

NANETS Treatment Guidelines

Well-Differentiated Neuroendocrine Tumors of the Stomach and Pancreas

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Abstract: Well-differentiated neuroendocrine tumors (NETs) of the stomach and pancreas represent 2 major subtypes of gastrointestinal NETs. Historically, there has been little consensus on the classification and management of patients with these tumor subtypes. We provide an overview of well-differentiated NETs of the stomach and pancreas and describe consensus guidelines for the treatment of patients with these malignancies.

Key Words: islet cell, gastric, carcinoid, guidelines, review

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WELL-DIFFERENTIATED NEUROENDOCRINE (CARCINOID) TUMORS OF THE STOMACH

Neuroendocrine tumors (NETs) of the stomach comprise less than 1% of gastric neoplasms.^{1–3} In the pre-endoscopy era, they comprised 1.9% of all carcinoids, but in more recent studies, 10% to 30% of all carcinoids are reported in the stomach.³ They can be subclassified into 3 distinct groups: those associated with chronic atrophic gastritis/pernicious anemia (type 1; 70%–80%), those associated with Zollinger-Ellison syndrome (ZES) with multiple endocrine neoplasia type I (MEN I) (type 2; 5%), and sporadic NETs of the stomach (type 3; 15%–20%).^{2,4}

Etiology

Both types 1 and 2 NETs of the stomach are associated with hypergastrinemia (Table 1). High levels of gastrin are thought to result in hyperplasia of the enterochromaffin-like cells in the stomach, ultimately leading to hyperplastic lesions and small, often multiple carcinoid tumors.^{2,4} In contrast to types 1 and 2 carcinoids, type 3 carcinoids develop in the absence of hypergastrinemia and tend to pursue an aggressive clinical course.^{2,4}

Type 1 carcinoids are generally small and frequently multiple; limited to the mucosa-submucosa, and metastases occur in less than 2.5% to lymph nodes and less than 2.5% to the liver.^{2,4} Type 2 carcinoids are almost always multiple and generally small (<1 cm) and are usually limited to the mucosa-submucosa, but are slightly more aggressive than type 1 carcinoids, with up to 30% showing lymph node metastases, and up to 10% may show liver metastases.^{4,5} Type 3 carcinoids are usually single, generally larger (>1 cm in 70%), and invasive through the submucosa and deeper in most cases (>75%); 70% had accompanying lymph node metastases, and 69% had distant metastases.⁴

Pathological Classification

Neuroendocrine tumors of the stomach can be classified histologically in the same fashion as carcinoid tumors arising at other sites. A variety of proposals regarding the classification and nomenclature of NETs have appeared, and many of these differ somewhat regarding specific terminology and criteria for grading and staging. Most proposed systems have indeed proven useful to stratify prognostic subgroups of NETs. Features such as the proliferative rate of the tumor and the extent of local spread (assessed based on similar parameters used for nonneuroendocrine carcinomas of the same anatomical sites) are shared by most systems. Recently, a multidisciplinary consensus group of experts in the field of NETs has recommended such an approach and has developed a “minimum pathology data set” (Table 2) of features to be included in pathology reports.⁶ The College of American Pathologists has also developed similar “tumor checklists” for NETs that specify many of the same parameters.^{7–10}

In general, NETs of the stomach and other NETs are divided into well-differentiated and poorly differentiated categories. The concept of differentiation is linked to the grade of the tumors (see below), but there are subtle differences between differentiation and grade. Differentiation refers to the extent to which the neoplastic cells resemble their nonneoplastic counterparts. In NETs, well-differentiated examples have characteristic “organoid” arrangements of the tumor cells, with nesting, trabecular, or gyriform patterns. The cells are relatively uniform and produce abundant neurosecretory granules, reflected in the strong and diffuse immunoreactivity of neuroendocrine markers such as chromogranin A (CGA) and synaptophysin. Poorly differentiated NETs less closely resemble nonneoplastic neuroendocrine cells and have a more sheet-like or diffuse architecture, irregular nuclei, and less cytoplasmic granularity. Immunoreactivity of neuroendocrine markers is usually more limited. Grade, on the other hand, refers to the inherent biologic aggressiveness of the tumor. Low-grade NETs are relatively indolent, high-grade tumors are extremely aggressive, and intermediate-grade examples have a less predictable, moderately aggressive course. In general, well-differentiated NETs are either low or intermediate grade, and poorly differentiated NETs are considered high grade in all cases

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TABLE 1. Subtypes of NETs of the Stomach

	Hypergastrinemia	Gastric Acid Secretion	Typical Size, cm	No. Tumors	Clinical Features
Type 1 (in setting of chronic atrophic gastritis type A)	Yes (as a result of achlorhydria)	Low	<1	Multifocal	Rarely invasive; endoscopic removal often adequate
Type 2 (in setting of ZES)	Yes (as a result of ectopic gastrin secretion)	High	<1	Multifocal	Rarely invasive; may respond to somatostatin analogs
Type 3 (sporadic)	No	Normal	>1	Solitary	Frequently invasive and metastatic

(Table 3). The concept that some well-differentiated tumors could nonetheless be biologically high grade has been proposed but is controversial.¹¹

Well-differentiated (low and intermediate grade) tumors have been variably termed *carcinoid tumor* (typical and atypical, respectively), *neuroendocrine tumor* (grade 1 and grade 2, respectively), or *neuroendocrine carcinoma* (low grade and intermediate grade, respectively), among other options. Table 4 displays a comparison of the various systems of nomenclature currently in use for NETs, along with for which organ systems each system is most commonly used. Although the criteria that define each category do not perfectly match between the various systems, there are several common themes. Each system recognizes 3 grades. In each, the low and intermediate grades are closely related, well differentiated, and distinguished largely by proliferative rate (or necrosis). Finally, each system generally recognizes that individual tumors rarely display hybrid well-differentiated and poorly differentiated features.

Most systems of grading rely extensively on the proliferative rate to separate low-, intermediate-, and high-grade NETs. Some systems (such as the World Health Organization [WHO] classification for lung and thymus) include the presence of necrosis as a feature to distinguish intermediate grade from low grade within the well-differentiated group. The proliferative rate can be assessed as the number of mitoses per unit area of tumor (usually expressed as mitoses per 10 high-power microscopic fields, or per 2 mm²), or as the percentage of neoplastic cells immunolabeling for the proliferation marker Ki67. The WHO classification of lung and thymus tumors relies only on the mitotic rate, whereas the system recently proposed for gastroenteropancreatic NETs (GEP NETs) by the European Neuroendocrine Tumor Society (ENETS) and also now recommended by the WHO uses either mitotic rate or Ki67 labeling index. A comparison of the most widely used grading systems is shown in Table 4. The cut-points to distinguish the 3 grades vary somewhat among the different systems, and some studies suggest that the optimal cut-points may differ between organ systems.^{12,13} For these reasons, it is recommended to specify the actual proliferative rate in the pathology report, in addition to designating a grade based on a system that is specifically referenced.

The use of mitotic counts versus Ki67 index is controversial. In Europe, where the ENETS system is already in widespread use, Ki67 labeling indices are commonly reported for all NETs. When the amount of tumor tissue is limited (eg, in a biopsy from a primary tumor or a metastatic focus), it may not be possible to perform an accurate mitotic count, because it is recommended to count 40 to 50 high-power fields—more than most biopsy samples include. In these cases, Ki67 staining provides a more accurate assessment of proliferative rate, and it is particularly helpful to separate well-differentiated (low or intermediate grade) tumors from poorly differentiated (high grade) neuroendocrine carcinomas, which usually have dramatically

different Ki67 labeling rates.^{14,15} However, when adequate tissue is present to perform an accurate mitotic count, there are no data to demonstrate that the Ki67 labeling index adds important additional information, and in some cases, the 2 measures of proliferative rate may provide conflicting information about grading.

As recently as a few years ago, no formal TNM-based staging systems existed for NETs. Data submitted to the Surveillance, Epidemiology, and End Results program of the National Cancer Institute separated tumors into localized, regional, and distant stages based on the presence of lymph node or distant metastases, but substratification of the extent of the primary tumor was not performed.¹⁶ Recently, TNM staging systems have been proposed (Table 5). The American Joint Committee on Cancer (AJCC) has recently published a new TNM staging manual that includes NETs of all anatomical sites,¹⁷ and the ENETS has previously published recommendations for TNM staging of GEP NETs^{18,19} There are some differences between these systems, particularly for primary tumors of the pancreas and appendix, but there is also considerable overlap. Additionally, the staging criteria for both systems rely predominantly on the size of the tumor and the extent of invasion into similar landmarks as used for the staging of nonneuroendocrine carcinomas of the same sites. It is recommended that the extent of involvement of these structures be specifically indicated in the pathology reports, in addition to providing a TNM stage based on a system that is specifically referenced.

Until very recently, the WHO classifications for NETs of the tubular gastrointestinal tract (2000) and pancreas (2004) used a hybrid classification system that incorporated both staging information (size and extent of tumor—limited to the primary site or metastatic) and grading information (proliferative rate) into a single prognostic prediction system, with a different name being applied to the tumors in each prognostic group.^{20–23} Although this system did allow prognostic stratification of NETs, it did not allow for grading information to be applied to advanced stages of disease, preventing prognostication once metastases occurred and therefore limiting information for therapeutic decision making.²⁴ Furthermore, the implications of this classification were that the name for a NET limited to the primary site was different than that to be used for the same tumor once metastases occurred in the future, a relatively common occurrence for some NETs. Because of these limitations, the most recent WHO classification that applies to all GEP NETs has abandoned the hybrid classification system in favor of separately grading and staging the tumors (Tables 3 and 4). This will bring the WHO system more closely in line with other widely used systems.

A variety of other pathological findings may be of use in the prognostication and management of patients with NETs (Table 1). Immunolabeling for general neuroendocrine markers (CGA and synaptophysin) may not be needed in histologically

TABLE 2. Minimum Pathology Data Set: Information to Be Included in Pathology Reports of Gastric NETs**For resection of primary tumors**

- Anatomical site of tumor
- Diagnosis (functional status need not be included in pathology report)
- Size (3 dimensions)
- Presence of unusual histological features (oncocyctic, clear cell, gland forming, etc)
- Presence of multicentric disease
- (Optional: immunohistochemical staining for general neuroendocrine markers)
 - Chromogranin
 - Synaptophysin
- Peptide hormones, if a specific clinical situation suggests that the correlation with a functional syndrome may be helpful
- Grade (specify grading system employed)
 - Mitotic rate (no. mitoses per 10 high-power field or 2 mm²; count 50 high-power fields in the most mitotically active regions, count multiple regions)
 - (Optional: Ki67 labeling index [count multiple regions with highest labeling density, report average percentage; “eyeballed” estimate is adequate])
- Presence of nonischemic tumor necrosis
- Presence of other pathological components (eg, nonneuroendocrine components)
- Extent of invasion (use anatomical landmarks for the AJCC T-staging of analogous carcinomas of the same anatomical sites)
 - Stomach: depth of invasion into/through gastric wall
 - Small bowel: depth of invasion into/through bowel wall
 - Large bowel: depth of invasion into/through bowel wall
 - Appendix: depth of invasion into/through appendiceal wall; presence and extent of mesoappendiceal invasion
 - Pancreas: presence of extrapancreatic invasion or invasion of bile duct, duodenum, or ampulla
 - All sites: involvement of serosal/peritoneal surfaces; invasion of adjacent organs or structures
- Presence of vascular invasion (optional: perform immunohistochemical stains for endothelial markers if needed)
- Presence of perineural invasion
- Lymph node metastases
 - No. positive nodes
 - Total no. nodes examined
- TNM staging (specify staging system used)
- Resection margins (positive/negative/close) (optional: measure distance from margin if within 0.5 cm)
- Proliferative changes or other abnormalities in nonneoplastic neuroendocrine cells

For biopsy of primary tumors

- Anatomical site of tumor
- Diagnosis (functional status need not be included in pathology report)
- Presence of unusual histological features (oncocyctic, clear cell, gland forming, etc)
- (Optional: immunohistochemical staining for general neuroendocrine markers)
 - Chromogranin
 - Synaptophysin
- Peptide hormones, if a specific clinical situation suggests that the correlation with a functional syndrome may be helpful
- Grade (specify grading system employed)

TABLE 2. (Continued)

- Mitotic rate (no. mitoses per 10 high-power field or 2 mm²; count up to 50 high-power fields)
 - Ki67 labeling index, for biopsies in which a diagnosis of high-grade neuroendocrine carcinoma cannot be excluded (count multiple regions with highest labeling density, report average percentage; “eyeballed” estimate is adequate)
 - Presence of nonischemic tumor necrosis
 - Presence of other pathological components (eg, nonneuroendocrine components)
- For resection of metastatic tumors**
- Location of metastasis(es)
 - Diagnosis (functional status need not be included in pathology report)
 - No. metastases resected
 - Extent of involvement of resected tissue (percentage)
 - Greatest dimension of largest metastasis
 - Presence of unusual histological features (oncocyctic, clear cell, gland forming, etc)
 - (Optional: immunohistochemical staining for general neuroendocrine markers)
 - Chromogranin
 - Synaptophysin
 - Peptide hormones, if a specific clinical situation suggests the correlation with a functional syndrome may be useful
 - Grade (specify grading system employed)
 - Mitotic rate (no. mitoses per 10 high-power field or 2 mm²; count 50 high-power fields in the most mitotically active regions, provide separate mitotic rate for each major separate site of disease)
 - (Optional: Ki67 labeling index [count multiple regions with highest labeling density, report average percentage; “eyeballed” estimate is adequate])
 - Presence of nonischemic tumor necrosis
 - Presence of other pathological components
 - Resection margins (positive/negative/close) (optional: measure distance from margin if within 0.5 cm)
 - Identification of primary site
 - Immunohistochemistry for CDX2, TTF1
- For biopsy of metastatic tumors**
- Location of metastasis
 - Diagnosis (functional status need not be included in pathology report)
 - Presence of unusual histological features (oncocyctic, clear cell, gland forming, etc)
 - Immunohistochemical staining for general neuroendocrine markers
 - Chromogranin
 - Synaptophysin
 - (Optional: peptide hormones, if a specific clinical situation suggests the correlation with a functional syndrome may be useful)
 - Grade for adequate biopsy specimens; fine-needle-aspiration specimens may not be adequate (specify grading system is used)
 - Mitotic rate (no. mitoses per 10 high-power field or 2 mm²; count up to 50 high-power fields)
 - Ki67 labeling index (count multiple regions with highest labeling density, report average percentage; “eyeballed” estimate is adequate)
 - Presence of nonischemic tumor necrosis
 - Presence of other pathological components (eg, nonneuroendocrine components)
 - Identification of primary site
 - Immunohistochemistry for CDX2, TTF1

TABLE 3. Grade Versus Differentiation in NETs

Differentiation	Grade
Well differentiated	Low grade (ENETS G1) Intermediate grade (ENETS G2)
Poorly differentiated	High grade (ENETS G3)

typical resected primary tumors, but it is very important in many cases to confirm the nature of the tumor based on biopsy specimens. Immunolabeling for specific peptide hormones is useful only in highly defined circumstances, however. Adverse prognostic factors not included in grading and staging, such as vascular or perineural invasion, should be documented. Adequacy of surgical resection should be indicated, and the number of involved lymph nodes (as well as the total number of nodes examined) should also be stated. Histological abnormalities of the neuroendocrine cells in the surrounding tissues (such as neuroendocrine hyperplasia in the lung or stomach) should be described. A variety of prognostic or treatment-related biomarkers has been investigated, and some may have significant utility in the future, but currently, none is recommended to be used routinely, outside specific research settings.

Imaging

Most NETs of the stomach are directly imaged and diagnosed during endoscopy. For larger lesions, endoscopic ultrasound (EUS) may be performed to assess whether the NETs of the stomach is invasive.

Cross-sectional imaging with computed tomography (CT) or magnetic resonance imaging (MRI) is recommended to assess for metastases in patients with type 1 or 2 NETs of the stomach more than 2 cm in diameter, or for patients with type 3 NETs of the stomach in whom metastatic risk is a concern.²⁵ Neuroendocrine tumors are generally vascular tumors that enhance intensely with intravenous contrast during early arterial phases of imaging with washout during the delayed portal venous phase. The key to detecting small NETs on CT is to maximize the contrast between the tumor and the adjacent normal parenchyma. For abdominal and pelvic imaging, we recommend multiphasic CT that includes the arterial phase and the portal venous phase. Rapid intravenous bolus of intravenous contrast is also recommended. Thin sectioning and the use of a negative oral contrast agent also may be helpful in detecting small primary tumor in the small bowel that may not otherwise be seen.

Magnetic resonance imaging is preferred over CT for patients with a history of allergy to iodine contrast material or for those with renal insufficiency. Neuroendocrine tumors can have variable appearances on noncontrast MRI. They can be hypo-

intense or isointense on T1-weighted images. Metastases to the liver typically are usually high signal on T2-weighted images. Because T2-weighted images are obtained without intravenous contrast, they do not have the problems of variations in the timing of phases of contrast enhancement. T2-weighted imaging can be especially useful for patients unable to receive contrast. However, these metastases, especially when cystic or necrotic, can mimic the appearance of other T2 high-signal-intensity lesions, such as hemangiomas and, occasionally, cysts. Dynamic contrast-enhanced imaging can provide additional information about the nature of the lesions and help to detect smaller lesions. We recommend T1-weighted, T2-weighted imaging, and multiphasic (arterial, portal venous, and delayed) dynamic MRI for NETs.

Somatostatin receptor scintigraphy (SRS) provides a second useful imaging modality for the detection of metastatic disease in patients with malignant NETs of the stomach.^{25,26} Indium In 111-labeled somatostatin analog [¹¹¹In-DTPA⁰] octreotide was developed for scintigraphy of NETs. It shares the receptor-binding profile of octreotide, which makes it a good radiopharmaceutical for imaging of somatostatin receptor 2- and receptor 5-positive tumors. The overall sensitivity of [¹¹¹In-DTPA⁰]octreotide scintigraphy seems to be about 80% to 90%.²⁷ Unlike cross-sectional imaging, which is generally site directed, [¹¹¹In-DTPA⁰]octreotide scintigraphy is done as whole-body imaging and thus can detect disease at unsuspected sites. Imaging is generally performed at 4 to 6 hours and at 24 hours. Imaging at 24 hours provides better contrast due to lower background activity. However, there is often physiological bowel activity that may produce false-positive results. At 4 to 6 hours, some lesions may be obscured by relatively high background activity; however, bowel activity is limited. In some cases, additional imaging at 48 hours may be needed when there is significant bowel activity at the 24-hour scan, which may potentially obscure lesions that provide additional information. SPECT (single photon emission CT) imaging with CT fusion may be helpful in resolving the nature of indeterminate lesions found on CT and enhance the sensitivity and specificity the study.

[¹¹¹In-DTPA⁰]octreotide scintigraphy can be performed for patients on long-acting octreotide but is best performed at the end of the dosing interval (3–6 weeks after the last dose). Although [¹¹¹In-DTPA⁰]octreotide scintigraphy can provide useful information about the site of disease, it does not give information about size. Some agents such as interferon may upregulate somatostatin receptors and thus can lead to increased uptake without disease progression, whereas glucocorticoids can downregulate somatostatin receptor expression, thus causing false-negative results. [¹¹¹In-DTPA⁰]octreotide scintigraphy is also sometimes performed to evaluate the feasibility of peptide

TABLE 4. Systems of Nomenclature for NETs

Grade	Lung, Thymus (WHO)	GEP NETs (ENETS)	GEP NETs (WHO 2010)
Low grade	Carcinoid tumor	NET grade 1 (G1)	Neuroendocrine neoplasm grade 1
Intermediate grade	Atypical carcinoid tumor	NET grade 2 (G2)	Neuroendocrine neoplasm grade 2
High grade	Small cell carcinoma	Neuroendocrine carcinoma grade 3 (G3), small cell carcinoma	Neuroendocrine carcinoma grade 3, small cell carcinoma
	Large cell neuroendocrine carcinoma	Neuroendocrine carcinoma grade 3 (G3), large cell neuroendocrine	Neuroendocrine carcinoma, grade 3, large cell neuroendocrine carcinoma

The grade of the tumor must be included in the pathology report, along with a reference to the specific grading system being used. Unqualified terms such as *neuroendocrine tumor* or *neuroendocrine carcinoma* without reference to grade do not provide adequate pathology information.

TABLE 5. Staging of NETs of the Stomach

AJCC				ENETS			
Primary Tumor (T)				T—Primary Tumor			
TX	Primary tumor cannot be assessed			TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor			T0	No evidence of primary tumor		
Tis	Carcinoma in situ/dysplasia (tumor size <0.5 mm), confined to mucosa			—	—		
T1	Tumor invades lamina propria or submucosa and ≤1 cm			T1	Tumor invades lamina propria or submucosa and size ≤1 cm		
T2	Tumor invades muscularis propria or >1 cm			T2	Tumor invades muscularis propria or size >1 cm		
T3	Tumor penetrates subserosa			T3	Tumor invades pancreas or retroperitoneum		
T4	Tumor invades serosa (visceral peritoneum) or other organs or adjacent structures			T4	Tumor invades peritoneum or other organs		
Regional Lymph Nodes (N)				N—Regional Lymph Nodes			
NX	Regional lymph node(s) cannot be assessed			NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis			N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis			N1	Regional lymph node metastasis		
Distant Metastasis (M)				M—Distant Metastases			
—	—			MX	Distant metastasis cannot be assessed		
M0	No distant metastasis			M0	No distant metastasis		
M1	Distant metastasis			M1	Distant metastasis		
Stage	T	N	M	Stage	T	N	M
0	Tis	N0	M0	0	Tis	N0	M0
I	T1	N0	M0	I	T1	N0	M0
IIA	T2	N0	M0	IIa	T2	N0	M0
IIB	T3	N0	M0	IIB	T3	N0	M0
IIIA	T4	N0	M0	IIIA	T4	N0	M0
IIIB	Any T	N1	M0	IIIB	Any T	N1	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

receptor radiotherapy (PRRT) as a scan with intense uptake at all known sites of disease is associated with a higher response rate after radiotherapy with somatostatin receptor targeting.

Prior studies have shown [¹¹C]-5-hydroxytryptophan (5-HTP) positron emission tomography (PET) to be a promising imaging modality for the detection of NETs.²⁸ The serotonin precursor 5-HTP labeled with ¹¹C was used and showed an increased uptake and irreversible trapping of this tracer in NETs.²⁸ [¹¹C]-5-HTP PET proved better than SRS for tumor visualization. However, the short half-life of ¹¹C ($t_{1/2}$ = 20 minutes) makes it difficult to apply in clinical practice. Other new PET imaging agents for NETs include ¹⁸F-FDOPA, ⁶⁸Ga-DOTA-TOC, ⁶⁸Ga-DOTA-NOC, and ¹⁸F-FPGluc-TOCA. In addition, ^{99m}Tc-depreotide, which has a greater affinity to somatostatin receptor 3, has also been used for tumor imaging. Although these novel imaging techniques are promising, clinical experiences are limited. These techniques are generally not available in the United States.

Follow-up radiological imaging may not be routinely required for types 1 and 2 carcinoids, but is warranted after resection of type 3 carcinoids. Among patients undergoing surveillance after complete resection, we recommend chest x-ray and periodic cross-sectional imaging of the abdomen and pelvis. The role of routine [¹¹¹In-DTPA⁰]octreotide scintigraphy has not been defined by prospective studies. Many experts, however, would advocate the use of [¹¹¹In-DTPA⁰]octreotide scintigraphy as a yearly study for follow-up for patients without evidence of

disease or on an as-needed basis to resolve difficult issues. For patients with advanced disease, we generally recommend the use of cross-sectional imaging for follow-up of known sites of disease. Chest x-ray can be used as a screening examination for patients without evidence of thoracic disease. [¹¹¹In-DTPA⁰]octreotide scintigraphy can be used to test in vivo for the presence of somatostatin receptors 2 and 5. It can also be used to evaluate if PRRT represents a good treatment option.

Biochemical Monitoring

Fasting serum gastrin levels are important to differentiate types 1 and 2 NETs of the stomach from type 3. 5-Hydroxyindoleacetic acid (5-HIAA) levels are generally not useful in patients with NETs of the stomach, because development of the carcinoid syndrome is uncommon.⁴ Furthermore, carcinoid syndrome, if it occurs in these patients, is reported to be characteristically atypical with normal serotonin and 5-HIAA levels, although a recent study reports the typical carcinoid syndrome can occur in rare patients with NETs of the stomach.⁵ Plasma CGA levels are recommended because CGA is frequently elevated in both patients with types 1 and 2 as well as type 3 NETs of the stomach,²⁵ and changes in CGA levels may be helpful in the follow-up.²⁵ Chromogranin A should be used with caution as a marker of disease activity in patients treated with somatostatin analogs, because these agents significantly reduce plasma CGA levels, a change that may be more reflective of changes in hormonal synthesis and release from tumor cells than an actual

reduction in tumor mass.^{25,29} In patients on stable doses of somatostatin analogs, consistent increases in plasma CGA levels over time may reflect loss of secretory control and/or tumor growth. Plasma CGA levels have also been shown to have a prognostic value in patients with metastatic disease.^{25,30}

Management of Localized NETs of the Stomach

Because types 1 and 2 NETs of the stomach generally pursue an indolent course, tumors less than 2 cm (up to 6) should be resected endoscopically, with subsequent interval follow-up.^{2,25,31} Patients with tumors measuring more than 2 cm, with recurrent tumors or with more than 6 polyps, generally require more aggressive management, and local surgical resection is recommended.^{2,25,31} In patients with type 1 NETs of the stomach arising in the setting of chronic atrophic gastritis, antrectomy may be performed to eliminate the source of gastric production. Antrectomy has been reported to result in tumor regression in such cases.^{32,33} In patients with type 2 NETs of the stomach secondary to ZES/MEN I syndrome, treatment with somatostatin analogs may be initiated and has resulted in tumor regression.³⁴ The surgical management of type 3 isolated sporadic NETs of the stomach requires more aggressive surgery, generally with partial gastrectomy and lymph node dissection.^{2,25,31}

Management of Metastatic NETs of the Stomach

In general, metastatic NETs of the stomach, which are infrequent and therefore usually included in general studies including other more frequent malignant carcinoids (especially midgut), are treated in a similar fashion as these other malignant carcinoids.

Hepatic Resection and Transplantation

A small percentage of patients (5%–15%) with metastatic liver disease with a limited number of hepatic metastases localized preferable to one lobe may be successfully treated with hepatic resection, providing both long-term symptomatic relief and likely increasing survival times.^{35–37} The number of patients with liver-isolated metastatic NETs in whom orthotopic liver transplantation (OLT) has been attempted remains small, resulting in the role of OLT in such patients being controversial and cannot, at this time, be routinely recommended.^{38,39} In a recent review of 85 cases, overall 5-year survival was 45%, and poor prognostic factors were prior extensive upper abdominal surgery, a neuroendocrine primary tumor in the duodenum or pancreas, and hepatomegaly.³⁹ Without any of these risk factors, the 5-year survival was 66%.³⁹ It has been proposed for the occasional, younger patient without any of these risk factors with a metastatic carcinoid tumor that is unresectable and limited to the liver that liver transplantation remains an option that should be considered.^{38–40}

Hepatic Artery Embolization

Hepatic arterial embolization is recommended as a palliative option in patients with hepatic metastases who are not candidates for surgical resection, have an otherwise preserved performance status, have disease primarily confined to the liver, and have a patent portal vein.^{35,41,42} The response rates associated with embolization, as measured either by decrease in hormonal secretion or by radiographic regression, are generally greater than 50%.^{35,41–43} Improved techniques have, in recent years, reduced the incidence complications related to embolization, making embolization an important and generally safe treatment.⁴³ A number of techniques may be used and include bland embolization, chemoembolization, embolization with chemotherapy beads, and embolization using radioisotopes. There are currently no data confirming superiority of any of these

techniques compared with the others. This technique should be especially considered for a patient with a functional carcinoid in which the hormone excess state cannot be controlled by other methods.

Radiofrequency Ablation and Cryoablation

Other approaches to the treatment of hepatic metastases include the use of radiofrequency ablation (RFA) and cryoablation, either alone or in conjunction with surgical debulking.^{35,42} These approaches can be performed using a percutaneous or laparoscopic approach. Although they seem to be less morbid than either hepatic resection or hepatic artery embolization, the clinical benefit of these approaches in patients with asymptomatic, small-volume disease has not been clearly established. Similarly, these approaches may not be applicable in patients with large-volume hepatic metastatic disease. Ablative techniques should therefore be considered as a treatment option only in carefully selected patients.^{35,42,44,45}

Systemic Treatment of Metastatic Disease

Patients with metastatic NETs of the stomach may develop an “atypical” carcinoid syndrome related to release of histamine and/or 5-HTP or rarely a typical carcinoid syndrome as seen in patients with metastatic midgut carcinoids.⁵ These patients frequently benefit from treatment with somatostatin analogs for symptom control.^{5,46}

The addition of α -interferon to therapy with somatostatin analogs has been reported to be effective in controlling symptoms in patients with carcinoid syndrome who may be resistant to somatostatin analogs alone.^{47,48} Treatment with α -interferon may therefore be considered in patients with metastatic NETs of the stomach refractory to somatostatin analogs. In clinical trials, doses of α -interferon have ranged from 3 to 9 MU subcutaneously, administered from 3 to 7 times per week.

The direct antineoplastic effects of somatostatin analogs either with or without interferon remain uncertain, although recent studies suggest they have a cytostatic effect in 40% to 70% of patients.^{48,49} Treatment with somatostatin analogs can therefore be considered in patients with NETs of the stomach and evidence of radiological progression. Whether this cytostatic effect of somatostatin alone or with interferon results in increased survival is largely unproven at present. A recent prospective study (PROMID study) demonstrates in patients with metastatic midgut carcinoid tumors involving less than 10% of the liver the use of octreotide long-acting release (LAR) resulted in an increased time to progression.⁵⁰ However, it is unclear whether similar effects occur with patients with more extensive metastases or with foregut (gastric, pancreatic, duodenal) or hindgut carcinoids as well.

Cytotoxic Chemotherapy

Because of its rarity, there have not been any specific studies of cytotoxic agents in only patients with malignant NETs of the stomach. However, with malignant carcinoids in general, cytotoxic chemotherapy plays only a limited role, and therefore, it is probable that similar results can be expected with malignant NETs of the stomach. Studies of single-agent therapy with 5-fluorouracil, streptozocin, or doxorubicin in patients with metastatic carcinoid tumors have shown that these agents are associated with only modest response rates.^{41,51,52} Trials of combination chemotherapy in this disease have failed to demonstrate superiority to single-agent therapy; furthermore, many of these combination regimens have been associated with significant toxicity.^{41,52,53} Dacarbazine (DTIC) has been evaluated

as a potential alternative to streptozocin-based therapy in carcinoid and pancreatic NETs (PNETs), although concerns regarding toxicity have limited its use for this indication.⁵⁴ Studies with the oral agent, temozolomide, have also shown only limited activity in carcinoid tumors. Although streptozocin-, dacarbazine-, or temozolomide-based therapy may therefore be considered in patients with metastatic NETs of the stomach, careful consideration needs to be given to the relative benefit of such an approach.⁵¹

Investigational Approaches

In the absence of an approved systemic treatment for metastatic carcinoid disease, treatment with investigational agents is appropriate for patients with metastatic NETs of the stomach. Recent studies using vascular endothelial growth factor

pathway inhibitors such as bevacizumab, sunitinib, and sorafenib have suggested that these agents may have antitumor activity.⁵⁵⁻⁵⁸ Similarly, the mTOR (mammalian target of rapamycin) inhibitor, everolimus, has shown activity in patients with advanced carcinoid in early studies.^{55-57,59} Randomized trials are currently ongoing to confirm activity with these agents, and they remain investigational in patients with metastatic carcinoid disease.⁵⁵⁻⁵⁷ Treatment with radiolabeled somatostatin analogs represents another investigational approach to the treatment of patients with advanced carcinoid tumors.^{60,61}

WELL-DIFFERENTIATED NETS OF THE PANCREAS

Well-differentiated NETs of the pancreas (PNETs) have an estimated incidence of less than 1 per 100,000 individuals.⁶²⁻⁶⁴ Pancreatic NETs are divided into 2 groups: those associated with

TABLE 6. Staging of NETs of the Pancreas

AJCC				ENETS			
Definitions of TNM				Proposal for a TNM Classification and Disease Staging for Endocrine Tumors			
Primary Tumor (T)				T—Primary Tumor			
TX	Primary tumor cannot be assessed			TX	Primary tumor cannot be assessed		
T0	No evidence of primary tumor			T0	No evidence of primary tumor		
T1	Tumor limited to the pancreas, ≤2 cm in greatest dimension			T1	Tumor limited to the pancreas and size <2 cm		
T2	Tumor limited to the pancreas, >2 cm in greatest dimension			T2	Tumor limited to the pancreas and size 2–4 cm		
T3	Tumor extends beyond the pancreas but without involvement of the celiac axis or the superior mesenteric artery			T3	Tumor limited to the pancreas and size >4 cm or invading duodenum or bile duct		
T4	Tumor involves the celiac axis or the superior mesenteric artery (unresectable primary tumor)			T4	Tumor invading adjacent organs (stomach, spleen, colon, adrenal gland) or the wall of large vessels (celiac axis or superior mesenteric artery)		
				<i>Note: For any T, add (m) for multiple tumors</i>			
Regional Lymph Nodes (N)				N—Regional Lymph Nodes			
NX	Regional lymph node(s) cannot be assessed			NX	Regional lymph nodes cannot be assessed		
N0	No regional lymph node metastasis			N0	No regional lymph node metastasis		
N1	Regional lymph node metastasis			N1	Regional lymph node metastasis		
Distant Metastasis (M)				M—Distant Metastases			
—				MX	Distant metastasis cannot be assessed		
M0	No distant metastasis			M0	No distant metastasis		
M1	Distant metastasis			M1a	Distant metastasis		
Endocrine and Exocrine Pancreas				Endocrine Pancreas			
Stage	T	N	M	Stage	T	N	M
0	T0	N0	M0	—	—	—	—
IA	T1	N0	M0	I	T1	N0	M0
IB	T2	N0	M0	—	—	—	—
IIA	T3	N0	M0	IIa	T2	N0	M0
IIB	T1	N1	M0	IIb	T3	N0	M0
	T2	N1	M0	—	—	—	—
	T3	N1	M0				
III	T4	Any N	M0	IIIa	T4	N0	M0
				IIIb	Any T	N1	M0
IV	Any T	Any N	M1	IV	Any T	Any N	M1

a functional syndrome due to ectopic secretion of a biologically active substance and those that are not associated with a functional syndrome (generally called nonfunctional PNETs [NF-PNETs]; Table 6).^{62–65} This distinction is important for clinical presentation, diagnosis, and treatment of these tumors.

Clinical Presentation and Etiology

Functional PNETs include insulinomas, gastrinomas, PNETs secreting vasoactive intestinal polypeptide (VIPomas), somatostatinomas, glucagonomas, growth hormone–releasing hormone secreting (GHRHomas), and a group of less common PNETs including PNETs secreting adrenocorticotropic hormone (ACTH; AfCTHomas) and causing Cushing syndrome, PNETs causing the carcinoid syndrome, PNETs causing hypercalcemia (via parathyroid hormone [PTH]–related peptide [PTH-rP] secretion), and, very rarely, PNETs ectopically secreting luteinizing hormone, renin, insulinlike growth factor 2, or erythropoietin.⁶² Functional PNETs and NF-PNETs also frequently secrete a number of other substances (chromogranins, neuron-specific enolase, subunits of human chorionic gonadotropin, neurotensin, ghrelin), but they do not cause a specific hormonal syndrome.^{62–65} In terms of relative frequency, NF-PNETs are at present the most frequently found PNET, occurring approximately twice as frequently as insulinomas, which are generally more frequent than gastrinomas, followed by glucagonomas > VIPomas > somatostatinomas > others.^{62,63,65,66}

Pancreatic NETs can occur both sporadically and in patients with various inherited disorders.^{62,67} Pancreatic NETs occur in 80% to 100% of patients with MEN I, in 10% to 17% of patients with von Hippel-Lindau syndrome (VHL), up to 10% of patients with von Recklinghausen disease (neurofibromatosis 1 [NF-1]), and occasionally in patients with tuberous sclerosis.⁶⁷ Each of these is an autosomal dominant disorder.⁶⁷ Of these disorders, MEN I is the most frequent, in patients with PNETs.^{67,68} Multiple endocrine neoplasia I is caused by mutations in chromosome 11q13 region, resulting in alterations in the *Menin* gene, which encodes for a 610–amino acid nuclear protein, menin, which has important effects on transcriptional regulation, genomic stability, cell division, and cell cycle control.⁶⁷ Patients with MEN I develop hyperplasia or tumors of multiple endocrine and nonendocrine tissues including parathyroid adenomas (95%–100%), resulting in hyperparathyroidism, pituitary adenomas (54%–65%), adrenal adenomas (27%–36%), various carcinoid tumors (gastric, lung, thymic; 0%–10%), thyroid adenomas (up to 10%), various skin tumors (80%–95%), central nervous system tumors (up to 8%), and smooth muscle tumors

(up to 10%).⁶⁷ In MEN I patients, 80% to 100% develop pancreatic NF-PNETs, but in most patients, they are small and microscopic, causing symptoms in only 0% to 13%.⁶⁷ Gastrinomas (>80% duodenal) develop in 54% of MEN I patients, insulinomas in 18%, and glucagonomas, VIPomas, GHRHomas, and somatostatinomas in less than 5%.⁶⁷ In VHL, 98% of all the PNETs that develop in 10% to 17% of the patients are NF-PNETs; in the 0% to 10% of NF-1 patients developing a PNET, they are characteristically duodenal somatostatinomas that do not cause the somatostatinoma syndrome, and in tuberous sclerosis, rare functional and NF-PNETs are reported.⁶⁷

Pathological Classification

The pathological classification of PNETs generally parallels that of NETs of the stomach and other NETs (described previously for NETs of the stomach), with some notable differences. Because PNETs do not arise in the luminal gut, separate TNM staging systems are used for PNETs (Table 6). The issue of functionality of NETs also impacts on the nomenclature for PNETs. Functioning NETs are defined based on the presence of clinical symptoms due to excess hormone secretion by the tumor (Table 7). Terms reflecting the clinical syndromes may be applied to these NETs, such as insulinoma, glucagonoma, gastrinoma, and so on. Although there are prognostic implications to some of the functional categories (eg, insulinomas are generally very indolent), the biology of most functioning NETs is still defined by the grade and stage of the tumor (although the clinical consequences of the hormone hypersecretion can be significant). Furthermore, the functional status of the tumor is defined by the clinical findings, not by the pathological appearance or immunohistochemical profile. Thus, the pathological diagnosis of functioning NETs should be the same as for analogous nonfunctional NETs of the same anatomical site, with the descriptive functional designation appended to the diagnosis when there is knowledge of a clinical syndrome.

Incidence, Clinical Features, and Diagnosis of Specific PNETs

Insulinoma

Insulinomas have an estimated annual incidence of 1 to 4 per million persons. Approximately 4% of patients with insulinoma have MEN I.⁶⁷ Insulinomas are usually single tumors (except in patients with MEN I), generally small (ie, <1 cm), and almost always (>99%) intrapancreatic in location and, in contrast to all other PNETs, are benign in more than 85% to 95% of patients.^{67,69–71} Insulinoma patients characteristically present

TABLE 7. Clinical Presentation of Pancreatic NETs

Tumor	Symptoms or Signs	Incidence of Metastases	Extrapancreatic Location
Insulinoma	Hypoglycemia resulting in intermittent confusion, sweating, weakness, nausea; loss of consciousness may occur in severe cases	<15%	Rare
Glucagonoma	Rash (necrotizing migratory erythema), cachexia, diabetes, deep venous thrombosis	Majority	Rare
VIPoma, Verner-Morrison syndrome, WDHA syndrome	Profound secretory diarrhea, electrolyte disturbances	Majority	10%
Gastrinoma, ZES	Acid hypersecretion resulting in refractory PUD, abdominal pain, and diarrhea	<50%	Frequently in duodenum
Somatostatinoma	Diabetes, diarrhea, cholelithiasis	Majority	Rare
Nonfunctional	May be first diagnosed due to mass effect		

with symptoms of hypoglycemia, especially neuroglycopenic symptoms (confusion, altered consciousness) and symptoms due to sympathetic overdrive (weakness, sweating), which are usually made worse by fasting.^{62,70,71} The diagnosis of insulinoma can be established by determining plasma proinsulin, insulin, C-peptide, and glucose levels, which are usually performed during a 72-hour fast.^{62,70,71} It is important to realize that insulin levels are increasingly being determined by immunochemiluminescent assays or specific immunoradiometric assays that do not cross-react with proinsulin and give lower values than that obtained with most insulin radioimmunoassays, which can effect the proposed criteria listed in many reviews for diagnosis, which were based on radioimmunoassay results.^{62,72}

Gastrinoma

Gastrinomas ectopically secrete gastrin, resulting in hypergastrinemia, which stimulates gastric acid hypersecretion, resulting in severe peptic disease (ZES).^{62,73,74} Currently, gastrinomas, in contrast to older studies, are found in the duodenum in more than 60% of patients with sporadic ZES (>85% with MEN I/ZES), are usually single in sporadic ZES and invariably multiple in MEN I/ZES, are usually small in the duodenum (<1 cm), and are malignant in 60% to 90% of cases.^{67,75–78} Recent studies show pancreatic tumors are more aggressive than duodenal tumors, are much more likely to metastasize to liver and/or bone, and are more likely to be present in the 25% of ZES patients with aggressive gastrinomas.^{62,79–81} Patients typically present with abdominal pain due to peptic ulcer disease (PUD), diarrhea, and reflux esophagitis.⁷³ Zollinger-Ellison syndrome should be suspected in patients with PUD with diarrhea, with ulcers in unusual locations, with severe PUD or with complications of PUD, with PUD without *Helicobacter pylori* present, with PUD with a family history of PUD or endocrinopathies, or with PUD with prominent gastric folds, presence of an endocrinopathy, or with hypergastrinemia.^{62,73,74,82,83} The diagnosis of ZES requires the demonstration of inappropriate hypergastrinemia (ie, hypergastrinemia present at time of acid hypersecretion).^{62,73,74,82,83} When ZES is suspected, the initial determination in most centers is a fasting gastrin level, because it will be elevated in 99% to 100% of ZES patients.^{62,82,83} The diagnosis can be complicated by the fact that other conditions, some of which are much more common than ZES, can cause hypergastrinemia in a range seen with ZES patients.^{62,73,74,82–85} These other conditions either can result in hypergastrinemia due to their causing hypochlorhydria/achlorhydria (atrophic gastritis, proton pump inhibitor [PPI] treatment) or can be associated with increased acid secretion similar to ZES.^{62,73,82,83,86} Recent studies^{86,87} show that the widespread use of PPIs can particularly complicate and delay the diagnosis of ZES. This occurs because PPIs, in contrast to histamine H₂-receptor antagonists, control the symptoms in most ZES patients with conventional doses used to treat idiopathic PUD/esophagitis and thus mask the diagnosis.^{62,83,86} Furthermore, PPIs cause hypergastrinemia in patients without ZES, commonly in the range that is seen with most ZES patients.^{83,86–88} To exclude physiological hypergastrinemia (associated with hypochlorhydria/achlorhydria), it is essential to measure gastric pH if hypergastrinemia is detected because it is 2 or less in all patients with ZES not taking anti-secretory drugs.⁸⁹ Because of the presence of other conditions that can also cause hypergastrinemia and an acidic pH, the diagnosis of ZES may require the assessment of basal acid output as well as a secretin provocative gastrin test.^{62,74,83,84} Gastrinomas ectopically express secretin receptors, and intravenous administration of secretin characteristically causes an exaggerated release of secretin by the gastrinoma (≥ 120 -pg/mL

increase post secretin is positive for gastrinoma,⁸⁴ if the patient is not taking PPIs).^{84,90} With some patients suspected of having ZES, there can be risk to stopping PPIs to assess fasting gastrin levels and perform acid secretory studies or secretin provocative testing; thus, it is best that these patients be referred to a clinical unit experienced in making the diagnosis of ZES.

The diagnosis of ZES in patients with MEN I can be complicated by the fact that the presence or absence of hyperparathyroidism with the resultant hypercalcemia can have a marked effect on fasting gastrin levels, basal acid output, and the secretin test results.^{67,68,91–93} Each of these parameters can markedly decrease after correction of the hyperparathyroidism, by an effective parathyroidectomy (≥ 3.5 glands removed) and thus can mask the diagnosis of ZES in MEN I patients.^{67,68,91–93}

Glucagonoma

Glucagonomas cause glucose intolerance (40%–90%), weight loss (80%), and a pathognomonic rash, migratory necrolytic erythema (70%–90%).^{62,66,94–96} Glucagonomas are generally single, large tumors (mean, 6 cm), associated with liver metastases in more than 60% of cases at diagnosis, and are almost entirely intrapancreatic in location.^{62,66,94–96} Although glucagonomas may be associated with glucose intolerance, clinically significant hyperglycemia occurs in only half of such patients. Patients with glucagonomas are frequently initially diagnosed by a dermatologist, after presenting with necrolytic migratory erythema. This rash, characterized by raised erythematous patches beginning in the perineum and subsequently involving the trunk and extremities, is found in more than two thirds of all patients.^{62,66,94–96} However, necrolytic migratory erythema is not specific for glucagonomas because it can also occur in cirrhosis, pancreatitis, and celiac disease.⁶² The diagnosis of a glucagonoma requires the demonstration of increased plasma glucagon levels (usually 500–1000 pg/mL; normal, <50 pg/mL) in the presence of the appropriate symptoms.^{62,66,94–96}

VIPomas (Also Called Verner-Morrison Syndrome, Pancreatic Cholera, or WDHA [Watery Diarrhea, Hypokalemia, and Achlorhydria] Syndrome)

VIPomas are PNETs ectopically secreting VIP, which leads to profound, large-volume diarrhea (>700 mL/d in 100%, >3 L/d in 70%–80%), hypokalemia, and achlorhydria.^{62,66,94,97,98} VIPomas are usually single tumors, metastatic at presentation in 70% to 80% of cases, and in adults are intrapancreatic in location in more than 95% of cases, whereas in children they often are ganglioneuromas/ganglioblastomas.^{62,66,94,97,98} The diagnosis requires the demonstration of an elevated plasma VIP level in a patient with large-volume secretory diarrhea.^{62,66,94,97,98}

Somatostatinoma

Somatostatinomas are PNETs that can occur in the duodenum or pancreas.^{62,66,94,99–101} In the literature, there is no general agreement of what is a somatostatinoma and whether a functional component is required for the diagnosis.^{62,94} Most of the cases reported in the literature are PNETs containing somatostatin by immunohistochemistry, without an specific somatostatinoma syndrome, which includes the presence of diabetes mellitus, gallbladder disease, weight loss, diarrhea, steatorrhea, and anemia.^{62,66,94,99–101} Somatostatinomas are usually single tumors; approximately 50% are intrapancreatic and the remainder primarily in the duodenum or the rest of the small intestine, and 50% to 60% are malignant; however, the malignancy rate is higher with pancreatic than duodenal tumors.^{62,66,94,99–101} The diagnosis of the somatostatinoma syndrome is confirmed by the presence

of a PNET with the appropriate symptoms and an elevated plasma somatostatin level.^{62,66,94,99,100} In contrast to pancreatic somatostatinomas, duodenal somatostatinomas, which can occur in up to 10% of patients with von Recklinghausen disease (NF-1), are usually not associated with metastatic disease and are rarely associated with the somatostatinoma syndrome.^{62,66,94,99,100}

Other Rare Functional PNETs

GHRHomas ectopically secrete growth hormone-releasing hormone, which results in acromegaly, which is generally clinically indistinguishable from that caused by pituitary adenomas.^{62,94,102} GHRHomas in the pancreas are generally single, large tumors at diagnosis; one third have liver metastases, and they are found in the pancreas in 30% of cases, 54% in the lung, and the remainder primarily in other abdominal locations.^{62,94,102} The diagnosis is made by establishing the presence of increased plasma growth hormone levels accompanied by increased plasma Growth hormone releasing factor levels.^{62,94,102} Pancreatic NETs causing hypercalcemia usually secrete PTH-rP as well as other biologically active peptides and are similar to pancreatic ACTHomas associated with ectopic Cushing syndrome in that both are usually large tumors at diagnosis, with 80% to 90% associated with liver metastases.^{62,94,103,104} With ACTHomas or PNETs causing hypercalcemia, the diagnosis is made by the presence of a PNET with the appropriated elevated hormonal assay result.

Nonfunctional PNETs

Nonfunctional PNETs are intrapancreatic in location, characteristically large (>5 cm in 70%), and at an advanced stage when first diagnosed, with 60% to 85% having liver metastases in most series.^{62,64,65,94,105} Because NF-PNETs are not associated with a clinical hormonal syndrome, they present clinically with symptoms due to the tumor per se, which include primarily abdominal pain (40%–60%), weight loss, or jaundice.^{62,64,65,94,105} In recent years, NF-PNETs are increasingly being discovered by chance on imaging studies being performed for various nonspecific abdominal symptoms.^{62,106} Even though NF-PNETs do not secrete peptides causing a clinical syndrome, they are not biologically inactive, because they characteristically secrete a number of other peptides, which are frequently used in their diagnosis. These include chromogranins, especially CGA (70–100%) and pancreatic polypeptide (PP) (50%–100%).^{62,64,65,94,105} The presence of an NF-PNET is suggested by the presence of a pancreatic mass in a patient without hormonal symptoms, who has an elevated serum PP or CGA level or a positive Octreoscan (SRS) (discussed in the next section). It is important to remember that an elevated PP level or CGA level is not specific for NF-PNETs.^{62,64,65,94,105}

Imaging

General

Imaging of the primary tumor location and the extent of the disease is needed for all phases of management of patients with PNETs. It is needed to determine whether surgical resection for possible cure or possible cytoreductive surgery is needed, to determine whether treatment for advanced metastatic disease is appropriate, and during follow-up to assess the effects of any antitumor treatment as well as the need for deciding whether additional treatments directed at the PNET are indicated.^{62,94,107,108} Functional PNETs (especially insulinomas, duodenal gastrinomas) are often small in size, and localization may be difficult.^{62,94,107,108} A number of different imaging modalities have been widely used including conventional im-

aging studies (CT, MRI, ultrasound, angiography),^{62,107,109–111} SRS,^{62,112–114} EUS,^{62,115,116} functional localizations studies measuring hormonal gradients,^{62,117–119} intraoperative methods particularly intraoperative ultrasound,^{62,120,121} and, recently, the use of PET preoperatively.^{28,114,122,123} A few important points in regard to each are made in the following section.

Conventional Imaging Studies for PNETs Studies (CT, MRI, Ultrasound, Angiography)

Even though PNETs are highly vascular tumors, and most of these studies are now performed with contrast agents, the results with conventional imaging studies are dependent to a large degree on the tumor size.^{62,107,109–111} Although conventional imaging studies detect more than 70% of PNETs that are greater than 3 cm, they detect less than 50% of most PNETs that are less than 1 cm, therefore frequently missing small primary PNETs (especially insulinomas, duodenal gastrinomas) and small liver metastases.^{62,107,109–111} At least one of these modalities is generally available in most centers, with CT scanning with contrast being most frequently use as the first imaging modality.

Somatostatin Receptor Scintigraphy

Pancreatic NETs, similar to carcinoid tumors, frequently (>80%, except nonmetastatic insulinomas) overexpress somatostatin receptors (particularly subtypes sst 2 and 5), which bind various synthetic analogs of somatostatin (octreotide, lanreotide) with high affinity.^{62,112–114,124} A number of radiolabeled somatostatin analogs have been developed to take advantage of this finding to image PNETs, with the most widely used worldwide and the only one available in the United States being ¹¹¹In-DTPA-octreotide (Octreoscan).^{62,112–114,124} Somatostatin receptor scintigraphy combined with CT detection (SPECT imaging) is more sensitive than conventional imaging for detection of both the primary (except nonmetastatic insulinomas) PNET and metastatic PNETs to liver, bone, or other distant sites.^{81,112–114,124,125} This sensitivity allows SRS to detect 50% to 70% of primary PNETs (less frequent with nonmetastatic insulinomas or duodenal gastrinomas) and more than 90% of patients with metastatic disease.^{62,112–114,126,127} It has the advantage of allowing total body scanning quickly at one time, and its use has resulted in a change in management of 24% to 47% of patients with PNETs.^{62,112–114,126,127} False-positive localizations can occur in up to 12% of patients, so it is important to interpret the result within the clinical context of the patient, and by doing this, the false-positive rate can be reduced to 3%.^{62,113,127,128}

Endoscopic Ultrasound

Endoscopic ultrasound combined with fine-needle aspiration can be useful in distinguishing a NF-PNET from adenocarcinoma or some other cause of a pancreatic mass.^{62,115,116} Fine-needle aspiration is rarely used to diagnose functional PNETs because they are suggested by symptoms, and the diagnosis is established by hormonal assays.^{62,94,116} Endoscopic ultrasound is much more effective for localizing intrapancreatic PNETs than extrapancreatic PNETs such as duodenal gastrinomas or somatostatinomas.^{62,94,115,116} Endoscopic ultrasound is particularly helpful in localizing insulinomas, which are small, almost always intrapancreatic, and frequently missed by conventional imaging studies and SRS.^{62,94,115,116} Endoscopic ultrasound can identify an intrapancreatic PNET in about 90% of cases.^{62,115} Endoscopic ultrasound can also play an important role in the management of patients with MEN I who

contain NF-PNETs in 80% to 100% of cases or in patients with NF-PNETs with VHL syndrome, which occur in 10% to 17%, which are often small and whose management is controversial.^{62,67,69,129–131} Endoscopic ultrasound can detect many of these small NF-PNETs, and it has been proposed that serial evaluations with EUS be used to select which MEN I or VHL patients should have surgery.^{62,67,69,130–132}

Functional Localization (Assessing Hormonal Gradients) and PET Scanning for PNETs

Assessment of hormonal gradients is now rarely used except in occasional patients with insulinomas or gastrinomas not localized by other imaging methods.^{62,110,117–119,133} When used, it is usually performed at the time of angiography and combined with selective intra-arterial injections of calcium for primary insulinomas or secretin for a primary gastrinoma or possible metastatic gastrinoma in the liver with hepatic venous hormonal sampling.^{62,110,117–119,133} Positron emission tomographic scanning for PNETs is receiving increasing attention because of its increased sensitivity.^{28,62,114,122,123} With PNETs, ¹¹C-5-HTP or ⁶⁸gallium-labeled somatostatin analogs have been shown to have greater sensitivity than SRS or conventional imaging studies and therefore may be clinically useful in the future. At present, neither of these methods is approved for use in the United States and are therefore not available in the United States.^{28,62,114,122,123}

Intraoperative Localization of PNETs

During surgery, the routine use of intraoperative ultrasound is recommended especially for PNETs,^{62,120,121} and for small duodenal tumors (especially duodenal gastrinomas), endoscopic transillumination^{62,134,135} in addition to routine duodenotomy is recommended.^{62,78,115,135–137} These are discussed in more detail in the surgical section below.

Follow-Up Imaging of PNETs

Among patients undergoing surveillance after complete resection, we recommend chest x-ray and periodic cross-sectional imaging of abdomen and pelvis. The role of routine [¹¹¹In-DTPA⁰]octreotide scintigraphy has not been defined by prospective studies. Many experts, however, would advocate the use of [¹¹¹In-DTPA⁰]octreotide scintigraphy as a yearly study for follow-up for patients without evidence of disease or on an as-needed basis to resolve difficult issues. For patients with advanced disease, we generally recommend the use of cross-sectional imaging for follow-up of known sites of disease. Chest x-ray can be used as a screening examination for patients without evidence of thoracic disease. [¹¹¹In-DTPA⁰]octreotide scintigraphy can be used to test *in vivo* for the presence of somatostatin receptors 2 and 5. It can also be used to evaluate if PRRT represents a good treatment option.

Biochemical Assessment and Monitoring

Specific hormonal assays are needed to establish the diagnosis of each functional PNET, as outlined in the discussion of each tumor type in the previous sections. Specifically, for insulinomas, an assessment of plasma insulin, proinsulin, and C-peptide is needed at the time of glucose determinations, usually during a fast.^{62,71,138} For ZES, serum gastrin is needed either alone or during a secretin provocation test.^{62,71,82,84,138} For VIPomas, a plasma VIP level is needed; for glucagonoma, plasma glucagon levels; for GRFomas, plasma growth hormone and GRF levels; for Cushing syndrome, urinary cortisol, plasma ACTH and appropriate ACTH suppression studies; for hypercalcemia with a PNET, both serum PTH levels and PTH-rP levels are indicated; and for a PNET with carcinoid syndrome, urinary

5-HIAA should be measured.^{62,66,94,138,139} Plasma CGA can be used as a marker in patients with both functional and NF-PNETs.^{62,138–140} Chromogranin A should be used with caution as a marker of disease activity in patients treated with somatostatin analogs, because these agents significantly reduce plasma CGA levels, a change that may be more reflective of changes in hormonal synthesis and release from tumor cells than an actual reduction in tumor mass.^{29,139} In patients on stable doses of somatostatin analogs, consistent increases in plasma CGA levels over time may reflect loss of secretory control and/or tumor growth.^{30,69,138–140}

Surgical Management of Localized PNETs

All experts agree that surgical resection of a functioning PNET should be considered whenever possible,^{36,62,64,141} except in the case of patients with MEN I with either ZES or small NF-PNETs (ie, <2 cm).^{62,67,142} The role of routine surgery is controversial in MEN I/ZES patients, because these patients are almost never cured without extensive resections (Whipple operations).^{67,74,78,115} Almost every MEN I patient (80%–100%) has small, microscopic NF-PNETs which in only 0% to 13% of patients do they grow larger and/or become symptomatic, and similar to the small gastrinomas in MEN I/ZES patients, without surgery, these patients have an excellent prognosis, if there are no PNETs that are greater than 2 cm.^{62,67,74,142,143} Many PNETs, especially insulinomas, small NF-PNETs (<2 cm), and small gastrinomas, can be treated by surgical enucleation.^{36,62,64,141} Local resection or enucleation of the PNET is generally recommended, and more advanced surgical resections such as Whipple resections are not routinely recommended and should be used in only carefully selected patients.^{36,62,64,78,115,141} In general, except for insulinomas (see below), PNETs are surgically approached by a laparotomy to allow an extensive exploration of the entire abdomen and search for lymph node metastases.^{36,62,64,141,144} Insulinomas in non-MEN I patients are increasingly being treated by laparoscopic approach; in 85% of patients, they are single tumors, they are almost invariably intrapancreatic, and if they can be localized preoperatively, they can be cured in 70% to 100% using a laparoscopic approach.^{62,115,145,146} At present, surgical cure rates for insulinomas approach 100%.^{62,70,71,147} For sporadic gastrinomas, 60% immediately postoperatively and 30% to 40% at 5 years.^{62,74,78,115,136,148} and for other PNETs, the cure rates are lower because many of the patients present with advanced disease.^{36,62,64,141} In general, surgical resection of the primary PNET should be attempted whenever it may be possible if the patient does not have another medical condition limiting life expectancy or increasing surgical risk, diffused metastatic liver disease, or one of the inherited PNET syndromes discussed in the previous sections. This recommendation is made because recent studies in patients with gastrinomas demonstrate for the first time that surgical resection decreases the subsequent rate of developing metastases and extends survival by preventing the development of advanced or progressive disease.^{149,150}

Medical Management of PNETs

Management of Symptoms Related to Hormone Hypersecretion

Management recommendations for patients with symptoms of hormonal hypersecretion related to a PNET is dependent on the hormone secreted.

Insulinoma

With insulinomas, dietary modification with frequent small feedings may help control the hypoglycemia. Administration of

diazoxide (200–600 mg/d) successfully controls hypoglycemia in 50% to 60% of patients.^{62,70,71,151,152} Diazoxide frequently leads to fluid retention requiring diuretics as well as nausea at higher doses and occasional hirsutism.^{62,70,71,151} Long-acting somatostatin analogs (octreotide, lanreotide) control hypoglycemic symptoms in up to 50% of patients with nonmetastatic insulinomas; however, they need to be used with care because, in some cases, they may worsen the hypoglycemia.^{62,153} Recent studies in small numbers of patients show that mTOR inhibitors (rapamycin, everolimus) may control hypoglycemia in patients with metastatic insulinomas.^{154–156}

Gastrinoma

Both histamine H₂-receptor antagonists and PPIs (omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole) can control the acid hypersecretion in almost every patient with ZES.^{74,75,83,157} However, with frequent use of H₂-receptor antagonists, high doses are required by many patients,^{74,75,83,157} making PPIs the drug of choice, because with their high potencies and long durations of action, once- or twice-a-day dosing is possible in most ZES patients.^{74,75,83,157,158} It is recommended that control of acid hypersecretion (<10 mEq/h before the last dose of drug [intact stomach] or <5 mEq/h) (previous gastric surgery) be documented whenever possible.^{62,74,83,159} Patients with ZES with complicated disease (MEN I, moderate to severe gastroesophageal reflux disease or prior Billroth 2 resection) may require more frequent dosing (usually twice a day instead of once a day), higher doses, and greater control of the acid hypersecretion, which can result in drug doses varying markedly from patient to patient.^{74,83,157,160,161} This requires, for the management of complicated ZES, the dose of antisecretory drug needed to control the acid hypersecretion be determined by titration in regard to symptoms and endoscopic findings in each patient.^{74,83,157,160,161} Long-term follow-up of patients with ZES treated with PPIs for up to 10 years demonstrates no evidence of tachyphylaxis and an excellent safety profile,^{62,74,75,83,157,158,162} although drug-induced achlorhydria can lead to nutrient deficiencies (vitamin B₁₂ is more of a concern than iron).^{62,83,162,163} In some patients with ZES, parenteral antisecretory drug treatment is required during their disease course, and both intermittent use of intravenous PPIs (2–3 times a day) (pantoprazole, lansoprazole, esomeprazole) or continuous administration of histamine H₂-receptor antagonists can be used.^{62,148,158,164,165} Somatostatin analogs are also effective in reducing both gastrin and acid secretion in ZES patients; however, they are rarely used because excellent oral medications are available.¹⁶⁶

Other Functional PNETs

Long-acting somatostatin analogs (octreotide, lanreotide) are generally successful in the initial management of patients with glucagonomas, VIPomas, and GRFomas and, in some patients, somatostatinomas.^{49,58,59,62,64,66,167} With long-term treatment, symptomatic breakthrough may occur, and the dose may need to be increased, frequency of administration increased, or, on occasion, the drug stopped and restarted. The availability of the long-acting depot forms of octreotide and lanreotide (octreotide LAR, lanreotide autogel) has greatly improved patient convenience because they allow once-a-month dosing in many patients.^{49,58,62,167,168} Adverse effects of treatment with somatostatin analogs occur in approximately 50% of patient with octreotide, are generally mild, and include flatulence, diarrhea/steatorrhea, nausea, gallstones, and glucose intolerance.^{49,58,62,64,167–169} In long-term treatment of patients with acromegaly with somatostatin analogs, only 5% developed ad-

verse effects severe enough to require stopping the drug.^{62,168,169} In these patients, 29% developed gallstones with long-term treatment; however, in only 1% did symptoms develop.¹⁶⁸ In occasional patients, if somatostatin therapy is not adequate, then stating α -interferon or the addition of α -interferon to somatostatin analogs may help control symptoms.⁶⁴

Management of Advanced PNETs

General

Pancreatic NETs demonstrate highly variable growth patterns, with most insulinomas being benign (>85%), whereas in most series, greater than 50% of the other symptomatic PNETs and the NF-PNETs demonstrate liver metastases.^{62,64} Furthermore, even within these groups, there is marked variability in tumor growth, with a prospective study demonstrating that up to 60% of metastatic gastrinomas to the liver demonstrated no growth or slow growth over a 2-year period, whereas the other 40% demonstrated rapid growth, with all the deaths occurring in the latter group.¹⁷⁰ Five-year survival rates of 90% to 100% are seen with patients with PNETs resected, or PNETs were so small they are not seen on imaging; incomplete resections have rates of 20% to 75%, and patients with diffuse liver disease have 5-year survival rates of 10% to 50%.^{35,62,65,80,171,172} Therefore, in a number of these patients, treatment for advanced metastatic disease is needed.

Hepatic Resection (Cytoreductive Surgery) and Transplantation for Metastatic Disease

Unfortunately, similar to described above for malignant NETs of the stomach, surgical resection of at least 90% of all visible tumor is possible in only 5% to 15% of patients with PNETs with hepatic metastases.^{35,37,62,173–175} The role of cytoreductive surgery in this situation is controversial.^{37,62,173–175} Whereas numerous uncontrolled studies provide evidence that surgical resection may improve symptom control and perhaps extend survival, neither result is proven at present.^{35,37,62,173–175} Nevertheless, because of the low efficacies of other tumor treatments, most conclude that surgical resection should be attempted in any patient with a malignant PNET if it is thought that at least 90% of the visible tumor could be removed.^{35,37,62,173–175} The number of patients with liver-isolated metastatic NETs in whom OLT has been attempted remains small, and the role of OLT in such patients is unclear.^{35,62} The role of liver transplantation in selected patients with advanced PNETs was discussed in more detail in the previous sections dealing with NETs of the stomach. As pointed out in this section, in a recent review of 85 cases of carcinoids and PNETs treated by liver transplantation, the overall 5-year survival was 45%, and poor prognostic factors were prior extensive upper abdominal surgery, presence of a PNET rather than a carcinoid tumor, and hepatomegaly.³⁹ Without any of these risk factors, the 5-year survival was 66%.³⁹ It has been proposed for the occasional, younger patient with a metastatic PNET that is unresectable and limited to the liver, especially if it is symptomatic and cannot be controlled by other available therapies, that liver transplantation remains an option that should be considered.^{35,38–40}

Hepatic Artery Embolization/Chemoembolization

As discussed above with NETs of the stomach, hepatic arterial embolization is recommended as a palliative option in patients with PNETs with hepatic metastases who are not candidates for surgical resection, have an otherwise preserved performance status, have disease primarily confined to the liver, and have a patent portal vein.^{35,41,42} Similar to gastric and other

carcinoid tumors, the response rates associated with embolization, as measured either by decrease in hormonal secretion or by radiographic regression, are generally greater than 50%.^{35,41–43} Improved techniques have, in recent years, reduced the incidence complications related to embolization, making embolization an important and generally safe treatment.^{35,41,42,176} A number of techniques may be used and include bland embolization, chemoembolization, embolization with chemotherapy beads, and embolization using radioisotopes. There are currently no data confirming superiority of any of these techniques compared with the others. This technique is considered especially for a patient with a functional PNET in which the hormone excess state cannot be controlled by other methods.^{41–43,62}

RFA and Cryoablation

Similar to those described in the previous sections for advanced carcinoid tumors, other approaches to the treatment of hepatic metastases in a patient with a malignant PNET include the use of RFA and cryoablation, either alone or in conjunction with cytoreductive surgery.^{35,42} These approaches can be performed using a percutaneous or laparoscopic approach. Although they seem to be less morbid than either hepatic resection or hepatic artery embolization, the clinical benefit of these approaches in patients with asymptomatic, small-volume disease has not been clearly established. Similarly, these approaches may not be applicable in patients with large-volume hepatic metastatic disease. Ablative techniques should therefore be considered as a treatment option only in carefully selected patients with advanced PNETs.^{35,42,44,45}

Peptide Receptor Radionuclide Therapy

The overexpression of somatostatin receptors by almost all PNETs is increasingly being investigated to target possible radiolabeled cytotoxic agents to the malignant PNET.^{60,61,177} One recent study⁶¹ reported results with 129 patients with malignant NETs treated with [¹⁷⁷Lu-DOTA-Tyr³]octreotate and found a complete response in 2%, partial in 32%, and stabilization in 34%. At present, no controlled studies have demonstrated this form of treatment prolongs survival, and this treatment is still investigational in the United States; however, this form of treatment is undergoing widespread evaluation because of its promising results.⁶²

Traditional Chemotherapeutic Agents

In contrast to carcinoid tumors, a number of chemotherapeutic agents either alone or in combination have been reported to have sufficient antitumor activity to be clinically useful in patients with advanced PNETs.^{35,41,51,52,75,178} The traditional chemotherapeutic agents with most effect in well-differentiated malignant PNETs are the combination of streptozocin/doxorubicin, streptozocin/fluorouracil, or streptozocin/doxorubicin/fluorouracil.^{5,17,179} A large retrospective analysis of 84 patients with either locally advanced or metastatic PNETs receiving a 3-drug regimen of streptozocin, 5-fluorouracil, and doxorubicin showed that this regimen was associated with an overall response rate of 39% and a median survival duration of 37 months.⁵¹ In patients with poorly differentiated PNETs, chemotherapy is recommended with the combination of cisplatin and etoposide or its analogs, because it has been shown to have a 40% to 70% response rate; however, the duration of the responses is short.^{35,41,51,52,180,181}

Biotherapy

Even though widely used in advanced PNETs for their possible effect on tumor growth, the clinical benefit of the direct

antineoplastic effects of somatostatin analogs either with or without interferon remains uncertain, although recent studies suggest they have a cytostatic effect in 40% to 70% of patients and cause a tumor reduction of less than 15% of cases with both agents.^{48,56,62} The tumoristatic effect can be long lasting in some patients with advanced PNETs, and it is seen more frequently in PNETs with a lower proliferative rate.^{48,64,182–184} Even though no study has shown that this results in prolonged survival in these patients, SS analogs are still frequently used first because they are well tolerated and because of their tumoristatic effect.⁶² A recent prospective study (PROMID study) demonstrates the use of octreotide LAR resulted in an increased time to progression in patients with metastatic midgut carcinoid tumors involving less than 10% of the liver.⁵⁰ However, it is unclear whether similar effects occur with patients with more extensive metastases or with malignant PNETs as well.

Newer Agents With Possible Use for Advanced PNETs

Recently, a number of newer chemotherapeutic agents with some efficacy in malignant PNETs have been described. The overall response rate associated with temozolomide-based therapy has been reported to be 34%, a rate similar to that of streptozocin-based therapy.¹⁸⁵ Temozolomide-based regimens represent an acceptable alternative to streptozocin-based therapy in patients with advanced PNETs. Temozolomide has been commonly administered as a single agent or in combination with capecitabine. There are currently no data comparing the efficacy of temozolomide monotherapy to combination therapy, and either regimen is considered acceptable.⁵⁴

Investigational approaches are appropriate for minimally symptomatic patients before streptozocin- or temozolomide-based therapy or for patients who fail streptozocin- or temozolomide-based therapy for advanced PNETs. Recent studies using vascular endothelial growth factor pathway inhibitors such as bevacizumab, sunitinib, and sorafenib have suggested that these agents may have modest antitumor activity in patients with malignant PNETs.^{55–57,186–188} In a randomized placebo-controlled trial, treatment with sunitinib was shown to result in significantly longer time to tumor progression and improved survival when compared with placebo.¹⁸⁹ The mTOR inhibitor everolimus has shown activity in early studies.¹⁸⁸

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