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# Neuroendocrine Tumors, Version 1.2015

## Clinical Practice Guidelines in Oncology

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## Overview

Neuroendocrine tumors (NETs) are thought to arise from cells throughout the diffuse endocrine system. They comprise a broad family of tumors, the most common of which are carcinoid tumors (most commonly arising in the lungs and bronchi [so-called bronchopulmonary], small intestine, appendix, rectum, and thymus) and pancreatic NETs. Other less common NETs include those arising in the parathyroid, thyroid, adrenal, and pituitary glands.

**Abstract**

Neuroendocrine tumors (NETs) comprise a broad family of tumors that may or may not be associated with symptoms attributable to hormonal hypersecretion. The NCCN Clinical Practice Guidelines in Oncology for Neuroendocrine Tumors discuss the diagnosis and management of both sporadic and hereditary NETs. This selection from the guidelines focuses on sporadic NETs of the pancreas, gastrointestinal tract, lung, and thymus. (J Natl Compr Canc Netw 2015;13:80–110)

### NCCN Categories of Evidence and Consensus

**Category 1:** Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2A:** Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

**Category 2B:** Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

**Category 3:** Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

**All recommendations are category 2A unless otherwise noted.**

**Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.**

### Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Neuroendocrine Tumors are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**



### Disclosures for the NCCN Neuroendocrine Tumors Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Neuroendocrine Tumors Panel members can be found on page 108. (The most recent version of these guidelines and accompanying disclosures are available at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

An analysis of the SEER database estimated that the incidence of NETs in the United States was 5.25 cases per 100,000 people in 2004.[1] This analysis suggested that the incidence of NETs is increasing and that the prevalence of individuals with NETs in the United States may exceed 100,000.[1] A recent independent analysis of the SEER database also found that the incidence of gastrointestinal NETs increased from 1975 to 2008.[2] The reasons for this increase are unclear, although it seems likely that improved diagnosis and classification is a factor.

Most NETs seem to be sporadic, and risk factors for sporadic NETs are poorly understood. NETs may also arise in the context of inherited genetic syndromes, including multiple endocrine neoplasia (MEN) types 1 and 2. MEN1, associated with mutations in the menin gene, is characterized by multiple tumors of the parathyroid, pituitary, and pancreatic glands.[3] MEN2, associated with mutations in the *RET* proto-oncogene, is characterized by the development of medullary thyroid cancer, pheochromocytoma (often bilateral), and hyperparathyroidism.[4] NETs have also been associated with von Hippel-Lindau disease, tuberous sclerosis complex, and neurofibromatosis.[5,6]

Patients with NETs may or may not have symptoms attributable to hormonal hypersecretion. These symptoms include intermittent flushing and diarrhea in patients with carcinoid syndrome,[7] hypertension in patients with pheochromocytoma,[8] and symptoms attributable to secretion of insulin, glucagon, gastrin, and other peptides in patients with pancreatic NETs.[9]

Text cont. on page 93.

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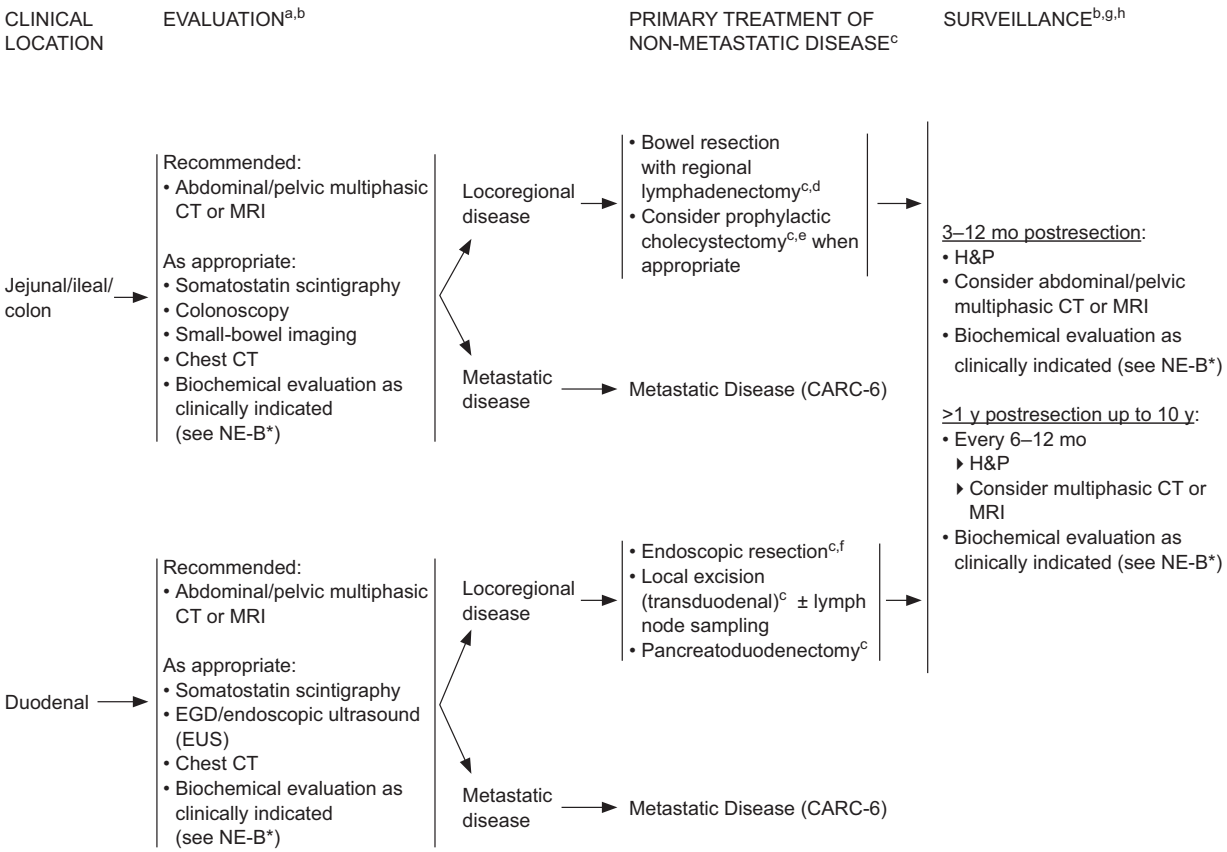
## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)




*Available online, in these guidelines, at NCCN.org.

[a]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).

[b]See Principles of Biochemical Testing (NE-B*).

[c]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

[d]Should include:
- Careful examination of the entire bowel, as multiple synchronous lesions may be present.
- Assessment of the proximity to or involvement of the superior mesenteric artery and superior mesenteric vein.

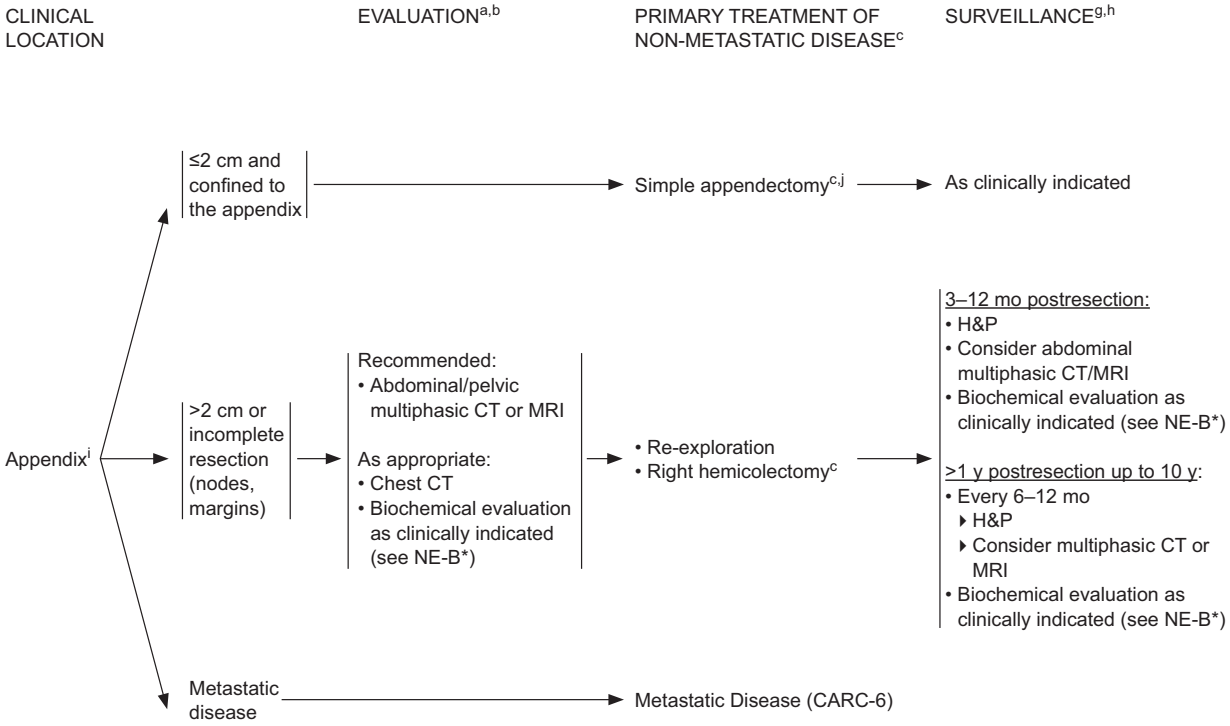
[e]If possible future need for octreotide.

[f]If endoscopic resection performed, follow-up EGD as appropriate.

[g]Earlier, if symptoms.

[h]Somatostatin scintigraphy and FDG-PET scan are not recommended for routine surveillance.

## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

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[a]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).

[b]See Principles of Biochemical Testing (NE-B*).

[c]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

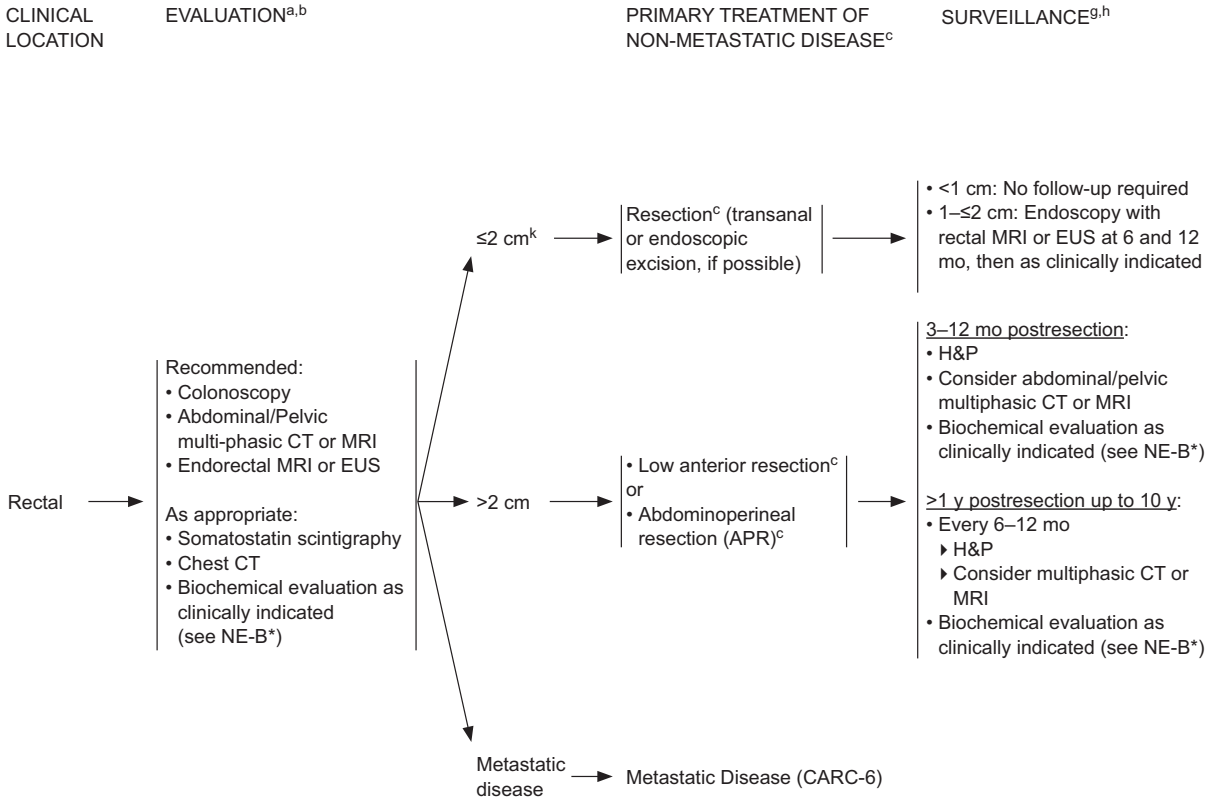
[g]Earlier, if symptoms.

[h]Somatostatin scintigraphy and FDG-PET scan are not recommended for routine surveillance.

[i]Some appendiceal carcinoids will have mixed histology, including elements of adenocarcinoma. Such tumors should be managed according to colon cancer guidelines. See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colon Cancer; to view the most recent version of these guiedlines, visit NCCN.org.

[j]Some institutions will consider more aggressive treatments for 1- to 2-cm tumors with poor prognostic features. See Discussion for details.

## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

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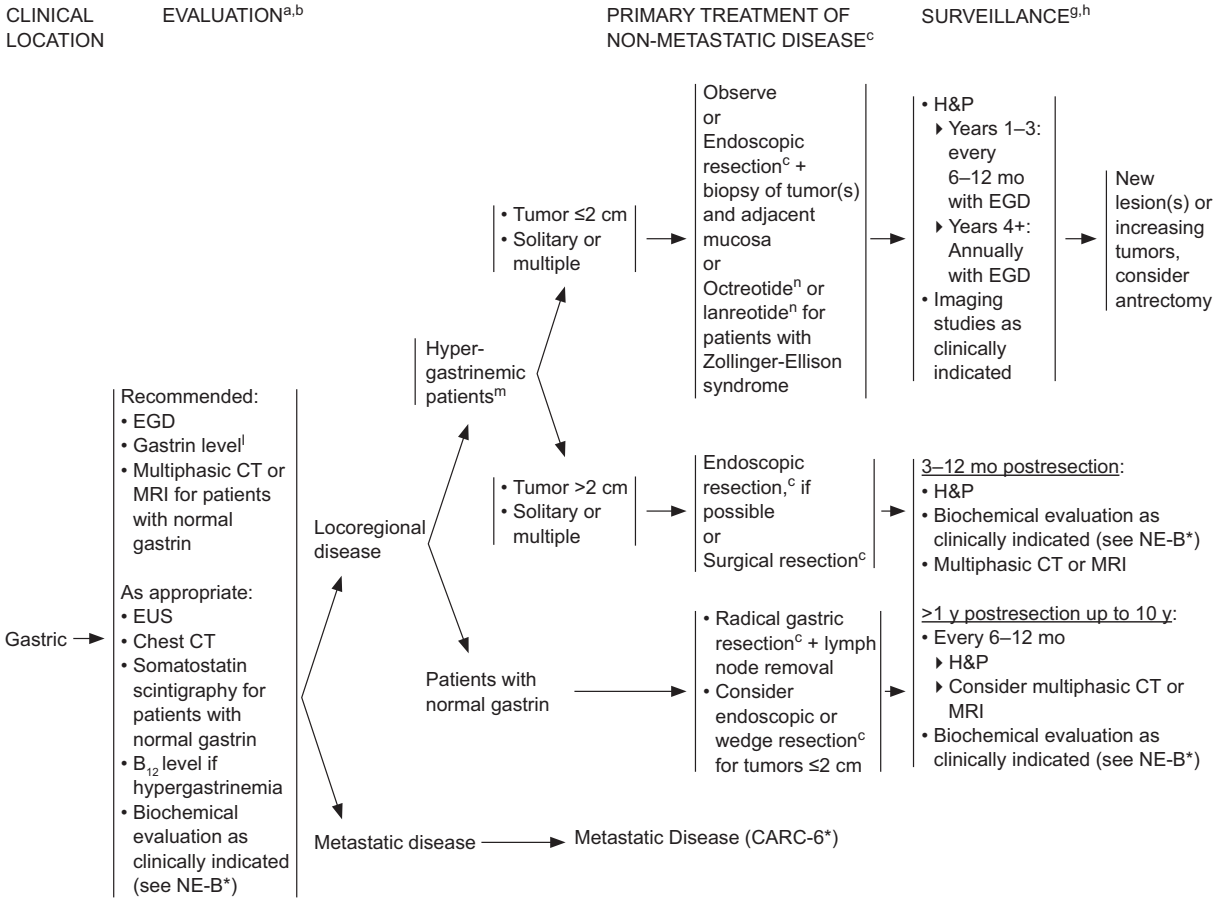
[a]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).
[b]See Principles of Biochemical Testing (NE-B*).
[c]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).
[g]Earlier, if symptoms.
[h]Somatostatin scintigraphy and FDG-PET scan are not recommended for routine surveillance.
[k]For 1- to 2-cm tumors, consider examination under anesthesia (EUA) and/or EUS with radical resection if muscularis propria invasion or node positive.

## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)




*Available online, in these guidelines, at NCCN.org.

[a]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).

[b]See Principles of Biochemical Testing (NE-B*).

[c]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

[g]Earlier, if symptoms.

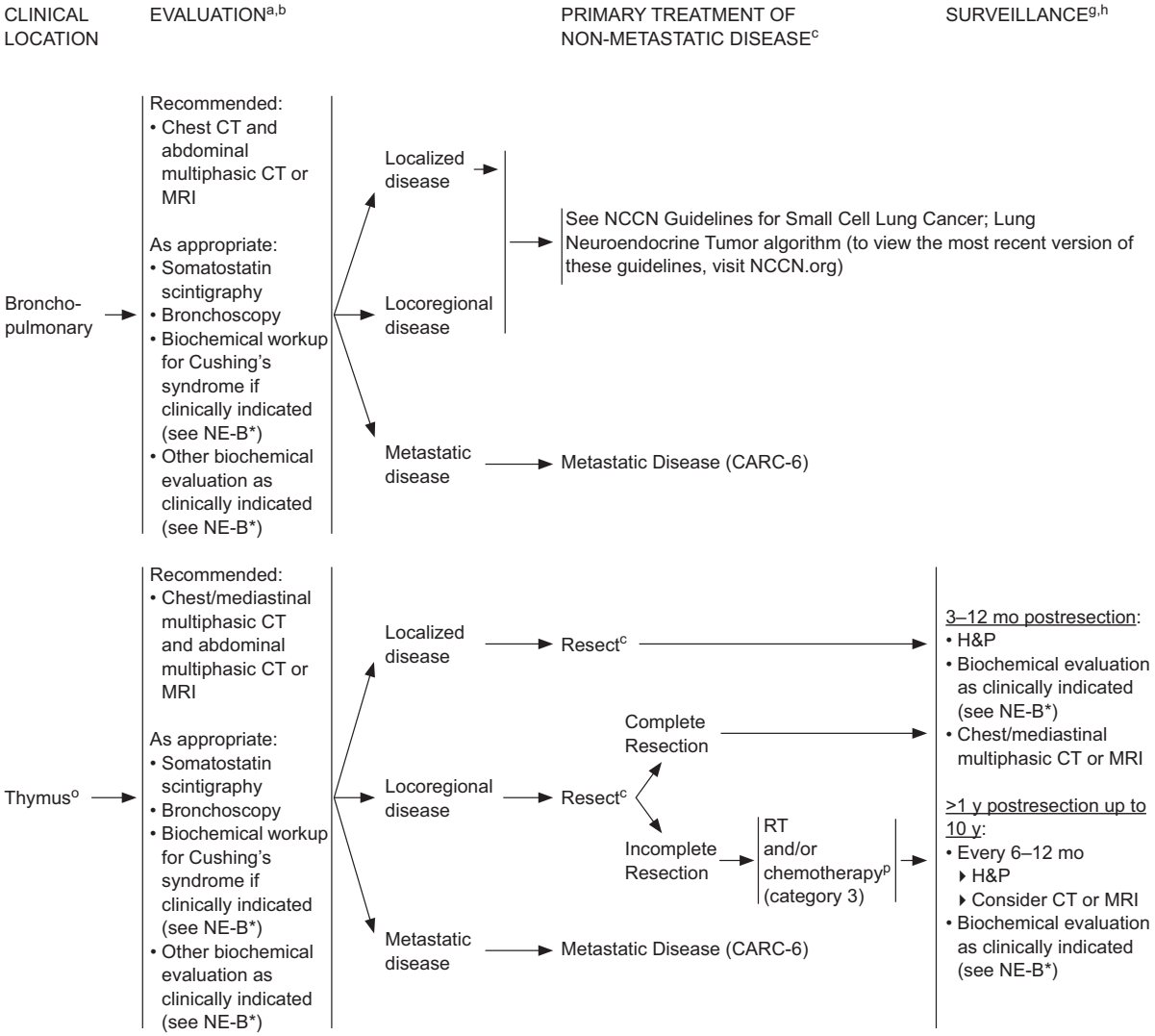
[h]Somatostatin scintigraphy and FDG-PET scan are not recommended for routine surveillance.

[l]Gastrin levels need to be completed while fasting and off protein pump inhibitors for 1 week.

[m]If gastric pH is low or there is clinical or radiographic evidence, see gastrinoma on PanNET-2.

[n]See Principles of Systemic Anti-Tumor Therapy (NE-D*).

## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)




*Available online, in these guidelines, at NCCN.org.

[a]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).

[b]See Principles of Biochemical Testing (NE-B*).

[c]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

[g]Earlier, if symptoms.

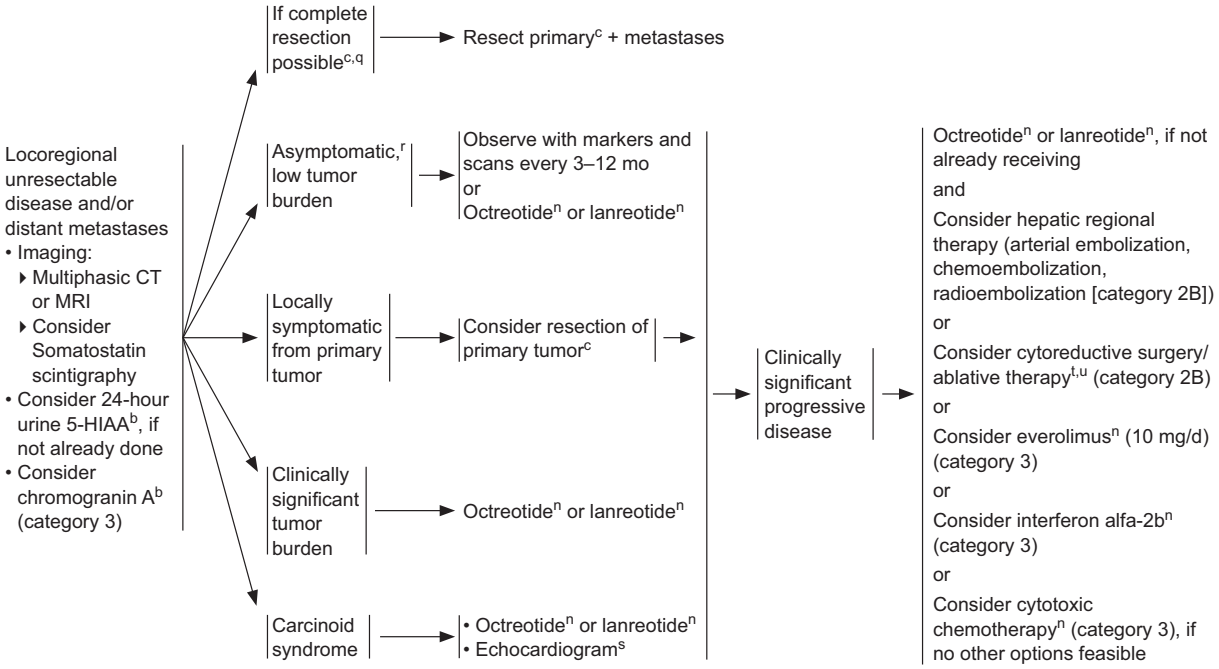
[h]Somatostatin scintigraphy and FDG-PET scan are not recommended for routine surveillance.

[o]Thymic carcinoids are often associated with MEN1. See Multiple Endocrine Neoplasia, Type 1 (MEN1-1*).

[p]Consider 5-FU or capecitabine at radiosensitizing doses. Cisplatin or carboplatin with etoposide may be appropriate for patients with atypical or poorly differentiated tumors.

## Neuroendocrine Tumors of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[c]




*Available online, in these guidelines, at NCCN.org.

[b]See Principles of Biochemical Testing (NE-B*).

[c]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

[n]See Principles of Systemic Anti-Tumor Therapy (NE-D*).

[q]Noncurative debulking surgery might be considered in select cases.

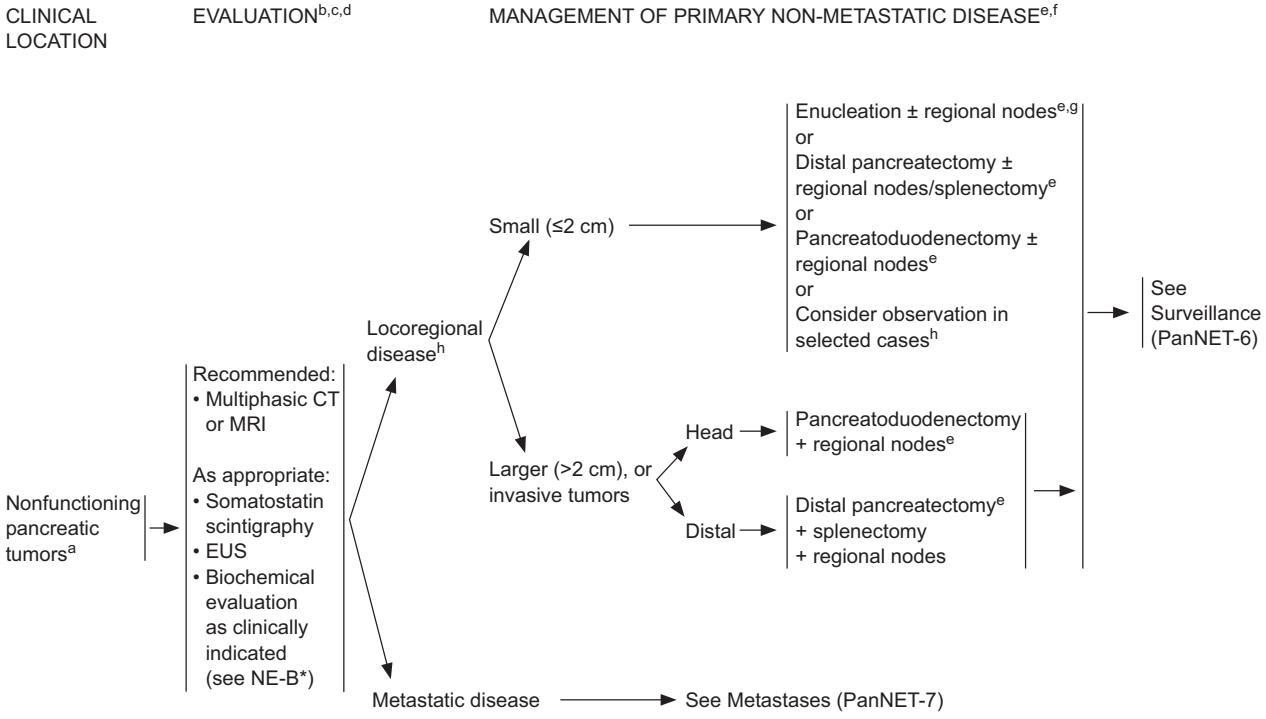
[r]Resection of a small asymptomatic (relatively stable) primary in the presence of unresectable metastatic disease is not indicated.

[s]If signs and symptoms of heart disease or planning major surgery.

[t]Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited. However, data on the use of these interventions are emerging.

[u]Only if near complete resection can be achieved.

## Neuroendocrine Tumors of the Pancreas




*Available online, in these guidelines, at NCCN.org.

[a]For tumors secreting hormones such as somatostatin, ACTH, PTHrP, and PP, follow the nonfunctioning pancreatic tumor pathway.

[b]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).

[c]See Principles of Biochemical Testing (NE-B*).

[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1*).

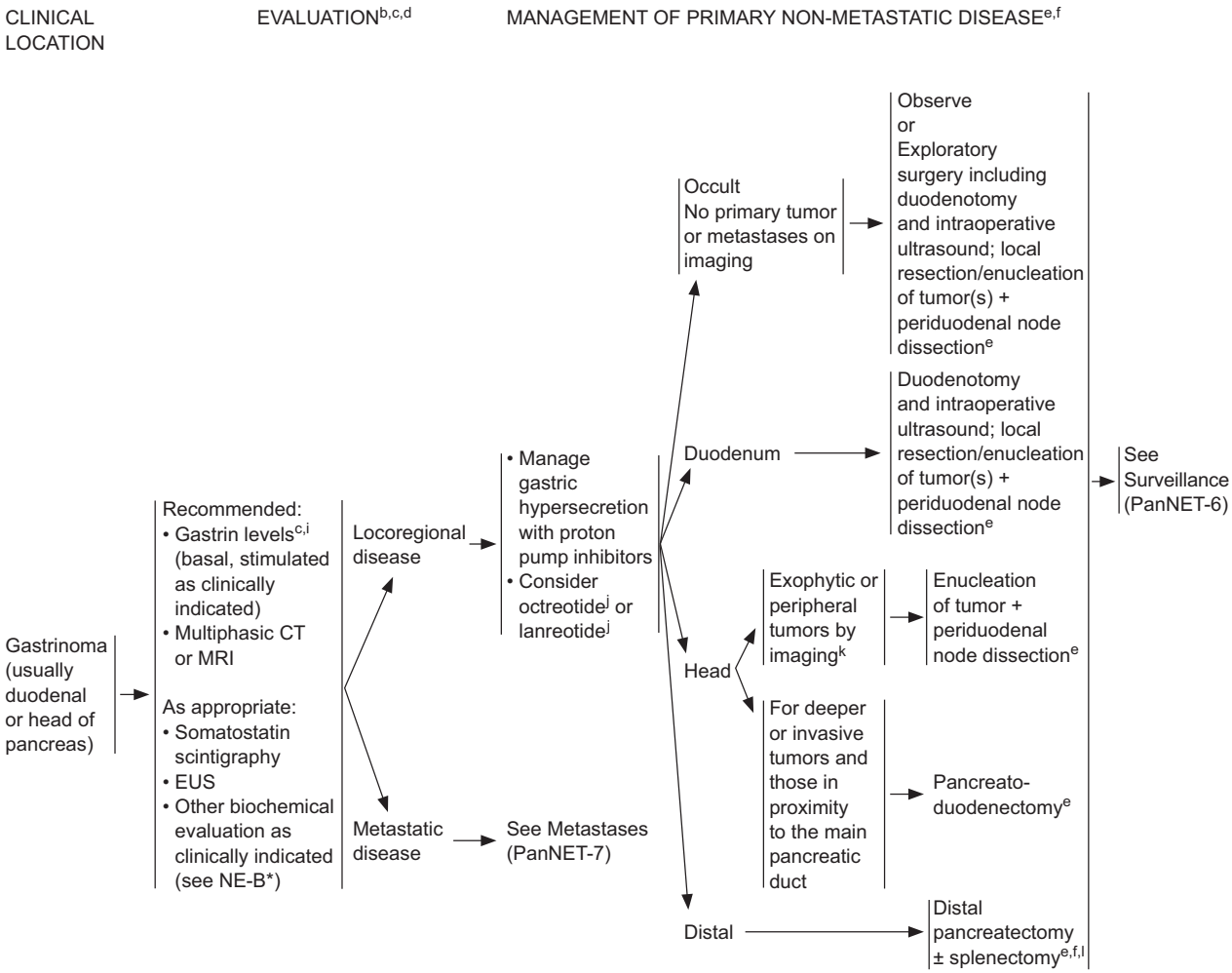
[e]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

[f]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.

[g]Neuroendocrine tumors of the pancreas that are 1–2 cm have a small, but real risk of lymph node metastases. Therefore, lymph node resection should be considered.

[h]Observation can be considered in select cases: tumors <1 cm, incidently discovered. Decision based on estimated surgical risk, site of tumor, and patient comorbidities.

## Neuroendocrine Tumors of the Pancreas

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[c]See Principles of Biochemical Testing (NE-B*).

[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1*).

[e]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

[f]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.

[i]Gastrin levels need to be completed while fasting and off proton pump inhibitors for 1 week.

[j]See Principles of Systemic Anti-Tumor Therapy (NE-D*).

[k]Not adjacent to the main pancreatic duct.

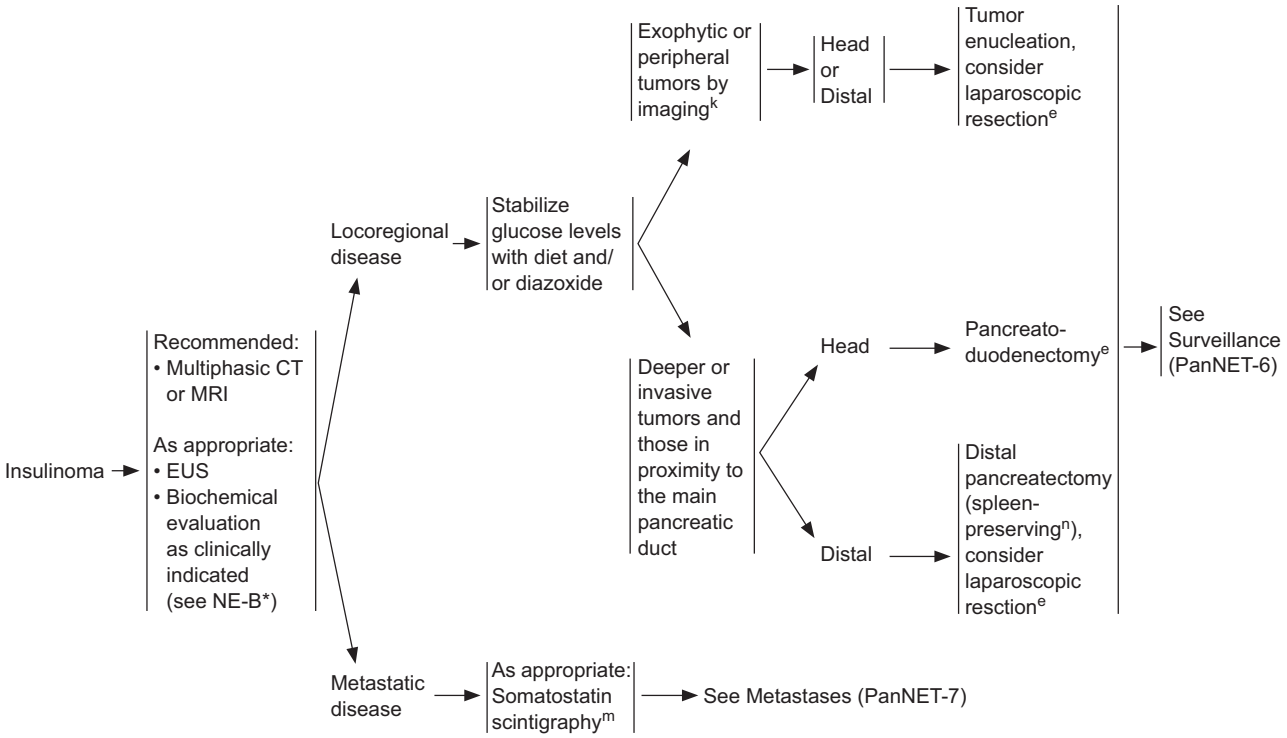
[l]There is some disagreement among panel members regarding the role of splenectomy in all cases.

## Neuroendocrine Tumors of the Pancreas

CLINICAL LOCATION

EVALUATION[b,c,d]

MANAGEMENT OF PRIMARY NON-METASTATIC DISEASE[e,f]




*Available online, in these guidelines, at NCCN.org.

[b]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).

[c]See Principles of Biochemical Testing (NE-B*).

[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1*).

[e]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

[f]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.

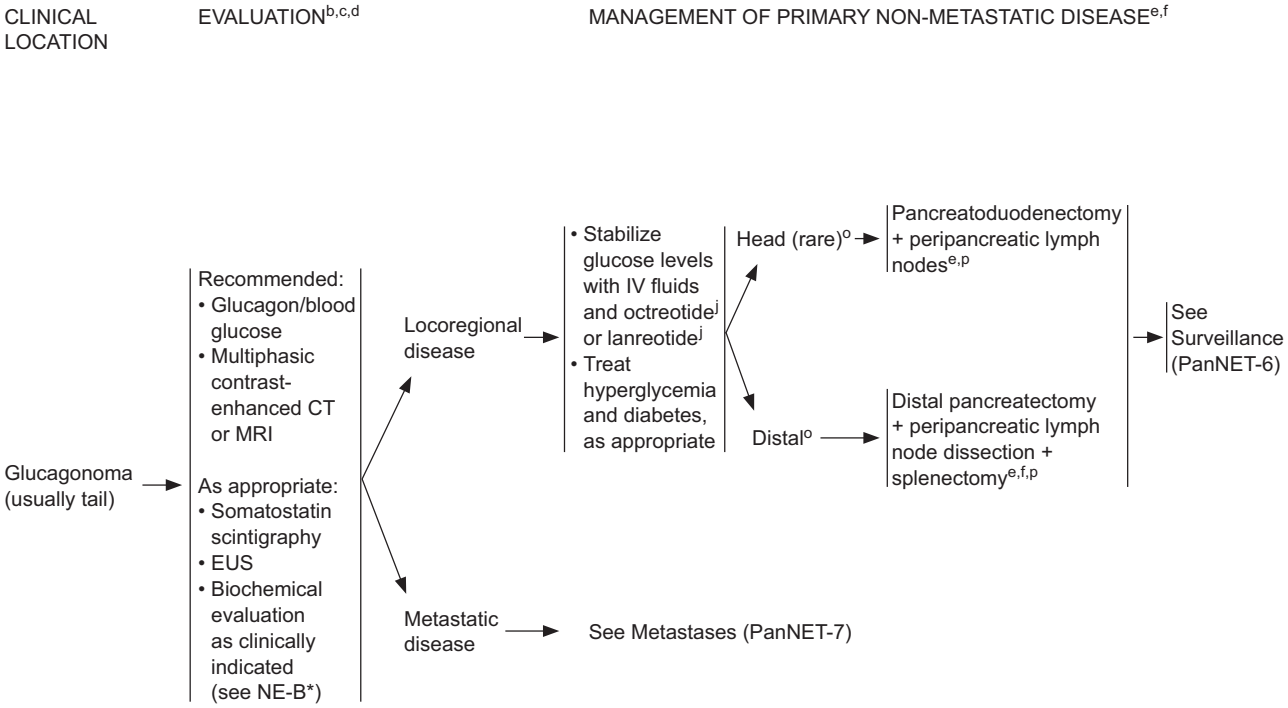
[k]Not adjacent to the main pancreatic duct.

[m]Somatostatin scintigraphy only if treatment with a somatostatin analog is planned. Somatostatin analogs should only be given if tumor demonstrates somatostatin receptors. In the absence of somatostatin receptors, somatostatin analogs can profoundly worsen hypoglycemia. (See Discussion for details).

[n]Splenectomy should be performed for larger tumors involving splenic vessels.

PanNET-3

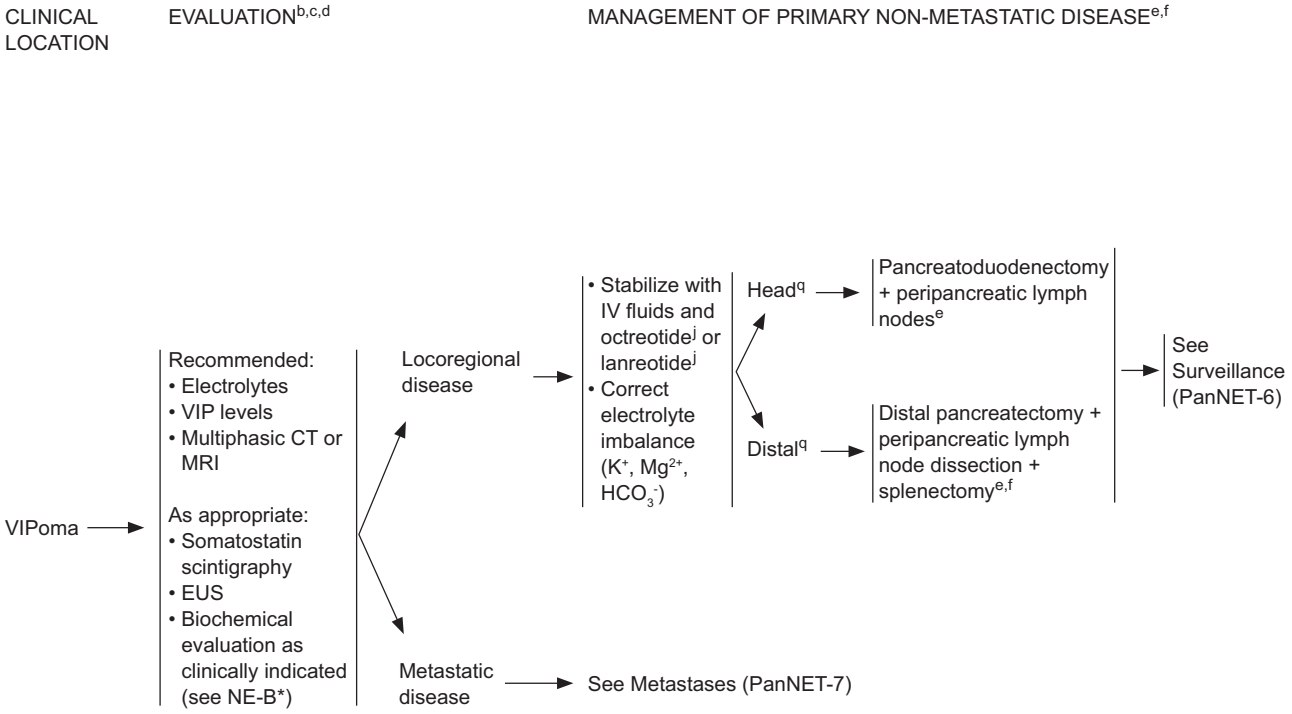
## Neuroendocrine Tumors of the Pancreas




*Available online, in these guidelines, at NCCN.org.

[b]See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).
[c]See Principles of Biochemical Testing (NE-B*).
[d]For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1*).
[e]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).
[f]Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
[j]See Principles of Systemic Anti-Tumor Therapy (NE-D*).
[o]Small (<2 cm), peripheral glucagonomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.
[p]Hypercoaguable state has been described. Perioperative anticoagulation can be considered.

## Neuroendocrine Tumors of the Pancreas

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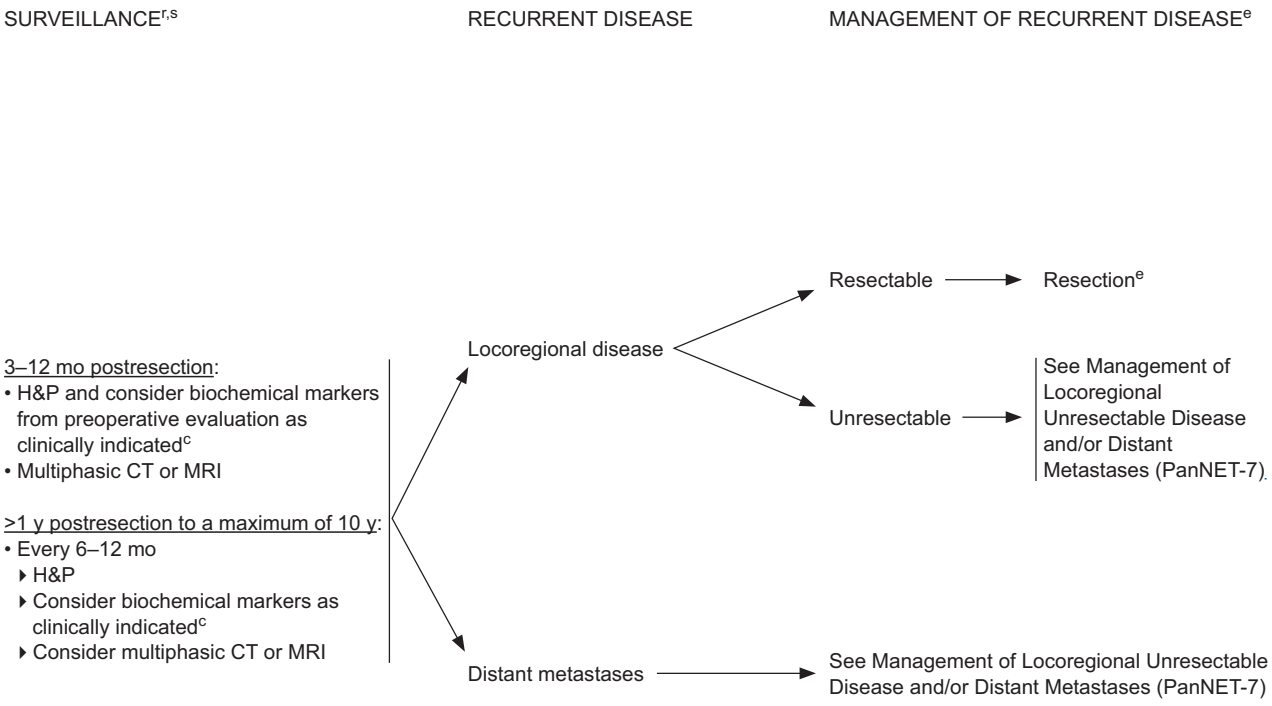
[b] See Principles of Pathology for Diagnosis and Reporting of Neuroendocrine Tumors (NE-A*).
[c] See Principles of Biochemical Testing (NE-B*).
[d] For all patients with PanNET, evaluate personal and family history for possibility of MEN1 and see Multiple Endocrine Neoplasia, Type 1 (MEN1-1*).
[e] See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).
[f] Preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcal group C), if considering surgery with possible splenectomy.
[j] See Principles of Systemic Anti-Tumor Therapy (NE-D*).
[q] Small (<2 cm), peripheral VIPomas are rare; enucleation/local excision + peripancreatic lymph dissection may be considered.

## Neuroendocrine Tumors of the Pancreas



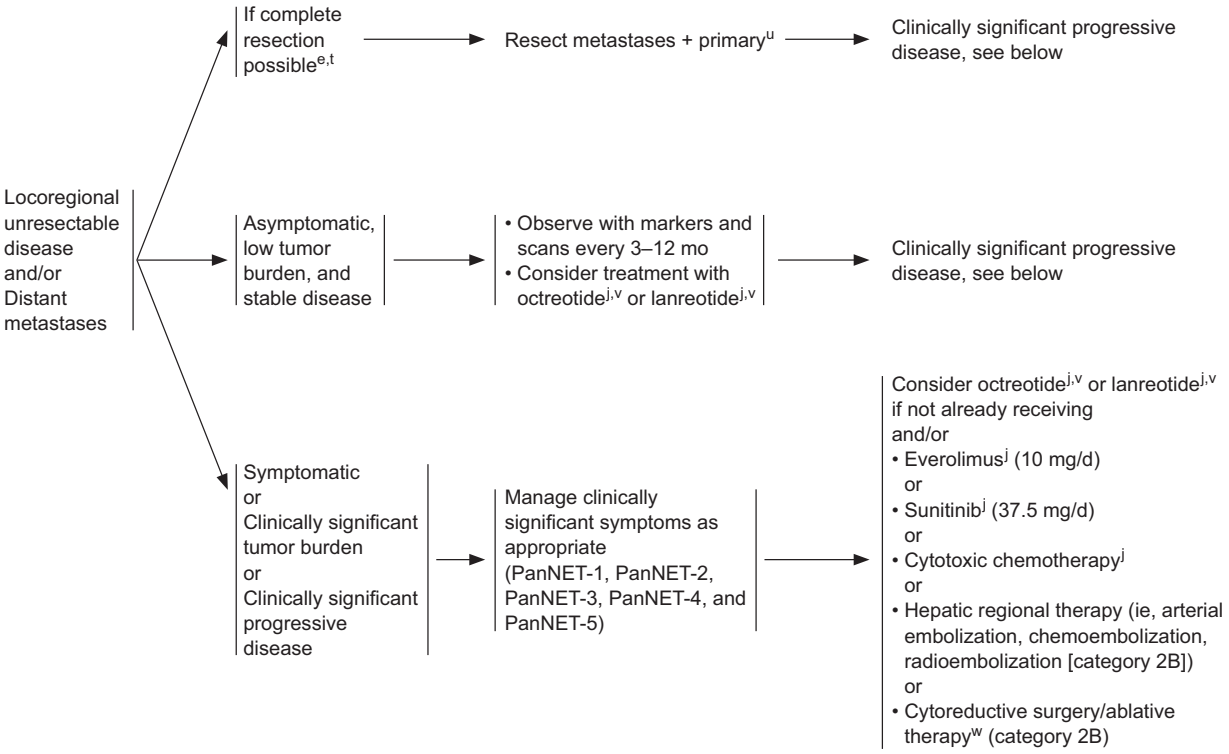

*Available online, in these guidelines, at NCCN.org.

[c]See Principles of Biochemical Testing (NE-B*).
[e]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).
[r]Earlier, if symptoms.
[s]Somatostatin scintigraphy and FDG-PET scan are not recommended for routine surveillance.

PanNET-6

## Neuroendocrine Tumors of the Pancreas

MANAGEMENT OF LOCOREGIONAL UNRESECTABLE DISEASE AND/OR DISTANT METASTASES[e]




*Available online, in these guidelines, at NCCN.org.

[e]See Surgical Principles for Management of Neuroendocrine Tumors (NE-C*).

[j]See Principles of Systemic Anti-Tumor Therapy (NE-D*).

[t]Noncurative debulking surgery might be considered in select cases.

[u]Staged or synchronous resection when possible. When performing staged pancreatoduodenectomy and liver resection, consider hepatectomy prior to pancreatic resection in order to reduce risk of perihepatic sepsis. De Jong MC, Farnell MB, Sclabas G, et al. Liver-directed therapy for hepatic metastases in patients undergoing pancreaticoduodenectomy: A dual-center analysis. Ann Surg 2010;252:142-148.

[v]Somatostatin analogs should be used with caution in patients with insulinoma as they may transiently worsen hypoglycemia. (See Discussion for details).

[w]Includes ablative techniques such as radiofrequency, microwave, and cryotherapy. There are no randomized clinical trials and prospective data for these interventions are limited, but data on their use are emerging.

PanNET-7

Text cont. from page 79.

Patients with hormonal symptoms are considered to have "functional" tumors, and those without symptoms are considered to have "nonfunctional" tumors.

Appropriate diagnosis and treatment of NETs often involves collaboration between specialists in multiple disciplines, using specific biochemical, radiologic, and surgical methods. Specialists include pathologists, endocrinologists, radiologists (including nuclear medicine specialists), and medical, radiation, and surgical oncologists.

The full version of these guidelines discuss the diagnosis and management of both sporadic and hereditary NETs and are intended to assist with clinical decision-making. Most of the guideline sections pertain to well-differentiated, low- to intermediate-grade tumors, although poorly differentiated/high-grade/large or small cell carcinomas are also addressed (see "Poorly Differentiated Neuroendocrine Tumors/Large or Small Cell Tumors" in the complete version of these guidelines, at NCCN.org). Medical practitioners should note that unusual patient scenarios (presenting in <5% of patients) are not specifically discussed in these guidelines. This selection from the guidelines focuses on sporadic NETs of the pancreas, gastrointestinal tract, lung, and thymus.

## NETs of the Gastrointestinal Tract, Lung, and Thymus (Carcinoid Tumors)

Approximately one-third of carcinoid tumors arise in the lungs or thymus, and two-thirds arise in the gastrointestinal tract. Sites of origin within the gastrointestinal tract include the stomach, small intestine, appendix, and rectum.[1] The prognosis for patients with carcinoid tumors varies according to stage at diagnosis, histologic classification, and primary tumor site (see "Histologic Classification and Staging of Neuroendocrine Tumors" in the complete version of these guidelines, at NCCN.org).

NETs of the gastrointestinal tract and lungs may secrete various hormones and vasoactive peptides. Bronchial and thymic NETs have been associated with adrenocorticotropic hormone (ACTH) production and are a cause of Cushing's syndrome.[10,11] NETs arising in the small intestine or appendix are more commonly associated with carcinoid syndrome, related to the secretion of serotonin, histamine, or tachykinins into the systemic circulation causing episodic flushing and diarrhea.[12] Approximately 50% to 66% of patients with carcinoid syndrome develop valvular cardiac complications consisting of tricuspid regurgitation and/or pulmonary stenosis.[13]

The metabolic products released by intestinal NETs are rapidly destroyed by liver enzymes in the portal circulation. Thus, the classic syndrome, occurring in approximately 8% to 28% of patients with NETs,[14,15] is not usually observed unless liver metastases or, rarely, retroperitoneal disease have occurred, in which case hepatic metastases release metabolic products directly into the systemic circulation via the hepatic veins.

These guidelines address 7 major subtypes of carcinoid tumors: (1) jejunal/ileal/colon, (2) duodenal, (3) appendix, (4) rectal, (5) gastric, (6) bronchopulmonary, and (7) thymus.

### Evaluation of NETs of the Gastrointestinal Tract, Lung, and Thymus

Patients who present with suspected carcinoid tumors should be evaluated with imaging studies to assess disease burden and possible primary location. Commonly used techniques include CT and MRI. NETs of the gastrointestinal tract and lungs are highly vascular and can appear isodense with liver on conventional CT scan, depending on contrast phase. Multiphase CT or MRI scans should therefore be used for evaluation of liver metastasis. Chest CT is also recommended as appropriate to assess for lung metastases. Because most NETs express high-affinity receptors for somatostatin,[12,16] radiolabeled somatostatin receptor scintigraphy, performed using the radiolabeled somatostatin analogue [$^{111}$In-DTPA]-octreotide may also be used in the initial evaluation of patients with NETs. Additional recommendations vary by disease site and include colonoscopy and small bowel imaging as appropriate for jejunal, ileal, and colonic NETs; endoscopic ultrasound (EUS) and/or esophagogastroduodenoscopy (EGD) as appropriate for duodenal and gastric NETs; proctoscopic examination for rectal NETs; and bronchoscopy as appropriate for bronchopulmonary and thymic NETs.

Biochemical evaluation can also be helpful in the initial diagnostic evaluation, particularly in patients with symptoms that are suggestive of hormone hypersecretion. Evaluation of serotonin secretion, using a 24-hour urine collection for 5-HIAA, is generally recommended in patients with metastatic lung or gastrointestinal carcinoid tumors, particularly if carcinoid

syndrome, manifested by symptoms of flushing and diarrhea, is suspected. A workup for Cushing's syndrome (discussed in "Evaluation and Treatment of Cushing's Syndrome" in the complete version of these guidelines, at NCCN.org) may also be indicated in cases of bronchopulmonary or thymic NETs if signs and symptoms of hypercortisolemia are suspected. Details of the evaluation and diagnosis of Cushing's syndrome from a bronchial NET were recently published.[17]

## Management of Locoregional Disease

The management of locoregional NETs of the gastrointestinal tract and lungs depends on tumor size and primary site and the general condition of the patient. Resection is the primary treatment approach for most localized carcinoid tumors. Although symptoms of hormone hypersecretion are more common in patients with metastatic disease, for patients with locoregional disease and symptoms of hormone hypersecretion, symptom control with a somatostatin analogue is paramount (see "Management of Locoregional Unresectable and/or Metastatic NETs of the Gastrointestinal Tract, Lung, and Thymus," page 96). Specific recommendations for the management of NET subtypes are described herein.

***Gastric NETs:*** Three types of gastric NETs are generally recognized: type 1 (associated with antrum sparing type A chronic atrophic gastritis), type 2 (associated with Zollinger-Ellison syndrome), and type 3 (sporadic).[18] Types 1 and 2 gastric NETs are both associated with hypergastrinemia; the major difference between them is that patients with type 1 gastric NETs generally have antrum-sparing atrophic gastritis with a loss of the usual negative feedback loop on the gastrin-producing cells of the antrum by acid, resulting in hypergastrinemia and excess stimulation of the endocrine cells of the fundus, and patients with type 2 gastric NETs have evidence of acid hypersecretion secondary to gastrinoma (Zollinger-Ellison syndrome).[18]

For hypergastrinemic patients whose tumors are 2 cm or smaller and either solitary or multiple, options include (1) endoscopic resection, if feasible, with biopsy of the tumor and adjacent mucosa; (2) observation; or (3) octreotide or lanreotide for symptom control in patients with gastrinoma and Zollinger-Ellison syndrome. For patients with hypergastrinemia with solitary or multiple tumors larger than 2 cm, endoscopic resection (if possible) or surgical resection is indicated. Patients with nonmetastatic gastric NETs and normal gastrin levels (type 3) have more aggressive tumors and are usually treated with radical resection of the tumor with regional lymphadenectomy. Alternatively, endoscopic or wedge resection can be considered for tumors 2 cm or less.[19]

***Thymic NETs:*** Localized and locoregional NETs in the thymus are treated with surgical resection, generally without adjuvant therapy. After incomplete resection of locoregional disease, however, radiation therapy (RT) and/or chemotherapy are recommended (category 3). If chemotherapy is offered, capecitabine or 5-FU at radiosensitizing doses may be considered. Cisplatin or carboplatin with etoposide may be appropriate for patients with atypical or poorly differentiated tumors.

***Bronchopulmonary NETs:*** For localized or locoregional bronchopulmonary tumors, please refer to the Lung Neuroendocrine Tumors algorithm in the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Small Cell Lung Cancer (to view the most recent version of these guidelines, visit NCCN.org).

***NETs of the Duodenum, Small Intestine, and Colon:*** For localized lesions arising in the duodenum, endoscopic resection is recommended if feasible. Transduodenal local excision with or without lymph node sampling and pancreatoduodenectomy are other options for primary treatment of nonmetastatic duodenal NETs. If endoscopic resection was performed, follow-up upper endoscopy (EGD) should be performed as appropriate.

For patients presenting with tumors in the jejunum, ileum, or colon, surgical resection of the bowel with regional lymphadenectomy is recommended. The surgical procedure should include careful examination of the entire bowel, because multiple synchronous lesions may be present. In addition, the proximity to or involvement of the superior mesenteric artery and superior mesenteric vein should be assessed during surgery. If future treatment with octreotide or lanreotide is anticipated, a prophylactic cholecystectomy should be considered given the association between long-term treatment with somatostatin analogues and the development of biliary symptoms and gallstones.[20]

***Appendiceal NETs:*** Most appendiceal NETs are identified incidentally during appendectomy per-

formed for appendicitis. Most appendiceal NETs have well-differentiated histology, and for most appendiceal tumors 2 cm or smaller and confined to the appendix, simple appendectomy is sufficient because metastases are uncommon.[21,22]

However, some controversy exists regarding the management of appendiceal NETs measuring less than 2 cm with more aggressive histologic features. A recent population-based study analyzing the SEER database found evidence that lymph node metastases can develop in some patients with appendiceal NETs 2 cm or smaller.[23] Some NCCN Member Institutions thus consider more aggressive treatment for 1- to 2-cm tumors with poor prognostic features, such as lymphovascular or mesoappendiceal invasion or atypical histologic features.

Patients with an incomplete resection or tumors larger than 2 cm are at risk for locoregional or distant metastases. These patients should be staged using abdominal/pelvic CT or MRI scans. If no distant disease is identified, they should undergo reexploration with a right hemicolectomy. Additionally, a small proportion of appendiceal NETs may also contain evidence of adenocarcinoma (ie, adenocarcinoid or goblet cell carcinoid). These tumors should be managed according to the NCCN Guidelines for Colon Cancer (to view the most recent version of these guidelines, visit NCCN.org).

***NETs of the Rectum:*** The treatment of rectal lesions is based on the size of the primary tumor. If the lesion is 2 cm or less, endoscopic or transanal excision is recommended. Given the higher risk of invasion with larger tumors, examination under anesthesia and/or EUS before the procedure should be considered for tumors 1 to 2 cm. A recent retrospective review found that metastases were present in 66% of 87 patients with well-differentiated rectal NETs 11 to 19 mm.[24]

Tumors larger than 2 cm, those with invasion of the muscularis propria, or those associated with lymph node metastases should be treated with low anterior resection or, in rare cases, an abdominoperineal resection.[25]

### Surveillance of Resected NETs of the Gastrointestinal Tract, Lung, and Thymus

Surveillance of bronchopulmonary and gastrointestinal NETs should include complete patient history and physical examination (H&P) and consideration of multiphasic CT or MRI (usually abdominal and/or pelvic). Most patients with NETs of the jejunum/ileum/colon, duodenum, rectum, and thymus, and type 3 gastric NETs with normal gastrin levels should be reevaluated 3 to 12 months after resection (earlier if the patient is symptomatic) and then every 6 to 12 months for up to 10 years.

Relevant biochemical evaluations can also be performed based on preresection findings. Chromogranin A may be used as a tumor marker (category 3); although not diagnostic, elevated levels have been associated with recurrence.[26] In addition, an analysis of a large prospective database showed that chromogranin A levels elevated twice the normal limit or higher were associated with shorter survival times for patients with metastatic NETs (hazard ratio [HR], 2.8; 95% CI, 1.9–4.0; $P<.001$).[27] Chromogranin A levels can be elevated in several concurrent medical conditions, including renal or hepatic insufficiency, and are also commonly elevated in the setting of concurrent proton pump inhibitors. Several panelists therefore caution that increasing chromogranin A levels in an asymptomatic patient with a tumor that looks stable on imaging does not necessarily indicate that a patient should be initiated on a new therapy.

5-Hydroxyindoleacetic acid (5-HIAA), a metabolite of serotonin, in a 24-hour urine sample may also be considered as a biochemical marker in some cases, particularly in patients with metastatic small-intestinal NETs. During monitoring of patients after treatment of a carcinoid tumor, decreasing levels of 5-HIAA indicate a response to treatment, whereas increasing or excessive concentration indicates that the treatment has not been successful. However, a patient with symptoms may still have a NET even if the concentration of 5-HIAA is normal. Diet and a variety of drugs can affect the 5-HIAA test. Therefore, patients should be advised not to eat avocados, bananas, cantaloupe, eggplant, pineapples, plums, tomatoes, hickory nuts/pecans, plantains, kiwi, dates, grapefruit, honeydew, or walnuts for 48 hours before the start of urine collection. Additionally, patients should avoid coffee, alcohol, and smoking for this period. Medications that can increase 5-HIAA include acetaminophen, ephedrine, diazepam, nicotine, glyceryl guaiacolate (an ingredient found in some cough medicines), and phenobarbital.

Somatostatin receptor scintigraphy is not routinely recommended for surveillance after definitive resection, but may be indicated to assess disease lo-

cation and disease burden for comparison in cases of subsequent possible recurrence.

In specific cases, follow-up recommendations for patients with resected gastrointestinal NETs differ from the above general recommendations. For rectal tumors smaller than 1 cm, prognosis is excellent and no follow-up is usually required. For rectal tumors that are between 1 and 2 cm, follow-up endoscopies with rectal MRI or EUS are recommended 6 and 12 months after primary therapy, and then as clinically indicated.

For appendiceal tumors 2 cm or smaller without aggressive features, follow-up examinations are performed as clinically indicated. Patients with small, well-differentiated appendiceal NETs are at very low risk for recurrence,[28–30] and some institutions recommend no follow-up in these patients. Other institutions recommend a follow-up examination 1 year after simple appendectomy and then with decreasing frequency. However, because recurrences have rarely been reported even after resection of small appendiceal tumors, any patients with symptoms of hormone hypersecretion should be more fully evaluated.

Follow-up recommendations also differ to some extent for patients with hypergastrinemia and type 1 or 2 gastric NETs. For these patients, follow-up endoscopies are recommended every 6 to 12 months for the first 3 years and annually thereafter if no evidence of progression is seen. Because gastrin levels remain persistently high in patients with atrophic gastritis, gastrin levels are generally uninformative in patients with type 1 gastric NETs. If clinically indicated, imaging studies should also be performed. Antrectomy to remove the source of gastrin production can be considered in patients with type 1 gastric NETs if new lesions or increasing tumor burden is observed.

## Management of Locoregional Unresectable and/or Metastatic NETs of the Gastrointestinal Tract, Lung, and Thymus

Baseline imaging recommendations for patients suspected to have distant metastatic disease include multiphase technique CT or MRI.[31,32] Baseline levels of chromogranin A (category 3) or 24-hour urine 5-HIAA may also be considered for monitoring subsequent progression (as discussed previously). Somatostatin scintography can also be considered both to assess sites of metastases and to assess somatostatin receptor status if treatment with octreotide or lanreotide is being considered. The most common sites of metastases from intestinal NETs include regional/mesenteric lymph nodes, liver, and bones.

***Resection of Metastatic Disease:*** In some cases, patients with limited hepatic metastases or other sites of disease can undergo complete resection of the primary tumor and metastases with curative intent. One study of 172 patients who underwent hepatic resection of metastatic NETs showed that long-term survival can be achieved in selected cases: the reported 10-year overall survival rate was 50.4%.[33] A recent meta-analysis reported 5-year overall survival rates ranging from 41% to 100% in patients undergoing hepatic resection.[34] Most patients with resected metastatic disease, however, will eventually experience recurrence.[35,36] Noncurative debulking surgery can also be considered in select cases, especially if the patient is symptomatic from either tumor bulk or hormone production.

Resection of the primary site in the setting of unresectable metastases is generally not indicated if the primary site remains asymptomatic and is relatively stable.[34] However, it is not uncommon for patients with small bowel primary tumors to experience symptoms of intermittent abdominal pain from episodic bowel obstruction or bowel ischemia related to the primary tumor and surrounding fibrosis. Palliative small bowel resection is recommended in these patients.

***Somatostatin Analogues for Control of Symptoms and Tumor Growth:*** Patients who have metastatic NETs and carcinoid syndrome should be treated using a somatostatin analogue (octreotide or lanreotide).[20] The long-acting release (LAR) formulation of octreotide is commonly used for the chronic management of symptoms in patients with carcinoid syndrome. Standard doses of octreotide LAR are 20 to 30 mg intramuscularly every 4 weeks. Dose and frequency may be further increased for symptom control as needed. Therapeutic levels are not achieved for 10 to 14 days after LAR injection. Short-acting octreotide (usually 150–250 mcg subcutaneously 3 times daily) can be added to octreotide LAR for rapid relief of symptoms or for breakthrough symptoms.[37–39]

Lanreotide has a similar mechanism of action as octreotide, but is administered as a deep subcutaneous injection. Studies have shown it to be effective at controlling symptoms in patients with carcinoid tumors, gastrinomas, or vasoactive intestinal peptide tumors (VIPomas).[40–43] The multinational phase III ELECT trial randomized 115 patients with carcinoid syndrome who were either naïve to or responsive to

octreotide to receive 120 mg of lanreotide or placebo.[44] Although the predefined difference in percentage of days the patient used rescue octreotide was not met, the panel believes that the difference seen (34% in the lanreotide arm vs 49% in the placebo arm; *P*=.02) was significant enough to warrant use of lanreotide for symptom control.

A cardiology consultation and echocardiogram to assess whether the patient has carcinoid heart disease should also be considered in patients with carcinoid syndrome and signs and symptoms of heart disease or with planned major surgery.[20] Cardiac heart disease is frequent in patients with carcinoid syndrome; in one study, 59% of patients with carcinoid syndrome were diagnosed with tricuspid regurgitation.[45,46] A recent study involving 250 patients with carcinoid syndrome showed that those with 5-HIAA levels of 300 mcmol or greater (57 mg) over 24 hours and with 3 or more flushing episodes per day were more likely to have carcinoid heart disease.[47]

In patients who have clinically significant tumor burden or progressive disease, initiation of either octreotide or lanreotide is recommended to potentially control tumor growth if they are not already receiving it. The recommendation to consider octreotide in these patients is based on the results of the PROMID study, a placebo-controlled phase III trial of 85 patients with metastatic midgut NETs, which showed median times to tumor progression of 14.3 and 6.0 months in the octreotide LAR and placebo groups, respectively (*P*=.000072).[48] After 6 months of treatment, stable disease was observed in 66.7% of patients in the octreotide LAR group and in 37.2% of patients in the placebo group. Results of long-term survival of patients in the PROMID study were recently reported.[49] Median overall survival was not significantly different at 84 months in the placebo arm and not reached in the octreotide arm (HR, 0.85; 95% CI, 0.46–1.56; *P*=.59). However, poststudy treatment included octreotide in 38 of 43 patients in the placebo arm, possibly confounding interpretation of long-term survival results.

The recommendation that lanreotide be considered for control of tumor growth in patients with clinically significant tumor burden or progressive disease is based on results of the CLARINET study. The CLARINET study randomized 204 patients with locally advanced or metastatic nonfunctioning pancreatic or intestinal NETs to receive either lanreotide or placebo, and then followed them for progression-free survival (PFS). Results from this trial showed that treatment with lanreotide for 2 years resulted in an improved PFS compared with placebo (PFS not reached vs 18 months, respectively; HR, 0.47; 95% CI, 0.30–0.73; *P*<.001).[50]

No clear consensus exists on the timing of octreotide or lanreotide initiation in asymptomatic patients with metastatic NETs and low tumor burden. Although initiation of octreotide or lanreotide can be considered in these patients, deferring initiation until evidence of tumor progression is seen may also be appropriate in selected patients.

Patients with clinically significant progression of metastatic bronchopulmonary and gastrointestinal NETs can pursue several other options, as discussed in subsequent sections.

***Hepatic-Directed Therapies for Metastatic NETs of the Gastrointestinal Tract, Lung, and Thymus:*** For patients with unresectable hepatic predominant progressive disease, hepatic-directed therapies may be considered, mainly with the palliative goals of extending life and relieving hormonal symptoms.[51–54]

Cytoreductive surgery or ablative therapies, such as radiofrequency ablation (RFA)[55] or cryoablation, may be considered if near-complete treatment of tumor burden can be achieved (category 2B).[56,57] For unresectable liver metastases, hepatic regional therapy (arterial embolization,[58] chemoembolization,[59–61] or radioembolization [category 2B])[61–68] is recommended.

***Everolimus for Advanced NETs of the Gastrointestinal Tract, Lungs, and Thymus:*** For patients with progressive metastatic carcinoid tumors, everolimus can also be considered (category 3). Everolimus is an inhibitor of mTOR that was well tolerated and showed evidence of antitumor effect in patients with advanced carcinoid tumors when given with octreotide LAR in a phase II trial.[69] In the randomized phase III RADIANT-2 trial, 429 patients with advanced NETs and carcinoid syndrome were randomized to receive octreotide LAR with everolimus or placebo.[70] Based on central review, patients receiving octreotide plus everolimus had a median PFS of 16.4 months, compared with 11.3 months for patients receiving octreotide alone (*P*=.026). This difference in the primary end point of PFS did not, however, meet the predefined threshold for statistical significance. Adverse events associated with everolimus included stomatitis, rash, fatigue, and diarrhea.[70] Other side effects have also been described.[71–73]

A recent report highlights the outcomes of 169 pretreated patients with advanced NETs of the pancreas (n=85) or other sites (n=84) who received everolimus through a compassionate use program.[74] An increased risk of adverse events in patients who had received previous radiolabeled peptide therapy or chemotherapy was noted.

***Systemic Therapy for Advanced NETs of the Gastrointestinal Tract, Lung, and Thymus:*** *With Cytotoxic Chemotherapy:* the benefits associated with cytotoxic chemotherapy in patients with advanced carcinoid tumors appear, at best, to be modest. Tumor response rates are generally low, and no PFS benefit has been clearly demonstrated.[75]

Capecitabine was tested in patients with metastatic carcinoid tumors in a recent phase II trial; no objective responses were reported although 13 of 19 patients were reported to have experienced stable disease.[76] The combination of capecitabine and oxaliplatin was assessed in a phase II study, with response rates of 23% in patients with poorly differentiated NETs and 30% in those with well-differentiated disease.[77] 5-FU was assessed in the phase III E1281 trial in combination with streptozocin or doxorubicin.[78] Response rates in both arms were approximately 16%. Dacarbazine was given after progression, with a response rate of 8%. Responses to temozolomide in advanced carcinoid are rare.[79]

*Interferon Alpha:* The panel lists cytotoxic chemotherapy for NETs of the gastrointestinal tract and lungs as a category 3 recommendation. Although some panelists believe the toxicity of systemic therapy does not warrant its widespread use in this population, others believe that it is an important alternative for patients without other options for treatment. Use of interferon alpha in the setting of advanced carcinoid tumors is a category 3 recommendation. Interferon alpha has been shown in several large, nonrandomized series to be associated with an antitumor effect in patients with advanced carcinoid tumors.[38,80–83] Because of its potential side effects,[38,80–83] interferon is usually not started until somatostatin analogue treatment has failed.[75]

***Radiolabeled Somatostatin Analogues for Advanced NETs of the Gastrointestinal Tract, Lung, and Thymus:*** Treatment with radiolabeled somatostatin analogues has been reported to result in tumor responses in patients with advanced carcinoid tumors.[84–88] Numerous large nonrandomized cohort analyses have also reported encouraging survival rates with this approach.[89–91] However, patients pursuing this form of therapy are often highly selected. A prospective phase II study of radiopeptide therapy in 90 patients with metastatic carcinoid tumors refractory to octreotide showed that treatment was associated with improvement in symptoms; radiographic regression, however, was relatively uncommon.[92] Currently, this approach remains investigational. Randomized trials to further evaluate the relative benefit and potential toxicities of radiopeptide therapy in advanced carcinoid tumors are needed.[93]

***Liver Transplantation for Liver Metastases of NETs of the Gastrointestinal Tract, Lung, and Thymus:*** Several series have now reported the results of liver transplantation patients with carcinoid tumors whose metastases are confined to the liver.[94–99] A recent meta-analysis showed that, although 5-year survival rates are encouraging, most patients undergoing liver transplantation ultimately develop recurrence.[100] The panel acknowledged the considerable associated risks and deemed liver transplantation to be investigational and not part of routine care at this time.

## NETs of the Pancreas

According to a population-based study, malignant pancreatic NETs account for approximately 1% of pancreatic cancers by incidence and 10% of pancreatic cancers by prevalence.[101] Although the peak incidence of occurrence is between ages 40 and 69 years, a significant number of patients diagnosed with pancreatic NETs are younger than 35 years.[101,102] Based on an analysis of pancreatic NETs in the SEER database from 1973 to 2000, the annual incidence per 1 million was 1.8 in women and 2.6 in men.[103] An estimated 40% to 91% of pancreatic NETs are nonfunctional. The remainder manifest with clinically evident hormonal symptoms.[9,103] Consistent with these numbers, recent analysis of the NCCN NETs Outcomes Database found that 22% of patients with pancreatic NETs had a hormonal syndrome.[14] Of these functioning tumors, up to 70% are insulinomas, and approximately 90% of these are benign. Approximately 15% are glucagonomas. Gastrinomas and somatostatinomas account for another 10%; most gastrinomas and somatostatinomas (80%–90%) are associated with a relatively high risk for metastases.[102] The remaining

rare pancreatic NETs include VIPoma, pancreatic polypeptidoma (PPoma), and the recently described cholecystokininoma (CCKoma).[104]

Pancreatic NETs occurring in patients with MEN1 are typically multiple and require different treatment strategies from those used for patients with sporadic pancreatic NETs, which are usually solitary (see "Multiple Endocrine Neoplasia" in the complete version of these guidelines, available at NCCN.org). Gastrinoma and insulinoma are the most common pancreatic NETs in patients with MEN1.[105]

## Evaluation of NETs of the Pancreas

Personal and family history should be evaluated for the possibility of MEN1 (see "Multiple Endocrine Neoplasia" in the complete version of these guidelines, available at NCCN.org). The recommended evaluation also includes multiphasic CT or MRI scan. Hormone-secreting tumors may result in significant clinical symptoms even when very small, and lesion identification can be difficult.[106] Somatostatin scintography and EUS can also be considered as appropriate.

Biochemical evaluation is also often considered in patients with pancreatic NETs because many pancreatic NETs secrete specific hormones.[102] Biochemical evaluation is generally guided by the presence of symptoms that might indicate excess hormone. The range of symptoms associated with hormonal secretion is diverse. Classic syndromes include those associated with insulinomas, which secrete insulin, resulting in fasting or nocturnal hypoglycemia. Gastrinomas secrete gastrin, and patients often present with recurrent peptide ulcers. Glucagonomas are associated with the development of diabetes mellitus and/or migratory necrolytic erythema. Patients with somatostatinomas may also present with diabetes mellitus and/or diarrhea/steatorrhea from secretion of somatostatin. VIPomas are characterized by watery diarrhea, hypokalemia, and achlorhydria (WDHA syndrome) from secretion of vasoactive intestinal polypeptide (VIP). The guidelines describe appropriate tests for each of these situations. For nonfunctioning tumors, pancreatic polypeptide (PP; category 3), chromogranin A (category 3), calcitonin, parathyroid hormone-related protein (PTHrp), and growth-hormone–releasing hormone may also be tested as appropriate.

Serum chromogranin A (category 3) may also be tested as clinically appropriate. Chromogranin A levels are elevated in 60% or more of patients with either functioning or nonfunctioning pancreatic endocrine tumors.[107–109] In addition, analysis of a large prospective database found that chromogranin A levels elevated twice the normal limit or higher were associated with shorter survival times for patients with metastatic NETs (HR, 2.8; 95% CI, 1.9–4.0; $P<.001$).[27] Chromogranin A levels also seem to be prognostic in patients treated with everolimus.[110] Care should be taken in measuring chromogranin A and interpreting the results, because spuriously elevated levels of chromogranin A have been reported in patients using proton pump inhibitors, those with renal or liver failure, those with hypertension, and those with chronic gastritis.

***Evaluation of Gastrinomas:*** Gastrinoma is often suspected in patients with severe gastroduodenal ulcer symptoms, such as dyspepsia, usually accompanied by diarrhea. Evaluation of a patient with suspected gastrinoma includes measurement of basal and stimulated gastrin levels.[111] Diagnosis of gastrinoma can be confounded by the concurrent use of proton pump inhibitors, which will elevate serum gastrin levels. Importantly, most patients who are found to have an elevated level of serum gastrin do not have a gastrinoma but have achlorhydria or are receiving proton pump inhibitors or antacids. Gastrin levels (basal or stimulated) must be measured after the patient is off proton pump inhibitor therapy for at least 1 week. After excluding retained gastric antrum based on history, a combination of fasting serum gastrin level greater than 10 times elevated and a gastric pH less than 2 is diagnostic of a gastrinoma. Patients who have clinical manifestations suspicious for a gastrinoma and a gastric pH less than 2 but with less than 10 times elevation of serum gastrin levels require further testing.[112]

In addition, imaging studies (multiphasic CT/MRI scan) often help in not only localizing the tumor but also confirming the diagnosis. Other tests, such as somatostatin scintography, EUS, and chromogranin A levels (category 3), may be performed as appropriate. Approximately 70% of patients with MEN1 and gastrinoma have tumors situated in the duodenum.

The *New England Journal of Medicine* recently published a case report outlining the diagnosis of gastrinoma in a patient presenting with severe, recurrent diarrhea.[113]

***Evaluation of Insulinomas:*** Insulinomas are generally small tumors that are best localized with EUS, which has been shown to localize approximately 82% of pan-

creatic endocrine tumors.[114] Insulinomas can also be localized by injecting calcium into selective pancreatic arteries and measuring the insulin levels in the right (usually) or left hepatic vein (Imamura-Doppman procedure).[115] Most experts recommend this test only for patients with persistent or recurrent insulinoma or when other localization tests are equivocal or negative.

Serum insulin, proinsulin, and C peptide should be tested.[116] If the diagnosis of insulinoma is uncertain, a 48- to 72-hour observed or inpatient observed fast may also be helpful. An insulin level greater than 3 mcIU/mL (usually >6 mcIU/mL), C peptide concentrations of at least 0.6 ng/mL, and proinsulin levels of greater than or equal to 5 pmol/L when fasting blood glucose is less than 55 mg/dL indicated the presence of these tumors.[116]

Multiphasic CT or MRI scans should be performed to rule out metastatic disease. Ninety percent of insulinomas have an indolent course and can be cured surgically. Insulinomas are less consistently octreotide-avid than other pancreatic NETs, and somatostatin scintography may consequently be less useful as an imaging technique for insulinomas than for other tumor subtypes. Somatostatin scintography should be performed only if octreotide or lanreotide is being considered as a treatment for metastatic disease. Octreotide or lanreotide should only be administered to patients whose tumors are somatostatin scintography–positive, and patients with insulinoma should be carefully monitored when receiving somatostatin analogues, because in some cases somatostatin analogues can profoundly worsen hypoglycemia (see "Preoperative Management," opposite column).[117]

The *New England Journal of Medicine* recently published a case report describing the diagnosis of insulinoma in a lactating patient presenting with periodic numbness and prolonged episodes of confusion and lethargy.[118]

***Evaluation of Glucagonomas and VIPomas:*** For patients with recent-onset diabetes, cachexia, and/or a necrolytic erythematous skin rash, the panel recommends a blood test for glucagon and blood glucose and multiphase contrast-enhanced CT or MRI. Somatostatin scintography and EUS can be performed as appropriate.

For suspected VIPomas with characteristic watery diarrhea, testing for VIP and electrolytes is recommended. A multiphase CT or MRI scan may be useful for identifying large tumors or metastatic disease, and is recommended routinely for suspected VIPoma. Somatostatin scintography and EUS can also be considered as appropriate. A recent case report describes the diagnosis and treatment of a patient with VIPoma.[119]

## Primary Treatment of Locoregional Resectable NETs of the Pancreas

Resection is the primary treatment approach for localized pancreatic NETs when possible, and can result in excellent outcomes. Exceptions include patients with other life-limiting comorbidities or high surgical risk.

***Preoperative Management:*** Surgical resection is the optimal treatment for locoregional pancreatic endocrine tumors. Before excision, however, any symptoms of hormonal excess must be treated. Octreotide or lanreotide can be considered for symptom control in most pancreatic NET subtypes.[20] Octreotide or lanreotide should be used with caution in patients with insulinoma because they can also suppress counterregulatory hormones, such as growth hormone, glucagon, and catecholamines. In this situation, octreotide and lanreotide can precipitously worsen hypoglycemia, and can result in fatal complications.[117] Somatostatin analogues should generally not be used in patients with insulinoma in patients with a negative result by somatostatin scintigraphy.

In addition, specific measures are often recommended based on symptoms. For insulinomas, the panel advises stabilizing glucose levels with diet and/or diazoxide. Everolimus can also be considered in this scenario.[120] For gastrinomas, gastrin hypersecretion may be treated with proton pump inhibitors. For patients with glucagonoma, appropriate measures should be taken to treat hyperglycemia and diabetes, including the use of intravenous fluids. All patients who might require splenectomy should receive preoperative trivalent vaccine (ie, pneumococcus, haemophilus influenzae b, meningococcus group c).

***Surgical Management of Nonfunctioning Pancreatic NETs:*** Most patients with localized pancreatic NETs should undergo surgical resection, absent any contraindications. Exceptions include patients with other life-limiting comorbidities, high surgical risk, or widely metastatic disease. Additionally, several studies have suggested that patients with incidentally discovered tumors smaller than 1 cm may in some cases be safely observed, depending on the site of the tumor.[121,122] Other studies, including an analysis of the SEER database, suggest that some small tumors (measuring <2 cm in size in these studies) can pursue a more aggressive course.[123–125] Therefore, the panel

includes observation alone as an option for selected cases of incidentally discovered pancreatic NETs measuring 1 cm, but recommends surgical resection for larger tumors absent contraindications.

Resection for larger (>2 cm) or malignant-appearing nonfunctional tumors should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes. Lymph node resection should also be considered for tumors of 1 to 2 cm, because of the small but real risk of lymph node metastases.[126,127]

***Surgical Management of Gastrinomas:*** The treatment approach for gastrinoma usually depends on the results of preoperative localization studies and on findings during exploratory laparotomy. In patients with occult gastrinoma (ie, no primary tumor or metastasis seen on imaging), the panel recommends either observation or exploratory surgery, including duodenotomy and intraoperative ultrasound with enucleation or local resection of tumors if identified at operation, and removal of periduodenal nodes.

Gastrinomas in the duodenum are treated with duodenotomy and intraoperative ultrasound, with local resection or enucleation of tumors and periduodenal node dissection.

Gastrinomas in the head of the pancreas that are exophytic or peripheral as determined by imaging and are not immediately adjacent to the pancreatic duct should be enucleated. The periduodenal nodes should also be removed. Gastrinomas in the pancreatic head that are deeper or invasive and those with proximity to the main pancreatic duct should be managed with pancreatoduodenectomy.

Gastrinomas in the distal pancreas are treated with distal pancreatectomy. The role of routine splenectomy in these cases is debated. Gastrinomas in some cases may be associated with lymph node metastases,[128] which are removed with splenectomy. However, no firm data support splenectomy in all cases. A third alternative is the Warshaw technique, which, with resection of splenic vessels but preservation of the spleen,[129] can achieve lymph node retrieval comparable to distal pancreatectomy with en bloc splenectomy.

***Surgical Management of Insulinomas:*** The primary treatment for exophytic or peripheral insulinomas, because they are primarily benign, is enucleation. This procedure can be performed laparoscopically for localized solitary tumors within the body and tail of the pancreas. Sporadic tumors are usually solitary, whereas familial tumors are multiple. If enucleation is not possible because of invasion or the location of the tumor within the pancreas, then pancreatoduodenectomy may be considered for tumors in the head of the pancreas or distal pancreatectomy with preservation of the spleen for smaller tumors not involving splenic vessels. Distal pancreatectomy can be performed laparoscopically, and a recent meta-analysis reported that laparoscopic procedures are safe for patients with insulinomas and may be associated with shorter hospital stays.[130]

***Surgical Management of Glucagonomas:*** Most glucagonomas are malignant and calcified and located in the tail of the pancreas, with regional node involvement. The recommended treatment is distal pancreatectomy with splenectomy and resection of the peripancreatic lymph nodes. For tumors in the pancreatic head, pancreatoduodenectomy with resection of the peripancreatic lymph nodes is recommended. Small (<2 cm) peripheral glucagonomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumors of the head or distal pancreas. A hypercoagulable state has been reported in 10% to 33% of patients with glucagonoma.[131,132] Therefore, perioperative anticoagulation can be considered because of the increased risk of pulmonary emboli.

***Surgical Management of VIPomas:*** Distal VIPomas are treated with distal pancreatectomy with resection of peripancreatic lymph nodes and spleen. Pancreatoduodenectomy with dissection of peripancreatic nodes is recommended for tumors in the head of the pancreas. Small (<2 cm) peripheral VIPomas are rare; enucleation or local excision with peripancreatic lymph dissection may be considered for small peripheral tumors of the head or distal pancreas.

***Surgical Management of Other Pancreatic NETs:*** The treatment recommendations for tumors secreting hormones such as somatostatinoma, ACTH, Parathyroid hormone-related protein, and pancreatic polypeptide are similar to those for nonfunctioning tumors. Tumors that are small (<2 cm) and peripheral can be enucleated with or without removal of regional nodes, or distal pancreatectomy can be performed with or without removal of regional nodes and with or without splenectomy. Deeper, larger (>2 cm), or invasive tumors are treated with pancreatoduodenectomy

if they are located in the head of the pancreas, and with distal pancreatectomy and splenectomy if they are distally localized. Resection for larger (>2 cm) or malignant-appearing tumors should include total removal of the tumor with negative margins (including adjacent organs) and regional lymph nodes.

***Surveillance of Resected Pancreatic NETs:*** Disease recurrence has been observed in 21% to 42% of patients with pancreatic NETs and can occur after many years.[133–135] Higher lymph node ratio and Ki-67 status may indicate a higher chance of recurrence.[133] Patients should undergo follow-up 3 to 12 months after resection, or earlier if the patient presents with symptoms, and then every 6 to 12 months for a maximum of 10 years with an H&P and appropriate biochemical markers. Multiphasic CT or MRI can also be considered. Less frequent surveillance may be appropriate for low-risk tumors such as well-differentiated stage I pancreatic NETs. Somatostatin scintography and 18F-fluorodeoxyglucose PET (FDG/PET) scan are not recommended for routine surveillance.

The optimal duration of surveillance is unknown. In one study of 123 patients with resected sporadic pancreatic NETs, most recurrences occurred within 5 years of resection, and all recurrences occurred within 10 years.[136] Surgical resection is recommended for resectable locoregional or oligometastatic recurrence.

## Management of Locoregional Unresectable and/or Metastatic NETs of the Pancreas

Patients with malignant NETs of the pancreas frequently present with liver metastases. In patients with limited hepatic disease, surgical excision of both the primary tumor and liver metastases should be considered with curative intent when possible and can be performed in a staged or synchronous fashion. A recent meta-analysis reported that 5-year overall survival ranges from 41% to 100% in this population of patients.[34] Noncurative debulking surgery can also be considered in select cases. When performing staged pancreatoduodenectomy and liver resection, hepatectomy should be considered before pancreatic resection to reduce the risk of perihepatic sepsis from the contaminated biliary tree.[137] Although resection may provide clinical benefit, most patients with metastatic disease will experience recurrence.[35,36] Additional resection or ablation may be possible. A recent study of 172 patients who had liver resection of metastatic NETs (55 with the primary tumor in the pancreas) showed that significant long-term survival can be achieved after recurrence in many patients, with a 10-year overall survival rate of 50.4%.[33]

Unfortunately, most patients with advanced pancreatic NETs have unresectable disease. For selected patients with unresectable disease who are asymptomatic and have low tumor burden and stable disease, observation can be considered, with marker assessment and imaging every 3 to 12 months until clinically significant disease progression occurs. In addition, however, treatment with lanreotide or octreotide can be considered (discussed later). The optimal time to begin therapy in this patient population is not known.

For symptomatic patients with unresectable disease, those who initially present with clinically significant tumor burden, or those with clinically significant disease progression, several different options can be considered. Systemic options include treatment with octreotide or lanreotide, biologically targeted agents (everolimus or sunitinib, category 2A), or treatment with cytotoxic chemotherapy (category 2A). These options, and hepatic-directed therapies, are discussed in more detail in the following sections.

***Somatostatin Analogues:*** Patients with pancreatic NETs and symptoms of hormone secretion should, in most cases, receive treatment with either lanreotide or octreotide and/or other medication to manage their symptoms. Patients without hormone-related symptoms who have uptake with somatostatin scintography can also be considered for treatment with octreotide or lanreotide. Results from the CLARINET study, in which 204 patients with gastroenteropancreatic NETs (including both carcinoid and pancreatic NETs) were randomized to receive treatment with either lanreotide or placebo, showed that treatment with lanreotide was associated with in an improvement in PFS (not reached vs 18 months with placebo; HR, 0.47; 95% CI, 0.30–0.73; $P<.001$).[50] Although no randomized studies to date have directly shown an antitumor effect of octreotide in pancreatic NETs, the PROMID trial showed an improvement in its primary end point of time to tumor progression (14.3 vs 6.0 months; $P=.000072$) in carcinoid tumors of the midgut.[48] Lanreotide and octreotide share the same mechanism of action, and the panel believes that either lanreotide or octreotide are appropriate options for tumor control in this setting.

Additional therapies can be given in place of or in addition to octreotide or lanreotide, as discussed later.

***Biologically Targeted Therapies:*** The biologically targeted agents everolimus and sunitinib have recently been confirmed to have antitumor activity and to improve PFS in patients with advanced pancreatic NETs.

Everolimus, administered orally at a dose of 10 mg once daily, was evaluated in a multicenter study (RADIANT-3) enrolling 410 patients with advanced, progressive, pancreatic NETs.[138] In this study, the median PFS duration for patients randomized to everolimus was 11.0 months, compared with 4.6 months for patients receiving placebo ($P<.001$). Subset analyses of RADIANT-3 showed that the PFS effect of everolimus is independent of prior or concurrent somatostatin analogue therapy or prior chemotherapy.[139,140] Adverse events associated with everolimus include stomatitis, hyperglycemia, and, in rare cases, pneumonitis.[138] Other side effects have also been described.[71–73] A recent report highlights the outcomes of 169 pretreated patients with advanced NETs of the pancreas (n=85) or other sites (n=84) who received everolimus through a compassionate use program.[74] A higher risk of adverse events was noted in patients with previous radiolabeled peptide therapy and chemotherapy.

Sunitinib, administered orally at a dose of 37.5 mg once daily, was compared with placebo in a multicenter randomized study of patients with advanced progressive metastatic pancreatic NETs.[141] The study was designed to enroll 340 patients but was discontinued after enrollment of 171 patients, before the predefined efficacy analysis. At discontinuation, patients who received sunitinib had a median PFS duration of 11.4 months, compared with 5.5 months for patients receiving placebo ($P<.001$). The objective response rate seen with sunitinib was 9.3%.[141] A large proportion of patients on the placebo arm subsequently received sunitinib at progression, and no significant difference in overall survival was observed between the arms.[142] Adverse events associated with sunitinib include fatigue and, in rare cases, congestive heart failure.[143] Other side effects have also been described.[144,145]

***Cytotoxic Chemotherapy for Advanced Pancreatic NETs:*** Cytotoxic chemotherapy is another option for patients with unresectable or metastatic pancreatic NETs (category 2A). Although several regimens have been associated with antitumor activity in this setting, no panel consensus exists on which cytotoxic chemotherapy regimen is best. Streptozocin is FDA-approved for use in patients with advanced pancreatic NETs. The combination of doxorubicin and streptozocin was initially reported to be associated with an overall response rate of 69% and a survival benefit in a relatively small randomized study of patients with advanced pancreatic NETs.[146] A more recent retrospective review from MD Anderson Cancer Center reported an objective response rate of 39% with the combination of 5-FU, doxorubicin, and streptozocin.[147] 5-FU was assessed in the phase II/III E1281 trial in combination with streptozocin or doxorubicin in patients with NETs of various locations, including the pancreas.[78] Response rates in both arms were around 16%. Dacarbazine was given after progression, with a response rate of 8%. The combination of capecitabine and oxaliplatin was assessed in a phase II study, with response rates of 23% in patients with poorly differentiated NETs and 30% in well-differentiated disease.[77]

More recently, oral temozolomide-based therapy has been used in patients with advanced pancreatic NETs. Temozolomide has been administered using different schedules, either alone or in combination with other agents.[79,148–151] A retrospective series reported that the combination of temozolomide with capecitabine was associated with an objective radiographic response rate of 70% and a median PFS of 18 months.[151] Another retrospective review of the temozolomide and capecitabine combination reported a 61% response rate in 18 patients, with 1 surgically proven complete pathologic response.[152] A small recent retrospective study (7 patients) reported a response rate of 43%.[153]

In addition, a recent phase II study assessed the safety and efficacy of temozolomide administered with bevacizumab, a monoclonal antibody targeted against vascular endothelial growth factor.[148] Of the 15 patients with pancreatic NETs, 5 had a radiographic response (with no responses in the 19 patients with carcinoid tumors), and the toxicity was acceptable. These results are consistent with prior studies of temozolomide-based therapy, and further support the activity of temozolomide in pancreatic NETs. The added benefit of bevacizumab cannot be assessed from this single-arm study.

The combination of temozolomide with everolimus has also been studied. A recent phase I/II study found the combination to be safe, with a partial response observed in 40% of patients.[154]

***Hepatic-Directed Therapies:*** Hepatic-directed therapies may be considered in patients with progressive hepatic-predominant metastatic disease to reduce tumor bulk and relieve symptoms of hormone hypersecretion.[53] The panel lists cytoreductive surgery or ablative therapy (RFA[55], cryotherapy, microwave[56,57]) as category 2B recommendations for these patients. Although some groups report that the risks of cytoreductive surgery outweigh its benefits,[155] others have reported good outcomes.[156,157]

Additional options include hepatic regional therapies, including bland hepatic arterial embolization,[58] radioembolization (category 2B),[62–68] and chemoembolization.[158] Although embolization in general is considered an effective approach in patients with hepatic-predominant disease,[51,52,54] only limited data compare the various embolization techniques, and the optimal embolization approach remains uncertain.

***Radiolabeled Somatostatin Analogues for Advanced Pancreatic NETs:*** Treatment with radiolabeled somatostatin analogues has been reported to result in tumor responses in patients with advanced pancreatic NETs.[84–88] Numerous large nonrandomized cohort analyses have also reported encouraging survival rates with this approach.[90,91] However, patients pursuing this form of therapy are often highly selected. At this time, this approach remains investigational, and randomized trials to further evaluate the relative benefit and potential toxicities of radiopeptide therapy in patients with advanced pancreatic NETs are needed.[93]

***Liver Transplantation:*** Several series have now reported the results of liver transplantation in patients with pancreatic NETs whose metastases are confined to the liver.[94–99,159] A recent meta-analysis showed that, although 5-year survival rates are encouraging, most patients undergoing liver transplantation ultimately develop recurrence.[100] The panel acknowledged the considerable associated risks and deemed liver transplantation to be investigational and not part of routine care at this time.

## NETs of Unknown Primary

In a SEER database analysis, a primary tumor site could not be found in as many as 4752 (13%) of 35,618 NETs.[1] When a NET of unknown primary is diagnosed, attempts are usually first made to identify the origin of the neoplasm to help guide treatment decisions. If the primary tumor cannot be identified, treatment decisions are generally guided by tumor histology (see "Histologic Classification and Staging of Neuroendocrine Tumors" in the complete version of these guidelines, at NCCN.org). Many of these tumors are poorly differentiated and aggressive.[160]

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