Handbook of Supportive and Palliative Radiation Oncology

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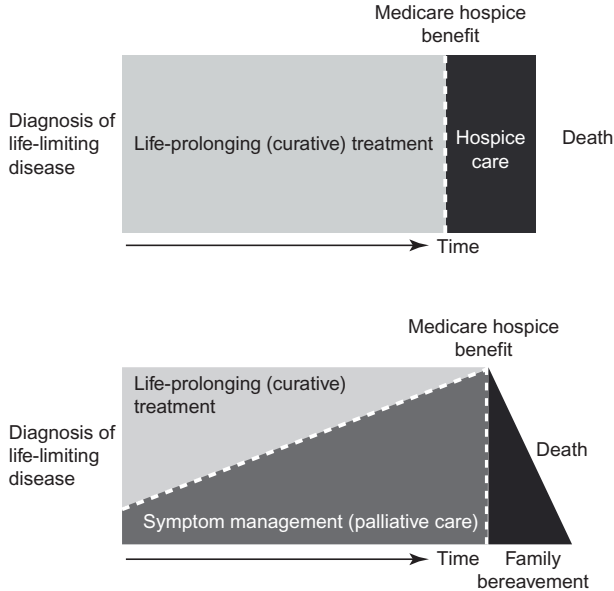
Preface

One common misconception about palliative care is that it is synonymous with hospice. While the palliative care field originated with hospice, it has since evolved to include care beyond the end of life and indeed the modern concept of palliative care endorsed by ASCO and other organizations is the early integration of palliative care into oncology care.



Perhaps, one reason why palliative care is so alluring is because it brings us back to the fundamentals and for many of us, our motivation for pursuing a career in medicine in the first place—*to relieve the pain and suffering of others*. We are reminded to be fully present to the "person" in front of us and to acknowledge their experience of illness as multidimensional affecting their physical, mental, emotional, and spiritual well-being.

Radiotherapy is very effective for symptom palliation and has played a key role in palliative oncology care for decades; however, palliative care education in radiation oncology training has been limited to date. As such, we hope this handbook will serve as a convenient, efficient, and valuable

resource to radiation oncology residents, fellows, and experienced practitioners. Moreover, this book can be used as a practical guide for palliative care professionals who are interested in improving their understanding of palliative radiation oncology.

We are pleased to share with you the first edition of the *Handbook of Supportive and Palliative Radiation Oncology*, which is divided into three sections. The first section of the handbook provides an overview of palliative oncology care. The second section is organized by symptoms and is designed to serve as a practical guide to manage symptoms patients initially present with, develop while "on treatment," and/or develop following the completion of radiation therapy. The third section is organized by disease site and provides concrete recommendations for managing the most common palliative radiation clinical issues encountered by radiation oncologists, including head and neck, gastrointestinal, and gynecological malignancies among others.

We would like to acknowledge the readers for their interest in learning more about palliative care and their openness to further refine their clinical skills to improve the quality of life of patients and their families. We would like to thank the authors of each chapter for their commitment to sharing their time and expertise in palliative radiation oncology. This handbook would not have been possible without them. Finally, we would like to thank our patients and their families who allow us to travel with them on their cancer journey and whose courage and compassion continue to inspire us each day.

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Chapter 1

General Approach to Palliative Care and Palliative Radiation Oncology

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Chapter Outline

Introduction 3
Life Expectancy and Prognostication 4
Religion and Spirituality 4
Relief of Pain and Suffering 8
Palliative Radiation Therapy 8
Efficacy of Palliative Radiation Therapy 10
Emerging Technologies 12
Radiation Therapy Planning and Delivery 13
Side Effects of Radiation Therapy 13
Guidelines and Quality Measures 14
Bone Metastasis 14
End-of-Life Radiation Therapy 14
Conclusion 15
List of Abbreviations 16
References 16

INTRODUCTION

The burden of cancer continues to increase in the United States and globally, with an estimated 14.1 million cancer cases worldwide in 2012 that is projected to increase to 19.3 million cases by 2025. In 2012, there were 8.2 million cancer deaths and 32.6 million people living with cancer [1]. Thus, the need for good palliative care (PC) is also increasing globally.

Ideally, PC is a multi- and interdisciplinary effort. Emerging in the PC world is the notion that there are two fundamental categories of PC. The first is generalized PC knowledge that every person who provides health care to patients with cancer should have. The second category is a more specialized skill set that caregivers who focus their time in PC should have [2]. This is partly in recognition of the shortage of PC specialists worldwide [2–4].

Handbook of Supportive and Palliative Radiation Oncology.

The function of PC is to reduce pain and suffering, allow discussions of goals of care, facilitate death with dignity, promote quality-of-life, and support patients, their families, and their caregivers. The assessment includes pain and symptom assessment as well as an assessment of the social and spiritual context. Patients whose spirituality is supported by the medical team have experienced better outcomes and quality of life [5–7]. After a complete assessment, prognostication about the illness trajectory, the expected timelines and maximizing the goals that are important to the patient come into play.

LIFE EXPECTANCY AND PROGNOSTICATION

Questions about life expectancy and the quality of that remaining life are extremely important to patients with metastatic cancer. Physicians and other health care providers often overestimate life expectancy, by as much as 3 months or more [8]. Accurate estimates of life expectancy are important to patients and physicians for many reasons. It helps set appropriate goals, avoid treatments that will have little or no benefit, and choose supportive care or treatments that will be effective within the remaining time.

From the literature on clinical prediction and prognostication, several themes emerge. Clinical prediction tends to overestimate survival, but those clinical estimates improve over time with repeated encounters. The strongest prognostic indicators are the patient's performance status, the presence of the symptom cluster known as the terminal syndrome (dyspnea, dysphagia, dry mouth, anorexia, and weight loss) and the presence of cognitive failure or confusion [9].

Many of the existing prognostic indicators are best near the EOL. A simple, easy to use and validated tool to predict life expectancy is very much needed. Several tools exist (Table 1.1) and have been studied in patients with advanced or terminal cancer. Each of these tools has limitations. Some are easier to perform and are more generalizable than others. The best use of these tools may be in deciding which patients may not live long enough to see the benefit of a particular treatment. This is particularly true for radiation therapy (RT) as symptom relief typically takes several days to a few weeks for effect. The exception to this is hemostasis, which can often be seen 24–48 hours after the first dose of radiation. Some have advocated chemotherapy delivery within the last month of life as a metric of overutilization of health care [24,25]. Similar metrics may follow for RT [26].

RELIGION AND SPIRITUALITY

Multiple studies have surveyed patients in various settings about their desire to have their health care team inquire about their spiritual or religious beliefs or pray with them. As the severity of illness increases, the proportion of patients who want their spiritual beliefs considered increases. Ninety-four percent of outpatients favor discussion of spirituality in the setting of grave illness [27]. Yet, in another series, 68% of inpatients said that no physician

TABLE 1.1 Tools to Help Assess Life Expectancy in Patients With Cancer

Tool	Factors	Comment
National Hospice Study (NHPCO) [10]	Karnofsky Performance Status (KPS)	Based on hospice patients
	Anorexia	If KPS ≥ 50 and none of 5 factors, median survival 6 months, with all 5, 6 weeks
	Weight Loss	
	Dyspnea	
	Dry mouth	
	Dysphagia	
Palliative Performance Scale (PPS) [11]	Ambulatory status	Correlated with survival
	Activity level	Applicable to cancer populations
	Disease status	
	Self-care	
	Intake	
	Consciousness	
Palliative Prognostic Index (PPI) [12,13]	KPS	Short-term survival of terminally ill cancer patients
	Dyspnea at rest	
	Oral intake	
	Edema	
	Delirium	
Palliative Prognostic Score (PaP) [14]	KPS	Valid for terminally ill or advanced cancer patients
	Anorexia, dyspnea	
	High total WBC	
	Low lymphocyte percent	
	Clinicians prediction of survival (weeks)	
Survival Prediction Score (SPS) [15]	Tumor details	Developed in a palliative radiation oncology setting
	KPS	
	Fatigue	
	Anorexia	
	Shortness of breath	

(*Continued*)

TABLE 1.1 (Continued)

Tool	Factors	Comment
Number of Risk Factors (NRF) [16]	KPS	Developed in a palliative radiation oncology setting
	Primary site	
	Metastasis	
Prognosis in Palliative Care Study [17,18] (PiPs)	KPS	Predicts 2 week and 2 month survival
	Mental test score	Prognostic with or without lab values
	Selected laboratory values	
	Selected symptoms	
	Primary site	
	Site of metastasis	
TEACHH [19]	Type of cancer	Developed in a palliative radiation oncology setting
	ECOGPS	
	Age	
	Chemotherapy (prior palliative)	
	Hospitalizations	
	Hepatic metastasis	
Recursive Partitioning Analysis [20]	KPS	Applies to brain metastasis patients only
	Extent of metastatic disease	
	Age	
Graded Prognostic Assessment [21]	KPS	Applies to brain metastasis patients only
	Extent of metastatic disease	Assessment criteria varies by primary site
	Age	
	Number of brain metastasis	
	Tumor subtype	

(*Continued*)

TABLE 1.1 (Continued)

Tool	Factors	Comment
Metastatic Spinal Cord Compression Index [22]	Age	Applies to patients with spinal cord compression only
	Gender	
	Primary site	
	Number of involved vertebrae	
	Other bone metastasis	
	Visceral metastasis	
	Interval to cord compression	
	Ambulatory status	
	Time to motor deficits	
Dutch Bone Metastasis Study Group [23]	KPS	Applies to bone metastasis patients only
	Primary tumor type	
	Visceral metastasis	

had ever assessed their spiritual or religious needs [28]. Many patients with advanced and life-threatening malignancies do not feel that their spiritual needs are met [29].

There are spiritual coping and methods that health care providers can use to deliver more holistic care to patients with cancer [30]. PC providers can also be taught how to incorporate a discussion of religion and spirituality into the care that they deliver and support those needs of the patients they care for. One commonly cited barrier noted by medical practitioners is the lack of training about how to provide such care [31].

Though many use the terms religion and spirituality interchangeably, there is a distinction between them. Spirituality takes into account one's view of transcendent and existential questions. Religion is a subset of spirituality surrounding a set of texts, practices, and beliefs shared by a particular community [32].

Though many physicians think religious figures and spiritual care experts should be the ones to discuss spirituality and religion, a national consensus conference determined that all members of the health care team are

responsible for addressing patient's spiritual issues in the context of the biopsychosocial framework. This consensus panel recommended that all patients be screened with a spiritual history and that any spiritual distress should be diagnosed and attended to using validated assessment tools [33].

One such validated tool is the FICA spiritual history tool [34]. This relatively simple tool uses the acronym FICA as follows: F represents faith, belief, or meaning; I stands for importance and influence; C for community; and A represents address or action in care. The key principles of this tool are to assess if a particular person has a set of beliefs or a particular faith that gives meaning to their lives. The next step is to assess how this faith or spirituality helps them cope with stress or how it affects their health care decisions. If they belong to a community of like-minded individuals, how does this community affect their lives? The last step is for the health care team to address these issues as part of the patient's care (Table 1.2).

RELIEF OF PAIN AND SUFFERING

Alleviating pain and suffering is a comprehensive multidisciplinary effort that uses a combination of counseling and educating, medications, and therapeutic interventions. This text aims to provide a comprehensive approach to symptom control in patients with advanced cancer [35,36].

PALLIATIVE RADIATION THERAPY

External beam RT is a key component of palliative cancer care. It is useful to treat pain due to osseous metastasis or local tumor invasion, bleeding, obstruction, dyspnea, or cough, and functional impairment due to brain metastasis or impingement of nerve roots or the spinal cord.

Key in the utilization of RT is the selection of the shortest fractionation regimen that is effective to maximize patient and caregiver convenience and minimize toxicity and cost [37–40].

Though many believe that longer courses of RT have a more durable effect, there is no data to support this belief. In the Radiation Therapy Oncology Group (RTOG), patient selection was designed to enroll only those with a long expected survival. There was no difference in efficacy between

TABLE 1.2 FICA Spiritual History Tool [34]

F	Faith, belief, or meaning	Do you have faith? What gives your life meaning?
I	Importance	Do these beliefs help you cope or make decisions?
C	Community	Do you belong to a community?
A	Address or action	Health care team incorporates this knowledge

8 Gy in a single fraction and 30 Gy in 10 fractions [37]. Similarly, in an analysis of those patients who survived more than 52 weeks in the Dutch Bone Metastasis Study, there was no difference in response rate, time to response, duration of response, and time to progression of pain (Table 1.3) [41]. Randomized trials have confirmed the equivalence of short courses of RT in lung cancer [42–44] and bladder cancer [45] and hypofractionated radiation regimens have been successfully used to treat gynecologic, gastrointestinal, and head and neck malignancies [39].

One reason commonly cited in favor of multifraction regimens for the treatment of bone metastasis over those with higher dose per fraction regimens is the potential for pathologic fracture. In the analysis of the RTOG 97-14, there was no difference in the long-term risk of pathologic fracture with the single fraction regimen of 8 Gy when compared to multifraction regimen of 30 Gy in 10 fractions [46]. The initial report of the Dutch Bone Metastasis Study did show higher rates of pathologic fracture in the single fraction arm, but a subsequent analysis that corrected for the percent of cortical destruction did not demonstrate a difference in fracture rates between treatment arms [47,48]. This was confirmed in a large meta-analysis [49]. For patients with >30% cortical destruction, prophy-lactic change there may be cases where higher doses of RT are appropriate, including bone metastases with a large soft tissue component, osteolytic lesions with impending pathologic fracture, or patients with a symptomatic pathologic fracture [50]. Longer courses in these settings may help promote remineralization and tumor control, which is important for those patients with a longer life expectancy. After pathologic fracture and surgical intervention, it may be difficult to assess efficacy of single-fraction treatment. Optimal fractionation remains controversial; a single trial of patients with neuropathic pain from bone

TABLE 1.3 Results From the Dutch Bone Metastasis Trial in Patients Surviving >1 Year

Metric	Single Fraction of 8 Gy	Multiple Fraction 24 Gy in 6 Fractions
Response rate	87%	85%
Complete response rate	62%	48%
Time to response	4 weeks	4 weeks
Duration of response (mean/median)	29 weeks/35 weeks	30/42 weeks
Progression of pain	55%	53%
Time to progression	17 weeks	18 weeks

TABLE 1.4 Palliative Radiation Fractionation Schemes for Bone Metastasis

Prognosis	Treatment Options
<1 month	• Supportive care • Single 8 Gy fraction RT
>1 month	• Supportive care • Single 8 Gy fraction RT • Higher dose for complicated bone metastasis
>1 month with risk of fracture	• Above options • Consideration of surgical stabilization

TABLE 1.5 Palliative Radiation Fractionation Schemes for Spinal Cord Compression

Prognosis	Treatment Options
<3 months	• Supportive care • 8 Gy × 1 • 8 Gy × 2 once weekly
>3 months Not a surgical candidate	• Supportive care • Short course RT 20–35 Gy in 5–14 fractions
>3 months	• Surgical decompression • Postoperative RT 30 Gy in 10 fractions

metastases did not show superiority for either 20 Gy in 5 fractions or a single 8 Gy fraction [51].

Various clinical scenarios are depicted in Tables 1.4–1.8 with appropriate treatment options based on a patient's life expectancy.

EFFICACY OF PALLIATIVE RADIATION THERAPY

RT provides time-efficient and effective pain relief with few side effects. It can be extremely useful in patients who are intolerant of opioid analgesics and can decrease the need for opioids thus reducing the systemic side effects of opioids. The vast majority of patients respond to RT, with 60–80% having a partial response and 25–30% experiencing a complete response to treatment. Radioresistant tumors, such as sarcoma or renal cell carcinoma, are palliated by RT and may benefit from fractionation schemes with higher dose per fraction [52].

TABLE 1.6 Palliative Radiation Fractionation Schemes for Brain Metastasis

Prognosis	Treatment Options
<1 month	• Supportive care • Steroids alone • Short course RT
>1 month Multiple brain metastasis All <4 cm	• Supportive care • SRS • Whole brain radiation therapy (WBRT) • WBRT +/− SRS
>1 month Multiple brain metastasis At least one >4 cm	• Supportive care • WBRT
>1 month Solitary brain metastasis	• Surgical resection • SRS • +/− WBRT

TABLE 1.7 Palliative Radiation Fractionation Schemes for Lung Tumors

Prognosis	Treatment Options
<1 month	• Supportive care • 8–10 Gy in a single fraction • 17 Gy in 2 fractions of 8.5 Gy, 1 week apart
>1 month	• Supportive care • 17 Gy in 2 fractions of 8.5 Gy, 1 week apart • 30–39 Gy at 3 Gy per fraction

TABLE 1.8 Palliative Radiation Fractionation Schemes for Bleeding

Prognosis	Treatment Options
<1 month	• Supportive care • 8–10 Gy in a single fraction • 17 Gy in 2 fractions of 8.5 Gy, 1 week apart
>1 month	• Supportive care • 17 Gy in 2 fractions of 8.5 Gy, 1 week apart • 20 Gy in 5 fractions

Pain relief is not immediate after the initiation of RT. Patients can experience some relief within a few days or a week after the completion of treatment but the full palliative may not be seen until 4–6 weeks after the completion of treatment. Patients who are not expected to live this long may be better palliated using pain medications or other interventions. Since pain relief is not immediate, and RT requires patient immobilization for 15–30 minutes for treatment delivery, adequate pain control prior to the initiation of therapy is important. A helpful guide to pain medication dosing has been described by the World Health Organization [53]. These regimens may include nonsteroidal antiinflammatory agents, narcotic analgesics, or adjuvant pain medicines such as corticosteroids, nerve-stabilizing medicines, or antidepressants.

The pain relief provided by RT is variable, but typically lasts several months or longer. In patients who experience progression of pain, retreatment can be considered. In the NCIC study of retreatment, the initial course of RT varied and included single-fraction and multifraction schedules with daily fraction sizes of 3–8 Gy [54]. Patients with persistent pain at 4 weeks were randomized to 8 Gy in a single fraction versus 20 Gy in five fractions. There was no difference at two months in the overall response to treatment, pathologic fracture, or development of spinal cord or cauda equina compression. Acute toxicities such as anorexia and diarrhea were less frequent in the single fraction arm [54].

RT palliates symptoms from tumors in the lung with varying frequencies. Hemoptysis is palliated 80–90% of the time, while more complex symptoms such as cough and dyspnea have lower rates of palliation, 60–90% of the time for cough and 40–60% of the time for dyspnea [55–60]. Symptoms from pelvic malignancies are palliated 60–94% of the time [61,62]. Palliative radiation to patients with rectal cancer can help avoid colostomy [63]. The efficacy of palliative radiation will also be addressed in the chapters that follow.

EMERGING TECHNOLOGIES

Several emerging technologies, such as stereotactic body radiation therapy (SBRT) are capable of delivering highly conformal high dose radiation to tumor sites while minimizing dose to adjacent normal tissues [64]. It requires fastidious attention to dose planning, patient setup, and localization and may be ideally suited for retreatment situations where the spinal cord has reached tolerance due to the initial definitive course of RT or a previous palliative course of treatment [65]. Treatment regimens for spine lesions include 30 Gy in 5 fractions, 27 Gy in 3 fractions, 40 Gy in 5 fractions, or 16–24 Gy in a single fraction [66–68]. Early results are promising and prospective, randomized data are likely to help define the best use of this technology [69]. Relatively little data exists on the long-term toxicity of very large single

doses and there may be a higher risk of long-term side effects than is typically seen with more established treatment approaches [70]. Spine radiosurgery is an area of active clinical investigation and the subject of a current randomized trial [71]. Routine use should be avoided until sufficient evidence justifies the substantive increase in cost relative to standard RT.

RADIATION THERAPY PLANNING AND DELIVERY

Patients with documented metastasis are referred for consultation with a radiation oncologist. All of the relevant clinical data and radiographic studies are reviewed and a history and physical are performed. Communication with the other oncologic and PC providers follows that evaluation as do orders for any additional diagnostic testing or procedures. If the multidisciplinary team determines that RT is the most appropriate palliative treatment for a patient, a simulation or radiation planning session is scheduled. At simulation the patient is positioned in a comfortable and reproducible position and a CT scan of the affected area that includes all of the organs at risk for dose calculations is obtained. Fluoroscopic simulation is an alternative to CT simulation.

Behind the scenes, a dedicated team of professionals works with the radiation oncologist to select the best means by which to deliver dose to the intended target and minimize the dose delivered to adjacent normal tissues. In the palliative setting, where patients often have difficulty with transfers or travel, the consultation, simulation, and initiation of single fraction therapy can be done in a single visit. Once the dosimetric analysis is complete, the physician and the physicist review the plan for accuracy. A verification simulation is performed prior to the delivery of dose to ensure that what was planned actually conforms to the patient setup on the treatment table. Portal images and/or CT verify that the setup is correct for the area being treated. Patients are in the treatment room for 15–20 minutes while the radiation is delivered. Treatment is generally without immediate side effects, other than the potential for discomfort on the treatment table or in the transfer to the treatment table. Generally, no special preparation or fasting is required. An antiemetic may be given prior to treatment if radiation-induced nausea is anticipated.

SIDE EFFECTS OF RADIATION THERAPY

Palliative RT is generally well tolerated with few acute or long-term side effects. The acute side effects are often predictable based on the region being treated. They are usually mild and manageable with conservative measures. Fatigue is the main systemic side effect; this fatigue is typically less than that associated with the disease or other treatment modalities. Local side effects include skin irritation, nausea, diarrhea, esophagitis, and mucositis. Side effects are related to both the daily dose of radiation and the total dose

delivered and can occur acutely, subacutely, or in the long term. Fewer acute side effects have been associated with single-fraction palliative radiation when compared to multifraction regimens [37,72]. A "pain flare" is a transient increase in bone pain that occurs around the first few fractions of radiation for bone metastasis. It is caused by tumor cell kill and has been reported in between 20% and 40% of patients [73]. This pain flare can be mitigated by the use of nonsteroidal or steroidal antiinflammatory medications.

Late effects are rare and occur several months to years following the delivery of radiation. They are generally irreversible and more serious than the acute side effects of RT. Larger daily doses of radiation correlate with a higher risk of long-term side effects, though the risk of serious side effects is still very low with established regimens. Patients with metastatic cancer may not live long enough to commonly suffer late side effects but with improvements in systemic therapies, some patients may be at risk for the development of late complications that can be associated with short course, high dose per fraction therapy. To date, this has not been clinically significant given the relatively short survival of patients with metastatic cancer and the modest total doses employed.

GUIDELINES AND QUALITY MEASURES

Bone Metastasis

Multiple randomized trials have compared single-fraction approaches to palliative radiation to multiple different multifraction approaches for the treatment of bone metastasis. The overwhelming evidence suggests equivalence in efficacy increased cost and inconvenience of multifraction approaches, yet there is still a great deal of variability of approaches in use by radiation oncologists. One survey revealed that 101 different dose fractionation schemes were employed worldwide for this single clinical circumstance [74]. The American Society for Radiation Oncology (ASTRO) and the American College of Radiology (ACR) have developed guidelines; four fractionation schemes are considered equivalent in the successful management of uncomplicated painful bone metastases [75–77]. The use of one of the four approved fractionation schemes is considered a measure of quality as determined by the National Quality Forum (NQF) [78]. In addition, single fraction RT for painful uncomplicated bone metastasis has been incorporated into the American Board of Internal Medicine's "Choosing Wisely" campaign, a program designed to help physicians become better financial stewards of health care use [79].

End-of-Life Radiation Therapy

The delivery of chemotherapy in the last month of life has been proposed as a metric of overutilization of resources [24]. The delivery of RT in the last

two weeks of life may be a similar indicator since palliative radiation takes time to achieve its effect and there are few conditions, namely bleeding and spinal cord compression, where radiation may be indicated in the last month of life in addition to other supportive measures.

Approximately 50% of patients receiving radiation at the EOL do not complete the planned course of radiation [26,80]. In the series described by Toole et al., 6 patients died during the course of radiation and 43 (68%) received radiation within 10 days of death. Thirteen patients (21%) spent more than half of their last month receiving RT [26]. In patients who died after being diagnosed with incurable lung cancer in the National Comprehensive Cancer Network (NCCN) NSCLC Outcomes Database, 10% received RT within 14 days of death and 16% of patients died during treatment [80].

As there is a delay between the delivery of RT and its therapeutic benefit, most patients at the very EOL rarely benefit from RT. Accurate estimates of life expectancy help patients avoid costly care that is unlikely to benefit them or relieve their suffering.

CONCLUSION

The treatment of patients with advanced cancer is a multidisciplinary effort requiring coordination between the radiation oncologist and other specialists including medical oncologists, surgeons, palliative medicine specialists, and psychiatrists. Prognostication and accurate estimates of life expectancy are essential for goal setting and provision of appropriate care while avoiding treatments unlikely to provide a benefit. Many patients have unmet spiritual needs at the EOL and a simple acronym (FICA) can help physicians take a spiritual history and start the conversation.

RT is an important tool for palliating symptoms such as pain due to osseous metastasis or local tumor invasion, bleeding, obstruction, dyspnea or cough, and functional impairment due to brain metastasis or impingement of nerve roots or the spinal cord. Short course treatments effectively palliate pain and other symptoms. Since pain relief is not immediate, adequate pain control prior to the initiation of therapy is important. The short- and long-term toxicity associated with palliative RT is typically self-limited and can be managed conservatively. Highly conformal RT shows great promise, especially in patients with recurrent pain in the spine after prior conventionally fractionated curative therapy.

Increasingly, quality metrics surrounding the appropriate use of palliative radiation are being utilized. Avoidance of RT, especially long courses of RT, at the EOL is important given the delay between delivery of RT and the palliative effect of RT. Whenever possible, the shortest course of RT likely to have the desired effect should be employed. This maximizes patient comfort and convenience and minimizes cost and toxicity.

LIST OF ABBREVIATIONS

CT	computed tomography
ECOGPS	Eastern Cooperative Oncology Group Performance Status
EOL	end of life
Gy	gray (unit of radiation therapy)
KPS	Karnofsky Performance Status
RT	radiation therapy
RTOG	Radiation Therapy Oncology Group
SRS	stereotactic radiosurgery
WBC	white blood count
WBRT	whole brain radiation therapy

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Chapter 2

Communication

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Chapter Outline

Introduction 23
ASK-TELL-ASK 23
Delivering Bad News: SPIKES 24
Responding With Empathy: NURSE 25
Discussing Prognosis: ADAPT 25
Conducting a Family Meeting/Goals of Care Discussion 26
FICA Spiritual History Tool 27
References 28

INTRODUCTION

- One of the core competencies of providing palliative care is the ability to communicate with patients and their families [1].
- While many of us think that we are excellent communicators, there is always room for improvement.
- Communication is a skill and no matter what level you are starting at, there is always room for growth and refinement.
- Some basic tools are provided in this chapter to help guide you on your journey toward mastery.
- Your journey will involve trial and error, taking risks (going outside your comfort zone), taking the time to debrief on what went well or not so well, and what improvements you can make.

ASK-TELL-ASK

- One of the simplest but most effective approaches to communicating with a patient is the "ASK-TELL-ASK" method [2].
- It demonstrates willingness to listen to and negotiate the patient's agenda and builds on the patient's present knowledge and understanding of his/her illness.

Handbook of Supportive and Palliative Radiation Oncology.

Ask	• Ask the patient to describe his/her present concerns and understanding of their illness ○ "What brings you here today?" ○ "To make sure we are on the same page, can you tell me what your understanding of your disease is?"
Tell	• Communicate with the patient using straightforward language • Provide information in small chunks
Ask	• Ask the patient his/her understanding of the information provided ○ "To make sure I did a good job of explaining to you, can you tell me what your understanding is of your treatment plan?" • Clarify the patient's understanding if needed

DELIVERING BAD NEWS: SPIKES

- One of the most challenging aspects of being an oncologist is delivering "bad news."
- SPIKES is a six-step strategy that provides a useful framework for clinicians [2–4].
- We encourage focusing on improving one step at a time.
- Modify and tailor this approach to what feels most authentic to you and what meets your patient's specific needs.

Setting	S—Setting • Arrange for a private location • Involve significant others • Sit down • Make a connection through eye contact • Manage time constraints and interruptions
Perception	P—Perception of condition and seriousness • Determine the patient's understanding of his/her illness including the seriousness of their illness • Correct misinformation • Tailor information to the individual's level of understanding
Invitation	I—Invitation to the patient to give information • Ask the patient if he/she wishes to know the details of the illness • Accept the patient's right not to know • Offer to answer questions at a later time
Knowledge	K—Knowledge: giving medical facts • Assess the patient's level of comprehension (including level of education) • Provide information in small chunks • Check periodically for patient understanding • Respond to the patient's reactions as they occur • Provide facts accurately about treatment prognosis, treatment options, etc.
Empathize	E—Explore emotions and sympathize • Listen for and observe the patient's emotion • Identify the patient's emotion

- Identify the reason for the emotion
- Show the patient that their emotion is recognized
- Be quiet
- Refer to next section on "Responding With Empathy"

Summarize and Strategize

S—Strategize and summarize
- Ask whether the patient needs any clarification
- Establish a clear plan for the future

RESPONDING WITH EMPATHY: NURSE

- NURSE is a useful guide to respond to patient emotions with empathy [2].
- While it can be tempting to ignore strong emotions, it is important to openly acknowledge and demonstrate empathy when patients are in distress [5].

Naming
- Identify the patient's emotion
- Name the patient's emotion out loud
  - "Some patients in this situation would be angry. . ."

Understanding
- Confirm that you understand the patient's concerns in the context of this emotion
- Resist the temptation to provide reassurance before understanding the patient's primary concern(s)
  - "This must be very difficult for you."
  - "If I am understanding you correctly, you are concerned about the effect of chemotherapy on your children."

Respecting
- Respond verbally and nonverbally to the patient's emotion through appropriate facial expression, touch, or change in posture
- Match the level of your response to the patient's level of emotion
- Praise coping skills
  - "I am very impressed with how well you have cared for your wife throughout her treatment . . ."

Supporting
- Provide support by expressing your concern, confirming your understanding of the patient's situation (above), or acknowledging the patient's efforts to cope
- Many terminal patients fear abandonment—provide reassurance about your continued commitment to support the patient
  - "I will be here to support you no matter what happens."

Exploring
- Explore the patient's concerns and emotions
  - "Tell me more about what you are feeling . . ."

DISCUSSING PROGNOSIS: ADAPT

- Approaching the topic of prognosis with a patient and their family can be challenging.
- ADAPT is a "talking map" to help clinicians navigate through conversations about prognosis [6].

Ask	• Ask what patient knows
	  ○ "What have other doctors told you about your prognosis or what to expect for the future?"
	• Ask what he/she wants to know [7,8]
	  ○ "How much do you want to know?"

Discover	• Discover what type of prognostic information would be most useful for the patient
	  ○ For some patients, numbers or statistics about how long they will live are helpful
	  ○ For others, information about living to a particular date or event (e.g., graduation, the birth of a grandchild) may be most helpful

Anticipate	• Anticipate ambivalence ○ Explore patient's concerns about discussing prognosis
Provide	• Provide information in the format the patient prefers
Track	• Track or respond to patient's emotion ○ Acknowledge or respond to patient's emotion

CONDUCTING A FAMILY MEETING/GOALS OF CARE DISCUSSION

- You have probably conducted several family meetings already whether formally or informally.
- The following approach provides a useful guide to conducting a family meeting [4,9–11].
- Note that an effective meeting includes adequate preparation and debriefing afterward.

Premeeting planning	• Clarify the goals of the meeting in your own mind • Review relevant medical history, treatment options, and prognostic information • Review advance care planning information including code status • Coordinate medical opinions between consultants and primary team prior to the meeting • Obtain relevant information related to patients psychosocial, spiritual, and family dynamics
Establish an appropriate setting	• Choose a quiet and private environment • Minimize distractions such as cell phones or pagers
Introductions/establish rapport	• Introduce yourself • Have participants identify themselves and their relationship to the patient • Establish the goals of the meeting ○ Include the patient's/family's primary goals and concerns
Assess patient/family understanding	• Determine what the patient or family already knows ○ "What is your understanding of your current medical condition?"
Review medical status	• Present the big picture • Review current status, plan, and prognosis • Provide patient/family members with the opportunity to ask questions

Silence/respond to emotions	• Allow silence • Give patient/family time to react • Acknowledge and respond to their reactions and emotions before moving forward
Present options	• Discuss treatment options including symptom management, palliative care and/or hospice (if appropriate) • Make a recommendation

Manage conflict	• Recognize conflict and name the problem out loud
	• Listen
	  ○ For example, if the person is angry, he/she may have the need to be heard and understood
	• Listen to yourself
	• Identify the cause
	  ○ Conflict may emerge due to conflict between patient and his/her family and/or patient/family and the health care team
	• Reconcile
	  ○ Find common ground
	  ○ Determine a mutually agreeable solution to the conflict (e.g., establish a time trial for a specific intervention)

Translate goals into care plan	• Consider addressing the following (as appropriate to your patient)
	  ○ Assignment of a health care proxy
	  ○ DNR status
	  ○ Palliative care/Hospice support
	  ○ Other considerations (e.g., diagnostic tests, therapeutic interventions, artificial hydration/nutrition, antibiotics or blood products, and future hospitalization/ICU)

Summarize and document	• Summarize consensus, disagreements, decisions, and the care plan • Clarify next steps including a plan for follow-up • Document in the medical record (who was present, what decisions were made, follow-up plan) • Debrief with the health care team members involved with the patient's care

FICA SPIRITUAL HISTORY TOOL

- An important component of palliative care is addressing a patient's spiritual needs and concerns in the context of his/her health care.
- FICA is a useful means of framing the discussion about spirituality with patients and their families [11].
- Even if you do not feel comfortable discussing a patient's spirituality, take the first step to acknowledge its importance in a patient's illness and make a referral to social work or clergy.

Faith and belief	• Inquire about patients faith and beliefs ○ "Do you consider yourself spiritual or religious?" ○ "Is spirituality something important to you?" ○ "Do you have spiritual beliefs that help you cope with stress or difficult times?" • If the patient responds "No," consider asking ○ "What gives your life meaning?"
Importance	• Explore the importance of their faith and beliefs ○ "What importance does your spirituality have in your life?" ○ "Has your spirituality influenced how you take care of yourself, your health?"
Community	• Inquire whether it is a source of social support ○ "Are you part of a spiritual community?" ○ "Is there a group of people who have been supportive to you during this time?"
Address	• Clarify the meaning of their faith and beliefs in the context of their health care ○ "How would you like me, your health care provider, to address these issues in your health care?" ○ "Does your spirituality influence you in your health care decision-making?" (e.g., advance directives, treatment)

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Chapter 3

Prognostication in Patients Receiving Palliative Radiation Therapy

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Chapter Outline

Introduction 29
Importance of Prognostication 29
Physician Accuracy 30
What Patients Want to Hear 30
Prognostic Factors 31
Prognostic Models 32
Future Directions 35
References 36

INTRODUCTION

Importance of Prognostication

- Prognostication (prediction of life expectancy) is one of the most difficult tasks faced by oncologists. It is particularly difficult in patients with advanced, incurable cancer as life expectancy in these patients can vary from days to months.
- However, it is also an essential skill as it can inform treatment decisions, including the type and aggressiveness of treatment as well as the decision to enroll on hospice.
- Hospice referrals require a physician predicted prognosis of ≤ 6 months.
- Patients who hold overly optimistic perceptions of their prognosis are more likely to want futile, aggressive care [1].
- Patients are more likely to defer aggressive medical care that is associated with lower quality of life near death, greater medical care costs, and worse caregiver bereavement outcomes when physicians provide prognostic information during end-of-life discussions [2–4].

Handbook of Supportive and Palliative Radiation Oncology.

- In theory, estimating prognosis can help with tailoring treatment to life expectancy
  - In a US SEER study, 18% of patients who received radiation therapy in the last month of life spent 10 of their last 30 days of life receiving radiation therapy [5].
  - In a study of 216 patients referred for palliative radiation therapy, 27% of patients spent 81–100% of their remaining lifespan on treatment [6].

PHYSICIAN ACCURACY

- Estimates of physician accuracy in prediction of life expectancy range from 20% to 60% [7–12].
- Physicians tend to communicate overly optimistic prognostic information to patients [7,10,12].
- Several physician related factors can influence predictions of survival
  - Length of the patient–physician relationship: Each year that a physician has known a patient has been shown to increase the likelihood of making an erroneous prediction by 12% per year [13].
  - Accuracy has not been found to be dependent on physician seniority [14].
  - Physicians tend to lack confidence in estimating life expectancy [15], which has been shown to make them more likely to withhold prognostic information [16,17].

WHAT PATIENTS WANT TO HEAR

- The majority of patients desire at least some information regarding their prognosis.
- The amount of information desired and desired manner of communication varies from patient to patient.
- Two studies assessing patient preferences showed similar outcomes. One studied 126 patients with incurable metastatic disease in Australia and the other assessed 352 cancer patients in Michigan, USA
  - About 80% of patients wanted to know average survival rates and qualitative prognostic information [18,19].
  - About 60% of patients wanted to discuss expected survival rates when first diagnosed with their illness [18,19].
  - About 15% of patients who expressed a preference to receive qualitative prognostic information did not receive it [18,19].
  - Only about half of patients wanted to receive quantitative prognostic information [18,19].

PROGNOSTIC FACTORS

- Tumor size, stage, grade, and genetics do not play as significant a role in predicting prognosis of patients with incurable disease.
- Other factors have been studied to determine if they help physicians estimate prognosis in patients with incurable cancer
- Performance status has been identified in numerous analyses as a potential prognostic indicator in patients with advanced cancer [20–22].
  - Tseng et al. assessed 113 physicians to determine what factors were important to them in determining life expectancy. Ninety two percent of these physicians indicated that performance status was "very important" when assessing a patient's life expectancy.
  - Performance status has been shown to be primarily helpful for predicting prognosis when it is in the middle to low range [22,23].
  - Steep deterioration in Karnofsky Performance Status (KPS) can indicate a serious worsening of prognosis [22–24].
  - Prognostic utility of KPS has been shown to increase when combined with clinical symptoms, such as edema, dyspnea at rest, and delirium [24,25]
- Clinical symptoms can be used in addition to performance status to help in predicting life expectancy
  - Cachexia-Anorexia syndrome: Loosely defined as anorexia and involuntary weight loss.
    - Thought to occur because of imbalanced interactions between inflammatory cytokines, neuropeptides, hormones, and tumor-derived products [26].
    - Has been shown to be related to poor survival in patients with metastatic cancer [27].
    - In a study of 484 patients with metastatic cancer receiving palliative care consults, longer survival was seen among patients with neither anorexia nor weight loss as compared to patients having anorexia and/or weight loss [27].
  - Several other symptoms have been noted to be related to survival, particularly when used in combination with each other
    - In a study of 181 hospitalized patients referred to a palliative care team, multivariate analysis showed that nausea, dysphagia, dyspnea, confusion, and absence of a depressed mood were independent prognostic factors for worse survival [28]. The authors commented that the absence of a depressed mood may be related to worse survival because patients with a depressed mood may get earlier psychosocial and palliative intervention. However, they admit that the correlation is largely unexplained.
    - In that same study, patient survival time decreased with increasing number of the above symptoms: patients with four risk

factors had a 60% absolute increased risk of dying at 1 month compared to those with no risk factors [28].

- Symptoms must be used cautiously, given the subjectivity involved and difficulty in accurately assessing these symptoms at the end of life.
- Further research required to establish the most predictive and reliably assessable symptoms.
- Laboratory values have also been identified as potential markers for life expectancy
- Elevated levels of LDH have been associated with numerous types of cancer [29,30]
  - LDH thought to be a potential marker for higher disease burden and a potential prognostic indicator in patients with metastatic disease.
  - In a study of 93 terminal cancer patients, median survival time in patients with LDH <313 was 27 days as compared to 14 days in the elevated LDH group [31].
- C-reactive protein (CRP) is any acute phase reactant that responds to inflammation, injury, and cancer
  - Acute phase reactant that responds to inflammation, injury, and cancer.
  - In a study of 44 patients with incurable cancer admitted to a palliative care unity, patients with a CRP of ≥ 2.2 had a significantly shorter survival than patients with a CRP <2.2, with a hazard ratio of 3.22 [32].
- Leukocytosis/lymphopenia have both been suggested as poor prognostic markers in nonhematologic malignancies [33,34].
  - In a study of 252 hospitalized patients with nonhematological malignancies, leukocytosis was associated with a significantly shorter mean survival time [35].
  - In a study of 1051 cancer patients receiving chemotherapy with either advanced Non-Hodgkin's lymphoma or metastatic breast cancer, lymphocyte count $\leq 700/\mu L$ was identified as independent risk factor for early death (death within 31 days after chemotherapy delivery) [36].
- While laboratory values are promising tools for predicting prognosis, they must be used with caution.
- Data regarding laboratory values is limited and available studies are small.
- Laboratory values are not always readily available in this patient population.

PROGNOSTIC MODELS

- Various models have been created which incorporate all of the above factors in order to predict prognosis.

- These models vary in terms of their ease of use and accuracy as well as the specific patient population that they apply to.
- A detailed review of prognostic models has been performed elsewhere [37]. Several models also exist that are site-specific (i.e., brain metastases, spinal cord compression). For the purposes of this handbook, four major prognostic models focusing on patients with any type of advanced cancer are reviewed below. (Please see Appendix for additional details.)
- *Palliative Prognostic Score (PaP)*: Prospective, multicenter study of 519 patients with advanced solid tumors and no longer receiving chemotherapy [38]:
  - Developed a prognostic model to divide patients into distinct prognostic groups using independent predictors of survival.
  - Final model included anorexia, dyspnea, KPS, total white blood cell count (WBC), lymphopenia, and physician's survival prediction in weeks.
  - Patients divided into three groups based on numerical score determined by relative weight of the different prognostic factors and the probability of surviving 1 month (Table 3.1, see book Appendix for calculation of score).
  - Validated in 451 patients entering hospice programs and in a separate population of 100 patients with advanced cancers being cared for by oncologists [39].
  - Helpful to predict survival at 30 days but not as useful to predict survival in patients with longer life expectancies.
- *Palliative Prognostic Index (PPI)*: Prospective study of 150 terminally ill cancer patients admitted to a palliative care unit and expected to live ≤ 6 months [40]:
  - Model created to divide patients into three prognostic groups based on predictors of survival. The study assessed the palliative performance score (PPS, a modified version of the Karnofsky Performance Status) as well as 20 other clinical symptoms.
  - Final model included the PPS, oral intake, edema, dyspnea at rest, and delirium and specifically assessed likelihood of living to 3 and 6 weeks, respectively (see book Appendix for calculation of score).

TABLE 3.1 Prognostic Groups From PaP Prognostic Model

	Group A	Group B	Group C
PaP score (see Appendix for details of calculation)	0–5.5	5.6–11.0	11.1–17.5
Probability of surviving 1 month (%)	>70	30–70	<30

- Using cut-off point of PPI >6, survival of less than 3 weeks predicted with sensitivity of 73% and specificity of 87%.
- Using cut-off point of PPI >4, survival of less than 6 weeks predicted with sensitivity of 70% and specificity of 85%.
- Validated in two prospective studies of hospice patients [41].
- Useful for predicting survival in patients with short survivals, but limited use in estimation of long-term survival (>6 weeks).

- *Number of Risk Factors model (NRF)*: Retrospective review of 395 patients seen in a radiation oncology department [20]:
  - Goal of this study was to create a simplified prognostic model that would split patients into distinct survival groups.
  - Final model consisted of primary cancer site (breast vs nonbreast), the site of metastasis (bone only vs metastases including nonbone sites) and KPS (>60 vs ≤60).
  - Three groups created based on the number of risk factors (nonbreast cancer, nonbony metastases, KPS <60) (Table 3.2).
  - Externally validated in 467 patients referred for radiation therapy at Princess Margaret Hospital [20].
  - Easy to use, but developed in select population receiving palliative radiation therapy, less useful for patients with shorter life expectancies.
- *TEACHH Model*: Retrospective study of 862 patients receiving palliative radiation at one radiation oncology center [42]:
  - Model created to divide patients into three distinct prognostic groups, focusing on the extremes of the prognostic spectrum (i.e., patients living <2 months and patients living >1 year).
  - Final model consisted of *T*ype of cancer (breast and prostate vs other), Eastern Cooperative Oncology Group (*E*COG) performance status (0−1 vs 2−4), *A*ge at treatment (<60 vs ≥60), prior palliative *C*hemotherapy (0 vs ≥1 course), *H*ospitalizations in the last 3 months (0 vs ≥1) and the presence of *H*epatic metastases.
  - Three groups created based on the number of risk factors (nonbreast/nonprostate cancer, ECOG PS 2−4, age ≥60, receipt of prior palliative chemotherapy, being hospitalized within the last 3 months and having hepatic metastases) (Table 3.3).

TABLE 3.2 Prognostic Groups From NRF Model

	Group A	Group B	Group C
Number of risk factors	0−1	2	3
Median survival (weeks)	60	26	9

TABLE 3.3 Prognostic Groups From TEACHH Model

	Group A	Group B	Group C
TEACHH number of risk factors	0–1	2–4	5–6
Median survival (months)	19.9	5.0	1.7

TABLE 3.4 Comparison of Prognostic Models

Model	Ease of Use (Simple or Complex)	External Validation (Yes or No)	Limitations
PaP	Complex	Yes	Designed for patients with limited life expectancies
PPI	Complex	Yes	Designed for patients with limited life expectancies
NRF	Simple	Yes	Developed for patient population receiving palliative radiation therapy. Less applicable to patients with very limited life expectancies.
TEACHH	Simple	No	Developed for patient population receiving palliative radiation therapy. Broad middle survival group

  - Patients grouped in order to identify those at the extremes of the prognostic spectrum (i.e., living longer than 1 year or <2 months) to aid in treatment decision making. The median survival of patients in group C is <2 months and of Group A is more than a year.
  - Large sample size and identifies patients at the extremes of the prognostic spectrum, but unable to provide ranges of life expectancy for each grouping. Also, it is specific to patients receiving palliative radiation therapy.
- Each model has specific strengths and weaknesses (Table 3.4).
- The ideal model would be both easy to use and apply across the prognostic spectrum.

FUTURE DIRECTIONS

- While various prognostic markers and prognostic models exist to determine prognosis, none are without limitations.

- Existing models do not incorporate treatment-related factors [43], which are becoming increasingly important in patients with metastatic cancer.
- Future research must focus on incorporating treatment-related factors into models as well as developing more refined models that can be used with increased reliability.
- For now, prognostic factors and models should be used as a guide in making treatment-related decisions and should be used with all other available information including patient goals and values.

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Chapter 4

Palliative Care, Hospice Care, Advance Care Planning, and Advance Directives

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You matter because of who you are. You matter to the last moment of your life, and we will do all we can, not only to help you die peacefully, but also to live until you die.

Dame Cicely Saunders

Chapter Outline

Background 39
Palliative Care 40
Definitions 40
Guidelines 41
Palliative Care Services 41
Interdisciplinary Team 42
Setting 42
Barriers 42
Outcomes 42
Hospice 45
Criteria for Enrollment in the Medicare Hospice Benefit 46
Hospice Services 47
Interdisciplinary Care Team 47
Setting 47
Reasons for Discharge 48
Barriers to Enrollment 48
Outcomes 49
Resources 50
Advance Care Planning and Advance Directives 50
Definitions 50
Utilization 50
Effectiveness 52
Documents 52
Resources 53
References 53

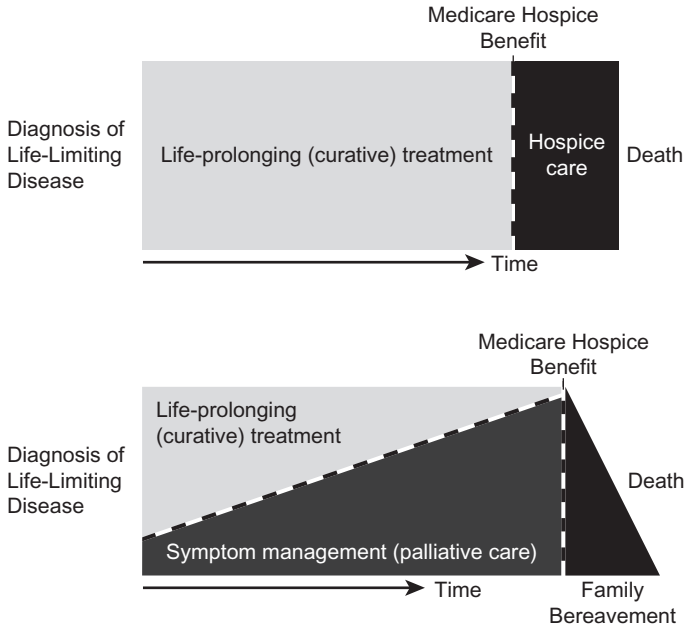
BACKGROUND

Hospice care was first recognized as a medical specialty in the 1940s in England. Dame Cicely Saunders worked with the terminally ill and went on to create St. Christopher's Hospice. It was not until the 1960s that this specialty

Handbook of Supportive and Palliative Radiation Oncology.

started to take hold in the United States and in 1982 the Medicare hospice benefit was created within the Tax Equity and Fiscal Responsibility Act. In order to qualify for the Medicare hospice benefit a provider must certify that, to the best of their judgment, a patient's life expectancy is 6 months or less.

It was not until the early 1970s that the term "palliative care" was used by Balfour Mount to describe his new program at the Royal Victoria Hospital in Montreal, modeled on St. Christopher's Hospice [1]. Although hospice care and palliative care programs share commonalities in the type of services provided, they differ in where they are utilized along the treatment trajectory. Hospice focuses on comfort rather than curative measures in the terminal phase of illness, while palliative care focuses on pain and symptom relief at any phase of a serious illness.



PALLIATIVE CARE

Definitions

The following definitions reflect the modern concept of palliative care:

- The World Health Organization (WHO) defines palliative care as: "An approach that improves the quality of life (QOL) of patients and their families facing the problems associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial, and spiritual" [2].
- The Centers for Medicare and Medicaid Services (CMS) have endorsed the following definition: "Palliative care means patient and family-centered

care that optimizes QOL by anticipating, preventing, and treating suffering. Palliative care throughout the continuum of illness involves addressing physical, intellectual, emotional, social, and spiritual needs and facilitating patient autonomy, access to information, and choice" [3].

- The Center to Advance Palliative Care defines palliative care as: "Specialized medical care for people with serious illnesses . . . focused on providing patients with relief from the symptoms, pain and stress of a serious illness—whatever the diagnosis. The goal is to improve QOL for both the patient and the family. Palliative care is provided by a team of doctors, nurses, and other specialists who work together with a patient's other doctors to provide an extra layer of support. It is appropriate at any age and at any stage in a serious illness and can be provided along with curative treatment" [4].

Guidelines

- The American Society for Radiation Oncology (ASTRO) has established three palliative guidelines [5]:
  - Palliative radiotherapy for bone metastases (2011).
  - Palliative thoracic radiotherapy in lung cancer (2011).
  - Radiotherapeutic and surgical management for newly diagnosed brain metastasis (2012).
- In 2012, the American Society of Clinical Oncology (ASCO), published a provisional clinical opinion (PCO) based on seven published randomized controlled trials (RCTs) that combined standard oncology care and palliative care should be considered early in the course of illness for any patient with metastatic cancer and/or high symptom burden [6].
- The National Consensus Project for Quality Palliative Care published the third edition of their guidelines in 2013. These guidelines "promote quality palliative care, foster consistent and high standards in palliative care, and encourage continuity of care across settings." There are eight domains of care: 1: Structure and Processes of Care; 2: Physical Aspects of Care; 3: Psychological and Psychiatric Aspects; 4: Social Aspects of Care; 5: Spiritual, Religious, and Existential Aspects of Care; 6: Cultural Aspects of Care; 7: Care of the Patient at the End of Life (EOL); and 8: Ethical and Legal [7].

Palliative Care Services

- Symptom management.
- Establishing goals of care that are in keeping with the patient's values and preferences
  - Code status.
  - Advance directives.
- Consistent and sustained communication between the patient and all those involved in his or her care.

- Psychosocial, spiritual, and practical support both to patients and their family caregivers.
- Coordination across sites of care.

Interdisciplinary Team

- Physicians.
- NPs/PAs.
- Registered nurses.
- Social workers.
- Spiritual Counselor.
- Pharmacists.

Setting

- Hospital
  - Consultative service.
  - Inpatient palliative care units.
  - Comanagement models.
- Ambulatory setting.
- Nursing home.
- Home.
- Hospice.

Barriers

- Key barriers to palliative care integration across three WHO domains:
  - Education domain: Lack of adequate education/training and perception of palliative care as end-of-life care.
  - Implementation domain: Inadequate size of palliative medicine-trained workforce, challenge of identifying patients appropriate for palliative care referral, and need for culture change across settings.
  - Policy domain: Fragmented health care system, need for greater funding for research, lack of adequate reimbursement for palliative care, and regulatory barriers [8].

Outcomes

- A metaanalysis of 19 studies concluded that palliative care and hospice teams improved patients' pain and other symptoms [9].
- In a landmark study, patients with newly diagnosed metastatic nonsmall cell lung cancer who were randomly assigned to early palliative care integrated with standard oncologic care had a better QOL, less depressive

symptoms, and longer median survival than did those who were assigned to oncologic care alone [10].
  - The ambulatory palliative care assessment in this trial focused on symptom management, patient, and family coping, and illness understanding and education [11].
  - In a later analysis, patients receiving early palliative care received the same number of chemotherapy regimens as did those in the control group but they were less likely to have chemotherapy continued close to death and more likely to enroll in hospice for a longer duration [12].
- The ENABLE II trial demonstrated higher scores for QOL and mood in patients with any life-limiting cancer (prognosis of approximately 1 year) who received psychoeducational palliative intervention in addition to standard care [13].
- The ENABLE III trial randomly assigned patients with advanced cancer to receive an in-person palliative care consult, structured palliative care telehealth nurse coaching sessions (once per week for six sessions), and monthly follow-up either early after enrollment or 3 months later.
  - Outcomes were QOL, symptom impact, mood, 1-year survival, and resource use (hospital/intensive care unit days, emergency room visits, chemotherapy in last 14 days, and death location).
  - Early-entry participants' patient-reported outcomes and resource use were not statistically different; however, their survival 1-year after enrollment was improved compared with those who began 3 months later [14].
- A randomized trial demonstrated that comprehensive outpatient palliative care in patients who continue to pursue disease modifying treatment, compared to usual care, improves symptom management, and patient satisfaction [15,16].
- Many clinicians fear that conversations about EOL issues with have a negative impact on patient's QOL, however, this has not panned out it the literature. Failure to have these conversations has documented adverse effects [17–21]:
  - Care inconsistent with values and goals.
  - Inferior QOL.
  - Prolonged death and increased suffering.
  - Inferior bereavement outcomes.
  - Increased costs without benefits.
- Palliative care with a strong emphasis on quality communication is a high-value intervention and results in [10,11,13,22–25]:
  - Better QOL.
  - Reduction in the use of aggressive care.

- Lower cost.
- 25% increase in survival [10].

Unfortunately, we do not have enough palliative care clinicians to reach all patients who would benefit from such specialized care. To bridge this gap, Dr. Susan Block created a tool to provide a systematic approach for non-palliative care clinicians. The tool is called the Serious Illness Conversation Guide and with her permission is included in the below table.

Serious Illness Conversation Guide

CLINICIAN STEPS

☐ **Set up**
- Thinking in advance
- Is this okay?
- Hope for best, prepare for worst
- Benefit for patient/family
- No decisions necessary today

☐ **Guide** (right column)

☐ **Act**
- Affirm commitment
- Make recommendations about next steps
  - Acknowledge medical realities
  - Summarize key goals/ priorities
  - Describe treatment options that reflect both
- Document conversation
- Provide patient with Family Communication Guide

CONVERSATION GUIDE	
Understanding	What is your understanding now of where you are with your illness?
Information preferences	How much information about what is likely to be ahead with your illness would you like from me? FOR EXAMPLE: Some patients like to know about time, others like to know what to expect, others like to know both.
Prognosis	***Share prognosis as a range, tailored to information preferences***
Goals	If your health situation worsens, what are your most important goals?
Fears / Worries	What are your biggest fears and worries about the future with your health?
Function	What abilities are so critical to your life that you can't imagine living without them?
Trade-offs	If you become sicker, how much are you willing to go through for the possibility of gaining more time?
Family	How much does your family know about your priorities and wishes? (Suggest bringing family and/or health care agent to next visit to discuss together)

Draft R4.3 5/22/15

HOSPICE

Eligibility: Medical guidelines for determining appropriateness of hospice referral: Documenting decline. Obtained from the Centers for Medicare and Medicaid Services.

A patient will be considered to have a life expectancy of 6 months or less if he/she meets the following criteria for decline in clinical status, when they are not considered to be reversible:

1. Progression of disease as documented by worsening clinical status, symptoms, signs, and laboratory results
   a. Clinical status
      i. Recurrent or intractable infections such as pneumonia, sepsis, or upper urinary tract infection.
      ii. Progressive inanition as documented by weight loss not due to reversible causes (depression, diuretics), decreasing anthropomorphic measurements (mid-arm circumference, abdominal girth), not due to reversible causes (depression, diuretics), decreasing serum albumin, or cholesterol, dysphagia leading to recurrent aspiration and/or inadequate oral intake documented by decreased food portion consumption.
   b. Symptoms
      i. Dyspnea with increased respiratory rate.
      ii. Cough, intractable.
      iii. Nausea/vomiting poorly responsive to treatment.
      iv. Diarrhea, intractable
      v. Pain, requiring increasing doses of analgesia.
   c. Signs
      i. Decline in systolic blood pressure below 90 or progressive postural hypotension.
      ii. Ascites.
      iii. Venous, arterial, or lymphatic obstruction due to local progression or metastatic disease.
      iv. Edema.
      v. Pleural/pericardial effusion.
      vi. Weakness.
      vii. Change in level of consciousness.
   d. Laboratory (when available, lab testing not required to establish hospice eligibility)
      i. Increasing $PaCO_2$ or decreasing PaO_2, or decreased SaO_2.
      ii. Increasing calcium, creatinine, liver function.
      iii. Increasing tumor markers (CEA, PSA).
      iv. Progressively decreasing or increasing sodium or increasing serum potassium.
2. Decline in Karnofsky Performance Status (KPS) or Palliative Performance Status from $<70\%$, due to progression of disease.
3. Increasing emergency room visits, hospitalizations, or physicians' visits related to hospice primary diagnosis.
4. Progressive decline in Functional Assessment Staging (FAST) for dementia (from $\geq$7A on the FAST).
5. Progression to dependence on assistance with additional activities of daily living.
6. Progressive stage 3–4 pressure ulcers despite optimal care.

PaO_2, arterial oxygen tension; *$PaCO_2$*, arterial carbon dioxide tension; *SaO_2*, arterial oxyhemoglobin saturation; *CEA*, carcinoembryonic antigen; *PSA*, prostate-specific antigen.
Source: Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD) for Hospice Determining Terminal Status (L32015) [accessed 28.08.2015].

Medical guidelines for determining appropriateness of hospice referral: Nondisease specific baseline guidelines plus comorbidities.

A patient will be considered to have a life expectancy of 6 months and be eligible for hospice services if he/she meets criteria for BOTH the following nondisease specific baseline guidelines AND disease-specific guidelines (shown on a separate table)

Both A and B should be met:

1. Physiologic impairment of functional status as demonstrated by Karnofsky Performance Status (KPS) or Palliative Performance Score (PPS) <70%. Note that two of the disease-specific guidelines (HIV and stroke/coma) establish a lower qualifying KPS or PPS.
2. Dependence on assistance for two or more activities of daily living (ADLs)
   a. Feeding.
   b. Ambulation.
   c. Continence.
   d. Transfer.
   e. Bathing.
   f. Dressing.

Comorbidities

Although not the primary hospice diagnosis, the presence of comorbid disease which is likely to contribute to a life expectancy of 6 months or less should be considered for hospice eligibility. Comorbid diseases may include:

1. Chronic obstructive pulmonary disease.
2. Congestive heart failure.
3. Ischemic heart disease.
4. Diabetes mellitus.
5. Neurologic disease (CVA, ALS, MS, Parkinson).
6. Renal failure.
7. Liver disease.
8. Neoplasia.
9. Acquired immune deficiency syndrome.
10. Dementia.

CVA, cerebrovascular accident or stroke; *ALS,* amyotrophic lateral sclerosis; *MS,* multiple sclerosis.

Source: Centers for Medicare & Medicaid Services. Local Coverage Determination (LCD) for Hospice Determining Terminal Status (L32015) [accessed 28.08.2015].

Criteria for Enrollment in the Medicare Hospice Benefit

1. Eligibility for Medicare part A, which is the benefit that covers hospice in addition to other care services (i.e., inpatient hospitalization, skilled nursing facility care, nursing home care, and home health services).
2. Medicare-approved hospice.
3. A statement signed by the patient indicating that they are choosing hospice care instead of regular Medicare. Of note, Medicare regulations allow for regular Medicare reimbursement for incidental medical expenses that are unrelated to the terminal illness (e.g., acute myocardial infarction in a patient with advanced cancer).
4. Certification by both the patient's personal physician and the hospice medical director that the patient has a terminal illness and is likely to

have less than 6 months to live if the disease follows its usual course. In addition, the patient's treatment goals should emphasize alleviating symptoms of illness and focusing on comfort and QOL rather than cure of the underlying disease.

Hospice Services

Once enrolled in the Medicare hospice benefit (MHB), all care related to their terminal illness must be covered by their hospice at an average hospice per diem reimbursement of $150 per day. As a result, many treatments may be cost prohibitive [26].

- Skilled nursing care.
- Symptom management.
- Psychosocial and spiritual care.
- Short-term inpatient care for difficult to control symptoms.
- Short-term respite is available for 5 days for every 30 days when caregivers are overwhelmed at home.
- Provides medications related to terminal condition, medical supplies and equipment.
- Bereavement care to surviving family and caregivers.

Interdisciplinary Care Team

- The patient's personal physician (typically the primary care physician or medical oncologist).
- Hospice physician (or medical director).
- NPs/PAs.
- Registered nurses.
- Home health aides.
- Social workers.
- Clergy or other counselors.
- Trained volunteers.
- Speech, physical, and occupational therapists, if needed.

Setting [27]

- Home
  - The majority of people receiving hospice get their care at home in a private residence. However, hospice care can also take place in residential facilities, assisted living, or nursing homes. A main caregiver is identified as the individual responsible for around-the-clock supervision of the patient. This person is with the patient most of the time and is trained to provide much of the hands-on care.

- Nursing home
  - Many nursing homes and other long-term care facilities have small hospice units. Some have staff trained to care for hospice patients while others contract with outside hospice agencies to provide care. This can be a good option for patients who want hospice care but do not have primary caregivers to take care of them at home.
- Residential hospice
  - Many communities have free-standing, independently owned hospices that feature inpatient care buildings as well as home care hospice services. A free-standing hospice can benefit patients who do not have a caregiver at home or those that do not want to die in their residence which comes up frequently with parents with young children.
- Inpatient setting
  - Hospitals may have a dedicated hospice program and/or a special hospice unit that they staff. Others consult outside hospice teams that visit patients, provide recommendations, patient support, and staff education/support.
  - To find a hospice in your area:
  - http://www.nhpco.org/find-hospice
  - http://www.hospicedirectory.org/
  - http://www.cancer.org/treatment/findingandpayingfortreatment/choosingyourtreatmentteam/hospicecare/hospice-care-how-to-find

Reasons for Discharge [28]

- Medical condition stabilizes (79%).
- Patient or family decision (12%).
- Decision is made to pursue more aggressive therapy (7%).

Barriers to Enrollment

- The first national survey of the enrollment policies of 591 hospices showed [26]:
  - 78% of hospice programs reported having at least one policy that could restrict access.
  - 61% of hospices won't accept a patient on chemotherapy.
  - 55% of hospices won't accept someone relying on parenteral nutrition.
  - 40% of hospices won't accept patients requiring transfusions.
  - 30% of hospices won't accept a patient who needs radiation therapy.
  - 32% of hospices won't accept a patient with an intrathecal catheter.
  - 30% of hospices require a caregiver at home.
  - 12% of hospices won't accept patients with tube feedings.
  - Only 30% of hospices offer some form of open access enrollment. This is possible for patients who are not yet eligible for hospice under

the MHB. These patients have the traditional hospice services while simultaneously retaining access to medical treatments such as palliative chemotherapy, radiation, and transfusions.

- Smaller hospices (average daily census of 60), for-profit hospices, and hospices in certain regions of the country consistently reported more limited enrollment policies.
- Larger hospices (average daily census of 200) were more likely to have no restrictive enrollment policies or open access enrollment [26].
- The average hospice stay is 2 weeks with average daily Medicare reimbursement rate of $150 per day.
  - The highest costs to the hospice are around admission (equipment, staff visits, medications, durable medical equipment) and death (staff visits, medications, etc.).
  - Per Meyers et al. [29]:
    - For 6 month hospice stay the hospice would be reimbursed $27,000.
    - For a 2 week hospice stay the amount decreases to $2100.
    - Palliative radiation costs can be as much as $10,000 and out of reach for many small hospices across the country.
  - Hospice and palliative radiation are not mutually exclusive; if an individual hospice organization is able to absorb the cost of radiation it would be an available treatment option.

Outcomes

- A secondary Analysis of The National Hospice Study revealed an improved quality of death in patients receiving hospice care [30].
- In a mortality follow-back survey, family members of patients who died in hospice were significantly more satisfied with the care than those of patients who died while receiving care in hospitals, nursing homes, or home health agencies [31].
- Family survivors are less likely to experience posttraumatic stress disorder and prolonged grief disorder after hospice care as compared to those whose loved ones died in a hospital or intensive care unit [32].
- Increasing evidence also suggests that hospice is associated with decreased direct (billed services) costs in the home setting, particularly for patients with cancer [33,34]. In contrast, data on the consequences of increased access to, and length of stay in, hospice among nursing home residents suggest that despite reduced hospital utilization, total Medicare spending is actually higher for hospice beneficiaries in nursing homes, by an average of around $6000 per person [35].
- Finally, the available data suggest that 80% of Americans prefer to die at home but that only approximately 25% do [36]. However, among the patients who die with hospice involved in their care, 75% die at home.

Resources

- https://library.tmc.edu/website/end-of-lifepalliative-education-resource-center-eperc/
- http://www.nhpco.org/about/hospice-care
- http://www.nhpco.org/resources
- http://www.helpguide.org/articles/caregiving/hospice-and-palliative-care.htm
- http://www.cancer.gov/about-cancer/advanced-cancer/care-choices/hospice-fact-sheet
- http://hospicefoundation.org/End-of-Life-Support-and-Resources/Grief-Support.aspx
- http://www.caregiverslibrary.org/caregivers-resources/grp-end-of-life-issues/hsgrp-hospice/hospice-vs-palliative-care-article.aspx

ADVANCE CARE PLANNING AND ADVANCE DIRECTIVES

Definitions

Advance care planning

Advance care planning (ACP) involves an ongoing discussion between patients, their families and health care professionals regarding goals, values, and beliefs. Exploration of these topics allows the patient to discover what is important to them and their family members regarding current and future medical care. The process of ACP informs and empowers patients to have a say about their current and future treatment [37].

Advance Directives

Advance directives (ADs) are the documents utilized to record treatment preferences. These documents vary depending on geographic location and include: Durable power of attorney for health care (health care proxy); living will and medical orders, such as do not resuscitate (DNR); and physician orders for life-sustaining treatment/medical orders for life-sustaining treatment (POLST/MOLST).

Utilization

- Planning for the EOL often occurs late or not at all. Several studies have shown that patients with serious medical illnesses do not discuss EOL preferences, or that the first discussions occur in the last days to months of life [17–19].
- For patients with advanced cancer [20]:
  - The first EOL discussion occurred median 33 days prior to death.
  - 55% of initial EOL discussions occurred in the hospital.
  - Only 25% of these discussions were conducted by the patient's oncologist.

- Misconceptions held by health care providers that were disproved:
  - It will make people depressed—*Incorrect*.
  - It will take away hope—*Incorrect*.
  - Involvement of Hospice or Palliative care will Reduce Survival—*Incorrect*.
  - We do not really know a patient's prognosis—*True, but with qualifications*.
  - Talking about prognosis is not culturally appropriate—*Incorrect*.
  - We do not like to have these discussions, and they are hard on us—*True*.

Why It Matters

- Patients lose good time with their families and for reflection and spend more time in the hospital and intensive care units.
- Patients and families want prognostic information, and it supports their ability to make decisions that are right for them.
- Several guidelines recommended by these authors about disclosing a poor prognosis:
  - Back AL, Arnold RM. Discussing prognosis: "How much do you want to know?"—Talking to patients who do not want information or who are ambivalent. J Clin Oncol 2006;24:4214–4217 [38].
  - Back AL, Arnold RM. Discussing prognosis: "How much do you want to know?"—Talking to patients who are prepared for explicit information. J Clin Oncol 2006;24:4209–4213 [39].
  - Back AL, Arnold RM, Tulsky JA. Mastering communication with seriously ill patients: balancing honesty with empathy and hope. Cambridge, United Kingdom, Cambridge University Press, 2009 [40].
- Minorities tend to have lower rates of ACP [41] and AD completion [42,43], with evidence that many AD documents as they currently exist are not culturally acceptable to them [42,44,45].
- Patient characteristics associated with a higher likelihood of completing an AD include [42,43,46–48]:
  - Older age.
  - Caucasian race.
  - History of a chronic disease, including AIDS and cancer.
  - High disease burden.
  - Higher socioeconomic status.
  - Prior knowledge about AD and EOL care options.
  - Higher level of education.
- When ADs are discussed the discussions are often inadequate [37]:
  - Many conversations focus on medical procedures only and fail to address key elements of quality discussions:
    - Prognosis.
    - Tradeoffs.

- Unacceptable states.
- Treatment outcomes.

Effectiveness

- A systematic review of the impact of ADs was performed in 2014 [49]. The results were notable for:
  - Decreased rate of hospitalization and the chances of dying in the hospital in two out of five studies.
  - Decreased use of life-sustaining treatment in 10 out of 22 studies.
  - Increased use of hospice or palliative care in five out of seven studies.
- Earlier conversations addressing EOL discussions about patients goals and priorities and coordinated ACP [17,37,50]:
  - Improves EOL care and enhances goal-concordant care.
  - Reduces the incidence of anxiety, depression, and posttraumatic stress in surviving relatives thus improves bereavement outcomes.
  - Reduces burden of decision-making for families.
  - Improves patient and family satisfaction with hospital care.
  - Are associated with less aggressive medical care near death, fewer hospitalizations, and earlier hospice referrals.

Documents

- *Durable Power of Attorney for Health Care*—A Durable Power of Attorney for Health Care (DPAHC, Health Care Proxy (HCP), or Health care Power of Attorney) is a signed legal document authorizing another person to make medical decisions on the patient's behalf in the event the patient loses decisional capacity [51].
- *Living Will*—The Living Will (LW) is a document detailing a person's preferences regarding their medical care in circumstances in which they are no longer able to express informed consent. Typically addresses resuscitation and life support but may also include preferences regarding tube feedings, implantable defibrillators, dialysis, etc.
- *Combined Directives*—ACP documents are being developed that include components of the LW along with a values history and instructional directive, while also designating a surrogate decision-maker. One example is the "Five Wishes," which combines the LW with the DPAHC [52].
- *Physician Orders for Life-Sustaining Treatment* (POLST)—The POLST paradigm is an approach to EOL planning emphasizing: (1) ACP conversations between patients, health care professionals, and loved ones; (2) shared decision-making between a patient and his/her health care professional about the care the patient would like to receive at the end of his/her life; and (3) ensuring patient wishes are honored. As a result of these conversations, patient wishes may be documented in a POLST form, which translates the shared decisions into actionable medical

orders. The POLST form assures patients that health care professionals will provide only the treatments that patients themselves wish to receive, and decreases the frequency of medical errors. It is meant to complement ADs, not replace them.

Resources

- State specific laws regarding LW's; http://www.caringinfo.org/i4a/pages/index.cfm?pageid=3289
- http://www.polst.org/educational-resources/
- Table 2. Randomized Controlled Trials of Decision Tools for ACP in:
  Austin C, Mohottige D, Sudore R, Smith A, Hanson L. Tools to promote shared decision making in serious illness: a systematic review. JAMA Intern Med 2015;175(7):1213−1221. DOI: 10.1001/jamainternmed.2015.1679 [53].
- Table 3. Randomized Controlled Trials of Decision Tools for Current Treatment:
  Austin C, Mohottige D, Sudore R, Smith A, Hanson L. Tools to promote shared decision making in serious illness: a systematic review. JAMA Intern Med 2015;175(7):1213−1221. DOI: 10.1001/jamainternmed.2015.1679 [53].

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Chapter 5

Palliative Care Assessment

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Chapter Outline

Introduction 57 References 64

INTRODUCTION

When a patient is referred for consideration of palliative radiotherapy, an overall assessment of patient and family must predicate all decision-making regarding the provision of radiation treatments. Questions about patient and family understanding of illness, patient and family understanding of prognosis, overall symptom burden, and the impact that radiotherapy will have on each of these areas must be weighed against the potential burdens of radiotherapy, including burdens of the actual treatment itself and the risks of both acute and late side effects of radiotherapy. The set of risks versus benefits of radiotherapy must be weighed in the context of patient and family overall goals to come to a mutual understanding of what treatments are most appropriate for the patient at any given time. This chapter explores the approach needed to undertake such an assessment for a patient referred for palliative radiotherapy.

- Historically, what are the differences between patients treated with curative or radical intent versus palliative intent?
  - "In a 'curable' situation, radiation therapy is radical treatment and a modest complication rate is licensed. In the event of failure, palliation often is a begrudgingly accepted bonus. Such unscheduled palliation is not the issue here. When the initial objective of radiation therapy is palliation, new ground rules must be applied. Possible serious complications or even slowly self-limiting side effects of treatment are no longer acceptable. Overall treatment time must be short. Cost must be minimized. Convenience of treatment must be considered" (JAMA, 1964, Robert Parker, Chair of Radiation Oncology, University of Washington) [1].

Handbook of Supportive and Palliative Radiation Oncology.

- Do such stark differences between palliative and curative radiation apply in the era of modern radiotherapy?
  - Sometimes, particularly for patients near the end of life. Advances in radiotherapy have made aggressive treatment of some metastatic lesions with treatments such as stereotactic ablative radiotherapy possible with minimal side effects. Fundamentally, though, questions about goals of radiotherapy (local tumor control versus strict symptom palliation) must be considered in the context of patient/family wishes in order to use a patient/family-centered approach to radiation [2–5].
  - Factors that should be considered when choosing to treat or not treat and to select appropriate dose-fractionation discussed at the end of this chapter.
  - In 2014, as part of the Choosing Wisely campaign to improve healthcare value, the American Society of Radiation Oncology (ASTRO) weighed in on the importance of defining goals of care and collaboration with palliative care teams:
    - "Don't initiate non-curative radiation therapy without defining the goals of treatment with the patient and considering palliative care referral" [6].
    - See Chapter 1, General Approach to Palliative Care and Palliative Radiation Oncology; Chapter 2, A Practical Guide to Communication in Palliative Care, Chapter 3, Prognostication in Patients Receiving Palliative Radiation Therapy; Chapter 4, Palliative Care, Hospice Care, Advance Care Planning, and Advance Directives; and this chapter, for more details of palliative care.
- How is palliative care defined (for patients/families referred to palliative care)?
  - Center to Advance Palliative Care (CAPC) definition:
    - Palliative care is specialized medical care for people with serious illnesses. This type of care is focused on providing patients with relief from the symptoms, pain, and stress of a serious illness—whatever the diagnosis. The goal is to improve quality of life for both the patient and the family. Palliative care is provided by a team of doctors, nurses, and other specialists who work with a patient's other doctors to provide an extra layer of support. Palliative care is appropriate at any age and at any stage in a serious illness, and can be provided together with curative treatment [7].
- World Health Organization (WHO) definition:
  - Palliative care is an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and

treatment of pain and other problems, physical, psychosocial, and spiritual. Palliative care:
  - provides relief from pain and other distressing symptoms;
  - affirms life and regards dying as a normal process;
  - intends to neither hasten nor postpone death;
  - integrates the psychological and spiritual aspects of patient care;
  - offers a support system to help patients live as actively as possible until death;
  - offers a support system to help the family cope during the patients illness and in their own bereavement;
  - uses a team approach to address the needs of patients and their families, including bereavement counseling, if indicated;
  - will enhance quality of life, and may also positively influence the course of illness;
  - is applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications.
- Of note, for the WHO definition, palliative radiotherapy may be delivered without intent to prolong life, but rather with a goal of improving symptoms.

- What fundamental questions must be answered in assessing a patient referred for palliative radiotherapy?
  - Palliative care assessment should include assessment of the following issues [8]:
  - What is the patient's overall level of distress (physical, psychosocial, spiritual, etc.)?
    - Definition of distress:
      - Distress is a multifactorial unpleasant emotional experience of a psychological (i.e., cognitive, behavioral, emotional), social, and/or spiritual nature that may interfere with the ability to cope effectively with cancer, its physical symptoms, and its treatment. Distress extends along a continuum, ranging from common normal feelings of vulnerability, sadness, and fears to problems that can become disabling, such as depression, anxiety, panic, social isolation, and existential and spiritual crisis [9].
    - Distress is the preferred term (rather than "psychosocial," "emotional," "psychiatric" because it is more acceptable) [9].
    - Screening should evaluate for practical problems, family problems, emotional problems, spiritual/religious problems, and physical problems.
    - Positive screens should lead to referral to other supportive team members (palliative care, social work, chaplaincy).

- See Chapter 1, General Approach to Palliative Care and Palliative Radiation Oncology, for more details on the spiritual aspects of palliative care.

- What is the patient's overall symptom burden?
  - Common symptoms that should be assessed per the NCCN Palliative Care Guidelines [8]:
    - Pain;
    - Dyspnea;
    - Anorexia/cachexia;
    - Nausea/vomiting;
    - Constipation;
    - Malignant bowel obstruction;
    - Fatigue;
    - Weakness;
    - Asthenia;
    - Insomnia and daytime sedation;
    - Delirium;
    - See Chapter 6, Pain Management; Chapter 7, Radiation-Induced Adverse Effects; Chapter 8, Management of Dyspnea and Central Airway Obstruction in Patients With Malignancy; Chapter 9, General Management: Bleeding; Chapter 10, Skin Toxicity in Palliative Radiation Therapy, for specific management of symptoms including pain, GI symptoms, dyspnea, bleeding, and skin challenges;
    - Collaboration with palliative care should be considered when symptoms persist in spite of palliative interventions by the primary oncology teams.
  - Multiple screening tools exist to assess for severe symptoms and should be utilized regularly, either a general tool or specific tool based on referral (see appendices):
    - Edmonton Symptom Assessment Score (ESAS);
    - MD Anderson Symptom Assessment Scores (bone, brain, spine);
    - EORTC Quality of life measures and for bone metastases;
    - Nonverbal pain assessment tools.

- What is the patient/family understanding of current illness status?
  - Data from Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) suggest that many patients do not understand the goals of their treatment (radiotherapy or chemotherapy) and such data may impact decision-making, so assessment of illness understanding is fundamental to the consultation.
  - Prospective data from the Cancer Care Outcomes Research and Surveillance Consortium; two analyses prospectively explored patient expectations regarding goals of treatment:
  - Weeks et al. NEJM 2012 [10]

1193 patients alive 4 months after diagnosis of stage IV lung or colorectal cancer completed surveys regarding expectations of chemotherapy;
69% of patients with lung cancer and 81% of patients with colorectal cancer did not report understanding that chemotherapy was not at all likely to cure their cancer.

- Chen et al. JCO 2013 [11].
  - 384 patients who received radiotherapy for stage IIIB or stage IV nonsmall cell lung cancer;
  - 78% of patients believed RT was very or somewhat likely to help them live longer;
  - 67% believed that RT was very or somewhat likely to help them with problems related to their cancer;
  - 64% did not understand that RT was not at all likely to cure them.
- Given importance in decision-making and described misinterpretation of goals of therapy, consider asking patients and families directly: "What is your understanding of your current situation?"
- Be prepared to discuss "serious news" if patient has not understood that disease is incurable.
- Responding to emotion is critical to conversations about serious news; consider NURSE acronym, from *Mastering Communication with Seriously Ill Patients* [12]:
  - Name the emotion;
  - Understand the emotion;
  - Respect (praise) the patient;
  - Support the patient;
  - Explore the emotion.
- See Chapter 2, A Practical Guide to Communication in Palliative Care, for more on communication skills regarding illness understanding.

- What is the patient/family's prognostic awareness? (see Chapter 3, Prognostication in Patients Receiving Palliative Radiation Therapy, for tools to help with prognostication.)
  - How much do patient/family want to know?
  - Consider discussion using ranges (years, months, dying patient) and/or best and worst case scenarios.
  - If patient and/or family do not want to know, consider whether prognosis will impact decision-making in palliative radiotherapy beyond the fact that the illness is incurable in deciding to explore further.
  - Response to emotion (NURSE as above).
- How involved would patient/family like to be in decision-making?
  - A direct question can help to improve medical decision-making, allowing patients to invite caregivers into the conversation, defer to family, or defer to the medical team [13–14].

- What are the patient's overall goals of care?
  - Even if not assessing patient/family interest in continuing further antineoplastic therapy, advanced care planning, or other details of therapy outside of the proposed radiation treatment, it is important to understand patient/family goals as regard radiotherapy.
  - Four questions can serve as a starting point for discussion of risks and benefits of radiotherapy (adapted from Atul Gawande, "The Best Day Possible" [15] and *Being Mortal* [16]):
    - What is your understanding of your health or condition? (as above)
    - What are your goals if your health worsens?
    - What are your fears?
    - What are the trade-offs you are willing to make and not willing to make?
  - See Chapter 2, A Practical Guide to Communication in Palliative Care, for communication techniques and Chapter 4, Palliative Care, Hospice Care, Advance Care Planning, and Advance Directives, for specifics of advanced care planning.

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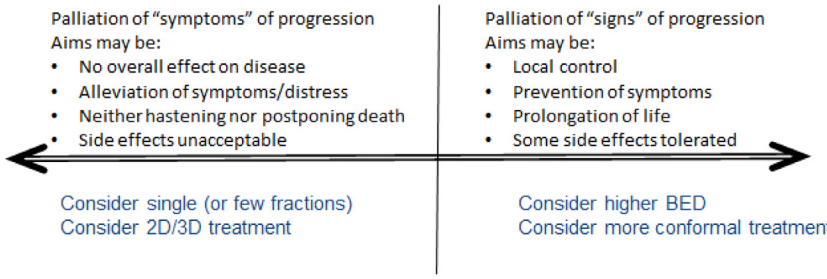
- What is the likelihood that palliative radiotherapy will help to relieve the symptom burden? [17] The following chapters discuss specifics of the likely efficacy of palliative radiotherapy by symptom and by site.
  - If asymptomatic, what is the goal of palliative radiotherapy?
  - Is local tumor control an important goal of radiotherapy for this patient at this time?
  - What other treatment options might help with symptom relief and must be weighed in the context of what palliative radiotherapy can offer?
  - What dose/fractionation and radiotherapy technique best achieve the balance of symptom control and patient convenience to patient?
- What are the factors that influence the appropriate selection of dose-fractionation scheme and appropriate radiotherapy technique? From Jones ASTRO CME [17] adapted from Van Oorshot et al. [18].



- Table describing factors that influence dose-fractionation and when not to treat with radiotherapy, from Jones and Simone, Palliative Radiotherapy, APM, 2014 [19].

Factors suggestive of a more aggressive approach (highly conformal or stereotactic treatment, or prolonged fractionation)	Factors suggestive of a less aggressive approach (less conformal treatment, short fractionation)	Factors suggestive of palliative care without radiotherapy intervention
Prognosis likely >6 months (see accompanying text)	Prognosis likely 1-6 months	Prognosis likely <1 month
Good performance status (KPS ≥70)	Poor performance status (KPS <70)	Very poor performance status/death imminent
Systemic disease well controlled	Large burden of systemic disease	Overwhelming burden of symptoms—radiotherapy affecting one symptom among many
Effective systemic treatments available*	Few or no proven effective systemic treatments available*	No effective systemic treatments available*
Large symptomatic tumor (less likely to respond to lower doses of radiotherapy)	Small symptomatic tumor (more likely to respond to lower doses of radiotherapy)	
High likelihood of significant late side effects due to normal tissue exposure	Low likelihood of significant late side effects	High likelihood of acute side effects that the patient may not survive
High morbidity of possible recurrence	Low morbidity of possible recurrence	
High morbidity of retreatment	Low morbidity of retreatment	Retreatment in an area that would exceed critical normal tissue tolerance
Few or no effective alternative palliative therapies	Range of effective alternative palliative therapies	If radiotherapy prohibits other effective palliative therapies (i.e., delay of referral to hospice)

*, effective systemic treatments may be based on the histology and biology of the primary cancer (i.e., metastatic hormone receptor positive metastatic breast cancer versus metastatic squamous cell carcinoma of the lung) and number and effect of prior treatment regimens; **, psychosocial issues (such as transportation issues, wanting to live to experience a specific event, wanting to spend time with family, etc.) that emerge in conversations with patients and family may cross categories in either direction.

- When should hospice or palliative care without radiotherapy be considered? [20,21]

Factors related to the patient
• Death is imminent
• Multiple progressive symptoms
• Inability to provide informed consent
• Transportation is impossible
Factors related to the treatment
• Potential side effect risks outweigh potential benefit
• Retreatment exceeds normal tissue tolerance
• Required course would be too lengthy
• Unnecessarily expensive treatment
Factors related to the health care system
• Radiotherapy facility is unavailable
• Lack of specialized radiotherapy technology
• Insufficient communication between radiation oncologist and palliative care

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Chapter 6

Pain Management

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Chapter Outline

Introduction 67
What Is Pain? 67
Common Pain Terminology 68
Pain Assessment 68
Patient Reported Outcomes 70
Management of Pain 71
Pharmacologic Management of Pain 71
Nonpharmacologic Management of Pain 73
Patient Case 1.1 73
Patient Case 1.2 74
Patient Case 1.3 76
Patient Case 1.4 77
Patient Case 1.5 77
Patient Case 1.6 77
Patient Case 1.7 78
Conclusion 80
Glossary 80
List of Abbreviations 81
References 81

INTRODUCTION

Pain is one of the common symptoms reported by cancer patients. This handbook chapter is a practical and quick guide to use while assessing and managing patients with cancer pain. We offer medication options to consider when treating patients as well as offer nonpharmacologic options worth considering.

WHAT IS PAIN?

Pain is "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage. While it is unquestionably a sensation in part or parts of the body, it is always unpleasant and therefore, an emotional experience" [1]. The above definition addresses the physical and emotional aspects of pain, however, we

Handbook of Supportive and Palliative Radiation Oncology.

should also be cognizant of the concept of total pain [2], which addresses other components such as the psychological, social, financial, cultural, and spiritual aspects of pain.

COMMON PAIN TERMINOLOGY

- Acute pain—It is pain that "follows injury to the body and generally disappears when the bodily injury heals." It can be associated with objective physical signs of sympathetic nervous system activity including tachycardia, hypertension, diaphoresis, mydriasis, and pallor [3].
- Chronic pain—Acute pain that persists for three months or longer [3]. Objective physical signs of sympathetic nervous system activity that may be associated with acute pain are likely to disappear in chronic pain (the patient with chronic pain may not appear to be in pain).
- Central pain—According to Chekka et al. [4], it is "regional pain caused by a primary lesion or dysfunction in the central nervous system usually associated with abnormal sensibility to painful (hyperalgesia) and non-painful (allodynia) stimulation."
- Neuropathic pain—Pain that results from a primary lesion in the nervous system [1]. Often associated with sensory changes (decreased sensation, allodynia, hyperalgesia, and other sensory changes).
- Nociceptive—Pain caused by noxious stimuli [5].

PAIN ASSESSMENT

- Pain is a subjective experience and performing a thorough assessment is one of the key steps in managing a patient's pain [6].
- Multiple scales exist; most of them document the patient's own self-reported level of pain and some of the scales document the patient's report of pain interference with activities and quality of life.
- It is essential to perform a pain assessment at the initial and every consecutive visit using *the same scale*.
- The following are the most commonly used pain assessment scales that can be used in clinical practice [7]:
  - Visual Analog Scale (VAS)
  - Numerical Rating Scale (NRS)
  - Patient rates pain using a numerical figure usually from "0" being no pain to "10" being the worst pain imaginable.
  - Limited as it captures one dimensional aspect of pain.
  - Wong-Baker FACES Scale [8] (Fig. 6.1)
  - Patient chooses the face that best depicts their level of pain. Useful in patients greater than 3 years of age.

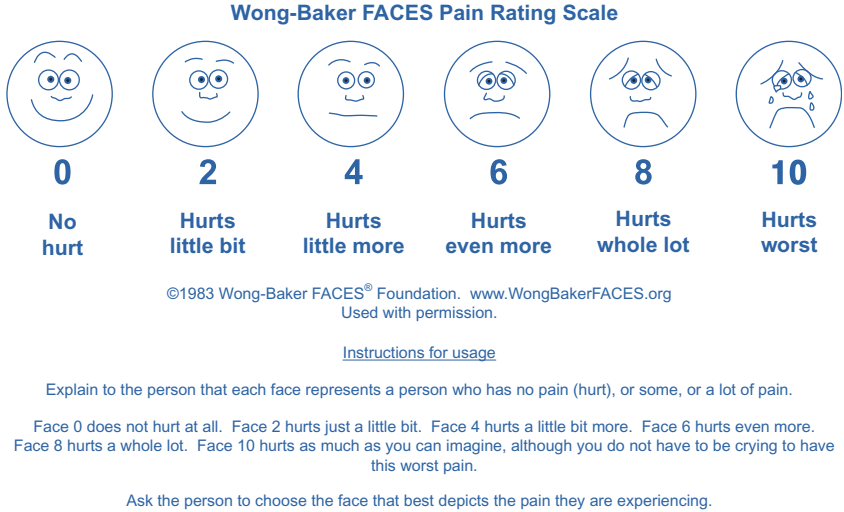

FIGURE 6.1 If patient is in severe pain, consider hospital admission for intravenous opioid titration for expedited pain relief. Be conservative with older patients.

  - Can also be used in the elderly.
  - Edmonton Symptom Assessment Scale: Pain is one of the 9 symptoms assessed with a scale 0 to 10 [9].
  - Brief Pain Inventory [10]
- Measures pain intensity and interference of pain in patient's life, as well as pain relief, pain quality, and patient perception of the cause of pain.
- Minimum requirements for pain assessment *must* include pain location, intensity, aggravating and alleviating factors, pain trajectory, and current pain regimen. One example of this is PQRST characteristics of pain [11]:
  - Palliating or precipitating factors (*P*)—"what makes it better or worse?"
  - Quality of pain (*Q*)—"what is it like?"
  - Region and/or Radiation (*R*)—"does it spread anywhere?"
  - Severity (*S*)—"How severe is it?"
  - Temporal factors (*T*)—"Is it there all the time, or does it come and go?"
- Other points to keep in mind:
  - The type of pain being treated (acute, chronic, acute on chronic) and how long it is anticipated to last for.
  - Safety and other concerns related to the prescribed pain regimen such as:
    - Opioids—Drug abuse potential, constipation, respiratory depression, and adverse effects.
    - NSAIDs—GI, renal, and other toxicity.
    - Antidepressants—Multiple drug−drug interactions.

  - Antiepileptics—Dose restrictions in renal failure and other concerns.
- Recommended screening tools to be used for the patients with substance abuse history:
  - Opioid risk tool [12].
  - CAGE substance abuse screening tool [13].
- Conduct an interview about any personal and/or family history of substance abuse and personal history of anxiety, depression or other.
- Tips to consider when managing patients with increased risk of opioid use disorder:
  - Use only one prescriber (or one team if a group practice).
  - Always consult with prescription monitoring programs if available in your state.
  - Contact retail/dispensing pharmacy if there is a high suspicion of opioid use disorder and the patient reports challenges/issues such as lost prescriptions.
  - Consider transdermal formulations such as the Fentanyl transdermal patch as they are difficult to tamper with. Consider other tamper-proof opioids, such as methadone or morphine (lowest street value medications).
  - For patients with repeated suspicious behavior (running out of medications, reports of repeated loss of medications or prescriptions), you may need to give a limited amount for 3–7 days instead of monthly refills (more time-consuming, more complex with insurance coverage, higher copays for the patient).
  - Factors that increase risk for opioid overdose include history of overdose, substance abuse disorder, higher opioid dosages, and concurrent benzodiazepine use.
  - Engage other members of a multidisciplinary team, e.g., social worker, psychiatry, patient representative, if needed, an addiction counselor.
  - Consider a peer review process for complex cases.
  - Establish goals of opioid treatment, timeline, and the plan of tapering at the first appointment and reinforce at each visit.
- Address potential system barriers such as:
  - Medication cost.
  - Access to analgesics of choice.
  - Local and national rules and regulations.
- Document all the above.

PATIENT REPORTED OUTCOMES

Patient-reported outcomes (PROs) such as pain and other symptoms are commonly measured not only in research, but more commonly now in routine clinical care for symptom screening and to enhance communication, particularly those addressing chronic illnesses that impact patient quality

of life and their activities of daily living. Use of PROs in performance evaluation is closely related to a growing interest in integrating PROs into electronic health records systems and patient portals [14]. Evidence demonstrates that patient reporting can improve communication, satisfaction, and symptom management [15,16]. There is evidence to support PRO in assessing baseline pain and changes in pain, analgesia, and analgesic-induced side effects in an effort to improve analgesia [17] (Tables 6.1 and 6.2).

MANAGEMENT OF PAIN

Pain management includes both the use of pharmacological and nonpharmacological approaches.

Pharmacologic Management of Pain

- The World Health Organization (WHO) and National Comprehensive Cancer Network (NCCN) Adult Cancer Pain Management have developed guidelines for the pharmacologic management of pain [18,19].
- The WHO analgesic "ladder" for cancer pain relief in adults recommends starting with a nonopioid then gradually escalating to a mild opioid and further escalating to a strong opioid as necessary [18].
  - Step 1: Use acetaminophen, NSAIDS or adjunct analgesic.
  - Step 2: Use a mild opioid with or without an adjunct analgesic.
  - Step 3: Use a strong opioid (e.g., morphine, hydromorphone, fentanyl, and hydrocodone) with or without an adjunct analgesic (variety of drug classes including anticonvulsants, antidepressants, muscle relaxants, and corticosteroids) (Table 6.3).

TABLE 6.1 Opioids—Initial Dosing Recommendations for Opioid-Naïve Patients[a]

Medication (Common Brand Name)	Oral	Parenteral
Morphine	7.5–15 mg q 3–4 h	2.5–5 mg q 3–4 h
Hydromorphone	2 mg q 3–4 h	0.2 mg q 3 h
Oxymorphone	5–10 mg q 3 h	0.5–1 mg q 3 h
Levorphanol	2 mg q 6 h	–
Codeine	30–60 mg q 3–4 h	15–30 mg q 3–4 h
Hydrocodone	5/325 mg q 4 h	–
Oxycodone	5–10 mg q 4 h	–
Tramadol	25–50 mg q 6 h	–

[a]*as needed for pain.*

TABLE 6.2 Equianalgesic Dosing Table

	Equianalgesic Doses (mg)		Caution in:
Drug	**Parenteral Dose**	**Oral Dose**	
Morphine	10	30	Renal insufficiency—avoid or dose reduce
Fentanyl[a]	0.1		
Hydrocodone	NA	30	
Hydromorphone	1.5	7.5	Renal insufficiency—dose reduce
Methadone[b]	1	2	
Levorphanol	2	4	
Oxycodone	10	20	Renal insufficiency—dose reduce
Oxymorphone	1	10	Renal insufficiency—dose reduce
Tramadol	100	120	Renal insufficiency—dose reduce

[a]*Unidirectional rotation. If opioid-naïve patients, consider, 10 mg IV morphine being equivalent to 100 mcg of fentanyl. If opioid-tolerant, 10 mg of IV morphine is equivalent to approximately 250 mcg of IV/transdermal fentanyl [19].*
[b]*See Table 6.3 for dose-dependent methadone conversion ratios. This is unidirectional.*
Source: Miaskowski C, Bair M, Chou R, D'Arcy Y, Hartrick C, Huffman L, et al. Principles of analgesic use in the treatment of acute pain and cancer pain. 6th ed. American Pain Society; 2008.

TABLE 6.3 Suggested Starting Doses for Nonopioids

Medication	Oral	Parenteral
Acetaminophen	650–1000 mg every 8 h	650–1000 mg every 8 h
Ibuprofen	400–600 mg every 6 h	N/A
Ketorolac	–	15–30 mg every 6 h (limit to 3–5 days)
Gabapentin	100–300 mg at bedtime	N/A
Pregabalin	150 mg daily	N/A
Dexamethasone	4 mg every 12 h	4 mg every 12 h
Cyclobenzaprine	5 mg every 8 h	N/A

A few pointers:

- Have a long-term treatment plan: prescribing medications, when and how to increase or decrease the dose of medications, and the frequency of follow-up appointments for monitoring of outcomes, side effects, and risk factors. Communicate this plan to the patient clearly. For example, patients treated for acute pain on opioids will more often than not be titrated off these medications slowly to avoid withdrawal.
- The FDA does not mandate any specific time interval to manage patients on controlled substances. Follow the administrative requirement for controlled substance prescribing in your respective state. For example, in New York State, the Prescribing Monitoring Program Registry (PMP) is an electronic system used to review a patient's prescription history of controlled substances [20].
- Be aware of important drug−drug interactions
  - Example: Patients being initiated on methadone who are currently on antidepressants with CYP3A4 inhibiting activity. These antidepressants could slow the metabolism of methadone and potentially increase serum levels and possibly cause toxicity issues.

Nonpharmacologic Management of Pain

- Other nonpharmacologic approaches to managing pain include alternative and complementary medicine, which includes guided imagery, music therapy, acupuncture, and massage therapy [21−23]. These various modalities have been shown to improve pain when used either alone or in combination with pharmacologic approaches.
- Acupuncture has been shown to be effective for cancer-related pain and postoperative pain [24]. Pain intensity levels decreased by 36% by 2 months from baseline in the treatment group compared to placebo [25].
- Music therapy is also able to relax patients and make pain bearable [26].
- Interventional pain management
  - Certain procedures (radiotherapy, nerve blocks, e.g., celiac plexus blocks for pancreatic cancer patients, intrathecal pump placements) can alleviate pain in oncology patients.
  - The appropriate service should be consulted when a patient is being considered for these alternative options for pain management.

PATIENT CASE 1.1

Mr. RJ is a 71-year-old man with a newly diagnosed locally advanced SCC of the supraglottic larynx. He has a sore throat and has trouble swallowing due to pain and mechanical dysphagia. The plan is to start radiation therapy. The following information is gathered during his pain assessment.

- Location of pain: Base of throat
- Quality: Ache, not constant
- Radiation: None
- Onset: A few weeks ago
- Intensity: 7/10 on the numerical pain rating scale
- Aggravating factors: Swallowing
- Alleviating factors: None
- No prior or current substance abuse, psychiatric history, or psychosocial issues

Mr. RJ also reports that he has tried over-the-counter acetaminophen and ibuprofen with not much relief. What pain medication would you recommend?

- Based on Mr. RJ's assessment, a short-acting opioid to be administered as needed may be worth considering. (See Table 6.1 for opioid options to consider as needed for opioid naïve patients.)
- Some options include:
  - morphine 7.5−15 mg by mouth every 3−4 hours as needed for pain.
  - oxycodone 5 mg PO q 3−4 h as needed for pain.
  - Hydromorphone 2−4 mg PO every 3−4 hours as needed for pain.
  - In the setting of aggravated dysphagia or where the patient is unable to swallow tablets, consider the liquid formulation.
- Other considerations:
  - It may be appropriate to start a constipation prophylaxis regimen particularly if the patient is taking the opioids frequently. Consider a stimulant laxative and a stool softener.
  - Maintain a pain diary to document usage and side effects.
  - Counsel patient to store opioids in a safe place, not to share medications with others.
  - Avoid driving if sedated.
- Opioid Adverse effects:
  - Patients on opioids can experience various side effects such as nausea, vomiting, itching, dizziness, confusion, hallucinations, and constipation (Table 6.4).

PATIENT CASE 1.2

Mr. RJ returns in 1 week with reports of good analgesia and some constipation. He states he is afraid to fall asleep because of increased pain should he miss a dose of the short-acting opioids. He reports that he is taking medications every 3 or 4 hours around the clock. What would be an appropriate next step?

- This patient would benefit from a long-acting opioid and a short-acting opioid for breakthrough pain
- Calculate the total effective 24 hour opioid dose.

TABLE 6.4 Opioid Adverse Effects and Possible Treatment Options

Side Effect	Treatment Option	Comments
Nausea	Antinausea meds, e.g., metoclopramide, ondansetron, and in very resistant cases neuroleptics in low doses have been reported to be effective	Nausea may resolve after 3–7 days as tolerance develops fairly quickly in most cases
Urinary retention	Opioid rotation	Unpredictable as to which opioid would cause less urinary retention
Sedation	Psychostimulant or slow titration	If sedation is persistent or significant, monitor for respiration depression. Respiration depression is more often preceded by sedation. High risk for respiratory depression include patients with sleep apnea, obesity, intrathoracic abnormalities, upper airway compromise, chronic CO_2 retention, such as COPD
Constipation	Initiate a bowel regimen as soon as opioids are started. No tolerance develops to constipation (constipation persists as long as patient requires opioids)	Fentanyl and methadone have been reported to be less constipation in small case reports. Untreated constipation can cause severe ileus requiring admission to the hospital
Delirium	Opioid dose reduction if possible or opioid rotation	Often multifactorial and requires thorough workup
	Consider inpatient admission for workup (delirium is multifactorial) and safety	
Hypoglycemia (only reported for methadone and tramadol)	Rule out other causes; if other causes are ruled out, consider opioid rotation	Rare
Pruritus	Antihistamines	The mechanism is not of a true allergy but based on histamine release
	If severe, consider opioid rotation	
QTC prolongation	Opioid rotation	Reported for methadone Oxycodone (doses higher than 100 mg)

(*Continued*)

TABLE 6.4 (Continued)

Side Effect	Treatment Option	Comments
Opioid overdose	Hold opioids	Monitor use of other sedating medications and patients at high risk of respiratory depression such as COPD and other restrictive lung disease, obesity and sleep apnea, other upper airway compromise
	Instruct families to call 911 if home	
	Dosing instructions: Dilute 1 mL (0.4 mg) of naloxone with 9 mL of NS in a syringe (final concentration = 0.04 mg/mL). Administer 1 mL of dilute naloxone IV push over 15 s. Repeat dose every 2–3 min as needed	

- Give this dose in a long-acting opioid formulation, e.g., Morphine extended release, oxycodone extended release, and fentanyl transdermal patches.
- Give 10–20% of the 24 hour total opioid dose of the long-acting opioid every 3 or 4 hours as needed for pain.
- In patients with dysphagia, the fentanyl transdermal patch might be an option to consider (avoidance of oral route). Methadone is available in liquid form, and may be appropriate for patients with difficulty swallowing tablets, however, some patients might not tolerate the taste (some patients find it bitter).
- Other considerations:
  - Start a scheduled constipation prophylaxis regimen, e.g., a stimulant laxative such as Senna 8.6 mg by mouth every 12 hours with a stool softener such as Docusate sodium 100 mg by mouth every 12 hours. Senna may be titrated up to four tablets twice daily as tolerated.
  - Maintain a pain diary to document usage and side effects.
  - Counsel patient to store opioids in a safe place, not to share medications with others.
  - Avoid driving if patient continues to be sedated.

PATIENT CASE 1.3

Mr. RJ starts radiation therapy and reports mucositis pain, skin pain, and allodynia and more opioid requirements.

- May consider starting gabapentin and titrating to effect (maximum dose 3600 mg). Gabapentin has been showing promising results and possibly reduces opioid requirements for patients with mucositis pain [27].
- Assess and escalate opioids as needed following the plan in case 1.2.

PATIENT CASE 1.4

Mr. RJ calls the doctor's office with a report of 10/10 pain rating. He sounds confused and is unable to report the location of his pain. He reports that he is unable to swallow much and unable to take his medications and he sounds very distressed.

- Mr. RJ might need an inpatient admission due to dose-limiting side effects (his medications might be causing confusion) and uncontrolled pain.
- Consider opioid rotation and IV administration of opioids.
- Opioid Rotation: In certain cases, a patient may need to be switched to another opioid due to a number of reasons (inadequate pain control, or intolerance to an opioid due to side effects). Additionally when converting from one opioid to another, one would need to factor in incomplete cross-tolerance. Using Table 6.2 for converting to another opioid, consider a 25–50% dose reduction in the total 24 hour opioid dose.
  - Calculate the total effective 24 hour opioid dose.
  - Choose another opioid and convert using conversion tables above.
  - Dose reduce by at least 25% to factor for incomplete cross-tolerance.

PATIENT CASE 1.5

Radiation is completed for Mr. RJ and he would like to know how long his pain will last for.

- Explain to him that the pain could last an additional 2–4 weeks.
- He can be tapered down on the opioids to the lowest effective dose as pain improves.

PATIENT CASE 1.6

You start to taper Mr. RJ off opioids as his pain symptoms have improved. After about 48 hours of tapering, the patient calls to complain of diarrhea, yawning, sweating, and dysphoria.

- This is physical withdrawal which is expected and a slower taper is required.
- Symptoms of withdrawal include dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation, piloerection or sweating, diarrhea, yawning, fever, and insomnia, and may present after discontinuation of opioids.
- Clonidine for withdrawal may be considered, and acetaminophen as needed.
- In some situations, one may need to refer to an addiction specialist for further opioid tapering.

PATIENT CASE 1.7

Mr. RJ comes back 6 months later with recurrent disease and complains of pain. What pain medication do you start with?

- Assume he is opioid naïve and start with PRN opioids.
- Additional general tips for prescribing opioids:
  - Be cognizant of controlled substance prescribing [28].
  - The recommended starting doses of common opioids are presented in Table 6.1.
  - Comparable doses of opioids with each other are presented in Table 6.2. These equianalgesic data are based on single dose studies and cannot be relied upon solely.
  - Clinicians should monitor their patients on opioids and dose carefully in renally or hepatically impaired patients.
  - For patients with mucositis pain and being managed with systemic opioids, may consider topical opioids. Opioids may be combined with magic mouthwash and patients instructed to swish and spit for pain relief of mucosal ulcers however this remedy may or may not be helpful to all patients [29].
  - Topical anesthetics although widely used have not been shown to be effective with larger studies.
  - Opioids can cause adverse effects including sedation, opioid neurotoxicity, urinary retention, nausea, vomiting, delirium, constipation, and respiratory depression. These side effects are treatable and can be prevented [30].
  - In pain crisis, consider referring patient to the hospital for rapid opioid titration using IV medications including PCAs.
  - Methadone is a long-acting medication with complicated pharmacokinetic and pharmacodynamic properties and it may be safe to consider consultation with a pain management specialist (Tables 6.5–6.7).

TABLE 6.5 Advantages and Disadvantages of Analgesics

Medication/ Medication Class	Advantage(s)	Disadvantage(s)
Nonopioid—Acetaminophen	No damage to gastric mucosa, no cognitive side effects, no constipation, minimal risk of addiction	No antiinflammatory effects, hepatotoxic at high doses; ceiling effect for analgesia
Nonopioid–NSAIDS	Antiinflammatory effects, no physical dependence, no	Hematological effects, GI effects, cardiovascular effects

(*Continued*)

TABLE 6.5 (Continued)

Medication/ Medication Class	Advantage(s)	Disadvantage(s)
	cognitive side effects, no psychological dependence	(prothrombotic), renal effects, CNS dysfunction, bone density effects, ceiling effect for analgesia
Opioids	No ceiling effect	Constipation and other side effects (see Table 6.2), tolerance, addiction
Coanalgesics—Gabapentinoids	Minimal drug–drug interactions; may be particularly helpful for neuropathic pain; may reduce opioid requirements in radiation induced mucositis	May take 3–7 days after reaching therapeutic doses (often requires 2700–3600 mg/day for gabapentin) to achieve expected analgesia, need dose adjustment in RI
Coanalgesics—antidepressants	May be particularly helpful for neuropathic pain	Potential for more drug–drug interactions, e.g., tamoxifen with SSRI's (decrease effect of tamoxifen), fentanyl with SSRI's (risk of SS); may take 3–7 days after reaching therapeutic doses to achieve expected analgesia

TABLE 6.6 Methadone Dosing

24-h Oral Morphine (mg)	Oral Morphine:Methadone Ratio
30–90	4:1
90–300	8:1
>300	12:1
>1000	20:1 (please consider pain specialist consult)
>2000	30:1 (please consider pain specialist consult)

Important notes about Methadone

- Methadone is a long-acting opioid (half-life 15–60 h) with a duration of analgesia od 6–12 h.
- Methadone can prolong the QTC interval; may order baseline EKG at the initiation of methadone.
- Methadone should be administered every 8 or 12 h. Will recommend a short-acting opioid to be given for breakthrough pain. If methadone is given for breakthrough pain, consider 10% of the daily methadone dose.
- Strongly consider consult with a pain specialist when initiating patients on methadone, unless you have had prior training.
- Often requires hospital admission for IV admin by designated pain specialists.

TABLE 6.7 Adjuvant Analgesics and Their Use in Various Types of Pain

Neuropathic pain	Gabapentinoids, antidepressants, ketamine*, anticonvulsants, lidocaine (topical)
Bone pain	Corticosteroids (e.g., dexamethasone; bone modifying agents such as bisphosphonates or denosumab; NSAIDS)
Muscle spasms	Muscle relaxants (e.g., cyclobenzaprine)

- For further assistance with pain, consider consultation with pain management specialists especially if:
  - Unsure about dose.
  - Unfamiliar with medication/dose.
  - Unexpected side effects.
  - Need help with pain diagnosis.
  - Patient with active or history of substance abuse.
  - Patient with history of psychiatric comorbidity.

CONCLUSION

There are several modalities to use in the management of pain. While there are general suggestions provided, treatment should be individualized for each patient. The most ideal pain management treatment plan should be multimodal in nature and incorporate both pharmacologic and nonpharmacologic approaches.

GLOSSARY

Breakthrough pain: Pain that flares in a patient on chronic opioid daily treatment.
Equianalgesic dose: An equivalent dose of a medication when compared to the dose of another medication.
High risk behavior: According to the Substance Abuse and Mental Health Services Administration, it includes:

- Selling prescription drugs;
- Prescription forgery;
- Stealing or borrowing another patient's drugs;
- Injecting oral formulation;
- Obtaining prescription drugs from nonmedical sources (friends, family, street);
- Concurrent abuse of related illicit drugs;
- Multiple unsanctioned dose escalations;
- Recurrent prescription losses;
- Lying about opioid use.

Incomplete cross-tolerance: An increased response to the new opioid when you change from an existing opioid to a new one (opioid rotation).
Opioid rotation: In certain cases, a patient may need to be switched to another opioid due to a number of reasons (inadequate pain control, or intolerance to an opioid due to adverse effects).
Opioid-tolerant: Using the Food and Drug Administration (FDA) definition, opioid-tolerant patients are taking 1 week or longer of at least:

- 60 mg oral morphine/day;
- 25 μg transdermal fentanyl/hour;
- 30 mg oral oxycodone/day;
- 8 mg oral hydromorphone/day;
- 25 mg oral oxymorphone/day; or
- An equianalgesic dose of any other opioid.

Opioid-naïve: Patients who do not meet the above definition of opioid-tolerant, and who have not taken opioid doses at least as much as those listed above for 1 week or longer.
Tolerance: Requiring increased amounts of opioids to achieve desired effect or a diminished response in analgesia with continued use of the same dose of an opioid.
Withdrawal: The development of the following symptoms after discontinuation of opioids: dysphoric mood, nausea or vomiting, muscle aches, lacrimation or rhinorrhea, pupillary dilation, piloerection or sweating, diarrhea, yawning, fever, and insomnia.

LIST OF ABBREVIATIONS

CNS	central nervous system
COPD	chronic obstructive pulmonary disease
GI	gastrointestinal
NS	normal saline
NSAIDS	nonsteroidal antiinflammatory drugs
PCA	patient controlled analgesia
RI	renal insufficiency
SS	serotonin syndrome
SCC	squamous cell carcinoma
SSRI	selective serotonin reuptake inhibitors

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Chapter 7

GI Symptoms: Radiation-Induced Adverse Effects

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Chapter Outline

Radiation-Induced Mucositis and Esophagitis 85
- Definition/Diagnosis 85
- Prevalence/Progression 86
- Treatment 87
- Esophagitis 89

Radiation-Induced Diarrhea 89
- Definition/Diagnosis 89
- Presentation/Prevalence/Progression 89
- Treatment 90

Radiation-Induced Constipation 92
- Definition/Diagnosis 92
- Presentation/Prevalence 93
- Treatment 94

Radiation-Induced Nausea and Vomiting 96
- Incidence 96
- Risk Factors 97
- Treatment 97

References 99

RADIATION-INDUCED MUCOSITIS AND ESOPHAGITIS

Definition/Diagnosis

Oral and gastrointestinal mucositis is an inflammation of the mucous membranes [1] and is a result of biological events involving the epithelium and submucosa induced by chemotherapy and radiotherapy [2]. Mucositis is a significant source of pain for many patients, and is thus of clinical relevance as it poses as a dose- and treatment-limiting side effect when it begins to interfere considerably with a patient's quality of life (QOL) [1]. As a result

Handbook of Supportive and Palliative Radiation Oncology.

TABLE 7.1 World Health Organization (WHO) Scale

Severity	Description
0	✓ No oral mucositis
1	✓ Erythema and soreness
2	✓ Ulcers, able to eat solid foods
3	✓ Ulcers, requires liquid diet
4	✓ Ulcers, alimentation not possible

Source: Taken from Davis MP, Feyer P, Ortner P, Zimmermann C. Chapter 11, Oral and gastrointestinal mucosal adverse effects. Supportive Oncology. Philadelphia: Elsevier Saunders; 2011. p. 102–113.

of its interference with cancer therapy, mucositis can potentially impact tumor response and long-term patient survival [3].

Oral mucositis primarily affects the soft palate, floor of the mouth, buccal mucosa, lateral margins, and ventral surface of the tongue and lips [2]. It is characterized by inflammation of the mucous membranes of the oral cavity and oropharynx and is distinguished by erythema, edema, atrophy, and often ulceration [1]. The World Health Organization (WHO) grades the severity of oral mucositis on a 0–4 grade point scale. Another research-based scale is the Oral Mucositis Assessment Scale (OMAS), which shows a strong correlation with more global scales such as the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) instrument. Table 7.1 summarizes the WHO measure.

Esophagitis is similar to mucositis both in presentation and management [4]. Symptoms of esophagitis include the onset of retrosternal chest pain and odynophagia [5]. Other symptoms that may aid in differential diagnosis include candidiasis, HSV, CMV, bacterial infections, and aspergillosis [5]. Chemotherapy (CT) and radiotherapy (RT)-induced esophagitis may produce an erosive esophagus that is clinically indistinguishable from infection—diagnosis of which requires an endoscopy or biopsy [5].

Prevalence/Progression

Mucositis

Eighty-five percent of patients undergoing RT for primary tumors of the oral cavity, oropharynx, or nasopharynx experience WHO grade 3 or 4 oral and/or oropharyngeal mucositis [3]. In another study of 75 patients receiving RT for head and neck cancer, 76% experienced severe oral pain, 51% required a feeding tube, and 37% were hospitalized for an average of 4.9 days [1].

The severity of the mucositis is governed mainly by the dosimetry of radiation to mucosal tissue. The risk factors corresponding to radiation

TABLE 7.2 Radiation Dosimetry and Toxicity Risk

Risk Factor	Risk Outcome
>2500 cGy	✓ Risk for developing clinically significant toxicity
≥ 5000 cGy	✓ Most severe lesions observed in these patients
Hyperfractionation	✓ Further increases risk
Concurrent chemoradiotherapy	✓ Severity of lesion can be escalated

TABLE 7.3 Clinical Progression of RT-Induced Mucositis Based on Conventional 7-Week Radiation Protocol (2 Gy/day, 5 × /week)

Time	Progression
End of 1st week	✓ Erythema ✓ Epithelial sloughing ✓ Oral discomfort
2nd or 3rd week	✓ Ulceration ✓ Severe pain
2–4 weeks	✓ Healing

dosimetry and the clinical progression of RT-induced mucositis are presented in Tables 7.2 and 7.3, respectively.

Esophagitis

Acute esophagitis occurs usually in week 3–4 of conventionally fractionated radiotherapy [6]. Patients with acute esophagitis will experience dysphagia, odynophagia, and heartburn; if not treated early, patients will experience weight loss and dehydration.

Treatment

Mucositis

Due to the challenging nature of mucositis treatment and the associated costs of managing the effects, the Mucositis Study Group of the Multinational Association for Supportive Care in Cancer and the International Society of Oral Oncology (MASCC/ISOO) saw the need for an evidence-based literature review to produce guidelines for mucositis management [7]. The guidelines were updated in 2007 and the guidelines for prevention and treatment of radiotherapy-induced mucositis are reproduced in Table 7.4.

TABLE 7.4 MASCC/ISOO Summary of Evidence-Based Clinical Practice Guidelines for Care of Patients With Oral and Gastrointestinal Mucositis

Oral Mucositis
Radiotherapy: Prevention
✓ The panel recommends the use of midline radiation blocks and 3-dimensional radiation treatment to reduce mucosal injury
✓ The panel recommends benzydamine for prevention of radiation-induced mucositis in patients with head and neck cancer receiving moderate-dose radiation therapy
✓ The panel recommends that chlorhexidine not be used to prevent oral mucositis in patients with solid tumors of the head and neck who are undergoing radiotherapy
✓ The panel recommends that antimicrobial lozenges not be used for the prevention of radiation-induced oral mucositis
Radiotherapy: Treatment
✓ The panel recommends that sucralfate not be used for the treatment of radiation-induced oral mucositis
GI Mucositis
Radiotherapy: Prevention
✓ The panel suggests the use of 500 mg sulfasalazine orally twice daily to help reduce the incidence and severity of radiation-induced enteropathy in patients receiving external beam radiotherapy to the pelvis
✓ The panel suggests that amifostine in a dose ≥ 340 mg/m^2 may prevent radiation proctitis in patients who are receiving standard-dose radiotherapy for rectal cancer
✓ The panel recommends that oral sucralfate not be used to reduce related side effects of radiotherapy; it does not prevent acute diarrhea in patients with pelvic malignancies undergoing external beam radiotherapy; and, compared with placebo, it is associated with more GI side effects, including rectal bleeding
✓ The panel recommends that 5-amino salicylic acid and its related compounds mesalazine and olsalazine not be used to prevent GI mucositis
Radiotherapy: Treatment
✓ The panel suggests the use of sucralfate enemas to help manage chronic radiation-induced proctitis in patients who have rectal bleeding

Source: Taken from Keefe DM, et al. Updated clinical practice guidelines for the prevention and treatment of mucositis. Cancer 2007; 109(5): 820–831.

TABLE 7.5 Symptoms and Symptom Management for Esophagitis

Symptoms	Management
Mild esophagitis	✓ Suspension of aluminum hydroxide, magnesium hydroxide, and oxetacain ✓ 5–10 mL of mouthwash swallowed every hour, consisting of: Maalox (4 oz), benadryl elixir (4 oz), viscous lidocaine (100 mL), and mycostatin oral suspension (1 oz)
More severe symptoms	✓ Require analgesic drugs (often including morphine)
Heartburn symptoms	✓ Proton pump inhibitors
Spasms	✓ Calcium antagonists
Candidiasis	✓ Oral nystatin or fluconazole

Esophagitis

The literature on the management for esophagitis is scarce; thus, institutional protocols have been developed [6]. The management of esophagitis has been described as being similar to mucositis [4] and is mainly supportive—often requiring dietary changes, topical agents, and narcotic pain medication [6]. Several suggestions for management of symptoms have been proposed and are listed in Table 7.5.

RADIATION-INDUCED DIARRHEA

Definition/Diagnosis

Diarrhea is defined as the urgent and frequent passage of loose or watery stools [8,9]. More specifically, some define diarrhea as the passage of three or more loose stools per day [9]. Another definition characterizes diarrhea as passing ≥ 200 g of stool per day based on a typical diet [9]. As in the case of constipation, however, a patient's perspective of diarrhea will vary and should be further clarified by health care providers. The grading of severity of diarrhea, as outlined by the National Cancer Institute, is displayed in Table 7.6.

Severe diarrhea can lead to dehydration, malnutrition, electrolyte imbalance, pressure ulcer formation, and weakening of the immune function [8]. It is debilitating and may, in some cases, even be life-threatening [8].

Presentation/Prevalence/Progression

Diarrhea is a well-known adverse effect resulting from abdominal or pelvic RT [11]. Radiation treatment often results in injury to the lower intestine and

TABLE 7.6 Common Toxicity Criteria (version 4.0) for Diarrhea

Grade	Description
1	An increase of <4 stools/day over baseline; mild increase in ostomy output compared to baseline
2	An increase of 4–6 stools/day over baseline; moderate increase in ostomy output compared to baseline
3	An increase of ≥7 stools/day over baseline; incontinence; hospitalization indicated; severe increase in ostomy output compared to baseline; limiting self-care ADL
4	Life-threatening consequences; urgent intervention indicated
	Death

Source: Adapted from National Cancer Institute. Common terminology criteria for adverse events (CTCAE). US Department of Health and Human Services, National Cancer Institute; 2010 [10].

damages intestinal mucosa; consequent prostaglandin release and bile salt malabsorption together stimulate increased intestinal peristalsis, resulting in diarrhea [8]. Moreover, radiotherapy to the abdominal region may disturb the colonization resistance of the gut flora, causing enteritis—an inflammation of the gastrointestinal tract that leads to severe diarrhea [12]. Approximately 50% of patients treated by pelvic and abdominal RT experience diarrhea and abdominal cramping as a result of acute enteritis [11].

Symptoms of RT-induced diarrhea usually occur during the third week of fractionated RT [11]. Enteritis is often accompanied by proctitis, an inflammation of the anus and rectum and acute radiation enteritis/proctitis occur within approximately 6 weeks of therapy [8]. Late radiation enteritis/proctitis occurs around 8–12 months after RT and may be delayed for years [8]. Onset of these late symptoms may manifest in the form of malabsorption and/or diarrhea [8].

Treatment

Standard therapy for diarrhea consists of oral opiates such as loperamide and diphenoxylate, which are effective in most patients with mild symptoms. However, a randomized trial published in 2000 showed octreotide (100 μg tid) to be significantly more effective than oral diphenoxylate (10 mg/day), with 61% of patients on octreotide resolved of diarrhea in three days versus only 14% of the patients treated with diphenoxylate [11,13].

RT-induced diarrhea requires a therapy procedure that differs from treatments designed to manage diarrhea arising from other causes [11]. Guidelines for management of cancer treatment-induced diarrhea published in 2004 by the American Society for Clinical Oncology recommends a

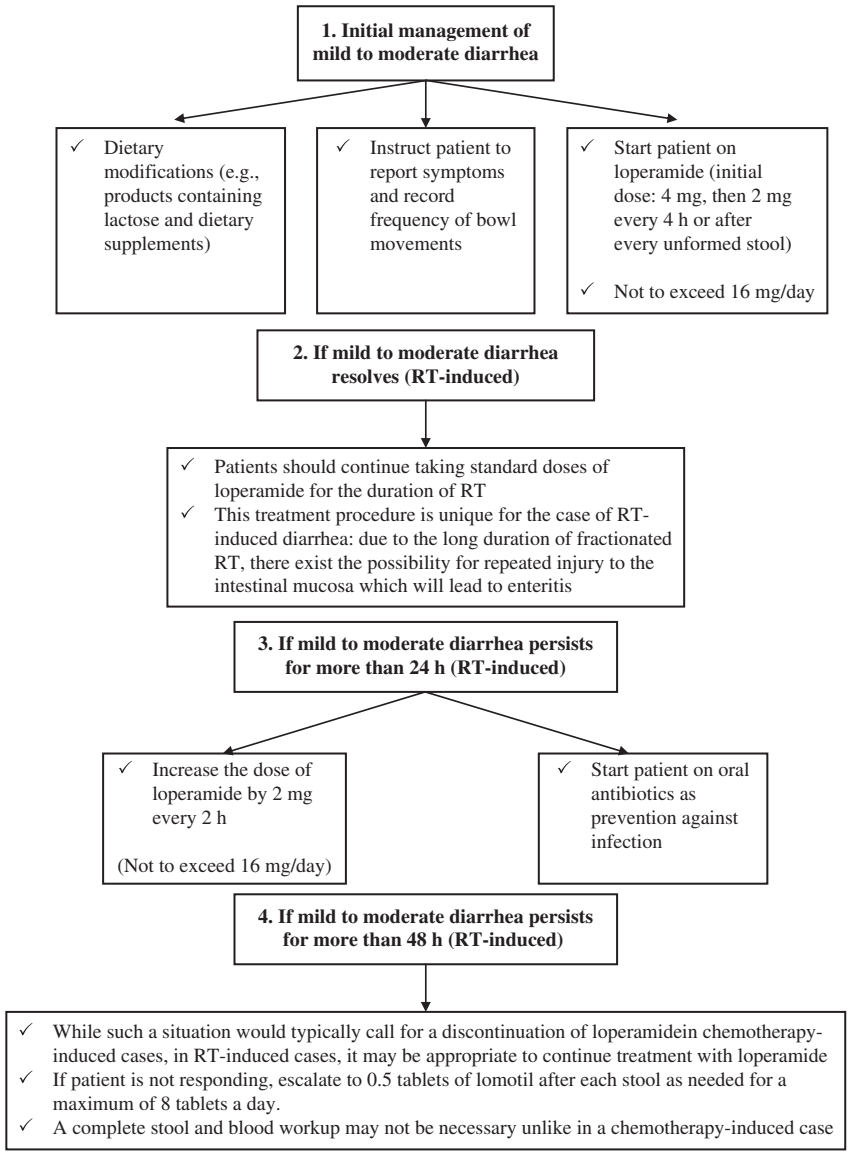

FIGURE 7.1 Visual summary of American Society for Clinical Oncology Guidelines for management of mild to moderate RT-induced diarrhea.

procedure to specifically manage RT-induced diarrhea [11]. We summarize the treatment procedure for managing mild to moderate RT-induced diarrhea in Fig. 7.1. A sample treatment might be: Loperamide (4 mg PO first then 2 mg following each episode of diarrhea up to max of 16 mg a day) and ensuring adequate hydration.

TABLE 7.7 Clinical Trial Findings on Preventative Measures Against Diarrhea in Patients Undergoing Pelvic RT

Treatment		Clinical Trial Finding
Sucralfate		✓ Mixed findings ✓ 3 European trials: Significant decline in occurrence of diarrhea in patients treated with 1–2 g of sucralfate 2–6 times daily when compared with placebo [13–15] ✓ Swedish trial: Significant decline in long-term bowel dysfunction in patients treated with sucralfate ✓ NCCTG trial and Australian trial: No improvement in diarrhea and significant worsening of some GI symptoms when compared with placebo group [16,17]
Salicylates	Sulfasalazine	✓ Turkish study: Sulfasalazine found to be effective [18] ✓ Until subsequent trial is conducted for confirmation, sulfasalazine should not be used outside of a clinical trial to treat patients undergoing pelvic RT [10]
	Olsalazine	✓ Turkish study: Increased diarrhea dramatically when compared with placebo [18]

The procedure outlined in Fig. 7.1 concerns cases of mild to moderate diarrhea. In cases in which mild to moderate diarrhea involves moderate to severe cramping, nausea and vomiting, diminished performance status, fever, sepsis, neutropenia, bleeding, or dehydration, and in cases of severe diarrhea, patients are classified as "complicated" [8].

In cases of complicated RT-induced diarrhea, patients require intensive monitoring and management in hospitals, intensive home care nursing programs, or adequate outpatient facilities that are capable of providing the level of care necessary [8]. In addition, these patients should undergo complete stool and blood workup and should be treated with octreotide in conjunction with intravenous antibiotics [8]. In most RT-induced diarrhea cases, however, it may be inappropriate to prescribe octreotide and a complete stool and blood workup may be unnecessary.

There have been several clinical trials which have focused on the prevention of diarrhea in patients undergoing pelvic RT [12]. The results of these studies are summarized in Table 7.7.

RADIATION-INDUCED CONSTIPATION

Definition/Diagnosis

Constipation is the slow passage of feces through the large intestine that results in infrequent bowel movements [8]. In the case that a bowel

TABLE 7.8 Rome III Criteria for Functional Constipation

1. Must include *two or more* of the following:
   a. Straining during at least 25% of defecations
   b. Lumpy or hard stools in at least 25% of defecations
   c. Sensation of incomplete evacuation for at least 25% of defecations
   d. Sensation of anorectal obstruction/blockage for at least 25% of defecations
   e. Manual maneuvers to facilitate at least 25% of defecations (e.g., digital evacuation, support of the pelvic floor)
   f. Fewer than three defecations per week
2. Loose stools are rarely present without the use of laxatives
3. Insufficient criteria for irritable bowel syndrome

Source: Adapted from Cherny NI, Werman B. Diarrhea and constipation. In: DeVita VT, Lawrence TS, Rosenberg SA, editors. Cancer principles & practice of oncology. 10th ed. Philadelphia: Wolters Kluwer Health; 2015.

movement does occur, the stool is dry and hard [8]. Constipation is defined under the Rome III criteria with an emphasis on the physical characteristics of the stool, the frequency of bowel movements, and other subjective measures of distress to the patient [9]. The criteria for functional constipation are presented in Table 7.8.

While guidelines have been laid out by the Rome III criteria, it is important to note that people differ with respect to the weights that they attribute to different aspects of this symptom cluster and patients may often consider themselves constipated even when they do not qualify as being constipated under the Rome III criteria [19]. As such, a diagnosis of constipation should primarily focus on a patient's complaint of the problem, and focus on his or her account of the situation [19]. Patients' assessment of their constipation can be assessed visually or with the aid of questionnaires and adjective scales [19]. Table 7.9 summarizes several formal methods of assessment.

Presentation/Prevalence

The presentation of constipation in patients as a direct adverse effect of radiation treatment is not well-documented. Constipation is often the result of a combination of factors rather than a single one [20]. Unlike the prevalence of diarrhea as an adverse result of radiation treatment, constipation is more often a result of chemotherapy regimens involving platinum compounds, vinca alkaloids, taxanes, thalidomide, bortezomib, and 5-HT_3 antagonist antiemetics, as well as opioid usage for the control of pain [8,9,19]. While a causative relationship between radiation and subsequent constipation is not often iterated, it has been noted as a possible side effect of radiation [21] and around 50% of patients admitted to a hospice report constipation [19]. In fact, constipation is often a more common problem than diarrhea in patients

TABLE 7.9 Formal Methods of Assessment for Constipation

Assessment Tools	Description
1. Constipation Assessment Scale (CAS) of McMillan and Williams	✓ Relevant for population undergoing active treatment for cancer ✓ An 8-item scale ✓ Average completion time: 2 min
2. Patient Assessment of Constipation-Symptoms (PAC-SYM) and Patient Assessment of Constipation-Quality of Life (PAC-QOL)	✓ Questionnaires directed at the patient's own perspective on constipation ✓ PAC-SYM has three subscales: (1) Stool symptoms; (2) rectal symptoms; (3) abdominal symptoms ✓ PAC-QOL is a QOL measure specific to constipation
3. More invasive options	✓ Often of questionable clinical value to oncology with the exception of a situation in which a combination of abdominal and a rectal exam has been insufficient in detection
4. Abdominal radiograph	✓ Will indicate extent of colonic fecal loading ✓ Aids in distinguishing between severe constipation and malignant obstruction

Source: Information obtained from Davis MP, Feyer PC, Ortner P, Zimmermann C. Chapter 11, Oral and gastrointestinal mucosal adverse effects. Supportive oncology. Philadelphia: Elsevier Saunders; 2011. p. 102–113.

with advanced cancer as a result of the wide use of opioid analgesics for pain management [8]. As such, we nevertheless proceed to discuss methods in treating constipation.

Treatment

Treatment of constipation is predominantly characterized by the use of laxative agents classified into two classes: (1) stool softening laxatives and (2) peristalsis-stimulating laxatives [19]. Constipation of increasing severity often responds best to a combination of these two types. Stool softening and peristalsis-stimulating laxatives are listed in Tables 7.10 and 7.11, respectively. A sample regimen would include: prune juice and stool softener (docusate 100 mg BID) and Senna; if no improvement is observed in 3 days, consider prescribing milk of magnesia, Ex-Lax, or MiraLax. If still no improvement: magnesium citrate or lactulose (30 cc po qd) may be initiated, and then fleets enema.

TABLE 7.10 Stool Softening Laxatives

Agents	Examples	Mechanism of Action and Efficacy Assessment
Osmotic agents	Organic: Lactulose	✓ Present in native form in small bowel ✓ Broken down by colonic flora into organic acids ✓ The resulting lowered pH is suspected to increase secretion and motility ✓ Relatively weak laxative ✓ Causes flatulence in approximately 20% of patients
	Inorganic: Magnesium hydroxide or sulfate	✓ Not absorbed and thus maintain osmotic potency throughout the intestine ✓ Able to stimulate peristalsis ✓ At higher doses produce a prominent purgative effect
Surfactants	Docusate	✓ Increases water penetration of stools ✓ Promotes secretion of water, sodium, and chloride into the jejunum and the colon ✓ May stimulate peristalsis at higher doses
	Poloxamer	✓ Increases water penetration of the stools
Macrogols		✓ Renders the intestines unable to absorb water ✓ Aids in stimulating gut contraction as a reflex response to distention ✓ Effective oral treatment for fecal impaction ✓ May require daily consumption of a liter of solution (not tolerable by all patients)
Chloride channel activators	Lubiprostone	✓ Affects Type 2 chloride channels on the apical surface of the luminal epithelium ✓ Increases secretions without disturbing electrolytes ✓ Secondary effect on motility ✓ Accelerates small and large bowel transit
Bulk-forming agents		✓ Enlarges stools by providing material that resists bacterial breakdown ✓ Effective in mild constipation. Doubtful efficacy in severe constipation ✓ Need to be taken with at least 200–300 mL of water (may be not possible for people who feel unwell)

TABLE 7.11 Peristalsis-Stimulating Laxatives

Drug	Mechanism of Action	Efficacy Assessment
✓ Senna ✓ Bisacodyl ✓ Danthron ✓ Sodium picosulfate	✓ All act on the myenteric plexus in order to stimulate intestinal contraction	✓ Carcinogenicity concerns with continued use appear to be unsupported. Danthron may cause perianal skin rash
✓ 5-HT_4 agonists (e.g., tegaserod, as currently licensed in some countries)	✓ Increase motility by reinforcing normal enteric neuronal stimulation of the peristalsis	✓ Effectiveness in scenarios where the enteric nervous system is damaged has not yet been demonstrated

TABLE 7.12 Rectal Laxatives

Interventions	Description
1. Suppositories	✓ Can have an osmotic softening effect (sodium phosphate or glycerine) or stimulate peristalsis (bisacodyl)
2. Enemas	✓ Lubricate (olive oil or arachis oil)
3. Manual evacuation of rectum	✓ Conduct with appropriate analgesia and sedation ✓ Last resort

In the case that oral laxatives prove inadequate, rectal laxatives can attempt to aid in ameliorating the situation. Table 7.12 lists several rectal interventions available.

Moreover, it is important to note that constipation is the most frequent and persistent side effect of opioid treatment. Thus, cancer patients undergoing radiation who are on opioids may experience exacerbated effects of constipation. Such patients on narcotic pain regimens should have an accompanying bowel regimen as well.

RADIATION-INDUCED NAUSEA AND VOMITING

Incidence

Radiation-induced nausea and vomiting (RINV) is one of the most characteristic adverse effects of radiation therapy and is often the first clear indication of radiation toxicity [22]. However, RINV continues to be underestimated by radiation oncologists [23] despite its clinically significant outcome of

potentially decreasing compliance with treatment [24]. If deprived of prophylactic treatment, approximately 50–80% of patients undergoing RT will experience such symptoms [23]. In a study of 1020 patients receiving RT conducted by Maranzano et al. in 2010, nausea and vomiting were reported by 28%, with a median time of 3 days until the first episode of vomiting [25]. Seventeen percent of patients in the study were given antiemetic drugs, with 12% given prophylactic treatment and 5% given rescue therapy. A second cohort of patients studied by Enblom et al. in 2009 showed higher incidence rates for nausea and vomiting, at 39% of patients [26].

Risk Factors

Guidelines for categorizing the risk of emesis due to RT are divided into four categories by the Multinational Association for Supportive Care in Cancer (MASCC) and the European Society for Medical Oncology (ESMO). These guidelines have been endorsed by the American Society of Clinical Oncology (ASCO) [27]. We summarize these categories in Table 7.13.

Treatment

The 5-HT_3 receptor antagonists are the first class of antiemetic drug design specifically as prevention against radiation-induced emesis [28]. There is a biological basis for the effectiveness of this class of drugs. Specifically, animal models have aided in providing insight into the pathophysiology of emesis and have helped illuminate the mechanism with which they act to prevent RINV [29]. 5-HT_3 receptor antagonists inhibit emesis by blocking the action of 5-HT at the site of 5-HT_3 receptors on the vagus nerve in the

TABLE 7.13 Emetic Risk Categories of Radiation

Emetic Risk	Risk of Emesis Without Antiemetic Prophylaxis (%)	Irradiated Area
High	>90	Total body irradiation (TBI), Total nodal irradiation (TNI)
Moderate	60–90	Upper abdominal irradiation, hemibody irradiation (HBI) and upper body irradiation (UBI)
Low	30–60	Cranium (all), craniospinal, head and neck, lower thorax region, pelvis
Minimal	<30	Breast and extremities

Source: Taken from Feyer P, et al. Radiation induced nausea and vomiting. Eur J Pharmacol 2014; 722:165–171.

gastrointestinal tract and in the hindbrain vomiting system [29]. These drugs are useful in both prophylactic and rescue settings. Breakthrough RINV is vomiting and/or nausea occurring within 5 days of radiation after the use of guideline-directed prophylactic antiemetic agents (agents used to prevent RINV). This type of RINV usually requires immediate "rescue" with additional antiemetics. The efficacy of 5-HT_3 receptor antagonists have been confirmed in many trials and the standard guidelines for antiemetic dosing by radiation risk group are now available. Namely, the American Society of Clinical Oncology recently released a practice guideline update for antiemetics that was published in 2011. A summary of their recommendations is reproduced in Table 7.14. A sample regimen might be as follows: Start on ondansetron 8 mg PO an hour prior to radiotherapy, and escalate to three times a day if needed. If this is ineffective, prochlorperazine (5–10 mg PO q 8 h PRN) or metoclopramide (5–10 mg PO q 8 h) may be added. For RINV prophylaxis, we recommend prophylactic administration of ondansetron 8 mg PO 1 hour prior to radiotherapy treatment.

TABLE 7.14 Antiemetic Dosing by Radiation Risk Category

		Dose	Schedule
High Emetic Risk			
5-HT_3 antagonist	Granisetron[a]	2 mg oral	5-HT_3 antagonist before each fraction throughout XRT. Continue for at least 24 hours following completion of XRT
		1 mg or 0.01 mg/kg IV	
	Ondansetron[a]	8 mg oral twice daily	
		8 mg or 0.15 mg/kg IV	
	Palonosetron[b]	0.50 mg oral	
		0.25 mg IV	
	Dolasetron	100 mg oral ONLY	
	Tropisetron	5 mg oral or IV	
Corticosteroid	Dexamethasone	4 mg oral or IV	Before fractions 1–5
Moderate Emetic Risk			
5-HT3 Receptor antagonist	Any of the above listed agents are acceptable, note preferred option b		5-HT3 antagonist before each fraction throughout XRT
Corticosteroid	Dexamethasone	4 mg IV or oral	Before fractions 1–5

(*Continued*)

TABLE 7.14 (Continued)

		Dose	Schedule
Low Emetic Risk			
5-HT3 Receptor antagonist	Any of the above listed agents are acceptable, note preferred options		5-HT3 either as rescue or prophylaxis. If rescue is utilized, then prophylactic therapy should be given until the end of XRT
Minimal Emetic Risk			
5-HT3 Receptor antagonist	Any of the above listed agents are acceptable, note preferred options		Patients should be offered either class as rescue therapy once prior to RT. If rescue is utilized, then prophylactic therapy should be given until the end of XRT
Dopamine receptor antagonist	Metoclopramide	20 mg oral	
	Prochlorperazine	10 mg oral or IV	

IV, intravenous; *XRT,* radiation therapy; *bid,* twice daily; *qid,* four times daily; *q,* every; *h,* hours.
[a]*Preferred Agents.*
[b]*No data are currently available on the appropriate dosing frequency with palonosetron in this setting. The Update Committee suggests dosing every second or third day may be appropriate for this agent.*
Source: Adapted from Basch E, et al. Antiemetics: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 2011;29(31):4189–4198.

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Chapter 8

Management of Dyspnea and Central Airway Obstruction in Patients With Malignancy

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Chapter Outline

Introduction 101
Pathophysiology of Dyspnea 102
Evaluation of Dyspnea 102
  Visual Analog Scale 103
Management of Potentially Reversible Etiologies of Dyspnea 103
Symptom Management for Dyspnea 105
  Opioids 105
  Benzodiazepines 106
  Oxygen Therapy 107
  Nonpharmacologic Therapies 108
Summary 108
Palliative Management of Malignant Central Airway Obstruction (CAO) 108
  Significance of CAO 108
  Diagnosis 109
  Management 109
Summary 115
References 116

INTRODUCTION

Dyspnea is a subjective sensation of breathlessness. The American Thoracic Society defines dyspnea as a "subjective experience of breathing discomfort that consists of qualitatively distinct sensations that vary in intensity. The experience derives from interaction among multiple physiologic, psychological, social, and environmental factors, and may induce secondary physiologic and behavioral responses" [1].

Dyspnea is experienced by 29–74% of patients with terminal cancer [2]. It is the most common severe symptom in the dying patient and more

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common in patients with poor functional capacity (KPS < 60). Dyspnea can arise from complex multisystem processes, making it challenging to control effectively. Most patients with cancer experience dyspnea in conjunction with other symptoms including psychosocial distress and pain. Therefore identifying and addressing these issues may help to more effectively improve dyspnea.

PATHOPHYSIOLOGY OF DYSPNEA

- Complex and poorly understood.
- Combination of central, neural, chemical, and mechanical feedback.
- Related to a patient's perceived sensation of breathlessness and their reaction to this sensation. Normal breathing is an autonomic function. The respiratory control centers in the brainstem control inspiratory muscles while expiration occurs passively. Respiration also plays a crucial role in acid–base homeostasis.
  - Chemoreceptors in the carotid bodies and ventral surface of the medulla monitor pH.
  - Chemoreceptors in the carotid and aortic bodies monitor oxygen and carbon dioxide levels and provide feedback to the respiratory control center.
  - A higher level of control involving the motor cortex and cerebellum can temporarily override the autonomic regulation of respiration such as in the case of emotional feelings or protective reflexes like a cough.
  - Dysregulation or abnormalities in any of these pathways may contribute to dyspnea.

EVALUATION OF DYSPNEA

- Since dyspnea is a subjective experience, using objective data, such as respiratory rate, arterial blood gases, and pulmonary functional tests, alone may underestimate a patient's symptom.
- Oxygen saturation has been shown not to have a correlation with a patient's intensity of dyspnea [3].
- Dyspnea scales have been developed to better elicit a patient reported level of dyspnea. Patients should be encouraged to rate the intensity of their dyspnea to enable providers to better manage their symptoms
  - Borg 0–10 scale (0 = nothing at all, 5 = strong, 10 = extremely strong) [4].
  - Modified Medical Research Council Cancer Dyspnea Scale (Grade 1 = not troubled by breathlessness except on strenuous exercise, 5 = too breathless to leave the house, or breathless when undressing) [5,6].

Visual Analog Scale

- A multidimensional approach should be utilized in evaluating the etiology of dyspnea, as the cause is often multifactorial.
  - Whenever possible, identify and treat any potentially reversible etiologies.
  - History includes inquiring onset of dyspnea.
  - Elicit whether symptoms are present at rest or positional and determine the acuity and severity of symptoms.
- Perform a focused cardiopulmonary history and physical examination.
  - Tachypnea may or may not be present in patients with dyspnea, and not all patients with tachypnea will experience dyspnea.
  - Cyanosis, if present, may suggest hypoxia, and pulse oximetry at rest and with exertion should be performed to assess for oxygen desaturation.
  - Lung examination should include evaluation for adventitial lung sounds and for findings suggestive of pleural effusions.
  - Cardiac examination should include assessment of jugular venous pressure and assessment for other findings to suggest heart failure or cardiac tamponade.
- Diagnostic testing can be useful to assess for potentially reversible etiologies.
  - Imaging often includes chest X-ray and chest computed tomography (CT).
  - A CT angiogram may be necessary to assess for pulmonary emboli.
  - Echocardiogram can be useful if cardiac etiology (such as pericardial effusion) is suspected.
  - In some instances, bronchoscopy may provide diagnostic information about airway lumen patency or yield specimens for microbiologic or pathologic analysis.

MANAGEMENT OF POTENTIALLY REVERSIBLE ETIOLOGIES OF DYSPNEA

- Management should be initially directed at all potentially reversible etiologies.
- Sometimes, a sole underlying cause cannot be pinpointed, in which case several interventions may be considered in parallel.
- In a palliative care setting, the risks and benefits of an intervention must be weighed against the patient's prognosis, the general health of the patient, and the patient's wishes.
- Treatment options are usually based upon the underlying pathophysiology (see Table 8.1).
- In some patients with malignancy, worsening dyspnea, hemoptysis, and stridor may suggest central airway obstruction (CAO). Urgent evaluation with direct examination of upper and lower airways may be required. Please refer to the section below on management of CAO.

TABLE 8.1 Potentially Reversible Etiologies of Dyspnea and Management Strategies

Pathophysiology	Possible Etiology	Possible Intervention
Airflow obstruction	Central Airway Obstruction (CAO) by tumor (intrinsic or extrinsic)	Radiation/chemotherapy/ bronchoscopy with laser therapy, brachytherapy, cryotherapy, or stent
	Radiation stricture	Balloon dilation or stenting
	Secretions/mucus impaction	Suction, nebulizer therapy, expectorant
Vascular obstruction	Pulmonary emboli	Anticoagulation
	Tumor thrombus	Interventional radiology
	Superior vena cava syndrome	Radiation/chemotherapy
	Cardiac tamponade	Pericardiocentesis
	Heart failure	Diuretics/medical therapy
	Anemia	Red blood cell transfusion, or if indicated iron and vitamin C, folate, B12 or erythropoietin
Decreased lung volume	Pleural effusion	Thoracentesis/Indwelling pleural catheter/pleurodesis
	Ascites	Paracentesis
	Pneumothorax	Chest tube
Altered ventilation	Anxiety	Psychotherapy, breathing techniques, benzodiazepines
	Depression	Antidepressant therapy
	Panic attack	Anxiolytic therapy
Infiltrative lung disease	Pulmonary fibrosis/drug induced pneumonitis	Corticosteroids/stop offending agent
	Radiation pneumonitis	Corticosteroids
	Pulmonary edema	Diuretics/management of underlying etiology
	Lymphangitic carcinomatosis	Corticosteroid, palliative chemotherapy
	Infection (pneumonia, TB, opportunistic)	Antimicrobial therapy

(*Continued*)

TABLE 8.1 (Continued)

Pathophysiology	Possible Etiology	Possible Intervention
Neuromuscular disorder	Phrenic nerve injury	Plication of the diaphragm, nocturnal noninvasive ventilation
	Paraneoplastic syndrome	Possibly treatment of cancer
Oxygen carrying capacity	Methemoglobinemia	Supplemental O_2, methylene blue, exchange transfusion
	Anemia	Red blood cell transfusion, or if indicated iron and vitamin C, folate, B12 or erythropoietin
Pain	Chest wall infiltration by cancer	Opioid, radiation
	Rib fracture	Opioid, radiation

SYMPTOM MANAGEMENT FOR DYSPNEA

Opioids

- Opioids have remained the primary tool in the management of dyspnea in advanced cancer patients.
- In addition to providing analgesia, opioids provide an additional antidyspneic effect.
  - When healthy opioid-naïve volunteers were given naloxone to counteract endogenous opioids in their bodies, they experienced sensation of dyspnea suggesting that opioids have a specific effect on dyspnea [7].
  - A metaanalysis of 18 double-blind, randomized, placebo-controlled trials on opioids for dyspnea from any disease showed a statistically significant positive effect of opioids in the treatment of dyspnea. Subgroup analysis showed a greater effect for oral or parenteral opioids when compared to nebulized routes [8].
- Morphine provides palliation of dyspnea for approximately 4 hours (See Table 8.2).
  - The average oral bioavailability of morphine is 30–40%, the onset of action is 15–30 minutes, the peak plasma concentration occurs within 30 and 90 minutes, and the half-life is 1.4–3.4 hours [9].
- Once an effective 24 hour opioid dose for dyspnea is determined, it can be converted to long-acting forms to provide baseline symptomatic relief of dyspnea [10].
  - Short-acting opioids may be titrated for breakthrough dyspnea and taken on an as needed basis.

TABLE 8.2 Initial Opioid Management of Pain

	Morphine	Breakthrough	Weight Based
Opioid-Naive	2.5 mg q 4 h PO	+ breakthrough	0.02 mg/kg q 4 h PO
Opioid-Exposed	5–10 mg q 4 h PO	+ breakthrough	0.04 mg/kg q 4 h PO

- Patients with prior opioid exposure often require approximately 25% higher doses of opioids than opioid-naïve patients to effectively reduce dyspnea and tachypnea for as long as 4 hours [11].
- Multiple routes of opioid delivery are available.
  - Opioids for dyspnea may be effective when administered orally, sublingually, rectally, or intravenously.
  - Many of the randomized controlled trials (RCT) exploring opioids for dyspnea have used a subcutaneous route [12,13].
  - Opioid receptors have been found in bronchial mucosa and nebulized options have therefore been explored for dyspnea. However, RCTs do not support the use of nebulized morphine in improving dyspnea [14].

Benzodiazepines

- Benzodiazepines are effective in controlling anxiety and panic, which may contribute to the sensation of dyspnea. Cancer patients with dyspnea often have some level of anxiety, fear, and sensation of impending death.
- There is no evidence that benzodiazepines alone are effective in relieving dyspnea in advanced cancer [15].
- However, benzodiazepines have been shown to act synergistically when utilized in combination with opioids.
  - In the inpatient setting, an RCT investigated the efficacy of scheduled morphine 2.5 mg every 4 hours with midazolam 5 mg every 4 hours versus patients with either scheduled morphine and breakthrough midazolam or scheduled midazolam and breakthrough morphine [16].
    - Ninety-two percent of patients with scheduled morphine and midazolam had dyspneic relief compared to those who had scheduled morphine and breakthrough midazolam (69%) or scheduled midazolam and breakthrough morphine (46%).
- No reported increase in drowsiness with the addition of scheduled midazolam.
- In an ambulatory setting, Navigante et al. studied the use of midazolam in combination with morphine.

- Starting doses were 2 mg for midazolam and 3 mg for morphine, with incremental increases of 25% of the preceding dosing every 30 minutes. If the dyspnea intensity was not reduced by at least 50%, the patient received the next step dose.
- The dose that reduced the intensity of dyspnea by at least 50% was considered the "effective dose" [17].

- Lorazepam has also been used.
  - Suggested doses are 25–50 mcg/kg (maximum 1 mg) as the starting dose.

Oxygen Therapy

- Although oxygen therapy is effective in the treatment of hypoxic respiratory failure, there has not been evidence to support the use of oxygen for palliation of dyspnea.
  - While some patients may feel reassured to have an oxygen supply as a "lifeline" when they become breathless, others may become more secluded and solitary as a result of a negative stigma associated with the oxygen delivery system.
  - There is growing evidence suggesting that the use of oxygen in these patients is of no benefit and may be detrimental [3,18,19]. It may cause discomfort, lead to deterioration in health status in certain conditions, and contribute to the financial burden on the health care system.
    - Unless there is documented hypoxemia, oxygen should not be prescribed for palliation of dyspnea in patients.
- Helium/oxygen gas mixtures have been used to treat patients with severe upper-airway obstruction associated with tumor, COPD, and asthma.
  - Heliox is a helium–oxygen gas mixture that reduces work of breathing by decreasing turbulent flow and thereby decreasing airway resistance.
  - The lower density and higher viscosity of the helium/oxygen gas mixture promote a more laminar flow in terminal airways and reduce resistance to flow thereby reducing work of breathing and improving alveolar ventilation [20].
  - In a double-blind, randomized, controlled Phase II trial of 12 lung cancer patients comparing Heliox 28 (72% helium and 28% oxygen) versus oxygen-enriched air, there was a significant improvement in exercise capability, oxygen saturation, and dyspnea scores for those who breathed Heliox 28 [21].
  - Use of helium/oxygen gas mixtures is a short-term bridge to definitive therapy due to the high cost of this specialty gas.

Nonpharmacologic Therapies

- Dyspneic patients will often benefit from therapies focused on increasing patient comfort.
  - Patients can use a handheld or fixed fan to blow cool air over the face. A randomized control trial demonstrated a significant reduction in breathlessness when a fan was blowing on the face compared to the leg, and this reduction was irrespective of the order of use of fan directed to the face or leg [22].
  - Placing the head of the bed at an elevation between 60 degrees and 90 degrees may help by optimizing diaphragm position.
  - Avoidance of irritants, like cigarette smoke and allergens, and good oral hygiene may also decrease the perception of dyspnea.
- The psychosocial component to dyspnea can be addressed with cognitive behavioral therapy.
  - Studies have shown that patients may benefit from weekly counseling sessions that help with breathing retraining, relaxation, and coping and adaptation strategies.
  - One multicenter, randomized controlled study of effects of nurse-run dyspnea clinic for lung cancer patients demonstrated improvement in dyspnea and performance scores compared with patients treated with standard of care with no specific interventions.
  - The intervention included teaching the patients breathing and relaxation techniques and providing psychosocial support [23].
  - Strategies such as these have been shown to reduce distress from dyspnea by more than 50% [24].
- Ultimately, the best management strategy most likely employs a combination of pharmacological and nonpharmacological methods to optimally palliate dyspnea.

SUMMARY

- Dyspnea is a disabling symptom experienced by many patients with advanced stages of cancer.
- Although the causes of dyspnea can be difficult to identify, physicians should employ a systematic approach to identify any potentially reversible causes.
- A combination of pharmacological and nonpharmacological management strategies should be utilized to optimally relieve dyspnea.

PALLIATIVE MANAGEMENT OF MALIGNANT CENTRAL AIRWAY OBSTRUCTION (CAO)

Significance of CAO

In a patient with malignancy, CAO is often a slow and insidious process. It may occur either by direct tumor invasion into an airway or by extrinsic

compression from a tumor leading to collapse of the airway. Most procedures to manage the CAO are palliative, but these interventions significantly reduce dyspnea, improve functional status, reduce postobstructive infections, enhance quality of life, and enable better radiographic evaluation for staging. Because these interventions are palliative, one should carefully assess the risk of any procedure with the potential for palliative benefit. The overall goals and likely outcomes should be clearly explained to the patient.

Diagnosis

- Patients with CAO frequently present with pneumonia and shortness of breath.
- Less severe CAOs are often asymptomatic but may be misdiagnosed as asthma or COPD.
- A focused history and physical exam are paramount for narrowing the differential diagnosis.
- Specific diagnostic tests may be useful in the diagnosis of CAO.
  - A chest X-ray is rarely diagnostic due to lack of soft tissue contrast, but may be useful as a screening tool to identify tracheal deviations suggestive of mass effect or radiopaque foreign body.
  - A CT scan of the chest often can provide greater level of detail
    - May identify the cause of the CAO, determine the location of the obstruction in the airway, and determine the length and dimension of the lesion, which can help determine treatment interventions.
- Advanced three-dimensional reconstruction of CT images can create internal and external renderings of the bronchial airways to help physicians better visualize and pinpoint the location of obstruction. Direct bronchoscopic visualization with rigid or flexible bronchoscopy is usually required to evaluate the CAO.
  - Can help to determine whether the CAO is due to endobronchial invasion or extrinsic compression.
  - Bronchoscopy allows for direct tissue sampling, so that a pathologic and molecular diagnosis can be established in order to better guide the therapeutic approach.

Management

Initial Stabilization

- In cases with severe CAO, endotracheal intubation may be required to secure the patient's airway and to provide positive pressure ventilation.
- Flexible bronchoscopy can then be performed after patient is intubated.
- If patient has an obstructive pneumonia, empiric antibiotic therapy should be initiated.

Bronchoscopy

- Bronchoscopy is an important diagnostic tool and can be used to evaluate and possibly treat the cause of obstruction.
- Bronchoscopic management of airway obstruction is palliative.
- A single institutional study revealed 42% of patients required more than one procedure to maintain airway patency [25].
- There are two types of bronchoscopy
  - The flexible fiber optic bronchoscopy is used widely in evaluating and diagnosing diseases of the airway due to its relative ease of use, and lack of a need for general anesthesia.
  - The rigid bronchoscope is often preferred by interventional pulmonologists given its superior control when managing difficult airway conditions.
    - In a severely obstructed airway, the beveled edge of the rigid bronchoscope can be used to shear large pieces of the endobronchial tumor and ventilation through the bronchoscope can be used to ventilate the distal airway.
    - Additionally, the large bore of the rigid bronchoscope can accommodate larger caliber suction catheters and larger biopsy forceps.
  - The rigid bronchoscope is more unwieldy than the flexible bronchoscope and requires greater training [26].

Bronchoplasty or Balloon Dilation

- Bronchoplasty or balloon dilation can be utilized to dilate a stenotic airway.
- Rigid dilators or sequential balloons may be passed through a stenotic segment of a central airway to dilate the stenosis.
- For balloon dilation, a series of dilations are performed with increasing balloon diameter to reduce risk of tracheobronchial rupture.
- Irrespective of the method of dilation, bronchoplasty provides immediate relief of extrinsic and intrinsic lesions, but the results are temporary.
  - Granulation tissue may form after bronchoscopy and cause recurrent stenosis due to mucosal tears from the procedure.
  - Often airway stents are placed for more durable results.

Airway Stents

- Airway stents may be used to maintain patency of the airway, and may be placed via flexible or rigid bronchoscopy.
- Metal and silicone stents may both be used.
  - Covered metal stents are most often used for malignant obstructions
    - Prevent tumor ingrowth and provide a larger internal: external diameter ratio compared to silicone stents.
    - Difficult to remove.

- Silicone stents
  - More easily removed if the obstructing mass responds to chemotherapy and/or radiation therapy.
  - Smaller diameter, which leads to a higher rate of migration.
  - Require a rigid bronchoscopy for placement.

Argon Plasma Coagulation

- Argon Plasma Coagulation (APC) is a noncontact electrocoagulation therapy applied via rigid bronchoscopy.
- A 5000−6000 V spark formed at the tip of a tungsten electrode ionizes argon gas, which then coagulates adjacent tissues causing them to undergo coagulative necrosis.
- Coagulation occurs 2−3 mm deep and there is very little risk of airway perforation [27].
- Can treat lesions lateral to probe or areas inaccessible by laser therapy making this therapy useful for hemorrhages.
- Does not vaporize tumor and some authors recommend repeat bronchoscopy 1−3 days after APC procedure to debulk the necrotic tissue.

Laser Therapy

- Lasers have been used for debulking since 1975.
- The Nd:YAG laser is most commonly used today. It can be used via a flexible bronchoscope and can achieve a tissue penetration of up to 10 mm [28].
- Laser photoresection has been used extensively for both benign and malignant airway lesions.
  - Malignant lesions have the best ablation rates with laser therapy alone;
  - Benign lesions were best managed by laser therapy and mechanical rigid dilation [29].
- Success can depend on location.
  - Tumors located in the trachea, right mainstem bronchus, and bronchus intermedius were treated successfully 97%, 94%, and 90% of the time;
  - Tumors in the left mainstem bronchus and left upper lobe were more difficult, but treated successfully in 86% and 58% of the time, respectively [30].
- Laser resection has a greater than 90% success in reestablishing patency in endobronchial masses that are central, intrinsic, and less than 4 cm in length [30,31].
- The most common reported complications from laser resection are bleeding (2.5%), and hypoxia (1.8%) [32].

Cryotherapy

- Endobronchial cryotherapy destroys tumors with cytotoxic effects of rapid freezing (−100°C/minute) and slow thawing of tissue.
  - The freezing creates intracellular ice crystals that expand in the cell causing cell membrane and organelle damage resulting in direct cell death.
  - Additionally, the freezing causes thrombosis of the microvasculature to the tumor [33].
- Using a flexible cryoprobe, adjacent tissue is frozen to extremely low temperatures (below −20°C to −40°C) [34].
- The role of cryotherapy for management of CAO is limited due to its delayed effect and the need to undergo multiple bronchoscopies to remove debris [35].

Palliative Surgery

- For patients with a localized tumor encasing a major bronchus, and who cannot tolerate a pneumonectomy, a tracheobronchial sleeve resection may be considered for both curative and palliative intent.
  - Helps preserve native lung function.
  - Associated with lower mortality rates than pneumonectomy [36].
- Tracheostomy can be performed to bypass a large obstructive neoplastic lesion proximal to the larynx and prevent respiratory compromise.
  - Patients can function with a temporary or permanent tracheostomy.
  - The side effects from tracheostomy are increased risk of infections, and perceived social stigma.

Palliative Chemotherapy

- The primary goal of palliative chemotherapy is to prolong survival and ease the symptoms by reducing the burden of disease.
- Each patient must be carefully evaluated and his or her goals of care must be known before deciding on pursuing palliative chemotherapy.
  - The American Society for Clinical Oncology guidelines recommend palliative chemotherapy only for solid tumor patients with good Eastern Cooperative Oncology group (ECOG) performance status (ECOG <3) [37].
  - Prigerson et al. showed that chemotherapy-refractory metastatic cancer patients with good ECOG performance status who received additional palliative chemotherapy will have significantly worse quality of life at the end of life than those who did not receive chemotherapy [38].
- If the patient has not received chemotherapy before, or their cancer has had previous response to the chemotherapy, palliative chemotherapy may be an option.

- Standard doublet therapy with cisplatin or carboplatin and a second agent such as a taxane is superior to single-agent therapy [39].
- In a Phase III RCT, cisplatin and pemetrexed was found to be more active in patients with nonsquamous histology, while cisplatin and gemcitabine were more active in squamous histology [40].

Palliative Radiation

- Palliative radiotherapy has a role in treatment of symptoms including cough, shortness of breath, hemoptysis, bronchial or tracheal obstruction, or superior vena cava obstruction.
- Many randomized trials have assessed palliative dose fractionation for locally advanced lung cancer, though many of these studies were completed before wide use of modern CT simulation and computerized treatment planning [41–43].
  - The studied regimens have ranged from as short as a single 10 Gy fraction to as lengthy as 50–60 Gy in 25–30 fractions.
  - Though there is not a single defined optimal dosing schedule, shorter fractionation schedules (10 Gy in 1 fraction, 17 Gy in 2 fractions over 2 week, and 20 Gy in 5 fractions) are equally efficacious in providing palliative relief with fewer side effects (1991; 1992) (See Table 8.3).

TABLE 8.3 Common Dose and Fractionation Scheme for Palliative Radiotherapy

Common Dose Fractionation	Benefit >2 Weeks	References
10 Gy × 1 fraction	Dyspnea 45%	MRC [44], Erridge [45]
	Cough 51%	
	Hemoptysis 88%	
8.5 Gy × 2 fraction q week	Dyspnea 49%	Sundstrom [46]
	Cough 44%	
	Hemoptysis 70%	
4 Gy × 5 fraction	Dyspnea 54%	Bezjak [47]
	Cough 46%	
	Hemoptysis 80%	
3 Gy × 10 fraction	Cough 56%	MRC [48]
	Hemoptysis 86%	

- Palliative improvement with either short- or longer-course radiation has been shown to improve dyspnea (40–97%), hemoptysis (77–92%), cough (60–91%), superior vena cave syndrome (51–96%), and pain (70–78%).
- When deciding on the most appropriate fractionation scheme, a patient's age, performance status, pulmonary function, presence of pleural effusion, and metastatic disease burden should be taken into account [42].

- Radiation for collapsed lung
  - 71% of patients who received 30–60 Gy to the obstructive tumor in the mainstem bronchus within 2 weeks after radiological evidence of atelectasis had complete reexpansion of their lungs, whereas only 23% of patients who received radiation greater than 2 weeks had reexpansion [49].
  - If there are plans for definitive radiation, then large dose per fraction (3–4 Gy/fraction) should not be pursued since it will limit the radiation dose for future treatment. If the lesion is amenable to endobronchial management (debridement, stent, or even brachytherapy), this should be considered first. Some patients have collapsed lobe on imaging but are asymptomatic (especially if both ventilation and perfusion are affected, i.e., a "matched defect").
  - If patient is neutropenic, consider prophylactic antibiotic due to risk of sepsis after reexpansion of lung.
- Radiation for intubated patient
  - Intubated patient with near complete consolidation due to either intrinsic or extrinsic airway obstruction (i.e., endobronchial disease, or hilar LN or mass that is central enough to compress on the airway) should be managed endobronchially first if there is endobronchial disease, since patient is already intubated. Debridement would have more immediate benefit than stent. If stent is placed, palliative dose would be the same even if no stent is present.
  - The addition of concurrent chemotherapy with external beam radiotherapy does not improve symptom improvement and may add unwanted toxicity [42].
- The use of highly conformal therapy such as stereotactic body radiotherapy (SBRT) for locally advanced lung cancer holds promise, but has not yet been extensively studied [42].
  - Single institution trials of SBRT showed no benefit in overall survival.
  - Approximately 25% of patients have partial or complete bronchial strictures resulting in secondary loss of normal lung volume [50].
- Side effects associated with palliative radiation therapy
  - Worsened fatigue, dysphagia, and esophagitis resulting in weight loss.
  - Increase shortness of breath with radiotherapy to the lung in patients with preexisting chronic obstructive pulmonary disease.
  - Patients should be counseled regarding the potential acute effects of radiation against benefits.

- Supportive care for intubated patient
  - In an intubated patient in the ICU, all options could be considered to determine what might be most effective to alleviate obstruction. Possibilities might include trial of bronchoscopy with cryotherapy or laser therapy, possible stent placement, or XRT. Decision about whether or not to proceed would depend on location of obstruction, acuity, and patient's overall prognosis and goals of care.

Brachytherapy (Intraluminal)

- High dose rate (HDR) endobronchial radiation can be used as an adjuvant therapy following stenting procedures to delay regrowth of the obstructive mass.
  - Polyethylene afterloading catheters are positioned in place with flexible or rigid bronchoscopy.
  - Intraluminal brachytherapy is limited to smaller tumors [51].
    - The effective dose distance of endochronichial HDR brachytherapy is 0.5−2 cm from the source.
  - Typical doses prescribed are 20−30 Gy total dose at 2 cm.
- Intraluminal brachytherapy is considered for symptomatic recurrence of intraluminal disease that has previously been treated with EBRT [42].
- The addition of endobronchial brachytherapy to external beam radiotherapy has not been shown to significantly add to symptom control.

Helium/Oxygen Therapy

- Heliox is a helium−oxygen gas mixture that reduces work of breathing by decreasing airway resistance by decreasing turbulent flow and thereby decreasing airway resistance.
- Has been used in multiple medical situations including postextubation laryngeal edema, tracheal stenosis, and angioedema [52].
- Two case studies demonstrated the use of the helium/oxygen mixture to manage severe upper-airway obstruction associated with tumor [53].
- Improvement in breathing and dyspnea is only temporary (CAO is still present).

SUMMARY

- Management of malignant central airway obstruction requires direct visualization with flexible or rigid bronchoscope to determine the extent and location of the obstruction.
- Although rigid bronchoscopy is difficult to perform without advanced training and requires general anesthesia, it does allow for greater debulking of the obstructive mass and provide greater choices of interventions for the pulmonologist as compared to flexible bronchoscopy.

- Multiple strategies to alleviate the obstruction are now available, including bronchial stent, cryotherapy, palliative external beam radiotherapy, and intraluminal brachytherapy.
- Decision about which strategy to employ should be based upon the patients overall condition and the therapies available.

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Chapter 9

Malignant Bleeding

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Chapter Outline

Scope of the Problem 119
Goals of Care, Communication, and Assessment 120
Local Therapies 121
- Dressings, Packing, and Topical Agents 121
- Radiation Therapy 121
- Endoscopic Procedures 122
- Transcutaneous Embolization 122
- Surgery 123

Treatment Options by Site of Hemorrhage 123
- Skin Lesions 123
- Hemoptysis 124
- Vaginal Bleeding 125
- Gastrointestinal Bleeding 126
- Hematuria 126

Systemic Therapies and Considerations 127
- Antifibrinolytics: Tranexamic Acid to Minimize the Risk of Bleeding 127
- Discontinuation of Causative or Exacerbating Agents 128

Conclusion 128
References 129

SCOPE OF THE PROBLEM

Approximately 10% of patients with advanced cancer will have at least one bleeding episode. For those patients with hematologic malignancies, that number rises to almost 30% [1]. These events vary in severity from low-grade oozing to major episodic bleeding to catastrophic bleeds. Bleeding events can be caused by local tumor invasion or abnormal tumor vasculature and can be categorized as epistaxis, hemoptysis, hematemesis, hematochezia, melena, hematuria, and vaginal bleeding. Immunotherapies, such as bevacizumab, nonsteroidal antiinflammatory agents, and anticoagulants, can exacerbate bleeding. These agents are routinely used in cancer patients due to their high-propensity to have painful bone metastasis and cancer-induced coagulopathies. Chemotherapy-induced thrombocytopenia also predisposes patients to bleeding. Tumor regression or prior radiation therapy can also cause bleeding.

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There are no randomized therapeutic trials of palliative interventions to provide hemostasis in the context of advanced malignancy and a lack of consistent outcome measures, time points, and methods of assessment in the literature that does exist. The literature discussed in this chapter includes reports of single modality interventions without consistent definitions of bleeding or response to therapy. There are very few good overviews of multimodality treatment of bleeding at all body sites due to advanced cancer. This is likely due to the heterogeneity of the patient population, the various sites affected by bleeding, and the fact that the modalities utilized to treat bleeding spans multiple medical specialties which make randomized trials difficult. Much of the literature is retrospective which makes prospective endpoint definition and evaluation nearly impossible. Some of this is inherent in the heterogeneity of the problem, the terminal nature of advanced cancer, and the availability of institutional resources and expertise.

GOALS OF CARE, COMMUNICATION, AND ASSESSMENT

In patients at high risk for bleeding or who are suffering from the effects of bleeding, goals of care should be explored as therapies are considered. The extent to which the bleeding is visible or disturbing to patients and the adverse effects on quality of life should be examined. The quantity of a patient's remaining life should be estimated and used to determine the most appropriate therapies. Prognostic models can be used to estimate life expectancy [2–8]. Radiation therapy can control bleeding within 24–48 hours in most cases; however, patients have to be comfortable lying on the table for the radiation planning and treatment process. Surgery can be helpful in the management of bleeding tumors; the expected difficulty and duration of the recovery should be considered in the context of a person's remaining life and goals of care.

For those patients at risk for catastrophic bleeding events, it is important to prepare the patient and their family for the visually and mentally disturbing effects of such a bleed. Encourage the use of dark sheets, towels, blankets, and clothing to dampen the visual shock of seeing massive bleeding from a loved one. Fast-acting sedatives, such as intravenous or subcutaneous midazolam, should be readily available; families should be instructed on their use if the patient is at home. Terminal or palliative sedation may be appropriate for bleeding at the end of life. Often, however, death occurs rapidly in this setting; unless intravenous access is already in place, there may be very little time.

For those patients not at the end of life who suffer a major but noncatastrophic episode of bleeding, establishment of intravenous access, stabilization with fluids, and hemodynamic monitoring can allow further investigation into the cause of bleeding and treatment, if appropriate. Laboratory analysis should include a complete blood count, a coagulation profile, a complete

metabolic panel with assessment of liver enzymes and function. Further investigation may include computed tomography of the area suspected of bleeding, angiography, and/or endoscopy. Comorbidities, current medications, and recent therapeutic interventions may also be contributing factors. The risks of further bleeding in the setting of anticoagulation should be balanced against the risks of further clotting.

LOCAL THERAPIES

Dressings, Packing, and Topical Agents

- Nonadherent dressings can be applied to bleeding lesions of the skin.
- Packing can be utilized for bleeding involving the nose, vagina, and rectum.
- Various topical agents, such as absorbable gelatin or collagen, utilized to control surgical bleeding can be utilized for accessible skin or mucosal surfaces.
- Vaginal packing can be soaked with paraformaldehyde. Moh's paste and Monsel's solution can be applied topically to areas of vaginal bleeding [9].

Radiation Therapy

- Radiation therapy has been demonstrated to decrease hemoptysis [10–20], hematuria [21–23], vaginal bleeding [24], and bleeding from the GI tract (melena, hematemesis, and hematochezia) (Table 9.1) [25].
- Radiation therapy to palliate bleeding can be effective within 24–48 hours of the delivery of the first dose. Patients must be hemodynamically stable to safely be transported to radiotherapy departments for treatment.
- Various fractionation schemes have been described in the palliative setting. These include short courses of 8–10 Gy in a single fraction, intermediate courses of 4–8 Gy in 3–5 fractions, or longer courses of 3 Gy in 10–15 fractions.
  - No scheme has been determined to be better than any other in the palliation of hemorrhage. At least one randomized trial of radiation fractionation suggests fewer side effects with shorter courses of treatment [26].
  - Some of these hypofractionated regimens have been used in patients that are medically frail with otherwise curable cancers. In these situations, the highest dose per fraction schemes may be less appropriate given that the longer life expectancy of these patients puts them at higher risk for the development of potential late complications of radiation therapy.

- For patients with advanced and metastatic cancers, shorter courses of radiation offer equal or better palliation with increased convenience and decreased cost [27].

- Delivery of additional radiation therapy may be difficult if the patient previously received radiation therapy to the same site. Re-irradiation can be considered if the benefits of retreatment outweigh the risks. Care must be taken to respect normal tissues constraints in most circumstances, especially of the spinal cord.

Endoscopic Procedures

- Bronchoscopy, esophagogastroduodenoscopy (EGD), cystoscopy, and colonoscopy have been utilized to identify and treat bleeding tumors in the organs visualized through each procedure.
- Cautery, argon plasma coagulation (APC), deployment of clips, injection of epinephrine or other sclerosing agents, laser, and other adjunctive therapies have been described. Varying rates of success and rebleeding occur.
- Endoscopic interventions are most successful in the treatment of less advanced and nondiffusely bleeding tumors. The existing literature describing the utility of these procedures are not limited to patients with advanced cancer.
- Two small series describe the application of a hemostatic powder to a bleeding tumor. Hemostasis was reported in 100% of patients but rebleeding remains a problem [28,29].
- APC is a noncontact thermal cautery with a depth of penetration of 2–3 mm.
  - Argon is a nonflammable gas that is ionized by a high-voltage spark.
  - Immediate hemostasis has been reported to be 100% but rebleeding occurs in 30% of patients [30].

Transcutaneous Embolization

- Transcutaneous embolization of vessels has been described to embolize bleeding vessels in many organ sites and malignant processes. Various mechanical devices and materials are utilized to achieve vascular embolization [31].
  - Mechanical devices, such as coils, are defined by the size of their core, diameter, and length.
  - Various biodegradable or permanent sclerosing agents can be injected depending on the indication for embolization.
  - Permanent agents, such as polyvinyl alcohol or microspheres, are used for embolization of malignant bleeding [32].
- Patients must be able to lie flat for the duration of the procedure.

- Limitations of vascular embolization include the ability to identify and catheterize the bleeding vessel and to selectively embolize the blood supply of the tumor and protect vessels supplying normal tissues.
  - Arterial access is accomplished through one of the major arteries, e.g., the femoral, popliteal, brachial, and radial arteries.
  - Care must be taken to ensure that preexisting coagulopathies are corrected and that the patient is hydrated as contrast agents are utilized to visualize the vasculature.
- Successful hemostasis occurs in 70–99% of patients [33].
- Rebleeding can occur early, usually due to incomplete embolization, or late, due to recanalization of the vessels.
- Complications include local site bruising or hematoma, bleeding, coil migration, vessel occlusion, and postembolization syndrome.
- Tumor necrosis induces pain, flu-like symptoms, nausea and vomiting which can last for several days [32,33].

Surgery

- Various surgical procedures can provide relief of bleeding when the level of bleeding, the patient's expected remaining life and lack of other good options warrant it.
- Surgical options range from ligation of vessels to resection of the tumor and/or bleeding organ.
- Laparoscopic procedures may result in less acute morbidity than open ones but may be associated with a higher cost.
- Additional considerations include the risks of anesthesia.

TREATMENT OPTIONS BY SITE OF HEMORRHAGE

Skin Lesions

- Skin lesions are very visible manifestations of metastatic disease that can ooze, bleed, have a foul odor, or be painful.
- Nonadherent dressings can be applied to manage bleeding.
- Local therapies include surgical excision, radiation therapy, and other ablative therapies.
- For superficial lesions, laser or cryotherapy may be sufficient.
- Electrochemotherapy combines a cytotoxic agent with electrical impulses that increase the permeability of the cell membrane, which enhances uptake of the cytotoxic drug.
  - Response rates of 77–87% have been reported with bleomycin. Local or general anesthesia is generally required to alleviate the painful muscle contractions caused by the electrical impulses [34].

- Intratumoral injection of interleukin-2 (IL-2) has been associated with response rates of 70–80%. It is delivered in doses of 3–18 MIU per session at 2–3 sessions per week. Isolated limb perfusion is usually reserved for melanoma and sarcoma [34].
- Palliative radiation can be very helpful in the management of pain and bleeding from skin metastases.
  - Given that the goal of radiation is to palliate symptoms rather than completely eradicate the tumor, hypofractionated regimens such as 8–10 Gy in a single fraction or 20 Gy delivered in 5 fractions should be considered.

Hemoptysis

- Depending on the amount of hemoptysis and the wishes of the patient, it may be necessary to protect the airway by intubation.
- Single lumen tubes allow passage of a standard flexible bronchoscope, but do not permit reliable lung isolation.
- Rigid bronchoscopy is useful for large volume bleeding to airway control and rapid suctioning, but requires expertise and is challenging to perform outside the operating room.
  - Temporary control of bleeding can be affected with balloon catheters via the scope.
  - Blood clots can be suctioned and visualization of the airways can help determine the source of the bleeding.
  - Various therapeutic interventions can be performed including balloon tamponade, iced saline lavage, Nd-YAG laser coagulation, electrocautery, or APC.
  - Reported hemostasis ranges from 60% for Nd-YAG laser to 100% for APC [35].
- For lesions not amenable to bronchoscopic intervention, bronchial artery angiography with embolization may be appropriate.
  - Angiographic signs of hemoptysis include tumor blush and active extravasation.
  - Many studies of bronchial artery embolization are not limited to those with cancer, thus accurate response rates are difficult to determine.
  - Care must be taken to visualize and avoid the spinal artery as spinal cord injury can result from bronchial artery embolization [36].
- Radiation therapy is very successful at palliating hemoptysis, with rates of hemostasis in 80–97% of patients [10,16].
  - Various fractionation regimens have been employed ranging from 17 Gy in two weekly fractions of 8.5 Gy, 20 Gy in 5 fractions of 4 Gy and 30–39 Gy in 10–13 fractions of 3 Gy.
  - No consistent significant differences in rates of palliation have been reported.

- Several studies, which were not powered to detect a survival benefit, and include otherwise curable patients, demonstrate conflicting results regarding survival.
  - Both longer fraction courses of 30–39 Gy in 10–13 fractions of 3 Gy [14,15] and shorter course of 17 Gy in 2 fractions of 8.5 Gy [17,19] have been shown to result in improved survival.
  - The increased convenience and decreased costs of the shorter courses and lack of data supporting longer courses of radiation favor their use [10,17,19].
  - Radiation myelitis has been reported rarely in patients who survive for at least 9 months; [37] three-dimensional conformal radiation therapy techniques can be used to decrease the dose to the spinal cord and mitigate this small risk.

Vaginal Bleeding

- Vaginal bleeding occurs commonly in advanced cervical and endometrial cancer and accounts for 6% of deaths from cervical cancer.
- Treatments should be tailored to the available resources and the wishes of the patient.
- Topical therapies include vaginal packing that can be soaked with paraformaldehyde or application of Moh's paste or Monsel's solution to areas of vaginal bleeding.
- If interventional radiology services are available, uterine or iliac artery embolization can be performed.
  - As with embolization in other settings, mechanical devices, such as coils, or sclerosing agents help achieve embolization.
- When interventional radiology is not available, surgical ligation of vessels is a more invasive treatment option [9].
- When radiotherapy is available, palliative radiation therapy can be directed to the uterus and/or cervix.
  - An early RTOG phase I/II investigated large (10 Gy) fraction radiation therapy for palliation of advanced pelvic malignancies, repeated at monthly intervals with misonidazole.
    - Though there was approximately 40% complete or partial response rate seen, there was an unacceptably high level of gastrointestinal complications seen [38].
  - Many other fractionation schemes are effective for the palliation of bleeding, including 3.7 Gy BID in 4 fractions, 20 Gy in 5 fractions, and 21 Gy in 3 fractions given over 3 weeks.
  - Care must be taken when using large fraction sizes in frail patients with curable disease who may live long enough to be at risk for late complications of radiation therapy.

TABLE 9.1 Palliative Radiotherapy Fractionation for Bleeding From Various Sites

	Palliative Intent	Curative Intent***
Skin lesions	8 Gy/1 fraction or 20 Gy/5 fractions	Per NCCN guidelines
Hemoptysis	17 Gy in 2 fractions, 1 week apart	2–3 fractions at 3–4 Gy followed by definitive radiation to the equivalent of ~60 Gy at 2 Gy/fraction
GI, GU or GYN bleeding	20 Gy in 5 fractions or 7 Gy × 1 repeated weekly up to 3 times (total 21 Gy)	If curable but medically frail, limit fraction size, or total dose

***For curative intent patients with bleeding, a few fractions (2–3) can be delivered at 3–4 Gy per fraction followed by definitive radiation to the appropriate curative dose.

Gastrointestinal Bleeding

- Though palliative radiation therapy has been utilized to treat bleeding from various gastrointestinal tumors, there is relatively sparse data reporting outcomes.
- Hemostasis from locally advanced gastric cancer has been reported in 50–73% of patients treated with radiotherapy.
  - A variety of palliative radiotherapy regimens have been employed [39].
  - The wide reported range of hemostasis may stem in part from the varying definitions of success which include no further bleeding, to decreased transfusion requirements, to an increase in hemoglobin levels.
- In rectal cancer, a recent systematic review reported the combined results of 23 retrospective and four prospective series. Hemostasis was achieved in 81% of patients [40].

Hematuria

- Tumor invasion of the bladder often causes hematuria.
- Initial therapies may include bladder irrigation and discontinuation of any medications that may increase the bleeding risk, such as NSAIDs or anticoagulants.
- Transurethral resection of the bladder with coagulation may control the bleeding. Other surgical options include cystectomy with urinary diversion.
- Nonsurgical options include radiation therapy.

- Various palliative fractionation schemes ranging from 3 to 8 Gy per fraction have been utilized and report 50–92% hemostasis [41].
- Renal artery embolization [32] can palliate flank plan or hematuria caused by malignant kidney tumors.
- Embolization of branches of the anterior trunk of the iliac artery can provide hemostasis of bladder tumors [42].
- Intravesicular formalin instillation is no longer routinely used for the treatment of hematuria due to discomfort, the risk of renal failure, and requirement for general or spinal anesthesia [43].
- Intravesicular instillation of alum or prostaglandins have varying rates of hemostasis.
  - Like formalin, it causes protein precipitation that occludes bleeding vessels.
  - Bladder spasms can be induced that can generally be controlled with the use of antispasmodics [43].
  - Prostaglandin treatment is generally reserved for the case of alum failure due to issues of cost, availability, and storage [42].

SYSTEMIC THERAPIES AND CONSIDERATIONS

- Blood and blood products can be given to resuscitate hemodynamically unstable patients and treat patients who are actively bleeding.
- The AABB (formerly the American Association of Blood Banks) provides evidence-based guidance on the transfusion of red blood cells, platelets, and plasma [44–46].
- The role of transfusions in the palliative care of patients with advanced malignancy is less clear. Symptomatic improvement in patients with advanced cancer has been described [42].
- Vitamin K can be used to correct bleeding in a patient on warfarin or with deficiencies in the vitamin K dependent clotting factors, which include factors II, VII, IX, and X. Vitamin K can be administered orally, subcutaneously, or intravenously.

Antifibrinolytics: Tranexamic Acid to Minimize the Risk of Bleeding

- Tranexamic acid has not been formally studied in advanced cancer.
  - In trauma patients, it reduces mortality due to bleeding by approximately one-third.
  - There have been minimal side effects associated with its administration.
  - There is no dose response for its therapeutic effect, but there is an increase in neurologic complications with increasing doses of tranexamic acid.

- In elective surgery, metaanalyses have demonstrated a reduction in blood loss and transfusion requirements by approximately one-third [47,48].
- Current studies are evaluating its use in gastrointestinal bleeding.
- None of the studies to date have demonstrated an increased thrombotic risk with the use of tranexamic acid.
- Recommended dosing is 10 mg/kg per dose, with no benefit to doses above 1 g, administered intravenously every 6−8 hours [49].

Discontinuation of Causative or Exacerbating Agents

- A thorough assessment of potential causative or exacerbating agents is a critical component of the assessment of patients who are bleeding. Full discourse on all of the medications that fall into this category are beyond the scope of this chapter.
- NSAIDs are often utilized in the care of patients with advanced malignancy to treat pain. These have definite antiplatelet and anticoagulant properties.
- Patients with advanced cancer are at increased risk of coagulopathies and are often anticoagulated with warfarin or enoxaparin.
- The risk of further bleeding must be weighed against the risks of additional deep venous or pulmonary thromboembolism.
- Patients with cancer who are anticoagulated suffer bleeding complications at a higher rate than those anticoagulated without malignancy [50].
- Chemotherapeutic agents and radiation therapy may add to the risk of bleeding by causing thrombocytopenia. These treatments can be held to let the bone marrow recover.

CONCLUSION

Bleeding due to advanced cancer is common. The approach to the bleeding cancer patient depends on the type of bleeding and the site of bleeding. It includes hemodynamic stabilization and care consistent with the patient's goals of care. Agents that exacerbate bleeding, e.g., anticoagulants, should be discontinued and blood products given as indicated.

Accessible sites, e.g., the nose, skin, and vagina, can be packed and treated with topical agents. More invasive therapeutic interventions include endoscopic treatment, percutaneous embolization, surgery, and radiation therapy. There are limitations of the available literature on the topic of bleeding in advanced cancer which include few prospective studies solely focused on the treatment of bleeding in advanced cancer, the lack of consistent endpoints, and no randomized trials of the various therapeutic interventions. Treatment should be individualized based on the patient's preferences and resource availability.

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Chapter 10

Skin Toxicity in Palliative Radiation Therapy

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Chapter Outline

Introduction 133
Acute Skin Toxicities From Radiation 134
Pathology and Timeline 135
Grading of Toxicity 136
Prevention 137
Treatment 139
Chronic Skin Toxicities From Radiation 140
Pathology 140
Grading 141
Prevention 143
Treatment 143
Radiation Recall Dermatitis 144
Conclusion 145
References 145

INTRODUCTION

- Radiation-induced skin toxicity is a commonly reported toxicity of definitive radiation therapy, with almost half of patients reporting grade 2 or higher skin reactions [1]. Multiple factors, both radiation- and patient-specific, contribute to the likelihood of developing skin toxicity. Radiation-specific factors include total dose, dose per fraction, beam energy, size of field, anatomic location of the radiation, and concomitant systemic treatments. Patient-related factors, particularly age and comorbidities, also influence the likelihood of developing toxicity.
- Skin is composed of an outer epidermis above a layer of dermis (Fig. 10.1). The epidermis has two layers, an outer protective layer and an underlying basal layer. The dermis is composed of collagen and elastic fibers that helps to give sturdiness to skin. The blood supply for the epidermis is supplied by the underlying dermis [2]. Hair follicles, sebaceous glands, and sweat glands are contained within the dermis and hypodermis. Sebaceous glands are associated with hair follicles and secrete sebum, which acts to lubricate and waterproof the skin and hair [2].

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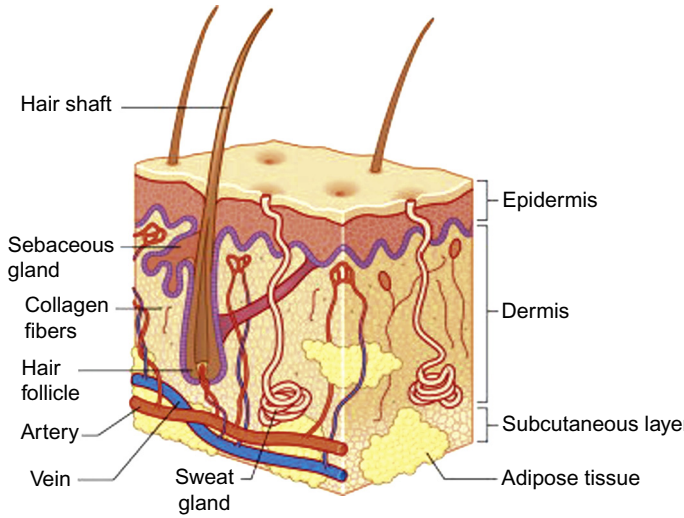

FIGURE 10.1 Skin anatomy.

Epidermal cells, hair follicles, and sebaceous glands all contain rapidly dividing cells that are exquisitely sensitive to radiation.

- Radiation can cause both acute and late toxicity to the skin. Acute toxicity, often occurring around 2 weeks after the start of radiation, can manifest as dryness, itchiness, pain, hair loss, and desquamation. Late toxicity, occurring months to years after the completion of radiation, can present as fibrosis, telangiectasias, changes in skin pigmentation, and wound healing issues.
- With most palliative doses of radiation (ranging from 8 Gy × 1 to 3 Gy × 10) the rates of acute and late skin toxicity are low. RTOG 9714 randomized patients with uncomplicated bony metastases to either single-fraction (SF, 8 Gy × 1) or multifraction (MF, 3 Gy × 10) radiation. There was a very low rate of acute skin toxicity in both arms (4% in SF vs 12% in MF), with the majority being grade 1. The late toxicity was even less common (2% SF vs 1% MF), with again the majority being grade 1 [3]. In studies done on re-irradiation, the acute skin toxicity was slightly higher, although still very low (16% in SF vs 22% in MF) at 7 days after radiation [4].

ACUTE SKIN TOXICITIES FROM RADIATION

- Acute reactions to the skin from radiation include erythema, hyperpigmentation, dryness, pain, itchiness, hair loss, and desquamation. The severity of acute reactions can vary greatly between patients due to multiple factors including total radiation dose, dose per fraction, beam energy

used, size of radiation field treated, concomitant systemic therapy, and anatomic location of the radiation. Additionally there are patient-related factors including age, connective tissue disorders, and comorbidities that are not fully understood but also play a role in determining the severity of the reaction.

Pathology and Timeline

- The initial reaction to radiation is often erythema, although not always visible to the human eye, that can occur within a few hours and is caused by capillary dilatation and increased capillary permeability [5].
- Ten to fourteen days after the start of radiation, sustained erythema, likely mediated by cytokines, becomes apparent (Fig. 10.2) [6].
- With continued radiation, generally with doses of radiation above 40 Gy, one can see moist desquamation characterized by vascular dilatation, epidermal necrosis, fibrinous exudates, and pain (Fig. 10.3). Histologically, fibrin thrombi obstruct arterioles, extravasation of erythrocytes and leukocytes, as well as edema can be seen [5,6].
- The peak skin reaction occurs between 1 and 2 weeks after the completion of radiation therapy with regeneration occurring between weeks 3 and 5 [6]. The majority of patients will have completely recovered from their acute toxicities by 3 months after treatment, although often much sooner.
- Hair follicles, sebaceous glands, and sweat glands are also affected by radiation and can lead to dry skin and hair loss. Although hair loss often doesn't occur for a few weeks, generally the damage was done early in

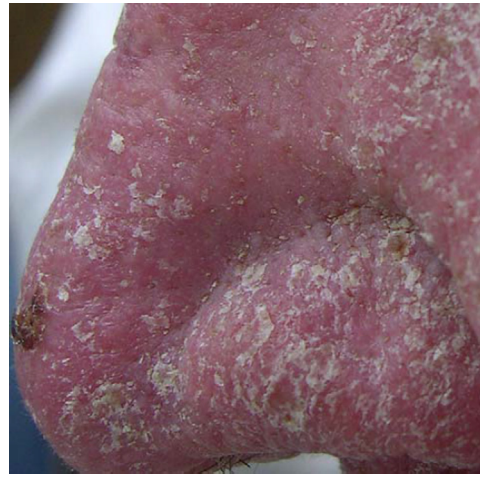

FIGURE 10.2 Acute grade 2 dermatitis (erythema and dry desquamation).

the radiation course [5]. New hair can take up to 1 year to regrow and in some situations the hair loss can be permanent.

Grading of Toxicity

- The two most widely used scales for grading acute adverse events due to cancer therapy are the National Cancer Institute's Common Toxicity Criteria for Adverse Events (CTCAE) version 4 [7] and the Radiation Therapy Oncology Group (RTOG)/European Organization for Research and Treatment of Cancer (EORTC) grading system [8]. Both of these tools have specific criteria for acute radiation toxicity to the skin (Tables 10.1 and 10.2) and allow for consistent grading between practitioners.

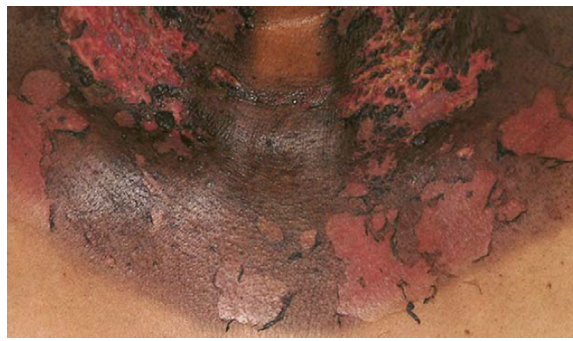

FIGURE 10.3 Acute grade 3 dermatitis (erythema, hyperpigmentation, and moist desquamation).

TABLE 10.1 CTCAE v. 4

Dermatitis Radiation **Definition: A finding of cutaneous inflammatory reaction occurring as a result of exposure to biologically effective levels of ionizing radiation**	
Grade	**Description**
1	Faint erythema or dry desquamation
2	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skinfolds and creases; moderate edema
3	Moist desquamation in areas other than skinfolds and creases; bleeding induced by minor trauma or abrasion
4	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated
5	Death

TABLE 10.2 RTOG/EORTC

Skin (Acute)	
Grade	**Description**
0	No change over baseline
1	Follicular, faint, or dull erythema/epilation/dry desquamation
2	Tender or bright erythema, patchy moist desquamation/moderate edema
3	Confluent, moist desquamation other than skinfolds, pitting edema
4	Ulceration, hemorrhage, necrosis

Prevention

- There is wide practice variation between institutions and even practitioners regarding the use of agents for prevention of radiation dermatitis. Most fall into one of two schools of thought regarding prophylaxis. Some believe in having patients use moisturizer up front, thinking that it can help prevent dry skin and delay the onset of acute toxicity. Others believe there is no benefit to initiation of moisturizer before the development of symptoms and cite concerns over confusion that could occur if the patient has a reaction to the lotion.
- Although there are many publications regarding the use of different products to prevent the development of radiation dermatitis, mostly within the breast and head and neck literature, the data can be contradictory and confusing. However on some topics, such as the use of routine washing and the use of antiperspirant, the literature is clear.
- *Hygiene*: Three trials evaluated and found no detriment to the use of routine washing with soap or shampoo and water during radiation therapy [9–11]. All three recommended continued normal hygiene practices during the course of radiation.
- *Antiperspirant*: Some practitioners believe the use of antiperspirant during radiotherapy could lead to a bolus effect on the skin, thereby worsening radiation toxicity. At least four randomized controlled trials have shown no difference in toxicity with the use of antiperspirant, even in preparations containing aluminum, compared to gentle washing alone [12–15].
- *Topical Steroids*: Multiple randomized controlled trials have been done examining the role of topical steroids to prevent or ameliorate acute radiation dermatitis. Although the trials are heterogeneous, the outcomes have consistently shown a benefit to use of topical steroids [16–20].
- *Topical Trolamine*: Trolamine, an oil-in-water emulsion with nonsteroidal antiinflammatory properties, has been relatively widely studied. The results

of the published data is mixed with some trials showing a benefit to the use [21,22] and others showing no benefit [23–26].

- *Topical Aloe vera*: As *Aloe vera* is a commonly used treatment for a variety of skin conditions, from dry skin to sunburns, it is a natural extension to believe it may be helpful to prevent radiation dermatitis. Results from one trial suggested a benefit to the use of *Aloe vera* gel in delaying the onset [27], however, multiple trials as well as a systemic literature review did not find evidence to suggest a benefit [28–30].
- *Topical Hyaluronic Acid*: Similarly the results from studies evaluating hyaluronic acid also show mixed results with some studies showing a benefit [31] and others failing to do so [32].
- *Topical Sucralfate*: Three different trials evaluating the use of topical sucralfate have shown three different outcomes: a benefit [33], no difference [34], and possibly a detriment [35].
- *Topical Petroleum Ointments*: Aquaphor, a petroleum-based ointment, is a very commonly recommended topical treatment during radiation therapy. The published data on Aquaphor for prevention is mostly as a control arm and thus is difficult to determine effectiveness. However, there is some data that suggests there is no benefit to petroleum-based treatment compared to control [16,26]. Additionally, the study by Gosselin et al., also looked at RadiaCare gel and again did not find a benefit over control [26].
- *Topical Calendula*: One randomized control trial has evaluated the use of calendula (vs trolamine) and found an improvement in rate of acute dermatitis and patient satisfaction with calendula [23].
- *Oral Agents*: Minimal data has been published on the use of oral agents for prevention of radiation dermatitis. Two randomized, although not blinded, control trials comparing oral proteolytic enzymes (a combination of papain, trypsin, and chymotrypsin) to no treatment showed improvement in acute radiation side effects, including dermatitis [36,37]. Preclinical data and a single small double blind randomized control trial have suggested that oral zinc supplementation may decrease acute radiation dermatitis [38,39]. Studies on other oral agents, such as oral sucralfate and oral pentoxifylline, have not shown benefit to the development or severity of acute radiation dermatitis [40,41].
- The Multinational Association for Supportive Care in Cancer (MASCC) published guidelines in 2013 after a thorough review of the literature.
  - A strong recommendation was made for washing of the skin and hair with water, either with or without a mild soap or shampoo, as well as allowing patients to use antiperspirants. Additionally, a strong recommendation for use of topical steroids to prevent radiation dermatitis was made [42].
  - The MASCC recommended against the prophylactic use of *Aloe vera* or trolamine. For multiple other agents, sucralfate, hyaluronic acid, silver

dressing, silver sulfadiazine cream, and others they did not make a recommendation for or against use due to insufficient evidence [42].

- *Other Skin Care Tips*: Other tips on skin care given to patients undergoing radiation therapy include staying out of the sun, wearing loose clothing, avoiding extreme heat or cold (i.e., heating pads or ice packs) directly onto the skin being treated, and avoiding products with alcohol or scents. Additionally, for those patients who are getting treated to the face or neck, it is advisable to use an electric razor rather than a manual one. For patients getting treated to the head, gentle brushing of hair and avoiding use of styling tools (i.e., curling irons, straightening irons) is recommended.

Treatment

- Despite a thorough literature review there is a paucity of well designed, blinded, randomized trials evaluating treatment options. The intervention with the most data is on the use of dressings, however, the outcomes of these studies are mixed, with some showing longer healing times with use of moist dressings [43,44], while others showed faster healing times [45]. Additionally, there are a few publications on the use of topical steroids, none of which showed a benefit compared to their control group [46,47]. Sucralfate has also been studied and has found to have no benefit when mixed with sorbolene cream versus sorbolene cream alone [48].
- In lieu of randomized evidence, many institutions and practitioners have developed treatment recommendations for patients.
  - Once a patient develops erythema, hypopigmentation, or dry desquamation, a common recommendation is for use of an emollient-based cream, such as Aquaphor, RadiaCare, or Biafine.
  - If the patient has pain or burning, a mixture of Aquaphor mixed with lidocaine jelly (1:1 formulation) can be prescribed.
  - Oral pain medication can also be used for severe skin reactions, although this is rarely, if ever, seen when treating a patient to palliative doses.
  - If a patient notes itchiness, a topical steroid cream can be recommended. Steroid creams can be layered underneath or alternated with an emollient-based cream.
  - If moist desquamation occurs, Domeboro soaks, Silvadene, or Xenaderm can be used. An example treatment regimen is offered in Fig. 10.4.
- Specific recommendations for patients undergoing treatment to the lower pelvis (i.e., gynecologic cancers):
  - A recently published review [49] on complications of pelvic radiation gives some suggestions regarding treatment of skin toxicity in this unique population.

At start of radiation:

- **Provide tips for prevention regarding hygiene, clothing, etc.**
- **To consider asking patient to start using an unscented gentle white lotion at least daily.**
- **To consider asking patient to use a topical steroid cream based on above data.**

When dry desquamation develops:

- **Recommend treatment with Aquaphor, 2–4 times daily**

If itch develops:

- **Add a topical steroid cream (i.e.,hydrocortisone) to patient's skin care regimen. Can alternate with Aquaphor or layer Aquaphor over the top.**

If burning/pain develops:

- **Recommend Aquaphor with lidocaine: Aquaphor mixed 1:1 with lidocaine jelly**

If moist desquamation develops:

- **Continue Aquaphor (+– lidocaine)**
- **To consider Domeboro soaks**

FIGURE 10.4 Example regimen for skin care during radiation therapy.

- Recommendations are made for prophylactic moisturizing, encouraging loose cotton clothing, and the use of a sitz bath with addition of sodium bicarbonate, Epsom salt, or Domeboro soaks.
- Early identification and treatment for Candida is also recommended.
- For patients who develop desquamation, nonadherent, silver clear nylon or hydrogel dressings can be applied [49].
- Additional recommendations may include the use of a peri bottle to assist with cleansing and instructions to pat rather than wipe after urination.

CHRONIC SKIN TOXICITIES FROM RADIATION

- Late toxicity from radiation can begin to appear anywhere from months to years after radiation therapy is completed. The late toxicity from radiation includes telangiectasias, fibrosis, hypo- or hyperpigmentation (Fig. 10.5), dryness, ulcers, and difficulty with wound healing. The likelihood and severity of developing a late radiation reaction is not completely understood but likely depends on multiple factors including total dose, dose per fraction, and patient-related factors.

Pathology

- Radiation-induced fibrosis is characterized by thickening and reduced compliance of the skin. Histologically, excessive collagen deposition,

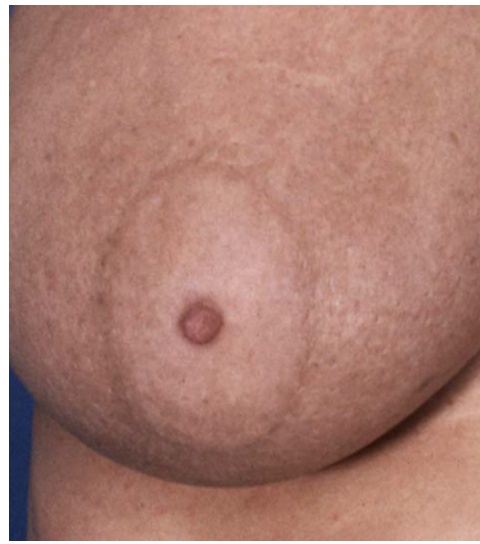

FIGURE 10.5 Late grade 1 dermatitis (hyperpigmentation).

atrophy, and excess mesenchymal cells are present [50]. Severity of acute injury does not seem to play a role in development of fibrosis, although total dose, dose per fraction, and other patient-related factors, such as age, have been shown to have an association [51,52].

- Telangiectasias (Fig. 10.6) are small dilated blood vessels close to the skin's surface. After radiation they appear as a result of damage to the microvascular endothelial cells and basement membrane [5]. Research into factors that influence the likelihood of developing telangiectasias have found an association with total dose of radiation, presence of severe acute injury (i.e., moist desquamation), as well as patient-related factors, such as age, long-term smoking, and certain comorbidities (allergies and hypertension) [52,53].
- Chronic dryness can be due to permanent damage to sebaceous and sweat glands.

Grading

- Similar to acute toxicity, commonly used grading tools include the RTOG/EORTC tool [8] as well as the Late Effect on Normal Tissue (LENT)/Symptom Objective Measures, Management, Assessment (SOMA) [54].
- The RTOG/EORTC grading tool has specific criteria for late skin toxicity (Table 10.3). The LENT/SOMA tool has a general grading system

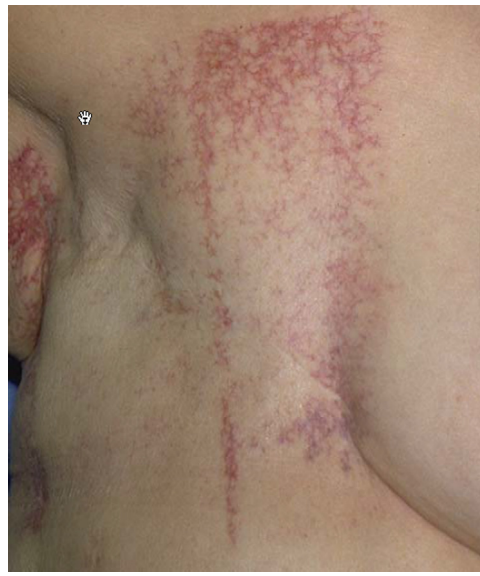

FIGURE 10.6 Late grade 2 dermatitis (telangiectasia).

TABLE 10.3 RTOG/EORTC

Skin (Late)	
Grade	**Description**
0	None
1	Slight atrophy, pigmentation change, some hair loss
2	Patch atrophy, moderate telangiectasia, total hair loss
3	Marked atrophy, gross telangiectasia
4	Ulceration
5	Death

(Table 10.4) as well as a more complex grading system for late skin toxicity with multiple factors separately assessed within categories of subjective, objective, management, and analytic. Examples of criteria within each category include scaliness/roughness, objective fibrosis/scar (Table 10.5), management fibrosis/scar, and color photographs.

TABLE 10.4 LENT/SOMA (General Grading System)

General	
Grade	**Description**
0	None
1	The most minor symptoms that require no treatment
2	Moderate symptoms, requiring only conservative treatment
3	Severe symptoms, which have a significant negative impact on daily activities, and which require more aggressive treatment
4	Irreversible functional damage, necessitating major therapeutic intervention

TABLE 10.5 LENT/SOMA (Symptom Specific—Fibrosis/Scar)

Objective—Fibrosis/Scar	
Grade	**Description**
0	None
1	Present/asymptomatic
2	Symptomatic
3	Secondary dysfunction
4	Total dysfunction

Prevention

- Little data has been published on the prevention of late toxicity from radiation. Early data suggests lower fibrosis scores at 18 months in patients who started pentoxifylline and vitamin E after the completion of radiation and continued for 6 months [55].

Treatment

- Similarly, minimal data is available regarding treatment of late toxicity from radiation.
- Pulse dye laser has been shown to improve the appearance of telangiectasias from radiation [56]. The MASCC skin toxicity study group gave a weak recommendation for the use of the pulsed dye laser to improve cosmetic appearance [42].

- The use of vitamin E and pentoxifylline in the treatment of radiation fibrosis has mixed results. A few studies have shown an improvement in fibrosis following use of pentoxifylline and vitamin E [57–59], however, other studies have not shown a benefit [60]. One study compared pentoxifylline combined with vitamin E, pentoxifylline alone, vitamin E alone, or placebo and found a benefit only in the combination of the two drugs [59].
- The MASCC Skin Toxicity Study Group notes insufficient evidence to make a recommendation either for or against the use of pentoxifylline for treatment of radiation-induced fibrosis [42].

RADIATION RECALL DERMATITIS

- Radiation recall dermatitis is a poorly understood and uncommon phenomenon where a skin reaction similar to an acute radiation dermatitis develops in a previously irradiated area. The onset of this reaction is most often associated with administration of a medication, either intravenously or orally. The severity of the reaction can range from mild to severe and does not appear to correlate with the severity of either the acute radiation reaction or late radiation changes.
- A large number of systemic agents (Fig. 10.7) have been linked to radiation recall reactions [61–67]. The time from radiation therapy to

Actinomycin D	Edatrexate	Pemetrexed
Adriamycin	Etoposide	Simvastatin
Azithromycin	Erlotinib	Sorafenib
Bleomycin	Everolimus	Sunitinib
Capecitabine	5-Flurouracil	Sunlight
Cetuximab	Gemcitabine	Tamoxifen
Cisplatin	Hydroxyurea	Temsirolimus
Cyclophosphamide	Interferon alpha	Trimetrexate
Cytarabine	Levofloxacin	Vemurafenib
Dacarbazine	Melphalan	Vinblastine
Daunorubicin	Methotrexate	Vinorelbine
Docetaxel	Oxaliplatin	
Doxorubicin	Paclitaxel	

FIGURE 10.7 List of agents thought to be associated with radiation recall reactions.

development of a radiation recall reaction varies widely from 7 days to 2 years, although some reports are up to 25 years postradiation.
  - In general, the shorter the time interval between the end of radiation therapy and the developing of a radiation recall dermatitis, the more severe the reaction [66,67].
  - It has been suggested that anything shorter than 7 days should be attributable to an acute radiation reaction rather than a radiation recall reaction [67].
- The time from drug exposure to the onset of dermatitis as well as the duration of the dermatitis varies greatly. Onset can occur immediately up to months after exposure [66,67]. The length of time the dermatitis persists also varies greatly from hours to weeks [66,67].
- Although there are suggestions that treatment with oral or topical steroids, antihistamines, or nonsteroidal antiinflammatory drugs shortens the reaction, there is no conclusive data on this topic.
- Additionally, whether a patient can be safely rechallenged with the offending agent is also controversial, with conflicting reports in the literature [67].

CONCLUSION

Radiation-induced skin reactions are common in definitive radiation but can also occur in palliative courses. Acute radiation toxicity, generally occurring during or shortly after treatment can range from mild (erythema, hyperpigmentation) to severe (moist desquamation). A wide variety of products exist to help prevent and treat acute radiation dermatitis, although further research is needed on efficacy of many of these products. Similarly, products to help prevent and treat late radiation toxicity, occurring months to years after radiation, also need further research.

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Chapter 11

Palliative Radiotherapy for Brain Metastasis

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Chapter Outline

Introduction 153
Evaluation 154
Palliative Radiotherapy Regimens 154
Whole Brain Radiation Therapy 154
Partial Brain Radiation Therapy 155
Stereotactic Radiosurgery 155
Hypofractionated Stereotactic Radiotherapy 156
Evaluation and Management of Common Clinical Concerns 156
Headache 156
Nausea/Vomiting 157
Anorexia 159
Seizure 160
Fatigue/Lethargy/Somnolence 161
Tearing/Conjunctivitis 161
Otitis Externa 162
Functional Deficits 162
Conclusion 164
List of Abbreviations 165
References 166

INTRODUCTION

Unlike most site-specific symptoms, the management of a patient with a primary central nervous system (CNS) tumor or brain metastasis is complicated both by the complexity and gravity of neurologic symptoms, as well as the added uncertainty of distinguishing between treatment- and disease-related side effects. Additionally, many patients, due to impairments in speech or cognitive processing, may have difficulty with clearly communicating their concerns.

Therefore given the ramifications of misdiagnosis in this patient population, it is vital to document both a thorough baseline neurologic examination as well as a list of the medications that the patient is taking at the time of evaluation. When there is uncertainty regarding the etiology of a patient's symptoms, there should be prompt additional investigation with further examination, imaging, or subspecialist input.

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Evaluation

- Prompt assessment of severity of acute symptoms with evaluation of performance status and acquisition of vital signs. If patient is in extremis, transfer to the emergency department for urgent brain imaging and neurosurgery/neurology consultation should be pursued.
- If initial evaluation does not necessitate enhanced care procedures, a complete history including neurologic symptoms (headache, nausea, focal neurologic deficits) should be elicited followed by:
  - Careful examination with a thorough neurologic exam, including evaluation of the cranial nerves, muscle tone and strength, sensation to touch, pain, and temperature, reflexes, and neurocognitive status.
  - As appropriate, labwork including a CBC and complete metabolic panel, renal function and liver function tests (LFTs), and/or blood cultures.

PALLIATIVE RADIOTHERAPY REGIMENS

Whole Brain Radiation Therapy

- Whole brain radiation therapy (WBRT) has been utilized for decades to relieve symptoms related to brain metastases or malignant gliomas, to decrease in-brain progression, and in the case of brain metastases, to reduce the risk of neurologic death [1–4].
- Additionally, WBRT has been demonstrated to increase survival compared to no treatment or to corticosteroids alone both in patients with primary CNS tumors and with brain metastases [5].
- While WBRT for the palliation of multiple brain metastases is becoming increasingly controversial due to concerns for neurocognitive impairment, it remains an appropriate treatment option for patients with diffuse brain metastases, leptomeningeal disease, or gliomatosis cerebri [6–8].
- Wide variation in dose/fractionation schemes exist for WBRT.
  - Comparisons of different treatment schemas have demonstrated no measurable differences in locoregional control, overall survival, or acute toxicity [9].
  - Therefore hypofractionated regimens, e.g., 20 Gy in 5 fractions should be considered when estimates of life expectancy (see Chapter 3: Prognostication in Patients Receiving Palliative Radiation Therapy) are less than 12 weeks.
- For patients with longer life expectancies or when there are concerns for neurocognitive impairment from radiation, more conventional fractionation schemes, e.g., 30 Gy in 10 fractions, 35 Gy in 14 fractions, or 37.5 Gy in 15 fractions, can be employed. Please see section on "Functional Deficits" for additional strategies to reduce neurocognitive decline when considering WBRT.

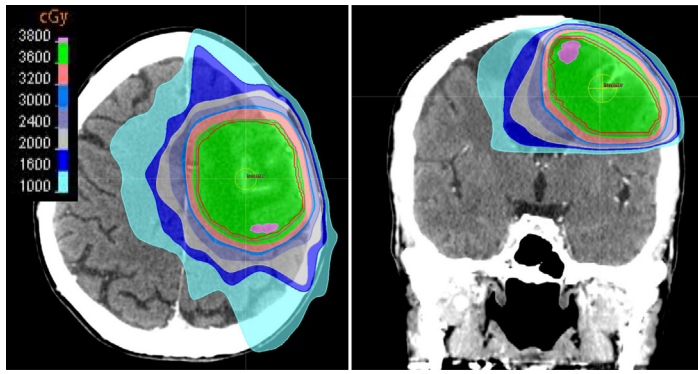

FIGURE 11.1 Partial brain irradiation.

Partial Brain Radiation Therapy

- Due to a growing concern for the neurotoxic effects of WBRT, alternative treatments that target metastases while providing greater preservation of normal brain tissue have become increasingly popular.
- Radiation approaches that treat brain metastases while including less than the entire brain in the treatment portal can vary significantly in approach:
  - Targeting the entire posterior fossa for lesions confined to the cerebellum
  - Contouring the gross tumor volume (GTV) of a large single lesion or multiple small lesions and adding a modest expansion of 0.5−1.0 cm to create a partial brain clinical target volume (CTV) (Fig. 11.1).
  - In cases of partial brain radiation therapy, where randomized data are lacking, dose and fractionation schemes similar to those used in WBRT are utilized to ensure a similar rate of local control.

Stereotactic Radiosurgery

- Stereotactic radiosurgery (SRS) has become a popular alternative to whole brain or partial brain radiation therapy, most commonly delivering a single, highly focused dose of radiation to a lesion while largely sparing uninvolved brain tissue.
- SRS has proven to be well-tolerated and highly effective for local control, with 1 year local control rates exceeding 90% [3−4,10−11].
- It is a technique that is most appropriate for uniformly shaped lesions smaller than 3 cm that are located at a safe distance from dose-limiting normal structures.
- RTOG 9005 identified the maximum tolerated dose (MTD) for brain lesions by size as: 24 Gy, 18 Gy, and 15 Gy for tumors measuring less

than or equal to 2, 2.1−3, and 3.1−4 cm, respectively [11]. In this study, the radionecrosis rate was 11% at 2 years.

- In practice, most physicians rarely employ SRS for lesions exceeding 3 cm and rarely prescribe doses as high as 24 Gy out of concern for inducing radionecrosis and due to efficacy of disease control at lower doses.
- While there is significant variability by institution, many physicians employ single doses of between 18 and 20 Gy for lesions measuring less than 3 cm.

Hypofractionated Stereotactic Radiotherapy

- Hypofractionated stereotactic radiotherapy (hSRT) uses the precision localization techniques of SRS, but rather than deliver radiation in a single dose, it employs smaller fractional doses of radiation for lesions that are not ideal for single dose treatment due to a larger size, irregular shape, or proximity to dose-limiting normal structures, such as the optic apparatus or brainstem.
- hSRT is usually administered across 2−9 treatments in doses higher than conventional WBRT fractions, but in doses smaller than those used for single-fraction SRS.
- Published reports using this approach also suggest that it is well-tolerated and results in local control rates of 40−90% [12−15].
- To date, the ideal dose and fractionation scheme for hSRT is not well-defined and may vary by size, location, histology, patient performance status, prior cranial irradiation, and burden of disease both intracranially and extracranially.
  - Published regimens vary widely, but commonly used schemes include 5 Gy × 5 fractions or 8 Gy × 3 fractions [16−17].
  - Of note, according to the American Society for Radiation Oncology (ASTRO) billing definitions, hSRT with 2−5 fractions are defined as SRS and is often interchangeably referred to as such [18].

EVALUATION AND MANAGEMENT OF COMMON CLINICAL CONCERNS

- Both alopecia and radiation dermatitis are common side effects experienced by patients receiving radiation to the brain, but the management of these symptoms are well-addressed in Chapter 10, Skin Toxicity in Palliative Radiation Therapy, and will not be readdressed in this chapter.

Headache

- Approximately 50% of patients with brain metastases will experience headaches and this symptom remains common among patients receiving WBRT or any other RT to the brain.

- In order to determine the etiology of the headache, this symptom deserves careful questioning regarding the nature of the pain (e.g., sharp, dull, worse lying down, or associated with nausea/vomiting) to elicit a possible etiology.
- The differential diagnosis for a headache in a patient with brain metastases or a primary CNS tumor is broad and may range from the benign to the severe (e.g., stress, herniation, hemorrhage, obstructing hydrocephalus).
- If there is concern that the symptom may be related to an acutely life-threatening etiology, such as hemorrhage, these patients should be emergently evaluated and appropriately directed to an emergency room.
- If there is a low level of clinical concern, conservative management is appropriate. This includes ensuring adequate hydration and an adequate blood glucose level.
  - If no obvious etiology is identified, treatment with over-the-counter analgesics including acetaminophen or NSAIDS is appropriate. Before prescribing, consider comorbidities that could serve as a contraindication to taking these medications.
  - Stress is also a common source of headaches and reassurance can be helpful to resolving symptoms.
- If there is a moderate level of clinical concern, oral steroids, e.g., dexamethasone 4 mg QD or BID, can be initiated.
  - Dosage should be chosen and adjusted by the burden of intracranial disease, patient tolerance, and response to therapy.
  - Patients with a known significant burden of intracranial disease may benefit from an increase in dosage, up to 16 mg/day.
  - Oral narcotics including short-acting oxycodone or morphine may be considered.
- If there is a high level of concern, prompt imaging and/or formal neurologic evaluation should be executed with management determined by findings. High dose steroids (dexamethasone 8–16 mg/day) may also be initiated in parallel (Table 11.1).

Nausea/Vomiting

- Nausea and vomiting are common symptoms in the CNS patient. A stepwise approach to the treatment of nausea and vomiting is outlined in Table 11.2.
- While prophylactic treatment is not necessary, once a patient develops nausea and vomiting, premedication prior to irradiation can be helpful in preventing symptoms.
- Patients should always be evaluated prior to medical management to rule out a life-threatening etiology (e.g., increased intracranial pressure

TABLE 11.1 Headache Characteristics and Associated Level of Concern

Headache Characteristic	Level of Clinical Concern		
	Low	Moderate	High
Onset	Slow		Sudden
Distribution	Band-like, Retro-orbital		Localized
Character	Dull		Intensifies with cough or defecation
Intensity [1–10]	1–3	4–6	7–10
Timing	Following treatment	Preceding treatment	Wakes patient from sleep, early morning, recumbent position
Associated symptoms	None	Nausea, aura, scotoma, phantosmia	Vomiting, confusion, disequilibrium

TABLE 11.2 Approach to Antinausea and Antiemetic Management

	Dosing	Mechanism
First-Line Agents		
Ondansetron (Zofran)	4–8 mg q 8 h:PRN SL/PO	Serotonin 5-HT3 receptor antagonist
Prochlorperazine (Compazine)	5–10 mg q 6 h:PRN PO	Dopamine D2 receptor antagonist
Lorazepam (Ativan)	0.5–1 mg q 4 h:PRN SL/PO	Benzodiazepine
Second-Line Agents		
Olanzapine (Zyprexa)	2.5–5 mg BID:PRN SL/PO	Mixed D1/5-HT2 receptor antagonist
Dexamethasone (Decadron)	4–8 mg QD (QAM or divided BID) PO/IV	Corticosteroid
Third-Line Agents		
Metoclopramide (Reglan)	10 mg QID: PRN PO	D2 receptor antagonist/mixed 5-HT3/4 antagonist/agonist
Scopolamine	1 patch TD q 72 h:PRN	mAch receptor antagonist

from obstructive hydrocephalus) that would require other immediate intervention.

- Multiple agents can be used to manage nausea and vomiting, however, agents of the same or similar class should not be administered concurrently.
- Additionally, the use of third-line agents should be used judiciously as metoclopramide increases gastrointestinal motility and may exacerbate symptoms, while the elderly and infirm may be particularly susceptible to the anticholinergic effects of scopolamine.
- If a patient reports persistent nausea/vomiting despite antiemetics, a detailed drug history may uncover other potential etiologies.
  - Changes in narcotics to newer generation drugs may be a source of worsening nausea.
  - Patients receiving chemotherapy may be symptomatic from the chemotherapeutic agent, and this may resolve with adjustment of antiemetic dosage or regimen, but is best determined by the prescribing oncologist.
  - Alternatively, a patient on a steroid taper may require a slower taper to resolve his or her symptoms.
- Of note, many patients are prescribed steroids prior to the initiation of radiation therapy to decrease expected reactive inflammation and to prevent or reduce neurologic symptoms. However, steroids are often continued in these patients despite resolution of their symptoms.
  - Prolonged steroid usage can be associated with serious side effects including agitation, insomnia, weight gain, gastritis, myopathy and associated weakness, hyperglycemia, and increased risk of infection.
- Therefore steroids should be weaned as quickly as possible. If the patient was asymptomatic when steroids were initiated and received fewer than 5 days worth of medication, they can be stopped immediately and without taper.
- Patients with refractory severe nausea and vomiting and escalating symptoms should be directed to a local emergency department for prompt evaluation and management.

Anorexia

- Many patients with CNS malignancies experience a loss of appetite.
- While a loss of appetite is a subjective concern, assessing the patient's weight, physical appearance, and serum electrolytes/albumin can provide additional information regarding their nutritional status and aid in determining if medical intervention is necessary.
- Anorexia can be caused as a direct effect of radiation therapy to the brain, but the cause is more often multifactorial and may be owed to medication-induced anorexia or dysgeusia, pain, dysphagia, persistent

TABLE 11.3 Medical Management of Anorexia

	Dosing	Notes
First-Line Agents		
Prednisone	20–40 mg PO daily	
Megestrol Acetate (Megace)	160 mg–800 mg PO daily	May increase risk of edema/thromboembolism
Second-Line Agents		
Cyproheptadine (Peritol)	8 mg PO TID	Limited data; effective for carcinoid syndrome

nausea, or depression/anxiety, as well as tumor-mediated anorexia/cachexia effects in the case of very ill patients.

- A thorough history, including the timing of the onset of symptoms in relation to the patient's treatment course, may be helpful in determining the etiology of the anorexia and determine if a simple modification of the patient's medication regimen or optimization of their antiemetics may be sufficient to resolve this concern.
- Alternatively, if the symptoms appear to be radiation or directly malignancy-related, the agents in Table 11.3 can be trialed.
- Cannabinoids, including Dronabinol and Marinol, while frequently cited as an effective appetite stimulant, have not proven efficacious in the advanced cancer population compared to megestrol acetate, either alone or in combination [19].
- In some states, medical marijuana has been approved for the treatment of pain, nausea, and chronic fatigue, but patients should be referred to a designated prescriber for additional evaluation.

Seizure

- Seizure is an uncommon, but potentially serious secondary effect of radiation therapy to the brain, most commonly triggered by reactive edema.
- Patients with disease involving the motor cortex or meninges are at a relatively higher risk of seizure.
- Among patients receiving SRS or hSRT, approximately 5–15% of patients will experience a seizure following treatment due to the rapid onset of edema associated with high dose radiation [16,20–21]. In some practices, a short course of lorazepam 0.5–1.0 mg BID or other antiepileptic agent is prescribed prophylactically in the days surrounding an SRS procedure, when radiation-induced seizures are most likely.

- In general, patients with primary brain tumors or those with brain metastases are placed on antiepileptic therapy only if they have already experienced a seizure or have undergone brain surgery.
  - In these cases, levetiracetam is frequently utilized at doses of 500–1000 mg BID for prophylaxis.
  - Levetiracetam can be tapered in the weeks following surgery for patients who remain seizure free.

Fatigue/Lethargy/Somnolence

- While fatigue is a widely recognized side effect of radiation therapy, it can be particularly profound among patients receiving radiation to the brain.
- The reasons for fatigue in this patient population are often multifactorial and can include the disease, depression, anxiety, pain, poor nutrition, dehydration, physical inactivity, and medications in addition to the radiation itself.
- When rapid onset of fatigue or somnolence is observed, care should be taken to rule out serious causes of lethargy including cerebral infarction/hemorrhage or cerebral edema.
- Once more serious causes are excluded, the agents in Table 11.4 can be trialed, preferably with the oversight of neurologic or palliative care services.

Tearing/Conjunctivitis

- For patients receiving WBRT or craniospinal irradiation, the posterior orbit is within the radiation treatment field and the lacrimal glands are

TABLE 11.4 Medical Management of Lethargy and Somnolence

Agent	Dosing	Notes
Prednisone	10–60 mg PO daily	
Methylphenidate (Ritalin)	Initial dosing: 2.5–5 mg PO QD-BID Maximal dose: 20–40 mg daily	May exacerbate headaches, anorexia, or insomnia in CNS patients
Modafinil (Provigil)	Initial dosing: 100 mg PO daily Maximal dose: 200 mg daily	May exacerbate headaches, nausea, or insomnia in CNS patients

often partially irradiated. Consequently, excessive eye tearing can be seen.

- With partial brain or periorbital radiation treatments that include partial eye irradiation, radiation-induced conjunctivitis causing a red eye with or without mucoid discharge can be experienced.
  - Cool compresses or lubricating eye drops can be administered as needed for relief.
  - Glucocorticoid containing eye drops should be avoided if infection cannot be excluded as steroids may cause corneal damage in the presence of a viral or bacterial nidus.

Otitis Externa

- Otitis externa is an inflammatory reaction involving the outer ear or ear canal that can result from whole brain or partial brain irradiation.
- Typically, patients will report having an earache or ear congestion that is exacerbated by pulling or tugging on the external ear.
- A thorough examination including otoscopic examination should be performed and can reveal diffuse inflammation with eczematous changes of the ear canal. Frequently, swelling of the canal can prevent visualization of the tympanic membrane.
- Rarely, the inflammation and pain can be accompanied by discharge from the ear.
- If the practitioner is confident that the symptoms are radiation-induced and noninfectious, a course of dexamethasone 0.1% otic suspension can be applied to the ear canal 3−4 times daily for 1−2 weeks.
- If there is uncertainty regarding the etiology of the inflammation, referral to an otolaryngologist is recommended.

Functional Deficits

- Functional deficits are a common presentation for brain metastases or primary CNS tumors and can be wide ranging from changes to affect, memory, and comprehension to discrete impairments in speech, vision, sensation, or motor function.
  - During radiation treatment, the new onset of functional deficits should trigger a prompt and thorough evaluation with possible additional imaging if an etiology is not identified.
  - Neurosurgical consultation may be warranted for concerns of progressive tumor growth, cerebral edema, infarction, or hemorrhage.
- Following completion of radiation therapy to the brain, patients and families may specifically report the delayed, and often, insidious onset of neurocognitive slowing or memory impairment.

- Some studies estimate that up to 50% of long-term survivors develop late cognitive deficits caused by radiation-induced injury of normal brain tissue [6–8].
- Older patients and those patients receiving WBRT are particularly vulnerable to this late effect of treatment for reasons that are not fully understood, though radiologic changes correlated with neurocognitive decline include ventriculomegaly and diffuse cortical leukoencephalopathy.
- Animals models have also demonstrated damage to the microvascular environment as well as direct neuronal loss following radiation to the brain [22–24].

- Due to concerns for neurocognitive decline following radiation therapy, two recent RTOG trials have shown preliminary success in reducing the extent of decline in patients receiving WBRT with the addition of either protective drug therapy or improved radiation techniques.
  - RTOG 0614 used memantine drug therapy as a neuroprotectant and demonstrated that patients displayed a longer time to cognitive decline and a decreased probability of cognitive function failure at 6 months with the addition of memantine.
    - In this study, memantine was administered coincident with the first day of radiation treatment and continued for a total of 6 months [25].
    - The dose schedule for memantine is as follows: 5 mg by mouth daily for week 1, 5 mg twice daily for week 2, 10 mg in the morning and 5 mg in the evening for week 3, and 10 mg twice daily for the remaining weeks 4–24.
    - Careful consideration of the benefits of memantine in this setting is warranted, however, these findings have yet to be replicated and other criticisms of the findings, including a high patient dropout rate, have been raised.
  - RTOG 0933 sought to minimize dose to the hippocampal region of the brain, an area that is thought to be associated with the consolidation of long-term memory.
    - In this study, patients received hippocampal sparing WBRT using an IMRT-based plan.
    - Cognitive and quality-of-life assessments were performed on these patients at baseline, and at 2, 4, and 6 months following radiation therapy.
    - The relative decline in measurements of delayed recall from baseline to 4 months was significantly lower than those observed in historical controls [26].
    - Concerns remain with this technique as the effect size was modest and practitioners may not feel comfortable with intentional underdosing of some brain tissue, particularly in patients with a high tumor burden.

- While both memantine and hippocampal sparing radiation therapy are not considered the standard of care for all CNS patients, they represent promising interventions for patients receiving WBRT and may be useful in select cases, at the discretion of the physician. At our institution, patients with a life expectancy greater than 1 year are considered the most ideal candidates for receipt of both memantine and hippocampal sparing strategies.

CONCLUSION

The management of patients with CNS malignancies can be a complicated but ultimately a rewarding pursuit. Advancements in medical therapies and an increase in variety of radiation techniques available have led to increased survival in both patients with metastatic disease to the brain and in patients with primary brain tumors. This has increased the frequency of need for symptom management. Patients with tumors of the CNS require careful monitoring during and following treatment to recognize and relieve symptoms related to therapy (Table 11.5).

TABLE 11.5 On Treatment Management Summary

Symptoms	Acute Management	Late Management
Headache	• 1st line: OTC Tylenol/ NSAID's first-line • 2nd line: Dexamethasone 4 mg QD or BID adjusted by burden of intracranial disease, patient tolerance, and response to therapy or Oxycodone 5–10 mg PO q4-6H PRN	• Severe or persistent symptoms require formal neurologic evaluation with imaging and high dose steroids
Nausea/ vomiting	• Commonly prescribed antiemetic's include: Ondansetron 4–8 mg PO TID PRN, Prochlorperaine 5–10 mg PO QID PRN, Lorazepam 0.5–1 mg PO q4H PRN, or Decadron 4 mg qD or BID	• Severe or persistent symptoms require formal neurologic evaluation with imaging • Consider nutritional support with IV fluids, supplements, etc.
Seizure	• General prophylaxis: Levitiracetem 500–1000 mg BID	• Continue with acute management if it is working

(*Continued*)

TABLE 11.5 (Continued)

Symptoms	Acute Management	Late Management
	• Pre-SRS: Ativan 0.5–1.0 mg BID pre- and posttreatment	• Refer to neuro-oncology if concern for persistent seizure activity despite prophylaxis
Anorexia	• Prednisone 20–40 mg PO daily • Megestrol Acetate 160–800 mg PO daily • 2nd line: Cyproheptadine 8 mg PO TID	• Steroids should not be used as a long-term strategy and should be tapered as quickly as possible • Megestrol should be used in caution in patients with thromoembolic history
Fatigue/ lethargy/ somnolence	• Prednisone 10–60 mg PO daily	• Steroids should not be used as a long-term strategy and should be tapered as quickly as possible • Methylphenidate 2.5–5 mg PO daily to BID (max dose: 20–40 mg daily) or Modafinil 100 mg PO daily (max dose: 200 mg daily) are superior long-term agents
Tearing/ conjunctivitis	• Cool compresses or lubricating eye drops • Glucocorticoid containing eye drops if infection is excluded	
Otitis externa	• Dexamethasone 0.1% otic suspension can be applied to the ear canal 3–4 times daily for 1–2 weeks • If uncertainty regarding etiology, refer to an otolaryngologist	

LIST OF ABBREVIATIONS

BID twice daily
GTV gross tumor volume
hSRT hypofractionated stereotactic radiotherapy
IV intravenous
mg milligram
MTD maximum tolerated dose
PO by mouth
PR per rectum

PRN as needed
PTV planning tumor volume
QD daily
QID four times daily
SL sublingual
SRS stereotactic radiosurgery
TID three times daily
WBRT whole brain radiotherapy

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Chapter 12

Palliative Radiotherapy for Malignant Epidural Spinal Cord Compression

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Chapter Outline

Introduction 169
Definition 170
Presentation 170
Pain 170
Myelopathy/Neurological Impairment 171
Prognostic Factors 171
Evaluation 172
History 172
Physical Examination 172
Imaging 173
Management 175
Dexamethasone 175
Radiotherapy 176
Highly Conformal Radiotherapy: Stereotactic Radiosurgery/ Stereotactic Body Radiation Therapy (SRS/SBRT) 179
Surgery 180
Surgical Stabilization 182
Recurrence 183
Summary 184
References 185

INTRODUCTION

Metastatic epidural spinal cord compression (MESCC) is an oncological emergency and needs to be diagnosed early and treated promptly. Patients with MESCC often experience debilitating pain and/or neurological impairment; these symptoms can significantly impact their functional independence and quality of life. Therefore, the primary goal of intervention is to maximize quality of life by relief of pain and preservation/restoration of neurological function as well as to maintain mechanical stabilization of the spine.

Approximately 5–10% of patients with cancer develop malignant spinal cord compression during the course of their disease [1]. The most common

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location is the thoracic spine (59–78%), followed by the lumbar spine (16–33%), and the cervical spine (4–13%) [2]. The most common histologies include lung, prostate, and breast cancers, each accounting for about 20% of patients with MESCC. Median survival in patients with MESCC is generally short and varies depending on the type of primary tumor. Median survival is about 4–6 months for patients with lung cancer, whereas for patients with breast cancer and multiple myeloma the median survival can be up to 18 months [1,2].

DEFINITION

Definition of epidural spinal cord compression varies in the literature. Some authors suggested that any radiographic evidence of thecal sac indentation should be considered epidural spinal cord compression (ESCC), whereas other authors differentiate between (symptomatic) ESCC and pending ESCC [3,4]. Recently, ESCC grading scale, an MRI-based grading system, was proposed by the Spinal Oncology Study Group [5]. Using the axial T2-weighted images at the site of most severe compression, the degree of ESCC is determined (See Table 12.1).

This grading system is a guideline from expert consensus but has not been robustly validated. Nevertheless, it may help guide treatment decision-making.

PRESENTATION

Common presenting symptoms include pain and myelopathy or neurological impairment [6–9]:

Pain

- The most common presenting symptom, occurring in approximately 80–95% of patients. Unexplained back pain in cancer patients warrants immediate evaluation.
- Typically precedes neurological deficits.

TABLE 12.1 Epidural Spinal Cord Compression (ESCC) Grading System

Grade 0: Bone-only disease
Grade 1: Epidural impingement
1a: Epidural impingement without deforming the thecal sac
1b: Thecal sac deformation without spinal cord abutment
1c: Thecal sac deformation, cord abutment, no cord compression
Grade 2: Moderate-grade spinal cord compression with visible CSF around the cord
Grade 3: High-grade spinal cord compression without visible CSF around the cord

- Local pain is thought to be due to periosteal stretching from tumor growth and/or local inflammatory process. It often responds to steroids.
- Radicular pain indicates neuroforaminal pathology due to nerve root compression or irritation and tends to be constant with dermatomal distribution of the involved nerve root.
- Mechanical pain is movement-related pain. It is indicative of bone etiology often caused by vertebral body collapse or compression as a result of instability. It is often worse with movement and is often refractory to steroids or narcotics.

Myelopathy/Neurological Impairment

- The presence of neurological impairment is indicative of high-grade ESCC.
- Motor weakness is the most common neurological symptom (indicative of impaired corticospinal tracks) [7–9].
- Approximately 60–85% present with motor weakness at the time of diagnosis [3].
- Sensory impairment (paresthesias, loss of sensation) often accompanies motor impairment (pinprick evaluates spinothalamic tracks; proprioception evaluates posterior columns).
- Sphincter control/continence and autonomic impairment such as urinary retention and hesitancy are often a late finding. Urinary retention is the most common and often correlates with the degree of motor deficit [10].
- Functional assessment can be objectively graded using Frankel classification [11].

Frankel Classification

Grade A	Paraplegia
Grade B	Sensory function only, complete paralysis
Grade C	Not ambulatory but has some motor function below compression level
Grade D	Ambulatory with some motor function below compression level
Grade E	No neurologic symptoms

- The cause of neurological impairment is thought to be commonly due to edema caused by increased vascular permeability when the epidural venous plexus is compressed by an epidural metastasis.
- Direct compression of the spinal cord by an expanding epidural mass can also lead to spinal cord ischemia and subsequent neurological injury.
- Bone fragments due to posterior displacement of fractured bone metastasis may also result in direct compression on the spinal cord [7].

PROGNOSTIC FACTORS

- The neurological status at the time of diagnosis (pretreatment neurological status), especially motor function and ambulatory status, correlates with the prognosis of MESCC.

- Multiple studies have shown that pretreatment ambulatory function is the most important prognostic factor for ambulatory ability after treatment [12,13].
- Rate of motor deficit development due to compression is prognostic for functional outcomes.
  - More rapid progression of motor weakness prior to intervention predicts a worse outcome [13]. Slower progression predicts a better outcome.
- Visceral metastases and short-course radiotherapy are associated with inferior local control after radiotherapy [14].
- Longer survival after radiotherapy was associated with absence of visceral metastases, no other bone metastasis, being ambulatory before radiotherapy, longer time interval between diagnosis and cord compression ($\leq$15 vs $>$15 months), longer duration of developing motor deficits before radiotherapy (1−14 vs $>$14 days) and breast/prostate/myeloma/lymphoma [14].
- Using these prognostic factors, a prognostic score to predict overall survival has been developed and validated (Table 12.2) [15,16].
- A score that predicts postradiotherapy ambulatory status has also been developed and validated [17,18].
  - Six prognostic factors were included: tumor type, interval between cancer diagnosis and spinal cord compression, presence of other bone or visceral metastases at the time of radiotherapy, pretreatment ambulatory status, and duration of motor deficits (Table 12.3).

EVALUATION

History

- A comprehensive history should include characteristics of pain, presence, extent and duration of neurological symptoms, performance status, extent/status of extraspinal metastatic cancer, and GI/GU functions (including urinary retention and continence).
- Neurological symptoms:
  - Include any motor, sensory, or autonomic (bladder/bowel) dysfunction.
  - Details of onset (acute vs gradual), time since onset, severity, and extent of the neurological symptoms.
- Detailed history of the pain characteristics may elicit whether pain is due to local/axial, radiculopathic, or mechanical causes.

Physical Examination

- Comprehensive examination to include: Inspection of spine alignment, palpation of focal tenderness/mass.
- Thorough neurologic examination including motor function, gait, sensation (pinprick, proprioception), reflexes (deep tendon reflex, abdominal, Babinski, Hoffman), clonus.
- Range of motion.

TABLE 12.2 Prognostic Score to Predict Overall Survival After Radiotherapy for MESCC

Prognostic Factor	Description	Score
Cancer type	Breast cancer	8
	Prostate cancer	7
	Myeloma/ lymphoma	9
	Lung cancer	3
	Other	4
Interval between cancer diagnosis and cord compression	*< 15 months*	4
	>15 months	7
Other bone metastasis	*Yes*	5
	No	7
Visceral metastasis	Yes	2
	No	8
Motor function prior to radiotherapy	Ambulatory	7
	Not ambulatory	3
Time developing motor deficits prior to radiotherapy	1–7 days	3
	8–14 days	6
	>14 days	8

Group	Sum Score	Median Survival	6-Month Overall Survival Rate
I	20–30	2.5 months	16%
II	31–35	7.5 months	48%
III	36–45	25 months	81%

Imaging

- MRI of the spine with and without gadolinium is the gold standard imaging modality for evaluation and should be performed immediately when metastatic spinal cord compression is suspected.
- MRI determines the location, extent of compression, single versus multiple lesions, and other epidural/cord compression sites. It also differentiates between metastasis and spondylodiscitis [19].
- The entire spine should be imaged because epidural compression may occur at multiple levels.

TABLE 12.3 Prognostic Score to Predict Postradiotherapy Ambulatory Status for MESCC

Prognostic Factors	Description	Score
Cancer type	Breast cancer	8
	Prostate cancer	7
	Myeloma/lymphoma	9
	Nonsmall cell lung cancer	5
	Small cell lung cancer	6
	Cancer of unknown primary	5
	Renal cell cancer	6
	Colorectal cancer	6
	Other	6
Interval from cancer diagnosis to cord compression	≤15 months	6
	>15 months	8
Visceral metastasis	Yes	5
	No	8
Motor function prior to radiotherapy	Ambulatory without aid	10
	Ambulatory with aid	9
	Not ambulatory	3
	Paraplegic	1
Time developing motor deficits prior to radiotherapy	1–7 days	4
	8–14 days	7
	>14 days	9

Group	Sum Score	Postradiotherapy Ambulatory Rate
I	21–28	10.6%
II	29–37	70.9%
III	38–44	98.5%

- To visualize the site of epidural compression:
  - Sagittal T1-weighted images with and without contrast and T2-weighted images.
- To confirm the degree of compression:
  - Axial T1-weighted images with and without contrast and T2-weighted images at the regions of interest based on sagittal imaging finding.
- Compression of the thecal sac and structures within the dura including the spinal cord and cauda equina by an extradural mass is diagnostic.
  - Direct tumor extension from bone metastasis into the epidural space is the most common.
  - Bone fragment due to vertebral metastasis into the spinal column is another cause.
- Spinal CT defines bony anatomy and the extent of bone involvement and is especially useful for evaluation of compression fracture, mechanical instability, and posterior bone fragment protrusion.
- Occasionally, biopsy or surgical decompression is considered when pathological diagnosis is needed in patients without known history of cancer diagnosis or if there is no evidence of other metastasis.

MANAGEMENT

Urgent consultation with both Neurosurgery and Radiation Oncology and multidisciplinary approach involving radiologists, neurosurgeons, radiation oncologists, medical oncologists, and neurologists provides the best assessment for intervention. Risk and benefit profiles of specific interventions are based on patient's neurologic status, performance status, extent of epidural disease, stability of the spine, status of extraspinal metastasis, and life expectancy. Treatment decision is often individualized based on these factors.

Dexamethasone

- All patients with suspected MESCC should receive prompt administration of dexamethasone when MESCC is suspected.
- A randomized trial by Sorensen et al. investigated patients treated with radiotherapy alone for spinal cord compression who were randomized to high-dose dexamethasone 96 mg/day vs. none; 81% of the patients who received dexamethasone were ambulatory, compared to 63% in the control arm, demonstrating the benefit of high-dose steroids [20].
- No consensus data on optimal dosing schedules of dexamethasone.
- High-dose dexamethasone is associated with severe gastrointestinal toxicity including bowel perforation, ulcer, and bleeding.
  - Sorensen et al. reported 11% of patients had serious GI side effects including perforation [20].

- A common inpatient regimen is immediate administration of dexamethasone 10 mg IV bolus followed by 4–8 mg q 6–8 hours, with taper completed in 2 weeks.
- An alternative is administration of a medium dose of dexamethasone (8 mg twice a day) from the day of MESCC diagnosis until the end of radiotherapy with taper completed in 2 weeks [21].
- Recommendation for outpatient regimen: initial dose of 4 mg q 6 hours of dexamethasone, with a taper started after surgery and/or radiotherapy. Taper usually consists of an empiric reduction in dose of 2–4 mg every 1–3 days as tolerated.
- Common side effects of dexamethasone include stomach irritation, insomnia, irritability, and fluid retention/lower extremity swelling. Prophylaxis against dexamethasone-induced ulceration with proton pump inhibitor or ranitidine 150 mg BID should be used.

Radiotherapy

Candidates for Prompt Palliative Radiotherapy

- Patients who are not surgical candidates.
- No evidence of spinal instability or compression caused by a bone fragment.
- Multilevel spinal cord compression.
- In the absence of mechanical instability, radiotherapy may be considered for minimal radiographic epidural extension without surgical decompression for patients who are appropriate surgical candidates.

Radiotherapy Planning Technique

- Either fluoroscopic simulation or CT simulation are appropriate.
- PA, AP/PA, or posterior oblique field design is commonly used, depending on the distance between body surface and spinal cord. Opposed lateral fields for mid/upper cervical spine may be used.
  - Posterior oblique may decrease the skin dose but may increase the dose to the lung for treatment to the thoracic spine.
- Radiation portals are centered on the site of ESCC. If PA or AP/PA fields are used, the field generally encompasses two vertebral bodies above and below the level of compression with a width of 8–10 cm (unless there is paraverterbral extension which should be included in the treatment field).
- With fluoroscopic simulation, dose is prescribed at cord depth or at mid-plane.
- 3D conformal treatment planning has become more popular in recent years. CT simulation has multiple advantages, including (1) more accurate definition of the treatment site and incorporation of paravertebral extension and (2) more accurate dose calculation accounting for body habitus.

- 30 Gy in 3 Gy per fraction × 10 fractions is most commonly used.
  - Other fractionations, e.g., 2 Gy × 20 fractions, 2.5 Gy × 15 fractions, 4 Gy × 5 fractions, and 8 Gy × 1 fraction may be considered (please see below for more information on dose/fractionation).

Side Effects

- Side effects are generally mild and depend on the location in the spine being treated.
- Acute (reversible): fatigue, nausea/vomiting, mucositis, esophagitis, bowel irritation.
- Late (very rare): myelopathy, pathological vertebral fractures.
- Antiemetics (typically a 5-hydroxytriptamine antagonist) can be administered 30–60 minutes prior to radiotherapy when treating fields between T8 and L3.

Dose/Fractionation

The majority of patients with MESCC receive radiotherapy, either alone or preceded by surgery. Various radiotherapy fractionation regimens were investigated. While studies have consistently shown that radiotherapy is an effective way to control pain and improve ambulatory outcomes, there is no evidence that neurological outcomes are improved with higher doses of radiotherapy. Dose/fractionation varies in published data.

Common fractionation used for MESCC:

Fractionation	Patient Population
3 Gy × 10 fractions	• Good prognosis. Life expectancy >3 months • Following decompressive surgery
4 Gy × 5 fractions	• Suitable for patients with intermediate-to-poor prognosis
8 Gy × 1 fraction	• May be considered for patients with very poor prognosis and limited life expectancy (<3 months)
2.5 Gy × 15 fractions	• Alternative for patients with good prognosis

Data From Randomized Clinical Trials

- Four trials compared short-course versus long-course radiotherapy for patients with short life expectancy without spinal instability.
- 8 Gy × 2 a week apart versus split course (5 Gy × 3 then 3 Gy × 5 with 4-day interval) [22].
  - Pain relief was reported in approximately 55% of the patients and was similar in these two groups.
  - The posttreatment ambulatory rates were approximately 70%, similar between the two groups.
    - About 90% of ambulatory patients remained ambulatory posttreatment,

  - but only roughly 30% of nonambulatory patients regained ambulation after radiotherapy.
- CONCLUSION: 8 Gy × 2 had equivalent palliation versus split course.

- 8 Gy × 1 versus 8 Gy × 2 a week apart [23].
  - No difference between the two arms for pain relief or ambulatory outcomes.
    - Approximately 50% of patients had pain relief.
    - Ambulation:
      - Up to 90% of ambulatory patients remained ambulatory.
      - But only 4% of paraplegic patients regained walking ability.
  - The median duration of response = 5 months. Median overall survival = 4 months in both groups.
  - CONCLUSION: 8 Gy in 1 versus 8 Gy in 2 had equivalent palliation effect.
- 10 Gy × 1 versus 4 Gy × 5 [24]
  - Response to RT = improvement or no progression of motor function at 5 weeks.
    - 79% after 10 Gy × 1 versus 68% after 4 Gy × 5 (not statistically significant).
  - Only 38% evaluable at 5 weeks.
  - CONCLUSION: 10 Gy × 1 was not inferior for motor function versus 4 Gy × 5.
- 4 Gy × 5 versus 3 Gy × 10 for poor-to-intermediate prognosis [25].
  - Response to RT = improvement or no progression of motor function at 4 weeks.
    - ~88% in both arms.
    - About 40–44% improved, 45% stable, and 12% deteriorated.
  - ~75% evaluable at 4 weeks.
  - Ambulatory rate at 1 month: 82% versus 75% (NS).
  - 6-month overall survival ~40%.
  - CONCLUSION: 4 Gy × 5 was not inferior for motor function and ambulatory status versus 3 Gy × 10.

Data From Prospective Studies

- A prospective observational multi-center study comparing 30 Gy in 10 fractions with 40 Gy in 20 fractions found that 30 Gy in 10 fractions was associated with similar outcomes, less treatment time, and lower costs [26].
- Another prospective study comparing short course (8 Gy × 1 or 4 Gy × 5) versus long course (3 Gy × 10, 2.5 Gy × 15, 2 Gy × 20) radiation schemes found similar motor function improvement (~35%) for various fractionations while improved local control and progression-free survival were associated with protracted fractionation [27].

Retrospective Studies

- The largest retrospective study evaluated five common radiotherapy dose-fractionation schedules received by 1304 patients with MESCC: 8 Gy × 1, 4 Gy × 5, 3 Gy × 10, 2.5 Gy × 15, and 2 Gy × 20 [28,29].
  - The functional outcomes were similar; approximately 30% of the patients had improvement in motor function, and about 70% of the patients were ambulatory posttreatment.
  - However, in-field recurrence differed significantly; patients who received protracted fractionation had lower 2-year in-field recurrence rates (~25% for 8 Gy × 1 and 4 Gy × 5, 14% for 3 Gy × 10, ~8% for 2.5 Gy × 15 and 2 Gy × 20).
  - Based on this result, the authors recommended 8 Gy × 1 for patients with poor expected survival and 3 Gy × 10 for other patients.
- Multiple retrospective studies also demonstrated improved pain in 50–70% of patients and preservation of ambulatory ability in ambulatory patients with radiotherapy alone.
- However, radiotherapy has limited ability to improve motor deficit; <30% of the patients regained the ability to ambulate [3].
- Patients with a very good survival prognosis (prognostic score >36 in Table 12.2) appear to benefit from radiotherapy with higher total doses (>30 Gy) and lower doses per fraction (<3 Gy) in terms of better local control and survival of MESCC [30].

Highly Conformal Radiotherapy: Stereotactic Radiosurgery/ Stereotactic Body Radiation Therapy (SRS/SBRT)

- SRS/SBRT permits high dose conformal photon radiation therapy to deliver higher biologically ablative doses to improve local control while sparing spinal cord with a steep dose gradient, using a single-fraction or hypofractionated regimen.
- SRS/SBRT was initially investigated in vertebral metastases without epidural extension and has demonstrated excellent pain relief of approximately 90% and local control of 80% regardless of histology [31,32].
- However, SRS/SBRT has limited application in most patients with MESCC since many patients who present with MESCC have poor performance status, extensive disease, and/or poor prognosis.
- A recent prospective study from a single institution by Ryu et al. demonstrated radiosurgical decompression of epidural metastasis using a single fraction of 16 Gy is feasible.
  - An overall 81% improvement in neurological function, with mean epidural tumor volume reduction of 65% at 2 months after radiosurgery [33].

  - Dose constraint of the spinal cord is a major limitation: the portion of epidural mass directly compressing the spinal cord has to receive less therapeutic dose to protect the spinal cord.
- The ASTRO evidence-based guideline for palliative radiotherapy for bone metastases recommended SRS/SBRT be limited within a prospective trial [34].
  - Only selected patients without high-grade epidural compression, with isolated bone metastasis confined to 1−2 vertebral bodies, with no neurological deficits, and good performance status may be considered for SRS/SBRT.
- Toxicities for SRS/SBRT are generally mild and include esophagitis, mucositis, dysphagia, diarrhea, radiculitis, paresthesia, and pain flare.
  - Radiation-induced myelopathy is approximately 0.6% [35].
  - Vertebral fracture has been reported as a delayed complication [36].

Surgery

- Prompt neurosurgical evaluation is critical for patients with suspected spinal cord compression. Goals of surgery include circumferential decompression of the spinal cord to preserve neurological function and preservation or restoration of mechanical instability.
- Postoperative radiotherapy usually follows surgery.
- Patient selection is an important consideration; combined surgery and postop radiotherapy should be limited to surgical candidates with an expected survival of minimum of 3 months, good performance status (Karnofsky performance score (KPS) of ≥ 70), and with limited MESCC.
- Radiosensitive tumors, such as lymphoma, myeloma, and germ cell tumors, may be treated with radiotherapy without upfront surgical decompression.

Candidates for Surgical Decompression

- Good prognosis with expected life expectancy of more than 3 months.
- Good performance status.
- Limited extent of epidural compression.
- Isolated site of high-grade epidural compression leading to motor deficit.

Indications for Surgical Decompression

- Rapid neurological progression.
- Spinal instability.
- Spinal cord compression due to retropulsion of bone fragments causing impingement on the spinal canal [37].
- Progressive neurological symptoms consistent with progression during radiotherapy.
- Occasionally when pathological diagnosis is required.

Surgical Decompression

- The current surgical standard is direct decompressive surgery with maximal debulking, resection of tumor and bone in the canal, decompression of the neural elements, and appropriate reconstruction of the spine to provide stabilization.
- Decompressive laminectomy with or without radiotherapy did not show benefit and is no longer used in clinical practice [38].
  - Laminectomy removes posterior elements of the spinal column only but without tumor resection.
  - Spinal cord is not immediately decompressed with laminectomy.
  - Furthermore instability is possible due to resection of the posterior elements.
- The treatment paradigm of decompressive surgery followed by postoperative radiotherapy was established by a randomized clinical trial by Patchell et al. [39].
  - One hundred one patients with a single site of metastatic spinal cord compression from solid malignancies were randomized to decompressive surgery followed by radiotherapy versus radiotherapy alone.
  - Conclusion: Patients with single metastatic spinal cord compression treated with decompressive surgery and radiotherapy were able to maintain ambulatory ability longer and were more likely to regain ambulatory ability, when compared to radiotherapy alone.
    - More patients remained ambulatory after surgery plus radiotherapy compared to radiotherapy alone (84% vs 57%).
    - Those who were not ambulatory prior to treatment: 62% in the surgery and radiotherapy group regained the ability to walk after therapy, compared to only 19% of the patients who received radiotherapy only.
    - Patients treated with surgery maintained the ability to walk much longer (122 days vs 13 days).
    - The need for corticosteroids and analgesics was reduced in the surgical plus radiotherapy group.
    - In 20% of the patients in the radiotherapy only group, significant progressive motor dysfunction during radiotherapy was noted and these patients underwent surgery.
    - Survival time improved with surgery followed by radiotherapy (median 126 days vs 100 days).
    - Criticisms of the study include [40]:
      - Poorer outcomes for radiotherapy-only patients compared to historical data (patients maintained ambulatory ability for median of 13 days).
      - Statistical power is questioned because the study ended prematurely after meeting an early stopping rule.
      - Slow accrual: 101 patients over 10 years.

- The results of the highly selected cohort of the Patchell study could not be confirmed in a match pair analysis more likely reflecting clinical routine [41], which showed similar rates of motor function improvement and posttreatment ambulatory rate between the surgery/radiation and radiation alone arms.

	Patchell et al. (2005) [40] (Surgery/Radiation vs Radiation Alone)	Rades et al. (2010) [41] (Surgery/Radiation vs Radiation Alone)
Improved motor function%		27 vs 26
Posttreatment ambulatory rate%	84 vs 57	69 vs 68
% of nonambulatory patients regained ambulation	62 vs 19	30 vs 26
1-year local control%		90 vs 91

- In recent years separation surgery, or limited decompressive surgery, has recently been proposed to combine with radiotherapy.
  - Separation surgery decompresses epidural mass with spinal stabilization and provides a separation between the tumor and the spinal cord.
  - This allows optimal and safe delivery of highly conformal radiation therapy (SRS/SBRT) to treat the remaining cancer.
  - This approach may decrease the perioperative risk related to radical decompression and at the same time allow decompression of high-grade ESCC.
  - Single institution experience reported promising durable local control including 1-year control of 95% in 186 patients in one series [42].
  - This approach remains to be further investigated.

Surgical Stabilization

- Mechanical instability includes fracture-dislocation, translational deformity, and significant collapse of vertebral body with associated mechanical pain.
- This can lead to mechanical injury to the spinal cord resulting in detrimental neurological function.
- The spinal instability neoplastic score (SINS) was developed by expert consensus from the Spine Oncology Study Group to evaluate mechanical stability [43,44].

- See Appendix E (Palliative Care Toolkit) for SINS classification.
- Factors that predict instability include >50% vertebral body collapse, bilateral facet destruction, pain associated with movement, progressive deformity, presence of subluxation, and location in the junctional segments of the spine.

- Surgical stabilization should be strongly considered in patients with mechanical instability (e.g., high SINS score).
- Percutaneous cement augmentation such as vertebroplasty and kyphoplasty is not indicated for patients with spinal cord compression.
  - Although this approach may be effective in reducing pain due to compression fracture in cancer patients, patients with epidural metastasis were excluded in the CAFÉ study [45].

RECURRENCE

- In-field recurrence after initial radiotherapy for MESCC has been shown to occur in approximately 10–25% of patients [14,28,29].
  - A match-pair study comparing 8Gy × 1 versus 4 Gy × 5 for life expectancy <6 months reported need for in-field re-irradiation did not differ: 18% versus 9% at 6-months (NS) [46].
- If patients are surgical candidates with life expectancy >3 months, decompressive surgery for recurrence in the previously irradiated area is preferred.
- Re-irradiation may be the only suitable intervention for many patients due to poor performance status or short expected survival. It is well tolerated and effective when the cumulative biologically equivalent dose (BED) is limited to BED $\leq 120\ Gy_2$ (using alpha/beta of two for radiotherapy-induced myelopathy) [47,48].
- An analysis of 579 evaluable patients entered on two randomized trials that assessed radiotherapy for MESCC [47] concluded that re-irradiation was safe and effective.
  - One-half of patients with in-field recurrences after different doses and fractionations received re-irradiation.
  - Ambulatory capacity before re-irradiation was the strongest prognostic factor for functional outcome [47].
  - Mean interval between radiotherapy courses was about 5 months.
  - Ambulation was maintained in 86% of the ambulatory patients.
  - However, all five nonambulatory patients did not regain ambulatory function after radiotherapy [47].
- Motor function after re-irradiation was associated with performance status, time to developing motor deficits, visceral metastases, and whether first course improved motor function [48].

- Spinal re-irradiation using short-course radiotherapy (8 Gy × 1, 3 Gy × 5, or 4 Gy × 5) was showed to have equivalent effectiveness.
  - Eighty-five percent of the patients had stable or improved motor function [49].
  - Six of sixteen nonambulatory patients regained ambulation after radiotherapy.
- If the cumulative BED is $>120\ Gy_2$, surgery should be considered, if possible. SBRT is an alternative for those who cannot undergo surgery.
- Re-irradiation with SBRT may be considered in selected patients with isolated local recurrence, and good performance status and life expectancy.
  - Improvement of neurological deficits has been described in a retrospective single institutional study [50].
  - Neurological outcomes correlate with pretreatment neurological status. Thus diagnosis before development of neurological deficit is crucial.
- Clinical decision for re-irradiation should be made on a case-by-case basis, with at least a 5 month interval between the radiotherapy courses.

SUMMARY

- Patients with history of cancer who present with persistent back pain should be promptly evaluated for MESCC because early diagnosis and intervention of spinal cord compression results in the best prognosis of ambulation.
- Surgical decompression is the best initial therapy for selected patients with moderate-grade (compression of the thecal sac) or high-grade (compression of the spinal cord) ESCC, followed by radiotherapy. Exceptions include patients with a highly radiosensitive tumor, patients with multiple levels of MESCC, patients with a poor performance status, and patients with a very limited survival prognosis.
- Those patients who are not surgical candidates should be considered for radiotherapy alone.
- Radiotherapy planning uses AP/PA, PA only, or a posterior oblique field arrangement. The treatment field should encompass the site of compression and two uninvolved vertebral bodies above and below the level of compression with a width of 8−10 cm.
- The radiation fractionation regimen depends on the survival prognosis. Patients with a poor survival prognosis should receive 8 Gy × 1 or 4 Gy × 5, those with an intermediate prognosis 3 Gy × 10, and those patients with a very good prognosis 2.5 Gy × 15 or 2 Gy × 20.
- Retreatment for recurrent MESCC with external beam radiotherapy is safe and feasible. Cumulative radiotherapy dose (BED) should be kept to $120\ Gy_2$ or below. Otherwise, neurosurgery (if possible) or SBRT should be considered in patients with good survival prognosis.
- SRS/SBRT should be preferentially limited within a prospective trial for patients with a very good survival prognosis and limited metastatic

epidural extension, as recommended by the ASTRO Evidence-Based Guideline. This requires multidisciplinary evaluation by neurosurgery, radiation oncology, and medical oncology.

- Spinal stability needs to be evaluated by neurosurgery; stabilization surgery may be needed. Percutaneous cement augmentation such as vertebroplasty and kyphoplasty is not indicated for patients with spinal cord compression.
- Additional randomized trials are required to further optimize the treatment of MESCC.

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Chapter 13

Palliative Radiotherapy for Bone Metastasis

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Chapter Outline

Introduction/Background 189
Pathophysiology 190
Presentation/Evaluation 190
Clinical Assessment 190
Imaging 192
Management Overview 192
External Beam Radiation Therapy 193
Randomized Controlled Trials 193
Recommendations 195
Exceptions 195
Side Effects 196
QOL Improvement and Palliative EBRT 198
Re-Irradiation 199
- Intention to Treat 199
- Per Protocol Population 200
- Toxicity 200
- Conclusions 200

Stereotactic Body Radiotherapy/ Stereotactic Radiosurgery 200
- Prospective Trial 200

External Beam Radiation Therapy Techniques 201
Radiopharmaceuticals for Diffuse Painful Bone Metastases 202
Beta Emitters 202
Summary 204
Alpha Emitters 204
- Radium-223 204

Bisphosphonates and Denosumab to Prevent SREs 205
Bisphosphonates in Combination With EBRT 205
Denosumab 206
Conclusion 206
References 207

INTRODUCTION/BACKGROUND

- Bone metastases present a variety of unique and complex clinical challenges that demand a multidisciplinary approach for optimal management.
- Bone is the third most common site of metastases, affecting patients with a wide variety of malignancies, most commonly breast, prostate, lung, kidney, and thyroid carcinomas.

Handbook of Supportive and Palliative Radiation Oncology.

- It is estimated that 68% of bone metastases arise from breast, prostate, and lung cancer [1].
- The prevalence of bone metastases is not well understood, as bone metastases are likely underdiagnosed worldwide.
- Prognosis is varied, ranging from a few months to a few years, depending on primary tumor type, extent of disease, prior therapies, and performance status.
- Treatment recommendations must take into account the clinical symptom, the site and number of bone metastases, prior therapies, overall prognosis, and goals of care.
- Goals should include pain control, prevention of pathologic fracture or neurological deficit, local control, and improvement in quality of life (QOL).

PATHOPHYSIOLOGY

- The pathophysiology of bone metastases is driven by disruptions in the unique bone microenvironment.
- Specifically, one of the pathways involves alterations of the OPG/RANKL/RANK signal transduction pathway promoting increased osteoclast formation, accelerating bone resorption, which in turn releases bone-derived growth factors resulting in further proliferation of tumor cells. These tumor cells then further disrupt the OPG/RANKL/RANK pathway resulting in a cycle of bone loss and tumor growth.

PRESENTATION/EVALUATION

- Bone metastases can cause significant morbidity for patients.
- Clinical manifestations include pain, pathologic fracture, neurological deficits due to spinal cord compression or nerve root compression, and hypercalcemia.
- Most commonly, bone metastases present with pain.
- Pain can be severe requiring aggressive medical management.
- As lesions progress, they can inhibit function and mobility.
- Ultimately, they can result in a pathologic fracture causing intense pain and immobility.
- When involving the spine or sacrum, they can cause nerve root impingement and spinal cord compression with devastating neurological deficits.
- Evaluation must involve clinical assessment as well as imaging.

CLINICAL ASSESSMENT

- On exam, bone metastases are often associated with tenderness to palpation as well as functional pain limiting mobility and range of motion.

- Patients must be evaluated for neurological deficits including weakness, paralysis, sensory abnormalities, or incontinence.
- Pathologic fracture/instability assessment
  - Neurosurgical or orthopedic evaluation should be considered for bone metastases involving the spine or weight bearing bones.
  - Risk of pathologic fracture is difficult to predict; most evidence comes from retrospective surgical series.
  - The Randomized Dutch Bone Metastases Study showed that in patients with femoral metastases, a cortical involvement less than 30% had a 97% negative predictive value for fracture [2].
  - Mirels Staging System (Table 13.1 and Appendix) [3].
    - Site of lesion: Upper limb, Lower limb, Trochanteric region.
    - Nature of lesion: Blastic, Mixed, Lytic.
    - Cortical Involvement: <1/3, 1/3−2/3, >2/3.
    - Pain: Mild, Moderate, Functional.
      - Patients receive 1−3 points for each of the four categories, increasing from right to left.
      - Total <8, the risk of fracture is low and radiotherapy alone is recommended.
      - Total = 8, the risk of fracture is moderate and best clinical judgment is recommended.
      - Total >8, the risk is high and surgery should be strongly considered.
    - Only applicable to long bones (not spine).

TABLE 13.1 Mirels' Scoring System for Impending Pathologic Fracture Risk

Score	Site of Lesion	Size of Lesion	Nature of Lesion	Pain
1	Upper limb	<1/3 of cortex	Blastic	Mild
2	Lower limb	1/3 to 2/3 of cortex	Mixed	Moderate
3	Trachanteric region	>2/3 of cortex	Lytic	Functional
Total Score	*Recommendation*			
<8	The risk of fracture is low and radiotherapy alone is recommended			
= 8	The risk of fracture is moderate and best clinical judgment is recommended			
>8	The risk of fracture is high and surgery and adjuvant radiation should be strongly considered			

  - Has been independently validated and proven superior to clinical judgment alone [4].
- Recommendation for surgical management of impending fractures should take into consideration risk of fracture, patient performance status, comorbidities, and patient wishes.

IMAGING

- More than one imaging modality may be required for complete evaluation depending on clinical presentation.
- X-rays are often the first imaging study obtained as they are quick and inexpensive. However, they are limited in their ability to detect small lesions.
- Bone scans are ideal for screening patients at risk for bone metastases or evaluating the extent of bone disease.
  - However, bone scintigraphy only detects osteoblastic lesions, and therefore, should not be used for patients at risk for primarily osteolytic lesions as seen in multiple myeloma.
  - Bone scans are nonspecific and do not definitively distinguish between metastatic disease and other common pathologies such as arthritis and trauma.
- CT scans are the best modality for defining the size of an osseous lesion/destruction and assessing the amount of cortical involvement, imperative for assessment of pathologic fracture risk. They are also often utilized to guide needle biopsies for tissue diagnosis.
- MRI scans are particularly useful for vertebral metastasis to assess for spinal cord compression and epidural extension.
- PET/CT scans are useful for whole body screening and are particularly sensitive for osteolytic lesions.

MANAGEMENT OVERVIEW

- Treatment should begin with medical pain control.
  - World Health Organization Analgesic Ladder should be utilized as a framework for treating cancer pain.
  - Nonsteroidal antiinflammatory medications Nonsteroidal antiinflammatory drugs (NSAIDs) are often effective.
  - Steroids can provide rapid relief of pain, but should not be administered for extended courses due to side effects.
  - Pain from bone metastases is often severe requiring narcotic medications.
  - For neuropathic pain, medications such as gabapentin and amitriptyline can be attempted, but are unlikely to be sufficient on their own.
  - Antidepressants and benzodiazepines may be effective adjuvant medications in selected patients.
  - Refer Chapter 6, Pain Management, for a more detailed discussion.

- Good pain control can be achieved through medications, but QOL can be significantly impaired due to medication side effects. In order to minimize pain medication requirements, thereby, improving QOL, a number of local and systemic therapies can be utilized.
  - External beam radiation is the primary treatment modality for local pain secondary to bone metastases.
  - Surgical management for bone metastases is largely reserved for prevention or management of pathologic fractures and for decompression and stabilization for spinal cord compressions.
  - Interventional techniques such as vertebroplasty and kyphoplasty can be utilized for relief of mechanical pain caused by compression fracture due to vertebral metastases; however, little data exists regarding the efficacy and safety of these methods. An ablative procedure such as radiofrequency ablation or cryotherapy is often combined with these interventional techniques to prolong tumor control at the site.
  - A variety of systemic therapies are available including radiopharmaceuticals, chemotherapy, targeted agents, and bisphosphonates.

EXTERNAL BEAM RADIATION THERAPY

- External Beam Radiation Therapy (EBRT) is the standard of care for localized bone pain resulting from bone metastases.
- It is a noninvasive, well tolerated, and cost-effective treatment modality.
- Pain relief can be rapid, occurring within days to weeks of radiation.
  - The Randomized Dutch Bone Metastases Study reported the mean onset of pain relief occurring at 3 weeks and full palliative effect occurring 4–6 weeks after completion of treatment [5].
  - Given this delay in peak effect, medical management of pain remains critically important during and following radiation therapy.
- Pain response from EBRT ranges from 60% to 80% [6].
- Multiple prospective randomized studies have evaluated different dosing and fractionation schemes.
- However, it was not until 2000, that a consensus meeting was held to define and regulate endpoints in an attempt to improve consistency and allow accurate and meaningful comparison of future trials [7].
- Recommended dose fractionation regimens are summarized in Table 13.2.

RANDOMIZED CONTROLLED TRIALS

- Radiation Therapy Oncology Group (RTOG) 74-02
  - RTOG 74-02 was one of the initial randomized controlled trials comparing fractionation regimens for bone metastases [8].
    - Patients with a single bone metastasis were randomly assigned to 40.5 Gy in 15 fractions or 20 Gy in 5 fractions.

TABLE 13.2 Recommended Dose Fractionation Regimens for Bone Metastases

Uncomplicated Bone Metastasis	Impending Pathologic Fracture	Extensive Soft Tissue Component	Re-irradiation	Stereotactic Body Radiotherapy (SBRT)
8 Gy in 1 fraction[a]	*Definitive RT*: 30 Gy in 10 fractions *Postoperative RT*: 30 Gy in 10 fractions	30 Gy in 10 fractions	• 8 Gy in 1 fraction • 20 Gy in 5 fractions	• 50 Gy in 5 fractions • 16 Gy in 1 fraction

[a]*8 Gy in 1 fraction is the preferred regimen for all uncomplicated bone metastases regardless of primary tumor type, location, or prognosis.*

  - Patients with multiple metastases were randomized to 30 Gy in 10 fractions, 15 Gy in 5 fractions, 20 Gy in 5 fractions, or 25 Gy in 5 fractions.
  - Initial analysis showed 90% of patients experienced some pain relief and 54% of patients received a complete response to pain with no statistically significant difference in relief rates between any of the arms [8].
  - This study was criticized for using physician assessment of pain response, and reanalysis was performed with an altered definition of a complete pain response.
  - The reanalysis defined a complete pain response as no pain, no analgesic use, and no re-irradiation [9]. With this change in definition, a statistically significant benefit was found in the more protracted arms (40.5 Gy in 15 and 30 Gy in 10).
  - How pain response was defined dramatically altered the outcomes of this trial, illustrating the importance of definitions and end points.
- Two randomized trials compared single-fraction radiation doses.
  - Hoskin et al. randomized patients to 4 Gy versus 8 Gy in a single fraction [10].
  - Jeremic et al. randomized patients to 4 Gy versus 6 Gy versus 8 Gy [11].
  - In both of these studies 8 Gy was superior to 4 Gy. There was no apparent benefit of 8 Gy over 6 Gy in the later trial.
- RTOG 97-14
  - RTOG 97-14 compared 30 Gy in 10 fractions with 8 Gy in one fraction [12].
  - Patient assessment of pain response was evaluated with the Brief Pain Inventory.

- There were no differences in complete or partial pain response between the two arm ($p = 0.6$).
- The re-treatment rate was 18% in the 8 Gy arm and 9% in the 30 Gy arm ($p < 0.001$).
- However, narcotic use and progressive pain scores were similar between the two arms, suggesting that the higher re-irradiation rate was not simply a result of decreased pain response or decreased durability of pain response.
  - It has been suggested that the increased re-irradiation rate in the single-fraction arm was due to patient willingness to undergo re-irradiation given the ease of this fractionation scheme.
  - Furthermore, perhaps physicians are more willing to deliver re-irradiation following a total dose of 8 Gy as opposed to higher doses.

- Metaanalysis
  - A recent metaanalysis of 16 randomized trials including over 2000 patients demonstrated equivalent efficacy for pain control between single fraction 8 Gy and multifraction radiotherapy [13].
  - Complete pain response rate was 23% in the single-fraction arms and 24% in the multifraction arms. Rates were measured at variable time periods ranging from 3 to 8 weeks, where reported.
  - Overall pain response rates were 58% and 59% in the single-fraction versus multifraction arms, respectively.

RECOMMENDATIONS

- 8 Gy in 1 fraction is the preferred treatment regimen for noncomplicated bone metastases regardless of primary tumor type, site of metastasis, or prognosis, as it has demonstrated equivalent pain relief, while maximizing patient convenience and cost-effectiveness.
- Studies have reported higher rates of re-irradiation after single-fraction radiation versus more prolonged courses [2, 12].
  - Whether this is due to a less prolonged pain response or patient and physician willingness to consider re-irradiation after single-fraction radiotherapy remains unclear.

EXCEPTIONS

- More prolonged courses are recommended for bone metastases with an extensive soft tissue component or impending pathologic fracture in order to achieve greater tumor control and induce bone remineralization.
- Single-fraction radiation has been associated with higher rates of pathologic fracture in femoral metastases treated with radiation alone without surgical stabilization [2].

- Consider 20 Gy in 5 fractions or 30 Gy in 10 fractions in these instances.
- After surgical stabilization, the optimal radiation regimen is unknown, as little data exists.
  - However, similar principles of increased remineralization are applied, and more protracted courses of radiation are generally recommended.
  - Consider 30 Gy in 10 fractions.

SIDE EFFECTS

- External beam radiotherapy for bone metastases is very well tolerated regardless of fractionation used.
- General side effects could include fatigue, pain flare, skin irritation, or hair loss in the targeted area.
- Other side effects depend on the area being treated and dose to normal structures.
- In the chest, patients can experience sore throat, dysphagia, or cough.
- In the abdomen, nausea or enteritis is possible.
- In the pelvis, patients may develop loose stool/diarrhea or bladder irritation.
- Side effects are generally mild and self-limited.
- Recommendations for medical management of side effects during treatment are summarized in Table 13.3.
- Pain flare
  - A definition of pain flare was defined as a 2-point increase in the maximum pain score (0−10 on the Numeric Rating Scale-11) compared to baseline with no decrease in analgesic intake, or a 25% increase in analgesic intake with no decrease in the maximum pain score [14].
  - Pain flare should be distinguished from progression of pain by requiring the worst pain score and analgesic intake to return to baseline after the increase within a 10-day follow-up period [14].
  - May occur in up to 40% of patients [14].
  - Consider NSAID or dexamethasone administration.
  - A pilot study of 33 patients treated with 8 mg dexamethasone prior to 8 Gy in 1 fraction palliative EBRT for bone metastasis [15].
    - 8 (24% of patients) experienced a pain flare within the 10 day follow-up period.
    - Only 1 (3% of patients) experienced a pain flare within the first 2 days (duration of action of dexamethasone).
    - The authors concluded that dexamethasone may be effective in the prophylaxis of pain flare following palliative EBRT for bone metastases.
  - Hird et al. published a Phase II trial evaluating the prophylactic role of prolonged dexamethasone administration [16].

TABLE 13.3 On Treatment Management

Symptoms	Acute Management
Sore throat	Recommend over-the-counter analgesic medications
Cough	Recommend over-the-counter cough suppressants
Nausea/ Vomiting	Recommend prescription antiemetics • Ondansetron 4–8 mg PO TID PRN • Compazine 10 mg PO QID PRN • Phenergan 12.5–25 mg PO QID PRN • Ativan 0.5–1 mg PO TID PRN • Compazine and Phenergan available as suppositories if needed
	Continue antiemetics for 1–2 weeks posttreatment as needed
Loose stools/ diarrhea	• Goal of 1–2 bowel movements per day • Low residue diet (low fiber, low dairy, limit caffeine to slow motility) • Start with bismuth subsalicylates (Pepto-Bismol or kaopectate) • Add loperamide 4 mg PO × 1, then 2 mg PO after each subsequent loose stool, maximum 16 mg/day • If not controlled try lomotil (diphenoxylate/atropine) or combine loperamide and lomotil
	Continue antidiarrhea medications for 1–2 weeks posttreatment as needed
Cystitis	• Check a urinalysis if dysuria, increased frequency • For dysuria try OTV azo-standard or prescription phenazopyridine 100 mg PO TID × 3–7 days—caution patient about urine discoloration with this medication
	For urgency add antispasmodic agents such as oxybutynin 5–10 mg PO q day
Pain flare	*Prophylaxis*: • Dexamethasone 4 mg twice a day PO daily for 5 days • Administer the first dose at least 1 h prior to initiation of radiation therapy
	Treatment: • Begin dexamethasone 4 mg twice a day PO daily if not already initiated • Aggressive pain management is recommended as pain can be severe and debilitating • Nonsteroidal antiinflammatory medications (NSAIDS) are often effective • Opiate management is often required • If opiates are initiated or increased, remember to recommend an aggressive bowel regimen to avoid opiate-induced constipation

  - 41 patients received 8 mg of dexamethasone daily started at least 1 hour prior to delivery of EBRT (8 Gy × 1) and for three consecutive days after EBRT.
  - Pain flare occurred in 9 (22% of patients).
- A double-blind, randomized, placebo-controlled Phase III trial evaluating the efficacy of dexamethasone in reducing pain flares following EBRT for painful bone metastases was reported by Chow et al. in 2015 [17].
  - Dexamethasone was delivered to 148 patients at 8 mg at least 1 hour prior to radiation and then 8 mg/day for the following 4 days postradiation therapy.
  - Placebo was administered in 150 patients.
  - 39 (26%) patients in the dexamethasone group versus 53 (35%) patients in the placebo group experienced a pain flare ($p = 0.05$).
  - Two grade 3 and one grade 4 biochemical hyperglycemic events occurred in the dexamethasone group compared with none in the placebo group.
  - Other toxicities were mild and well balanced between the two groups.
  - This study supports the use of routine dexamethasone to reduce the incidence of pain flare.
- When discussing side effects of radiation, patients should be made aware of the possibility of a pain flare, and prophylactic dexamethasone therapy should be considered.

QOL IMPROVEMENT AND PALLIATIVE EBRT

- The goal of palliative therapy goes beyond resolution of symptoms to improvement in QOL.
- As discussed earlier, pain relief is a proven benefit of palliative EBRT for bone metastases, but does this translate to an improvement in QOL?
- The international consensus on palliative radiotherapy endpoints for future clinical trials in bone metastases defined end points largely in terms of patient-assessed pain score and analgesic consumption [18].
- The 2012 update published the recommendation for the inclusion of validated QOL instruments in all future clinical trials [19].
- McDonald et al. performed a literature review of all prospective and retrospective studies investigating the QOL following palliative radiation therapy for bone metastases [20].
  - Only three randomized controlled trials were found to include validated QOL tools.
  - Most commonly utilized tools were the Brief Pain Inventory, Edmonton Symptom Assessment Scale, European Organization for Research and Cancer Treatment (EORTC) QOL questionnaires.

- The review confirmed that the majority of patients did experience improvement in QOL after EBRT.
- Validated QOL assessment tools should be included in all future randomized controlled trials in bone metastases. (See Appendix for further details regarding these tools.)

RE-IRRADIATION

- Re-irradiation of bone metastases is safe and effective with response rates varying from 33% to 84% in retrospective studies using a variety of dose/fractionation regimens [21].
- Cumulative radiation doses to critical normal structures must be considered carefully, as in all re-irradiation scenarios.
- Chow et al. published results of an international Phase III randomized controlled trial comparing 8 Gy in 1 fraction versus 20 Gy in 5 fractions for re-irradiation of bone metastases [22].
  - 425 patients were randomly assigned to each treatment group.
  - 250 (48%) of all patients who received their assigned treatment had reduced pain at treatment site or reduced need for analgesia.
  - Pain severity was scored with the Brief Pain Inventory.
  - Primary endpoint was pain relief at 2 months after completion of re-EBRT.
  - Pain relief was defined as at least a 2 point reduction in worst pain score (without increase in analgesic use) or reduction in oral analgesic intake, or both.
  - The intention to treat analysis showed noninferiority of 8 Gy in 1 fraction as compared to 20 Gy in 5 fractions with less toxicity.
  - However, almost one-third of patients were not assessable at 2 months due to deaths, loss to follow up, or poor documentation.
    - 140 (33%) in the 8 Gy arm and 132 (31%) in the 20 Gy arm were counted as missing data in the intention to treat analysis.
  - In the patients who received the protocol treatments and were available for follow up (per protocol population), analysis did not meet the prespecified noninferiority margin.

Intention to Treat

- 118 (28%) patients in the 8 Gy arm had an overall pain response.
- 135 (32%) patients in the 20 Gy arm had an overall pain response.
- $p = 0.21$.
- 4.00% response difference (upper limit of the 95% CI 9.2, less than the prespecified noninferiority margin of 10%).

Per Protocol Population

- 116 (45%) patients in the 8 Gy arm had an overall pain response.
- 134 (51%) patients in the 20 Gy arm had an overall pain response.
- $p = 0.17$.
- 6.00% response difference (upper limit of the 95% CI 13.2, greater than the prespecified noninferiority margin of 10%).

Toxicity

- Lack of appetite at 14 days was 56% in the 8 Gy arm and 66% in the 20 Gy arm; $p = 0.011$.
- Diarrhea at 14 days was 23% in the 8 Gy arm and 31% in the 20 Gy arm; $p = 0.018$.
- Pathologic fracture, spinal cord, or cauda equine compression rates were not significantly different.

Conclusions

- Re-irradiation with 8 Gy in 1 fraction for painful bone metastases appears noninferior and less toxic than 20 Gy in 5 fractions.
- Findings, however, were not robust in a per protocol analysis, suggesting that trade-offs between efficacy and toxicity may exist.
- Given the current available data, either 8 Gy in 1 fraction or 20 Gy in 5 fractions can be delivered for re-irradiation of painful bone metastases per clinician judgment and patient preference.

STEREOTACTIC BODY RADIOTHERAPY/STEREOTACTIC RADIOSURGERY

- Oligometastatic disease is a unique clinical scenario for which ideal management options are still being investigated.
- It is hypothesized that patients with <5 metastases have potentially curable disease and should be treated aggressively with curative intent.
- Stereotactic body radiotherapy (SBRT)/Stereotactic radiosurgery (SRS) allows for ablative, potentially curative, doses while protecting critical normal structures.

Prospective Trial

- Milano et al.
  - Milano et al. prospectively evaluated 121 patients with five or fewer metastatic lesions involving 1−3 sites from any primary disease site treated with curative intent SBRT [23].
  - The majority of patients received 50 Gy in 10 fractions.

- Patients with breast cancer had improved outcomes compared to patients with nonbreast cancers.
- Breast cancer patients:
  - 2-year OS, freedom from distant metastases (FFDM) and LC rate was 74%, 52%, and 87%, respectively.
  - 6-year OS, FFDM and LC rate was 47%, 36%, and 87%, respectively.
  - None of the 17 bone lesions recurred after SBRT compared to 10 of 68 lesions involving other organs.
- Nonbreast cancer patients:
  - 2-year OS, FFDM, and LC rate was 39%, 28%, and 74%, respectively.
  - 6-Year OS, FFDM, and LC rate was 9%, 13%, and 65%, respectively.
- A larger SBRT target volume was associated with decreased OS and LC for nonbreast cancers.
- This study offers good support for the use of SBRT in select cases, particularly in breast cancer patients with good prognosis and for bone metastases.
- Further studies are needed to establish the role of curative intent therapy in patients with oligometastatic disease.

- It is also theorized that SRS/SBRT may provide greater and more durable pain control than conventional EBRT.
- Multiple single institution studies have reported pain control rates of approximately 90% with SRS/SBRT [24, 25].
- RTOG 0631 is currently open to enrollment and is randomizing 16 or 18 Gy in 1 fraction with SBRT to 8 Gy in 1 fraction with conventional EBRT for spinal metastases with the primary endpoint of pain control.
- SBRT for bone metastases appears to provide excellent pain control and local control; however there is a lack of randomized evidence.
- Selected patients with painful oligometastasis or isolated recurrence requiring re-irradiation with good prognosis may be considered as SRS/SBRT candidates.

EXTERNAL BEAM RADIATION THERAPY TECHNIQUES

- Radiation therapy for bone metastases is usually performed with 2–3 fields with either a fluoroscopy or CT simulation.
- Attention should be taken to minimize treatment time as radiation positioning can often worsen pain.
- Typically 6–15 MV photons are used; however, electron therapy can be beneficial in superficial lesions, i.e., ribs, sternum, or skull, as electrons allow adequate target coverage while minimizing dose to deeper structures.

- The use of more complex, highly conformal techniques, such as intensity-modulated radiation therapy (IMRT) or SBRT should be reserved for areas that have been heavily radiated previously or in the unique instance of oligometastatic disease in patients with good performance status and prognosis.

RADIOPHARMACEUTICALS FOR DIFFUSE PAINFUL BONE METASTASES

- When patients have diffuse bone metastases, localized therapies such as EBRT cannot address diffuse nature of pain.
- Hemibody radiation therapy techniques were utilized historically, but these have fallen out of favor due to toxicities.
- Radiopharmaceuticals are a compelling alternative.
- Calcium and phosphorous analogs are combined with a radioactive isotope with beta minus or alpha particle emission. These analogs preferentially accumulate in bone, particularly in areas of active bone turnover, allowing localized radiation delivery to these areas.
- Of particular interest, is that they can be safely combined with other therapeutic modalities including EBRT and chemotherapy.
- Efficacy of radiopharmaceuticals for pain palliation has been demonstrated in multiple RCTs.

BETA EMITTERS

- Strontium-89 (Sr-89)
  - Sr-89 is a calcium analog approved for use in metastatic prostate cancer in 1993 [26].
  - It is a pure beta minus emitter.
  - Average energy is 0.58 MeV.
  - Average range in soft tissue is 2.4 mm.
  - Half-life is 50.5 days [27].
  - The efficacy of Sr-89 for reducing pain has been shown in multiple randomized clinical trials.
    - A large multicenter Canadian trial prospectively randomized patients to Sr-89 versus placebo after localized EBRT [28].
      - 126 patients with hormone resistant metastatic prostate cancer were randomized to either a single injection of 10.8 mCi versus placebo.
      - There were no significant differences in survival or pain relief at the index site.
      - However, QOL, delay of pain progression, and tumor marker levels were all improved in the Sr-89 arm.

- Oosterhof et al. reported a Phase III randomized clinical trial comparing Sr-89 versus local EBRT in castrate resistant metastatic prostate cancer [29].
  - Over 200 patients were randomized to either one intravenous injection of 150 MBq of Sr-89 versus localized EBRT.
  - An overall survival benefit was seen in the EBRT group, 11 months versus 7.2 months, $p = 0.0457$.
  - There was no difference in pain response, progression free survival, time to progression or toxicity.
- A systematic review evaluating the efficacy of Sr-89 in patients with metastatic prostate and breast cancer reported some pain response to Sr-89 in 80% of patients and a complete pain response in 10% of patients [30].
  - Mean duration of response ranged from 3 to 6 months. As many as 10 injections every 3 months have been administered safely.
- A second review reported complete pain responses from 8% to 77% with an average complete pain response rate of 32% [31].
  - Onset of treatment ranged from 4 to 28 days with mean duration of response of 15 months.

- Sr-89 can also be combined safely with chemotherapy.
- Multiple randomized clinical trials have evaluated the efficacy and safety of combination Sr-89 and chemotherapy.
  - Sciuto et al. compared Sr-89 with cisplatin versus Sr-89 with placebo [32].
    - 70 patients were randomized to 150 MBq Sr-89 with 50 mg/m^2 cisplatin versus Sr-89 150 MBq plus placebo.
    - Pain relief was significantly improved in the cisplatin arm compared to the placebo arm, 91% versus 63%, $p < 0.01$.
    - Median duration of response and progression of bone disease were also improved in the cisplatin arm.
    - No survival differences or hematologic toxicities were observed.
  - Tu et al. reported a survival benefit with the addition of Sr-89 to doxorubicin [33].
    - They randomized 72 patients to doxorubicin with or without Sr-89.
    - Median survival was 27.7 months in patients who received Sr-89 and 16.8 months in patients who received doxorubicin alone, $p = 0.001$.

- Samarian-153 (Sm-153)
  - Samarian-153 (Sm-153), also a beta minus emitter, was approved in the 1990s.
    - It is created by neutron bombardment in a nuclear reactor and is chelated by ethylenediaminetetra-methylenephosphate (EDTMP) to increase affinity for bone.

  - Its mean energy is 0.23 MeV with average range of 0.6 mm and half-life of 1.9 days. It has 28% gamma emission [34].
  - A Phase III placebo controlled trial compared 0.5 or 1.0 mCi/kg of Sm-153 to placebo in 118 patients in a variety of cancers [35].
    - Sm-153 was associated with a significant improvement in pain relief ($p = 0.016$) with complete pain relief in 31% of patients by 4 weeks.
  - In another randomized Phase III trial, 152 patients with bone metastatic castrate resistant prostate cancer were randomized to receive either radioactive or nonradioactive samarium [36].
    - Complete pain relief was seen in 38% versus 18% of patients in the radioactive Samarian arm versus the non-radioactive arm, respectively ($p = 0.008$).
    - Sm-153 has also been shown to be safe and efficacious when combined with docetaxel in Phase I and II trials [37, 38].
- Rhenium-186 (Re-186)
  - Rhenium-186 (Re-186) is another beta minus and gamma emitting radionuclide.
  - Mean energy is 0.349 MeV, average range is soft tissue is 1.1 mm, and the half-life is 3.7 days.
  - The PLACORHEN study was a Phase III randomized study comparing Re-186 to placebo in 111 men with bone metastases from castrate resistant prostate cancer [39].
    - Mean pain response was 27% versus 13% in the treatment arm versus placebo arm, respectively ($p = 0.05$).

SUMMARY

- Sr-89, Sm-53, and Re-186 have all been shown to be efficacious and safe in Phase III randomized controlled trials.
- They have also been compared to each other head to head, but no significant difference in efficacy or toxicity has been described.
- These radiopharmaceuticals should be considered for patients with diffuse bone metastases for palliation of pain and expected survival >3 months.
- The addition of Sr-89 to doxorubicin has been shown to provide a significant overall survival benefit when compared to doxorubicin alone.

ALPHA EMITTERS

Radium-223

- Radium-223 is an alpha emitter.
- Radium-223 has been shown to prolong overall survival in patients with bone-metastatic castrate resistant prostate cancer.

- Alpha emitters have a significantly shorter range than beta emitters in the range of 2–10 cell diameters, minimizing myelotoxicities.
- A randomized controlled Phase III trial (ALSYMPCA) randomized 922 patients with symptomatic bone-metastatic castrate resistant prostate cancer to either six injections of Ra-223 (50 kBq/kg) every 4 weeks or placebo [40].
  - All patients had at least two bone metastases, with no visceral metastases, and had previously received docetaxel or were medically unable to receive docetaxel.
  - Primary end point was overall survival.
  - At the interim analysis, median overall survival was significantly higher in the Ra-223 arm (14.0 months) compared to the placebo arm (11.2 months), $p = 0.0019$.
  - The trial was closed early due to this benefit in the treatment arm.
- Radium-223 has now been approved for patients with bone-metastatic castrate resistant prostate cancer.
- Further studies are needed to test its safety with concurrent chemotherapy and its efficacy in other cancers.

BISPHOSPHONATES AND DENOSUMAB TO PREVENT SREs

- Bisphosphonates are an important systemic therapy for the treatment and prevention of skeletal complications.
- Bisphosphonates are pyrophosphate analogs that bind to exposed bone mineral. During bone resorption, they are internalized by osteoclasts and induce cell apoptosis, reducing the rate of bone resorption and remodeling [41].
- They have poor oral bioavailability, and are typically administered intravenously monthly.
- They have become standard of care in the management of multiple myeloma and solid tumors with confirmed bone metastases.
- Zoledronic acid has been shown in a prospective randomized trial to be more efficacious than pamidronate in breast cancer and advanced multiple myeloma [42].
- For castrate resistant prostate cancer and other solid tumors, zoledronic acid has also been shown to reduce skeletal related events (SREs) [43, 44].
- Complications related to bisphosphonate therapy include osteoradionecrosis of the mandible and renal toxicity.

BISPHOSPHONATES IN COMBINATION WITH EBRT

- The use of bisphosphonates in combination with EBRT has been evaluated in two prospective trials.
  - Vassiliou et al. evaluated 45 patients with bone metastases from a variety of solid tumors treated with EBRT (30–40 Gy over 3–4.5 weeks) with monthly ibandronate 6 mg IV for 10 cycles [45].

  - A complete pain response was seen in 57% and a partial response in 43%.
  - The mean pain scores (graded from 0 to 10) were reduced from 6.3 to 0.8 at 3 months.
  - Opiate use also decreased significantly from 84% to 24% at 3 months.
  - Bone density assessed by CT, performance status and functioning scores all significantly improved.
  - Treatment was well tolerated.
- A prospective study by Kouloulias et al. evaluated 33 patients with bone metastases from breast cancer treated with EBRT (30 Gy in 10 fractions) with monthly IV pamidronate for 24 months [46].
  - The therapy was well tolerated.
  - 88% complete pain response and a 12% partial response.

DENOSUMAB

- Denosumab is a human monoclonal antibody which binds to the RANK ligand, inhibiting the production and normal maturation process of osteoclasts.
- Two large prospective randomized studies have shown improved efficacy of denosumab when compared to zoledronic acid.
  - Stopek et al. randomized over 2000 breast cancer patient to either monthly denosumab or monthly zoledronic acid.
    - Denosumab was found to be more efficacious in terms of delaying time to first and subsequent SREs ($p = 0.001$) [47].
  - A second randomized controlled trial compared denosumab to zoledronic acid in castrate resistant prostate cancer [48].
    - Over 1900 patients were randomized.
    - Median time to first SRE was 17.1 months in the zoledronic acid arm and 20.7 months in the denosumab arm ($p = 0.008$ for superiority).

CONCLUSION

Bone metastases are a common and morbid occurrence in cancer patients. A multidisciplinary approach to management is needed to navigate the vast array of clinical scenarios and treatment options. For local treatment EBRT remains the mainstay of treatment. Surgery is important for treatment of and prevention of pathologic fractures. Radiopharmaceuticals offer good palliation of pain with diffuse bone metastases, with Radium-223 demonstrating a survival benefit in bone-metastatic castrate resistant prostate cancer. Bisphosphonates and denosumab should be considered to prevent SREs. Treatment recommendations should depend on prognosis and performance status.

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Chapter 14

Site-Specific Symptom Management: Palliative Radiotherapy for Advanced and Metastatic Lung Cancer

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Chapter Outline

Introduction 211
Evaluation 211
General History and Physical Exam 211
Treatment Recommendations 213
General Pulmonary Symptoms 213
Hemoptysis 217
Postobstructive Pneumonia 218
Mesothelioma 218
Superior Vena Cava Syndrome 220
Asymptomatic Metastases 222
Expected Acute Side Effects 224
On-Treatment Management 224
References 227

INTRODUCTION

Management of symptoms from locally advanced or metastatic lung cancer can be challenging due to their multifactorial nature. The use of palliative radiation therapy is generally accepted as a safe and effective means of symptom management in select patients. The doses and fractionation schemes in the literature are varied, though some may be more suitable based on other factors such as performance status, immediacy of symptom relief, and need for durability of control. Treatment-related toxicities vary with the schema and targets, and therapeutic ratio should be considered when offering treatment.

EVALUATION

General History and Physical Exam

- When patients present with either locally destructive or metastatic disease in the thorax, evaluation will often be directed by the nature of the complaint.

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- Given the diversity of critical structures in the thorax, location of the tumor in question will determine additional workup.
- After a general history and physical exam, a more focused history should be performed.
  - Evaluate presence of dyspnea at rest, associations with cough or chest pain, and exacerbating factors.
  - Qualifying and documenting dyspnea on exertion in relation to common exertions (i.e., number of blocks before resting, flights of stairs) can be useful in subjectively determining if a patient's functional respiratory status is improving or declining.
  - Assess for causes of baseline dyspnea, given that concomitant pulmonary disorders such as emphysema and chronic obstructive pulmonary disease (COPD) are prevalent in populations with small cell lung cancer (SCLC) and nonsmall cell lung cancer (NSCLC).
- Further workup depends on presenting symptoms
  - Initial imaging of the chest often includes chest X-ray followed by computed tomography (CT) of the chest. When medically possible, patients should have contrast-enhanced CT chest.
  - Dyspnea in the setting of malignancy can be multifactorial, given the possibility for any combination of embolism, infection, tumor, or effusion.
    - Presence of a pleural effusion should be sampled by thoracentesis if possible. This not only is therapeutic in the setting of removing compressive fluid, but also allows staging and prognostic information in the setting of malignant cells in the effusion.
    - Bronchoscopy can also be important for direct evaluation, tissue diagnosis, and the potential opportunity for therapeutic interventions such as endobronchial stents.
    - If there is suspicion for overlying infection, standard infectious workup should also be initiated, which would include complete blood count with differential and blood cultures.
    - As always, a thorough pain history is required. Duration of pain, character, severity, and exacerbating/alleviating factors are all equally important in thoracic malignancies.
    - In patients presenting with chest pain and/or shortness of breath, CT angiogram of the chest is often warranted to rule out pulmonary embolism (given malignancy as predisposition to hypercoagulable state). Differentiating symptoms such as pain or dyspnea related to an embolism versus local effects of tumor can be crucial in initiating effective palliation of symptoms.
- Patients suspected to have superior vena cava syndrome (SVCS) should have a thorough history taken relating to the duration and severity of classical symptoms.

- Symptom assessment should include facial edema and cyanosis (refer to the later section on management of SVCS for additional symptoms and implications). Consider a venogram.

- Complaints of dysphagia should be evaluated by endoscopy. Esophagogastroduodenoscopy (EGD) can be useful in determining the nature of dysphagia, including differentiating between extrinsic compression from an intrathoracic tumor and a tumor arising from or invading the esophagus directly. This can potentially be therapeutic providing the opportunity to dilate or stent obstructions if appropriate.
- Hoarseness should be further evaluated by fiberoptic nasal endoscopy to assess of the presence of primary laryngeal tumors as opposed to symptoms secondary to recurrent laryngeal nerve paralysis.

TREATMENT RECOMMENDATIONS

Patients with new or worsening respiratory symptoms often present with a suite of interrelated characteristics such as dyspnea, cough, and pleuritic chest pain. In this section we will explore treatment recommendations for general pulmonary symptoms as well as some specific scenarios such as SVCS.

General Pulmonary Symptoms

- Radiation has been shown to improve general pulmonary symptoms [1–13].
- Various fractionation schemes for radiation therapy have been studied. Table 14.1 has a summary of more commonly used and/or studied fractionation schemes and the relative benefit for several clinically relevant endpoints such as symptom control, toxicity, and survival.
- In 2001 [1], a Cochrane review of palliative radiation regimens for locally advanced NSCLC examined the contributions of available randomized evidence at the time. Though updated later in 2006 [2] and most recently in 2015 [3], the recommendations in these reviews have been largely unchanged.
  - As of the 2015 release, fourteen randomized trials were analyzed.
  - Inclusion required that the studies compare at least two radiation regimens based on effectiveness in palliation of symptoms from NSCLC.
  - One goal of these reviews was to identify subsets of patients that would benefit more from a particular regimen on the basis of symptom relief, performance status, convenience, or even survival.
  - Symptom control
    - While all trials reported improvement in symptoms with radiation, only three of the trials included showed a difference in symptom control with respect to the radiation regimen.

TABLE 14.1 Select Commonly Used Regimens With Available Randomized Evidence. Gray Boxes Indicate Insufficient Information for That Endpoint for a Particular Regimen. For Symptom Control, Durability, QOL, and OS, + Indicates Strength/Abundance of Evidence for Benefit. For Toxicities, + Indicates Tolerability of Treatment and − Indicates Increased Toxicity. For Tx Length, Higher + Indicates Longer Total Treatment Time

Regimen	BED_{10} (Gy)	Symptom Control	Durability	QOL	Tx Length	Toxicities	OS
30 Gy/10 fx [6,7,10]	39.00	+++	++	++	+++	+	++
20 Gy/5 fx [5,12]	28.00	+++		++	++	+	+
17 Gy/2 fx (weekly) [7–9]	31.45	++	+		++	+[a]	−
16 Gy/2 fx (weekly) [7,12]	28.80	++	−		++	+	+
10 Gy/1 fx [5,6,8]	20.00	+		+/−	+	+	−
39 Gy/13 fx [7]	50.70	++			++++	+/−[b]	+
45 Gy/18 fx [4]	56.25	++	+		++++	+	+
50 Gy/25 fx [11]	60.00	++			+++++	+/−	+

fx, fractions; *Gy*, Gray; BED_{10}, biologically equivalent dose assuming alpha/beta = 10 Gy for tumor control, *QOL*, quality of life; *Tx*, treatment.
[a]*Select instances of radiation myelopathy in this group.*
[b]*Increased acute esophagitis.*

- Teo et al. [4] compared 45 Gy in 18 daily fractions with 31.2 Gy in 4 fractions given once weekly. While there were no differences in survival or radiologic tumor regression, they reported significant improvement in symptoms (assessed monthly) in the 45 Gy arm.
- Bezjak et al. [5] randomized patients with 20 Gy in 5 fractions or 10 Gy in 1 fraction. Patients in the 20 Gy arm had significant improvement in lung cancer-related symptoms and patient-reported global quality of life (QOL) without any differences in toxicity. There was also a survival benefit (6 months compared to 4.2 months) in favor of the fractionated regimen.
- Erridge et al. [6] compared a more commonly used regimen of 30 Gy in 10 fractions with a single fraction of 10 Gy. They found no differences in survival, toxicity, or QOL between the arms. While a significant difference was found with respect to symptom palliation (dyspnea, chest pain) in favor of the 30 Gy regimen, this still met their prespecified parameters for equivalence.

- Survival: Multiple trials showed survival differences between the arms studied.
  - As mentioned earlier, the Bezjak et al. study [5] showed improved survival in the fractionated arms as compared to the hypofractionated regimens.
  - Three randomized trials from the Medical Research Council (MRC) were included in these reviews and each looked at slightly different regimens.
    - The earliest of the MRC studies compared 30 Gy in 10 fractions, 27 Gy in 6 daily fractions, or 17 Gy in 2 weekly fractions [7].
    - The second compared the use of 17 Gy in 2 weekly fractions with 10 Gy in a single fraction in patients with poor performance status [8].
    - The final MRC study included compared 36−39 Gy in 12−13 fractions with 17 Gy in 2 weekly fractions in patients with good performance status [9]. Overall, there was a statistically significant survival difference in favor of the more protracted fractionated regimen (31% vs 36% at 1 year and 9% vs 12% at 2 years) and difference in symptom control was reported between these regimens in all three MRC trials.
  - Kramer et al. [10] randomized patients to 30 Gy in 10 fractions or 16 Gy in 2 weekly fractions. There was a 1-year survival advantage in favor of the 30 Gy/10 fx arm (19.6% vs 10.9%). On subgroup analysis, this advantage was only significant in the patients with better performance status.

  - Another study enrolled asymptomatic unresectable patients with locally advanced NSCLC and randomized them to either 50 Gy in 25 fractions to the primary tumor/mediastinum or 20 Gy in 5 fractions to the same targets followed by another 20 Gy again 4 weeks later [11]
    - Survival favored the standard fractionation regimen (18% vs 6%), though this trial was criticized for split course design with a significant interval break, theoretically allowing for accelerated tumor repopulation.
  - Senkus-Konefka et al. [12] randomized patients to either 20 Gy in 5 fractions or 16 Gy in 2 fractions given 1 week apart. Survival was statistically significantly higher in the more hypofractionated arm (5.3 months vs 8 months in the 16 Gy arm).
  - The metaanalysis of survival in these trials showed an overall difference in 1-year survival barely achieving significance but favoring more fractionated regimens.
- Toxicity: Practitioners often balance potential differences in symptom relief durability with an increased chance of toxicities.
  - The three MRC trials mentioned showed a nonsignificant increase in severe (Grade 3–4) rates of esophagitis in shorter regimens, though the results were very heterogeneous and no definitive relationship was found.
  - Radiation-induced myelopathy was described in a small number of patients in the MRC trials [7–9] (five total patients) and another trial that had a single incident in the 50 Gy/25 fraction arm [13]. No clear relationship was found with respect to regimen, though this was a very rare event.
    - The authors of the metaanalysis calculated the $BED_{1.7}$ (for spinal cord) of each of the regimens where radiation myelopathy was noted, and each had (biologically equivalent dose) BED >100.
    - A prospective nonrandomized study of patients treated with 16 Gy in 2 fractions given 1 week apart ($BED_{1.7} = 91$ Gy) showed no incidents of myelopathy [14].
    - While the analysis of this uncommon toxicity has many weaknesses, use of regimens with $BED_{1.7} < 100$ or the use of a spinal cord block should be considered.
  - Pneumonitis rates ranged from 1.6% to 6.0% in these trials, but did not show a statistically significant difference in lower or higher fraction regimens.
- Endobronchial Brachytherapy (EBB): In 2011, the American Society of Radiation Oncology (ASTRO) released guidelines for palliative thoracic radiation therapy [15] that draws on many of the same randomized trials as above and has similar conclusions with respect to optimal external beam radiotherapy (EBRT) regimens. The ASTRO guidelines also evaluated and included EBB trials.

- EBB is a different method of delivering radiation therapy by direct insertion of a radioactive source into a target within a major bronchus.
- The guidelines identified six randomized trials that studied various combinations of EBB alone or in conjunction with EBRT.
- Inclusion criteria required at least a portion of the tumor within a central (main or lobar) bronchus in order to achieve potential benefit from EBB.
- Langendijk et al. [16] randomized patients with a luminal tumor component to EBRT with or without EBB. Dose of EBRT was at the discretion of the treating physician and the dose of EBB was 15 Gy in 2 fractions (insertions).
  - There was no difference in median survival, but there was a significantly increased rate of lung re-expansion (57% vs 35%) and improved dyspnea in the arm including EBB.
- With regards to EBB alone, Stout et al. [17] randomized patients to either 30 Gy in 8 fractions EBRT or a single 15 Gy EBB insertion. This showed improved palliation of symptoms with EBRT (83% vs 59%) with a slightly increased survival (9.4 vs 8.2 months).
- Dose optimization studies with respect to EBB have not shown a clear benefit with any particular regimen [18,19].
- A recent updated Cochrane metaanalysis of EBB reported no conclusive evidence that the addition of EBB to EBRT improved palliation but that EBB should be considered in patients previously treated by EBRT [20].

- In summary:
  - No obvious external beam radiotherapy regimen is overall superior for palliation of general respiratory symptoms.
  - Higher BED regimens may improve symptoms and even survival, but possibly with higher risk of toxicities (See Table 14.1).
  - EBB could be considered in patients previously treated with EBRT or in conjunction with EBRT in properly selected patients with a luminal tumor component to potentially improve dyspnea and lung re-expansion, though metaanalysis of evidence did not produce strong recommendations.
    - Selection of a regimen should take into account the patient's performance status and prognosis, patient convenience, durability of response, and anticipated toxicities, as patients with poorer performance status may be considered for more hypofractionated regimens.

Hemoptysis

- Outside of the Cochrane analyses, another notable review source analyzed many of the same trials with some exceptions. Fairchild et al.

(2008) [21] attempted to further specify the various pulmonary symptoms to be palliated, and examined BED-related trends in responses. Hemoptysis was specifically addressed in five of the trials included in this review. When divided by higher dose or lower BED arms, the respective rates of hemoptysis resolution were 73.7% and 68.9% (not statistically significant).

- Use of EBB after previous EBRT in the setting of hemoptysis has been studied, with up to 92% relief of hemoptysis rate if coming from endobronchial lesions [22].
- For additional details on the management of hemoptysis, refer to the chapter on hemoptysis in this textbook (See Chapter 9: Malignant Bleeding).

Postobstructive Pneumonia

- In addition to direct pulmonary symptoms such as dyspnea, cough, and pain mentioned earlier, there are also symptomatic issues that are secondary to the malignancy such as recurrent postobstructive pneumonia.
- Both EBB and EBRT may be used for relief of obstruction that leads to pneumonia (EBB for intraluminal causes and EBRT for external compression and intraluminal causes).
- One study of patients that had an endobronchial recurrence after previous EBB or EBRT showed an 82% response rate with respect to postobstructive pneumonia after repeat EBB (8–10 Gy single insertion) [22].
- An earlier study showed a comparable rate (88% response in postobstructive pneumonia) after EBB, though many of these patients also received EBRT with variable dose fractionation schemes [23].
- It is generally recommended that palliative radiation to an obstructive lesion be performed after resolution of acute infectious symptoms treated with an appropriate course of empiric antibiotics.

Mesothelioma

- While mesothelioma can present with any of the same above symptoms to palliate, there have been variable responses in this particular disease.
- Though curative-intent treatment regimens for mesothelioma include surgery with adjuvant chemotherapy and radiation, this rare often-fatal malignancy can often blur the lines between definitive and palliative treatments.
- More so than parenchymal lesions from NSCLC, mesothelioma often presents with more pleuritic pain symptoms.
- Given the low incidence of mesothelioma in the general population, evidence for treatment comes often from retrospective series and small prospective trials.

- MacLeod et al. [24] reviewed the available literature related to mesothelioma treated with radiation therapy specifically for pain symptoms. All studies were level 2 or 3 evidence, and heterogeneity precluded quantitative evaluation. Two trials prospectively evaluated pain, with mixed results.
- Linden et al. [25] did not find a significant pain control benefit to the addition of radiation (40 Gy in 20 fractions).
- Bissett et al. [26] used older radiation techniques (Cobalt 60 machines) and found 68% pain improvement measured by prospective pain scores. The review authors were unable to make definitive conclusions on pain relief with radiation based on limited evidence, though options are often limited in this disease.
- Jenkins et al. [27] published one of the larger retrospective series from a single institution where patients were treated to 36 Gy in 12 fractions.
  - 54% rate of reduction in chest pain symptoms with radiation.
  - Four patients here presented with SVCS, of which three had symptom relief.
  - One patient presented with dysphagia and had relief after radiation.
  - Only two patients developed grade three toxicities (one pneumonitis, one nausea).
  - Response to radiation was predicted by performance status and prognostic category.
- The largest retrospective study available looked at 189 patients with mesothelioma that received radiation for any reason [28].
  - 50% local reduction in pain with median dose of 36 Gy.
  - The median duration of pain relief was significantly higher in patients treated with fraction sizes higher than 4.0 Gy (98 days vs 69 days).
  - Potentially confounded because patients with disease encompassing >66% of the hemithorax were generally given less than 4.0 Gy fractions.
- Cochrane review of radiation in mesothelioma was published, but the lack of randomized evidence prevented them from making any definitive conclusions [29].
- Recent European Society for Medical Oncology (ESMO) clinical practice guideline recommended consideration of palliative radiation in the setting of chest wall pain/invasion with mesothelioma [30].
- Currently there are open trials in the United Kingdom studying post-surgical radiation to the surgical tract and will reportedly include pain evaluation.
- Overall, while radiation-related pain relief in mesothelioma shows variable response rate in the literature, performance status, prognosis,

and patient goals of care can help identify subsets that may have higher chance of benefit.

Superior Vena Cava Syndrome

- SVCS is a clinical diagnosis made based on the presence of characteristic features in the setting of obstruction of the SVC. The constellation of symptoms is related to the reduction of venous flow through the SVC, causing an increase in venous pressure in more proximal vessels.
  - Can lead to facial plethora/edema, cyanosis, edema in upper extremity, and distention of subcutaneous vessels of the neck and chest.
  - Symptoms of laryngeal edema (stridor) and cerebral edema (headaches, visual changes, syncope) can occur, and can be potentially life threatening. The neurologic symptoms occur in 2–10% of documented cases, while stridor was noted in 4% of patients [31].
- While compression by a malignancy is more common [32], impingement of the SVC by any process can lead to a similar clinical picture. Within malignant causes, primary lung carcinomas comprise a majority of cases [32], though SVCS can also be caused by lymphomas, metastatic parenchymal lesions, malignant lymphadenopathy, or other less common thoracic tumors.
- Historically, the presence of SVCS was regarded as a relative emergency, at least partially due to rarer complications related to cerebral or laryngeal edema.
- An older review of SVCS outcomes looked at 1986 patients, of which a single death was documented as the result of SVCS [33].
- Initial management of patients with SVCS is often guided by the severity of symptoms and the nature of the underlying malignancy.
- Strategies aimed at relief of the obstruction must be weighed against treatment of the overall oncologic process.
  - If life-threatening symptoms occur, such as airway compromise or symptoms of cerebral edema, relief of compression may take precedent over other diagnostic tests or treatments.
  - In the presence of any neurologic symptoms with SVCS, evaluation for concomitant brain metastases is crucial given the high prevalence of brain metastasis.
  - If symptoms are nonurgent or stable for a period of time (as in a majority of presentations), the patient may be better served by completing the staging workup and obtaining tissue diagnosis for those without a diagnosis of malignancy. Some evidence exists that empiric radiation therapy prior to tissue diagnosis in emergent thoracic scenarios can obscure the subsequent biopsy results [34].
  - When treating the obstruction itself, several approaches exist, including early conservative measures, steroids, radiation, chemotherapy,

and endovascular stenting. A Cochran review of treatment strategies is summarized here:

- Early conservative measures can include elevation of the patient's head to reduce pressure secondary to edema, though there is no empirical evidence that this is effective [31].
- Steroids: No studies directly evaluate the role of steroids in palliation on SVCS. However, these can be used during radiation management in order to mitigate temporary worsening obstruction due to tumor edema.
- Chemotherapy versus Radiotherapy: similar response rates with either.
  - In patients with SCLC, the authors of the Cochran review noted relief in 76.9% with chemotherapy and 77.6% with radiation therapy.
  - There was a slightly lower response rate in NSCLC for both treatment types (59% with chemotherapy and 63% with radiation).
- Data from randomized trials were included:
  - Spiro et al. reports an unplanned subset of a randomized trial with SCLC receiving chemoradiation versus chemotherapy: 37 patients had SVCS, and no difference in SVCS recurrence [35].
  - A randomized phase II trial included 34 patients with NSCLC presenting with SVCS, randomized to multiagent chemotherapy or radiation therapy with cisplatin [36]. The rates of SVCS relief and relapse were not different between the two arms.
- Endovascular stenting
  - Stenting is the most rapid and effective treatment with respect to relief of symptoms in patients that are able to tolerate the procedure.
  - Another advantage to stenting is that tissue diagnosis is not required, nor does upfront stenting obscure future pathologic diagnosis attempts.
  - This is a technique that requires technical expertise and may be difficult to generalize to all centers.

- Several fractionation schemes have been studied.
  - Overall consensus is to use fractions of 3.0−4.0 Gy.
  - Commonly used fractionation schemes include 30 Gy in 10 fractions, 37.5 Gy in 15 fractions, and 20 Gy in 5 fractions.
  - Multiple studies show that the time to beginning of improvement after radiation therapy is about 72 hours. This should be considered when weighing the timing of other treatments.

- Treatment recommendations by SVCS classification
  - Life threatening symptoms (~5% of patients [37]).
    - Assess for signs of significant cerebral or laryngeal edema.
    - Immediate endovascular stenting is recommended for these patients.
    - Immediate RT or chemotherapy should be considered (histology dependent) if stenting not available/unsafe.
  - Less severe symptoms
    - Tissue diagnosis.
    - Staging.
    - Multidisciplinary opinion.
  - SCLC and other chemoradiosensitive histologies: Initiation of chemotherapy if medically possible.
  - NSCLC and other nonchemoradiosensitive histologies: Consideration of early radiation or stenting.

Asymptomatic Metastases

- The treatment of asymptomatic metastases to the lung/thorax is sometimes controversial.
- Traditional canon is that palliative treatments should be used for active/impending symptoms.
- In recent years, treatment of oligometastatic disease has been an increasingly popular topic [38]. In certain malignancies, metastatic disease can be controlled effectively for years with a variety of systemic/targeted therapies and local treatments such as metastasectomy [39].
- While still not definitive therapy per se, targeting thoracic metastases with local therapy such as surgery or radiation in the setting of disseminated disease is an increasingly studied paradigm.
- Stereotactic body radiation therapy (SBRT) for selected patients with oligometastasis to the lung has been established in recent years with safe delivery of higher doses per fraction to small defined metastases.
  - Currently there are no randomized data comparing SBRT to surgery or no local treatment, but several prospective trials have shown promising results.
    - One multiinstitutional Phase I/II trial was conducted enrolling patients with 1–3 lung metastases from a variety of different primary sites [40].
      - The Phase I aspect of the trial escalated the dose from 48 Gy to 60 Gy in 3 fractions with no dose-limiting toxicities and all patients in the Phase II aspect were prescribed 60 Gy in 3 fractions.
      - Local control (actuarial) with SBRT was 100% and 96% at 1 and 2 years, respectively.
      - Median survival was 19 months and 2-year survival was 38%.

- The treatment was well-tolerated, with 7.9% incidence of any grade 3 toxicity (including a single incident of grade 3 pneumonitis) and no grade 4–5 toxicities.

- Another recent study examined patients with oligometastatic NSCLC specifically with ≤5 active metastases that were treated to 50 Gy in 10 fractions [41].
  - Grade 3 pulmonary toxicity (cough, pneumonitis) was 8% with no toxicities of grade 4–5.
  - Partial metabolic response rate (by PET) at 30% and a complete response rate of 30% for a total 60% response.
  - In-field failures occurred in 15% of patients.
  - The median survival was 23 months and 1-year overall survival of 67%.
  - This study had a slightly lower lesion control rate than others, likely partially attributed to lack of respiratory motion control compensation in the SBRT technique and the use of a lower BED treatment.

- A third recent prospective trial combined SBRT with erlotinib in patients with metastatic NSCLC of limited scope, defined as less than six sites of extracranial disease and no more than three pulmonary lesions [42]. Multiple fractionation schemes were permitted, including 19–24 Gy for single fraction, 27–33 Gy for 3 fractions, or 35–40 Gy in 5 fractions.
  - Median OS was 20.4 months and median progression-free survival was 14.7 months.
  - Of the 47 evaluable sites treated, three showed in-field progression (6.4%).

- Patient selection is key in predicting benefit from local therapies in disseminated disease.
  - De Vin et al. [43] proposed a prognostic model for patients with oligometastatic disease treated with SBRT.
    - Patients with adenocarcinoma fared significantly better with respect to survival compared to nonadenocarcinoma, though this may reflect differences in natural disease history rather than response to SBRT.
    - BED_{10} of ≥75 Gy compared to <75 Gy was a significant predictor of survival.
    - Several patient-related factors identified that predicted survival after SBRT including dose, histology, primary location, and gender (female patients had improved survival).
  - A metaanalysis examined individual data on patients with oligometastatic NSCLC treated with either surgery or SBRT [44].
    - Patients were divided into risk groupings based on recursive partitioning analysis that identified lower nodal stage, histologic

type, and metachronous presentation as positive predictors of survival after local therapy.
  - Though there was no control group in this analysis, these patient-related factors may help guide the decision to offer local therapy to oligometastatic disease.
- In summary, while SBRT can be used safely and effectively for localized or oligometastatic thoracic lesions, randomized trials will be needed to demonstrate that it provides disease-free or overall survival benefits for patients. Patient selection is an important part of determining the potential benefit of these local therapies, and BED of the SBRT regimen chosen may predict response.

EXPECTED ACUTE SIDE EFFECTS

- Acute toxicities of radiation therapy are dose and fractionation-dependent.
- In general, patients may experience standard toxicities, such as skin changes (erythema, pruritis, desquamation) and fatigue.
- Treatment of larger fields that are potentially occupied by remaining healthy lung tissue should be done with care.
- Standard lung constraints should be respected, though these were generally developed for either standard fraction sizes (such as 1.8 Gy to 2.0 Gy per fraction) or SBRT.
- Doses associated with palliative radiation can range from 2.0 Gy to 8.0 Gy in fraction-size, and therefore exist between conventional EBRT and SBRT dose constraints. If constraint violation is in question, calculation of BED is recommended to aid clinical decision-making.
- Hypofractionated regimens have been associated with some acute onset symptoms within 24–48 hours of treatment including fevers, rigors, chest pain, or sweating [45]. These symptoms are not serious and rarely require intervention, but should be part of expectant counseling for patients.
- While nausea/vomiting can occur in patients on treatment in general, patients receiving treatment for mesothelioma seem to experience this at a higher rate.

ON-TREATMENT MANAGEMENT

- General management on treatment should include at least weekly vital signs including orthostatic blood pressure readings to monitor for dehydration and accurate weight to monitor for accelerated weight loss.
- Skin changes like erythema and dry desquamation should be managed with topical emollients.
- Though uncommon in doses such as these, moist desquamation should be treated with antimicrobial topical agents such as silver sulfadiazine.

- Radiation-induced esophagitis
  - Can be managed with topical analgesics such as viscous lidocaine alone or in mixtures with antacids and antihistamines (occasionally referred to as "magic mouthwash" or "oncology mouthwash"). These often offer only temporary relief of esophagitis symptoms but can be effective if optimally timed for meals or oral intake.
  - Escalated pain symptoms in this setting sometime require narcotics for management. Transdermal narcotics can be effective at providing long-acting analgesia without requiring oral administration.
  - Overuse of narcotics should be regarded with caution given the potential for respiratory depression in a population that may have significant dyspnea at baseline.
- Occasionally costochondritis can develop and cause mechanical chest pain.
  - This may be more common with SBRT and can be acute or subacute (6 months to 1 year) after treatment.
  - Usually conservative measures including over-the-counter nonsteroidal antiinflammatory medications are adequate to treat this until they resolve spontaneously.
- Acute cardiac toxicities are uncommon, and may manifest as pericarditis or pericardial effusion.
  - If pericarditis is suspected on the basis of chest pain or hemodynamic changes, evaluation by cardiology or emergency medicine is recommended.
  - Pericardial friction rub on exam and diffuse ST segment elevations on electrocardiogram are characteristics. This can usually be managed conservatively with antiinflammatories.
  - Constraints proposed by an MD Anderson review of pericardial effusion in treatment of esophageal tumors with definitive radiation include mean dose <26 Gy and V30 $<46\%$ [46], though these may not be directly applicable to the various dose regimens and fraction sizes used in palliative thoracic radiation.
  - Another study pooling protocol patients at a single institution reported an actuarial rate of 3.9% for pericarditis at 6 months, which suggested that fraction size may predict development of pericarditis or effusion [47].
- Possibly the most challenging on-treatment toxicities to manage are those related to the patients' respiratory symptoms.
  - Patients may present with a history of respiratory issues and are often receiving palliative radiation due to an acute exacerbation of these symptoms.
  - Worsening dyspnea or cough on treatment could represent radiation toxicity, tumor progression, embolism, infection, or development of a pleural effusion.

TABLE 14.2 On-Treatment and Chronic Management of Toxicities

Symptoms	Acute Management	Late Management
Respiratory symptoms: • Cough • Shortness of breath • Dyspnea on exertion	• Consider differential diagnosis given proclivity to develop pulmonary embolism, postobstructive pneumonia, or pleural effusion. If acute presentation, workup including CT angiogram may be indicated • If no reversible causes are found, treat symptomatically with: • Antitussive syrups (including those containing codeine, guaifenesin) • Tessalon perles 1–2 caps TID PO • Mucinex-600 mg PO BID	• Subacute/late radiation pneumonitis, a course of steroids may be indicated (40–60 mg prednisone q Day then taper) or indomethacin (25 mg PO BID-TID) if more mild • Optimize medical management of comorbidities such as COPD/emphysema • Pulmonary rehabilitation programs • May require home oxygen
Odynophagia or dysphagia secondary to esophagitis	• Temporary relief can be provided by various 1:1:1 combinations of viscous lidocaine, antacids like Maalox, and antihistamines like diphenhydramine ("Magic Mouthwash"), usually 5 mL taken immediately prior to a meal or PRN through the day • Carafate 2 tsp swallow QID • Accelerated pain may require narcotic management; consider elixir formulations or smaller tablets such as oxycodone for ease of administration	• Long-term esophagitis rare but chronic dysphagia can occur with strictures • May require endoscopy with esophageal dilation which can be repeated • May require nutritional support if pain or dysphagia limit diet
Costochondritis	• Confirm reproducible mechanical pain on exam to differentiate from cardiac or pulmonary chest pain • Conservative measures with over-the-counter nonsteroidal antiinflammatory medications • Many resolve spontaneously	• May develop 6–12 months after treatment with SBRT, though managed similarly • Consider physical therapy

(*Continued*)

TABLE 14.2 (Continued)

Symptoms	Acute Management	Late Management
Skin toxicities	• Usually mild at these doses • Managed with topical emollients for preventative care or treatment of erythema/dry desquamation • Moist desquamation managed with silver sulfadiazine	
Pericarditis	• Uncommon; if acute symptomatic pericarditis is suspected based on symptoms or EKG, emergency department evaluation may be indicated • Can be managed with antiinflammatories, however, this should be done under the guidance of a cardiologist	

- As these are all managed in very different ways, there should be a low threshold to order repeat diagnostic imaging or infectious work-ups while on treatment.
- Depending on etiology, a trial of inhaled bronchodilators may be useful.
- As earlier, concurrent steroids may be effective in reducing transient tumor swelling when treating compression-related symptoms. Working closely with the patient's pulmonologist is advised (Table 14.2).

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Chapter 15

Palliative Radiation Oncology for Gastrointestinal Tract Malignancies

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Chapter Outline

Introduction/Background	**231**	**Anorectal Cancer**	**244**
Esophageal Cancer	**232**	Liver Metastases	246
Dysphagia	232	**On Treatment Management**	**249**
Gastric Cancer	**236**	**Conclusion**	**249**
Pancreatic Cancer	**237**	**List of Abbreviations**	**252**
Hepatobiliary Cancer	**242**	**References**	**252**

INTRODUCTION/BACKGROUND

- Gastrointestinal (GI) tract malignancies include a diverse group of diseases including esophageal, gastric, pancreatic, hepatobiliary, small bowel, colon, rectal, and anal cancers.
- Unfortunately over 50% of these malignancies present at locally advanced or metastatic stages making palliative treatments an integral part of their management.
- Locally advanced disease within the GI tract can cause a variety of symptoms including, but not limited to, dysphagia, bleeding, obstruction, nausea/vomiting, malnutrition, dehydration, and pain [1].
- A multidisciplinary approach is required for optimal palliation.
- This chapter addresses the most common symptoms and their management with a focus on radiation therapy.
- We will conclude by exploring a unique topic within gastrointestinal metastatic disease: liver metastases.

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ESOPHAGEAL CANCER

- Despite advances in the multidisciplinary treatment of esophageal cancer, the 5-year overall survival rate remains low at approximately 15%, with over 50% of patients presenting with locally advanced or metastatic disease [2].
- Local progression of disease within the esophagus can cause severe morbidity including dysphagia, pain, and bleeding.

Dysphagia

- Malignant dysphagia is a complex medical problem with debilitating consequences for the patient.
- It can progress rapidly from difficulty swallowing solids to the inability to swallow liquids and saliva, placing the patient at risk for severe nutritional deficits and aspiration pneumonia.
- Evaluation must include swallow evaluation with consideration of feeding tube placement.
- Many treatment options exist for the management of malignant dysphagia with no clear consensus on optimal treatment paradigms as few studies have directly compared modalities with formal quality of life end points or measurements.
- Many times, in the setting of disseminated disease, systemic therapy can be initiated first with improvement of dysphagia.
- Beyond systemic therapy, options include surgical bypass or resection, external beam radiotherapy (EBRT) or brachytherapy (BT), endoscopic dilation, stenting, or endoluminal ablation [3].
- Given the limited prognosis and generally poor prognosis of these patients, surgical management is often deferred in favor of a less invasive approach.
- Most commonly utilized is stenting and/or radiation therapy [4].
- Endoscopic dilation is often used for immediate relief of symptoms, but on its own requires serial dilations with increased risk of esophageal perforation [5].
- Stenting has also been shown to provide rapid relief of dysphagia. However, the durability of this response is similarly limited due to stent migration and local tumor progression [6].
- Table 15.1 summarizes management recommendations of dysphagia by prognosis.

Radiation Therapy

- Radiation therapy has the advantage of treating the cause of dysphagia, gross tumor, rather than just the symptom, resulting in a more durable response.

TABLE 15.1 Management of Dysphagia Summary

Prognosis	Treatment Option
<3 month	Stenting +/− EBRT (20 Gy in 5 fractions or 30 Gy in 10 fractions) or BT (7–28 Gy in fractions of 5–7 Gy)
3–6 months	EBRT (20 Gy in 5 fractions or 30 Gy in 10 fractions) +/− BT (8 Gy in 2 fractions)
>6 months	CRT (30–50 Gy) after initial systemic therapy with stable disease

EBRT, External beam radiotherapy; *BT,* brachytherapy; *CRT,* chemoradiation.

- Two randomized controlled studies have compared BT to stenting.
  - Homs et al. compared high dose rate (HDR) BT with stent placement [7].
    - Between 1999 and 2002, 209 patients from nine hospitals in the Netherlands were randomized to either stent placement or single dose BT. Stents deployed were all self-expanding metal stents, and BT was delivered in a single fraction of 12 Gy.
    - Relief of dysphagia occurred more rapidly after stent placement than after BT, but relief persisted longer in the BT group.
    - There were also improved quality of life scores and fewer complications in favor of BT (21% vs 33%, $p = 0.02$).
  - Berquist et al. also compared HDR BT with self-expanding metal stent placement [8].
    - The BT regimen was 7 Gy in 3 fractions delivered over 2–4 weeks.
    - A total of 65 patients were randomized.
    - At 1 month, the patients who underwent stent placement had significantly higher quality of life scores for dysphagia ($p = 0.05$), but most other quality of life scores declined.
    - Dysphagia scores improved at 3 months in the BT group with little deterioration of other quality of life scores.
    - Dysphagia recurrence was higher in the stent group.
    - When immediate relief of dysphagia is indicated and prognosis is poor, stenting is the preferred approach as onset of relief is rapid.
  - If prognosis is greater than 3 months, HDR BT is recommended.
    - Dose recommendations from the American Brachytherapy Society are 7–28 Gy in fractions of 5–7 Gy [9].
    - Lower doses should be utilized in patients who have previously undergone EBRT to the esophagus for either definitive or palliative management.

- A recent multicenter randomized trial compared conventional metal stent placement with stents combined with low dose rate (LDR) BT [10].
  - Zhu et al. randomized 160 patients to either a conventional metal stent or a stent loaded with Iodine-125 seeds.
    - Overall survival was improved in the BT group with a median overall survival of 177 days versus 147 days ($p = 0.0046$).
    - Side effects from treatment were similar between the two groups.
    - This approach combines the rapid onset of relief provided by stent placement with the prolonged durability of response provided by BT with no increase in treatment length.
- EBRT alone also provides significant relief of dysphagia.
  - Multiple retrospective studies have shown a significant palliation of dysphagia in 70–90% of patients undergoing EBRT alone [11–14].
  - Palliative treatment regimens range from 30 Gy over 2 weeks to 50 Gy over 5 weeks.
  - Relief of dysphagia typically takes >2 weeks, so if severe, stenting +/− EBRT or BT is typically preferred.
  - Choice of regimen should be based on patient goals, performance status, and preference.
- EBRT can also be used in combination with stenting, BT, and chemotherapy.
  - Javed at al. compared metal stenting alone versus stenting followed by EBRT [15].
    - A total of 84 patients were randomized to either metal stent placement alone or metal stent placement followed by 30 Gy in 10 daily fractions of EBRT.
    - Dysphagia scores improved in both groups after stent placement, but the response was more durable in the radiation group (7 vs 3 months, $p = 0.002$).
    - Overall median survival was also significantly higher in the radiation group (180 vs 120 days, $p = 0.009$).
    - Of note, QOL scores improved after stenting and declined immediately following radiation.
    - This reinforces the idea that if prognosis is <3 months, stenting alone is a reasonable option.
    - However, if prognosis is >3 months, adjuvant EBRT should be strongly considered after stent placement.
    - At our institution, we recommend multimodality management with stent placement followed by radiation therapy in patients with moderate to severe dysphagia and prognosis >3 months.
  - Rosenblatt et al. performed a randomized trial comparing BT alone versus BT followed by EBRT [16].
    - A total of 219 patients were randomized.
    - All patients received BT consisting of 8 Gy in 2 fractions within 1 week.

  - The EBRT group went on to receive 30 Gy in 10 daily fractions.
  - Dysphagia relief was significantly improved with combined therapy, for an absolute benefit of 18% at 200 days from randomization ($p = 0.019$).
  - Furthermore, scores for dysphagia ($p = 0.00005$), odynophagia ($p = 0.006$), regurgitation ($p = 0.00005$), chest pain ($p = 0.0038$), and performance status ($p = 0.0015$) were all significantly improved.
  - However, weight, toxicities, and overall survival were not different between the study arms.
  - Combination of BT and EBRT appears effective and well tolerated and should be considered in patients with reasonable performance status and prognosis approaching 6 months.
- A Phase I/II prospective trial from Canada evaluated the efficacy and toxicity of short course EBRT (30 Gy in 10 fractions) with concurrent single course of chemotherapy with 5-flurouracil (5-FU; 1000 mg/m^2, days 1−4) and mitomycin-C (10 mg/m^2, day 1) [17].
  - Twenty-two patients were enrolled and all completed therapy.
  - A complete resolution of dysphagia was achieved in 68% of patients with a median time of complete response of 5 weeks.
  - The median dysphagia free interval was 11 weeks, and 73% of these patients remained dysphagia free until death.
  - However, 32% of patients had transient worsening of dysphagia secondary to treatment induced esophagitis immediately following therapy.
  - Given the increased acute side effects with concurrent chemoradiation, this approach should be reserved for patients with a prognosis >6 months and a good performance status.
- At our institution, highly selected patients with a good performance status/prognosis with response to chemotherapy are treated with consolidative chemoradiation to 45−50 Gy over 5 weeks.

Side Effects of Radiotherapy to the Esophagus

- Potential acute side effects of radiotherapy to the esophagus include fatigue, esophagitis/dysphagia, nausea, vomiting, anorexia, weight loss, and pneumonitis.
  - Esophagitis
    - Begin with over-the-counter analgesic medications.
    - Consider topical anesthetics, such as compounded formulations with viscous lidocaine.
    - Systemic opioids, via transdermal patches or liquid formulation, may be required if pain becomes severe.

  - Nausea and vomiting should be managed aggressively with medications.
  - If anorexia, weight loss approaching 5% of the patient's body weight, dysphagia, or esophagitis are severe, a PEG tube should be considered for nutritional support.
  - Radiation pneumonitis
    - Treat with prednisone 50–60 mg for 1 week with an extended taper.
    - Supplemental oxygen may be required.
  - Esophageal perforation
    - This is a rare, life-threatening event requiring emergent medical intervention.
    - Signs and symptoms can include severe chest pain, tachycardia, hemorrhage, and hemodynamic instability.
- The most common late effect of esophageal radiation is stenosis and stricture often requiring serial endoscopic dilatation.

GASTRIC CANCER

- Cancer of the stomach is the fourth most common cancer and the third leading cause of cancer mortality worldwide [18].
- Local progression of gastric cancer may manifest with gastric outlet obstruction, pain, or bleeding.
- Palliative options include surgical bypass, endoscopic stenting, endoluminal ablation, or radiation therapy.
- Although, EBRT is used widely for palliation of gastric malignancies, little data exists in the literature regarding its efficacy and tolerance.
- Studies show a wide range of symptom relief with EBRT, ranging from 20% to 75% [19,20].
- Common dose fractionation regimens include: 8 Gy in 1 fraction, 20 Gy in 5 fractions, and 30 Gy in 10 fractions.
- Addition of concurrent chemotherapy can be considered in patients with a good performance status in order to obtain a greater and more durable palliation of symptoms.
- Kim et al. retrospectively evaluated symptom relief with radiation therapy in 37 patients with advanced gastric cancers [21].
  - Nearly 66% of the patients received concurrent chemotherapy; the majority received single agent 5-fluorouracil.
  - A variety of radiation dose fractionation regimens were utilized with a median dose of 35 Gy in 14 fractions.
  - Palliation of bleeding, obstruction, and pain were seen in 70%, 81%, and 86% of patients, respectively.
  - Relief from bleeding and obstruction was sustained for a median duration of 11.4 and 6.2 months, respectively.

- The median duration of pain control had not been reached at last follow-up.

Side Effects of Radiotherapy to the Stomach

- Acute side effects from gastric radiation include fatigue, nausea, vomiting, gastritis/reflux symptoms, enteritis, anorexia, dehydration, or dysphagia.
- Management includes antiemetics, acid reflux medications, antidiarrheal medications, aggressive hydration, and medical pain management.
- If a feeding tube is required, a jejunostomy tube should be placed as opposed to a gastric tube.

PANCREATIC CANCER

- Despite advances in multimodality therapy for adenocarcinoma of the pancreas, survival rates remain poor.
- Only 10–25% of patients present with resectable disease and among these patients, 5-year survival rates are as low as 10–20%, with median survival of 13–18 months [22].
- Median survival of patients with locally advanced, unresectable disease is approximately 8–14 months [23].
- Recently, in the metastatic setting, FOLFIRINOX (leucovorin, 5-fluorouracil, irinotecan, and oxaliplatin) has improved the median survival from 6.8 months with gemcitabine alone to 11.1 months [24].

Local Disease

- Despite the poor prognosis of this disease, patients can benefit from aggressive local therapy for palliation, preventing local progression of disease, subsequently limiting or delaying significant morbidity.
- Local progression of pancreatic cancer can result in severe back and abdominal pain, biliary obstruction, intestinal obstruction, anorexia, cachexia, and fatigue.
- A number of treatment paradigms exist for local control of pancreatic cancer, including supportive care, chemotherapy, EBRT, chemoradiation therapy, and stereotactic body radiation therapy (SBRT).
- Multiple prospective trials have compared various regimens with conflicting results and little consensus.
- Prospective randomized trials are summarized in Table 15.2.
- Given the lack of consensus, any of these approaches are reasonable and the decision should be dictated by patient preference and performance status.
- Further trials with quality of life end points are warranted given the poor prognosis of this disease.

TABLE 15.2 Prospective Randomized Trials (Phase III) for Locally Advanced Pancreatic Cancer

Trial (Year Published) (References)	Randomization	Number of Patients	Median Survival (Months)	1 Year Survival (%)
CRT vs Chemotherapy				
ECOG (1985) [29]	EBRT (40 Gy in 20 fractions) + 5-FU	47	8.3	26
	5-FU alone	44	8.2	32
GITSG 9283 (1988) [30]	EBRT (54 Gy in 30 fractions) +5-FU and SMF	22	9.7	41
	SMF alone	21	7.4	19
FFCD/SFRO (2000-2005) [31]	EBRT (60 Gy in 30 fractions) + 5-FU/ CDDP	59	8.6	32
	Gemcitabine alone	60	13	53
ECOG E4201 (2003–2005) [32]	EBRT (50.40 Gy in 28 fractions) + Gemcitabine	34	11.1	50
	Gemcitabine alone	37	9.2	32
CRT vs EBRT				
GITSG 9273 (1981) [33]	EBRT (60 Gy in 30 fractions, split course) alone	25	5.3	10
	EBRT (40 Gy in 20 fractions, split course) + 5-FU	83	9.7	35
	EBRT (60 Gy in 30 fractions, split course) + 5-FU	86	9.3	46
ECOG E8282 (2005) [34]	EBRT (59.4 Gy in 33 fractions) alone	49	7.1	NA
	EBRT (59.4 Gy in 33 fractions) + 5-FU/MMC	55	8.4	NA
CRT Regimens				
GITSG 9277 (1985) [35]	EBRT (60 Gy in 30 fractions, split course) + 5-FU	73	8.5	33

(*Continued*)

TABLE 15.2 (Continued)

Trial (Year Published) (References)	Randomization	Number of Patients	Median Survival (Months)	1 Year Survival (%)
	EBRT (40 Gy in 20 fractions) + doxorubicin	70	7.6	27
Taipei (2003) [36]	EBRT (50.40–61.2 Gy in 28–34 fractions) + 5-FU	16	6.7	31
	EBRT (50.4–61.2 Gy in 28–34 fractions) + Gemcitabine	18	14.5	56

CRT, chemoradiation; *ECOG*, European Cooperative Oncology Group; *EBRT*, External beam radiotherapy; *5-FU*, 5-flurouracil; *GITSG*, Gastrointestinal Tumor Study Group; *SMF*, streptozocin, mitomycin-C, and 5-flurouracil; *FFCD/SFRO*, Fèdèration Francophone de Cancèrologie Digestive/ Sociètè Francophone de Radiothèrapie Oncologique; *CDDP*, cisplatin; *MMC*, mitomycin-C.

- For patients with good performance we recommend more definitive local therapy with either fractionated concurrent chemoradiation or SBRT.
- A common fractionated regimen is 50.40 Gy in 1.8 Gy daily fractions with concurrent continuous infusion 5-FU.
- More recently SBRT is being utilized with the theory that ablative doses of radiotherapy may improve local control while minimizing acute side effects and duration of treatment, particularly important given the poor prognosis of these patients.
  - Chang et al. report a retrospective analysis of 77 patients with unresectable adenocarcinoma of the pancreas treated with single fraction SBRT to a dose of 25 Gy [25].
    - Local control was good with freedom from local progression at 6 months and 12 months of 91% and 84%, respectively.
    - The progression free survival was poor due to metastatic progression; 26% at 6 months and 9% at 12 months.
    - The overall survival rates at 6 months and 12 months were 56% and 21%, respectively.
    - Acute toxicity was low with only 5% of patient experiencing a grade ≥ 2 toxicity.
    - Late toxicity was significant, however, with 9% of patients experiencing a grade ≥ 3 toxicity.
    - Furthermore, the rates at 6 months and 12 months of grade >2 toxicity were 11% and 25%, respectively.

- Due to the high late toxicity, other SBRT fractionation schemes have been explored.
  - Moningi et al. report on their single institution experience with 25–33 Gy in 5 fractions for locally advanced pancreatic cancer (LAPC) and borderline resectable pancreatic cancer (BRPC) [26].
    - A total of 88 patients were included, 74 of whom had LAPC.
    - The majority of patients received chemotherapy prior to SBRT.
    - Radiation targets and doses were modified to achieve strict dose constraints to adjacent structures.
    - The PTV was edited to avoid overlap with duodenum, small bowel, and/or stomach, and PTV dose was reduced from 33 Gy if required to meet dose constraints.
    - The median overall survival was 18.4 months, and median progression free survival was 9.8 months.
    - Surgery was performed in 21.6 % of patients, with margin negative resections in 84%.
    - Only three patients experienced acute grade ≥ 3 toxicity, and only five patients experienced late grade ≥ 2 toxicity.
    - This study highlights the efficacy and safety of fractionated SBRT with strict dosimetric parameters.
- At Moffitt Cancer Center, we have implemented a similar institutional protocol for the treatment of borderline and LAPC.
  - Mellon et al. reported on 159 patients treated on this protocol, 49 of whom had LAPC [27].
    - Patients began with chemotherapy for 2–3 months with regimen at the discretion of the treating medical oncologist but the majority being gemcitabine-based.
    - Patients then underwent SBRT in five consecutive daily fractions with mean total radiation doses of 30 Gy to tumor and up to 40 Gy to tumor-vessel interfaces with a dose painting technique.
    - Restaging scans were performed 4–6 weeks after completion of radiotherapy for evaluation of resectability.
    - Median overall survival for LAPC patients was 15.0 months.
    - Five LAPC patients underwent R0 resections.
    - For those who did not undergo resection, 1 year locoregional control was 78%.
    - Only 7% of patients experienced a grade ≥ 3 toxicity.
- Recently, a multiinstitutional, Phase II, prospective trial was completed that confirmed the safety and feasibility of this approach of a five fraction SBRT regimen following gemcitabine-based chemotherapy [28].
  - Herman et al. evaluated 49 patients with LAPC treated with up to three doses of neoadjuvant gemcitabine (1000 mg/m^2) followed by SBRT to 33 Gy in 5 fractions and adjuvant gemcitabine until disease progression or toxicity.

  - Median overall survival was 13.9 months.
  - Rate of acute and late grade ≥ 2 toxicity was 2% and 11%, respectively.
  - Patients reported a significant improvement in pain 4 weeks following SBRT ($p = 0.001$).
  - Of note, this trial only included patients with a life expectancy >6 months and an Eastern Cooperative Oncology Group (ECOG) performance status of 0−1.
- These three studies highlight the feasibility, the safety, and the efficacy of fractionated SBRT in LAPC. However, this strategy should be reserved for patients with a good performance status and life expectancy >6 months.
- For patients with poor performance status, we recommend either supportive care alone or chemotherapy alone with radiation therapy reserved for palliation of symptoms.

Symptom Palliation

- Approximately 70% of patients with pancreatic cancer will develop significant abdominal or back pain [37].
  - The majority of these patients will be managed with systemic opioid analgesics, but approximately one-third of patients will not achieve adequate pain control with oral medications alone [38].
  - In these instances, celiac plexus neurolysis should be considered.
    - Eisenberg et al. reported a metaanalysis of 1145 patients treated with celiac plexus neurolysis [39].
    - They reported a 70−90% response with acceptable toxicity.
- Gastric outlet obstruction and biliary obstruction are common complications of locally destructive pancreatic cancer.
  - Management of these clinical syndromes is primarily surgical and endoscopic.
  - Radiation can play a role and will be discussed in the gastric and hepatobiliary sections, respectively.
- Gastrointestinal bleeding is a rare, but life-threatening complication from local infiltration of pancreatic cancer, which can present as hematemesis, melena, or hematochezia.
  - Local infiltration can involve the stomach, duodenum, or colon.
  - Hemostatic methods for hemorrhage include endoscopic hemostasis, transcatheter arterial embolization, or surgery.
  - If endoscopic, interventional, and surgical methods fail, EBRT can be considered. Suggested regimens include 30 Gy in 10 fractions, 20 Gy in 5 fractions, or 12 Gy in 3 fractions. Choice of regimen should depend on patient's clinical status, performance status, and disease burden with more extended courses reserved for patients with a better functional

status and lower disease burden and shorter courses preferred for patients with a poor performance status and greater disease burden.
  - Prognosis is extremely poor in these patients and supportive measures should be initiated.

Metastatic Disease

- Pancreatic cancer can metastasize to the liver, peritoneum, lung, brain, and bone.
- Radiation therapy can be effective for palliation of metastases to all of these sites.
- Radiation technique, dose, and fractionation should depend on the site of disease, prognosis, performance status, and patient preference.
- See the section "Liver Metastases" for further recommendations.
- For peritoneal metastases, we recommend 30 Gy in 10 fractions to the symptomatic site with bowel being the dose-limiting organ.
- For lung and brain metastases, consider stereotactic techniques if patient has a good performance status and relatively good prognosis. Refer to the corresponding chapters for specific recommendations (see Chapter 14, Site-Specific Symptom Management: Palliative Radiotherapy for Advanced and Metastatic Lung Cancer and Chapter 11, Palliative Radiotherapy for Brain Metastasis).
- For all uncomplicated bone metastases, we recommend 8 Gy in 1 fraction. See the chapter on bone metastases for further recommendations (see Chapter 13, Palliative Radiotherapy for Bone Metastasis).

HEPATOBILIARY CANCER

- Hepatocellular carcinoma (HCC) is the second leading cause of cancer mortality worldwide [40].
- Primary treatment is surgical resection when feasible.
- Unfortunately, the majority of patients present with unresectable disease secondary to the extent of disease or underlying liver dysfunction.
- Other potentially curative options include liver transplant and percutaneous ablation.
- Palliative treatment options include transarterial chemoembolization (TACE), Yittrium-90 (Y-90) radioembolization, EBRT, or systemic chemotherapy.

Y-90 Radioembolization

- Several retrospective and prospective studies have shown the efficacy and feasibility of Y-90 radioembolization in HCC.
  - Retrospective studies comparing Y-90 to TACE show similar survival rates and safety profiles [41,42].
  - Salem et al., in fact, reported a better response rate, a longer time to progression, and less toxicity in favor of radioembolization [41].

- Y-90 dose ranges from 80 to 135 Gy and is generally well tolerated but can lead to acute fatigue, nausea, vomiting, anorexia, abdominal pain, fever, hepatobiliary toxicity, ulcers of the GI tract, radiation pneumonitis, or radiation-induced liver disease (RILD).

Stereotactic Body Radiation Therapy

- SBRT can also be utilized for the management of HCC.
  - A Phase I/II study used a single fraction of radiotherapy with doses ranging from 14 to 26 Gy [43].
    - The treatment was well tolerated with a 98% tumor control rate at 6 weeks.
  - In a study by Weiner et al., 28 patients were enrolled on a single institution, prospective SBRT protocol [44].
    - The planned dose was 55 Gy, which was reduced to meet a mean liver dose constraint of <20 Gy or to spare 700 cc to <20 Gy.
    - Fiducial markers, respiratory gating, and daily imaging were all used to decrease dose to uninvolved liver.
    - Despite these efforts, two patients developed RILD and died.
- Although the risk of RILD is less after SBRT when compared to conventional fractionation regimens, RILD remains a real and devastating risk of SBRT to the liver, and patients must be counseled accordingly.
- Doses should be adjusted based on Child-Pugh score and typically range from 25 to 60 Gy in 3–6 fractions.
- Indeed, other investigators have confirmed the importance of personalizing the dose to the patient based on their underlying liver function and the individual patient's tumor volume characteristics [45,46].

Biliary Obstruction

- Biliary obstruction is a common manifestation of locally advanced cholangiocarcinoma, adenocarcinoma of the gall bladder, and adenocarcinoma of the pancreatic head.
- Biliary obstruction can present with painless jaundice, pruritis, and clay colored stool.
- It is primarily managed by endoscopic procedures and stenting.
- Percutaneous biliary drainage and surgical management are also commonly utilized.
- When standard treatments fail, palliative radiotherapy can be considered.

Palliative Radiation Therapy for Biliary Obstruction or Pain

- For EBRT, typically doses of 30–50 Gy in 1.8–3 Gy fractions are utilized depending on performance status and prognosis.

- Dose-limiting structures include the duodenum, liver, stomach, and spinal cord.
- To enhance radiation response, intraluminal BT is often employed to increase dose to the gross tumor volume while sparing these dose-limiting organs.
- Either LDR or HDR BT can be utilized, and both are delivered through a percutaneous drainage catheter placed by an interventional radiologist.
- Common BT doses range from 20 Gy to 30 Gy delivered in 3–5 fractions.
- Concurrent chemotherapy, typically 5-fluorouracil, can also be added to enhance tumor response.

ANORECTAL CANCER

- Approximately 10–15% of patients present with locally advanced or unresectable rectal cancer [47].
- When deep invasion into local structures is present, adequate surgical resection may be extremely morbid or even impossible.
- In these instances, neoadjuvant therapy is recommended in order to allow for potentially curative resection.
  - A Phase III randomized trial by Braendengen et al. established chemoradiotherapy (CRT) as standard of care over radiotherapy alone for locally advanced rectal cancer [48].
  - Patients were randomized to either 50 Gy in 2 Gy per fraction alone or the same radiation regimen with concurrent 5-FU and adjuvant 5-FU for 16 weeks after surgery.
  - An R0 resection was achieved in 84% of the CRT group and 68% in the RT group ($p = 0.09$).
  - Local control, time to treatment failure, cancer-specific survival all favored the CRT group.
  - Acute toxicity was worse with the combined therapy with no difference in late toxicity.
- Short course radiotherapy (25 Gy in 5 fractions) can be considered in patients with very limited metastatic disease prior to resection of both the primary and metastases.
- This regimen can also be utilized in patients with poor performance status, poor prognosis, or symptoms (pain/bleeding). If patients cannot tolerate five treatments, consider 8 Gy in a single fraction.
- Neoadjuvant CRT is preferred when significant downstaging of disease is required for complete surgical resection [49].
- For patients who cannot undergo surgical resection after neoadjuvant treatment, either due to extent of disease or due to medical comorbidities, higher radiation doses in excess of 60 Gy should be considered in order to maximize local control and palliation [50].

Recurrent Disease

- Recurrent disease in patients who have not had prior radiation therapy is approached similarly to unresectable or locally advanced disease with an aggressive multimodality approach.
- No standard regimen exists, but a number of studies have shown efficacy of a neoadjuvant approach with radiation or CRT followed by surgical resection with or without intraoperative radiotherapy (IORT) or adjuvant chemotherapy.
- Recurrent disease in a previously irradiated patient, presents a more challenging clinical scenario.
- Re-irradiation is possible, but puts patients at risk for significant toxicity.
  - Mohiuddin et al. presented long-term results of re-irradiation in 103 patients [51].
    - Re-irradiation consisted of 30 Gy in 1.2 Gy BID fractions or 36 Gy in 1.8 Gy daily fractions followed by a boost to GTV to a dose of 6−20 Gy with concurrent continuous infusion 5-FU.
    - Radiation was delivered with opposed laterals or a three-field technique to the presacral area and GTV.
    - The 5-year OS rate was 19%.
    - Late toxicity, consisting of severe, persistent diarrhea, small bowel obstruction, fistula formation, and stricture occurred in 22 (21%) patients.
    - The authors report effective palliation of symptoms with 100% resolution of bleeding with control lasting till time of death in 80% of patients.
    - Pain completely resolved in 55% of patients, and partially responded in 28% of patients with median duration of pain control of 9 months.
  - Das et al. reported on 50 patients treated with a hyperfractionated regimen [52].
    - Patients received 30−39 Gy in 1.5 Gy BID fractions.
    - The majority of patients received concurrent chemotherapy.
    - The 3-year freedom from progression was 33% and 3-year overall survival was 39%.
    - The 3-year rate of late grade 3−4 toxicity was 35%.
    - Both regimens show significant late toxicity, although many of these toxicities (SBO, fistula, or stricture) may be due to tumor progression as opposed to radiation effect.

Metastatic Disease

- Most common sites of metastasis include liver, lung, brain, and bone.
- Palliative treatment recommendations should take into account site of the lesion, patient prognosis, performance status, and preference.

- See corresponding chapters in section 3 for detailed recommendations (Brain metastasis and primary CNS tumors, Spinal cord compression, and Bone Metastases).
- See Table 15.3 for a summary of anorectal treatment recommendations.

Liver Metastases

- Liver metastases can originate from almost any primary site.
- Common malignancies to metastasize to the liver are colorectal, breast, and lung cancers.
- Liver metastases are often asymptomatic and are found on staging and follow-up imaging.
- However, they can also cause a variety of local and systemic symptoms including abdominal pain/distention, nausea, vomiting, anorexia, night sweats, or fevers.
- Prognosis is generally poor, but varies widely with primary site of disease, prior therapies, and extent of hepatic and extrahepatic disease.
- Treatment recommendations strongly depend on these same characteristics.

Surgical Resection

- In patients without extrahepatic disease, determination of whether the patient's liver tumors are surgically resectable, either initially or following downstaging therapy, is key to determine whether there may be any future potential for curative intent treatment.
- Although criteria for surgical removal can vary between institutions and among surgical oncologists, the presence of adverse preoperative prognostic features has historically been cause for caution.
  - For example, in a series of over 1000 consecutive cases of liver metastases from colorectal cancer, findings of the largest tumor >5 cm, more than one liver metastasis, a disease-free interval <12 months, a preoperative CEA >200 ng/mL, and the presence of a node positive primary tumor were found to be predictive when combined as a clinical risk score [53].
  - More recent data, however, have reported no survival difference between patients undergoing an R0 resection of 1–3, 4, 5–7, or 8–11 metastases [54].
- Thus, patients with limited hepatic disease may benefit from a multidisciplinary initial consultation to determine whether, even if the disease is initially unresectable, an anatomic liver resection might be feasible with downstaging and enough future liver remnant function.
- Moreover, the presence of upfront poor prognostic factors does not necessarily preclude ultimate resection and long-term cure.
  - In a recent report of 612 consecutive patients with metastatic colorectal cancer, 102 were 10 year survivors and of these, 7% had synchronous

TABLE 15.3 Anorectal Cancer Treatment Recommendations

Locally Advanced Rectal Cancer		Recurrent Anorectal Cancer		Metastatic Anorectal Cancer	
ECOG 0-2/ surgical candidates	• Neoadjuvant CRT with 50 Gy in 2 Gy/ fractions + 5-FU • Surgical Resection • Adjuvant 5-FU for 16 weeks	No prior RT	No standard exists, but consider multimodality therapy with neoadjuvant CRT followed by resection and adjuvant chemotherapy	Liver	• Surgical resection • Radiofrequency ablation • Hepatic arterial infusional chemotherapy • Chemoembolization • Radioembolization • SBRT
				Lung	• Surgical resection • SBRT • Systemic therapies
ECOG ≥ 3/ surgical candidates	Consider neoadjuvant short course radiation therapy to 25 Gy in 5 fractions	Prior RT	Consider a hyperfractionated regimen with concurrent 5-FU: • 30 Gy in 1.2 Gy BID fractions • 36 Gy in 1.8 Gy daily fractions • 30–39 Gy in 1.5 Gy BID fractions	Brain	• Surgical resection • SRS • Systemic therapies
Nonsurgical candidates	> 60 Gy RT with concurrent 5-FU if patient can tolerate it			Bone	• 8 Gy × 1 for uncomplicated bone metastases • 20 Gy in 5 fractions or 30 Gy in 10 fractions if there is a significant soft tissue component or pathologic fracture risk. • Systemic therapies

ECOG, Eastern Cooperative Oncology Group; *CRT*, chemoradiation; *5-FU*, 5-fluorouracil; *RT*, radiation therapy; *SBRT*, stereotactic body radiation therapy; *SRS*, stereotactic radiosurgery; *BID*, twice daily at least 6 h apart.

disease, 36% had a disease-free interval <12 months, 25% had bilobar liver metastases, 50% had a node positive primary cancer, 39% had >1 metastasis, and 35% had a tumor size >5 cm [55].

- For initially unresectable liver metastases, a number of other treatment options in addition to the standard of histology specific systemic therapy are available, such as hepatic arterial infusional chemotherapy for colorectal cancers [56], local ablation therapies that can be delivered percutaneously in interventional radiology [57], chemoembolization strategies [58], radioembolization, and SBRT [59].

Y-90 Radioembolization

- Radioembolization with Y-90 can also be utilized in the metastatic setting for local control [60].
- Although Y-90 therapy is well tolerated without significant toxicity and is given in the outpatient setting, it is still unclear when patients might benefit the most from such liver directed therapy when systemic therapy is an option.
  - The SIRFLOX randomized, multicenter trial compared Y-90 radioembolization combined with mFOLFOX6 to mFOLFOX6 alone in the first line setting [61].
    - PFS was 20.5 months with the addition of Y-90 compared to 12.6 months.
    - Despite this improvement, there was no significant difference in overall PFS or response rate (RR).
    - There was, however, an improvement in hepatic RR, 78.7% versus 68.8%, $p = 0.042$ without a significant increase in toxicity.
    - This study suggests there may be benefit to combining therapies earlier in the disease course of mCRC liver metastases.
- Thus, for palliation of patients with significant hepatic disease burden, there may be an emerging role for radioembolization as an adjunct to systemic therapy.

Stereotactic Body Radiation Therapy

- With SBRT, investigators have reported on the high rates of local control and the low toxicity rates in studies that enrolled patients with liver metastases from multiple sites, typically 1–5 in number and <6 cm in size [62], with some investigators treating larger lesions [63].
- Recent data suggests excellent local control with regimens such as 60 Gy in 5 fractions [64] and a single dose of 35–40 Gy [65].
- Although the dosing parameters vary, most series confirm that with precision ablative radiotherapy, patients can benefit from this noninvasive modality that offers them convenience, absence of significant toxicity, and excellent hepatic control.

- Local control of liver metastases with SBRT ranges from 70% to 100% at 1 year and 60−90% at 2 years (Table 15.4).
- A recent survey showed that the majority of US practices surveyed had adopted SBRT, with over half incorporating liver SBRT into the practice [66].

Central Biliary Obstruction

- Central biliary obstruction from metastatic tumor can be problematic, precluding the administration of systemic therapy.
- Another role for palliative radiotherapy is to offer external beam radiation in the hope of decreasing tumor burden enough to improve local biliary outflow so that patients can resume systemic therapy.
- This can be delivered with a short course of EBRT or with SBRT depending on extent of disease burden.
- For those patients with disease suitable for SBRT, recent data supports the efficacy and safety of this approach [73].

Whole Liver Irradiation

- Finally, Whole Liver Irradiation (WLI) with EBRT can be considered if the patient has pain from local extent of disease distending the liver capsule and is not a candidate for other modalities [74].
- Improvement in pain has been reported in up to 90% of patients.
- Survival is not improved with WLI.

ON TREATMENT MANAGEMENT

- Given the anatomical extent of the gastrointestinal tract, radiation therapy for GI malignancies can lead to a variety of acute symptoms.
- Aggressive symptom management for radiation-induced side effects may be required (Table 15.5).

CONCLUSION

- Locally advanced, metastatic and recurrent gastrointestinal malignancies can cause significant morbidity.
- Palliative management of these diseases demands multidisciplinary management.
- Treatment recommendations should be tailored to the individual patient and guided by prognosis, performance status, and patient preference.
- Radiation therapy can provide significant relief of symptoms while decreasing tumor burden and providing local tumor control.
- Advances in radiation therapy will hopefully allow us to increase palliative effects while minimizing acute and late toxicities.
- Further studies are needed to compare different treatment regimens with regards to palliative outcomes and quality of life measurements.

TABLE 15.4 Prospective Trials (Phase I/II) of Stereotactic Body Radiation Therapy for Liver Metastases

Series	Dose/Fraction #	# of Patient/# of Tumors	Outcomes	Toxicity
Herfarth et al. [67]	14–26 Gy/1 (dose escalation trial)	35/55	• 1 year LC: 71% • 1 year OS: 72%	No significant toxicity
Schefter et al. [68]	36–60 Gy/3	18/NR	60 Gy in 3 fractions was found to be safe and is currently being tested in a Phase II study	No dose-limiting toxicity
Mendez-Romero et al. [69]	30–37.5 Gy/3	25/17	• 2 year LC: 68% • 2 year OS: 62%	2 patients with grade 3 liver toxicity
Hoyer et al. [70]	45 Gy/3	64/141	• 2 year LC for tumor/patient: 86%/63% • 2 year PFS: 19% • 1 year OS: 67% • 2 year OS: 38% • 5 year OS: 13%	One patient died due to hepatic failure. One patient required surgery for a colonic perforation. Two patients developed duodenal ulcers
Rusthoven et al. [62]	30–60 Gy/3 (dose escalation trial)	47/49 Lesions assessable for LC; 63 for survival	• 1 year LC: 95% • 2 year LC: 92% • Median survival: 20.5 months	One patient (2%) developed Grade ≥3 toxicity
Lee et al. [63]	27.7–60 Gy/3	68/NR	• 1 year LC: 71% • Median survival: 17.6 months	10% Grade 3/4 acute toxicity
Goodman et al. [71]	18–30 Gy/1 (dose escalation trial)	26/40	• 1 year LC: 77% • 2 year OS: 50.4% • Median survival: 28.6 months	No grade ≥3 toxicities
Scorsetti et al. [72]	75 Gy/3	42/52	• 2 year LC: 91% • 2 year OS: 65% • Median survival: 29.2 months	No grade ≥3 toxicities

LC, local control; *OS*, overall survival; *NR*, not reported; *PFS*, progression free survival.

TABLE 15.5 On Treatment Management

Symptoms	Acute Management
Esophagitis	• Avoid spicy foods and consider soft diet and/or liquid diet • Proton pump inhibitor or histamine-2 blockers daily • Start with Magic Mouthwash to be swallowed up to 5 ×/day prior to meals, combination of Lidocaine, Mylanta, and Benadryl • Liquid pain medication (Morphine or Oxycodone) and/or fentanyl patch
Nausea/ Vomiting	Recommend prescription antiemetics • Ondansetron 4–8 mg PO TID PRN • Compazine 10 mg PO QID PRN • Phenergan 12.5–25 mg PO QID PRN • Ativan 0.5–1 mg PO TID PRN • Marinol 2.5–10 mg PO BID if other antiemetics are not working and patient has anorexia • Compazine and Phenergan available as suppositories if needed Continue antiemetic's for 1–2 weeks posttreatment as needed
Weight loss/ Dehydration	• Nutrition consultation and encourage small more frequent high calorie meals • IV fluids as necessary • For appetite stimulation, consider low dose steroids, Megace 400–800 mg PO daily or Marinol 2.5–10 mg PO BID • Consider PEG tube if needed
Loose stools/ Diarrhea	• Goal of 1–2 bowel movements per day • Low residue diet (low fiber, low dairy, limit caffeine to slow motility) • Start with bismuth subsalicylates (Pepto-Bismol or kaopectate) • Add loperamide 4 mg PO × 1, then 2 mg PO after each subsequent loose stool, maximum 16 mg/day • If not controlled try lomotil (diphenoxylate/atropine) or combine loperamide and lomotil Continue antidiarrhea medications for 1–2 weeks posttreatment as needed
Cystitis	• Check a urinalysis if dysuria, increased frequency • For dysuria try OTV azo-standard or prescription phenazopyridine 100 mg PO TID × 3–7 days—caution patient about urine discoloration with this medication • For urgency add antispasmodic agents such as oxybutynin 5–10 mg PO q day
Hemorrhoids/ Proctitis	• Start with over-the-counter hemorrhoid creams • If pain is internal, recommend a gel product that can be inserted (careful consideration in neutropenic patients) • Sitz baths
Skin irritation/ Breakdown	• Keep skin well moisturized • Recommend moisturizers without alcohol or scent • Instruct patient to keep treatment area clean and dry prior to radiation therapy • Consider silver sulfadiazine for large areas of contiguous dry or wet desquamation • Sitz baths

LIST OF ABBREVIATIONS

BRPC borderline resectable pancreatic cancer
BT brachytherapy
CRT chemoradiotherapy
EBRT external beam radiotherapy
GI gastrointestinal
GTV gross tumor volume
HCC hepatocellular carcinoma
HDR high dose rate
IORT intraoperative radiotherapy
LAPC locally advanced pancreatic cancer
LDR low dose rate
PTV planning target volume
RILD radiation-induced liver disease
SBRT stereotactic body radiation therapy
TACE transarterial chemoembolization
Y-90 Yittrium-90

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Chapter 16

Palliative Radiotherapy for Advanced and Metastatic Gynecologic and Genitourinary Malignancies

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Chapter Outline

Introduction 257
Evaluation 258
Female Patients 258
Male Patients 259
All Patients 259
Treatment Recommendations 259
Primary Gynecologic Malignancies 259
Recurrent Disease 265
Primary Genitourinary Malignancies 266
Treatment Planning 269
Conclusion 272
List of Abbreviations 272
References 273

INTRODUCTION

Locally advanced, metastatic and recurrent pelvic malignancies, including gynecologic and genitourinary (GU) cancers, can cause severe symptoms. Common symptoms at presentation of gynecologic cancers include vaginal bleeding, foul-smelling discharge, pelvic pain, and obstructive symptoms related to compression of the pelvic viscera and lymphatic vessels. In the case of GU malignancies hematuria, urinary retention, or obstruction, dysuria, and pelvic pain are the most common symptoms requiring palliative intervention [1–3].

Handbook of Supportive and Palliative Radiation Oncology.

Bleeding is common with vulvar, vaginal, cervical, endometrial, and ovarian cancers and is typically related to tumor friability and invasion of the vasculature. Similarly, malignancies arising from the urinary tract will most commonly present with hematuria due to tumor friability and destruction of the local anatomy. Complete urinary obstruction often is related to interruption in the normal urine outflow by tumors arising from the bladder, prostate, and urethra and less commonly by very advanced vaginal, vulvar, and cervical tumors. Pelvic pain can be related directly to the tumor mass due to extension to the pelvic side wall and/or floor with nerve compression/invasion, or pressure on other structures of the pelvis including the bones and viscera. Obstruction related to compression of the small and large bowel, or lymphatic structures can cause various symptoms including nausea, vomiting, colicky abdominal pain, lymphedema, and deep venous thrombosis.

Radiation therapy (RT) is effective for palliation of common symptoms associated with advanced gynecologic and GU malignancies, particularly for hemostasis of vaginal bleeding, hematuria, and relief of pain. There are various published techniques for delivering palliative RT, including high-dose single-fraction regimens, hypofractionated short-course regimens, brachytherapy, and transvaginal electron cone therapy.

EVALUATION

Female Patients

- Complete history including gynecologic history and symptoms (vaginal bleeding, discharge, pelvic pain).
- Careful examination with a thorough abdominal and pelvic exam, including vaginal, bimanual, and rectovaginal exam. May need examination under anesthesia (EUA) with cystoscopy and proctoscopy in conjunction with gynecologic oncologist to best determine site of bleeding.
- Biopsy for histologic confirmation typically done. However for emergent circumstances, e.g., in a patient with a clinical cervical cancer with intractable vaginal bleeding despite vaginal packing, biopsy may be omitted or delayed until stabilized.
- Labs including complete blood counts (CBC) to assess hemodynamic stability, blood urea nitrogen (BUN)/creatinine to assess renal function, basic metabolic panel for electrolytes, and liver function tests (LFTs) for liver function.
- Clinical and imaging evaluation of extent of disease for staging and to determine whether to proceed with palliative or definitive management. Usually at least a computed tomography (CT) of the chest, abdomen, and pelvis (CAP), but positron-emission tomography (PET)/CT and pelvic magnetic resonance imaging (MRI) are also helpful in cervical cancer to determine extent of metastatic and locoregional disease, respectively.

Male Patients

- Complete history including urinary symptoms (frequency, obstructive symptoms, hematuria, dysuria), pelvic pain, bowel function, erectile function.
- Careful examination with a thorough abdominal and pelvic exam including digital rectal examination (DRE).
- Biopsy for histologic confirmation typically done. May be omitted or delayed in setting of enlarged, firm prostate gland and significantly elevated prostate specific antigen (PSA).
- Labs including CBC to assess hemodynamic stability; BUN/creatinine to assess renal function; LFTs for liver function, PSA, and testosterone; alkaline phosphatase for early measure of bone involvement.
- Clinical and imaging evaluation of extent of disease for staging and to determine whether to proceed with palliative or definitive management. Usually at least a CT CAP, but bone scan and/or pelvic MRI can also be helpful to determine extent of metastatic and locoregional disease, respectively.

All Patients

- Assessment of performance status, medical comorbidities, life expectancy.
- Assessment of severity of acute symptoms.
- If recurrent disease determine prior treatment(s) received, including receipt of prior RT.

TREATMENT RECOMMENDATIONS

- There are various doses and fractionation schedules that have been published for palliation of pelvic symptoms related to gynecologic and GU malignancies (Table 1).
- The decision on which schema to use should be based on the goals of care, whether the expected outcome is palliative versus definitive, expected symptom control is short-term versus durable and whether side effects will be tolerated.
  - For most patients with symptomatic advanced pelvic disease the goals of care are durable palliation with minimal time commitment and minimal toxicities.
  - Other considerations for particular schemas include patient performance status, life expectancy, prior treatments, and patient convenience.

Primary Gynecologic Malignancies

Most of the data reported for gynecologic malignancies lump together all five major primary disease sites (vulvar, vagina, cervix, uterus, and ovarian cancers). The studies described below focus mainly on the fractionation schemes used and specific sites are mentioned where indicated (Table 16.1).

TABLE 16.1 Summary of Dose and Fractionation of Palliative Regimens for Gynecologic Malignancies

Dose/Fractionation	Symptom Control		Potential Side Effects	Ideal Candidate
	Bleeding	Pain		
10Gy/1 fraction repeated 1–2 times each month Ideal treatment to maximize efficacy and minimize toxicity is 10Gy × 2	41–100% Increased response with increased dose delivered	33–100%	• Minimal acute toxicity • High late GI toxicity, 11% grade 3, 19% grade 4 • Increased side effects with increased dose delivered	• Life expectancy <1 year • Unable to come back and forth to treatment center for consecutive treatments • Applicable to gyn and other pelvic malignancies • Can be used for re-irradiation
"Quad shot" 14–18 Gy/4 fractions given twice a day ×2 days repeated 1–2 times each month	90%	68–91%	• Grade 1–2 acute genitourinary and gastrointestinal toxicity	• Applicable to gyn and other pelvic malignancies
"0-7-21" 18–24 Gy/3 fractions given on days 0, 7, and 21	92%	76%	• Grade 1–2 acute GI toxicity	• Allows frequent re-assessment for toxicity/benefit
Brachytherapy 5 Gy × 2 fractions 1 week apart	93%	NA	• No acute toxicity reported, but more invasive technique	• Tumor limited to vagina, easily accessible • May go on to receive definitive therapy

10 Gy × 1

- The most simple hypofractionated radiotherapy regimen that has been well-documented for use in palliation of gynecologic malignancies is whole pelvic treatment with 10 Gy in a single fraction with repeat doses up to three total treatments given every 4 weeks.
  - The standard pelvic fields used are typically either AP/PA or a four-field box and include from L5/S1 superiorly to the lower edge of the obturator foramen inferiorly with 1−2 cm outside the pelvic brim laterally, usually not larger than 15 × 15 cm, but sometimes extended to 18 × 18 cm to cover nodal or vaginal/vulvar extension (Fig. 16.1B).
  - For repeated treatments, the field is typically reduced to account for tumor regression.
  - Boulware et al. from M.D. Anderson Cancer Center reported on this technique in the late 1970s [4]. They treated 86 women between 1954 and 1975 with 10 Gy × 1 and added subsequent treatments in patients with a favorable clinical response.
    - In total, 31 women received 1 fraction, 35 received 2 fractions, and 20 all 3 fractions.
    - Response was evaluated clinically during follow up examinations and in women who received a greater number of treatments; there was increased control of vaginal bleeding, 45%, 85%, and 100% for 1, 2, and 3 treatments.
    - Median survival in each group was low, only 3 months, 7 months, and 9 months, respectively, and treatment durability was not addressed.
    - Of the gynecologic cancers included, the best response to treatment was in women with cervical, vaginal, and vulvar cancers, and was

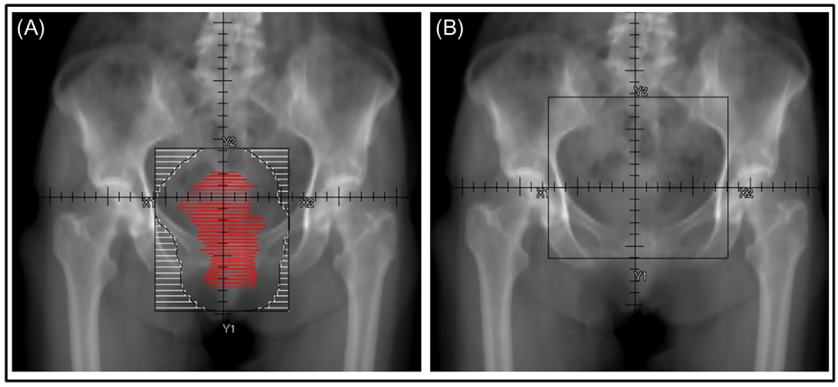

FIGURE 16.1 (A): Digitally reconstructed radiograph (DRR) of a patient with vaginal cancer with 3-dimensional contour of a gross tumor volume (GTV) and anteroposterior (AP) beam with 2 cm block margin. (B): AP X-ray for 2-dimensional planning with a 15 × 15 cm pelvic field for a patient with cervical cancer.

poor in endometrial and ovarian cancers, possibly suggesting that these histologies are less responsive to this regimen. However, as discussed below, this regimen has been used successfully in women with ovarian cancer.

- Similarly, Hodson et al., Chafe et al., and Halle et al. published single-institution experiences with this regimen from 1983 to 1986 which included a total of 69 patients treated in North America with 90–100% response in rates of vaginal bleeding [5–7].
  - In the study by Hodson et al., all of the 27 patients received 3 fractions for a total of 30 Gy to the pelvis given over 3 months.
  - The other two reports were both from the University of North Carolina with the initial report by Dr. Chafe and a longer-term follow up by Dr. Halle which ultimately included 42 patients. Of these patients, 25 received 1 fraction and 17 continued with subsequent fractions "to further reduce bulky disease in the pelvis or control continued bleeding."
  - In patients with follow-up there was 90% CR or PR of bleeding with initial treatment, but only 27% remained permanently free from bleeding. Tumor control rates were initially 25% at 6 months and declined to 14% at 12 months.
  - Minimal acute toxicity was originally reported, but in the follow-up by Halle et al. there was a 12% rate of serious treatment complications, 80% of which occurred >10 months posttreatment.
  - Unlike the prior study from MDACC, neither improved outcomes nor increased rates of toxicities were correlated with increased number of fractions received. The authors' conclusion was that this is good treatment for patients with a life expectancy <1 year [4].
- RTOG 7905 was published in 1987 and was a Phase I/II trial in 46 patients with advanced pelvic malignancies (43% gynecologic cancers) using the same radiotherapy regimen with 10 Gy repeated at 4-week intervals for a total of three treatments [8].
  - This study added misonidazole, a radiosensitizer which depletes radioprotective thiols and induces the formation of free radicals thereby sensitizing hypoxic cells to the cytotoxic effects of ionizing radiation, at a dose of 4 g/m^2 4–6 hours prior to RT.
  - Eighty percent (37 patients) completed all 3 treatments, with 6 achieving CR, 10 PR, 19 minimal or no response, and the remainders were not able to be evaluated due to no follow-up.
  - The study closed early due to unacceptably high rates of late GI toxicity: 11% grade 3, 19% grade 4, and projected 49% grade 3 or greater by 1 year.
- Single-fraction palliative RT is still used (without radiosensitizers) and has been reported by Onsrud et al. from Norway and Mishra et al. from India in 2001 and 2005, respectively [9,10].

  - Mishra et al. showed particularly good results in 100 patients with 100% relief of vaginal bleeding, 49% relief of vaginal discharge, and 33% relief of pain.
  - Symptom assessment was performed after each fraction. Relief of vaginal bleeding increased with each fraction from 31% after the first fraction to 100% after the third fraction. Interestingly, relief from vaginal discharge and pain were rated highest at the evaluation following the second fraction. There is no information reported on the durability of symptom control.
  - Vomiting and diarrhea were the most common acute side effects and at a median follow-up of 9 months, late effects were minimal with 4% subcutaneous fibrosis of the anterior abdominal wall, 3% radiation cystitis, and 3% radiation proctitis.
- Adelson et al. showed that this regimen is also effective for women with ovarian cancer [11]. They treated 42 women (26 single fractions, 8 with 2 fractions, and 8 with 3 fractions) and evaluated the women after each treatment.
  - The patients who were evaluable at follow-up had high rates of bleeding cessation in 71.4%, decreased pain in 55%, and tumor size reduction in 75%.
  - However, treatment durability was not evaluated as the median survival from the start of RT was only 5.1 months. Late GI and GU toxicity was high (23%) and the authors concluded, similarly, that 2 fractions $\times$ 10 Gy is the best and safest fractionation for effective palliation.
- In general, this treatment is convenient and effective for relief of pelvic symptoms from gynecologic malignancies.
- The studies show excellent rates of relief of vaginal bleeding as well as some benefit, although less, with vaginal discharge and pelvic pain.
- The treatment can be given as a single fraction with reevaluation for a second and even third fraction at 4-week intervals if the patient has a reasonable performance status and may continue to benefit from therapy.
- It has minimal acute toxicities, but does have high rates of late toxicity, especially gastrointestinal and is therefore generally reserved for patients with life expectancy $<$1 year.

Quad Shot

- After high rates of late GI toxicity were shown in RTOG 7905, RTOG 8502 was opened with a goal to minimize late toxicity and utilized multiple daily fractions of palliative radiotherapy.
  - The dose used was 3.7 Gy $\times$ 4 fractions given over 2 days with BID treatments for a total dose of 14.8 Gy and could be repeated at 3–6 week intervals up to 3 times for a total dose of 44.4 Gy.

- The initial Phase II protocol studied 142 patients (40% gynecologic) and showed 32% complete or partial remission of disease, 45% in patients who received all three courses, with minimal acute and late toxicity (one patient with each) [12] RTOG 8502 subsequently enrolled a second group of patients using the same treatment regimen, but randomized to either a 2- or 4-week interval between repeat courses of treatment and showed no difference in outcome [13].
- At the completion of the three course regimen, bleeding/obstruction were completely or partially palliated in 98% patients and pain in 68%.
- There is not a discussion of the durability of the results, but similarly to the patients in the 10 Gy studies, the median survival of all patients was 5−6 months.

- In all, 61 patients with cervical cancer were enrolled in RTOG 8502 and had equivalent response rates to single large fraction RT, but with less toxicity [14]. More recently, Caravatta et al. escalated the dose per fraction with modern planning techniques from 3.5 to 4.5 Gy to a total dose of 18 Gy over 2 days [15].
  - The primary evaluation of palliative response was performed with clinical evaluation at 15 days posttreatment and then subsequently every 2 months.
- Overall, there was an 89% complete or partial symptom remission with a median duration of palliation of 5 months (range 1−12 months) and no late toxicities.
  - In summary, the Quad shot is convenient and effective for vaginal bleeding, obstruction, and pain. There are minimal acute and late toxicities and this regimen can be used for patients with life expectancies >6 months and even >1 year.

Other Palliative External Beam Regimens

- Yan et al. from Princess Margaret Hospital published a 3 fraction regimen of 18−24 Gy total dose given on days 0, 7, and 21 [16].
  - From 1998 to 2008 they treated 51 patients with incurable gynecologic cancers, life expectancy <1 year or unable to follow intense treatment regimens due to severe comorbidities.
  - With a median follow up of 1.4 months, vaginal bleeding improved in 92% and pain improved completely or partially in 76%.
  - Most of the acute toxicity was gastrointestinal (10/33 patients with data) and included grade 1−2 diarrhea, proctitis, abdominal pain, and nausea.
  - A benefit of this regimen is that it is a short treatment program, but allows a break between fractions for evaluation of response and patient performance status prior to proceeding with each treatment.
- In ovarian cancer, 35 Gy in 14 fractions has also been used with good durable palliation [17]. The median duration of palliation was 4 months

with 90% of patients palliated until time of death, 90% vaginal bleeding control, 85% rectal bleeding control, and 83% pain relief.

- For women with bleeding at the time of diagnosis of a gynecological primary, but for whom definitive management is a consideration, it is reasonable to start with 1−2 larger fractions of external beam radiotherapy prior to definitive management. It is best to start with something like 4 Gy × 1 or 4 Gy × 2 so as to allow for definitive doses while respecting doses to organs at risk (OARs).

Electron Cone and Brachytherapy

- In the early part of the 1900s transvaginal electron cone therapy was used as part of definitive therapy for cervical cancers and sometimes as part of palliative therapy for vaginal bleeding, giving 5−8 Gy/day directly to the cervical mass [18,19].
- Brachytherapy has been shown to be effective at palliating vaginal bleeding from cervical cancer prior to more definitive treatment using an intracavitary cervical ring applicator [20].
  - This was demonstrated in 15 women with stage IB2-IVB disease using 2 fractions of 5 Gy given 5−7 days apart and prescribed to the applicator surface. Complete or partial response of vaginal bleeding was shown in 93% of patients. Due to the intrinsically invasive nature of brachytherapy, it is rarely used in the palliative setting, but when prescribed to the applicator surface, can be used to stop vaginal bleeding prior to a more definitive course of therapy as it adds minimal additional dose to the OAR.

Recurrent Disease

- In patients who have not had prior pelvic RT, the above options are all reasonable, depending on assessment of performance status and life expectancy.
- In patients who have received prior RT to the pelvis, re-irradiation may be given to smaller areas with careful field design to limit dose in regions of prior treatment [1]. With longer intervals between courses of radiation, there may be some recovery of the normal tissues, but in general, re-irradiation after prior definitive doses should be reserved for patients with limited life expectancies due to the concerns for increased late toxicities. The primary OARs in the pelvis are the bladder, rectum, bowel, and femoral heads. The Quantitative Analyses of Normal Tissue Effects in the Clinic (QUANTEC) data can be used as a general guideline for determining the risk of toxicity to these structures with additional pelvic radiotherapy [21−23]. However, further caution should be used in patients who were treated with hypofractionation or brachytherapy, as the QUANTEC data is based on conventional fractionation. The ABS worksheets can be helpful as a reference for

converting brachytherapy doses into the radiobiologic equivalent dose in 2 Gy fractions (EQD2) as well as giving an associated biologic equivalent dose (BED) for late effects [24].

Primary Genitourinary Malignancies

- Published literature regarding high-dose single fraction RT for primary GU malignancies is almost nonexistent.
- In RTOG 7905 only two patients had primary tumors arising from the prostate. The majority of the published regimens vary from a short hypofractionated scheme to a more conventional 2−3 week course of treatment.
- Unlike the GYN literature, the GU series report results separated by primary of origin rather than by dose fractionation scheme. Table 16.2 summarizes dose and fractionation schemes for GU malignancies by primary site.

Renal Cell Carcinoma

- Although renal cell carcinoma has been regarded as a relatively radioresistant malignancy, worthwhile palliative response can be achieved in the metastatic setting with conventional palliative regimes.
- Lee et al. demonstrated good pain control from bony metastatic disease by delivering of 30 Gy in 10 fractions with 83% of patients reporting site-specific pain relief after treatment and a median duration of site-specific pain response of 3 months (range, 1−15 months) [25].
- The emergence of extracranial stereotactic RT prompted its use in metastatic and primary inoperable renal cell carcinoma. The group at the Karolinska Institute in Sweden reported the outcomes of 58 patients with either metastatic or primary nonoperable renal cell carcinoma with total number of treated metastatic sites being 162.
  - Over 70% of the metastatic sites were in the lungs but 8 patients had primary inoperable malignancies and 12 had metastasis to the remaining kidney.
  - Most common dose-fractionations schedules were 32−40 Gy delivered in 4 fractions and 45 Gy in 3 fractions all through the course of approximately 1 week.
  - Local control rate was >90% with complete tumor regression in 30%. For the eight patients that had an inoperable primary tumor five were alive with no recurrence and symptom free at 4 years [26].

Bladder Cancer

- The first trial of palliative radiotherapy in tumors arising from the bladder was published over 15 years ago and consequently used relatively simple radiation treatment techniques.

- Patients with symptomatic, muscle invasive bladder cancer, unsuitable for surgical resection, chemotherapy, or definitive radiation treatment were randomized between two fractionation regimens.
  - A standard arm of 35 Gy in 10 fractions was compared to 21 Gy delivered in 3 fractions in 1 week.
  - At the end of treatment 50% of the patients in each arm had noticed significant improvement in their symptoms (the most common symptoms being urinary frequency and hematuria).
  - At 3 months overall improvement in hematuria, urinary frequency, and dysuria was 90%, 82%, and 72%, respectively, with no difference among either treatment regimen.
  - Median time to symptom progression after response was 6 months with a median survival of 7.5 months [27].
- More recently Kouloulias et al. [28], published a large retrospective review using weekly radiation doses between 5.75 Gy and 6 Gy for 5−6 weeks in patients with advanced bladder cancer with hematuria and pelvic pain.
  - The authors reported resolution of the hematuria in 90% and 95% of the patients, respectively, with grade 3 or higher acute urinary toxicity between 0% and 9%.
  - Median survival ranged between 10 and 14 months, with a mean hematuria free survival of 13 months, which suggests that simple interventions can provide long-lasting meaningful palliative responses

Prostate Cancer

- The management of advanced incurable locally symptomatic prostate cancer is quite challenging. Multiple fractionation schemes have been reported, ranging from long courses of 60 Gy in 30 fractions to shorter hypofractionated schemas such as 20 Gy in 5 fractions and the "quad shot" regimen.
- The group at M.D. Anderson Cancer Center reported in 1997 their experience with long courses of palliative RT for locally advanced symptomatic hormone ablation refractory prostate cancer.
  - A total of 29 patients received a mean dose of 60.4 Gy (10−80.2 Gy) using mainly photons.
  - More than half of the patients were treated due to obstructive urinary symptoms and a third were treated following progression on digital rectal exam with or without symptoms.
  - The 4-year local control, defined as the absence of new or progressive urinary obstructive symptoms, new or progressive disease on DRE, or biopsy confirmation of local active disease was 61% with the majority of the patients remaining symptom free. The majority of the failures were distant.
  - Interestingly, patients treated to a dose >60 Gy had a local control of 90% compared to 29% for those receiving less than 60 Gy [29].

- Hindson et al. in 2007 reported on 35 patients with advanced symptomatic (hematuria, bladder outlet obstruction or rectal obstruction) hormone refractory prostate cancer that received 60 Gy at 2−3 Gy per fraction.
  - Overall response rate was about 60% with patients presenting with more than one symptom reporting a higher response rate of 83%.
  - Bladder outlet and rectal obstruction showed a partial response in 18 patients with no complete responders, but all of them continued to show partial improvement at 6 months.
  - Of the five patients presenting with hematuria alone, three maintained a complete response 6 months posttreatment. Median survival was 13.7 months; they did not find any dose−response correlation [30].
- Additional data regarding less protracted regimens has become available in the past few years, as 25% of the patients enrolled in RTOG 8502 (discussed previously) had primary tumors arising from the GU tract, suggesting the efficacy of such fractionation in this population.
- More recently, Din et al. from the United Kingdom retrospectively analyzed their experience in 58 men with symptomatic locally advanced prostate cancer using simple fluoroscopic simulation with an opposed APPA (10×10) beam arrangement with the center of the field at the superior edge of the symphysis pubis.
  - Patients received 20 Gy delivered in 5 daily fractions.
  - Overall response rate at 4 months was 89%. Response rate at 6 weeks, 4 months, and 7 months for hematuria was 81%, 42%, and 29%, respectively.
  - Urinary outflow obstruction improvement was seen in two-thirds of the population with more than half of them maintaining this response at 7 months.
  - Pain response was above 60% in the first 4 months but dropped to 38% at 7 months, suggesting progression of disease [31].
- A systematic review of published trials on palliative pelvic radiotherapy for symptomatic incurable prostate cancer listed nine studies (all retrospectives chart reviews) with total doses and fraction sizes varying from 8 to 78 Gy and 2 to 8 Gy, respectively.
  - All nine studies had pre- and posttreatment quality of life assessment.
  - The overall symptom response rate was 75% with response rates for hematuria, pain, bladder outlet obstruction, rectal discomfort, and ureteric obstruction of 73%, 80%, 63%, 78%, and 62%, respectively [32].
- More recently the group at Oslo University Hospital in Norway published the results on 47 men with symptomatic incurable prostate cancer. This was a prospective multicenter study that looked at patient-reported outcome over a target symptom identified by the patient as the main problem.
  - Patients received 30−39 Gy in 10−13 daily fractions.
  - Almost 50% had lower urinary obstructive symptoms, with 25% complaining of hematuria and 20% of pelvic pain. Symptoms were assessed at baseline and 12 weeks after treatment.

- Improvement or complete resolution of the target symptom was achieved in 62%, 80%, and 72% of the patients at the end of radiotherapy, after 6 weeks, and at 12 weeks, respectively.
- It is important to mention that at 12 weeks there was a 100% response rate for hematuria with lower urinary obstruction symptom relief seen in 8 out of 18 patients and only 1 patient reporting worsening symptoms.
  Mild to moderate diarrhea was the most common toxicity with no grade 4 complications seen [33].

Penile and Urethral Cancer

- Locally advanced incurable urethral and penile carcinomas can cause significant symptoms from urinary obstructive symptoms to pain and hematuria as well as severe emotional distress.
- Palliative RT is commonly used in these scenarios to help relief some of the aforementioned symptoms.
- Common regimens include 30 Gy in 10 daily fractions as well as slightly more protracted 45 Gy in 15 fractions when there is no evidence of metastatic disease in the hopes to maintain a longer duration of response.
- Because of the rare occurrence of these tumors there is a lack of published data when definitive treatment is not possible with most of the clinical practice being extrapolated from experiences in other GU and gynecological sites.

Treatment Planning

- Treatment planning should be as simple as possible.
- Patients are supine with arms at sides (if treating AP/PA) or on chest /overhead for four-field technique.
- No need for custom immobilization or contrast in most cases.
- For tumors extending into the vagina it can be helpful to mark the lowest extent of disease with a gold fiducial marker, radiopaque vaginal packing or a BB.
- Gross tumor volume should be contoured and then fields designed with at least 2 cm to beam edge (Fig. 16.1A). Symptomatic patients may have difficulty holding still, so generous margins are essential to ensure adequate tumor coverage in many cases.
- Most simple field design is AP/PA, but increased homogeneity with four-field.
- For patients treated emergently 2D planning or clinical setup may be used. In that case a standard 15×15 cm pelvic field AP/PA is typically used (Fig. 16.1B).
- Table 16.3 details acute and late management for on-treatment issues seen during treatment of both GU and GYN malignancies.

TABLE 16.2 Summary of Dose and Fractionation of Palliative Regimens for Genitourinary (GU) Malignancies

Primary Site	Symptom Control			Median Duration of Response (months)	Fractionation (Gy/Fraction)	References
	Bleeding	LUOS[a]	Pain			
Renal	–	–	83%	3	30 G/10	Lee et al. [25]
			84%	NR	30–40/10–15	Fossa et al. [34]
Bladder	90%	82%	–	6	35/10 vs 21/3	Duchesne et al. [27]
	80%	–	–	5	20–30/5–10	Lacarriere et al. [35]
	90%	–	–	13 (HFS[b])	36–39.6/6–12	Kouloulias et al. [28]
Prostate	100%	60%	–	6	60/30 (md[c])	Hindson et al. [30]
	–	50%	–	36	60/30 (md)	Lankford et al. [29]
	91%	44%	77%	7	20/5	Cameron et al. [32] and [33]
	100%	62%	72%	NR	30–39/10–13	Din et al. [31]

[a] *LUOS, Lower Urinary Obstructive Symptoms.*
[b] *Hematuria Free Survival.*
[c] *Median Dose.*

TABLE 16.3 On Treatment Management

Symptoms	Acute Management	Late Management
Nausea/ Vomiting	• Recommend prophylactic antiemetics • Commonly prescribed antiemetic's include: ondansetron 4–8 mg PO TID PRN, Compazine 10 mg PO QID PRN, Phenergan 12.5–25 mg PO QID PRN, ativan 0.5–1 mg PO TID PRN • Compazine and Phenergan available as suppositories if needed • Continue antiemetic's for 1–2 weeks posttreatment as needed	• Continue with acute management if it is working • GI motility agents can help such as metoclopramide 5–10 mg BID × 12 weeks maximum • Cannabinoids can be added including marinol 2.5–10 mg PO q 6–8 h PRN, nabilone 1–2 mg PO q 8–12 h PRN • Consider nutritional support with IV fluids, supplements, etc.
Diarrhea	• Goal of 1–2 bowel movements per day • Low residue diet (low fiber, low dairy, limit caffeine to slow motility) • Start with bismuth subsalicylates (Pepto-Bismol or kaopectate) • Add loperamide 4 mg PO × 1, then 2 mg PO after each subsequent loose stool, maximum 16 mg/day • If not controlled try lomotil (diphenoxylate/atropine) or combine loperamide and lomotil • Continue antidiarrhea medications for 1–2 weeks posttreatment as needed	• Continue with acute management if it is working • Consider adding octreotide as an antisecretory agent (given SC, IV, or IM) • Be aware as narcotic drugs are tapered that motility can increase
Proctitis	• Hydrocortisone rectal suppositories can help with acute and late effects	• Hydrocortisone retention enemas for 1 h up to all night • Oral steroids usually prednisone 10–40 mg PO q day • Consider oral antiinflammatories such as sulfasalazine 500 mg PO QID or balsalazide 2.25 g PO TID × 8–12 weeks

(*Continued*)

TABLE 16.3 (Continued)

Symptoms	Acute Management	Late Management
		• Add Pentoxyfylline and vitamin E for 3–6 months • Refer to GI for sigmoidoscopy and consideration of topical formalin • Hyperbaric oxygen
Cystitis	• Check a urinalysis if dysuria, increased frequency • For dysuria try OTV azo-standard or prescription phenazopyridine 100 mg PO TID × 3–7 days—caution patient about urine discoloration with this medication • For urgency add antispasmodic agents such as oxybutynin 5–10 mg PO q day	• Continue with acute management if it is working • Add Pentoxyfylline and vitamin E for 3–6 months • Consider adding Elmiron (pentosan polysulfate sodium) 100 mg PO TID • Refer to urology for cystoscopy and consideration of topical formalin

CONCLUSION

Radiotherapy is effective in the palliation of many symptoms of advanced gynecologic and GU malignancies. It spares these patients from morbid pelvic surgeries and may delay more toxic systemic therapy.

Although technology is advancing and we are capable of performing more conformal and higher dose treatments, some of the older and simpler techniques and fractionation schedules may in fact be the most effective with the least long-term toxicities. In general, short courses of treatment are preferable and may be able to provide reasonable durability of symptom control with minimal time commitment and low rates of toxicities. The particular treatment regimen may be tailored to the individual patient by considering specifics such as the expected outcome (palliative vs definitive), expected duration of symptom control (short-term vs more durable), and whether side effects will be tolerated. Other considerations include patient performance status, life expectancy, prior treatments, and patient convenience.

LIST OF ABBREVIATIONS

ABS American Brachytherapy Society
AP/PA anterior-posterior/posterior-anterior
BID twice a day

CR complete response
PR partial response
RT radiation therapy
RTOG Radiation Therapy Oncology Group

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Chapter 17

Palliative Radiotherapy for Advanced and Metastatic Head and Neck Cancers and Skin Metastases

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Chapter Outline

Evaluation 275
General History & Physical Examination (H&P) 275
Symptoms 280
Goals of Care, Performance Status 280
Treatment Recommendation 281
Supportive Care 281
Palliative Chemotherapy 282
Radiotherapy for Aggressive Local Control or Potential Cure 283
Radiotherapy for Palliation 285
Stereotactic Body Radiotherapy and Brachytherapy 287
Expected Acute Side Effects From Radiation 288
Dermatitis 288
Mucositis 289
Xerostomia 290
Edema 290
Dysgeusia 290
On Treatment Management 291
Multidisciplinary 291
Steroids 291
Skin Care 291
Oral Care 291
References 294

EVALUATION

General History & Physical Examination (H&P)

- Cancer in the head and neck region can affect respiratory function, airway patency, and hemodynamic stability; therefore, it is important to obtain vital signs and assess patients for medical stability before proceeding with a full evaluation.

Handbook of Supportive and Palliative Radiation Oncology.

- In a stable patient, evaluation should begin with a general history and physical exam.
  - Important points to cover in the general history:
    - History of the present illness.
      - Diagnosis, original site of disease.
        - For head and neck tumors originating from the oropharynx, HPV status should be obtained if available.
      - Prior treatments received (surgery, radiation, chemotherapy, and experimental agents).
        - For surgeries in the head and neck region, review of prior operative notes can be of value.
        - Time elapsed from the last dose of chemotherapy/restaging exams.
        - Prior radiation therapy: Area treated, duration of treatment and dose, short- and long-term effects of therapy.
          - Detailed records including radiation plans, dose-volume histograms, on treatment assessments, and completion summaries should be obtained for prior radiation treatment delivered to the head and neck region.
        - Current systemic disease status (oligometastatic vs diffuse).
        - Serious health problems, prior operations.
          - Contraindications to radiation such as active connective tissue diseases.
          - Recurrent pneumonias may be indicative of aspiration. A dedicated assessment for this may be indicated.
        - Social history should note alcohol intake and all forms of tobacco usage.
- A focused history should then assess:
  - Pain: Accurate assessment of pain in patients with cancers in the head and neck area helps guide effective analgesic treatment.
    - *OPQRST*: Onset, provocation/palliation, quality, radiation, severity, and time course.
    - Because pain may correspond with disease progression, note temporal aspects of pain.
    - Distinguish between visceral, somatic, and neuropathic pain.
    - Somatic and neuropathic pain are common in the head and neck.
    - Although less common, visceral pain can be referred from the heart, lungs, and diaphragm to the jaw and neck.
    - Other types of referred pain include head and neck pain from invasion of the clivus. Referred otalgia may result from nerve stimulation/damage secondary to the following causes:
      - CN V: Trigeminal neuralgia, oral cavity carcinoma.
      - CN VII: Dental pain, TMJ dysfunction, parotitis, parotid tumors.

- ☐ CN IX: Pharyngitis, tonsillitis, oropharyngeal carcinoma.
- ☐ CN X: GERD, laryngopharyngeal carcinoma.
- ☐ C2 and C3: Neuropathy, metastatic invasion.

- Bleeding: Patients with bleeding should be evaluated urgently to prevent hemodynamic compromise. Appropriate treatment depends on the underlying etiology.
  - Local causes of bleeding include ulceration, exposure of intratumoral vessels, ischemic/inflammatory insult to surrounding vessels, and direct tumor extension into major vessels (e.g., carotids), which may be life-threatening.
  - Medications that increase risk of bleeding (e.g., NSAIDs and anticoagulants) should be identified and discontinued, if indicated.
- Airway/Breathing: Airway obstruction is the most imminent threat to ventilation and oxygenation. Obstruction of the nasal cavity, oral cavity, and/or oropharynx may produce dyspnea.
  - Initial presentation of airway obstruction may be inability of patient to lie supine.
  - Acute respiratory distress from airway obstruction should be assessed by physical exam: tachypnea, use of accessory muscles, and inspiratory stridor.
  - Oxygen saturation is a poor indicator of acute airway obstruction severity, as saturation may be maintained by compensatory mechanisms in spite of impending clinical demise.
  - If airway compromise is imminent, urgent intubation or tracheostomy should be performed in collaboration with anesthesia or ENT surgery until a more permanent solution is achieved.
  - Whether to proceed with tracheostomy, debulking, palliative radiation, or observation will depend on degree of airway obstruction and expected potential for shrinkage in response to ongoing or future therapies.
    - ☐ In patients with bulky disease in the midline neck (e.g., anaplastic thyroid cancer), tracheostomy may be more challenging as tumor may impede surgical access.
    - ☐ Advance planning (i.e., referral to head and neck surgery and multidisciplinary discussion with the patient regarding goals of care) is necessary as emergency tracheostomy may be exceedingly difficult.
- Speaking: Speech is produced by a complex series of active and static interactions among structures along the vocal tract.
  - Optimal articulation requires proper movement and/or alignment of the lips, teeth, tongue, hard palate, soft palate, uvula, epiglottis, and larynx, as well as the nasal cavity, oral cavity, pharynx, and laryngeal cavity.

- Both primary and metastatic cancers may impair speech by disrupting the anatomic relationships between these structures and their functions.
- CNs V, VII, IX, X, XI, and XII all carry efferent fibers involved in speech. Damage to these may produce speech-impairing deficits.
- Speech impairments should prompt timely referral to a speech-language pathologist, who may complete a comprehensive assessment of speech and aid in rehabilitation.

- Swallowing: Swallowing depends on complex neuromuscular coordination that enables the passage of solid or liquid from the oral cavity to the esophagus.
  - The process of swallowing can be divided into three phases, each of which with its own neurologic control.
    - Oral phase (*voluntary*): Bolus entry -> oral containment -> salivary moistening -> mastication -> trough formation -> tongue elevation -> bolus propelled into pharynx.
    - Pharyngeal phase (*involuntary*): Nasopharyngeal closure -> pharyngeal constriction -> oropharyngeal closure -> laryngeal closure -> hyoid elevation -> pharyngeal peristalsis -> bolus propelled into esophagus.
    - Esophageal phase (*involuntary*): Upper esophageal sphincter relaxation -> esophageal peristalsis (striated then smooth muscle) -> lower esophageal sphincter relaxation -> bolus propelled into stomach.
  - If the mechanisms of swallowing are impaired, pulmonary aspiration may occur, leading to complications ranging from chemical pneumonitis to pneumonia.
  - Pulmonary aspiration may be assessed with a bedside swallow test. A patient is asked to swallow a glass of water while oxygen saturation is measured. A desaturation of $\geq 2\%$ in the minutes after swallowing may indicate silent aspiration.
  - Deficiencies of cough, gag reflex, and motor speech functions also suggest an increased risk of aspiration.
  - Videofluroscopic swallowing study enables more accurate diagnosis of swallowing dysfunction and may be used to rule out aspiration.
  - Multidisciplinary care with involvement of a speech-language pathologist is helpful for diagnosis and treatment of dysphagia and aspiration.
- Nausea: While nausea may arise from a multitude of causes, identification of the underlying etiology is essential to guiding therapy, and is usually gleaned from a careful history.

- Common iatrogenic causes include chemotherapy, radiotherapy, and initiation of opioids.
- Other causes include anxiety, severe pain, anticipatory nausea, CN VIII damage/vestibulopathy, constipation, bowel obstruction, brain metastases, uremia, encephalopathy, gastritis, gastric ulcer disease, and metabolic derangements (hyponatremia and hypercalcemia).
- Etiology may be confirmed based on responsiveness to selected treatment.
- Nonpharmacologic interventions, such as frequent small feedings of cold meals and avoidance of triggering stimuli, may be helpful for nausea from variety of causes.
- Pharmacologic/interventional treatments should address the underlying cause: for example, prochlorperazine or ondansetron for chemo-induced and opioid-induced nausea, meclizine for vestibulopathy, dexamethasone for brain metastases, PPI or H2 blockers for gastritis, metoclopramide for gastroparesis, lorazepam for anxiety, and surgery/stenting for bowel obstruction.

○ Nutrition/Weight loss: Nutritional status may be compromised by dysphagia, nausea, dysgeusia, and loss of appetite, as well as the metabolic effects of cancer itself.

- History should focus on uncovering specific causes of malnutrition/weight loss. However, in the majority of advanced cancer patients, anorexia occurs secondary to effects of cancer itself.
- Assess ability of patient to increase oral intake, and consult a dietician for careful monitoring of nutritional intake, which should be followed closely throughout treatment and recovery.
- Gastrostomy tube should be considered for patients with poor performance status, dysphagia, odynophagia, inadequate hydration, high risk of pulmonary aspiration, 5% weight loss over 1 month, or 10% weight loss over 6 months, if aligned with goals of care.
- Nasogastric tubes are extremely unpleasant for patients and should only be considered for short-term use under extenuating circumstances. Also, they may be difficult to place in a patient with anatomic abnormalities in the head and neck (either due to tumor or due to prior surgeries/radiation).
- If nasogastric tube is indicated in a patient with prior head and neck surgery, consult with surgeon prior to placement.

○ Neurologic impairment: Numbness, tingling, weakness, and neuropathic pain may result from direct invasion or vascular compromise of nerves in the head and neck secondary to progression of cancer.

- Focal neurologic deficits in the head and neck may manifest as facial paralysis, dysphagia, speech impairments, and diplopia.

  - These deficits negatively impact quality of life and may serve as a great source of frustration to patients.
  - Neuropathic pain can be especially challenging to treat.
    - In many cases neuropathic pain is refractory to gabapentin and pregabalin.
    - Methadone may provide superior relief of neuropathic pain but ought to be prescribed cautiously or in conjunction with a palliative care specialist, as it carries a high risk of unintended overdose.
- Physical exam: A focused head and neck exam may include:
  - Head: Hair, skull, facial contours, salivary glands, skin.
  - Eyes: Vision, alignment, movements, pupils, light reflexes, fundi. Exophthalmos, diplopia, and ptosis may indicate the presence of metastases in the orbit or cavernous sinus.
  - Ears: Auricles, canals, tympanic membranes, hearing. Dedicated hearing evaluation may be indicated.
  - Nose and Sinuses: Mucosa, septum, sinus tenderness.
  - Oral Cavity and Pharynx: Lips, buccal mucosa, gingiva, teeth, retromolar trigone, hard and soft palate, tongue, tonsils, speech, swallow evaluation, assessment for trismus. Consideration should be given for a dental evaluation prior to any treatment in the head and neck region based on symptoms and life expectancy.
  - Neck: Lymph nodes, trachea, thyroid, range-of-motion.
- Fiberoptic nasolaryngoscopy, if indicated, enables better visualization of mucosal structures in the nasopharynx, oropharynx, larynx, and hypopharynx and extent of disease in these areas. It also allows for assessment of airway patency, and vocal cord function.

SYMPTOMS

See Table 17.1.

Goals of Care, Performance Status

- Goals of care should be determined by the patient and physician based on a realistic discussion of near- and long-term hopes and expectations.
- Although there is a lack of data regarding the prognostic implications of disease metastatic to the head and neck area, patients with recurrent and/or metastatic head and neck cancers generally have median survival less than 1 year, even with aggressive treatment [1].
- Poor performance status may complicate the logistics of simulation and treatment. Specifically, patients with tumors compressing the tracheal region may be unable to lie flat. Frequent monitoring or individualized radiation techniques and setup may be needed.

TABLE 17.1 Guide to Common Symptoms

Site	Symptoms	Acute Concerns
Oral cavity	Dysphagia, odynophagia, dysarthria, bleeding, trismus, tooth loss, infection	Airway compromise, aspiration risk
Larynx	Dyspnea, dysarthria, hoarseness	Airway compromise, aspiration risk, vocal cord dysfunction
Skin	Cosmetic changes, bleeding, ulceration	Infection, necrosis
Neck	Bleeding, dysphagia, dyspnea	Airway compromise, aspiration risk, vessel patency, hemorrhage
Neurologic	Cranial nerve palsy, weakness, numbness	Focal neurologic deficits, aspiration risk

- If prognosis is limited and/or performance status is poor, weigh the quality of life benefits of forgoing radiotherapy against the therapeutic benefits of receiving it.
- Encourage patients for whom time is short to make time for personal and professional goals.
- Allow for delays in radiotherapy, if necessary, for patients to fulfill these goals.

TREATMENT RECOMMENDATION

Supportive Care

- Diligent supportive care of advanced cancer patients with disease in the head and neck region requires early recognition and treatment of nausea, nutritional deficiency, anemia, and pain.
- Feeding tubes or parenteral nutrition, if necessary, should be anticipated based on swallowing function, nutritional status, and goals of care.
- If there is concern for airway compromise, ENT specialists or otolaryngologists should be involved and potentially available for airway management, which may include tracheostomy tube placement.
- It is technically challenging and morbid to perform a tracheostomy in proximity to areas of gross disease.
- Referral to experienced head and neck providers and advanced planning, including a thorough discussion of the patient's goals of care, are indicated.

- Effective treatment of pain should be of high priority. A significant proportion of cancer patients requiring analgesics in the outpatient setting are undertreated [2];
- Cancer patients likely have opioid preferences based on past experience: use this as a starting point.
- Set functional goals to guide pain management (e.g., "I want to be able to eat soft foods").
- Treatment of neuropathic pain can be particularly challenging.
- For refractory moderate to severe neuropathic pain, consider methadone; however, prescribe with caution or in collaboration with palliative care specialist given complex pharmacokinetic profile and risk of unintended overdose.

Palliative Chemotherapy

- For patients with advanced, metastatic head and neck cancer, palliative chemotherapy alone is not curative. However, it may provide prolonged survival but with significant risk of associated toxicity.
- EXTREME trial (Vermorken *NEJM* 2008): 442 patients with untreated recurrent or metastatic SCC of the head and neck were randomized to either [1] cisplatin/carboplatin + 5-FU or [2] cisplatin/carboplatin + 5-FU and cetuximab (EGFR inhibitor).
  - Patients receiving cetuximab showed improved median survival (10.1 months vs 7.4 months), PFS (5.6 months vs 3.3 months), and increased response rate (36% vs 20%).
  - However, toxicity was greater with cetuximab (26 vs 16 patients had adverse events): mostly anemia, neutropenia, and thrombocytopenia, but nine patients in the cetuximab arm had sepsis (vs 1 in the chemo-alone, $p = 0.02$) [1].
- Investigations of novel targeted agents and immunotherapy for various metastatic cancers, including head and neck cancers, are ongoing, with promising early results.
- A variety of chemotherapy agents administered to patients with advanced cancers may contribute to symptoms in the head and neck, which may be exacerbated by radiotherapy and hence potentially dose-limiting.
- Mucositis is one of the most common side effects of chemotherapy, in general, and can be treated with frequent saline and analgesic rinses. Other potential treatments include antimicrobials, amifostine, benzydamine hydrochloride, l-glutamine, GM-CSF, and superoxide dismutase inhibitors.
- Other potential head and neck side effects of chemotherapy include dermatitis, xerostomia, tongue swelling/tenderness, dysgeusia, neuropathy, mucosal pain, odynophagia, increased propensity for infection/dental abscess.

- Patients are likely to benefit from regular dental care.
- EGFR-inhibitors are also used in a variety of cancers (head and neck, lung, breast, colorectal) and may cause alopecia, hypertrichosis, dry skin, dermatitis, and mucositis.

Radiotherapy for Aggressive Local Control or Potential Cure

- While most tumors arising in the head and neck region stem from primary tumors within the head and neck, other potential sources of disease include metastases from distant primaries (e.g., prostate, renal cell, bladder, lung, and breast), as well as various cutaneous malignancies.
- If a patient with distant metastases to the head and neck region has a low enough systemic disease burden to justify pursuit of aggressive local treatment (oligometastatic disease), then aggressive local treatment may be indicated.

Head and Neck Primaries

- The most common form of primary treatment failure in head and neck cancer is locoregional recurrence, occurring in 20–30% of patients [3,4].
- Patients with locoregional recurrence who lack distant metastases may still achieve long-term survival if aggressive treatment options are pursued, albeit with significant risks of toxicity.
- In a patient with locoregional recurrence who previously received radiation therapy (RT), the length of disease-free interval (e.g., approximately 6 months) before recurrence is thought to inversely correlate with radioresistance.
- If disease-free interval is $<$6 months, disease recurrence within the previously irradiated field may not benefit from re-irradiation with curative intent; however, data are limited, and this observation is likely not valid in cases of miss or marginal miss, which may be more common in the intensity modulated radiation therapy (IMRT) era [5].
- Locoregional recurrences in patients with good performance status and limited resectable disease should be treated with curative-intent surgical resection. Postoperative re-irradiation may be appropriate if risk of future recurrence is high [6].
- Unfortunately, most patients with local recurrence are medically or technically inoperable. In this setting, aggressive re-irradiation, potentially given in combination with concurrent systemic therapy, offers palliative benefit and a potential chance of cure, although this is debatable.
- Considerations prior to full-dose re-irradiation with or without chemotherapy include willingness of patient to tolerate potentially morbid treatment with significant mortality risk, degree of radioresistance (based on

length of disease-free interval), and anticipated RT dose to critical structures based on pattern of recurrence (e.g., spinal cord, optic nerve, optic chiasm, and carotid arteries).

- Given the high morbidity associated with curative-intent re-irradiation, advanced treatment modalities with increased conformality, such as IMRT, may enable dose-escalation with less risk of severe complications [7–9].
- While concurrent chemotherapy with re-irradiation may address the issue of radioresistance among recurrent tumor cells, re-irradiation alone has conferred survival rates of 13–22% at 3 years [10,11].
- Attention to professional guidelines is indicated, [6] as is consideration for referral to a high volume head and neck center.
  - Prescription dose and treatment volumes should be tailored to the individual patient and clinical scenario.
    - One potential option is to treat to a total dose of 60 Gy with concurrent chemotherapy (ideally different agents than those used during the first course of treatment).
    - Treatment volumes should focus on gross disease or areas at highest risk of recurrence in the postoperative bed.
    - Given the potential toxicity, elective nodal irradiation is not generally recommended.
  - Even in the case of re-irradiation, an attempt should be made to spare normal structures as much as possible; however, priority should be given to limiting the dose administered to a previously irradiated spinal cord. Data are limited, but institutional experience has suggested there is likely some recovery of cord tolerance over time.

Important Trials

- RTOG 9911 (Langer *J Clin Oncol* 2007): 105 patients with local H&N SCC recurrence underwent chemo-re-irradiation.
  - RT: 60 Gy/1.5 Gy fx b.i.d. q 2 weeks × 4 cycles.
  - Chemo: cisplatin 15 mg/m^2 IV daily × 5 and paclitaxel 20 mg/m^2 IV daily × 5 q 2 weeks × 4 cycles. G-CSF was given days 6–13 of each 2-week cycle.
  - Median survival = 12.1 months, estimated OS 1 year = 50.2%, 2 year = 25.9%.
  - 26% of patients did not complete chemotherapy, 28% had Grade ≥ 4 acute toxicity, 21% had Grade ≥ 4 acute hematologic toxicity, and eight treatment-related deaths occurred (8%): five acute, three late (including two carotid hemorrhages) [12].
- RTOG 9610 (Spencer *Head Neck* 2008): 79 patients with local H&N SCC recurrence underwent chemo-re-irradiation.

- 60 Gy/1.5 Gy b.i.d. fx. Chemo: 4 weekly cycles of 5-FU 300 mg/m^2 IV bolus and hydroxyurea 1.5 g PO.
- Median survival was better for patients with > 1 year disease-free interval prior to chemo-re-irradiation (9.8 months vs 5.8 months, $p = 0.036$).
- Estimated OS rate for all patients were 2 year = 15.2% and 5 year = 3.8%.
- 25.3% of patients had acute Grade ≥4 toxicity, 19.4% had Grade 3, 3% had Grade 4 late toxicity, and six treatment-related deaths occurred (8%): two hemorrhage, four neutropenia [13].

Radiotherapy for Palliation

- For patients with advanced cancer in the head and neck region for whom aggressive treatment is either inappropriate or inconsistent with goals of care, RT with palliative intent may potentially alleviate symptoms and improve quality of life.
- Similar treatment principles apply for patients with advanced, metastatic cancer from a head and neck primary and those with metastatic spread from distant sites, such as GU, lung, and breast.
- For a symptomatic tumor in the head and neck region, RT is typically more likely to produce a local response than chemotherapy.
- Treatment volume for palliative RT
  - Should target only gross disease with an individualized margin to account for uncertainty and setup error.
  - Focus on areas of tumor responsible for symptoms.
- More conformal techniques, such as IMRT, may be considered if durable palliation is desired, if there is concern for intolerable or unwanted treatment-related side effects, or potentially for protection of critical structures in the case of re-irradiation. The benefits of using IMRT or other advanced techniques should be balanced against the increased cost and the need to start treatment within a shorter time frame.
- Skin metastases may bleed or be otherwise symptomatic and thus may also benefit from palliative radiotherapy.
  - Electrons may be preferable to photons for superficial lesions, depending on depth of invasion and surrounding anatomy.
  - The use of a bolus enables the 100% isodose line to be approximated to the surface of the targeted lesion.
  - If surface anatomy is complex, dose heterogeneity inherent to electron beam therapy may result in hot and cold spots. This can be addressed with a custom bolus.

Palliative Radiotherapy Regimens for Head and Neck Cancer

See Table 17.2.

TABLE 17.2 Guide to Palliative RT Regimens for Head and Neck Cancer

Regimen	Dose | Fractionation | Timing	Clinical Role
Quad Shot	44 Gy in 3.7 Gy fx b.i.d. for 2 consecutive days | 3 cycles separated by 2–3 weeks interval	Untreated, incurable, inoperable disease; favorable balance of response/toxicity
High-dose palliation	50 Gy in 2.5 Gy fx or 3.125 Gy fx | daily. Higher doses may also be considered in select cases (e.g., 55–60 Gy)	Good performance status; long-term control symptomatically beneficial
Low-dose palliation	20 Gy in 4 Gy fx or 30 Gy in 3 Gy fx | daily	Poor performance status; limited prognosis
Low-dose hypofractionation	30 Gy in 6 Gy fx, boost to 36 Gy as tolerated | 2 fx per week, at least 3 days apart	Poor performance status; limited prognosis; flexible treatment schedule
0–7–21	24 Gy in 8 Gy fx | delivered days 0, 7, 21	Very limited performance status and/or prognosis
Single fraction	8 Gy × 1	Other regimens not feasible or indicated
Hypofractionated palliation	40 Gy in 2.5 Gy fx, escalation to 50 Gy as tolerated | daily	Untreated, incurable, inoperable disease
IHF2SQ for palliative chemorads	48 Gy in 3 Gy fx b.i.d. on days 1 and 3 of weeks 1, 3, 5, and 7 of concurrent platinum-based chemo	Untreated, incurable, inoperable locally advanced disease; performance status too low for conventional chemorads

- RTOG 85–02 QUAD SHOT regimen: 44.4 Gy in 3 cycles of 3.7 Gy fx b.i.d. for 2 consecutive days, with 2–3 week intervals in between [14].
  - Several studies have demonstrated favorable rates of response and acceptably low toxicity profiles with QUAD SHOT [15,16].
  - MSKCC QUAD SHOT experience [17]: 44 patients completed at least one cycle of QUAD SHOT; 16 patients (36%) completed all 3 cycles. Palliative response (relief of presenting symptom or clinical/radiographic tumor response) was achieved in 75% of all patients, which was significantly associated with increased number of cycles received ($p = 0.01$). Median OS = 6.27 months (range 0.23–30.4 months). Grade 3 toxicity = 5% (dermatitis and mucositis), Grade 2 = 30% (fatigue and mucositis) [17].
- High-dose palliation may be used for patients with high performance status in whom longer-term local control may provide symptomatic benefit: 50 Gy/2.5 Gy fx or 50 Gy/3.125 Gy fx [18].

- Low-dose palliation is appropriate for patients with poorer performance status or more limited prognosis: 20 Gy in 5 fractions or 30 Gy in 10 fractions [19].
- Low-dose hypofractionated regimen: 30 Gy in 5 fractions at 2 per week, with at least 3 days apart (plus optional 6 Gy boost) [20].
- "0−7−21": Patients with very limited performance status and prognosis may be treated with 24 Gy in 3 fractions, delivered on day 0, day 7, and day 21 [21].
- Single fraction: 8 Gy × 1 may be used for symptom control when other regimens are not feasible or indicated.
- Hypofractionated palliative RT [22]: 110 patients with unresectable HNSCC received 40 Gy/16 fx, with escalation to 50 Gy when tolerable. Response rate: complete = 10%, complete and partial = 73%. Percentage of symptoms relieved: <50% = 26%, 50−75% = 57%, and >75% = 17%. Overall PFS at 12 months was 55.1% (95% CI 40.3−69.9%). Statistically significant correlates of PFS were weight >50 kg ($p = 0.049$) and RT dose > 40 Gy ($p = 0.012$). Toxicity was acceptable [22].
- IHF2SQ regimen for palliative chemoradiotherapy [23]: 78 patients with unresectable HNSCC treated with 2 fx of 3 Gy per day (day 1 and 3), during the 1st, 3rd, 5th, and 7th week of concurrent platinum-based chemo. Complete or partial response in 53%. Median OS = 12.9 months, median PFS = 10.3 months. Toxicity was acceptable [23].
- Comparison of fractionation schemes:
  - Low toxicity of QUAD SHOT [24]: 66 patients with advanced head and neck cancer treated with palliative radiotherapy.
  - Palliative response rates: QUAD SHOT = 83%, 70 Gy/35 fx = 77%, 30 Gy/10 fx = 67%, 37.5 Gy/15 fx = 86%, 20 Gy/5 fx = 60% ($p = 0.42$).
  - Grade ≥3 toxicity: QUAD SHOT = 9%, other regimens = 37% ($p = 0.01$) [24].
  - Potential benefit of dose escalation [25]: Retrospective review of 148 patients with head and neck cancer who underwent palliative RT. Median dose was 50 Gy (range 2−70); median fraction number was 20 (range 1−40). Median OS = 5.2 months. Increasing radiation dose was significantly associated with improved OS (HR 0.97, 95% CI 0.96−0.99, $p < 0.01$) and treatment response (OR 1.05, 95% CI 1.01−1.08, $p < 0.01$) [25].

Stereotactic Body Radiotherapy and Brachytherapy

- Stereotactic body radiotherapy (SBRT) may allow for hypofractionation and dose escalation, potentially improving rates of durable local control

in patients with a longer life expectancy. SBRT also offers the practical benefit of reduced treatment time compared with conventional RT.

- Several small studies have shown that advanced stage head and neck cancer patients treated with palliative SBRT have favorable symptom control rates with relatively low rates of toxicity [26–28].
  - SBRT for head and neck cancer [29]: 44 patients with primary, recurrent, or metastatic head and neck cancer underwent either single-dose ($n = 18$; 13–18 Gy) or fractionated RT ($n = 37$; 36–48 Gy) to 55 malignant lesions.
    - Overall complete and partial response rate = 77%. Tumor control rates at 1 year: primary = 83.3%, recurrent = 60.6%. Median OS: primary = 28.7 months, recurrent = 6.7 months, metastatic = 5.6 months.
    - Grade 3 + toxicity in 7 patients (16%) [29].
  - Phase II study of SBRT for re-irradiation with cetuximab [30]: 56 patients with recurrent head and neck cancer treated with SBRT to 36 Gy/6 fx with concomitant cetuximab (2 week treatment course).
    - At 3 months, response rate = 58.4%, disease control rate = 91.7%; 1 year OS = 47.5%.
    - Patients with Grade ≥ 3 toxicity = 18 (32%). Skin toxicity: all grades = 41 (73%), Grade $\geq 3 = 5$ (9%). Treatment-related death = 1 (hemorrhage) [30].
- SBRT may be a reasonable alternative to curative intent fractionated RT for primary treatment of inoperable head and neck cancer in elderly patients and those with poor performance status. While data is limited, published control rates, survival, and toxicity are encouraging [31,32].

- Brachytherapy may also provide therapeutic advantages in both curative and palliative situations by enabling dose-escalation, normal tissue avoidance, and the practical benefit of shortened treatment times.
  - Regimens vary widely across institutions, but high-dose-rate intraoperative techniques are most commonly utilized [33].
  - Modern studies of high-dose-rate brachytherapy for head and neck cancer recurrences report local control rates at 1–2 years approaching 70%, with Grade ≥ 3 toxicity occurring in $<20\%$ of patients [34,35].

EXPECTED ACUTE SIDE EFFECTS FROM RADIATION

Dermatitis

- Radiation dermatitis occurs in the majority of patients who receive radiotherapy for advanced cancer in the head and neck region. Risk varies based on total RT dose, fraction size, treatment time, beam type and energy, and skin volume exposed [36].
  - Grade 1: Faint erythema or dry desquamation.

  - Grade 2: Moderate to brisk erythema; patchy, most desquamation mostly confined to skinfolds; moderate edema.
  - Grade 3: Moist desquamation other than skinfolds; bleeding with minor trauma/abrasion.
  - Grade 4: Skin necrosis or ulceration of full thickness dermis; spontaneous bleeding.
- Skin changes are sharply demarcated, as they reflect the associated treatment field.
- Other risk factors include poor nutrition, preexisting dermatologic conditions, overlapping skinfolds, concurrent cetuximab, connective tissue diseases, HIV, diabetes, receipt of radiosensitive agents, and inherited disorders of DNA repair [36,37].
- Basic management strategies: Counseling about skin care, daily use of Aquaphor, and consideration of low to moderate dose topical steroids (e.g., mometasone 0.1%). Consider topical antibiotic (e.g., mupirocin) if evidence of infection.

Mucositis

- Radiation-induced mucositis is a common side effect of radiation to the head and neck that may potentially result in pain, dysphagia, dehydration, nutritional deficiencies, weight loss, feeding tube dependency, and pulmonary aspiration [38].
- Stomatitis (mucositis of the oral cavity) is of particular concern with chemoradiation, as various chemotherapy agents are independently associated with stomatitis, frequently in the anterior structures of the oral cavity.
- There is no reliable prophylaxis for radiation-induced mucositis; nonetheless, patients should be encouraged to maintain excellent oral hygiene and undergo dental evaluation prior to treatment.
- Aggressive use of analgesics may be required if pain is function limiting.
- In the event of dysphagia/odynophagia, speech and swallow evaluation and therapy may be indicated.
- Feeding tube placement should be considered only as a temporizing measure and must be aligned with patient's goals of care.
- Basic management strategies: consider regular oral rinses with baking soda/salt solution. Mild to moderate pain: consider Maalox/Benadryl/Lidocaine (MBL/Magic Mouthwash), or application of oral lidocaine gel to specific areas of pain. Acetaminophen and NSAIDs can also be considered, although care should be taken in patients with liver or renal dysfunction or those receiving systemic chemotherapy. Moderate to severe pain: consider opioid use (both short- and long-acting), potentially in conjunction with a bowel regimen.

Xerostomia

- Xerostomia is caused by hyposalivation that results from irradiation of the salivary glands.
- Xerostomia may impair speech, chewing, and swallowing, cause pain and ulceration, and predispose to infection as well as rapidly progressing caries [39].
- IMRT and proton beam therapy may enable improved sparing of salivary glands, which may be worth pursuing in selected patients considering that management of xerostomia is challenging.
- Potential therapies include the cholinergic agonists cevimeline and bethanechol, acupuncture, and oral lubricants [39].
- Avoidance of sugar and good oral hygiene practices, with prophylactic daily fluoride rinses, may help prevent rapidly progressing caries.
- Medications that may contribute to xerostomia include antihistamines, anticholinergics, beta-blockers, diuretics, some anticonvulsants, antipsychotics, hypnotics, and morphine.

Edema

- Radiotherapy may cause lymphedema of the larynx and pharynx, leading to difficulty speaking and dysphagia.
- Laryngeal edema is often more pronounced in the case of re-irradiation.
- RTOG Scale for laryngeal edema (to be determined by flexible fiberoptic exam) [40]:
  - Grade 0: No edema.
  - Grade 1: Slight edema.
  - Grade 2: Moderate edema.
  - Grade 3: Severe edema.
  - Grade 4: Necrosis.
- To prevent laryngeal edema, mean laryngeal dose should be ≤ 43.5 Gy [41].
- If airway is threatened, make sure ENT surgery is aware and available for acute management.

Dysgeusia

- Temporary radiation-induced dysgeusia occurs as a result of damage to the taste buds and/or chorda tympani.
- Avoidance of the anterior tongue in the treatment field is an effective strategy for preserving taste, even if the base of the tongue is irradiated [42].
- Dysgeusia may have a large negative impact on quality of life, contributing to weight loss and nutritional deficiencies.
- Other causes of dysgeusia include chemotherapeutics, especially taxanes and vincristine.

- Consultation with a nutritionist may be required to ensure that patient is able to maintain adequate dietary intake.

ON TREATMENT MANAGEMENT

Multidisciplinary

- Patients with advanced cancer in the head and neck are at high risk of developing a multitude of complications, both disease-related and iatrogenic.
- Early involvement of ENT surgeons, dentists, palliative care specialists, nutritionists, and speech-language pathologists is critical.

Steroids

- Corticosteroids may be used to reduce inflammation and edema in the head and neck (consider Decadron 2−4 mg PO QD to BID for severe inflammation/edema).
- May also relieve neuropathic pain and nausea.

Skin Care

- Moderate potency topical steroids, such has 0.1% mometasone, have been shown to be effective as prophylaxis against discomfort, burning, and itching associated with radiation dermatitis [43].
- Skin dryness can be alleviated by Aquaphor or other moisturizers.
- Pruritis can be treated with Gold Bond or 1% hydrocortisone ointment.
- Sun exposure to treatment site should be limited either by covering affected area or with SPF 50 or greater sunscreen.
- For moderate to severe radiation dermatitis, Domeboro compresses and Aquaphor/xylocaine, topical lidocaine, or Pramasone may be beneficial.

Oral Care

- Prior to receiving head and neck radiation, patients should undergo a dental evaluation to assess baseline oral health and determine the need for restorative work or extractions.
- Typical recommendations for maintaining good oral hygiene include: regular brushing, soft toothbrush, mild toothpaste, baking soda gargle, floss gently as tolerated, use a humidifier, reduce intake of spicy foods, and avoid intake of alcohol and use of tobacco products.
- Daily prophylactic fluoride use is also recommended, as patients are at increased risk for caries.
- Close dental follow-up is recommended, as patients are at high risk for dental complications (Table 17.3).

TABLE 17.3 On Treatment Management

Symptoms	Acute Management	Late Management
Dermatitis	• Avoid sun exposure and use at least SPF 50 sunscreen • Dryness: Aquaphor to affected area daily • Pruritus, mild pain: Gold Bond, low potency topical steroids (hydrocortisone 1% ointment), moderate potency topical steroids (mometasone 0.1%) • Early signs of infection: Topical antibiotics (mupirocin) • Simple, nonpurulent cellulitis (Strep and MSSA coverage): cephalexin 500 mg PO QID × 7 days, Augmentin 875/125 mg PO BID × 7 days, or clindamycin 300 mg PO TID × 7 days (clinda provides partial MRSA coverage)	• Maintain good wound care hygiene; consider involving wound care nurse specialist • Severe pain: Domeboro compresses and either Aquaphor/xylocaine, topical lidocaine, or Pramasone • Purulent cellulitis (MRSA suspected): Bactrim 160/800 mg 1–2 tabs PO BID × 7 days or doxycycline 100 mg PO BID—note these do not adequately cover *Streptococcus* and must be combined with either cephalexin 500 mg PO QID or amoxicillin 500 mg PO TID
Mucositis	• Pretreatment dental evaluation • Maintain good oral hygiene: Regular brushing and flossing, daily fluoride use, avoid tobacco and alcohol • Discomfort: Baking soda/salt gargle, mild toothpaste, soft toothbrush, avoid spicy foods • Moderate pain: Maalox/Benadryl/Lidocaine (MBL/Magic Mouthwash) or oral lidocaine gel and Tylenol/NSAIDs: Tylenol 975 mg PO TID and naproxen 500 mg PO BID (adjust for hepatic and renal impairment) • Severe pain: Consider opioid use (short and long acting) with a bowel regimen • Consider feeding tube placement only as temporizing measure after assessing whether it is aligned with patient's goals of care	• Dysphagia/odynophagia: Speech and swallow evaluation, monitor for dehydration, nutritional deficiencies, and pulmonary aspiration • Consider feeding tube placement after assessing whether it is aligned with patient's goals of care

(*Continued*)

TABLE 17.3 (Continued)

Symptoms	Acute Management	Late Management
Xerostomia	• Pretreatment dental evaluation • Consider IMRT for salivary gland sparing, as xerostomia can be difficult to treat • High risk of caries: Daily fluoride rinses, regular brushing and flossing, avoid sugar, tobacco, and alcohol	• Consider discontinuation of medications that contribute to xerostomia: Antihistamines, anticholinergics, beta-blockers, diuretics, some anticonvulsants, antipsychotics, hypnotics, and morphine • Regular dental follow-ups to monitor for and prevent caries • While treatment may be challenging, consider: Cevimeline 30 mg PO TID or bethanechol 25 mg PO TID (cholinergic agonists), oral lubricants, and acupuncture
Edema	• Limit mean laryngeal dose • Severe edema: Consider Decadron 2–4 mg PO QD to BID • If airway is threatened, make sure ENT is aware and available for acute management	• Continue Decadron as needed • For dysphagia and speech difficulty: Speech therapist referral • Consider intubation and/or feeding tube placement only if aligned with patient's goals of care
Dysgeusia	• Avoid anterior tongue in treatment field • First line: Small, frequent meals; cold, bland foods; avoid metal silverware; season food to taste; add fats and sauces to foods • Second line: Zinc sulfate 50 mg PO TID	• Consider other possible causes of dysgeusia, including chemotherapy, antihypertensives, antiemetics, antidepressants, depression, oral infections, and zinc deficiency • Consider nutritionist consultation to ensure adequate dietary intake • Monitor for weight loss • Regular dental follow-ups to improve oral hygiene and monitor for oral infections

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Index

Note: Page numbers followed by "*f*" and "*t*" refer to figures and tables, respectively.

A

Acid–base homeostasis, 102
Acupuncture, 73
Acute pain, 68
Acute skin toxicities from radiation, 134–140, 135*f*, 136*f*. *See also* Chronic skin toxicities from radiation
  grading of toxicity, 136
  Multinational Association for Supportive Care in Cancer (MASCC) guidelines for management, 138–139
  pathology and timeline, 135–136
  peak skin reaction, 135
  prevention, 137–139
  specific recommendations for patients undergoing treatment, 139–140
  tips on skin care, 139
  treatment options, 139–140
ADAPT (talking map), 25–26
Advance care planning (ACP), 50
  documents, 52–53
  priorities and coordinated, 52
  utilization of, 50–52
Advance directives (ADs), 50
  documents, 52–53
  patient characteristics and, 51
  systematic review of the impact of, 52
Airway stents, 110–111
Aloe vera, 138
Alpha emitters, 204–205
  radium-223, 204–205
American College of Radiology (ACR), 14
American Society for Radiation Oncology (ASTRO), 14, 41
Anorectal cancer, 244–249
  metastasis, 245–246
  as recurrent disease, 245
  treatment recommendations, 247*t*
Argon plasma coagulation (APC), 111, 122
"ASK-TELL-ASK" method, 23–24
Asymptomatic metastases, 222–224

B

Beta emitters, 202–204
  rhenium-186 (Re-186), 204
  samarian-153 (Sm-153), 203–204
  strontium-89 (Sr-89), 202–203
Biliary obstruction, 243
  palliative radiation therapy for, 243–244
Bisacodyl, 96*t*
Bisphosphonates, 205
Bladder cancer, 266–267
Bleeding
  assessment, 120–121
  communication with patients about catastrophic bleeding events, 120–121
  fractionation schemes for palliative radiation therapy, 11*t*
  goals of care, 120–121
  local therapies
    dressings, 121
    endoscopic procedures, 122
    packing, 121
    radiation therapy, 121–122
    surgical procedures, 123
    topical agents, 121
    transcutaneous embolization of vessels, 122–123
  scope of problem, 119–120
  systemic therapies and considerations, 127–128
    antifibrinolytics, 127–128

Bleeding (*Continued*)
causative or exacerbating agents, discontinuation, 128
tranexamic acid, 127–128
vitamin K, 127
treatment options by site of hemorrhage
embolization of branches, 127
gastrointestinal bleeding, 126
hematuria, 126–127
hemoptysis, 124–125
intravesicular instillation of alum or prostaglandins, 127
palliative radiotherapy fractionation for, 126*t*
palliative radiotherapy regimens, 126, 126*t*
renal artery embolization, 127
skin lesions, 123–124
uterine or iliac artery embolization, 125
vaginal bleeding, 125
Block, Dr. Susan, 44–45
Brachytherapy, 265
for head and neck cancers, 287–288
intraluminal, 115
Brain metastasis/bone metastases, 153
clinical assessment, 190–192
imaging modality, 192
Mirels' Scoring System, 191–192, 191*t*
evaluation, 154, 190
evaluation and management of common clinical concerns, 156–164, 164*t*
anorexia, 159–160, 160*t*
antinausea and antiemetic management, 158*t*
conjunctivitis, 161–162
fatigue, 161
functional deficits, 162–164
headache characteristics, 158*t*
lethargy, 161, 161*t*
nausea and vomiting, 157–159
otitis externa, 162
seizure, 160–161
somnolence, 161, 161*t*
tearing, 161–162
management, 192–193, 197*t*
alpha emitters, 204–205
beta emitters, 202–204
bisphosphonates, 205
bisphosphonates in combination with EBRT, 205–206
denosumab, 206
exceptions in radiation therapy, 195–196
external beam radiation therapy (EBRT), 193, 198–199, 201–202
pain control, 192
preferred treatment regimen for noncomplicated, 195
prospective trials, 200–201
QOL improvement, 198–199
radiopharmaceuticals for diffuse painful metastases, 202
randomized controlled trials on fractionation regimens, 193–195, 194*t*
re-irradiation, 199–200
side effects of radiation therapy, 196–198
stereotactic body radiotherapy/ stereotactic radiosurgery, 200–201
zoledronic acid, 205
palliative radiotherapy regimens for
hypofractionated stereotactic radiotherapy (hSRT), 156
partial brain radiation therapy, 155, 155*f*
stereotactic radiosurgery (SRS), 155–156
whole brain radiation therapy (WBRT), 154
pathophysiology, 190
presentation, 190
Brief Pain Inventory, 69
Bronchoplasty or balloon dilation, 110
Bronchoscopy, 110, 122
Burden of cancer, 3
patient's overall symptom burden, 60

C

CAGE substance abuse screening tool, 70
Calendula, topical, 138
Central airway obstruction (CAO), 103–104
diagnosis, 109
diagnostic tests, 109
three-dimensional reconstruction of CT images, 109
management, 109–115
airway stents, 110–111
argon plasma coagulation (APC), 111
brachytherapy (intraluminal), 115
bronchoplasty or balloon dilation, 110
bronchoscopy, 110
endobronchial cryotherapy, 112
helium–oxygen gas mixture therapy, 115
initial stabilization, 109
laser therapy, 111
palliative chemotherapy, 112–113

palliative radiotherapy, 113–115, 113*t*
palliative surgery, 112
silicone stents, 111
significance, 108–109
Central biliary obstruction, 249
Central pain, 68
"Choosing Wisely" campaign, 14
Chronic pain, 68
Chronic skin toxicities from radiation, 140–144. *See also* Acute skin toxicities from radiation
grading system, 141–142
LENT/SOMA, 143*t*
RTOG/EORTC, 142*t*
late toxicity, 140, 141*f*
prevention of, 143
LENT/SOMA (symptom specific—fibrosis/scar), 143*t*
pathology, 140–141
treatment, 143–144
use of vitamin E and pentoxifylline, 144
Clinical prediction, 4
Colonoscopy, 122
Combined directives, 52
Communication with patient
about catastrophic bleeding events, 120–121
ADAPT (talking map), 25–26
approaching the topic of prognosis, 25–26
"ASK-TELL-ASK" method, 23–24
conducting a family meeting/goals of care discussion, 26–27
delivering "bad news", 24–25
FICA Spiritual History Tool, 27–28
NURSE, 25, 61
responding to patient emotions with empathy, 25
SPIKES, 24–25
Constipation, as radiation-induced adverse effects
definition, 92–93
diagnosis, 92–93
formal methods of assessment for, 94*t*
peristalsis-stimulating laxatives, 96*t*
presentation of, 93–94
prevalence, 93–94
rectal laxatives, 96*t*
Rome III criteria for functional, 92–93, 93*t*
stool softening laxatives, 95*t*
treatment, 94–96
Costochondritis, 225
C-reactive Protein (CRP), 32
Curative radiation *vs* palliative radiation, 57–58
Cyproheptadine, 160*t*
Cystoscopy, 122

D

Danthron, 96*t*
Decision-making in palliative care, 61
Denosumab, 206
Dexamethasone, 98*t*, 158*t*
Diarrhea, as radiation-induced adverse effects
American Society for Clinical Oncology Guidelines for management, 91*f*
common toxicity criteria, 90*t*
complicated, management of, 92
definition, 89
diagnosis, 89
presentation, 89–90
prevalence, 89–90
preventative measures against, 92*t*
progression, 89–90
symptoms of, 90
treatment, 90–92
Diphenoxylate, 90
Discharge, reasons for, 48
Distress, defined, 59
Docusate, 95*t*
Dolasetron, 98*t*
Dronabinol, 160
Durable Power of Attorney for Health Care (DPAHC), 52
Dutch Bone Metastasis Study Group, 5*t*
Dysgeusia, 290–291
Dysphagia. *See* Malignant dysphagia
Dyspnea, 101–102
American Thoracic Society definition, 101
evaluation of, 102–103
cardiopulmonary history and physical examination, 103
diagnostic testing, 103
scales, 102–103
management of potentially reversible etiologies of, 103–104, 104*t*
management of symptoms
benzodiazepines, 106–107
nonpharmacologic therapies, 108
opioids, 105–106, 106*t*
oxygen therapy, 107
pathophysiology of, 102
symptoms, 101–102

E

Edmonton pain assessment scale, 69
Edmonton Symptom Assessment Score (ESAS), 60
Electron cone therapy, 265
Emetic risk categories of radiation, 97*t*
Endobronchial brachytherapy (EBB), 216–217
Endobronchial cryotherapy, 112
EORTC Quality of life measures and for bone metastases, 60
Epidural spinal cord compression (ESCC). *See also* Metastatic epidural spinal cord compression (MESCC)
  common presenting symptoms
    myelopathy/neurological impairment, 171
    pain, 170–171
  definition, 170
  grading system, 170*t*
    Frankel classification, 171
Esophageal cancer, 232–236
Esophagitis, as radiation-induced adverse effects, 225
  definition, 85–89
  diagnosis, 85–89
  prevalence/progression, 87
  symptoms and symptom management for, 86, 89*t*
  treatment, 89
  World Health Organization (WHO) Scale, 86*t*
Esophagogastroduodenoscopy (EGD), 122
External beam radiation therapy (EBRT), 193, 201–202, 232, 234–235, 242
  benefits of, 198–199
  bisphosphonates in combination with, 205–206
  efficacy and toxicity of, 235

F

FICA Spiritual History Tool, 8, 8*t*, 27–28
Fluoroscopic simulation, 13
5-Flurouracil (5-FU), 235

G

Gastric cancer, 236–237
Gastrointestinal (GI) tract malignancies, 231
Genitourinary malignancies, 266
  summary of dose and fractionation of palliative regimens, 270*t*
  on treatment management, 271*t*
  treatment planning, 269–271
Graded Prognostic Assessment, 5*t*
Granisetron, 98*t*
Gynecologic and genitourinary (GU) cancers, 257–258. *See also* Genitourinary malignancies; Gynecologic malignancies
  evaluation
    all patient, 259
    female patient, 258
    male patient, 259
  treatment recommendations, 259–271
    radiation therapy (RT) for, 258
Gynecologic malignancies, 259–265
  brachytherapy, 265
  dose and fractionation of palliative regimens for, 260*t*
    external beam regimens, 264–265
    Quad shot, 263–264
    10 Gy in a single fraction, 261–263, 261*f*
  electron cone therapy, 265
  recurrent disease, 265–266

H

Hair follicles, 133–134
Head and neck cancers and skin metastases
  airway/breathing obstruction, 277
  bleeding, 277
  common symptoms, 281*t*
  expected acute side effects from radiation, 288–291
    dermatitis, 288–289
    dysgeusia, 290–291
    laryngeal edema, 290
    mucositis, 289
    xerostomia, 290
  fiberoptic nasolaryngoscopy, 280
  general history and physical exam, 275–280
  goals of care, 280–281
  locoregional recurrences, 283
  nausea, 278–279
  neurologic impairment, 279–280
  nutrition/weight loss, 279
  pain, 276–277
  performance status, 280–281
  speech impairments, 277–278
  swallowing, 278
  on treatment management, 292*t*

corticosteroids, 291
multidisciplinary, 291
oral care, 291–293
skin care, 291
treatment recommendation, 281–288
brachytherapy, 287–288
concurrent chemotherapy with re-irradiation, 284
form of primary treatment failure, 283
full-dose re-irradiation, 283–284
important trials, 284–285
palliative chemotherapy, 282–283
radiotherapy for aggressive local control or potentially cure, 283–285
RT with palliative intent, 285–287, 286*t*
stereotactic body radiotherapy (SBRT), 287–288
supportive care, 281–282
Health care Power of Attorney, 52
Health Care Proxy (HCP), 52
Helium–oxygen gas mixture therapy, 107, 115
Hemoptysis, 217–218
Hepatocellular carcinoma (HCC), 242–244
Hospice care, 39–40, 63
Hospice referral
documenting decline, 45–46
medical guidelines for determining appropriateness of, 46
Hospice services, 47
barriers to enrollment, 48–49
interdisciplinary care team, 47
outcomes in patients receiving hospice care, 49
reasons for discharge, 48
setting, 47–48
home, 47
inpatient, 48
nursing home, 48
residential hospice, 48
5-HT_3 receptor antagonists, 97–98, 98*t*
Hyaluronic acid, topical, 138
Hypofractionated stereotactic radiotherapy (hSRT), 156

I

Interdisciplinary care team, 47
Intraluminal brachytherapy, 115

K

Karnofsky Performance Status (KPS), 31

L

Lactulose, 95*t*
Laryngeal edema, 290
Laser therapy, 111
Leukocytosis/lymphopenia, 32
Life expectancy, 4. *See also* Prognostication
tools to assess, 5*t*
Liver metastases, 246–249
treatment recommendation for
central biliary obstruction, 249
criteria for surgical removal, 246–248
SBRT, 248–249, 250*t*
surgical resection, 246–248
on treatment management, 249, 251*t*
whole liver irradiation (WLI) with EBRT, 249
Y-90 radioembolization, 248
Living Will (LW), 52
Loperamide, 90
Lorazepam, 107, 158*t*
Lubiprostone, 95*t*
Lung cancer, advanced or metastatic
chronic management of toxicities, 226*t*
evaluation, 211–213
complaints of dysphagia, 213
general history and physical exam, 211–213
hoarseness, 213
presenting symptoms, 212
of superior vena cava syndrome (SVCS), 212–213
expected acute side effects of radiation therapy, 224
on-treatment management, 224–227, 226*t*
for respiratory symptoms, 225–227
treatment recommendations
for asymptomatic metastases, 222–224
chance of toxicities, 216
commonly used and/or studied fractionation schemes, 214*t*
endobronchial brachytherapy (EBB), 216–217
for general pulmonary symptoms, 213–217
for hemoptysis, 217–218
for mesothelioma, 218–220
for postobstructive pneumonia, 218
for superior vena cava syndrome, 220–222
survival differences, 215–216

M

Magnesium hydroxide, 95*t*
Malignant dysphagia, 232–236
  management of, 233*t*
    external beam radiation therapy (EBRT), 234–235
    high dose rate brachytherapy (HDR-BT), 233
    low dose rate brachytherapy (LDR-BT), 234
    radiation therapy for, 232–235
  side effects of radiotherapy to the esophagus, 235–236
Malignant spinal cord compression, 169–170
Marinol, 160
MD Anderson Symptom Assessment Scores, 60
Medicare hospice benefit (MHB)
  average hospice per diem reimbursement, 47
  criteria for enrollment, 46–47
Megestrol Acetate, 160*t*
Mesothelioma, 218–220
Metastatic epidural spinal cord compression (MESCC), 169
  evaluation
    comprehensive physical examination, 172
    history, 172
    imaging, 173–175
  management, 175–183
    administration of dexamethasone, 175–176
    palliative radiotherapy, 176–179
    re-irradiation, 183–184
    surgery, 180–182
    surgical stabilization, 182–183
  prognostic factors, 171–172
    prognostic score to predict ambulatory status for MESCC, 174*t*
    prognostic score to predict overall survival, 173*t*
  recurrence after initial radiotherapy for, 183–184
Metastatic Spinal Cord Compression Index, 5*t*
Methylphenidate, 161*t*
Metoclopramide, 97–98, 98*t*, 158*t*
Midazolam, 106–107
Modafinil, 161*t*
Mucositis, as radiation-induced adverse effects, 289
  clinical progression of RT-induced, 87*t*
  definition, 85–89
  diagnosis, 85–89
  evidence-based clinical practice guidelines for care of patients, 88*t*
  inflammation of the mucous membranes, 86
  prevalence/progression, 86–87
  radiation dosimetry and toxicity risk, 87*t*
  treatment, 87–88
  World Health Organization (WHO) Scale, 86*t*

N

National Cancer Institute (NCI) Common Toxicity Criteria (CTC) instrument, 86
National Comprehensive Cancer Network (NCCN) NSCLC Outcomes Database, 15
National Consensus Project for Quality Palliative Care, 41
National Hospice Study (NHPCO), 5*t*
National Quality Forum (NQF), 14
Nausea and vomiting (RINV), radiation-induced
  antiemetic dosing by radiation risk category, 98*t*
  emetic risk categories of radiation, 97*t*
  incidence, 96–97
  risk factors, 97
  treatment, 97–98
Neuropathic pain, 68
Nociceptive pain, 68
Nonverbal pain assessment tools, 60
Number of Risk Factors model (NRF), 34, 34*t*
Number of Risk Factors (NRF), 5*t*
Numerical Rating Scale (NRS), 68
NURSE, 25, 61

O

Olanzapine, 158*t*
Olsalazine, 92*t*
Ondansetron, 98*t*, 158*t*
Opioid risk tool, 70
Opioid use disorder, managing patients with, 70
Oral Mucositis Assessment Scale (OMAS), 86

P

Pain
  acute, 68
  assessment, 68–70
    case scenarios, 73–80

minimum requirements, 69
recommended screening tools, 70
safety and concerns, 69–70
central, 68
chronic, 68
definition, 67–68
management of, 71–73
acupuncture, 73
adjuvant analgesics and their use in various types of pain, 80*t*
consultation with pain management specialists, 80
equianalgesic dosing table, 72*t*
interventional pain management, 73
methadone dosing, 79*t*
music therapy, 73
nonpharmacologic, 73
opioid adverse effects and possible treatment options, 75*t*
opioids—initial dosing recommendations for, 71*t*
pharmacologic, 71–73
suggested starting doses for nonopioids, 72*t*
using analgesics, 78*t*
WHO analgesic "ladder" for cancer pain relief, 71–72
neuropathic, 68
nociceptive, 68
Pain flare, 13–14
Palliative care assessment, 59–62
assessment of symptoms, 60
patient/family understanding of current illness status, 60–61
screening, 59
tools, 60
Palliative care (PC), 40
alleviating pain and suffering, 8
barriers to, 42
decision-making in, 61
definitions, 40–41
Centers for Medicare and Medicaid Services (CMS), 40–41
Center to Advance Palliative Care, 41
Center to Advance Palliative Care (CAPC), 58
World Health Organization (WHO), 40, 58–59
emerging technologies, 12–13
ENABLE III trial, 43
ENABLE II trial, 43
function of, 4
goals of care and collaboration with palliative care teams, 58
guidelines, 41
interdisciplinary team, 42
need for, 14
outcomes, 42–44
patient's overall goals of care, 62
religion and spirituality, role of, 4–8
services, 41–42
setting, 42
Palliative Performance Scale (PPS), 5*t*
Palliative Prognostic Index (PPI), 5*t*, 33–34
Palliative Prognostic Score (PaP), 5*t*, 33
prognostic model, 33*t*
Palliative radiation therapy, 8–10, 57–63, 113–115. *See also* Radiation-induced adverse effects
for biliary obstruction, 243–244
for bladder cancer, 266–267
for collapsed lung, 114
common dose and fractionation schemes, 113*t*
curative radiation *vs*, 57–58
Dutch Bone Metastasis Study, 8–9, 9*t*
efficacy of, 10–12, 62
fractionation schemes
for bleeding, 11*t*
for bone metastasis, 10*t*
for brain metastasis, 11*t*
for lung tumors, 11*t*
for spinal cord compression, 10*t*
guidelines and quality measures, 14–15
bone metastasis, 14
end of life radiation therapy, 14–15
for head and neck cancers and skin metastases, 285–287
expected acute side effects from radiation, 288–291
guide to palliative RT regimens, 286*t*
for intubated patient, 114
for MESCC, 176–179
candidates for, 180*b*
data from prospective studies, 178
data from randomized clinical trials, 177–178
data from retrospective studies, 179
dose/fractionation regimens, 177–179
planning technique, 176–177
side effects, 177
stereotactic radiosurgery/stereotactic body radiation therapy (SRS/SBRT), 179–180

Palliative radiation therapy (*Continued*)
pain relief following, 12
for penile and urethral cancer, 269
planning and delivery, 13
for prostate cancer, 267–269
rates of palliation, 12
for renal cell carcinoma, 266
side effects, 13–14
late, 14
side effects associated with, 114
supportive care for intubated patient, 115
use of modern CT simulation and computerized treatment planning, 113–114
Palonosetron, 98*t*
Pancreatic cancer, 237–242
clinical trials, 238*t*
complications of locally destructive, 241–242
local progression of, 237–241
borderline resectable pancreatic cancer (BRPC), 240
metastasis, 242
protocol for the treatment of, 240
symptom palliation, 241–242
Partial brain radiation therapy, 155, 155*f*
Patient/family's prognostic awareness, 61
Patient-reported outcomes (PROs), 74
Penile and urethral cancer, 269
Petroleum ointments, 138
Physician accuracy, 30
Physician Orders for Life-Sustaining Treatment (POLST), 52–53
Poloxamer, 95*t*
Postobstructive pneumonia, 218
Prednisone, 160*t*, 161*t*
Prescribing Monitoring Program Registry (PMP), 73
Prochlorperazine, 97–98, 98*t*, 158*t*
Prognosis. *See also* Prognostication
communication with patient, 25–26
estimating, 30
prognostic indicators, 4
Prognosis in Palliative Care Study (PiPs), 5*t*
Prognostication, 4
estimating prognosis, 30
future directions on prognostic markers and prognostic models, 35–36
importance of, 29–30
information desired and desired manner of communication, 30
physician accuracy, 30
prognostic factors, 31–32
prognostic models, 32–35, 33*t*
comparison of, 35*t*
Number of Risk Factors model (NRF), 34, 34*t*
Palliative Prognostic Index (PPI), 33–34
Palliative Prognostic Score (PaP), 33, 33*t*
TEACHH model, 34–35, 35*t*
Prostate cancer, 267–269

R

Radiation-induced adverse effects
constipation
definition, 92–93
diagnosis, 92–93
formal methods of assessment for, 94*t*
peristalsis-stimulating laxatives, 96*t*
presentation of, 93–94
prevalence, 93–94
rectal laxatives, 96*t*
Rome III criteria for functional, 92–93, 93*t*
stool softening laxatives, 95*t*
treatment, 94–96
diarrhea
American Society for Clinical Oncology Guidelines for management, 91*f*
common toxicity criteria, 90*t*
complicated, management of, 92
definition, 89
diagnosis, 89
presentation, 89–90
prevalence, 89–90
preventative measures against, 92*t*
progression, 89–90
symptoms of, 90
treatment, 90–92
esophagitis
definition, 85–89
diagnosis, 85–89
prevalence/progression, 87
symptoms and symptom management for, 86, 89*t*
treatment, 89
World Health Organization (WHO) Scale, 86*t*
mucositis
clinical progression of RT-induced, 87*t*
definition, 85–89
diagnosis, 85–89
evidence-based clinical practice guidelines for care of patients, 88*t*

inflammation of the mucous membranes, 86
prevalence/progression, 86–87
radiation dosimetry and toxicity risk, 87*t*
treatment, 87–88
World Health Organization (WHO) Scale, 86*t*
nausea and vomiting (RINV)
antiemetic dosing by radiation risk category, 98*t*
emetic risk categories of radiation, 97*t*
incidence, 96–97
risk factors, 97
treatment, 97–98
Radiation recall dermatitis, 144–145
agents associated with reactions, 144*f*
Radiation therapy (RT), 4. *See also* Palliative radiation therapy; Radiation-induced adverse effects
for bleeding events, 121–122
fractionation schemes, 121–122
gastric cancer, 236–237
for malignant dysphagia, 232–235
palliative, 8–10
side effects to stomach, 237
side effects to the esophagus, 235–236
Radium-223, 204–205
Recursive Partitioning Analysis, 5*t*
Religion, role in PC, 4–8
Renal cell carcinoma, 266
Rhenium-186 (Re-186), 204

S

Salicylates, 92*t*
Samarian-153 (Sm-153), 203–204
Saunders, Cicely, 39–40
Scopolamine, 158*t*
Sebaceous glands, 133–134
Senna, 94, 96*t*
Silicone stents, 111
Skin, structure of, 133–134, 134*f*
Skin toxicity, radiation-induced
acute, 134–140, 135*f*, 136*f*
grading of toxicity, 136
Multinational Association for Supportive Care in Cancer (MASCC) guidelines for management, 138–139
pathology and timeline, 135–136
peak skin reaction, 135
prevention, 137–139
specific recommendations for patients undergoing treatment, 139–140
tips on skin care, 139
treatment options, 139–140
chronic, 140–144
grading system, 141–142
LENT/SOMA grading system, 143*t*
LENT/SOMA (symptom specific—fibrosis/scar), 143*t*
pathology, 140–141
prevention of late toxicity, 143
RTOG/EORTC grading system, 142*t*
cutaneous inflammatory reaction, 136*t*
dermatitis, 288–289
grading of toxicity, 136
Common Toxicity Criteria for Adverse Events (CTCAE) version 4, 136, 136*t*
RTOG/EORTC grading system, 136, 137*t*
incidence rate, 133
palliative doses and, 134
radiation recall dermatitis, 144–145
agents associated with reactions, 144*f*
Sodium picosulfate, 96*t*
SPIKES-A six-step protocol, 24–25
Spinal instability neoplastic score (SINS), 182–183
Spiritual care experts, 7–8
Spirituality, role in PC, 4–8
Stereotactic body radiation therapy (SBRT), 12–13, 114, 179–180, 200–201
for hepatocellular carcinoma (HCC), 243
for liver metastases, 248–249, 250*t*
for pancreatic cancer, 239–241
Stereotactic body radiotherapy (SBRT)
for head and neck cancers, 287–288
Stereotactic radiosurgery (SRS), 155–156, 179–180, 200–201
Strontium-89 (Sr-89), 202–203
Sucralfate, 92*t*
Sucralfate, topical, 138
Sulfasalazine, 92*t*
Sulfate, 95*t*
Superior vena cava syndrome, 220–222
Surgical decompression, 180–182
candidates for, 180*b*
combined with radiotherapy, 182
decompressive laminectomy, 181
indications for, 180*b*
treatment paradigm, 181–182
Survival Prediction Score (SPS), 5*t*
Sweat glands, 133–134
Systemic chemotherapy, 242

T

TEACHH model, 5*t*, 34–35, 35*t*
Tegaserod, 96*t*
Telangiectasias, 141
Terminal syndrome, 4
Transarterial chemoembolization (TACE), 242
Transcutaneous embolization of vessels, 122–123
  limitations, 123
  mechanical devices and materials, 122
Trolamine, 137–138
Tropisetron, 98*t*

V

Visual Analog Scale (VAS), 68, 103

W

Whole brain radiation therapy (WBRT), 154, 163–164
Whole liver irradiation (WLI) with EBRT, 249
Wong-Baker FACES Scale, 68

X

Xerostomia, 290

Y

Yittrium-90 (Y-90) radioembolization, 242–243, 248