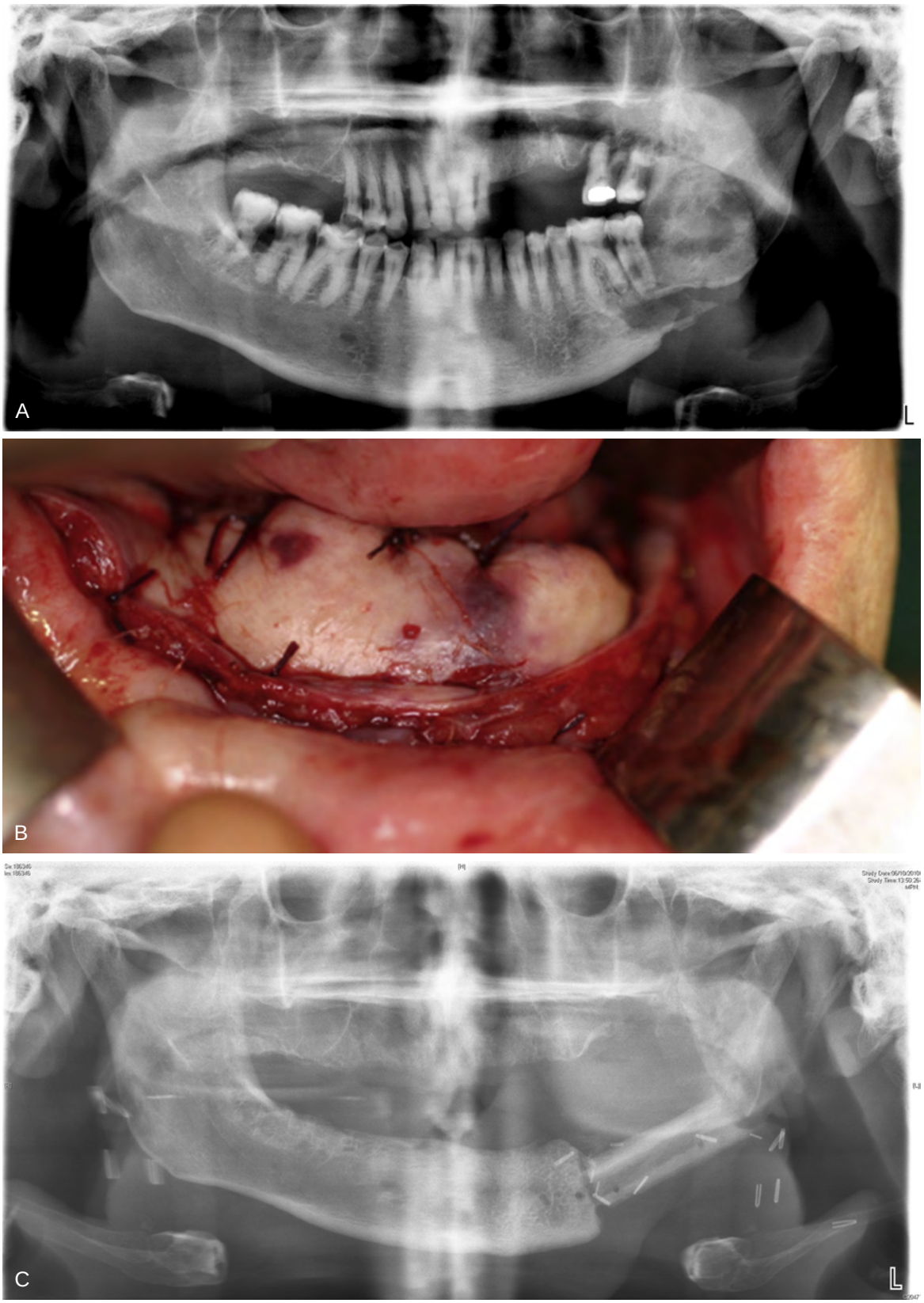


• **Fig. 45.5** **A,** The condyle appears unaffected by osteoradionecrosis. **B,** The entire condyle has been replaced.

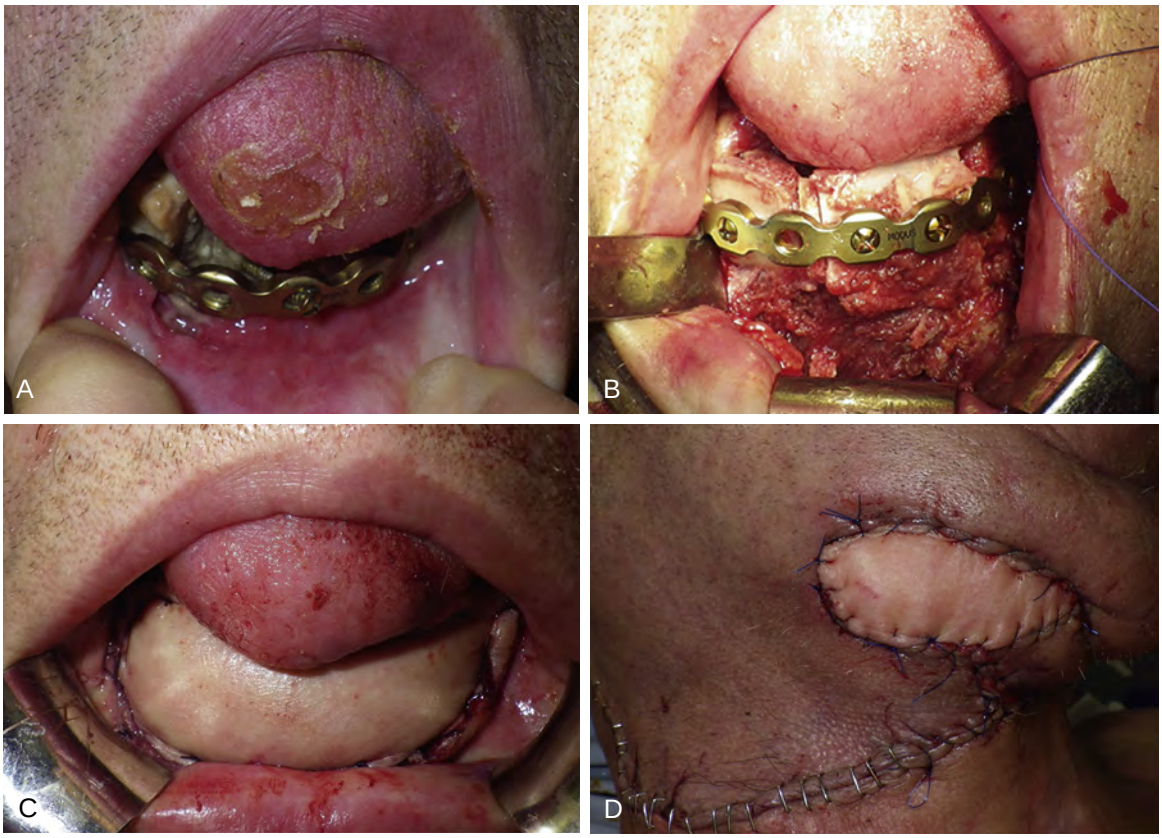
teeth need to be extracted in the contralateral side if this has been irradiated, this segment of bone is usually replaced by extending the length of the vascularized bone graft. However, as a useful alternative, a soft tissue component of the composite free vascularized flap can be transposed to cover the extraction defects, as was employed to prevent ORN on the contralateral side in Fig. 45.6B, rather than replace a very long area of mandible (see Fig. 45.5A and B). Unfortunately, early signs of ORN can be seen in the condyle (Fig. 45.6C), which was later excised.

In terms of the soft tissue requirement in planning the reconstruction of an ORN case, in addition to the soft tissue requirement to close any defect, two additional factors may need to be considered. First, the ipsilateral neck should be opened even when the anastomosis is to be contralateral. Bearing in mind that radiotherapy damages all tissues, both hard and soft; ideally an ellipse of free vascularized skin and subcutaneous tissue should be used to close the neck. This acts as an island of new tissue between the two sides of the neck incision, or any cervical fistula that may be present. Failure to do this can result in a protracted course for the neck to heal as well as an orocutaneous fistula. Second, where there has been significant bony destruction, particularly if there is a pathologic fracture, both the internal and external soft tissue may contract and fibrose, necessitating insertion of a considerably increased width of soft tissue to enable the mandibular position to be corrected.

For the aforementioned reasons, unless the length of bone required exceeds the length of a hemi-mandible, a scapula flap may be preferable to a fibula, because the scapula is able to impart a greater amount of soft tissue replacement (Fig. 45.7) to the donor site, which can almost always be closed primarily with a scapula but not a fibula. Pedicle length can be problematic, particularly when the flap needs to be anastomosed in the contralateral neck. To some extent, this may be resolved by placing the bony component as far over to the contralateral neck as possible, even if it means resecting apparently healthy mandibular bone. Alternatively, the flap can be based on the thoracodorsal vessels and scapula angle with its pedicle used to reconstruct the defect.



• **Fig. 45.6** **A,** While the osteoradionecrotic bone on the left requires excision, the carious teeth on the right are liable to be problematic later. **B,** Soft tissue reconstruction in **A.** By extending the fibula skin paddle to the right to cover the extraction sockets, further osteoradionecrosis has been avoided as can be seen several years later after plate removal **(C).** However, the condyle on the left is becoming osteoradionecrotic. (This was before the author changed his practice to nearly always replace the condyle.)



• **Fig. 45.7** **A,** Osteoradionecrosis around reconstruction plate. **B,** Bony component of scapula has been inset. **C,** Wide oral component of scapula. **D,** Cervical component of scapula.

The vascularized iliac crest graft is a useful method of reconstruction, particularly where the ipsilateral neck can be used for the anastomosis, because the pedicle is short. Treating ORN cases using the muscle component for the oral cavity and the soft tissue component for the neck and cheek was described by Urken and colleagues[33] in a study that included a large number of bilateral cases. However, careful preoperative patient selection is vital in terms of the viability of the skin pedicle, as the perforators may be absent or not arising from the deep circumflex iliac artery.

Although the bone component is limited in the composite radial forearm flap, this flap has been described as a useful method of reconstructing ORN. The excellent soft tissue component of this flap may render it a particularly useful method of reconstruction, and its long pedicle may be used to reach the opposite side of the neck. At the end of the day, any composite flap can be used to treat ORN. In determining which flap to use, not only should factors pertinent to the patient be considered but also which flap the surgeon feels most comfortable with. Particularly with lateral defects, a soft tissue only flap may be an option. Function and esthetics are unlikely to be as good as when a composite flap is used, but the surgery will inevitably be more straightforward. Although the time of surgery will be shorter, this is unlikely to be an issue because patients whose performance status renders them fit for a soft tissue free tissue transfer are likely to be fit for a composite free tissue transfer. In rare instances when a free vascularized composite reconstruction is apparently successful in terms of tissue viability but which gradually degrades over a period of months or years, then this is one of the circumstances wherein a soft tissue only free tissue transfer is appropriate. The temptation to put a new composite flap is great but in the author's experience repeated composite free tissue transfer is subject to a rule of diminishing returns: the paradox of the successful but functionally failed free flap (Fig. 45.8) is very difficult to deal with, and a long period of wound dressing may be the only option.



• **Fig. 45.8** Seemingly successful fibula reconstruction with cervical skin; however, an oro-cervical fistula developed.

No particular method of reconstruction seems to cause fewer or more complications. However, as a consequence of reviewing the results of this series, we always insert a free tissue transfer into the neck and oral cavity when reconstructing for ORN, either subcutaneously or exposed as a skin paddle.[32] Since doing this, fewer wounds have broken down seriously.

Conclusion

In most patients, the management of ORN does not represent a serious challenge and the condition will have little impact on the patient's quality of life. However, the reverse is true in a small minority and they represent one of the most complex and difficult challenges is maxillofacial and particularly reconstructive surgery.

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Preface

Oral, Head and Neck Oncology and Reconstructive Surgery is the first multidisciplinary text that provides the reader with a comprehensive system for managing cancers of the oral cavity and pharynx, representing the most common adult head and neck cancers, excluding thyroid cancer. In particular, it highlights recent technological innovations that have affected head and neck oncologic and microvascular reconstructive surgery, such as virtual surgical planning, transoral robotic surgery, and rehabilitation; intensity modulated radiation therapy; as well as emerging therapeutics, such as immunotherapy and molecularly targeted therapy. The text brings together expert head and neck surgeons from different training backgrounds (oral and maxillofacial surgery, otolaryngology, and general surgery), radiation oncologists, medical oncologists, dentists, pathologists, radiologists, and speech/language pathologists to present their respective "institutional approach" toward a particular problem or disease.

The first part of the book focuses on basic principles that are applicable to most any tumor type in the head and neck; the second section includes only the most common head and neck cancers, with the notable exclusion of thyroid cancer, sino-nasal cancers/skull base tumors, and sarcomas. All of the chapters in the second part of the book, except for the chapters on melanoma and salivary gland malignancies, deal exclusively with squamous cell carcinoma of the head and neck (HNSCC).

For almost a century, surgeons and oncologists have prescribed for patients with head and neck cancer various combinations of surgery, radiation therapy, and chemotherapy, which have resulted only in a state of equipoise. Advances in microvascular reconstruction, intensity modulated radiation therapy, and coordinated multidisciplinary care have improved quality of life outcomes for patients; but overall survival at five years still hovers between 50–60%. This is only marginally better than it was a century ago and is certainly not in keeping with improvements seen for some other solid cancers, most notably breast and colorectal cancer. But there is now reason for optimism.

As this textbook comes to print, the practice of oncology is being transformed as a result of our understanding that the presence of an endogenous anti-cancer immune response before treatment plays an important prognostic role in the long-term therapeutic effects seen following conventional therapy as well as immunotherapy. Adoptive cell transfer with tumor-infiltrating lymphocytes or receptor-engineered T cells, as well as checkpoint inhibitors, such as cytotoxic T lymphocyte antigen-4 (CTLA-4) anti-programmed death-1 (anti PD-1), that take the brakes off pre-existing anticancer immunity are resulting in objective clinical responses or durable stable disease in patients with a wide spectrum of cancers, including head and neck squamous cell carcinoma. Furthermore, as knowledge of tumor biology and the human genome has evolved, it is apparent that cancer therapies are becoming increasingly precise, thus enabling a truly personalized approach to oncologic treatment. In addition to numerous immunotherapy agents, an expanding portfolio of molecularly targeted drugs is being explored for the treatment of cancer, the result being an unprecedented investment by pharmaceutical companies, the federal government, and academia in drug development.

However, much work needs to be done if these agents are to be rationally integrated into the definitive setting. Surgery remains the primary modality of treatment for most patients with oral cavity squamous cell carcinoma, salivary gland malignancy, advanced skin cancer, and T4 larynx cancer, among others, and with the development of transoral robotic surgery, it is an increasingly popular therapeutic modality for T1/T2 oropharynx cancer. Therefore the responsibility to ensure that patients are enrolled into practice-changing clinical trials is paramount and rests squarely on the surgeon's shoulders.

From a research perspective, HNSCC has the potential to be particularly informative because of readily accessible primary tumor tissue that is available before definitive surgical resection and the ease in which tissue can be harvested from the resected primary site and draining lymph nodes, thus making neoadjuvant trial designs attractive to scientists. The ability to interrogate the tumor microenvironment, draining lymph nodes and peripheral blood by flow cytrometry, fluorescent multiplex immunohistochemistry, single cell or T-cell receptor (TCR) sequencing, whole genome, whole exome, and RNA sequencing, proteomics, tumor antigen T-cell profiling in the blood and circulating tumor DNA and will provide new insights into the biology of effective cancer therapy moving forward. It will also accelerate the development of next generation biomarkers that direct therapy and predict outcomes.

American head and neck surgeons are, in many cases, leading this effort as principal investigators on dozens of cooperative group, investigator-initiated, and industry-sponsored trials, and some of these leaders have authored chapters in this textbook. It is quite possible that these trials will result in an entirely new treatment paradigm—one that may or may not include surgery, radiation, and chemotherapy in the manner or sequence in which it is currently employed.

Textbooks are often already out of date on the day of their publication, but they make excellent points of reference when considering major milestones in the standard of care. We cannot predict the result of ongoing advances in precision oncology, targeted molecular therapy, immunotherapy or early detection; however, it is clear that by the time the second edition of this book is published, there will be significant changes in treatment paradigms and, for the first time, improved survival for patients with this most capricious disease.

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SECTION A

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20. Advanced Tongue Cancer (Special Considerations Requiring Total Glossectomy), 410

21. Early Floor of Mouth Cancer, 420

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27. Early Palatomaxillary Cancer, 560

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29. Advanced Palatomaxillary Cancer (Special Considerations Related to Reconstruction), 586

30. Advanced Palatomaxillary Cancer (Special Considerations Related to Nasal Involvement), 596

31. Lip Cancer, 608

TABLE A **WHO Classification of Tumors**

Code	Description
8070	Squamous cell carcinoma, conventional
8075	Acantholytic squamous cell carcinoma
8560	Adenosquamous carcinoma
8083	Basaloid squamous cell carcinoma

Code	Description
8051	Carcinoma cuniculatum
8052	Papillary squamous cell carcinoma
8074	Spindle cell squamous carcinoma
8051	Verrucous carcinoma
8082	Lymphoepithelial carcinoma
8550	Acinic cell carcinoma
8430	Mucoepidermoid carcinoma
8200	Adenoid cystic carcinoma
8525	Polymorphous adenocarcinoma
8147	Basal cell adenocarcinoma
8562	Epithelial-myoepithelial carcinoma
8310	Clear cell carcinoma
8480	Mucinous adenocarcinoma
8290	Oncocytic carcinoma
8500	Salivary duct carcinoma
8982	Myoepithelial carcinoma

Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *World Health Organization classification of tumours pathology and genetics of head and neck tumours*. Lyon: IARC; 2005.

TABLE B **Summary of Changes to the American Joint Committee on Cancer Staging Manual (8th edition)**

Change	Details of Change
Anatomy-primary site	Occult primary tumor: staging of the patient presents with EBV-unrelated and HPV-unrelated metastatic cervical lymphadenopathy is not included
Definition of primary tumor (T)	Clinical and pathological depth of invasion (DOI) are now used to increase the T category
Definition of primary tumor (T)	Extrinsic tongue muscle invasion is no longer used in T4 because this is a feature of DOI
Definition of regional lymph node (N)	Separate N staging approaches have been developed for HPV-related and HPV-unrelated cancers
Definition of regional lymph node (N)	Separate N category approaches have been developed for patients treated without cervical lymph node dissection (clinical cN) and patients treated with cervical lymph node dissection (pathological pN)
Definition of regional lymph node (N)	Extranodal extension (ENE) is introduced as a descriptor of all HPV-unrelated cancers

TABLE B Summary of Changes to the American Joint Committee on Cancer Staging Manual (8th edition)—cont'd

Change	Details of Change
Definition of regional lymph node (N)	ENE in HPV-negative cancers: Only clinically and radiographically overt ENE—ENE(+)—should be used for cN
Definition of regional lymph node (N)	ENE in HPV-negative cancers: any pathologically detected ENE is considered ENE(+) and is used for pN
Definition of regional lymph node (N)	ENE in HPV-negative cancers: Presence of ENE is designated pN2a for a single ipsilateral node <3 cm and pN3b for all other nodes
Definition of regional lymph node (N)	Classification of ENE: Clinically overt ENE is classified as ENE, and is considered ENE(+) for cN
Definition of regional lymph node (N)	Classification of ENE: Pathologically detected ENE is classified as either ENE_{mi} (<2 mm) or ENE_{ma} (>2 mm) for data collection purposes only, but both are considered ENE(+) for definition of pN

Adapted from Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In: Amin MB, et al, eds. *AJCC cancer staging manual*. 8th ed. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

TABLE C ICD-O-3 Topography Codes

Code	Description
C00.0	External upper lip (exclude vermilion border)
C00.1	External lower lip (exclude vermilion border)
C00.2	External lip NOS (exclude vermilion border)
C00.3	Mucosa of upper lip
C00.4	Mucosa of lower lip
C00.5	Mucosa of lip, NOS
C00.6	Commissure of lip
C00.8	Overlapping lesion of lip
C00.9	Lip, NOS
C02.0	Dorsal surface of tongue, NOS
C02.1	Border of tongue
C02.2	Ventral surface of tongue, NOS
C02.3	Anterior two-thirds of tongue, NOS
C02.8	Overlapping lesion of tongue
C02.9	Tongue, NOS
C03.0	Upper gum
C03.1	Lower gum
C03.9	Gum, NOS
C04.0	Anterior floor of mouth
C04.1	Lateral floor of mouth
C04.8	Overlapping lesion of floor of mouth
C04.9	Floor of mouth, NOS
C05.0	Hard palate
C05.8	Overlapping lesion of palate
C05.9	Palate, NOS
C06.0	Cheek mucosa
C06.1	Vestibule of mouth
C06.2	Retromolar area

Adapted from Ridge JA, Lydiatt WM, Patel SG, et al. Lip and oral cavity. In: Amin MB, et al, eds. *AJCC cancer staging manual*. 8th ed. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

SECTION B

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33. Early HPV-Related Base of Tongue Cancer, 649

34. Advanced HPV-Related Oropharynx Cancer, 677

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36. Soft Palate Cancer, 761

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8052	Papillary squamous cell carcinoma
8074	Spindle cell squamous carcinoma
8051	Verrucous carcinoma
8082	Lymphoepithelial carcinoma (non-nasopharyngeal)

From Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *World Health Organization classification of tumours: pathology and genetics of head and neck tumours*. Lyon: IARC; 2005.

TABLE C HPV-Negative Oropharyngeal and Hypopharyngeal Cancer: ICD-0-3 Topography Codes

Code	Description
C12.9	Pyriform sinus
C13.0	Postcricoid region
C13.1	Hypopharyngeal aspect of aryepiglottic fold
C13.2	Posterior wall of hypopharynx
C13.8	Overlapping lesion of hypopharynx
C13.9	Hypopharynx, NOS
C01.9	Base of tongue, NOS
C02.4	Lingual tonsil
C05.1	Soft palate, NOS
C05.2	Uvula
C09.0	Tonsillar fossa
C09.1	Tonsillar pillar
C09.8	Overlapping lesion of tonsil
C09.9	Tonsil, NOS
C10.0	Vallecula
C10.2	Lateral wall of oropharynx
C10.3	Posterior pharyngeal wall
C10.8	Overlapping lesion of oropharynx
C10.9	Oropharynx, NOS
C11.1	Pharyngeal tonsils

From Lydiatt WM, Ridge JA, Patel SG, et al. Oropharynx (p16-negative) and hypopharynx. In Amin MB, et al., eds. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017. http://dx.doi.org/10.1007/978-3-319-40618-3_10.

TABLE D WHO Classification of HPV-Mediated Tumors

Code	Description
8070	Squamous cell carcinoma, nonkeratinizing
8070	HPV-mediated squamous carcinoma
8070	P16+ squamous carcinoma
8083	Basaloid squamous carcinoma

From Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *World Health Organization classification of tumours pathology and genetics of head and neck tumours*. Lyon: IARC; 2005.

TABLE E HPV-Mediated (P16+) Oropharyngeal Cancer: ICD-0-3 Topography Codes

Code	Description
C01.9	Base of tongue, NOS
C02.4	Lingual tonsil
C05.1	Soft palate, NOS
C05.2	Uvula
C09.0	Tonsillar fossa
C09.1	Tonsillar pillar
C09.8	Overlapping lesion of tonsil
C09.9	Tonsil, NOS
C10.0	Vallecula
C10.2	Lateral wall of oropharynx
C10.3	Posterior pharyngeal wall
C10.8	Overlapping lesion of oropharynx
C10.9	Oropharynx, NOS
C11.1	Pharyngeal tonsils

From O'Sullivan B, Lydiatt WM, Haughey BH, et al. HPV-mediated (p16+) oropharyngeal cancer. In Amin MB et al. (eds). *AJCC cancer staging manual,* 8th edition, New York: Springer; 2017. http://dx.doi.org/10.1007/978-3-319-40618-3.

SECTION C

Larynx

37. Early Supraglottic Larynx Cancer, 777

38. Advanced Supraglottic Larynx Cancer, 785

39. Early Glottic Larynx Cancer, 799

40. Advanced Larynx Cancer, 818

41. Subglottic Larynx Cancer, 830

TABLE A **ICD-0-3 Topography Codes**

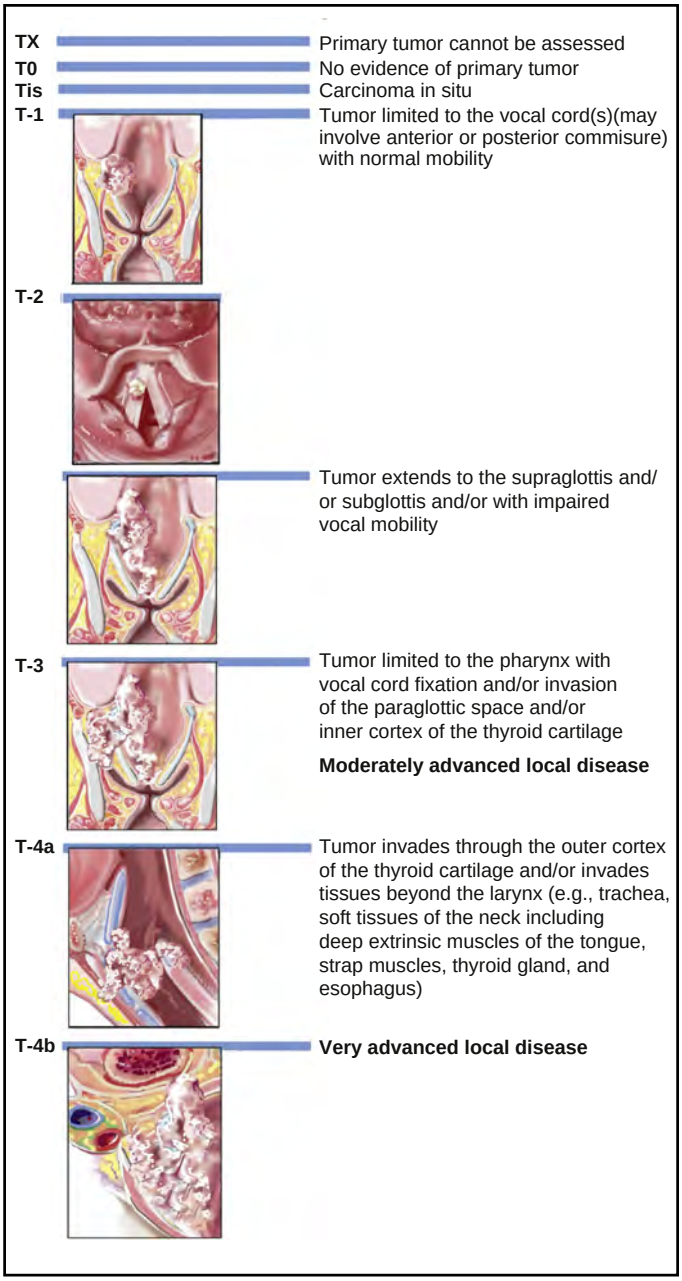
Code	Description
C10.1	Anterior (lingual) surface of epiglottis
C32.0	Glottis
C32.1	Supraglottis (laryngeal surface)
C32.2	Subglottis
C32.8	Overlapping lesion of larynx*
C32.9	Larynx, NOS*

*Stage by location of tumor bulk or epicenter.
Source: International statistical classification of diseases and related health problems, 10th revision (ICD-10).

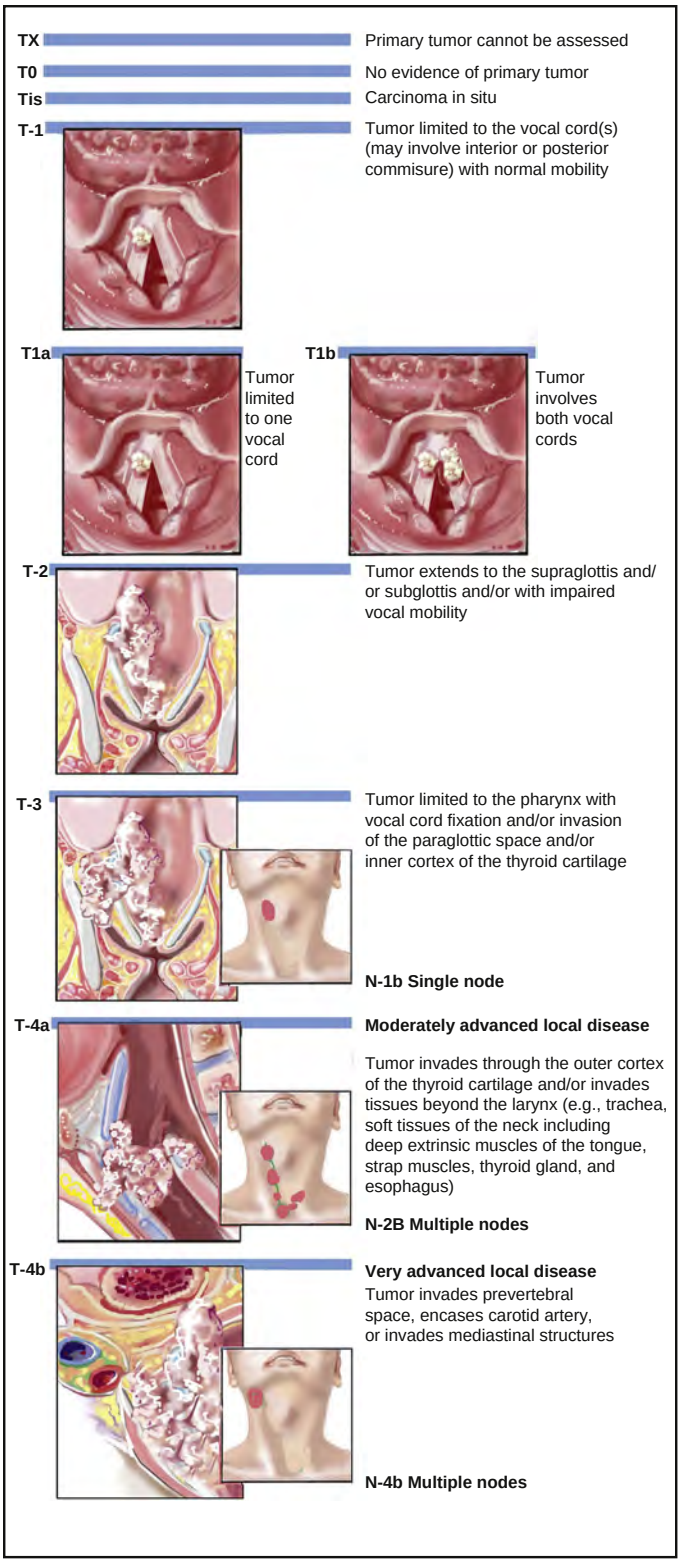
TABLE B **WHO Classification of Tumors**

Code	Description
8070	Squamous cell carcinoma
8075	Acantholytic squamous cell carcinoma
8560	Adenosquamous carcinoma
8083	Basaloid squamous cell carcinoma
8052	Papillary squamous cell carcinoma
8074	Spindle cell squamous carcinoma
8051	Verrucous carcinoma
8082	Lymphoepithelial carcinoma
8430	Mucoepidermoid carcinoma
8200	Adenoid cystic carcinoma
8240	Typical carcinoid
8249	Atypical carcinoid
8041	Small cell carcinoma, neuroendocrine type
8045	Combined small cell carcinoma, neuroendocrine type

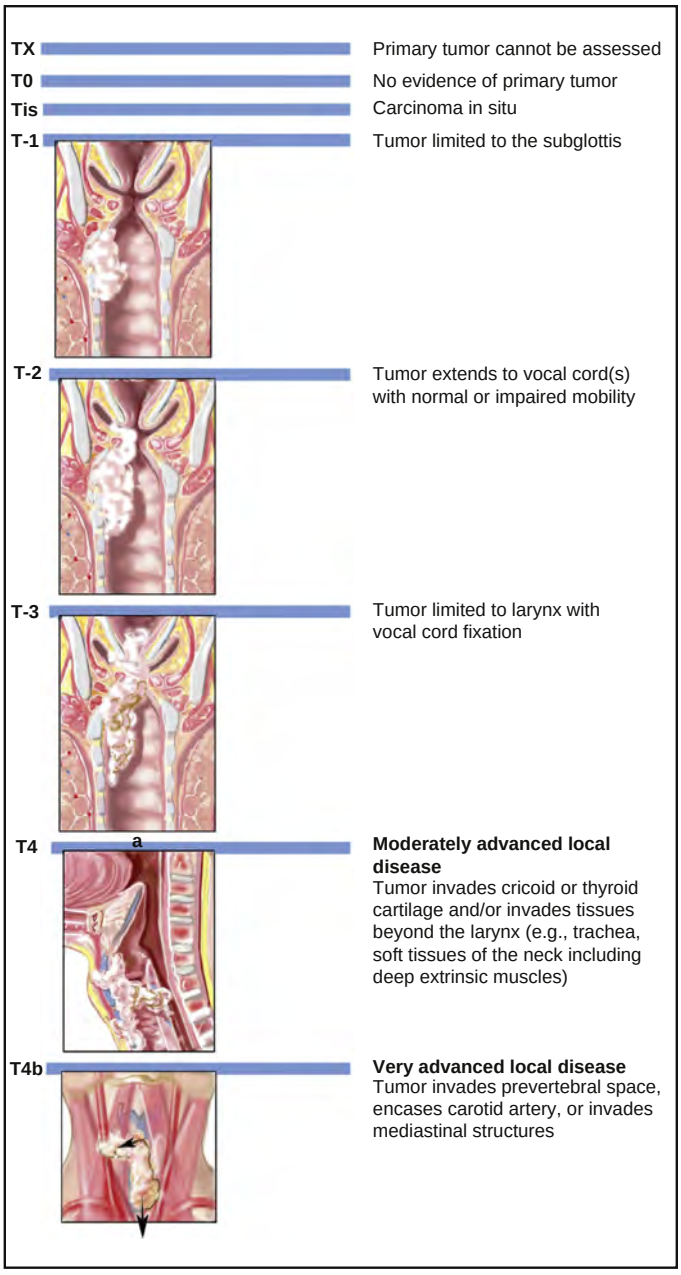
From Barnes L, Eveson JW, Reichart P, Sidransky D, eds. *World Health Organization classification of tumours: pathology and genetics of head and neck tumours.* Lyon: IARC; 2005.



• **Fig. C-1** Locoregional spread of supraglottic cancer arranged by stage.



• **Fig. C-2** Locoregional spread of glottic cancer arranged by stage.



• **Fig. C-3** Locoregional spread of subglottic cancer arranged by stage.

SECTION D

Other

42. Major Salivary Gland Cancer, 850

43. Melanoma, 876

44. Aggressive Non-melanoma Skin Cancer, 892

45. Osteoradionecrosis, 911

Mucosal Melanoma

TABLE A ICD-0-3 Topography Codes

Code	Description	Code	Description
C00.0	External upper lip	C06.9	Mouth, NOS
C00.1	External lower lip	C09.0	Tonsillar fossa
C00.2	External lip, NOS	C09.1	Tonsillar pillar
C00.3	Mucosa of upper lip	C09.8	Overlapping lesion of tonsil
C00.4	Mucosa of lower lip	C09.9	Tonsil, NOS
C00.5	Mucosa of lip, NOS	C10.0	Vallecula
C00.6	Commissure of lip	C10.1	Anterior (lingual) surface of epiglottis
C00.8	Overlapping lesion of lip	C10.2	Lateral wall of oropharynx
C00.9	Lip, NOS	C10.9	Oropharynx, NOS
C01.9	Base of tongue, NOS	C11.0	Superior wall of nasopharynx
C02.0	Dorsal surface of tongue, NOS	C11.1	Posterior wall of nasopharynx
C02.1	Border of tongue	C11.2	Lateral wall of nasopharynx
C02.2	Ventral surface of tongue, NOS	C11.3	Anterior wall of nasopharynx
C02.3	Anterior two-thirds of tongue, NOS	C11.8	Overlapping lesion of nasopharynx
C02.4	Lingual tonsil	C11.9	Nasopharynx, NOS
C02.8	Overlapping lesion of tongue	C12.9	Pyriform sinus
C02.9	Tongue, NOS	C13.0	Postcricoid region
C03.0	Upper gum	C13.1	Hypopharyngeal aspect of aryepiglottic fold
C03.1	Lower gum	C13.2	Posterior wall of hypopharynx
C03.9	Gum, NOS	C13.8	Overlapping lesion of hypopharynx
C04.0	Anterior floor of mouth	C13.9	Hypopharynx, NOS
C04.1	Lateral floor of mouth	C14.0	Pharynx, NOS
C04.8	Overlapping lesion of floor and mouth	C14.2	Waldeyer's ring
C04.9	Floor of mouth, NOS	C14.8	Nasal cavity
C05.0	Hard palate	C31.0	Maxillary sinus
C05.1	Soft palate, NOS	C31.1	Ethmoid sinus
C05.2	Uvula	C32.0	Glottis
C05.8	Overlapping lesion of palate	C32.1	Supraglottis (laryngeal surface)
C05.9	Palate, NOS	C32.2	Subglottis
C06.0	Cheek mucosa	C32.8	Overlapping lesion of larynx
C06.1	Vestibule of mouth	C32.9	Larynx, NOS
C06.2	Retromolar area		
C06.8	Overlapping lesion of other and unspecified parts of mouth		

To access the AJCC cancer staging forms, please visit www.cancerstaging.org.
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From Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE B **WHO Classification of Tumors**

Code	Description
8720	Melanoma, NOS
8722	Balloon cell melanoma
8770	Mixed epithelioid and spindle cell melanoma
8771	Epithelioid cell melanoma
8772	Spindle cell melanoma

From Barnes L, Eveson JW, Reichart P, eds. *World Health Organization classification of tumours pathology and genetics of head and neck tumours*. Lyon: IARC; 2005.

TABLE C **Definitions of American Joint Committee on Cancer TNM Staging**

Category	Criteria
Primary Tumor (T)	
T3	Tumors limited to the mucosa and immediately underlying soft tissue, regardless of thickness or greatest dimension; for example, polypoid nasal disease, pigmented or nonpigmented lesions of the oral cavity, pharynx, or larynx
T4	Moderately advanced or very advanced
T4a	Moderately advanced disease Tumor involving deep soft tissue, cartilage, bone, or overlying skin
T4b	Very advanced disease Tumor involving brain, dura, skull base, lower cranial nerves (IX, I, XI, XII), masticator space, carotid artery, prevertebral space, or mediastinal structures
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastases
N1	Regional lymph node metastases present
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis present

From Lydiatt WM, Brandwein-Gensler M, Kraus DH, et al. Mucosal melanoma of the head and neck. In Amin MB, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

Cutaneous Squamous Cell Carcinoma of the Head and Neck

TABLE D **ICD-0-3 Topography Codes**

Code	Description
C00.0	Vermilion border of upper lip (excludes external upper lip)
C00.1	Vermilion border of lower lip (excludes external lower lip)
C00.2	Vermilion border of lip, NOS (excludes external lip, NOS)
C44.0	Skin of lip, NOS
C44.2	External ear
C44.3	Skin of other and unspecified parts of the face
C44.4	Skin of scalp and neck
C44.8	Overlapping lesions of skin

To access the AJCC cancer staging forms, please visit www.cancerstaging.org. ©American Joint Committee on Cancer 2017.

From Califano JA, Lydiatt WM, Nehal KS, et al. Cutaneous squamous cell carcinoma of the head and neck. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE E **WHO Classification of Tumors**

Code	Description
8070	Squamous cell carcinoma
8211	Tubular carcinoma
8407	Microcystic adnexal carcinoma
8409	Porocarcinoma
8403	Spiradenocarcinoma
8940	Malignant mixed tumor
8400	Hiradenocarcinoma
8480	Mucinous carcinoma
8408	Digital papillary carcinoma
8200	Adenoid cystic carcinoma
8401	Apocrine carcinoma
8540	Paget disease of breast
8542	Extramammary Paget disease
8110	Pilomatriceal carcinoma
8103	Proliferating trichilemmal tumor
8410	Sebaceous carcinoma
8982	Myoepithelial carcinoma

From LeBoit PE, Burg G, Weedon D, eds. *World Health Organization classification of tumours, pathology and genetics of skin tumours*. Lyon: IARC Press; 2006.

TABLE F American Joint Committee on Cancer TNM Staging

Category	Criteria
Primary Tumor (T)	
TX	Primary tumor cannot be identified
Tis	Carcinoma in situ
T1	Tumor <2 cm in greatest dimension
T2	Tumor 2 cm or larger, but <4 cm in greatest dimension
T3	Tumor 4 cm or larger in maximum dimension or minor bone erosion or perineural invasion or deep invasion*
T4	Tumor with gross cortical bone/marrow, skull base invasion and/or skull base foramen invasion
T4a	Tumor with gross cortical bone/marrow invasion
T4b	Tumor with skull base invasion and/or skull base foramen involvement
	*Deep invasion is defined as invasion beyond the subcutaneous fat or >6 mm (as measured from the granular layer of adjacent normal epidermis to the base of the tumor); perineural invasion for T3 classification is defined as tumor cells within the nerve sheath of a nerve lying deeper than the dermis or measuring 0.1 mm or larger in caliber, or presenting with clinical or radiographic involvement of named nerves without skull base invasion or transgression
Regional Lymph Nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–); *or* in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–); *or* metastasis in any node(s) and clinically overt ENE [ENE(+)]
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) and ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L). Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+)
Pathological Nodes (pN)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node, 3 cm or smaller in greatest dimension and ENE(+); *or* >3 cm but not >6 cm in greatet dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–); *or* in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension, ENE(–)
N2a	Metastasis in a single ipsilateral or contralateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)

TABLE F American Joint Committee on Cancer TNM Staging—cont'd

Category	Criteria
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–); *or* in a single ipsilateral node >3 cm in greatest dimension and ENE(+); or multiple ipsilateral, contralateral, or bilateral nodes, any with ENE(+)
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)
N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral contralateral, or bilateral nodes, any with ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid *(U)* or below the lower border of the cricoid *(L)*. Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+)

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the Stage Group is…
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1	N1	M0	III
T2	N1	M0	III
T3	N1	M0	III
T1	N2	M0	IV
T2	N2	M0	IV
T3	N2	M0	IV
Any T	N3	M0	IV
T4	Any N	M0	IV
Any T	Any N	M1	IV

From Califano JA, Lydiatt WM, Nehal KS, et al. Cutaneous squamous cell carcinoma of the head and neck. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

Cutaneous Melanoma

TABLE G Summary of Changes to the American Joint Committee on Cancer Staging Manual (8th edition)

Change	Details of Change
Definition of Primary Tumor (T)	All principal T-category tumor thickness ranges are maintained, but **T1** now is subcategorized by tumor thickness states at 0.8-mm threshold.
Definition of Primary Tumor (T)	Tumor mitotic rate was removed as a staging criterion for **T1** tumors, but remains an overall important prognostic factor that should continue to be recorded for all patients with T1 to T4 primary cutaneous melanoma. • **T1a** melanomas now are defined as nonulcerated and <0.8 mm thick. • **T1b** melanomas now are defined as 0.8 to 1.0 mm in thickness regardless of ulceration status *or* ulcerated melanomas <0.8 mm thick.
Definition of Primary Tumor (T)	**T0** definition has been clarified. **T0** should be used if there is no evidence of a primary tumor (e.g., in a patient who presents with axillary metastasis and no known primary tumor). Staging may be based on clinical suspicion of a primary cutaneous melanoma, with the tumor categorized as **T9** (**Tis,** not **T0,** designates melanoma in situ.)
Definition of Primary Tumor (T)	Tumor thickness measurements now are recorded to the nearest 0.1 mm, not the nearest 0.01 mm, because of the impracticality and imprecision of measurements, particularly for tumors >1 mm thick. Tumors ≤1 mm may be measured to the nearest 0.01 mm if practical, but should be reported rounded to the nearest 0.1 mm (e.g., melanomas measured to be in the range of 0.75 to 8.4 mm are reported as 0.8 mm thick; hence **T1b**).
Definition of Primary Tumor (T)	**Tis** (melanoma in situ). **T0** (no evidence of a primary tumor) and **TX** (tumor thickness cannot be determined) may now be used as the T category designation for stage groupings.
Definition of Regional Lymph Node (N)	Number of tumor-involved regional lymph nodes is maintained.
Definition of Regional Lymph Node (N)	Previously empirically defined "microscopic" and "macroscopic" descriptors are redefined as "clinically occult" (i.e., clinical stage I/II with nodal metastasis determined at sentinel node biopsy) and "clinically detected" regional node disease (clinical stage III), respectively.
Definition of Regional Lymph Node (N)	Sentinel node tumor burden is considered a regional disease prognostic factor that should be collected for all patients with positive sentinel nodes, but it is not used to determine N-category groupings.
Definition of Regional Lymph Node (N)	Non-nodal regional disease (e.g., microsatellites, satellites, and in-transit cutaneous and/or subcutaneous metastases) is more formally stratified by **N** category according to the number of tumor-involved lymph nodes. • Presence of microsatellites, satellites, or in-transit metastases is now categorized as **N1c, N2c,** or **N3c** based on the number of tumor-involved regional lymph nodes, if any.
Definition of Regional Lymph Node (N)	"Gross" extranodal extension no longer is used as an N-category criterion, but the presence of "matted nodes" is retained.
Definition of Distant Metastasis (M)	**M1** is now defined by both anatomic site of distant metastatic disease and serum lactate dehydrogenase (LDH) value for all anatomic site subcategories.
Definition of Distant Metastasis (M)	Description of distant anatomic sites of disease are classified in **M** subcategories.
Definition of Distant Metastasis (M)	Descriptors were added to the **M1** subcategory designation that provide LDH status—designated as "0" for "not elevated" and "1" for "elevated" level—for all sites of distant disease (e.g., skin/soft tissue/nodal metastasis with elevated LDH is now **M1a(1)** not **M1c**).
Definition of Distant Metastasis (M)	New **M1d** designation was added to include distant metastasis to the central nervous system (CNS) with or without any other distant sites of disease; **M1c** no longer includes CNS metastasis.
Definition of Distant Metastasis (M)	Elevated LDH level no longer defines **M1c.**
AJCC Prognostic Stage Groups	No overall changes were made in T subcategories, but definitions of **T1a** and **T1b** were refined. In addition, although the stage group for cT1bN0 remains clinical stage IB, the stage group for pT1bN0 now is pathological stage IA.

TABLE G Summary of Changes to the American Joint Committee on Cancer Staging Manual (8th edition)—cont'd

Change	Details of Change
AJCC Prognostic Stage Groups	N category now comprises four stage groups rather than three, and these groups are based on multivariable models, including T-category elements (tumor thickness and ulceration) and N-category elements (number of tumor-involved nodes, satellites/in-transits/microsatellites), demonstrating a significant impact of primary tumor factors in assigning stage groups.
AJCC Prognostic Stage Groups	Clarification is provided that stage IV is not further stage-grouped (i.e., M1c is stage IV not stage IVC).

From Gershenwald J, Scolyer RA, Hess KR, et al. Melanoma of the skin. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE H ICD-0-3 Topography Codes

Code	Description
C44.0	Skin of lip, NOS
C44.1	Eyelid
C44.2	External ear
C44.3	Skin of other and unspecified parts of face
C44.4	Skin of scalp and neck
C44.5	Skin of trunk
C44.6	Skin of upper limb and shoulder
C44.7	Skin of lower limb and hip
C44.8	Overlapping lesion of skin
C44.9	Skin, NOS
C51.0	Labium majus
C51.1	Labium minus
C51.2	Clitoris
C51.8	Overlapping lesion of vulva
C51.9	Vulva, NOS
C60.0	Prepuce
C60.1	Glans penis
C60.2	Body of penis
C60.8	Overlapping lesion of penis
C60.9	Penis, NOS
C63.2	Scrotum, NOS

From Gershenwald J, Scolyer RA, Hess KR, et al. Melanoma of the skin. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE I American Joint Committee on Cancer TNM Staging

Category	Thickness	Ulceration status
Primary Tumor (T)		
TX, primary tumor thickness cannot be assessed (e.g., diagnosis by curettage)	Not applicable	Not applicable
T0, no evidence of primary tumor (e.g., unknown primary or completely repressed melanoma)	Not applicable	Not applicable
Tis (melanoma in situ)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8–1.0 mm	With or without ulceration
T2	>1.0–2.0 mm	Unknown or unspecified
T2a	>1.0–2.0 mm	Without ulceration
T2b	>1.0–2.0 mm	With ulceration
T3	>2.0–4.0 mm	Unknown or unspecified
T3a	>2.0–4.0 mm	Without ulceration
T3b	>2.0–4.0 mm	With ulceration
T4	>4.0 mm	Unknown or unspecified
T4a	>4.0 mm	Without ulceration
T4b	>4.0 mm	With ulceration

Regional Lymph Nodes (N)

	Extent of Regional Lymph Node and/or Lymphatic Metastasis	
Category	Number of Tumor-Involved Regional Lymph Nodes	Presence of In-transit, Satellite, and/or Microsatellite Metastases
XX	Regional nodes not assessed (e.g., SLN biopsy not performed, regional nodes previously removed for another reason) Exception: pathological N category is not required for T1 melanomas, use cN.	No
N0	No regional metastases detected	No
N1	One tumor-involved node or in-transit, satellite, and/or microsatellite metastases with no tumor-involved nodes.	
N1a	One clinically occult (i.e., detected by SLN biopsy)	No
N1b	One clinically detected	No
N1c	No regional lymph node disease	Yes
N2	Two or three tumor-involved nodes or in-transit, satellite, and/or microsatellite metastases with one tumor-involved node	
N2a	Two or three clinically occult (i.e., detected by SLN biopsy.)	No
N2b	Two or three, at least one of which was clinically detected	No
N2c	One clinically occult or clinically detected	Yes

TABLE I **American Joint Committee on Cancer TNM Staging—cont'd**

Regional Lymph Nodes (N)

	Extent of Regional Lymph Node and/or Lymphatic Metastasis	
Category	**Number of Tumor-Involved Regional Lymph Nodes**	**Presence of In-transit, Satellite, and/or Microsatellite Metastases**
N3	Four or more tumor-involved modes or in-transit, satellite, and/or microsatellite metastases with two or more tumor-involved nodes, or any number of matted nodes without or with in-transit, satellite, and/or microsatellite metastases	
N3a	Four or more clinically occult (i.e., detected by SLN biopsy)	No
N3b	Four or more, at least one of which was clinically detected, or presence of any number of matted nodes	No
N3c	Two or more clinically occult or clinically detected and/or presence of any number of matted nodes	Yes

Distant Metastasis (M)

	Criteria	
Category	**Anatomic Site**	**LDH Level**
M0	No evidence of distant metastasis	Not applicable
M1	Evidence of distant metastasis	See below
M1a	Distant metastasis to skin, soft tissue including muscle, and/or nonregional lymph node	Not recorded or unspecified
M1a(0)		Not elevated
M1a(1)		Elevated
M1b	Distant metastasis to lung with or without M1a sites of disease	Not recorded or unspecified
M1b(0)		Not elevated
M1b(1)		Elevated
M1c	Distant metastasis to non-CNS visceral sites with or without M1a or M1b sites of disease	Not recorded or unspecified
M1c(0)		Not elevated
M1c(1)		Elevated
M1d	Distant metastasis to CNS with or without M1a, M1b, or M1c sites of disease	Not recorded or unspecified
M1d(0)		Normal
M1d(1)		Elevated

Suffixes for M category: (0) LDH not elevated, (1) LDH elevated.
No suffix is used if LDH is not recorded or is unspecified.

From Gershenwald J, Scolyer RA, Hess KR, et al. Melanoma of the skin. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE J American Joint Committee on Cancer Prognostic Stage Groups

Clinical (cTNM)

Clinical staging includes microstaging of the primary melanoma and clinical/radiologic/biopsy evaluation for metastases. By convention, clinical staging should be used after biopsy of the primary melanoma, with clinical assessment for regional and distant metastases. Note that pathological assessment of the primary melanoma is used for both clinical and pathological classification. Diagnostic biopsies to evaluate possible regional and/or distant metastasis also are included. Note there is only one stage group for clinical stage III melanoma.

When T is…	And N is…	And M is…	Then the Clinical Stage Group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IB
T2a	N0	M0	IB
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
Any T, Tis	≥N1	M0	III
Any T	Any N	M1	IV

Pathological (pTNM)

Pathological staging includes microstaging of the primary melanoma, including any additional staging information from the wide-excision (surgical) specimen that constitutes primary tumor surgical treatment and pathological information about the regional lymph nodes after SLN biopsy or therapeutic lymph node dissection for clinically evident regional lymph node disease.

When T is…	And N is…	And M is…	Then the Clinical Stage Group is…
Tis	N0	M0	0
T1a	N0	M0	IA
T1b	N0	M0	IA
T2a	N0	M0	IA
T2b	N0	M0	IIA
T3a	N0	M0	IIA
T3b	N0	M0	IIB
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T0	N1b, N1c	M0	IIIB
T0	N2b, N2c, N3b or N3c	M0	IIIC
T1a,b/T2a	N1a OR N2a	M0	IIIA
T1a,b/T2a	N1b/c or N2b	M0	IIIB
T2b/T3a	N1a-N2b	M0	IIIB
T1a/T3a	N2c or N3a/b/c	M0	IIIC
T3b/T4a	Any N ≥N1	M0	IIIC
T4b	N1a-N2c	M0	IIIC

TABLE J **American Joint Committee on Cancer Prognostic Stage Groups—cont'd**

When T is…	And N is…	And M is…	Then the Clinical Stage Group is…
T4b	N3a/b/c	M0	IIID
Any T, Tis	Any N	M1	IV

Pathological Stage 0 (melanoma in situ) and T1 do not require pathological evaluation of lymph nodes to complete pathological staging.

From Gershenwald J, Scolyer RA, Hess KR, et al. Melanoma of the skin. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE K **WHO Classification of Tumors**

Code	Description
8720	Melanoma
8720	Nevoid melanoma
8720	Melanoma of childhood
8721	Nodular melanoma
8742	Lentigo maligna melanoma
8743	Superficial spreading melanoma
8744	Acral lentiginous melanoma
8745	Desmoplastic melanoma
8761	Melanoma arising in a giant congenital nevus
8780	Melanoma arising from a blue nevus

From LeBoit PE, Burg G, Weedon D, eds. *World Health Organization classification of tumours, pathology and genetics of skin tumours.* Lyon: IARC Press; 2006.

Major Salivary Glands

TABLE L **ICD-0-3 Typography Codes**

Code	Description
C07.9	Parotid gland
C08.0	Submandibular gland
C08.1	Sublingual gland
C08.8	Overlapping lesion of major salivary glands
C08.9	Major salivary gland, NOS

From Lydiatt WM, Mukherji SK, O'Sullivan BO, et al. Major salivary glands. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE M **WHO Classification of Tumors**

Code	Description
8550	Acinic cell carcinoma
8430	Mucoepidermoid carcinoma
8200	Adenoid cystic carcinoma
8525	Polymorphous adenocarcinoma
8562	Epithelial-myoepithelial carcinoma
8310	Clear cell carcinoma
8147	Basal cell adenocarcinoma
8410	Sebaceous carcinoma
8140	Adenocarcinoma
8500	Salivary duct carcinoma
8982	Myoepithelial carcinoma
8941	Carcinoma ex pleomorphic adenoma
8980	Carcinosarcoma
8041	Small cell carcinoma
8012	Large cell carcinoma
8082	Lymphoepithelial carcinoma
8070	Squamous cell carcinoma
8290	Oncocytic carcinoma
8974	Sialoblastoma

From Barnes L, Eveson JW, Reichart P, eds. *World Health Organization classification of tumours. pathology and genetics of skin tumours*. Lyon: IARC Press; 2005.

TABLE N American Joint Committee on Cancer TNM Staging

Category	T Criteria
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
T1	Tumor 2 cm or smaller in greatest dimension without extraparenchymal extension*
T2	Tumor >2 cm but not >4 cm in greatest dimension without extraparenchymal extension*
T3	Tumor >4 cm and/or tumor having extraparenchymal extension*
T4	Moderately advanced or very advanced disease
T4a	Moderately advanced disease. Tumor invades skin, mandible, ear canal, and/or facial nerve
T4b	Very advanced disease. Tumor invades skull base and/or pterygoid plates and/or encases carotid artery
	*Extraparenchymal extension is clinical or macroscopic evidence of invasion of soft tissues. Microscopic evidence alone does not constitute extraparenchymal extension for classification purposes
Regional Lymph Nodes: Clinical (cN)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–); *or* in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–); *or* metastasis in any node(s) with clinically overt ENE(+)
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)
N3b	Metastasis in any node(s) with clinically overt ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoids *(U)* or below the lower border of the cricoids *(L)*. Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+)
Pathological Nodes (pN)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(–)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* >3 cm but not >6 cm in greatest dimension and ENE(–); *or* metastases in multiple ipsilateral lymph nodes, none >6 cm in greatest dimension and ENE(–)
N2a	Metastasis in a single ipsilateral or contralateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node >3 cm but not >6 cm in greatest dimension and ENE(–)
N2b	Metastasis in multiple ipsilateral nodes, none >6 cm in greatest dimension and ENE(–)
N2c	Metastasis in bilateral or contralateral lymph nodes, none >6 cm in greatest dimension and ENE(–)

TABLE N American Joint Committee on Cancer TNM Staging—cont'd

Category	T Criteria
N3	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–); *or* in a single ipsilateral node >3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any with ENE(+)
N3a	Metastasis in a lymph node >6 cm in greatest dimension and ENE(–)
N3b	Metastasis in a single ipsilateral node >3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any with ENE(+)
	Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L)Similarly, clinical and pathological ENE should be recorded as ENE(–) or ENE(+)
Distant Metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis

From Lydiatt WM, Mukherji SK, O'Sullivan BO, et al. Major salivary glands. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

TABLE O American Joint Committee on Cancer Prognostic Stage Groups

When T is…	And N is…	And M is…	Then the Stage Group is…
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T0, T1, T2, T3	N1	M0	III
T4a	N0, N1	M0	IVA
T0, T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

From Lydiatt WM, Mukherji S, O'Sullivan BO, et al. Major salivary glands. In Amin MB, Edge SB, Greene FL, et al. *AJCC cancer staging manual,* 8th ed. New York: Springer; 2017.

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