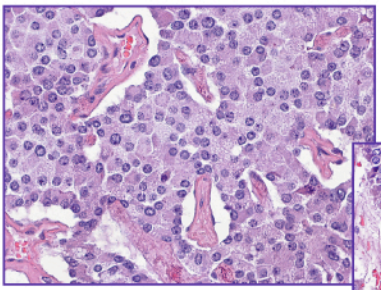
print ISSN 0028–3835 | Neuroendocrinology 84(3) 151–216 (2006) | 84 | 3 | 06 | online ISSN 1423–0194 | www.karger.com/nen

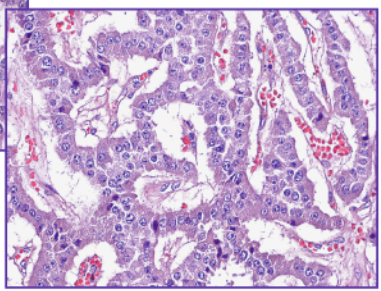
ISBN 978–3–8055–8267–4

Neuro-endocrinology

ENETS Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors

Part 1 – Stomach, Duodenum and Pancreas





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3 figures, 1 in color, and 7 tables, 2006

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Printed in Switzerland on acid-free paper by
Reinhardt Druck, Basel
ISBN 978–3–8055–8267–4

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Vol. 84, No. 3, 2006

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Neuro
-endocrinology

Neuroendocrinology 2006;84:155–157
DOI: 10.1159/000098006

Published online: February 20, 2007

Consensus Guidelines for the Management of Patients with Digestive Neuroendocrine Tumors: Why Such Guidelines and How We Went about It

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The Starting Point

The demand for standards in the stratification and treatment of patients with gastroenteropancreatic (neuro)endocrine tumors (NETs) prompted the European Neuroendocrine Tumor Society (ENETS) to define guidelines [1, 2]. Guidelines had been proposed, however, no attempt was made to reach consensus on specific issues [3, 4]. Given that published evidence on many aspects pertaining to digestive NETs is and continues to be limited, complete consensus in the diagnostic and management arena is unlikely to be achieved. Nonetheless, ENETS has sought to define the European standards in this intriguing field. Therefore, the circulation of ideas with discussion of different opinions and comparison of experiences (both published and according to expert specialists) were deemed indispensable in undertaking such a difficult task. The Society organized two conferences to discuss the previously published ENETS Guidelines, with the aim of arriving at consensus standards on the diagnosis and treatment of digestive NETs. The first consensus conference was held in Frascati, Italy, in November 2005 and focused on foregut tumors; the second conference is planned for November 2006 and will be devoted to midgut and hindgut tumors.

How We Worked

Sixty-two experts active in the field of digestive NETs from 20 different countries attended the first Consensus Conference. Attendees were invited on the basis of their proven expert scientific and clinical experience in NETs. The attendees represented all medical disciplines involved in managing patients with digestive NETs. They were assigned to four working groups according to their specific clinical expertise: (1) Pathology and Genetics (11 participants); (2) Surgery (10 participants); (3) Imaging and Radiology (10 participants), and (4) Medicine and Clinical Pathology (31 participants). The complete list of delegates is provided at the end of this commentary, as well as at the end of each of the six following papers.

The Conference was divided sequentially into 8 sessions devoted to specific topics on an anatomical basis (Gastric NET, Sessions 1 and 2; Duodenal NET; Pancreatic NET, Sessions 1–4; Poorly Differentiated Endocrine Carcinomas of foregut origin). A working booklet was prepared in advance by the organizing committee, using as a basis the published text of the ENETS Guidelines so that specific questions could be prepared and presented to different working groups. The booklet was provided to the participants only at the conference venue.

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0028–3835/06/0843–0155$23.50/0

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At the conference, following a short case presentation in a plenary session (which underlined typical problems in diagnosis and management in each tumor session), each working group gathered separately to discuss group-specific questions. Each session had a chairperson responsible for the case presentation and for conducting the general assembly toward consensus. Each working group had a group leader responsible for presenting specific questions and preparing group statements to the general assembly. Once agreement was reached within each group, consensus statements were discussed and approved or rejected by all participants gathered in the general assembly. This procedure was rigorously followed for all eight sessions. In addition, the TNM staging proposal prepared by the Pathology and Genetics working group was amended and finally approved by the plenary session of the Consensus Conference. The program, the booklet with specific queries and the original file with rough consensus statements are made available via the ENETS site (www.neuroendocrine.net).

What Was Achieved

The following seven papers are a significant and tangible result of the Conference. The reported work was organized after a meeting of the Organizing Committee and entailed the design of the paper and the assignment of each task to leading participants involved in the different sessions. The papers were designed to incorporate the present consensus statements within the previously published ENETS Guidelines [2]. The authors were free to approach the work however they wished, though, in the end, a common format would be agreed upon. This format proved to be flexible enough to accommodate different subjects and the individual views of the authors so that, as can be seen here, not all papers display exactly the same structure. The frame was, as well, consistent enough to highlight the specific consensus statements in a practical and user-friendly way. In addition, a TNM-staging/grading proposal for foregut endocrine tumors was also put forward by the expert pathologists, discussed by all experts and has already been published [5].

Final Remarks

All participants contributed a great effort equally and delegates generously devoted their time, experience and enthusiasm to building the following consensus guidelines. We thank them for their dedication and good will. We believe that the following papers will be practical and useful instruments for all professionals dealing with patients with digestive NETs. These consensus guidelines underline the possibility of achieving practical standards in such a complex tumor disease and should provide a good framework for patient management and aid in directing future investigative efforts.

Acknowledgements

The first consensus meeting held in Frascati, Italy, was supported by a generous grant to ENETS from Ipsen Beaufour Pharmaceutical.

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ENETS Guidelines

Neuro
-endocrinology

Neuroendocrinology 2006;84:158–164
DOI: 10.1159/000098007

Published online: February 20, 2007

Well-Differentiated Gastric Tumors/ Carcinomas

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Introduction

Gastric endocrine tumors (GET) are increasingly recognized due to expanding indications of upper gastrointestinal endoscopy. Often silent and benign, GET may however be aggressive when sporadic and may sometimes mimic the course of gastric adenocarcinoma.

Epidemiology and Clinicopathological Features

Current incidence of GETs is estimated at around 8% of digestive endocrine tumors [1–3]. Yearly age-adjusted incidence is around 0.2 per population of 100,000. GETs may occur in two different situations: sporadic GETs (type 3 tumors) are very rare tumors without predisposing factors for their development. They are most often located in the fundus/gastric corpus, but antral localization is possible. Gastric ECLomas develop from gastric enterochromaffin-like cells (ECL cells) in response to chronically elevated gastrin. The latter may occur in two opposing conditions [4–18]: achlorhydria secondary to (auto-immune) atrophic fundic gastritis (type 1 tumors), or in response to hypergastrinemia resulting from tumoral secretion from gastrinomas (Zollinger-Ellison syndrome), mostly in patients presenting with multiple endocrine neoplasia type 1 (type 2 tumors). Table 1 summarizes the main characteristics of GETs.

Type 1 tumors (ECLomas in the course of atrophic gastritis) occur mostly in women and are rarely responsible for symptoms [19]. They are non-functioning tumors, typically found during upper GI endoscopy performed for dyspepsia or for macrocytic (but also iron deficiency) anemia [7, 12, 15, 17, 19]. ECLomas present frequently as multiple (2–10) polyps, usually <1 cm in diameter in the gastric fundus. Type 1 tumors are almost

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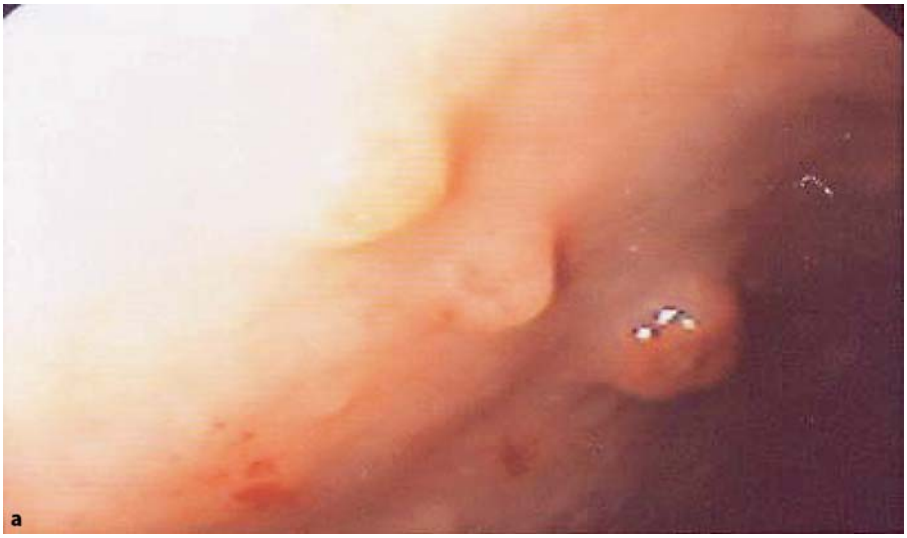

Fig. 1. Type 1 (**a**), type 2 (**b**) and type 3 (**c**) gastric ECLomas.

exclusively benign lesions with little risk of deep invasion of the gastric parietal wall [20]; the latter depends on tumor size [19, 21]. Type 2 tumors (ECLomas in the course of Zollinger-Ellison syndrome) are almost exclusively seen in MEN 1 patients [6, 22–24], occurring in 23–29% of such cases (as compared with 1–3% in sporadic gastrinomas) [24–26]. They appear as small (<1–2 cm) polyps and may involve the entire fundic mucosa. They are generally asymptomatic.

Type 3 tumors are usually solitary and mostly belong to WHO group 2: Ki 67 >2%, >2 cm in diameter with infiltrative growth; they occur mostly in men over 50 years of age [4–6, 19, 20, 27]. They may be discovered incidentally, but are often responsible for pain, weight loss, and iron-deficiency anemia. Atypical carcinoid syndrome due to histamine production is extremely rare (fig. 1).

Minimal Consensus Statements on Epidemiology and Clinicopathological Features

The yearly age-adjusted incidence of gastric type 1 and 2 endocrine tumors is approximately 0.2 per population of 100,000; however, these tumors are probably underdiagnosed. Type 1 tumors are the most common endocrine tumors of the stomach (70–85%) and they are usually benign (WHO group 1). Type 2 tumors,

Table 1. General characteristics of gastric endocrine tumors (GETs) [adapted from 5, 13 and 14]

	Type 1	Type 2	Type 3
Proportion among GETs, %	70–80	5–6	14–25
Tumor characteristics	often small (<1–2 cm) and multiple, polypoid	often small (<1–2 cm) and multiple, polypoid	unique, often large (>2 cm) polypoid and ulcerated
Associated conditions	chronic atrophic gastritis	gastrinoma/NEM 1	none
Pathology	well-differentiated	well-differentiated	well or moderately differentiated
Serum gastrin levels	↑	↑	normal
Gastric pH	↑↑	↓↓	normal
Metastases, %	2–5	10–30	50–100
Tumor-related deaths, %	0	<10	25–30

Table 2. WHO classification of gastric endocrine tumors

Tumor type	WHO classification	Metastases	Invasion beyond submucosa	Histological differentiation	Tumor size, cm	Vascular invasion	Ki 67 %
Benign (low risk)	group 1	–	–	well-differentiated	≤1	–	<2
Benign or low-grade malignant (intermediate risk)	group 1	–	–	well-differentiated	>1	±	<2
Low-grade malignant	group 2	+	+	well-differentiated	>2	+	>2
High-grade malignant	group 3	+	+	poorly differentiated	any	+	>15

however, are much rarer; however up to 35% of cases are metastatic at presentation. Type 1 gastric carcinoids occur more frequently in women and 70–80% of tumors are classically diagnosed in the 5th and 7th decades, although with the more extensive use of endoscopy the age limit may be younger particularly in those patients with multiple autoimmune diseases.

Clinical subtyping of ECL cell tumors (that is, distinction between type 1 and 2 tumors) is important and effective in patient management. Type 1 have almost universally good prognosis with rare tumor-related death at follow-up. Among type 2 gastric carcinoids, death due to metastatic gastric carcinoid is exceptional.

Small gastric carcinoids are usually asymptomatic and very occasionally (<1%) patients may complain of flush and present the 'atypical carcinoid syndrome'.

Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests

Imaging techniques such as CT scan and MRI are of very limited value for small type 1 and 2 tumors. These lesions are recognized by upper GI endoscopy. Endoscopic ultrasonography (EUS) may help to determine tumor invasion in the depth of the gastric wall (table 2). In case of small (<1 cm) ECLomas, upper GI endoscopy is usually the only recommended imaging procedure.

When there is a risk of metastases (table 1), and mainly in cases of sporadic tumors (type 3), an extensive search should be performed. EUS is useful in assessing regional lymph-node involvement and allows histological confirmation by fine-needle aspiration. Transabdominal ultrasonography, and mainly CT scan and MRI, have high sensitivity/specificity in looking for liver metastases. Somatostatin receptor scintigraphy (SRS) is recommended in these patients with well-differentiated tumors to search for liver, bone and lymph node metastases.

Laboratory tests are of major interest, especially in patients with type 1 or 2 ECLomas. In these patients, basal serum gastrin levels should be determined and are always elevated [11, 28, 29], as well as serum chromogranin A levels [30]. Further tests should be performed depending on the clinical context. In the majority of the cases (type

1 tumors), no symptoms of ZES are present and upper GI endoscopy does not show any lesion related to peptic disease. The search for autoimmune disease should include anti-parietal cell and anti-intrinsic factor auto-antibodies, present in about 50% of the patients with GAC [5]. Determination of basal and pentagastrin-stimulated acid output by gastric aspiration is rarely necessary to establish the diagnosis and confirms achlorhydria in difficult cases. In patients with ZES, laboratory tests are limited to chromogranin A and serum gastrin levels measurement [22, 23, 31, 32]. In patients with type 3 sporadic tumors, which occur independent of hypergastrinemia, determination of serum chromogranin A level is useful in patients with well-differentiated tumors.

Minimal Consensus Statements on Diagnostic Procedures

Diagnosis is made at gastroscopy and biopsy samples should be taken from the antrum (2 biopsies) and fundus (4 biopsies) in addition to biopsies of the largest polyps. For type 1 and small type 2 tumors, endoscopy and biopsy usually suffice. For type 1 and type 2 tumors EUS should be performed in tumors above 1 cm in size. CT, MRI, SRS are not required with the exception of larger tumors and invasive tumors at EUS. The minimal biochemical tests in patients with type 1 and type 2 tumors includes serum gastrin and chromogranin A levels. These tests should be performed at diagnosis and chromogranin A may be useful at follow-up (although there are no strong data to support the latter).

Pathology and Genetics

Pathological diagnosis is mandatory in all cases and is easily obtained from tumor biopsies performed during gastroscopy (for type 3 GETs), or preferably upon examination of a whole tumor (polyp) removed using endoscopic mucosal resection (EMR) (ECLomas type 1 and 2). In case of multiple polyps, biopsies of fundic non-polypoid mucosa should also be performed in order to establish the diagnosis of associated atrophic gastritis. In this latter condition, polyps may be of various origin and correspond to hyperplastic or inflammatory polyps, adenomas or even early gastric adenocarcinomas, as well as ECLomas. Multiple biopsies of different lesions should thus be performed, especially if macroscopic appearance of one lesion differs from that of the others. Pathological diagnosis of GET is performed using conventional hematoxylin-eosin staining, immunohistochemical staining with chromogranin and synaptophysin [5, 8, 10, 18, 22]. Determination of mitotic index by counting 10 HPF and calculation of Ki-67 index by immunohistochemistry are mandatory [33]. The tumors should be classified according to the WHO knowing that the great majority of GETs fall within group 1 tumors (table 2).

Most ECLomas are preceded (or accompanied) by linear or micronodular hyperplasia or dysplasia of ECL cells [34]. This condition is associated with a 26-fold increase in the risk of developing ECLomas in patients with chronic atrophic gastritis [34]. Type 3 tumors may be well or moderately differentiated. Proliferative index using Ki-67 antibody is frequently elevated [20]. Genetic testing for hereditary tumor syndrome should only be performed in case of suspected or established diagnosis of Zollinger-Ellison syndrome. As outlined above, the presence of ECLomas in a patient with ZES makes the diagnosis of MEN 1 very likely.

Minimal Consensus Statements on Pathology and Genetics

Histology is always necessary to establish a diagnosis. Cytology may be helpful, but should be confirmed by histology. The minimal ancillary tests to support the histological diagnosis include immunohistochemistry for chromogranin A and synaptophysin. Both the mitotic count in 10 HPF (2 mm^2) and the Ki-67 index (the latter performed using immunohistochemistry, although the techniques and counting standards need to be established) are mandatory in all cases. Immunohistochemistry for p53 or SSR2A receptors in type 1 or type 2 tumors is not recommended.

Germline DNA testing is only recommended in the presence of a positive family history of MEN-1 or if multiple tumors are present in the absence of atrophic gastritis in the rare instances when MEN-1 diagnosis has not been done previously. Genetic analysis should also be performed in suspected cases of MEN-1. Genetic testing when performed should include mutational screening and sequencing, allowing for analysis of the entire coding gene and splice sites and genetic counseling should be sought prior to testing in all patients. Informed consent is mandatory prior to genetic testing. Somatic (tumor) DNA testing is not recommended.

Endoscopic/Surgical Therapy

In patients with type 1–2 ECLomas, it is generally accepted that annual surveillance is sufficient for patients with tumors <10 mm. When tumors are larger, endoscopic resection is recommended for up to 6 polyps not involving the muscularis propria (EUS is thus necessary) [19]. In the remaining patients, local surgical tumor resection should be performed. Antral resection to avoid

repeated and chronic gastrin stimulation of ECL cells is effective in 80% of type 1 tumors [21, 35, 36]. In case of malignant development or recurrence despite local surgical resection, partial or total gastrectomy with lymph node dissection should be performed. In patients with type 3 tumors, surgical treatment should not differ from that of gastric adenocarcinomas (partial or total gastrectomy with lymph node dissection).

Minimal Consensus Statements on Endoscopic/ Surgical Treatment

Tumors <10 mm should undergo surveillance. For larger tumors local endoscopic ablation (following EUS) should be performed. Endoscopic mucosal resection (EMR) is recommended for lesions close to and above 1 cm but without invasion of the muscularis propria. In the presence of deep gastric parietal wall invasion and positive margins following EMR, antrectomy and local resection is performed in type 1 ECLomas. Antrectomy is effective in most patients (type I, >80%) and more radical surgery is required if lymph nodes are positive. In type 2, only local excision is recommended. Presence of multiple tumors does not per se influence surgical management.

Medical Therapy

The antiproliferative effect of somatostatin analogues on ECL cells has been shown in both animals and humans [37–41]. Although tumor regression of ECLomas has been reported, the use of somatostatin analogues is not justified in current practice. Intravenous cytotoxic chemotherapy may be used in patients with metastatic tumors (mainly type 3). Cytotoxic protocols depend on tumor differentiation.

Minimal Consensus Statements on Medical Therapy

Biotherapy is not currently recommended in patients with type 1 and 2 tumors except in patients with functioning tumors and in type 2 patients if indicated for the underlying tumor disease (i.e. other endocrine tumors). Exceptions may be made in case of metastatic disease in reference centers. There is usually no place for chemotherapy in patients with type 1 or type 2 tumors (with the exception of metastatic disease which is rare). Peptide receptor radionuclide therapy (PRRT) may be considered as a treatment option (no data currently available to support its use in this setting) on a compassionate basis or as part of academic research studies in patients with distant metastases, provided no other treatment options are available. A positive somatostatin receptor scintigraphy is required prior to use of PRRT (preferably using ^{90}Y- or ^{177}Lu-labeled analogues).

Follow-Up

No clinical study clearly indicates how often patients with type 1–2 ECLomas should undergo endoscopic surveillance, depending on the number and size of polyps and previous EMR. Recommendation is that surveillance should be performed every 2 years (type 1) or yearly (type 2) with EMR of polyps when >10 mm. In patients with chronic atrophic gastritis, the risk of gastric adenocarcinoma developing from intestinal metaplasia would also justify biopsies on flat mucosa. In patients with type 3 tumors, follow-up should depend on tumor subtype. In well-differentiated tumors and after curative resection, imaging (according to the initially positive study and to local experience) and chromogranin A should be performed at 6-month intervals for the first 2 years, and then yearly for 3 more years. In well-differentiated metastatic tumors, follow-up investigations (CT/MRI) should be done every 3 months.

Minimal Consensus Statements on Follow-Up

Gastroscopy should be performed every 2 years in patients with type 1 tumors and yearly in the case of type 2 tumors.

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ENETS Guidelines

Neuro
-endocrinology

Neuroendocrinology 2006;84:165–172
DOI: 10.1159/000098008

Published online: February 20, 2007

Well-Differentiated Duodenal Tumor/ Carcinoma (Excluding Gastrinomas)

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Introduction

Duodenal neuroendocrine tumors (NETs) are located in the duodenum and may or may not be associated with a functional clinical syndrome. The term duodenal NET includes all duodenal tumors with neuroendocrine (NE) features as determined by histological/immunohistochemical methods including positivity for NET cytosolic markers [neuron-specific enolase (NSE), PGP 9.5] or secretory vesicle proteins [chromogranin A (CgA), synaptophysin] and also frequently the presence of specific gastrointestinal (GI) hormones [1–6]. The term duodenal NET in this paper refers to tumors included in different studies classified as: duodenal carcinoid; duodenal gastroenteropancreatic (GEP) tumor; duodenal pancreatic endocrine tumor (PET); duodenal gastrinoma; duodenal somatostatinoma; gangliocytic paraganglioma; ampullary carcinoid or somatostatinoma; argentaffin carcinoid producing serotonin of the duodenum; psammomatous somatostatinoma; duodenal neuroendocrine carcinoma, poorly differentiated and small-cell neuroendocrine carcinoma of the duodenum [4]. The latter will be covered in the paper on poorly differentiated tumors and thus only referred to here. The clinical and management aspect of duodenal gastrinomas are included in the 'Endocrine tumors of the pancreas – gastrinoma' section and duodenal gastrinomas will only be consider in this section in comparison with the other duodenal NETs.

Epidemiology and Clinico-Pathological Features

Minimal Consensus Statement on Epidemiology

Duodenal NETs comprise 1.8% of all carcinoid tumors in the ERG Group (1950–1969); 2–3% of the Third NCS Survey (1969–1971); 1.9% of the early SEER Registry (1973–1991); 3.8 % of the Late SEER Registry (1992–1999), and 2.8% of the PAN-SEER Registry (1973–1999) [3, 7, 8]. Primary duodenal neoplasms occur in 0.03–0.05% of all autopsies [9]. Duodenal NETs comprise 1–3% of all primary duodenal tumors [2].

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Clinicopathological Features – General

In other studies, duodenal NETS were classified generally into five different tumor types [1]. These included duodenal gastrinomas; somatostatinomas; nonfunctional duodenal NETs which were not associated with a clinical syndrome but often demonstrated hormones with immunohistochemistry including serotonin and calcitonin; duodenal gangliocytic paragangliomas, and poorly differentiated neuroendocrine carcinomas [1, 4]. Many studies also differentiated ampulla of Vater or periampullary NETs because numerous studies demonstrated they differed from other duodenal NETs clinically, histologically and in their growth behaviors [10–15]. Ampullary NETs are frequently associated with von Recklinghausen's disease and often show somatostatin immunoreactivity, but almost never produce the clinical features of the somatostatinoma syndrome [4, 6, 10, 13, 16–20].

In older studies reporting on the 5 types of duodenal NETs, duodenal gastrinomas were the most frequent (mean 48.3% of all duodenal NETs, range 27–58%, 9 series) [4, 6, 10, 11, 21–27]; followed by somatostatinomas (mean 43 ± 6%, range 23–75%, 9 series) [4]; nonfunctional serotonin-containing tumors (mean 27.6 ± 7.2%, 6 series) [4]; nonfunctional calcitonin-containing NETs (mean 9 ± 2.5%, 4 series) [4], and finally rare gangliocytic paragangliomas or neuroendocrine carcinomas.

More than 90% of all duodenal NETs arise in the first and second part of the duodenum [4, 21, 22, 24, 26]. This has been well studied for duodenal gastrinomas [5, 6, 10, 21, 22, 24, 25, 27, 28] where 58% arise in D1, 33% arise in D2, 5% in D3 and 4% in D4 [29–33]. Approximately 20% (mean 18 ± 5%, 6 series) of duodenal NETs occur in the periampullary region [4].

Duodenal NETs are generally small with a mean size of 1.2–1.5 cm in seven series [4] and >75% are <2 cm in diameter [4, 5, 10, 11, 24, 25, 28]. Duodenal NETs are usually limited to the submucosal or mucosa; however, they are associated with regional lymph node metastases in 40–60% [1, 4, 30, 34–36]. Liver metastases generally occur in <10% of all patients with duodenal NETs (mean 9 ± 6%, 5 series) [4].

Duodenal NETs are generally single lesions with multiple tumors detected in only 9 ± 3% (5 series) [4, 11, 21, 24–26]. Multiple tumors should lead to a suspicion of multiple endocrine neoplasia type 1 (MEN1). MEN1 occurs in 6 ± 2.5% of all patients with duodenal NETs (mean, 8 series) [4, 6, 10, 21–23, 25–27]. However, MEN1 occurs in 20–30% of all patients with duodenal NETs with Zollinger-Ellison syndrome [34, 37–39].

Duodenal gangliocytic paragangliomas generally occur in the periampullary region [1, 12, 26, 40, 41]. These tumors may be large and invade the muscularis propria, but generally pursue a benign course [4, 11, 15, 42].

A WHO classification has recently been proposed for duodenal/jejunal NETs that will allow a better comparison to NETs in other locations [1]. This classification is summarized in the specific section below with a few other important points covered in the general clinicopathological section above.

Minimal Consensus Statement on Clinicopathological Features – Specific

Classification

1 Well-differentiated neuroendocrine tumor (carcinoid) (50–75%). (Percentage of all duodenal NETs. Modified from Kloppel et al. [1].)
  Benign: nonfunctioning, confined to mucosa-submucosa, nonangioinvasive, ≤1 cm in size.
- Gastrin-producing tumor (upper part of the duodenum)
- Serotonin (5-HT)-producing tumor
- Gangliocytic paraganglioma (any size and extension, periampullary)
  Benign or low-grade malignant (uncertain malignant potential): confined to mucosa-submucosa, with or without angioinvasion, or >1 cm in size
- Functioning gastrin-producing tumor (gastrinoma), sporadic or MEN-associated
- Nonfunctioning somatostatin-producing tumor (ampullary region) with or without
- Neurofibromatosis type 1 nonfunctioning serotonin-producing tumor

2 Well-differentiated neuroendocrine carcinoma (malignant carcinoma) [25–50%]
  Low-grade malignant: invasion of the muscularis propria and beyond or metastases
- Functioning gastrin-producing carcinoma (gastrinoma), sporadic or MEN-associated
- Nonfunctioning somatostatin-producing carcinoma (ampullary region) with or without neurofibromatosis type 1
- Nonfunctioning or functioning carcinoma (with carcinoid syndrome)
- Malignant gangliocytic paraganglioma

3 Poorly differentiated neuroendocrine carcinoma [<1–3%]
- High-grade malignant

Clinicopathological Features

Although >95% of duodenal NETs synthesize GI peptides/amines, 90% are not associated with a functional syndrome. In the 10% that cause a functional syndrome the relative frequency is: ZES (10%) > carcinoid syndrome (4%) > other (<1%). Duodenal NETs occur in greatest frequency in the proximal duodenum and 40–60% have lymph node metastases. 20% of duodenal NETs occur in the periampullary region and these differ from other duodenal NETs in their biological behavior and also with respect to clinical, histological and immunohistochemical features.

Prognosis and Survival

Duodenal NETs characteristically metastasize first to proximal lymph nodes and only infrequently (<10%) to the liver or distant sites. For all patients with well-differentiated duodenal NETs (carcinoid) the 5-year survival rate is 80–85% [28, 43], whereas for patients with well-differentiated duodenal carcinomas or variant duodenal carcinoid it is significantly ($p < 0.01$) less at 72% [28].

For patients with duodenal NETs associated with Zollinger-Ellison syndrome the 5-year survival is >90% [30, 35, 36]. The 5-year survival with different tumor extent with duodenal NETs is thought to be similar to all GI foregut NETs which is 80–95% for local disease, 65–75% with regional involvement only and 20–40% for the 5–10% of patients with liver or distant disease [8, 27, 43]. Invasion of the duodenal NET into the muscularis mucosa, increased primary tumor size, and increased mitotic activity correlate with the occurrence of metastatic disease or aggressive growth [5, 10, 11, 25]. Ampullary NETs are reported to share different growth patterns than do nonampullary duodenal NETs. Two studies report [10, 13] that there was no relationship between these tumors and the development of metastases with primary tumor size.

Clinical Presentation

The mean age of presentation is in the 6th decade (range 15–91 years) and there is a slight male predominance (65 ± 5%, 9 series) [4]. Because 90% of duodenal NETs are not associated with a functional clinical syndrome, either symptoms due to the tumor itself or the discovery of the tumor by chance (usually at upper GI endoscopy) lead to the diagnosis. The most common presenting symptoms are pain (37 ± 8%, range 9–64%, 6 series), jaundice (18 ± 4%, range 7–32%), nausea/vomiting (4 ± 8%), bleeding (21 ± 3%), anemia (21 ± 3%, range 1–28), diarrhea (4%) and duodenal obstruction (1%) [5, 10, 24, 25, 43, 44]. Symptoms due to ZES are present in 10 ± 3% of all patients with duodenal NETS followed by carcinoid syndrome in 4 ± 2%, and rarely due to Cushing's syndrome, acromegaly due to a GRF-secreting tumor, somatostatinoma syndrome, insulinoma, glucagonoma or due to the development of polycythemia rubra vera [4, 16, 18, 19, 44–46]. An increasing percentage of duodenal NETs are being diagnosed in asymptomatic patients during a UGI endoscopy (up to 33%). The most common nonspecific symptom that led to the endoscopy was dyspepsia [10]. Periampullary NETs more frequently present with jaundice (50–60 vs. 7–15%) and also more frequently cause pain, nausea, diarrhea or vomiting [10, 11, 13, 15]. Periampullary NETs are more frequently associated with von Recklinghausen's disease (18%) and the presence of somatostatatin immunoreactivity (25–100%); however, a clinical somatostatinoma syndrome is very rare with these tumors [4, 6, 10, 11, 13, 47].

Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests

Diagnostic Imaging – General

Because duodenal NETs are generally small in size (mean 1.2–1.5 cm) (>75% <2 cm) [4, 5, 10, 11, 21, 22, 24, 25, 27, 28], they are frequently missed (>80%) with conventional imaging studies (CT, MRI, ultrasound, angiography) [15, 29, 30, 33, 48–52]. Studies in duodenal gastrinomas demonstrate that conventional imaging studies detect ≤15% of gastrinomas <1 cm in diameter, 20–50% 1–3 cm in diameter and 95% >3 cm in diameter [48, 50, 53].

Although there are no systematic studies with all duodenal NETs, studies with somatostatin receptor scintigraphy (SRS) in duodenal gastrinomas show it is unlikely to be a more sensitive method to localize small duodenal primaries (<1 cm). SRS misses 50% of tumors <1 cm in diameter [30, 52, 54]. However, SRS will likely prove to be the most sensitive modality for detecting lymph node metastases, which occur in 40–60% of all patients with duodenal NETs [1, 4, 30, 34–36].

To detect the primary duodenal NET, UGI endoscopy with biopsy is the most sensitive modality with endoscopic ultrasound (EUS) used to confirm the diagnosis and locally stage the disease [55–59]. Some duodenal NETs such as gastrinomas may be primarily submucosal in location and these may be missed on both UGI endoscopy and/or EUS resulting in detection rates as low as 30–60% for duodenal gastrinomas causing ZES, which were diagnosed by hormone assays [60–62].

For full staging of duodenal NETs, helical CT is generally used [55, 56], although studies with gastrinomas suggest SRS may be more sensitive [52, 54, 63, 64].

In patients with advanced metastatic disease, bone metastases can develop especially in those with diffuse liver metastases. It is important they be sought because in other NETs their detection has been shown to generally change management [64–71]. Somatostatin receptor scintigraphy, bone scanning and MRI of the spine best detect them.

Minimal Consensus Statement on Diagnostic Procedures – Specific

Endoscopy

UGI endoscopy with biopsy is the most sensitive method to detect and diagnose most duodenal NETs, followed by endoscopic ultrasound to locally stage the disease extent.

Imaging and Nuclear Medicine

Helical CT or MRI of the abdomen and somatostatin receptor scintigraphy should be used to fully assess disease extent and detect possible distant metastases. In patients with advanced disease, including especially patients with liver metastases, bone, somatostatin scanning and an MRI of the spine should be performed to seek bone metastases.

Laboratory Tests

Serum chromogranin A (CgA) should be obtained in all patients with duodenal NETs. CgA is found in 75–100% of duodenal NETs [4, 5, 6, 10, 27, 28] and an elevated serum CgA occurs in 56–100% [10, 49, 72, 73]. Serum gastrin, somatostatin, GRF and cortisol with urinary 5-HIAA or cortisol determinations should be obtained if suggestive symptoms occur or if the duodenal NET contains these hormones on immunohistochemistry. Patients with MEN1 with a duodenal NET should have serum somatostatin, gastrin, CgA, prolactin, glucagon, insulin and parathormone determinations as well as serum glucose and ionized calcium assessments. Patients with von Recklinghausen's disease should have serum somatostatin, CgA, and calcitonin levels assessed.

Pathology and Genetics

Histopathology – General

Duodenal NETs demonstrate light microscopic features typical of GI NETs in having trabecular, acinar, ribbon or cribiform structures which are uniform, have few mitosis, little necrosis and are separated by stroma [1, 5, 23, 24]. On silver staining 75–80% of duodenal NETs are argyrophilic [5, 6, 23, 24], they are usually argentaffin negative (0–12% positive) [5, 6, 23], 75–100% show positivity for chromogranin A [4–6, 10, 27], 80–100% for neuron-specific enolase (NSE) [5, 6, 10, 28] and 91% for Leu-7 [6]. Greater than 85% of duodenal NETs synthesize GI peptides/amines and 40 ± 16% (7 series) synthesize >1 hormone/amine [4, 5]. Their relative frequency is: gastrinomas (48%) > somatostatinomas (43%) > nonfunctioning serotonin containing tumors (27%) > nonfunctioning calcitonin containing tumors (9%) > poorly differentiated carcinomas, gangliocytic paragangliomas [4]. Duodenal NETs uncommonly (<5%) produce insulin, PP, glucagon or ACTH.

Duodenal somatostatinomas tend to occur periampullary and histologically they frequently contain psammoma bodies (49–68%) [4, 6, 10, 25–28]. This is in contrast to other duodenal NETs, which uncommonly contain psammoma bodies (4.8%) [4, 11, 21, 24–28, 74].

Duodenal gangliocytic paragangliomas contain epithelial (with PP and somatostatin cells), ganglia, and spindle cells [4, 26, 75]. They characteristically contain gangliocytic differentiation and S-100 protein immunoreactive Schwann cells [26, 75]. They also show positive staining for NSE in 94–100%, PGP 9.5 in 100%, synaptophysin in 94–100%, S-100 in 90%, PP in 75–92%, serotonin in 48–69%, chromogranin in most series in 10–15% and infrequently (<1%) calcitonin, gastrin or ACTH [4, 40, 75, 76].

Poorly differentiated nonfunctional duodenal carcinomas characteristically invade the muscularis propria, metastasize to lymph nodes and more distant sites and show features of other poorly differentiated tumors as discussed in a separate consensus paper [1, 2, 77].

Minimal Consensus Statement on Histopathology and Genetics – Specific [1]

Histopathology

50–75% of duodenal NETs are well-differentiated, 25–50% well-differentiated carcinomas and <1–3% poorly differentiated carcinomas. All duodenal NETs should have routine histology with hematoxylin-eosin staining, as well as staining for chromogranin A, and synaptophysin. S-100 staining should be performed on suspected gangliocytic paragangliomas and gastrin, somatostatin and serotonin if the clinical setting is suggestive. Duodenal NETs should have a mitotic index determined by mitotic counting and a Ki-67 to assess proliferative rate. Cytology is not routinely recommended.

Genetics

Patients with a duodenal NET with MEN1, a family history suggestive of MEN1 or with multiple duodenal NETs should be considered for germline DNA testing for MEN1 (following genetic counseling).

Surgical Therapy

Curative Surgery – General

Potential curative resection is possible in most patients with duodenal NETs because only 9 ± 6% (5 series) [4] have distant metastases at diagnosis with the remainder having either no metastases or a primary with lymph node metastases (40–60%) [1, 4, 5, 30, 34, 35, 44, 49]. Numerous surgical/endoscopic methods have been reported to be effective at removing duodenal NETs, including endoscopic removal by snare or stripping; laparoscopic removal; transduodenal local excision or aggressive resection by a pancreaticoduodenectomy using either a Whipple resection or a pylorus-sparing pancreaticoduodenectomy [15, 28, 49, 51, 60, 78–88]. The optimal method for removing duodenal NETs remains unclear because their natural history is still largely unknown. In addition, the long-term relative results of resection performed with endoscopy, laparoscopy, transduodenal local resection or by pancreaticoduodenectomy have not yet been determined. Finally, the sensitivity of available tumor imaging modalities in assessing local progression pre- or postresection has not been determined, primarily because of the low frequency of these tumors [15, 44, 49, 60, 89].

Minimal Consensus Statement on Surgical Therapy – Specific

Curative Surgery

All duodenal NETs should be removed unless in the presence of distant metastases or of medical conditions that markedly limit life expectancy or increase surgical risk. Small duodenal NETs (≤1 cm) can be locally resected by endoscopy procedures if there is no evidence of lymph node metastases on tumor localization studies and preferably endoscopic ultrasound examination. However, if the duodenal NET is in the periampullary region, local surgical resection may be required. Large duodenal NETs (i.e. ≥2 cm) or duodenal NETs of any size with lymph node metastases should be treated surgically with local resection (1st part duodenum), distal duodenectomy (4th part duodenum) or pancreaticoduodenectomy (frequently required in the 2nd and 3rd part of the duodenum). Treatment of intermediate size duodenal NETs (i.e. 1–2 cm) is controversial with some recommending endoscopic removal if no lymph node metastases are present on tumor localization studies (helical CT/MRI, endoscopic ultrasound), whereas others recommend surgical treatment of these NETs [15, 28, 44, 49, 60]. With ampullary NETs, a number of studies report no correlation between the NET size and the presence of malignancy [13–15, 42] and thus a pancreaticoduodenectomy is generally recommended for these tumors.

Palliative Surgery

In the uncommon patient with a duodenal NET who has hepatic metastases that are potentially resectable without distant metastases and no medical conditions markedly limiting life expectancy or increasing surgical risk, surgical resection and/or ablative therapy should be considered.

Medical Therapy

Minimal Consensus Statement on Medical Therapy

For the <10% of patients with functional hormonal syndromes due to a duodenal NET, appropriate specific therapy for the hormone excess state should be instituted. Specifically, treatment of the acid hypersecretion with proton pump inhibitors in patients with Zollinger-Ellison syndrome; treatment with somatostatin analogues for carcinoid syndrome, and treatment of ectopic Cushing's syndrome medically or by adrenalectomy. For patients with advanced metastatic disease, alpha interferon can be attempted, however, experience is limited. For patients with progressive advanced metastatic disease or with symptomatic diffuse metastatic disease, the combination of streptozotocin and 5-fluorouracil/doxorubicin is recommended in tumors with a low to moderate proliferative rate. Cisplatin/carboplatin plus etoposide is recommended in such patients with poorly differentiated tumors (see relevant consensus paper). For patients with metastatic/inoperable disease with no other options, peptide receptor radionuclide therapy (PRRT) should be considered if the octreoscan is positive. Although there is extensive experience with this therapy with other GI NETs, especially with lutetium-177- or yttrium-90-labeled somatostatin analogues [90–94], there is minimal experience specifically with duodenal NETs.

Follow-Up

Minimal Consensus Statement at Follow-Up

In patients with a nonfunctional duodenal NET completely removed at endoscopy, follow-up endoscopic examinations, abdominal ultrasound or CT and serum chromogranin A levels are recommended at 6, 24 and 36 months. In patients with postsurgical resection, helical CT, somatostatin receptor scintigraphy and serum chromogranin levels are recommended at 6 and 12 months, then yearly for at least 3 years. If any abnormalities are detected, endoscopic ultrasound should be performed. For patients with unresectable advanced metastatic disease, if no treatment is given because the disease is not progressive or symptomatic, the patient should be re-evaluated at 3- to 6-month intervals by chromogranin A, helical CT and/or ultrasound and somatostatin receptor scintigraphy. For patients with metastatic/inoperable disease receiving antitumor treatment (chemotherapy, interferon-alpha, PRRT) follow-up needs to be dictated by the protocol used and expected toxicities.

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ENETS Guidelines

Neuro
-endocrinology

Neuroendocrinology 2006;84:173–182
DOI: 10.1159/000098009

Published online: February 20, 2007

Gastrinoma (Duodenal and Pancreatic)

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Introduction

Gastrinomas are neuroendocrine tumors (NETs), usually located in the duodenum or pancreas, that secrete gastrin and cause a clinical syndrome known as Zollinger-Ellison syndrome (ZES). ZES is characterized by gastric acid hypersecretion resulting in severe acid-related peptic disease (peptic ulcer disease, PUD; gastro-esophageal reflux disease, GERD) [1–3] and diarrhea. In this section ZES, due to both duodenal and pancreatic gastrinomas, will be covered together because clinically they are similar [2, 3]. Specific points related to gastrinomas associated with the genetic syndrome of multiple endocrine neoplasia type 1 (MEN1) will also be mentioned. Some specific points related to duodenal gastrinomas will also be covered in the duodenal carcinoid section.

Epidemiology and Clinicopathological Features

Minimal Consensus Statement on Epidemiology and Clinicopathological Features

Epidemiology and Site of Origin [3, 4]

The incidence of gastrinomas is 0.5–3/million population/year. They are the most common functional and, malignant pancreatic endocrine tumor (PET) syndrome and comprise up to 30% of these tumors [3, 4]. Duodenal tumors, which were originally thought to be uncommon (i.e. <20%), now make up 50–88% of gastrinomas in sporadic ZES patients and 70–100% of gastrinomas in MEN1/ZES patients. In rare cases, gastrinomas occur in other nonpancreatic, nonduodenal abdominal (stomach, liver, bile duct, ovary) (5–15%) and extra-abdominal (heart, small cell lung cancer) locations [5–8].

Clinicopathological Features [1, 9, 10]

The WHO classification [10] subdivides gastrinomas, similar to other gastroenteropancreatic neuroendocrine tumors (GEP-NETs), into three general categories: (1) well-differentiated endocrine tumors with benign or uncertain behavior at the time of diagnosis (10–30%); (2) well-differentiated endocrine carcinomas with low-grade malignant behavior (50–80%), and (3) poorly dif-

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ferentiated endocrine carcinomas with high-grade malignant behavior (1–3%). The 50–80% of gastrinomas of the pancreas and duodenum that fall into the category of well-differentiated endocrine carcinomas are usually larger than 1 cm and show local invasion and/or proximal lymph node metastases [6, 11]. Liver metastases occur much more frequently with pancreatic gastrinomas (22–35%) than duodenal gastrinomas (0–10%) [6, 12]. Pancreatic gastrinomas are generally large in size (mean 3.8 cm, 6% <1 cm), whereas duodenal gastrinomas are usually small (mean 0.93 cm, 77% <1 cm). While the pancreatic gastrinomas may occur in any portion of the pancreas, duodenal gastrinomas are predominantly found in the first part of the duodenum including the bulb [7]. At surgery 70–85% of gastrinomas are found in the right upper quadrant (duodenal and pancreatic head area), the so-called 'gastrinoma triangle' [4, 5, 13]. MEN1 is an autosomal-dominant syndrome that is present in 20–30% of patients with ZES [14]. In these patients duodenal tumors are usually (70–100%) responsible for the ZES. The duodenal tumors are almost always multiple [15–17] and originate from diffuse gastrin cell proliferations [18].

Histologically, most gastrinomas are well-differentiated and show a trabecular and pseudoglandular pattern. Their proliferative activity (i.e. the Ki-67 index) varies between 2 and 10%, but is mostly close to 2%. Immunohistochemically, all gastrinomas stain for gastrin.

Prognosis and Survival [5, 6, 19–22]

Approximately one fourth of ZES patients have gastrinomas that pursue an aggressive course and aggressive growth occurs in 40% of patients with liver metastases. At diagnosis, 5–10% of duodenal gastrinomas and 20–25% of pancreatic gastrinomas are associated with liver metastases. Liver metastases are the most important prognostic factor, the 10-year survival being 90–100% without liver metastases and 10–20% with. Poor prognostic factors besides liver metastases include: inadequate control of gastric acid hypersecretion; presence of lymph node metastases ($p = 0.03$); female gender ($p < 0.001$); absence of MEN1 ($p < 0.001$); short disease history from onset to diagnosis ($p < 0.001$); markedly increased fasting gastrin levels ($p < 0.001$); presence of a large primary tumor (>3 cm) ($p < 0.001$); a pancreatic primary gastrinoma ($p < 0.001$); development of ectopic Cushing's syndrome or bone metastases ($p < 0.001$); the presence of various flow cytometric features, molecular features (high HER2/neu gene expression ($p = 0.03$), high 1q LOH, increased EGF of IGF1 receptor expression), or histological features including angioinvasion, perineural invasion, >2 mitoses per 20 HPF, Ki-67 index >2 [5, 6, 19–24].

Clinical Presentation [2, 14, 25–28]

At the onset of symptoms, the mean age of patients with sporadic gastrinomas is 48–55 years; 54–56% are males, and the mean delay in diagnosis from the onset of symptoms is 5.2 years. All of the symptoms except those late in the disease course are due to gastric acid hypersecretion. The majority of ZES patients present with a single duodenal ulcer or GERD symptoms and ulcer complications. Multiple ulcers or ulcers in unusual locations are a less frequent presenting feature than in the past. Abdominal pain primarily due to PUD or GERD occurs in 75–98% of the cases, diarrhea in 30–73%, heartburn in 44–56%, bleeding in 44–75%, nausea/vomiting in 12–30% and weight loss in 7–53%. At presentation, >98% of patients have an elevated fasting serum gastrin level, 87–90% have marked gastric acid hypersecretion (basal acid output greater than 15 mEq/h) and 100% have a gastric acid pH ≤2. Patients with MEN1 with ZES (20–30%) present at an earlier age (mean 32–35 years) than patients without MEN1 (i.e. sporadic disease). In 45% of MEN1/ZES patients, the symptoms of ZES precede those of hyperparathyroidism, and they can be the initial symptoms these patients present with. However, almost all MEN1/ZES patients have hyperparathyroidism at the time the ZES is diagnosed, although in many patients it can be asymptomatic and mild and therefore can be easily missed if ionized calcium and serum parathormone levels are not performed. Twenty five percent of all MEN1/ZES patients lack a family history of MEN1, supporting the need to screen all ZES patients for MEN1.

Diagnostic Procedures for ZES and MEN1: Laboratory Tests, Imaging and Nuclear Medicine

[2, 27, 29, 30]

Diagnosis of ZES – General

The diagnosis of ZES generally requires the demonstration of an inappropriate elevation of fasting serum gastrin by demonstrating hypergastrinemia in the presence of hyperchlorhydria or an acidic pH (preferably ≤2). In most cases the first study done nowadays is the fasting serum gastrin (FSG) determination. The FSG alone is not adequate to make the diagnosis of ZES because hypergastrinemia can be caused by hypochlorhydria/achlorhydria (chronic atrophic fundus gastritis, often associated with pernicious anemia) as well as other disorders causing hypergastrinemia with hyperchlorhydria besides ZES (*Helicobacter pylori* infection, gastric outlet obstruction, renal failure, antral G cell syndromes, short bowel syndrome, retained antrum). No level of FSG alone can distinguish ZES from that seen in achlorhydric states.

Recent data show that the widespread use of proton pump inhibitors (PPIs) is making the diagnosis of ZES more difficult and is delaying the diagnosis. This is occurring with PPIs because they are potent inhibitors of acid secretion with a long duration of action (i.e. up to 1 week), which has two effects that can lead to misdiagnosis of ZES. First, this results in hypergastrinemia in patients without ZES frequently with peptic symptom history thus mimicking ZES. This means the PPI needs to be stopped to make the proper diagnosis; however, it can be difficult to stop the drug in some patients, especially those with severe GERD. Second, the potent inhibition of acid secretion results in control of symptoms in most ZES patients with conventional doses used in idiopathic peptic disease, in contrast to H2 blockers where conventional doses were frequently not adequate. The result is that PPIs mask the diagnosis of ZES by controlling the symptoms in most patients and that breakthrough symptoms,

which may lead to a suspicion of ZES and are frequently seen with H2 blockers, are infrequent with PPIs.

Patients with ZES with PUD have *H. pylori* infections in 24–48% in contrast to patients with idiopathic peptic disease who have *H. pylori* in >90%. Therefore, lack of *H. pylori* should lead to a suspicion of ZES in a patient with recurrent peptic ulcer disease [30].

Minimal Consensus Statement on Diagnosis of ZES and MEN1 – Specific ZES [2, 27, 29, 30]

ZES should be suspected if: recurrent, severe or familial PUD is present; PUD without *H. pylori* is present; PUD resistant to treatment or associated with complications (perforation, penetration, bleeding) is present; PUD occurs with endocrinopathies or diarrhea; PUD occurs with prominent gastric folds on barium studies or at endoscopy (present –92% of ZES patients), or with hypercalcemia or hypergastrinemia [25].

Biochemistry/Laboratory Studies for ZES

Initially to make the diagnosis, FSG and gastric pH should be determined (following interruption of PPI for at least 1 week with H2-blocker coverage, if possible). If FSG is <10-fold elevated and gastric pH ≤2, then a secretin test and basal acid output should be performed. Also, if repeated fasting serum gastrin are performed on different days <0.5% of ZES patients will have all normal values. If a BAO is performed, >85% of patients without previous gastric acid-reducing surgery will have a value >15 mEq/h [26].

MEN1 [14, 17, 31]

MEN1 should be suspected if there is a: family or personal history of endocrinopathies or recurrent peptic disease; history of renal colic or nephrolithiases; history of hypercalcemia or pancreatic endocrine tumor syndromes.

Biochemistry/Laboratory Studies for MEN1

All patients with ZES should have serum parathormone levels (preferably an intact molecule assay – IRMA), fasting calcium levels and prolactin levels. Recent studies show that an ionized calcium level is much more sensitive than a total calcium- or albumin corrected-calcium determination.

Genetic Study for MEN1

If the family history is positive for MEN1, suspicious clinical or laboratory data for MEN1 are found or multiple tumors are present raising the possibility of MEN1, then MEN1 genetic testing should be done. If the genetic testing is positive for MEN1, genetic counseling should be performed.

Minimal Consensus Statement on Diagnosis of Other Hormonal Syndromes in ZES Patients [5, 23, 32]

Ectopic Cushing's syndrome develops in 5–15% of patients with advanced metastatic disease and has a very poor prognosis. It should be routinely assessed for in patients with advanced metastatic disease by careful clinical examination, history and routine 24-hour urinary cortisol determinations and serum cortisol assessment.

A secondary hormonal syndrome develops in 1–10% of patients, especially those with metastatic disease or MEN1. These should be assessed for by a careful clinical history and routine hormonal assays are not recommended.

Imaging – General [33, 34]

Tumor localization studies are required in all patients with ZES. All aspects of management of ZES require knowledge of tumor extent. It is important to remember that 60–90% of gastrinomas are malignant and that the natural history of the gastrinoma is now the most important determinant of long-term survival in many studies.

Tumor localization studies are necessary to determine whether surgical resection is indicated; to localize the primary tumor; to determine the extent of the disease and whether metastatic disease to the liver or distant sites is present, and to assess changes in tumor extent with treatments.

Numerous localization studies have been recommended including conventional imaging studies (CT, MRI, ultrasound), selective angiography, functional localization methods (angiography with secretin stimulation for hepatic venous gastrin gradients, portal venous sampling for gastrin gradients), somatostatin receptor scintingraphy (SRS) and endoscopic ultrasound (EUS) as well as various intraoperative localization methods, including intraoperative ultrasound, intraoperative transillumination of the duodenum [35] and routine use of a duodenotomy [21, 33, 34, 36–39]. Prospective studies show for primary gastrinomas that conventional imaging studies localize 10–40%, angiography 20–50% and SRS 60–70%. The use of SRS changes management in 15–45% of patients [33, 34, 40]. SRS's sensitivity is equal to all conventional imaging studies combined [34]. For SRS, as well as all conventional studies, tumor size is an important variable and tumors <1 cm are missed in >50% of cases [41, 42]. Therefore, because most duodenal tumors are <1 cm they are frequently missed. EUS is particularly sensitive for pancreatic lesions; however, its ability to detect small duodenal tumors is controversial [21, 43, 44]. Functional localization studies are not limited by tumor size but are invasive studies [45, 46]. Prospective studies show for metastatic gastrinoma to the liver that CT and ultrasound detect their presence in 30–50% of patients with metastases, MRI and angiography in 60–75% and SRS in 92% [33, 34]. At surgical exploration duodenotomy is essential to detect up to one-half of duodenal tumors and its use increases the cure rate.

Intraoperative transillumination of the duodenum is frequently used to help identify the site for the duodenotomy. Intraoperative ultrasound should be routinely used to assess and identify pancreatic lesions [35, 37, 38].

Minimal Consensus Statement on Imaging – Specific

Tumor localization studies are required in all patients with ZES biochemically established. Most recommend initially a UGI endoscopy with careful inspection of the duodenum followed by a helical CT and SRS. If these studies are negative and surgery is being considered, endoscopic ultrasound should be performed. If results are still negative, selective angiography with secretin stimulation and hepatic venous sampling should be considered. SRS is the best study to initially stage the disease and detect both liver and distant metastases. Intraoperative ultrasound and routine duodenotomy for duodenal lesions preferably preceded by transillumination of the duodenum should be done in all patients at surgery. Bone metastases occur in up to one-third of patients with liver metastases and should be sought in all patients by using SRS and an MRI of the spine [47, 48].

Pathology [1, 9]

Histopathology – General

The diagnosis of a gastrinoma requires the presence of a NET immunohistochemically expressing gastrin and associated with ZES. Gastrin-producing NETs without ZES are not considered gastrinomas. Gastrinomas do not show any histological features that distinguish them from other NETs. The histological features that are predictive of the biological behavior of a gastrinoma are discussed in the section on clinicopathological features and include angioinvasion, mitotic activity and the proliferative index determined by Ki-67 staining. Approximately 50% of gastrinomas, like other NETs, may produce hormonal peptides other than gastrin, but they may or may not be released in sufficient quantities to cause serum elevations or a respective hormonal syndrome. In MEN1/ZES patients with duodenal gastrinomas, multiple pancreatic endocrine tumors are invariably present microscopically and often also macroscopically. In almost 100% of these patients the gastrinoma is in the duodenum, and only exceptionally in the pancreas. In these patients, immunohistochemical studies with multiple hormones should be done on all primaries and metastases to help determine their origin.

Minimal Consensus Statement on Histopathology – Specific

Histological examination on HE-stained sections must be accompanied by immunostaining for chromogranin A, synaptophysin, gastrin and Ki-67. Both a mitotic index using a mitotic count and a Ki-67 index are recommended. In MEN1 patients, all primaries and metastases should also be stained for other hormones (PP, glucagon, insulin, somatostatin) to determine the full spectrum of hormone expression. Cytology is generally not useful except in an intraoperative setting for tumor confirmation.

Medical Therapy (Gastric Acid Hypersecretion)

Medical Treatment – General

Gastric acid hypersecretion can be >10 normal in ZES (mean 45 mEq/h) and it is essential it be controlled acutely and long-term in all patients to prevent peptic complications [2, 26]. Both H2-blockers and PPIs can control acid hypersecretion in all patients who can take oral medications and are cooperative [27, 49, 50]. PPIs are the drugs of choice because of their long duration of action allowing once or twice a day dosing to control symptoms in >98% of patients. H2 blockers, to be effective, are usually required at higher doses than are those drugs used in conventional peptic disease (frequently up to 10 times the usual dose) and 4- to 6-hourly dosing is frequently needed [49–52]. Patients with complicated disease (presence of MEN1 with hypercalcemia, presence of severe GERD symptoms, presence of previous Billroth II resection) need higher doses of all antisecretory drugs and may need more frequent dosing even with PPIs [53–56]. Patients have been treated for up to 15 years with PPIs with no evidence of tachyphylaxis and no dose-related side effects. Vitamin B_{12} deficiency but not iron deficiency has been reported with long-term PPI use in ZES, but it is unclear if it causes clinically important vitamin B_{12} deficiency [57–59]. Both intravenous PPIs (intermittent use) and continuous infusion of high doses of H2 blockers satisfactorily control acid secretion when parenteral drugs are needed. Because of this intermittent use, PPIs are recommended [52, 60]. In MEN1/ZES patients, correction of hyperparathyroidism can reduce the fasting gastrin level and BAO, and increase the sensitivity to acid antisecretory drugs [54, 61]. Postcurative resection in up to 40%, the patients continue to show mild acid hypersecretion and require low doses of antisecretory drugs [62]. Parietal cell vagotomy can reduce the BAO long-term and decrease the dosage of antisecretory drugs needed [63].

Minimal Consensus Statement about Medical Treatment – Specific

Acid hypersecretion needs to be controlled acutely and long-term in all ZES patients to prevent acid-related peptic complications. PPIs are the drugs of choice because of their long duration of action allowing once or twice a day dosing to control symptoms in >98% of patients. The recommended starting dose is equivalent to omeprazole 60 mg q.d. in sporadic ZES and 40–60 mg b.i.d. in MEN1/ZES. Patients with complicated disease (presence of MEN1 with hypercalcemia, presence of severe GERD symptoms, and presence of previous Billroth II resection) need higher doses of PPIs and should be started on 40–60 mg b.i.d. On follow-up visits, PPI drug dosage can be reduced in most patients with sporadic ZES and a 30–50% of MEN1/ZES patients. Patients have been treated for up to 15 years with PPIs with no evidence of tachyphylaxis. With long-term treatment serum vitamin B_{12} levels should be monitored once per year.

Surgical Therapy

Surgical Therapy – General [21, 64]

In contrast to the past, there is now general agreement that patients with sporadic ZES, with resectable disease and without serious contraindications to surgery or with concomitant illnesses limiting life expectancy, should undergo routine surgical exploration for cure by a surgeon experienced in treating these tumors. Surgical resection should be performed at laparotomy and not laparoscopically. The role of surgery, type of surgery, and timing of surgery in patients with MEN1/ZES remains controversial [21, 61, 65, 66]. Total gastrectomy should only be performed in patients who cannot or will not take oral antisecretory drugs (<1–2%). Parietal cell vagotomy at the time of exploratory surgery is generally not performed but it may have a role in selected patients because it reduces the acid secretory rate and drug dosage in patients who are not cured [63, 67]. Whipple resections can result in curing patients with pancreatic head/duodenal gastrinomas in both sporadic and MEN1/ZES patients. However, its use is not generally recommended. It may have a role in the few selected patients with long life expectancy with multiple or large gastrinomas in this region that are not removable by enucleation [21].

After curative resection it is essential to regularly evaluate patients for continuing cure by performing both fasting serum gastrin assessments as well as secretin testing. Repeated conventional imaging studies are not needed if the fasting gastrin and secretin test remain normal. Whether SRSs will detect recurrent tumors before fasting gastrin elevations or a return of a positive secretin test is unknown at present [68].

Minimal Consensus Statement on Surgical Treatment – Specific

Surgery is the only treatment that can cure gastrinomas. Surgery has been shown to decrease the rate of development of liver metastases which is the most important prognostic factor for long-term survival [5, 19, 69] and to increase survival [89]. Long-term curative resection without a pancreaticoduodenectomy (Whipple resection) occurs in 20–45% of patients with sporadic ZES when the surgery is performed by a surgeon skilled in the treatment of this disease, but in 0–1% of patients with MEN1/ZES [16, 21, 65, 70, 71]. Tumors in the pancreatic head area should be enucleated, distal pancreatic resection performed for caudally-located tumors and duodenotomy performed routinely to detect small duodenal gastrinomas. A lymph node dissection should be performed even if no primary tumor is found because lymph node primary tumors are reported, although controversial [21, 72]. Surgery for attempted cures is recommended in patients with sporadic ZES without liver metastases or concurrent illnesses limiting life expectancy. Routine surgical exploration is controversial in patients with MEN1/ZES since these patients usually have multiple duodenal gastrinomas, frequently with lymph node metastases, are rarely cured and have an excellent life-expectancy if only small tumors (<2 cm) or no tumors are present on preoperative imaging studies. Surgery is recommended if imaging studies identify tumors >2 cm in diameter to possibly decrease the subsequent development of metastatic spread to the liver. However, the efficacy of this approach remains unproven [65].

In contrast to insulinomas, laparoscopic resection of gastrinomas is not recommended because frequently the primary is not seen on preoperative imaging studies, the tumors are submucosal in the duodenum and they frequently have lymph node metastases [21]. Whipple resections are not generally recommended. It may have a role in the few selected patients with long life expectancy who have multiple or large gastrinomas in this region that are not removable by enucleation [21].

Integrated Therapy of Advanced Disease

Advanced Disease Treatment – General

It is important to consider treatment for advanced disease because it is becoming the main determinant of long-term survival in ZES patients now that acid hypersecretion can be controlled medically [5, 19]. The presence of any liver metastases decreases life expectancy in ZES patients. Ten-year survival with no liver metastases is 96%, single or limited metastases in both lobes (<5/lobe) is 78–80% and with the presence of diffuse metastases it is 16%. The survival of a patient who develops liver metastases during follow-up when there were no liver metastases at the initial evaluation is decreased to 85% [5, 19]. In 40% of patients with unresectable liver metastases the tumor demonstrated aggressive growth and all of the deaths due to disease progression occurred in these

patients [73]. One fourth of ZES patients have tumors that demonstrate aggressive growth and progress to cause death while in the remaining 75% the tumor growth is indolent and death from tumor is uncommon [6, 19]. Cytoreductive surgery, chemotherapy, hepatic artery embolization or chemo-embolization, biotherapy (somatostatin analogues/interferon), peptide receptor radionuclide therapy and liver transplantation have all been recommended as valuable in ZES patients with advanced disease [74–76].

Minimal Consensus Statement on Advanced Disease Therapy – Specific

Cytoreductive Surgery/Radiofrequency Ablation (RFA)

Cytoreductive surgery should be considered for the 5–15% of patients with liver metastases confined to one lobe or who have liver metastases that could be completely removed or ≥90% removed at surgery [64, 77–79]. At the time of cytoreductive surgery RFA can be used for isolated metastases. RFA can also be used alone if there are <10 lesions seen in the liver.

Hepatic Artery Embolization or Chemoembolization [79, 80]

This treatment should be considered in a patient with unresectable liver metastases if they are symptomatic or the hepatic deposits are increasing in size, the portal vein is patent and distant disease is not present. Selective embolization of peripheral arteries is usually preferred. There are no studies that show this methodology prolongs life in these patients.

Chemotherapy [76]

Streptozotocin and doxorubicin with or without 5-fluorouracil should be considered for patients with rapidly growing diffuse liver metastases that fail embolization or chemoembolization or have distant metastases outside the liver. The response rate varies from 5 to 50% in various series. Whether chemotherapy extends survival is controversial at present.

Biotherapy (Somatostatin Analogues/Interferon) [81–84]

Both interferon-alpha and somatostatin analogues have been used for their anti-tumor effects in patients with metastatic gastrinomas. Anti-growth effects are reported in 30–50% of patients with almost all cases responding by showing stabilization of tumors that had been growing prior to treatment. Both interferon and somatostatin are reported to be more effective in slow-growing tumors with low proliferative rates. Less than 10% of gastrinomas demonstrate a decrease in tumor size with treatment with either somatostatin or interferon-alpha. At present, the use of these biotherapy agents for anti-growth effects is controversial and their routine is not recommended until ongoing randomized trials clarify their role.

Peptide Receptor Radionuclide Therapy [85]

In patients with metastatic, inoperable tumors that are positive with SRS, of which most gastrinomas are, there may be a role for PRRT. Until this is more carefully studied with larger numbers of patients, its exact role at present is unclear.

Liver Transplantation [86]

In patients with disease confined to the liver who are young and otherwise generally healthy, liver transplantation may be considered. Patients with a Whipple resection or aggressive gastrinoma should be excluded.

Follow-Up

Long-Term Follow-Up – General

Patients with advanced metastatic disease, post-curative resection, with MEN1/ZES, and with active acid-related peptic disease problems frequently require a different follow-up schedule than the typical ZES patient with active but limited disease. Patients with metastatic disease require a relatively short follow-up initially (3–6 months) to determine whether progressive disease is present and antitumor treatment is indicated. Patients receiving antitumor treatment need follow-ups at 3- to 6-month intervals to assess the effect of treatment and to evaluate toxicity. Patients with MEN1/ZES after initial treatment of the MEN1 problems (hyperparathyroidism, pituitary disease) should be seen in 6- to 12-month intervals. Patients with postcurative resection can be evaluated yearly unless symptoms of recurrence occur.

Minimal Consensus Statement on Follow-Up – Specific

For patients with advanced metastatic disease follow-up should be at 3- to 6-monthly intervals with tumor imaging (CT, SRS), fasting serum gastrin and acid secretory control (6 months). At least yearly, assessment for ectopic Cushing's with a urinary cortisol and serum cortisol should be considered. For patients with advanced metastatic disease or who are receiving chemotherapy or other antitumor treatments, follow-up may need to be shorter to assess for specific toxicities. For patients with MEN1/ZES, follow-up should be yearly with an assessment of tumor extent with imaging (CT abdomen and chest [rule out thymic carcinoid], SRS), biochemical assessment for MEN1 diseases (ionized calcium, serum PTH, prolactin, glucagon), fasting serum gastrin, acid control, UGI endoscopy to evaluate for gastric carcinoid [14, 87, 88]. For patients with post-curative resection, yearly evaluation with fasting gastrin levels, secretin provocative test and acid secretory control should be done if the patient is still taking PPIs/H2 blockers. SRSs should be performed at 2-year intervals. Typical ZES patients without any of the above-mentioned special problems should be seen yearly with tumor assessment (CT, SRS), fasting gastrin determination, and acid control.

Final Remarks

The management of gastrinomas has many similarities to that of the management of other pancreatic endocrine tumor syndromes; however, it also has some important specific areas that need attention. First, the gastric acid hypersecretion is unique to ZES and requires appropriate management initially and at every phase of follow-up. Although PPIs have greatly simplified management, special circumstances such as the need for parenteral drugs, patients with MEN1, severe GERD or a previous Billroth II resection require special attention. The possible long-term effects of PPI treatment, such as the development of vitamin B_{12} deficiency or possibly increased development of gastric carcinoids, are also requiring special attention. Second, gastrinomas have the highest percentage of any GEP-NET of patients with MEN1 (20–30%). Its identification and management initially and during follow-up are critical because both differ from that of the nonMEN1/ZES patient. Particularly important are possible genetic counseling, assessment for thymic and gastric carcinoid, multiple hormonal syndromes, management of the hyperparathyroidism, and assessment for other tumors these patients are increasingly developing (soft tissues and muscle tumors, CNS tumors such as meningiomas, melanomas). Third, ZES is the most common malignant functional PET and in contrast to the other less common PETs the patients often present with minimal tumor burdens and the primary tumors can be difficult to find. Therefore, careful imaging and an appreciation of the prognosis of the disease with different tumor extents are essential in determining the appropriate treatment at a given stage. Fourth, in contrast to the other symptomatic PETs, the role of surgery in patients with MEN1/ZES is controversial. Fifth, in contrast to other functional PETs with advanced disease the symptoms of the hormone excess state can be controlled in almost every patient with PPIs. Therefore the indication for treatment of the advanced disease is either the symptoms due to the tumor mass per se or tumor progression, not refractory hormonal symptoms.

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ENETS Guidelines

Neuro
-endocrinology

Neuroendocrinology 2006;84:183–188
DOI: 10.1159/000098010

Published online: February 20, 2007

Well-Differentiated Pancreatic Tumor/Carcinoma: Insulinoma

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Epidemiology and Clinicopathological Features

Minimal Consensus Statement on Epidemiology

Insulinomas are the most common functioning endocrine tumors of the pancreas, with an estimated incidence of 1–3 per million per year. There is an age-specific incidence peak in the fifth decade of life and the incidence is slightly higher in women than in men. Approximately 10% are multiple, less than 10% can be malignant, and 5–10% are associated with the MEN-1 syndrome. These latter tumors are usually multiple and can be malignant in up to 25% of cases. After initial recognition of the key symptoms, careful laboratory testing, sophisticated imaging and eventually meticulous surgery follows in most cases. It is evident that a multidisciplinary team approach is required [1, 2].

Histopathology of Insulinomas – General

The WHO classifies functioning endocrine tumors of the pancreas into 3 well-defined categories: [1] well-differentiated endocrine tumors, with benign or uncertain behavior at the time of diagnosis; [2] well-differentiated endocrine carcinomas with low-grade malignant behavior, and [3] poorly differentiated endocrine carcinomas, with high-grade malignant behavior. Most insulinomas are classified as well-differentiated endocrine tumors, according to the WHO criteria (WHO 1), but occasionally they belong to the WHO 2 or 3 group [3].

Minimal Consensus Statements on Histopathology and Genetics – Specific

Histopathology

A detailed description of the macroscopic, microscopic and immunohistochemical findings, in order to support the diagnosis of insulinoma and to allow for its correct classification according to the current WHO classification is indispensable. The necessary

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0028–3835/06/0843–0183$23.50/0

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Table 1. Requirements for the histopathological diagnosis of an insulinoma

Macroscopic evaluation	Microscopic evaluation	Immunohistochemistry
Tumor size (largest diameter)	Mitotic index (expressed as the number of mitoses in 10 HPF)	Chromogranin A expression (yes/no; if yes, % of cells positive) Insulin expression (yes/no; if yes, % of cells positive)
Lymph node metastases (yes/no; if yes, number and location of metastatic lymph nodes)	Angioinvasion (yes/no)	Synaptophysin expression (yes/no; if yes, % of cells positive) Insulin expression (yes/no)
Extra-pancreatic invasion (yes/no)	Perineural invasion (yes/no)	Ki-67 index (expressed in % of cells positive)
Distant metastases (yes/no/unknown)		Insulin expression (yes/no; if yes, % of cells positive)

information is listed in table 1. Evaluation of the mitotic index and Ki67 index is required. Ancillary tests include the immunohistochemical detection of chromogranin A and synaptophysin. The immunohistochemical determination of insulin expression by tumor cells is not absolutely necessary for diagnosis. Some insulinomas do not stain positively for insulin despite the correct diagnosis. This might be caused by the rapid release of insulin from the insulin-producing cells [3]. Cytology is not recommended as a standard diagnostic procedure.

Genetics

Germline DNA testing for hereditary tumor syndromes is only recommended in specific situations: a familial history or clinical findings suggesting MEN-1 or von Hippel-Lindau disease (VHL); the presence of multiple tumors; or the demonstration of precursor lesions in the peritumoral pancreatic tissue. Mutational analysis should be performed to test for menin or VHL mutations (following informed consent).

Diagnostic Procedures: Clinical Assessment with Laboratory Tests, Imaging and Nuclear Medicine

Clinical Assessment with Laboratory Tests – General

Hypoglycemic symptoms can be grouped into those resulting from neuroglycopenia (commonly including headache, diplopia, blurred vision, confusion, dizziness, abnormal behavior, lethargy, amnesia, whereas rarely, hypoglycemia may result in seizures and coma) and those resulting from the autonomic nervous system (including sweating, weakness, hunger, tremor, nausea, feelings of warmth, anxiety, and palpitations) [4, 5]. Because symptoms occasionally are not specific and insulinoma can mimic several pathological conditions, a broad differential diagnosis should be considered but major distinction should be made between patients with insulinoma and noninsulinoma pancreatogenous hypoglycemia (NIPHS) [6]. However, Whipple's triad remains fundamentally sound. This triad consists of:

1 Symptoms of hypoglycemia.
2 Plasma glucose level ≤2.2 mmol/l (≤40 mg/dl).
3 Relief of symptoms with administration of glucose.

Minimal Consensus Statements Clinical Assessment – Specific

The diagnosis of insulinoma can be absolutely established using the following 6 tight criteria [4, 5]:

- Documented blood glucose levels ≤2.2 mmol/l (≤40 mg/dl).
- Concomitant insulin levels ≥6 μU/l (≥36 pmol/l; ≥3 μU/l by ICMA).
- C-peptide levels ≥200 pmol/l.
- Proinsulin levels ≥5 pmol/l.
- β-Hydroxybutyrate levels ≤2.7 mmol/l.
- Absence of sulfonylurea (metabolites) in the plasma and/or urine.

Further controlled testing includes the 72-hour fast, which is the gold standard for establishing the diagnosis of insulinoma [7]. When the patient develops symptoms and the blood glucose levels are ≤2.2 mmol/l (≤40 mg/dl), blood is also drawn for C-peptide, proinsulin and insulin. Failure of appropriate insulin suppression in the presence of hypoglycemia substantiates an autonomously secreting insulinoma [4, 5, 8].

Imaging and Nuclear Medicine – General

The spectrum of endogenous hyperinsulinism not only includes insulinoma, but also NIPHS/nesidioblastosis. Nesidioblastosis affects approximately 4% of adults with hyperinsulinemic hypoglycemia [9]. The role of imaging is first to detect and provide precise anatomical localization and second to stage the tumor prior to surgery. Insulinomas are usually solitary and the majority is intra-pancreatic in location. They are characteristically small with ap-

proximately two thirds being ≤2 cm at presentation, making them notoriously difficult to localize radiologically. What is the ideal imaging modality for insulinoma evaluation? The three most useful modalities are: gadolinium-enhanced dynamic magnetic resonance imaging (MRI); 3-phase computed tomography (CT), and endoscopic ultrasound. Invasive techniques such as selective celiac and mesenteric arteriography, venography and venous sampling are progressively being abandoned, and together with somatostatin receptor imaging and positron emission tomography (PET) with ^{11}C-5-hydroxytryptophan (5-HTP) as tracer (HTP-PET) or ^{11}C-l-DOPA (DOPA-PET) should be considered as complementary techniques for specific indications. A strikingly wide discrepancy with regard to the results for localization between different centers for each of these techniques presumably reflects the specialist expertise and the availability of equipment. Still, no single modality is 100% effective. Any proposed imaging algorithm should take into account cost, sensitivity, availability and local expertise [1].

Minimal Consensus Statements on Imaging and Nuclear Medicine – Specific

Transabdominal Ultrasound

Like in many other abdominal disorders, transabdominal ultrasound yields the widest range of success and failure of all preoperative localization tests. It is noninvasive, free of radiation exposure, readily available, relatively inexpensive, and anatomically precise. Key major drawbacks include its extreme dependence on operator expertise and limitations based on patient habitus, which usually is unfavorable in this setting since most of insulinoma patients are obese.

Computed Tomography (CT)

As the majority of benign insulinomas tend to be small at presentation and, therefore, seldom alter the contour of the pancreas, 3-phase CT should be used to maximize detection. Insulinomas are typically hypervascular and their appearance is that of a hyperattenuating lesion in both the arterial and portal venous phases. Liver metastases also tend to be hypervascular and, therefore, the arterial phase shows the number and size of liver metastases better than the venous phase. Spread to regional nodes is best seen during the arterial phase. The reported sensitivity of CT for the detection of insulinomas is in the range of 30–85%, depending on tumor size [10]. Combined 3-phase CT and endoscopic ultrasound may further increase this sensitivity up to 100% [11].

Magnetic Resonance Imaging (MRI)

MRI techniques have reported high sensitivities, ranging from 85 to 95%, in the detection of insulinomas and for determining the presence of metastatic disease. As compared to CT, MRI is superior in the detection of small lesions. The enhancement pattern of these tumors on MRI is due primarily to their hypervascularity. Insulinomas are low in signal intensity on fat-suppressed T_1-weighted images and moderately high in signal intensity on fat-suppressed T_2-weighted images, although variations do exist. Small metastases, like the primary tumor, exhibit homogenous enhancement [12–16].

Endoscopic Ultrasound

In experienced hands, endoscopic ultrasound (EUS) is currently considered the best preoperative procedure to localize insulinomas with a reported sensitivity of 94%. The high spatial resolution of this technique allows the detection of very small lesions and their precise anatomical localization. The sensitivity of this technique is the highest for lesions located in the head and body of the pancreas as compared to localization in the tail. Combined with 3-phase CT, the sensitivity rises to 100%. Endoscopic ultrasound imaging is also able to identify patients that qualify for laparoscopic, minimal invasive surgery [17, 18].

Angiography

Angiography combined with calcium stimulation and transhepatic portal venous sampling (THPVS) previously was considered the gold standard of insulinoma localization [19]. Angiography combines both anatomic localization of a tumor with functional information provided by THPVS, which can confirm that a visualized angiographic abnormality is an insulinoma. Additionally, in the instance in which the angiogram fails to demonstrate the tumor, THPVS will still be able to localize the tumor to a particular region of the pancreas [19]. Noninvasive imaging techniques have evolved such that angiography and THPVS should today be considered only for problem cases [19].

Intraoperative Ultrasound

Intraoperative ultrasound (IOUS) has been highly useful in localizing these small tumors. Additionally, it demonstrates the relevant operative anatomy, defining the relationship of the tumor to the pancreatic and bile ducts, and adjacent blood vessels. Intraoperative localization techniques, which include both careful palpation of the pancreas and the use of IOUS, remain the most reliable way to localize insulinomas, and to determine the correct surgical procedure (enucleation vs. middle pancreatectomy). Moreover, it is mandatory in patients in whom multiple lesions are suspected [20, 21].

Laparoscopic Intraoperative Ultrasound

Laparoscopic IOUS in experienced hands can identify >85% of insulinomas [22, 23].

^{111}In-Pentetreotide Scintigraphy

^{111}In-pentetreotide scintigraphy is only positive in 46% of benign insulinomas because not all insulinomas express somatostatin receptor subtypes that bind ^{111}In-pentetreotide. In malignant insulinomas, the relative distribution of somatostatin receptor subtypes is different from benign tumors and a higher rate of scan-positivity with this technique can be expected [24–26].

Positron Emission Tomography

The results of ^{18}F-fluorodeoxyglucose (^{18}F-FDG) PET imaging of insulinomas are disappointing, presumably because of their low proliferative potential. Promising results, however, have been obtained using ^{11}C-5-HTP, ^{18}F-DOPA, and ^{67}Ga-DOTA-DPhe^1-Tyr^3-octreotide (^{67}Ga-DOTATOC) [27, 28].

Surgical Therapy

Minimal Consensus Statements on Surgery

During operation, the entire pancreas is explored. In the presence of the MEN-1 genotype, multiple tumors have to be excluded. Tumor enucleation is preferred. When the tumor is located in the neck, body, or tail of the pancreas and is anatomically unsuitable for enucleation, central or distal pancreatectomy are safe and effective alternatives [29]. Blind distal resections in search of an occult insulinoma are not recommended anymore. In specific cases laparoscopic surgery seems feasible [23, 30].

Medical Therapy

Medical Therapy – General

Dietary management is designed to prevent prolonged periods of fasting. Medical management is reserved only for patients who are unable or unwilling to undergo surgical treatment, for preoperative control of blood glucose levels or for unresectable metastatic disease.

Minimal Consensus Statements on Medical Therapy – Specific

Diazoxide (50–300 mg/day, can be increased up to 600 mg/day) suppresses insulin secretion by direct action on the beta cells and by enhancing glycogenolysis [31]. Diazoxide is the most effective drug for controlling hypoglycemia. However, side effects are: edema, weight gain, renal impairment, and hirsutism. Verapamil and diphenylhydantoin have also been reported to be successful in the control of hypoglycemia [32–34]. In refractory cases, glucocorticoids such as prednisolone can be effective as well. Somatostatin analogs like octreotide and lanreotide can be useful in preventing hypoglycemia in those patients with somatostatin receptor subtype 2-positive tumors, but can worsen hypoglycemia in those patients with tumors that do not express this receptor subtype [35, 36]. Interferon-alpha has been shown to be beneficial in selected cases [37].

Minimal Consensus Statements on Malignant Insulinomas Management

Malignant insulinomas account for only about 5–10% of all insulinomas. The primaries are usually single and generally larger than benign insulinomas. The median disease-free survival after curative resection is 5 years, but recurrence occurs in more than 60% at a median interval of 2.5–3 years. Median survival with recurrent tumors is less than 2 years [38]. Palliative resection may prolong median survival. When surgical options to address malignancy have been exhausted, other debulking procedures such as radiofrequency thermoablation, cryotherapy, hepatic artery embolization and chemoembolization, and peptide receptor radionuclide therapy have been utilized, yielding good, but regretfully only temporary, palliation [39, 40]. Systemic chemotherapeutic options include combinations of doxorubicin and streptozocin, which can result in a significant (up to >60%) tumor regression rate, and remission from hypoglycemic symptoms can be extended up to 1.5 years [41].

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ENETS Guidelines

Neuro
-endocrinology

Neuroendocrinology 2006;84:189–195
DOI: 10.1159/000098011

Published online: February 20, 2007

Rare Functioning Pancreatic Endocrine Tumors

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Introduction

Pancreatic endocrine tumors (PETs) represent a heterogeneous group of tumors depending on functional status and histological differentiation. Functioning tumors are defined when clinical symptoms are related to peptide/hormone overproduction. Tumors secreting pancreatic polypeptide, human chronic gonadotrophin subunits, calcitonin, neurotensin or other peptides do not usually produce specific symptoms and should be considered as non-functioning tumors. In addition, it is important to note that several of these rare functioning tumors (RFTs) may have extra-pancreatic localizations such as VIPomas (10%), somatostatinoma (~50%), GRFoma (70%) and adrenocorticotropic-secreting tumors (ACTHoma) (85%) [1].

Epidemiology and Clinicopathological Features

General

The incidence of clinically detected PETs has been reported to be 4–12 per million, which is much lower than that reported from autopsy series (about 1%) [2, 3]. Considering functioning PETs, insulinomas are the most common (17% incidence), followed by gastrinoma (15%). The remainder incorporates RFTs and includes: VIPoma (2%), glucagonoma (1%), carcinoid (1%), somatostatinoma (1%), and the rest are comprised of adrenocorticotropic-secreting tumors (ACTHoma), GRFomas, calcitonin-producing tumors, parathyroid hormone-related peptide tumors, and other exceedingly rare neoplasms [4–14].

Similar to insulinomas and gastrinomas, the majority of RFTs are well-differentiated tumors [15]. Most RFTs present as malignant disease (WHO group 2) and liver metastases are common [8, 10, 14, 16, 17]. The 5-year survival rate is reported to be 60–100% for localized disease,

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40% for regional disease, 29% for distant metastases, and 80% for all stages [2, 3]. In a publication from 1993 [18], the 5-year survival rate for advanced PETs approached 60 months from diagnosis. RFTs can occur at any age with an equal sex distribution [10, 14, 17]. Overall, about 15–30% of patients with PETs have multiple endocrine neoplasia type 1 (MEN-1). In MEN-1 patients, multiple tumors occur either synchronously or metachronously [19]. The incidence of MEN-1 in patients with RFTs is not known but in recent studies appears to be about 2% for VIPomas and glucagonomas [20, 21]; the incidence of MEN1 in somatostatinomas and GRFomas may be higher.

Patients with malignant tumors may present with mixed syndromes, or the tumors may change clinically over time.

Minimal Consensus Statements on Epidemiology and Clinicopathological Features – Specific

RFTs represent less than 10% of all PETs. The majority of patients with RFTs of the pancreas present with metastatic disease and only some with local disease. Most RFTs are diagnosed as WHO group 2. Not enough data in the literature is currently available to give accurate estimates on survival. The average age at diagnosis is estimated to be 50–55 years, with equal gender distribution. Patients with malignant tumors may present with mixed syndromes or tumors may change clinically over time. The most frequent familial condition associated with RFT is MEN-1.

Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests

Diagnostic Procedures – General

The standard imaging procedures for RFTs, like other PETs, include endoscopic ultrasonography (EUS), contrast-enhanced helical CT or MRI of the abdomen (for both primary tumor and detection of metastases) in combination with somatostatin receptor scintigraphy (SRS). Image-fusion data, combining CT and SRS (SPECT), appears promising [22] in helping to accurately locate tumoral residues and plan surgery. EUS is a proven method in detecting most PETs and can be combined with EUS-FNA [23, 24]. SRS is a routine investigation for both primary tumors and metastases [25–27] and should be performed prior to treatment planning, especially surgery [68]. Gallium-labeled somatostatin analogue PET is also a promising detection method and despite the limited experience to date, the technique appears interesting, even in the detection of small tumors [28, 29]. Standard PET with ^{18}F-glucose is not efficient in detecting well-differentiated tumors but may have some value in the detection of aggressive poorly differentiated PETs [30]. Recently, data using positron emission tomography with 5-HTP or ^{18}F-DOPA has also shown promising results and may be an option for the detection of small well-differentiated tumors [30–32].

Biological tests in the presence of RFTs should include both specific markers (VIP, glucagon, somatostatin, GRF, ACTH) and general markers (chromogranin A and pancreatic polypeptide) [14, 16, 17, 33, 34].

Minimal Consensus Statements on Diagnostic Procedures – Specific

Imaging and Nuclear Medicine

The combined use of CT scan (or MRI) and SRS is always recommended. Endosonography is not universally recommended as a first-line procedure in the investigation of RFT of the pancreas; it may be used in circumstances where CT, MRI and SRS are inconclusive, especially preoperatively; however, in patients with RFTs presenting with liver metastases, EUS is rarely necessary. Insufficient data is available to recommend PET methods on a routine basis and availability is limited. If certain circumstances in the suspicion of RFTs and all above recommended imaging are negative [68]. Gallium-labeled somatostatin analogues positron emission tomography may be performed; however, this is not universally available. Other examinations which may be useful are ^{18}F-DOPA-PET or ^{11}C-5-HTP PET (although availability and costs may have to be considered).

Laboratory Tests

The minimal biochemical work-up for RFTs includes specific biochemical analyses related to specific hormonal activity (example serum glucacon in suspicion of glucagonoma) and general markers chromogranin A and pancreatic polypeptide. Serum parathormone and calcium should also be performed as a baseline screening for MEN-1. All biochemical tests should be performed at first visit.

Pathology and Genetics

Histopathology and Genetics – General

Pathological diagnosis is mandatory in all cases and is easily obtained on tumor biopsy performed either in cases of hepatic metastases (e.g. ultrasound-guided biopsy) or of the primary tumor (preferably using EUS-FNA if locally-advanced, or at surgery). Pathological diagnosis of RFTs is performed using conventional HE staining, immunohistochemical staining with chromogranin and synaptophysin [15]. Determination of mitotic index by

counting 10 HPF and calculation of Ki-67 index by immunohistochemistry is mandatory [35]. The tumors should be classified according to WHO system knowing that the vast majority of RFTs fall within group 2 tumors. Genetic testing for hereditary tumor syndromes should be performed in case of suspected familial predisposition to MEN-1 or if the presence of other associated endocrinopathies (e.g. elevated serum calcium or PTH suggesting hyperparathyroidism and prolactinoma, respectively).

Minimal Consensus Statements on Histopathology and Genetics – Specific

Histopathology

Histology is always necessary to establish a diagnosis. Cytology may be helpful, but should be confirmed by histology. The minimal ancillary tests to support the histological diagnosis include immunohistochemistry for chromogranin A, synaptophysin and specific hormones according to the clinical setting. Both the mitotic count in 10 HPF (2 mm^2) and the Ki-67 index (the latter performed using immunohistochemistry, although the techniques and counting standards need to be established) are mandatory in all cases. Immunohistochemistry for p53 and SSR2A receptors is not routinely recommended, with the exception of staining for SSR2A if SRS is not available.

Genetics

Germline DNA testing is only recommended in the presence of a positive family history of MEN-1, if there are suspicious clinical findings or if multiple tumors or precursor lesions are present. Genetic analysis should also be performed in suspected cases of MEN-1. Genetic testing, when performed, should include mutational screening and sequencing allowing the analysis of the entire coding gene and splice sites and genetic counseling should be sought prior to testing in all patients. Informed consent is mandatory prior to genetic testing. Somatic (tumor) DNA testing is not recommended.

Surgical and Cytoablative Therapies

Curative Surgery and Cytoablation – General

Indications for surgery depend on clinical symptoms, tumor size and location, malignancy and metastatic spread. Curative surgery should be sought also in metastatic disease, including 'localized' metastatic disease to the liver [36]. The type of surgery depends on the location of the primary tumor – pancreatico-duodenal resection (Whipple's operation), distal pancreatectomy, tumor enucleation or enucleation in combination with resection. If malignancy is suspected, adequate lymph node clearance is mandatory.

In case of surgery for liver metastases, complete resection (RO) of metastases should always be considered both in functioning and non-functioning tumors. Liver surgery includes metastasis enucleation, segmental resection(s), hemi-hepatectomy or extended hemi-hepatectomy [37]. Intraoperative US should be performed for detection of all liver metastases. Prior to performing liver surgery, metastatic disease should be confined to the liver. Surgery should be undertaken only if 90% of the tumor mass can be successfully removed. Liver surgery can be done concomitantly with surgery of the primary tumor or on a separate occasion. In patients with RFTs, specific measures to avoid hormonal crisis are required during surgery (notably perioperative somatostatin analogue infusion) and specified anesthetic considerations [10]. Palliative surgery (to primary or metastases) may also be performed following multidisciplinary discussions and includes palliative or debulking resections (resection of >90% of tumor burden) to control symptoms related to hormonal hypersecretion [10, 14, 17, 33]. Bilateral adrenalectomy should be performed in selected cases with ACTH secretion resulting in Cushing syndrome [38, 39]. Liver transplantation may be indicated for a small number of patients, without extrahepatic metastases [40], in whom life-threatening hormonal symptoms persist despite maximal medical therapy and where standard surgery is not feasible.

Selective embolization alone or in combination with intra-arterial chemotherapy (chemoembolization – using streptozotocin, doxorubicin, mitomycin C, etc.) is an established procedure effective in controlling symptoms and controlling tumor progression [41]. Symptomatic responses of about 60% are reported with approximately a 40–50% tumor response [42–46]. It has not been established whether chemoembolization is more efficient than embolization alone. In experienced centers, the mortality rate is low, however, significant morbidity may occur (hepatic or renal failure). The postembolization syndrome is frequent with fever (sometimes prolonged), right upper quadrant pain, nausea, elevation of liver enzymes and a decrease in albumin and PT [41]. Adequate analgesia and hydration are recommended during and following treatment and prophylaxis with somatostatin analogues is always indicated when embolizing functioning tumors. Contraindications of TACE are complete portal vein thrombosis, hepatic insufficiency and a previous pancreaticoduodenectomy, which may expose the patient to severe complications of TACE.

Other local ablative methods which may be used alone or in combination with surgery, including radiofrequen-

cy ablation (RFA), cryotherapy and laser therapy [47–53]. Local ablative methods are usually reserved to treat limited disease (<8–10 metastases of <4–5 cm in diameter).

Minimal Consensus Statements on Surgery and Cytoablative Therapies – Specific

Curative surgery is always recommended whenever feasible after careful symptomatic control of the clinical syndrome [10]; the latter may be achieved by medical or locoregional treatments. Curative surgery should include oncological resection with lymphadenectomy. Surgery of liver metastases may be performed during treatment of the primary tumor. The best treatment option for liver metastases in RFTs is liver resection when feasible or chemoembolization. In patients with advanced stages, debulking surgical strategies have a major role. Liver transplantation may be reserved for rare circumstances in patients where extra-hepatic disease is ruled out. Bilateral adrenalectomy should be performed in selected cases with Cushing syndrome. Loco-regional ablative therapies recommended for the treatment of malignant RFTs of the pancreas include transarterial chemoembolization and radiofrequency ablation.

Medical Therapy

Medical Therapy – General

Both somatostatin analogues and interferon have been shown to be effective in the control of symptoms in functioning PETs [54] and this also includes RFTs [8, 10, 14]; in fact about 80–90% of patients with VIPoma and glucagonoma improve very promptly, overcoming diarrhea and skin rash, and 60–80% have a reduction in VIP and glucagon levels. Symptomatic relief is not always related to reduction in circulating hormone levels, indicating that somatostatin analogues have direct effects on the peripheral target organ. Escape from symptomatic control can be seen quite frequently but an increase in the dose of somatostatin analogues can help temporarily. The anti-tumor efficacy of somatostatin analogues appears less pronounced according to recent data, with objective tumor responses of <10% [55–58]; however, disease stabilization of up to 40% has been reported and these agents may be of value in subgroups of patients with slowly-progressive well-differentiated tumors expressing sst2 receptor subtype (i.e., a positive SRS) [56, 58]. In the control of symptoms, somatostatin analogue therapy should be initiated with short-acting substance (octreotide 100 μg subcutaneously ×2–3) for 1–2 days with titration according to clinical response. The patient can then be transferred to slow-release Lanreotide-SR® i.m., Lanreotide autogel® s.c. or Sandostatin–LAR® i.m. (every 4 weeks) [59]. Likewise, interferon may be indicated in metastatic low-proliferating tumors and can be effective in VIPomas not responding to somatostatin analogs [60], but this requires confirmation in a controlled manner [56, 58].

Systemic chemotherapy is indicated in patients with metastatic and progressive RFTs using combinations of streptozotcin and 5-FU and or doxorubicin with objective response rates in the order of 35% [61, 62]. This is considerably lower than the 69% reported by Moertel et al. [63] in 1992. Chemotherapy in the adjuvant setting has not been explored to date. Peptide receptor radionuclide therapy (PRRT) has been made possible due to development of chelators suitable for radiometal labeling allowing for coupling of modified somatostatin analogues with trivalent metal ions (indium, gallium, yttrium, lutetium, etc.), thus allowing for further potential in diagnostic and therapeutic applications. Limited experience is available concerning PRRT in the treatment of RFTs; however, its efficacy in other advanced PETs with positive SRS has been demonstrated [64, 65].

Minimal Consensus Statements on Medical Therapy – Specific

Somatostatin analogues are an effective treatment in the control of symptoms in RFTs, especially in patients with VIPomas and glucagonomas. They may also be indicated as an antiproliferative treatment in selected cases based on positive SRS. Interferon may also be useful in selected patients with RFTs.

Systemic chemotherapy is reserved for patients with metastatic and progressive RFTs using streptozotocin plus 5-FU and or doxorubicin. Chemotherapy is not recommended in an adjuvant setting outside of a prospective evaluation. Peptide receptor radionuclide therapy can be used for RFTs in case of inoperable metastatic disease if the tumors have a high uptake (grade 3–4) on SRS.

Follow-Up

Follow-Up – General

As in other cases of PETs, follow-up in RFTs should include careful appraisal of clinical, biological and morphological parameters at regular intervals. No formal recommendation to date has been proposed. Given the high incidence of metastatic disease in RFTs, most patients are usually followed at intervals of between 3 and 6 months with appropriate biological and imaging tests.

Minimal Consensus Statements on Follow-Up – Specific

Follow-up for patients with RFTs should be at intervals of 3 to 6 month in metastatic disease and yearly in patients without metastatic disease. Following treatment, in patients with no evidence of residual disease, pertinent biochemical assessment (i.e. hormones known to be elevated prior to treatment, both specific and non-specific) should be initially performed and, when negative, further tests are not usually required. For patients with residual disease, specific markers coupled with CT-scan and SRS should be performed.

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ENETS Guidelines

Neuro
-endocrinology

Neuroendocrinology 2006;84:196–211
DOI: 10.1159/000098012

Published online: February 20, 2007

Well-Differentiated Pancreatic Nonfunctioning Tumors/Carcinoma

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Introduction

Nonfunctioning pancreatic neuroendocrine tumors (NET) are defined by their histopathological differentiation. Neuroendocrine cells are characterized by the expression of marker molecules like neuron-specific enolase (NSE), an unspecific cytosolic marker or vesicle proteins like chromogranin A or synaptophysin, indicating large and dense hormone-storing core vesicles and neuropeptides- or small neurotransmitter-storing synaptic vesicles, respectively [1–4]. These proteins define the neuroendocrine origin of the tumor cells. The term 'nonfunctioning' refers to the absence of clinical symptoms of hormonal hypersecretion. However, nonfunctioning tumors may well show immunohistochemical positivity for hormones, neuropeptides or neurotransmitters.

Massimo Falconi and Ursula Plöckinger both contributed equally to the paper. They and the following authors listed in alphabetical order equally contributed to the preparation of the Guidelines.

Classification and Epidemiology

The WHO classifies nonfunctioning pancreatic NETs according to the uniform classification scheme for endocrine tumors, independent of the site of the primary: (1) well-differentiated endocrine tumor, with benign or uncertain behavior at the time of diagnosis; (2) well-differentiated endocrine carcinoma, with low-grade malignant behavior, and (3) poorly differentiated endocrine carcinoma, with high-grade malignant behavior [5] (table 1). Most (60–100%, according to the series) are classified as well-differentiated endocrine carcinomas [6, 7].

Due to new and more sensitive imaging techniques, the number of neuroendocrine pancreatic incidentalomas has increased. The autoptic incidence is 1.6–10% per year [8], while the clinical incidence is 3.5–4/million/year [9]. Pancreatic endocrine tumors represent about 2–10% of all pancreatic tumors [9, 10]. In earlier series the percentage of nonfunctioning tumors out of all pancreatic endocrine tumors was estimated to be 18–66% [11–17]. In contrast, recent, large monocentric [7, 18, 19] or multicentric studies [20] classify 68–80% as nonfunc-

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0028–3835/06/0843–0196$23.50/0

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Table 1. Criteria for assessing the prognosis of endocrine pancreatic tumors

Biological behavior	WHO classification	Metastases	Invasion	Histological differentiation	Tumor size, cm	Angioinvasion	Ki67, %
Benign (low risk)	group 1	–	–	well-differentiated	≤2	–	<2
Benign or low-grade malignant (intermediate risk)	group 1	–	–	well-differentiated	>2	±	usually around 2
Low-grade malignant	group 2	+	+	well-differentiated	usually >3	+	usually >2
High-grade malignant	group 3	+	+	poorly differentiated	any	+	usually >20

tioning pancreatic neuroendocrine tumors. The peak incidence is during the fifth decade [6], with equal distribution among the sexes.

Minimal Consensus Statements on Classification and Epidemiology

Nonfunctioning pancreatic neuroendocrine tumors are defined by the absence of a hormone hypersecretion syndrome. The classification of the tumor as of neuroendocrine origin refers to the immunohistochemical positivity of chromogranin A and/or synaptophysin. Pathological grading is done according to the WHO classification of endocrine tumors; the majority are well-differentiated carcinomas. Pancreatic neuroendocrine tumors are rare.

Clinical Presentation

Due to the lack of symptoms related to hormonal hypersecretion, nonfunctioning pancreatic neuroendocrine tumors are diagnosed late in the course of the disease. The clinical signs and symptoms are due to the tumor mass, with local invasion and/or distant metastases. Abdominal pain is the major presenting symptom (35–78%), followed by weight loss (20–35%), anorexia and nausea (45%). The patient may present with intra-abdominal hemorrhage (4–20%), jaundice (17–50%) or a palpable mass (7–40%) [21–25]. Fifty-nine percent to 80% of the patients present with synchronous liver metastases at diagnosis [10, 25]. Given the mostly large primary (>5 cm), localizing the tumor at the head of the pancreas, followed by the body and tail, is straightforward [26].

Prognosis

Most neuroendocrine pancreatic tumors are well-differentiated (WHO group 2) endocrine carcinomas (table 1) [27]. Overall 5-year survival is 30–63%, with a median survival from diagnosis of 72 months [12, 25, 28, 29]. Actuarial 5- and 10-year survival rates after diagnosis of liver metastases were 46 and 38%, respectively. [10]. However, aggressive treatment may increase 5-year survival to 63 or 82% [25, 30]. Rapid progression of liver metastases (more than 25% volume increase within 6–12 months) and the development of bone metastases confer a poor prognosis [10]. Histopathological staging (table 1), including tumor differentiation, tumor size, proliferation marker and angioinvasion, correlates with survival. All patients with low-risk tumors were alive after 47 months, 10% of those with intermediate-risk tumors had died after 94 months, while 35% of patients with low-grade malignant tumors died after a period of 42 months. Few patients with a high-grade malignant tumor were alive after 4 months [27].

Minimal Consensus Statements on Clinical Presentation and Prognosis

Nonfunctioning pancreatic neuroendocrine tumors present as large tumors, with signs and symptoms related to the tumor burden. At diagnosis, the prevalence of synchronous metastases is 80%. Prognosis depends on the presence or absence of liver/bone metastases and histopathological classification. Overall 5-year survival is 60%.

Hereditary Tumor Syndromes

MEN-1. Multiple endocrine neoplasia type 1 (MEN-1) is a hereditary tumor syndrome with autosomal inheritance and high penetrance. The main manifestations of the disease are primary hyperparathyroidism, pituitary adenomas and pancreatic neuroendocrine tumors. Nonfunctioning pancreatic neuroendocrine tumors occur besides functional tumors. MEN-1-related tumors occur at an earlier age and demonstrate a more benign course than do sporadic tumors. They may be multiple and vary in size from small microadenomas to large tumors. The malignant potential is related to the size of the tumor [31]. Recent data indicate a prevalence of 55% for nonfunctioning pancreatic neuroendocrine tumors in MEN-1 patients [32]. However, only a small number of patients (8%)

with nonfunctioning pancreatic neuroendocrine tumors have MEN-1 syndrome [17].

Von Hippel-Lindau Disease (VHL). VHL is an autosomal-dominant disease with almost complete penetrance, characterized by the development of several types of neoplasia. Nonfunctioning pancreatic neuroendocrine tumors are part of the syndrome in up to 16% of the patients; frequently coexist with pheochromocytomas and may even precede the manifestation of other lesions [33–36].

Tuberous Sclerosis. An association of nonfunctioning pancreatic NETs with tuberous sclerosis has also been suggested [37, 38].

Minimal Consensus Statements on the Manifestation of Nonfunctioning Pancreatic NET in Hereditary Tumor Syndromes

Nonfunctioning pancreatic neuroendocrine tumors are part of the MEN-1 syndrome. They occur at an earlier age than do sporadic pancreatic NETs, may precede other manifestations of the syndrome and determine the prognosis of the patients. Nonfunctioning pancreatic NET are a rare, but recognized part of von Hippel-Lindau disease and may be seen in patients with tuberous sclerosis.

Diagnostic Procedures Imaging

Somatostatin-Receptor Scintigraphy (SRS)

SRS has a sensitivity and specificity for pancreatic neuroendocrine tumors of 90 and 80%, respectively [39, 40]. SRS is the central modality for localization of the primary and definition of the extent of the disease. Whole-body imaging allows for detection of distant metastases and thus influences therapeutic decisions [41]. SRS is indicated as the first staging procedure and whenever the demonstration of extrahepatic metastases is necessary for therapeutic decisions. The following details indicate the recommended standard procedure: a double or triple head gamma-camera and a medium energy, parallel hole collimator, peaks at 172 and 245 keV with a window of 20%. ^{111}In-octreotide 200 MBq for planar, 200–220 MBq for SPECT images. At an acquisition time of 15 min and 4 h post injection (p.i.) anterior and posterior abdominal views, at 24 h p.i. anterior and posterior views of the upper abdomen, head, chest and pelvis, as well as left and right lateral, anterior and posterior oblique views of the upper abdomen. Optional delayed images at 30–48 h p.i. are recommended. Whole body imaging should be performed with a scanning speed of 3 cm/min. SPECT images should be acquired at 24 h p.i. with a 6° step rotation for 360°/40–60 s [42].

Positron emission tomography (PET) and/or PET CT, using Ga-DOTATOC to visualize somatostatin receptors is a promising new tool. However sufficient data are still lacking [43–45]. Additional tracers used so far (^{11}C-labelled L-Dopa, ^{18}F-labelled L-Dopa and ^{11}C-5-hydroxytryptophan) are not useful in nonfunctioning pancreatic NET [46, 47].

Ultrasonography (US)

With US, most, especially small lesions, appear hypoechoic [48–50], while larger lesions are more heterogeneous, due to the different degree of hyalinized stroma, hemorrhage and cystic degeneration [48, 50]. Cystic areas are hypoechoic to anechoic.

Computed Tomography (CT)

Non-contrast-enhanced computed tomographic images (NCE-CT) display iso- or hypodense lesions compared to the adjacent pancreatic parenchyma. In addition, calcification and hemorrhage are accurately depicted on NCE-CT. With contrast enhancement, the hypervascularity of endocrine tumors is apparent and characteristic [48, 51, 52]. In addition areas of cystic degeneration are visualized as regions of reduced vascularity by contrast-enhanced CT. Images should be obtained with multidetector CT (2.5 mm section thickness) at the peak arterial phase of contrast enhancement and reconstructed at 1.25 mm thickness [42, 53, 54].

Magnetic Resonance Tomography (MRT)

MRT displays hypointense or hyperintense lesions compared to the adjacent pancreatic parenchyma on T_1- or T_2-weighted MRT images, respectively. Fat-saturated T_1-weighted images during the injection of gadolinium chelates demonstrate the hypervascularity of endocrine tumors [48, 55, 56]. The hyperintensity is best depicted on fat-suppressed T_2-weighted images. High-resolution, fat-saturated T_2-weighted images, acquired during breath-hold acquisition, and volumetric T_1-weighted images (3 mm slice thickness) at the peak arterial phase of contrast enhancement, using a high-field (1.5 T) MRT, employing high-performing gradients and phased array surface coils, are recommended. Injection rates of contrast material for the evaluation of hypervascular lesions average 3–5 ml/s. MRT with a hepatocyte-specific contrast agent may depict small (<1 cm) liver metastases and thus influence decision-making with respect to surgical therapy.

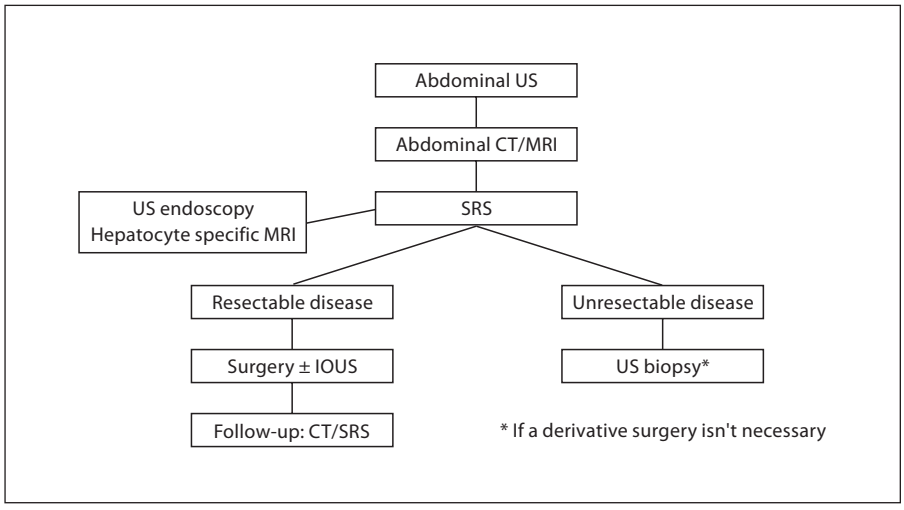

Fig. 1. Suggested algorithm of different diagnostic options for the identification, typing and staging of non-functioning pancreatic NETs. US = Trans-abdominal ultrasound; CT = computed tomography; MRI = magnetic resonance; SRS = somatostatin receptor scintigraphy; IOUS = intraoperative ultrasound.

To differentiate the hypervascular pancreatic neuroendocrine tumor from hypovascular pancreatic adenocarcinoma, contrast-enhanced techniques (multidetector CT or MRT) [53, 54, 57, 58] are useful. In addition, T_2-weighted MR images differentiate the hyperintense neuroendocrine pancreatic tumor from the frequently scirrous, and thus hypointense, adenocarcinoma. Other helpful signs of differentiation are the mean larger volume, the occasionally cystic component and the lack of infiltration of peripancreatic fat and vessels of neuroendocrine tumors in comparison to the more aggressive growing adenocarcinoma [59, 60].

In patients with a high degree of clinical suspicion but negative non-invasive imaging studies (US, CT and/or MRT), further diagnostic investigations may include contrast-enhanced US (sensitivity and specificity 94 and 96%, respectively) [61] or endoscopic ultrasound (EUS) with biopsies (sensitivity 82–86%) [62–64]. The sensitivity of CT and MR imaging is in the range of 75–79%, using comparable technical standards and equipment [65]. For follow-up, the technique which best visualizes the individual tumor should be used. However, with progressive disease and before therapeutic decisions, a thorough staging (SRS, US and CT/MRT) is recommended.

Minimal Consensus Statement on Imaging

US combined with state of the art contrast-enhanced CT/ MR imaging (including MRCP) is recommended. The decision whether to use CT or MRT depends on the preference, skill and expertise of the radiologist and the availability of the different techniques at each institution. Somatostatin receptor scintigraphy is the most sensitive, single screening method for extrahepatic disease manifestation. A possible algorithm is provided in figure 1.

Laboratory Tests

Chromogranin A (CgA) is a general tumor marker for neuroendocrine tumors [66]. Its concentration is supposed to correlate with the tumor mass. This correlation may be lost during SSA therapy [67]. In addition, basal and meal-stimulated pancreatic polypeptide (PP) may be useful for early detection of pancreatic involvement in MEN-1. The issue is controversial, as it has been demonstrated to substantiate the presence of a tumor in 75% of those tested [68], while others found no statistical difference between patients and controls for the meal-stimulated PP concentration [69].

Nonfunctioning pancreatic neuroendocrine tumors may secrete hormones and/or neurotransmitters, with plasma concentrations clearly above the normal range (e.g. so-called 'silent' tumors), but they are insufficient to induce a hypersecretion syndrome. However, the clinical impact of silent tumors compared to non-secreting, nonfunctioning tumors is as yet unknown. Thus, extensive screening for secreted hormones is not justified.

Minimal Consensus Statements on Laboratory Tests for Diagnosis and Follow-Up

CgA is a recommended tumor marker, while the sensitivity and specificity of meal-stimulated PP are controversial. PP may be useful for early detection of pancreatic tumors in MEN-1. Extensive hormonal screening is not justified.

Table 2. Requirements for the histopathological diagnosis of a pancreatic endocrine tumor

Macroscopic evaluation	Microscopic evaluation	Immunohistochemistry
Tumor size (largest diameter)	Mitotic index (expressed as the number of mitoses in 10 HPF)	Chromogranin A expression (yes/no; if yes, % of cells positive)
Lymph node metastases (yes/no; if yes, number and location of metastatic lymph nodes)	Angioinvasion (yes/no)	Synaptophysin expression (yes/no; if yes, % of cells positive)
Extrapancreatic invasion (yes/no)	Perineural invasion (yes/no)	Ki-67 index (expressed in % of cells positive)
Distant metastases (yes/no/unknown)		

HPF = High-power field.

Pathology and Genetics

Histopathology

Most nonfunctioning pancreatic neuroendocrine tumors present as well-differentiated tumors without distinctive histopathological features [5]. The growth pattern is usually of the nesting type. While fine needle aspiration cytology is not recommended as a standard diagnostic procedure, it may be useful in establishing the correct pre- or intraoperative diagnosis in the absence of a tissue specimen. New techniques, like monolayer cytology [70] or 'cellblock' sections, may improve the sensitivity of the procedure. Pre-operative histology is not required but is recommended. Histology is the gold standard in establishing a preoperative and definitive diagnosis. To demonstrate the endocrine nature of the neoplastic cells, immunohistochemical detection of CgA and synaptophysin are necessary and sufficient in most cases. To exclude tumors which may be confused with endocrine lesions, expression of vimentin, nuclear localization of beta-catenin for solid pseudopapillary tumors, and expression of trypsin for acinar cell carcinoma are useful [5]. While hormones/neurotransmitters like pancreatic polypeptide, glucagon, insulin, somatostatin, calcitonin and serotonin [5] may be expressed by silent neuroendocrine tumors, their immunohistochemical determination is not necessary for diagnosis and/or tumor subtyping. In contrast, the evaluation of the mitotic index is mandatory and that of the Ki67 index, at least in the primary tumor, is required.

Genetics

Germline DNA testing for hereditary tumor syndromes is only recommended in specific situations. These include a family history or clinical findings suggesting MEN-1 or von Hippel-Lindau disease (VHL), the presence of multiple tumors or the demonstration of precursor lesions, such as nesidioblastosis-like features or microadenomas, in the peritumoral pancreatic tissue [71, 72]. Mutational analysis should be performed to test for menin or VHL mutations.

Minimal Consensus Statement on Histopathology and Genetics

The pathological report should contain a detailed description of the macroscopic, microscopic and immunohistochemical findings, in order to support the diagnosis of an endocrine tumor and to allow for its correct classification, according to the current WHO criteria (table 2). Germline DNA testing, e.g. mutational analysis, is only justified in clinical situations strongly suggesting MEN-1 or VHL disease.

Surgical Therapy

Indications

According to the WHO classification, the size of the endocrine tumor correlates with malignant growth. Therefore, in localized tumors larger than 2 cm, aggressive surgery and, if required, resection of nearby organs (stomach, colon, kidney, adrenal gland) and/or major vessel resection, is indicated [73, 74]. In contrast, no data exist with respect to a positive effect of surgery on overall survival in small (<2 cm), possibly benign or intermediate-risk pancreatic endocrine tumors. Thus, the possibility of surgical cure has to be weighed against the operative morbidity, mortality and long-term complications asso-

ciated with pancreatic surgery [75–77]. In patients with nonfunctioning pancreatic endocrine tumors as part of the MEN-1 syndrome, especially with small lesions, surgical intervention is still controversial [78–80].

Type of Surgery

The type of surgery depends on the localization, the size and suspected malignancy of the tumor. Small, nonmalignant, easily accessible tumors can be treated by local atypical resection (enucleation or middle pancreatectomy). Middle pancreatectomy is advisable for lesions in the pancreatic body and close to the Wirsung duct. With atypical resection, pancreatic parenchyma can be preserved, avoiding exocrine and endocrine pancreatic insufficiency, while on the other hand the risk of a postoperative pancreatic fistula is high [81–83]. Localization of the tumor in the pancreatic head or suspected malignancy require larger, more typical resections, i.e. pancreaticoduodenectomy or left pancreatectomy [84, 85].

Surgical Strategies for Multiple Nonfunctioning Pancreatic Neuroendocrine Tumors in MEN-1

Multiple nonfunctioning pancreatic NETs are part of MEN-1 and may cause up to 20% of MEN-1-related deaths [86–89]. Histopathological parameters cannot differentiate between benign and malignant disease in the absence of metastases or local invasion, and tumor size has no correlation to prognosis [31, 79, 90]. Careful microdissection of the pancreas demonstrates multiple, small (100 μm to 5 mm) microadenomas [72, 91], indicating clinically unapparent, yet histologically visible disease in MEN-1. While only a minority of the microadenomas acquire the potential to grow unrestrictedly, larger lesions may be genetically unstable; develop secondary mutations and will grow into clinically relevant lesions. While surgical resection of the visible tumors fails to cure the patient, prophylactic surgery aims to remove these lesions before malignancy develops. However, while recent data show that early diagnosis and surgery improve survival [92], others suggest a more conservative approach, as their data indicate, that only tumors larger than 2 cm are associated with an increased risk of malignancy [79]. Therapeutic strategies thus range from follow-up, to enucleation of visible lesions [86] or aggressive interventions with enucleation of tumors in the head of the pancreas combined with distal, subtotal (80%) pancreatic resection as prophylaxis against tumor recurrence [78, 93, 94].

Minimal Consensus Statement on Curative Surgery

Localized, small, malignant tumors should be operated on aggressively, while in small (<2 cm) possibly benign tumors the surgical risk/benefit ratio should be carefully weighted. In MEN-1 patients with multiple tumors prophylactic surgery aims to remove the lesions before malignancy develops.

Surgical Debulking of Locally Advanced Pancreatic NETs

Aggressive surgery, with curative intent for locally advanced nonfunctioning pancreatic NETs may prolong survival (5-year survival up to 80%, 72 and 77%, respectively) [75, 77, 85, 95]. However, all available data are retrospective analyses; most refer to a mixed – functioning and nonfunctioning – tumor cohort, and surgery is only part of a multimodal treatment approach. Thus, the effect of surgery alone is hard to estimate. In addition, surgery is mostly done in patients with less extensive disease and the prolonged survival of patients with debulking procedures may be primarily related to the stage of the tumor. Furthermore, most investigations give univariate survival analysis, which may be potentially misleading. Thus, the data are still inconclusive and only prospective randomized multicenter trials will provide an answer.

No data support debulking procedures in unresectable, locally advanced nonfunctioning pancreatic NETs. With partial resection of the primary, the risk of bleeding is high, tumors recur and survival advantage is not supported by the data [75, 77, 90, 95–97].

Surgery in Metastatic Nonfunctioning Pancreatic NETs

Surgery of the Primary. In metastatic disease, resection of the primary alone fails to improve survival. In selected, low-risk patients with a low volume of liver metastases, but life-threatening or unbearable symptoms, surgery of the primary may prevent tumor related complications (gastrointestinal hemorrhage or biliary/gastric outlet obstruction) and allow for a more effective treatment by limiting the disease to the liver [77].

Surgery for Liver Metastases. In the absence of extrahepatic disease, synchronous resection of the primary and liver metastases should be considered. The 5-year survival of patients treated with hepatic resection in recent series ranges from 47 to 76%, and this compares well with the 30–40% 5-year survival in untreated patients [98–101]. However, the rate of tumor recurrence is high, up to 76% [85, 98, 102–104], and half of these are seen within 2 years after resection [102]. Surgery should only

be undertaken if at least 90% of the tumor mass can be removed successfully. This may be possible in only up to 10% of the patients [98]. A prerequisite to hepatic surgery is sufficient hepatic reserve after resection. In addition, mortality and morbidity of palliative hepatic surgery should be less than 3–5% and 30%, respectively [103, 105, 106]. The type of surgery depends on the location of the metastases. The following procedures can be chosen: enucleation, one or more segmental resections, hemihepatectomy or extended hemi-hepatectomy. Intraoperative US must be performed for detection of all liver metastases. If feasible, the surgical procedure should include cholecystectomy to prevent possible side effects of somatostatin analogue or embolization therapy (gallstones or gallbladder necrosis, respectively).

If radical resection is not achievable, biliary and gastric outlet obstruction should be treated by surgical bypass rather than endoscopic or percutaneous procedures. Long-term survival, even in the presence of liver metastases, makes the surgical approach preferable since the short-term patency of endoscopic stents is poor [58, 107–109].

Minimal Consensus Statement on Palliative Surgery

Debulking of an unresectable primary is not recommended, with the exception of individual patients to avoid tumor-related complications. Surgery of liver metastases may be justified if at least 90% of the tumor mass can be reduced. This may be the case in only 10% of the patients. Surgery should only be performed in experienced centers with mortality, and morbidity less than 5 and 30%, respectively.

Locoregional Ablative Therapy

Loco-regional ablative therapy is defined by a panel of mostly nonsurgical interventions, aiming at palliative reduction of hepatic lesions in patients without manifestation of extrahepatic disease. Locoregional ablative procedures have been used mainly in functioning metastatic NETs to reduce endocrine active tumor volume and thus improve symptoms of hypersecretion. There are insufficient data to define the role of loco-regional ablative strategies in nonfunctioning pancreatic NETs. Most investigations report on mixed tumor groups, the data are analyzed retrospectively and the procedure is part of a multimodal treatment. However, locoregional ablative therapies are widely used in clinical practice in patients who have failed systemic chemotherapy and/or are not candidates for other procedures, due to the extent of liver involvement. The following options are available: selective (chemo-)embolization, radiofrequency ablation, and radio-embolization.

Selective (Chemo-)Embolization (TACE)

Selective embolization of peripheral arteries induces temporary, but complete ischemia. It has been suggested that embolization-induced ischemia sensitizes the tumor tissue to cytotoxic drugs, whose tumor concentration is increased by the slowing down of blood flow. The procedure can be performed repeatedly. Open questions are the type of drug (5-FU, doxorubicin and mitomycin C), dosage, intervals and timing of the procedure. Moreover, it has not been established whether chemo-embolization is more efficient than embolization alone. Results of (chemo-)embolization in 428 patients (14 trials, not all data are given in each trial) indicate a symptomatic response in 50–100%, biochemical response in 22–92%, and tumor volume response in 25–86% of the patients, overall median survival of 20–80 months and 5-year survival of 40–55% [110–123]. Positive prognostic factors are prior removal of the primary, metastatic liver involvement of less than 75%, diameter of the liver metastases < 5 cm and no extrahepatic metastasis [116, 123]. Mortality (0–3.3%) of the procedure is low; however, as morbidity may be significant, chemo-embolization should be performed in experienced centers. As it is not clear whether TACE prolongs survival, its main indication is the treatment of otherwise untreatable functionally active liver metastases [124].

Radiofrequency Ablation (RFA)

RFA is an alternative treatment limited to patients with no more than 8–10 lesions, and a diameter of the lesions below 4 cm. Depending on the tumor location, RFA can be performed laparoscopically or percutaneously [125–130]. Existing data report on all kinds of endocrine tumors. In the largest series so far (34 and 25 patients, 234 and 189 neuroendocrine metastases) symptomatic improvement occurred in 95 and 65%, partial or significant tumor volume reduction was observed in 65 and 68% of the patients, and median survival after RFA was 1.6 and 4.4 years, respectively. During the median follow-up of 1.6 years, 41% of the patients remained stable. Mortality was low and morbidity was 5–12% [131, 132]. In some patients, RFA may be used to convert an unresectable disease into a resectable one [105]. No data exist as to whether RFA has any effect on survival.

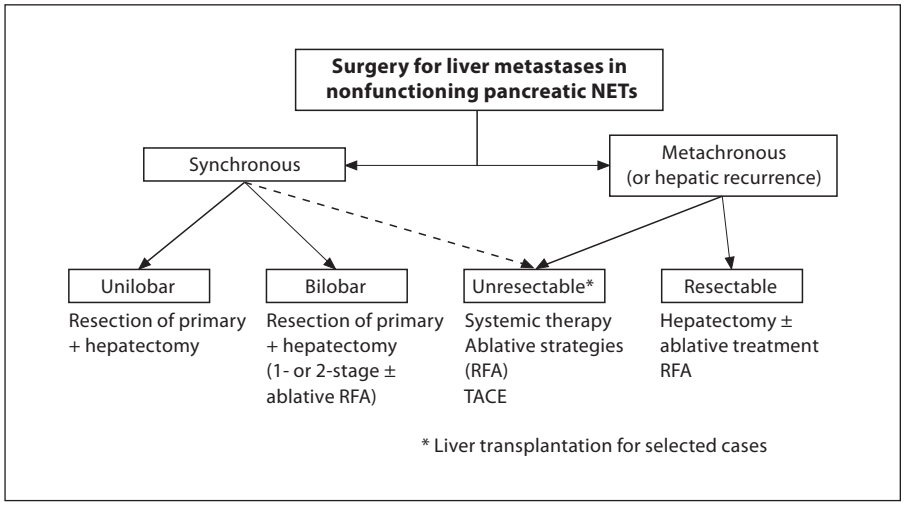

Fig. 2. Suggested algorithm of different treatment options for liver metastases in nonfunctioning pancreatic NETs. Hepatectomy = Oncological resection of the metastases; RFA = radiofrequency ablation; TACE = transarterial hemoembolization.

Radioembolization

Selective internal radiation therapy (SIRT) relies on the selective uptake by the tumor of yttrium-90 microspheres, following arterial hepatic injection. Due to the predominant arterial flow to liver tumors relative to normal liver tissue, the microspheres become trapped in capillary beds of tumorous lesions and deliver ionizing radiation to the tumor. Experience with this technique in NETs is lacking [133, 134]. An algorithm for the treatment of liver metastases is given in figure 2.

Minimal Consensus Statement on Locoregional Ablative Therapy

(Chemo-)embolization and radiofrequency ablation have been used as loco-regional ablative therapy per se or as an adjunct to palliative surgery. Experience is limited, however, palliation seems possible in patients with a tumor burden of less than 75%, small metastases (<5 cm) and no extrahepatic metastases.

Liver Transplantation

In a few, highly selected cases liver transplantation may be an option. However, experience with liver transplantation is limited. Patients considered for transplantation have to be free of extrahepatic metastases, unresponsive to medical therapy, or not otherwise treatable. Patients with aggressive carcinomas should be excluded from liver transplantation. Most transplanted patients have recurrences within months to years, possibly due to postoperative immunosuppressive treatment and/or undiagnosed extrahepatic metastases prior to the procedure. Hence, improved methods for the detection of extrahepatic metastases are necessary before liver transplantation can be used or recommended [135–146].

Minimal Consensus Statement on Liver Transplantation

Liver transplantation may be an option in a patient without extrahepatic metastases, and low proliferation rate when all other therapeutic options have failed.

Medical Therapy

Biotherapy

Numerous studies have evaluated the effect of SSA or interferon on tumor proliferation. General conclusions should be interpreted with caution, as most studies report on a mixed tumor cohort. Demonstration of progressive disease before initializing somatostatin analogue/interferon therapy has been a prerequisite in only a small number of studies. No placebo group was included in any of the studies and most trials were performed in patients pre-treated with other therapeutic modalities. The duration of therapy was rather short in most trials, and standardized schemes for evaluating therapeutic efficacy had not been universally employed. There are only a small number of studies for SSA and none for interferon using a randomized, prospective, multicenter approach including only tumors with demonstrated progress. Most trials

Table 3. Somatostatin analogue therapy in patients with progressive tumor disease

SSA	Dose	Patients*	Tm volume n eligible patients	CR	PR	SD	PD	Median survival (months) after		Ref.
								therapy	diagnosis	
Lanreotide	3,000 μg/day	22	22	0	1	7	14		69	155
Lanreotide	30 mg/2 weeks	35	35	0	1	20	14	29	64	149
Octreotide	600-1,500 μg/day	52	52	0	0	19	33			148
Octreotide	1,500–3,000 μg/day	58	58	0	2	27	29	22	62	169
Octreotide	600 μg/day	21	10	0	0	5	5		63	170
Lanreotide	15,000 μg/day	30	24	1	1	11	11		69	171
		218	201	1 (0.5%)	5 (3%)	89 (44%)	106 (53%)			

SSA = Somatostatin analogs; CR = complete response; PR = partial response; SD = stable disease; PD = progressive disease.
* Patients are from mixed cohorts of neuroendocrine tumors.

used secondary endpoints, such as tumor shrinkage or a decrease of tumor markers for the evaluation of drug efficacy. Endpoint analysis, i.e. time to progression or overall survival, was reported only in a minority of trials.

Somatostatin Analogues (SSA)

In nonfunctioning pancreatic NETs somatostatin analogue (SSA) therapy aims at the stabilization of tumor growth. Partial and complete remission can be observed in fewer than 10% of the patients, while stabilization of tumor growth occurs in 24–57% of patients with documented tumor progress before somatostatin analogue therapy. Distant metastases and progressive disease during the first 6 months of therapy are negative predictors for a persistent stabilization of the disease [147]. SSA therapy should be initiated as first-line medical therapy, whenever tumor progress is documented and surgical or ablative treatment is no option (table 3). However, in low-differentiated tumors with a high Ki67 index (>15%) chemotherapy should be the first-line treatment strategy in patients without surgical or ablative therapeutic options.

The tolerability of somatostatin analogues (nausea, newly developed diarrhea, abdominal pain) should be tested by initiating therapy with a short-acting analogue (e.g. octreotide). Thereafter, depot formulations, usually lanreotide-SR i.e. (every 2 weeks), lanreotide autogel s.c. or octreotide-LAR i.m. (every 4 weeks), are effective. The efficacy of lanreotide and octreotide is comparable [148–150]. Minor, initial side effects, usually subsiding within a few weeks, are abdominal discomfort, bloating and sometimes steatorrhea [148, 149, 151, 152]. In patients with steatorrhea, pancreatic enzyme supplementation may be of help. Major side effects are the development of gallstones (about 50%, rarely symptomatic). In a few cases, persistent steatorrhea resulting in malabsorption may occur [152, 153]. Follow-up of patients on SSA therapy should be performed in 6-month intervals. With documented, progressive disease during SSA therapy, SSA should be withdrawn.

Interferon

Interferon is given for the same indications as somatostatin analogues. However, data on interferon in nonfunctioning pancreatic NETs are rare. Results of 48 patients from 3 trials could be analyzed [28, 29, 154]. Progression has not usually been demonstrated before therapy and interferon was part of a multimodal therapeutic approach. Stabilization of the disease could be achieved in 23%, whereas partial remission of biochemical markers or tumor volume could be demonstrated in 48 and 23% of the patients, respectively. Progressive disease was observed in 23% (table 4). The usual dose is rIFNα2b 3–5 million units 3–5 times per week subcutaneously. Due to a larger range of side-effects, interferon is generally used as a second-line therapy for symptomatic control in functioning carcinoid tumors and is only rarely indicated as an antiproliferative therapy in nonfunctioning pancreatic NETs. Interferon treatment may be particularly recommended for low-proliferating nonfunctioning tumors with a proliferation index less than 2–3%. However, this still must be confirmed in randomized clinical trials. Pegylated interferon, i.e. a long-acting formulation of interferon, is available but still not regis-

Table 4. Therapy with interferon-alpha in patients with nonfunctioning pancreatic neuroendocrine tumors

Interferon	Dosage	Patients	CR	PR (biochem/radiol)	SD	PD	Year	Ref.
hIFN/IFnα2b	3–6 million U/day	9	–	6 (67%)/6 (67%)	??	??	1986	154
hIFN/IFnα2b	5 million U/3/week	14	–	6 (43%)/3 (21%)	3 (21%)	4 (29%)	1990	29
hIFN/IFnα2b	6 million U/day or 5 million U3/week	25		10 (40%)/2 (8%)	6 (24%)	8 (32%)	1993	28
		48		46 % /23 %	23%	31%		

NI = Not indicated; CR = complete response; PR (biochem/radiol) = partial response, reduction of tumor marker by more than 50%/reduction of tumor volume by more than 50%; SD = stable disease; PD = progressive disease.

tered for this indication. Studies comparing pegylated interferon with interferon s.c. are required.

Minor side effects are a flu-like syndrome, easily relieved by paracetamol, anorexia with weight loss and fatigue. Major side effects are hepatotoxicity, autoimmune reactions, depression and mental disturbances. Severe bone marrow depression is rare.

The combination of somatostatin analogues and interferon-alpha does not increase therapeutic efficacy as has been shown in a randomized prospective study by Faiss and co-workers [155, 156].

Minimal Consensus Statement on Biotherapy

Biotherapy, preferentially SSA therapy, can be used as first-line medical therapy in progressive tumors with a slow proliferation index. Stabilization of the disease may occur in about 50% of the patients. Side effects are less with SSA than with interferon. Combination therapy of SSA and interferon does not increase therapeutic efficacy.

Chemotherapy

For more than three decades, a combination of streptozotocin plus 5-FU or doxorubicin has been the gold standard for treatment of different types of endocrine pancreatic tumors. Early data indicated objective tumor responses in up to 60% of the patients [157]. More recent studies using MRI/CT evaluation have reduced the objective tumor responses down to 16–30% [158–161]. In a recent trial using 5-FU, doxorubicin and streptozotocin the response rate was 39%, 2-year progression-free survival 31% and 2-year overall survival was 74% [162]. Similar results were achieved in 50 patients with pancreatic NETs, half of them nonfunctioning, using dacarbazine (response rate 33%, median survival 39.2 months) [163]. Therefore, new randomized trials comparing cytotoxic treatment with new biological agents are necessary to clearly delineate the role of cytotoxic treatment. Preliminary data indicate that temozolamide alone or in combination with octreotide may induce antitumor responses in a small number of patients [164]. In addition, tyrosine kinase inhibitors or anti-angiogenic treatment strategies may prove useful [165]. For the time being, streptozotocin plus 5-FU is indicated for metastatic nonfunctioning tumors, if locoregional approaches are not feasible or are in patients with localized progressive bulky tumors [158]. Patients with tumors presenting a higher proliferation index, i.e. above 20% Ki67-positive cells, usually receive a combination of cisplatinum plus etoposide [159].

Adjuvant Chemotherapy

No studies have clearly indicated the value of cytotoxic treatment in an adjuvant setting. Yet, before prospective randomized trials for adjuvant chemotherapy can be suggested, the most effective cytotoxic therapy has to be delineated in malignant nonfunctioning pancreatic NETs. Thus, at present, adjuvant chemotherapy is not a therapeutic option in patients with pancreatic nonfunctioning NETs.

Minimal Consensus Statement on Chemotherapy

Chemotherapy is indicated as medical therapy in progressive tumors after biotherapy has failed. Streptozotocin and 5-FU or doxorubicin are used in tumors with a low proliferation index (Ki67 <20%), while cisplatin and etoposide are indicated in fast growing tumors. Stabilization of the disease may occur in about 30–50% of the patients. No data exist to support the use of adjuvant therapy in pancreatic nonfunctioning NETs.

Treatment Recommendations in Stable Disease

In patients with stable disease and low tumor burden after previous interventions, no medical therapy should

be initiated. Stable disease may prevail for some time. Unfortunately, there is no single predictive marker for tumor growth. Regular monitoring with CgA determinations and imaging methods will ultimately demonstrate the progression of the tumor disease.

Peptide Receptor Radionuclide Therapy

PRRT with somatostatin analogues coupled with beta-emitting radionuclides (e.g. ^{90}Y or ^{177}Lu) may be rewarding in patients with inoperable nonfunctioning pancreatic endocrine tumors which show sufficient uptake on the diagnostic SRS [166, 167]. After treatment with radiolabeled somatostatin analogues ([^{90}Y-DOTA^0, Tyr^3] octreotide or [^{177}Lu-DOTA^0, Tyr^3] octreotate), tumor shrinkage, i.e. complete or partial remission, was observed in 3 or 17% and 1 or 29%, stable or progressive disease in 61 or 12% and 39 or 18% of the patients (n = 182 and n = 76), respectively. After therapy with [^{177}Lu-DOTA^0, Tyr^3], octreotate median time to progression was over 36 months, which compares favorably with other treatment modalities, especially chemotherapeutic regimens [166]. The results may be influenced by the type of tumor-treated; various administered doses and dosage schemes; the amount of SSA uptake due to different receptor density; the estimated tumor burden, and liver involvement [166]. Side effects are nausea and vomiting at administration of the drug. In addition, abdominal pain and mild reversible hair loss were observed, as were anemia, leukocytopenia and thrombocytopenia. In men, testosterone and inhibin-B decreased, with a reactive increase in LH and FSH. Damage to the kidneys can be prevented by co-administration of amino acids.

Minimal Consensus Statements on PRRT

PRRT is a new therapeutic option in tumors with high somatostatin receptor density. [^{90}Y-DOTA^0, Tyr^3] octreotide or [^{177}Lu-DOTA^0, Tyr^3] octreotate can be used. However, PRRT is still experimental, as randomized comparison to various treatments is lacking.

Follow-Up

Benign or Borderline Nonfunctioning Pancreatic NETs

Follow-up aims to evaluate the results of surgical therapy and/or the indications for additional treatment. Follow-up includes clinical, laboratory (CgA) and radiological examinations [149, 168]. In general, the follow-up intervals should be close during the initial phase, following diagnosis, after therapeutic interventions or with progressive disease. No follow-up is probably necessary after complete resection of a benign nonfunctioning pancreatic NET (WHO 2000), as resection is curative. However, as long-time experience with the WHO classification is lacking follow-up every 12 months (CgA, US) is recommended even in patients with favorable prognostic factors. Patients with pancreatic lesions of uncertain behavior (WHO 2000), who have undergone radical surgery, cannot be considered cured. Therefore, long-term follow-up, every 12 months with US or MRI/CT scans and biochemical markers (CgA) is suggested [149, 168]. SRS should be done 6 months after surgery.

Malignant Nonfunctioning Pancreatic NET

Patients with radically resected malignant tumors should be followed up every 6 months with biochemical markers, US and/or MRI/CT scans to detect recurrences [149, 168]. A stricter follow-up can be advocated for poorly differentiated carcinomas in which radical resection was achieved. In this latter group, early relapse is quite often observed.

Advanced Malignant Nonfunctioning Pancreatic NET

In patients with rapid tumor growth, i.e. a proliferation index >30%, follow-up should be performed every 3 months. Initial follow-up investigations should include clinical, biochemical markers, ultrasound and/or MRT/CT.

All therapeutic schemes should be monitored closely and terminated as soon as there is further progression, indicating ineffective therapy. If no further therapeutic modalities are available, monitoring the disease should be kept at a minimum for the sake of the patient's convenience, as well as for the reduction of health costs.

Minimal Consensus Statements on Follow-Up

Follow-up investigations should be adjusted to the type of tumor (benign or malignant) and the stage of the disease (radically resected or progressive disease). The results of follow-up investigations clarify whether therapy is indicated or effective. Clinical examination, CgA determination and radiological investigations (US, CT/MRT) are recommended.

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ENETS Guidelines

Neuro
-endocrinology

Neuroendocrinology 2006;84:212–215
DOI: 10.1159/000098013

Published online: February 20, 2007

Poorly Differentiated Carcinomas of the Foregut (Gastric, Duodenal and Pancreatic)

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Introduction

Poorly differentiated endocrine carcinomas (PDEC) of the gastrointestinal tract are rare tumors. A PDEC is defined as 'a malignant epithelial tumor composed of highly atypical, small- to intermediate-sized tumor cells growing in the form of large, ill-defined aggregates, often with necrosis and prominent angioinvasion and/or perineural invasion' [1]. In the older literature, these tumors have been variously described as high-grade neuroendocrine carcinomas, small-cell carcinomas, oat cell carcinomas, undifferentiated carcinomas or anaplastic carcinomas. When applying the WHO criteria for PDEC, care should be taken to separate PDEC from mixed exocrine-endocrine tumors and exocrine tumors containing only small numbers of endocrine cells. Separation of PDEC from mixed exocrine-endocrine tumors is not always clear in the older literature. Due to the rarity of gastrointestinal PDEC, comprehensive studies are still lacking on the epidemiology, clinical presentation, genetic alterations, histopathology, natural history and treatment of these tumors. Our knowledge of gastrointestinal PDEC is therefore limited and mainly based on a small series of patients and case reports.

Primary small cell carcinoma of the stomach was first described in 1976 [2]. So far, more than 100 cases of gastric small cell carcinomas have been reported [3]. PDECs of the stomach account for approximately 6% of gastric endocrine tumors [4]. Males are more frequently affected than females (M:F ratio 3:1) and the mean age at diagnosis is 64 years [3, 5]. Most patients have regional or distant metastases at presentation and lack hormone overproduction syndrome. The clinical outcome is poor, with death due to tumor disease within 12 months of the di-

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agnosis in about half of the patients [3, 4]. Primary tumors are evenly distributed in the stomach and present as single lesions with an average size of 4.2–6.3 cm [3, 6]. Histopathological features of gastric PDEC include small- to intermediate-sized tumor cells growing in solid sheets, prominent angioinvasion, deep wall invasion and lymph node/distant metastases [6]. Tumor cells are strongly positive for cytosolic markers of neuroendocrine differentiation (NSE, PGP9.5) but show weak or absent positivity for chromogranin A or hormonal products [4]. Gastric PDECs frequently contain an adenocarcinomatous or squamous component in addition to the endocrine component [3]. Surgical treatment with removal of the entire tumor is seldom possible. Patients can be treated according to the so-called Mayo program (streptozotocin + 5-FU alternated with adriamycin) or with a combination of cisplatin + etoposide [7–9].

PDECs of the duodenum are rare tumors with less than 30 cases reported in the literature [10, 11]. Duodenal PDECs are primarily located in the ampulla of Vater [10] and account for 2–3% of the ampullar tumors [11]. The mean age of patients is 70 years with a male preponderance (M:F ratio 3:1). Most patients present with jaundice and abdominal pain. Regional and/or distant metastases are usually present at diagnosis and a majority of patients die from tumor disease. The primary tumor present as a single lesion with a mean size of 2.5 cm. Half the tumors are associated with adenomas in the adjacent mucosa [11]. The histopathological features of ampullar PDEC include separation into two groups, large-cell neuroendocrine carcinomas and small-cell neuroendocrine carcinomas. A majority of tumors of both types stain positive for synaptophysin and chromogranin A [11]. Surgical treatment that has been employed includes endoscopic resection, local excision and pancreaticoduodenal resection [7]. Effective response has been obtained with adjuvant chemotherapy, e.g. with a combination of 5-FU, TNF and interferon [12].

PDECs of the pancreas are rare tumors with less than 50 cases reported in the literature [13]. PDECs of the pancreas account for 1% of all malignant pancreatic tumors and 2–3% of pancreatic endocrine tumors [14–17]. Elderly patients are primarily affected with a male preponderance (M:F ratio 4:1) [13]. Presenting symptoms include jaundice, weight loss, abdominal pain and hepatomegaly. Symptoms due to hormone overproduction are rare, although cases with Cushing's syndrome [18] and carcinoid syndrome [19] have been reported. Pancreatic PDECs are predominantly located in the pancreatic head, measure 4 cm in diameter and typically invade adjacent organs or metastasized at the time of diagnosis. The outcome is generally poor and most patients die within 2 years of diagnosis. However, curative resection with long survival has been reported in individual patients [13]. Histopathological features of pancreatic PDEC include small- to intermediate-sized tumor cells growing diffusely or in irregular nests, often with extensive necrosis and high mitotic rate. Tumor cells are positive for synaptophysin and PGP9.5 but chromogranin A staining is usually negative or only focally positive [17].

Epidemiology and Clinicopathological Features

Minimal Consensus Statements on Epidemiology and Clinicopathological Features

Epidemiology

Poorly differentiated endocrine carcinomas of the stomach, duodenum and pancreas are rare tumors accounting for less than 2% of gastric carcinomas and less than 3% of duodenal carcinomas. They are probably underestimated since they may resemble undifferentiated carcinomas. A positive staining for synaptophysin may be the only indicator of endocrine differentiation.

Clinicopathologic Staging

Poorly differentiated endocrine carcinomas belong to the WHO group 3 of highly malignant tumors, frequently of small cell type, displaying solid growth pattern, necrosis, high mitotic rate, high Ki67 indices and frequent accumulation of mutated p53. There is no information available on the average clinicopathologic staging of these tumors.

Prognosis and Survival

The prognosis for patients with poorly differentiated endocrine carcinomas is generally poor. Patients with treated metastatic disease have an expected survival time of 6–12 months [4].

Diagnostic Procedures: Imaging, Nuclear Medicine and Laboratory Tests Including Pathology

Minimal Consensus Statements on Diagnostic Procedures

Imaging and Endoscopy

Stomach, Duodenum and Pancreas. CT, MRI, endoscopy with biopsy or EUS, FDG-PET. Comments: imaging procedure should be determined from the clinical situation. A minimal diagnostic procedure should include gastroscopy, CT or MRI [20, 21]. FDG-PET may be useful in the primary diagnosis and for staging. SRS is not recommended but should be evaluated in the clinical setting.

Biochemical Diagnosis

Stomach, Duodenum and Pancreas. Biochemical work-up should be performed at the time of diagnosis. NSE may be useful as a tumor marker [15]. Screening for chromogranin A and hormones is usually negative. Genetic testing is not indicated, except in cases with positive family history.

Histopathology

Stomach, Duodenum and Pancreas. HE, chromogranin A, synaptophysin, NSE, Ki67. Comments: histopathology is required for the diagnosis. Routine histopathology and immunohistochemical staining for general neuroendocrine markers should be performed. Staining for specific hormones is usually negative. Additional neuroendocrine and non-neuroendocrine markers may be useful in the differential diagnosis. Cytology with fine-needle aspiration is not recommended, but may be helpful in some instances.

Surgical and Cytoreductive Therapy

Minimal Consensus Statements on Surgery and Cytoreductive Therapy

Curative Surgery

Stomach. Partial or total gastrectomy with lymph node dissection as recommended for adenocarcinomas.

Duodenum. Pancreatico-duodenal resection (Whipple's procedure) for larger tumors. Duodenal resection for tumors located in the distal duodenum.

Pancreas. Pancreatic resection or pancreatico-duodenal resection (Whipple's procedure).

Comments. Curative surgery should be attempted in localized disease [7, 22]. Debulking surgery and surgery for liver metastases are not recommended.

Cytoreductive Therapy

Stomach, Duodenum, Pancreas. Cytoreductive therapy is generally not recommended, but TACE may be indicated in selected patients.

Medical Therapy

Minimal Consensus Statements on Medical Therapy

Stomach, Duodenum, Pancreas. Systemic chemotherapy with cisplatin and etoposide

Comment. Systemic chemotherapy is indicated in inoperable disease, provided the patient has adequate organ function and performance status. Combined treatment with cisplatin/carboplatin and etoposide has been reported to induce remission in 55–80% of patients with response duration of 8–11 months [9, 23–25]. Chemotherapy may be considered in selected cases as adjuvant treatment; however, there are no data available to corroborate this opinion and studies are thus required. Somatostatin analogue treatment or interferon therapy is not recommended.

Follow-Up

Minimal Consensus Statements on Follow-Up during and after Treatment

Stomach, Duodenum, Pancreas. All patients should be closely followed every 2–3 months with US, CT and MRT or other radiological methods depending on the affected organ. PRRT may be considered if SRS is strongly positive. Biochemical markers positive at diagnosis should be followed.

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