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Consensus Guidelines for the Management and Treatment of Neuroendocrine Tumors

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Abstract

Neuroendocrine tumors are a heterogeneous group of tumors originating in various anatomic locations. The management of this disease poses a significant challenge because of the heterogeneous clinical presentations and varying degrees of aggressiveness. The recent completion of several phase 3 trials, including those evaluating octreotide, sunitinib, and everolimus, demonstrate that rigorous evaluation of novel agents in this disease is possible and can lead to practice-changing outcomes. Nevertheless, there are many aspects to the treatment of neuroendocrine tumors that remain unclear and controversial. The North American Neuroendocrine Tumor Society published a set of consensus guidelines in 2010, which provided an overview for the treatment of patients with these malignancies. Here, we present a set of consensus tables intended to complement these guidelines and serve as a quick, accessible reference for the practicing physician.

Key Words

neuroendocrine tumors, carcinoid, neuroendocrine/diagnosis, neuroendocrine/treatment, neuroendocrine/pathology, pheochromocytoma

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Neuroendocrine tumors (NETs) are a heterogeneous group of tumors originating in various locations, including gastrointestinal tract, lung, and pancreas. The disease management poses a significant challenge because of the heterogeneous clinical presentations and varying degree of aggressiveness. The recent completion of several phase 3 trials, including those evaluating octreotide, sunitinib, and everolimus, demonstrate that rigorous evaluation of novel agents in this disease is possible and can lead to practice-changing outcomes. Nevertheless, there are many aspects to the treatment of NETs that remain unclear and controversial.

The North American Neuroendocrine Tumor Society (NANETS) was founded in 2006; and at that time, its board members convened a consensus guidelines committee in an effort to develop an expert consensus opinion on the treatment of these uncommon diseases. Although other comprehensive guidelines exist (ie, National Comprehensive Cancer Network Neuroendocrine Tumor guidelines, European Neuroendocrine Tumor Society (ENETs) guidelines), it was felt that the NANETS guidelines could enhance and complement these existing guidelines through the use of expert opinion added to evidenced-based recommendations. The first set of consensus guidelines[1–7] was published in 2010 and were intentionally comprehensive in scope. Here, we present a set of consensus tables intended to complement these guidelines and serve as a quick, accessible reference for the practicing physician. Consensus tables were developed and revised during a series of meetings between October 2011 and October 2012. Eight tables were created to define treatment and workup recommendations. These tables include the following: (1) Pathology; (2) NETs of the thorax; (3) Gastric NETs; (4) Pancreatic NETs; (5) NETs of the small bowel and cecum (‘‘midgut’’); (6) NETs of the colon and rectum (‘‘hindgut’’); (7) Pheochromocytoma, paraganglioma, and medullary thyroid cancer; and (8) High-grade neuroendocrine carcinoma. The tables include 2 categories of recommendations as either *Consider* or *Recommend*. Emphasis was placed on the development of sound guidelines based on the data when available and consensus expert opinion; controversial topics were also addressed. Each table includes guidelines for workup, treatment, and follow-up. When the disease-specific full consensus guidelines documents are next updated these consensus tables will be incorporated.

It should be noted that there was unanimous decision that all patients should be considered for clinical trials when possible. In addition, all members believe that the approach to patient management should include a team of experts that include, but are not limited to, medical and surgical oncologists, radiologists, gastroenterologists, interventional radiologists, and pathologists. Additionally, some of the controversial topics included in the tables were brought back to NANETS members and further refined during subsequent meetings and teleconferences. This introduction has been structured to further address some of these key issues.

Key Updates Since Publication of 2010 NANETS Consensus Guidelines

Since the 2010 publication of the NANETS Consensus Guidelines in Pancreas, a number of practice-changing studies have been published.

The RAD001 in Advanced Neuroendocrine Tumors-3 (RADIANT-3) study,[8] published in 2011, is a randomized phase 3 study evaluating the efficacy of everolimus in advanced pancreatic NETs. In this international multisite

study, 410 patients with low- or intermediate-grade, progressive, advanced pancreatic NETs were randomized to receive everolimus, 10 mg oral daily, or placebo. The median progression-free survival (PFS) was 11.0 months with everolimus compared with 4.6 months with placebo (hazard ratio, 0.35; 95% confidence interval, 0.27—0.45; P G 0.001). The response rate was 5% in the everolimus arm compared with 2% in the placebo arm. The median overall survival has not been reached.

In another phase 3 study published in 2011, 171 patients with advanced, well-differentiated, progressive pancreatic NETs were randomized to receive sunitinib, 37.5 mg orally daily, or placebo.[9] The study was discontinued prematurely after an independent data and safety monitoring committee observed more serious adverse events and deaths in the placebo arm and a difference in PFS that favored the sunitinib arm during an unplanned interim analysis. The median PFS was 11.4 months in the sunitinib arm compared with 5.5 months in the placebo arm (hazard ratio, 0.42; 95% confidence interval, 0.26—0.66; P G0.001). Response rates in the sunitinib and placebo arms were 9.3% and 0%, respectively. The median overall survival could not be estimated given the high number of censored events in both groups.

In addition to the aforementioned treatment advances, there were 2 key publications on NET pathology reporting.[4,10] A formal assessment of grade and differentiation using the minimum pathology data set described below in the pathology consensus table should be required for all patients before initiating therapy given the implications on treatment. There are different treatment algorithms for well-differentiated versus poorly differentiated NETs.

Key Controversial Topics

Several controversial topics were identified during the course of guidelines development (Table 1). A few of these topics are highlighted here.

Indications for Targeted Therapies

Based on the aforementioned phase 3 clinical trials, sunitinib and everolimus are Food and Drug Administration approved and recommended for patients with progressive metastatic pancreatic NETs. Everolimus was also studied in metastatic functional (ie, hormone secreting) carcinoid tumors in a large phase 3 clinical trial. Although this study did not meet its primary endpoint of PFS, there was a trend toward longer PFS in the treatment arm.[11] At the current time, we do not have sufficient evidence to recommend routine use of everolimus in carcinoid tumors; the level of recommendation for everolimus in the treatment of advanced carcinoid is listed as ‘‘consider’’.

Indications for Cytotoxic Therapies

Cytotoxic therapies such as streptozocin, 5-fluorouracil, or temozolomide should be considered in the palliation of patients with advanced pancreatic NET and symptoms related to tumor bulk. There are no prospective randomized data for a temozolomidebased regimen; however, a single-institution series showed promising activity,[12] and randomized clinical trials using temozolomide are planned. Cytotoxic therapies are currently listed as ‘‘consider’’ for pancreaticNET. There is currently no known role for cytotoxic therapies in advanced carcinoid.

Indication and Dosing of Somatostatin Analogs Refractory carcinoid syndrome is an unmet medical need. Carcinoid syndrome is caused by the secretion of serotonin and other bioactive amines into the systemic circulation and is manifested by flushing and diarrhea, fibrosis of the right-sided heart valves, and intestinal mesentery. Currently available somatostatin analogs include octreotide and lanreotide and can ameliorate the symptoms of carcinoid syndrome. Over time, however, patients with the carcinoid syndrome may become refractory to somatostatin analogs. For this reason, NET physicians often increase the dose and/or frequency of somatostatin analogs in an attempt to control refractory carcinoid syndrome. Such an approach has anecdotally improved symptoms although has never been tested in a rigorous and/or randomized fashion. The committee ‘‘recommends’’ that somatostatin analog doses could be escalated or interval shortened in an attempt to control these symptoms, but note that no prospective data exist.

The placebo-controlled, double-blind, prospective, randomized study on the effect of octreotide LAR in the control of tumor growth in patients with metastatic neuroendocrine midgut tumors PROMID trial also demonstrated antitumor efficacy of octreotide in advanced midgut carcinoid tumors.[13] Despite this evidence in midgut tumors, there are no prospective data for the use of somatostatin analogs as antiproliferative agents in pancreatic NETs, although ongoing clinical trials are poised to answer this question.

Serum Biomarkers in Diagnosis and Surveillance

Plasma chromogranin A (CgA) and 24-hour urinary 5-hydroxyindoleacetic acid (5-HIAA) levels can be elevated as surrogate markers of possible progression or response. 5- Hydroxyindoleacetic acid is not as useful in patients

with foregut (bronchial or gastric) or hindgut (rectal) NETs or in most patients with pancreatic NETs that do not secrete serotonin. Chromogranin A is a 49-kd protein that is contained in the neurosecretory vesicles of the NET cells and is commonly detected in the plasma of patients with endocrine neoplasms. Elevated plasma CgA levels have been associated with poor overall prognosis in patients with NETs.[14] Additionally, early decreases may be associated with favorable treatment outcomes in some studies. The committee ''recommends'' following CgA levels in patients with advanced disease in patients who have elevated CgA levels at diagnosis and ''considers'' following CgA in resected disease.

Role of Surgical Debulking

Progression of liver metastases is the predominant cause of mortality in many NET patients. The median survivals of 24 to 128 months are reported with treatment.[15–17] For this reason, hepatic resection, radiofrequency ablation, and hepatic arterial embolization have been used to control tumor burden. In patients in whom all hepatic metastases seem to be resectable, and in whom no (or mild nonclinically significant) extrahepatic disease is observed, resection should be ''considered''.[18–21] The lack of randomized data and selection bias may confound quantitative interpretation of reported results. Nevertheless, resection should be considered in carefully selected patients, particularly with functional tumors, where the tumors can be removed safely. Asymptomatic patients, in the setting of resectable disease, should also be ''considered'' as candidates for surgical debulking.

In recent years, we have witnessed many advances in NET trial design, conduct, and accrual—culminating in the FDA approval of 2 new biologic agents in this disease. There is ongoing research in biomarkers, imaging, and novel agents. Below we present 8 consensus tables summarizing available data and expert consensus in the field of NETs (Tables 2—9).

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TABLES

Table 1: Controversial Topics

Pancreas
Use of octreotide for tumor control in patients with advanced pancreatic NETs
Indications for initiating targeted therapies or cytotoxic chemotherapy in patients with advanced pancreatic NETs
Midgut
Specific recommendations for dosing of octreotide LAR in refractory carcinoid syndrome
Indications for initiating octreotide for tumor control in patients with advanced carcinoid tumors
Dose escalation of octreotide for tumor control in patients with advanced carcinoid tumors
Indications for right hemicolectomy in patients with appendiceal carcinoids with high-risk features, which could be defined by size, infiltration into mesentery, located at base, and higher grade of tumor
Frequency of echocardiograms in functional midgut tumors
Pheochromocytoma
Indications for systemic chemotherapy in patients with advanced pheochromocytoma/paraganglioma
Surgery
Role of surgical debulking in asymptomatic patients with metastatic liver predominant NET
Role of surgical debulking in patients where an R0 resection cannot be achieved
Embolization
Role of bland embolization, radioembolization and chemoembolization
All
Use and frequency of chromogranin A in following patients on or off treatment
Use of everolimus and sunitinib in patients without pN
Use of somatostatin scintigraphy imaging to follow disease

Table 2: Neuroendocrine Tumor Pathology

Thoracic NET Pathology		
Mitotic rate should be obtained. Use of the World Health Organization (WHO) and International Association for the Study of Lung Cancer grading system is recommended. If specimen is inadequate, a second biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Grading (proliferative rate)		
Mitotic rate	Recommend	Mitoses/10 HPF*
Ki67	Consider	
Typical carcinoid	Recommend	< 2 mitoses/10 HPF
Atypical carcinoid	Recommend	≥ 10 mitoses/10 HPF
High grade (small cell or large cell neuroendocrine carcinoma)	Recommend	> 10 mitoses/10 HPF
Presence of necrosis	Recommend	Absent: typical carcinoid; present: atypical carcinoid
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	May be appropriate
Biopsy or resection of primary tumor		
Anatomic site of tumor	Recommend	
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	Lung primary: invasion into pleura, main stem bronchus, pericardium, chest wall, or diaphragm. Thymic primary: invasion through tumor capsule, invasion into pleura, lung, pericardium, or adjacent structures
Nodal metastases	Recommend	
Resection margins	Recommend	Positive/negative
Vascular or perineural invasion	Recommend	Present/absent
Presence of nonneuroendocrine components	Recommend	Present/absent

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Gastric NET Pathology		
Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained, the higher grade is assigned. If specimen is inadequate, a second biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Grading (proliferative rate)		
Mitotic rate	Recommend	
G1		< 2 mitoses/10 HPF*
G2		2–20 mitoses/10 HPF
G3		> 20 mitoses/10 HPF
Ki 67	Recommend	
G1		< 3%
G2		3%–20%
G3		> 20%
Histology differentiation	Recommend	Poorly differentiated NECs (G3) are highly aggressive and need distinguishing from other NE
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
Cytokeratin	Consider	Marker for carcinoma
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Biopsy or resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	Present/absent
Nodal metastases	Recommend	
Distant metastases	Recommend	Pathologic metastasis (pM) denotes metastases location
Presence of nonneuroendocrine components	Recommend	Present/absent
Biopsies of nontumoral gastric mucosa	Recommend	Helps differentiate types of gastric NETs
Histology/immunohistochemistry		
Atrophic gastritis present		
Enterochromaffin-like (ECL) hyperplasia present		
Parietal cell hypertrophy present		

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Pancreatic NET Pathology		
Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained, the higher grade is assigned. If specimen is inadequate, repeat biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Subtype		
Small cell, non–small cell (ie, large cell)	Recommend	
Grading (proliferative rate)	Recommend	
Mitotic rate		
G1		< 2 mitoses/10 HPF*
G2		2–20 mitoses/10 HPF
G3		> 20 mitoses/10 HPF
Ki 67		
G1		< 3%
G2		3%–20%
G3		> 20%
Histology differentiation	Recommend	Poorly differentiated NECs (G3) are highly aggressive and need to be distinguished from other NETs
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
Cytokeratin	Consider	Marker for carcinoma
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Biopsy or resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	
Nodal metastases	Recommend	
Distant metastases	Recommend	pM denotes metastases location
Presence of nonneuroendocrine components	Recommend	Present/absent

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Midgut NET Pathology		
Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained, overall grade is defined by the higher of the two. If specimen is inadequate, a second biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Grading (proliferative rate)	Recommend	
Mitotic rate		
G1		< 2 mitoses/10 HPF*
G2		2–20 mitoses/10 HPF
G3		> 20 mitoses/10 HPF
Ki 67		
G1		< 3%
G2		3%–20%
G3		> 20%
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
Cytokeratin	Consider	Marker for carcinoma
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	
Nodal metastases	Recommend	
Distant metastases	Recommend	pM should be used to denote metastases location
Presence of nonneuroendocrine components	Recommend	Present/absent

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Hindgut NET Pathology		
Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained grade is the higher of grade determined by mitotic rate or Ki67. If specimen is inadequate, a second biopsy is recommended.		
Test or Procedure	Recommendation	Comment
Grading (proliferative rate)	Recommend	
Mitotic rate		
G1		< 2 mitoses/10 HPF*
G2		2–20 mitoses/10 HPF
G3		> 20 mitoses/10 HPF
Ki 67		
G1		< 3%
G2		3%–20%
G3		> 20%
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	
Nodal metastases	Recommend	
Distant metastases	Recommend	pM denotes metastases location
Presence of nonneuroendocrine components	Recommend	Present/absent

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Pheochromocytoma/Paraganglioma Pathology		
Distinction between benign and malignant disease is difficult to ascertain pathologically.		
Test or Procedure	Recommendation	Comment
Patient and tumor characteristics		
Age	Recommend	Younger age increases suspicion of genetic disease
Extra-adrenal location	Recommend	Extra-adrenal location increases the risk of malignancy
Pathology reporting		
Multicentricity	Recommend	Can increase suspicion of genetic disease
Accompanying medullary hyperplasia	Recommend	Can increase suspicion of genetic disease
Ki67	Consider	Rates >2%–3% can be associated with malignancy
Periadrenal adipose tissue	Consider	
Large nests/diffuse growth	Consider	
Focal or confluent necrosis	Consider	Can be associated with malignancy
Cellularity	Consider	
Tumor cell spindling	Consider	
Cellular monotony	Consider	
Mitotic rate	Consider	>3/10 HPF* can be associated with more aggressive behavior
Atypical mitosis	Consider	
Hyperchromasia	Consider	
Profound nuclear pleomorphism	Consider	
Immunohistochemistry		
CgA	Recommend	Marker of neuroendocrine phenotype
Synaptophysin	Consider	Marker of neuroendocrine phenotype
S-100	Consider	Marker for sustentacular supporting framework
Cytokeratin	Consider	Negative staining supports pheochromocytoma/paraganglioma over carcinoid tumor or NET

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Table 2: Neuroendocrine Tumor Pathology (Continued)

Poorly Differentiated NET Pathology		
Test or Procedure	Recommendation	Comment
Subtype		
Small cell, non–small cell (ie, large cell)	Recommend	
Grading (proliferative rate)		
Mitotic rate (G3)	Recommend	> 10 mitoses/10 HPF* for lung
		> 20 mitoses/10 HPF for Gastroenteropancreatic-NET
Ki 67	Recommend	> 20%
Immunohistochemistry		
CgA	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
Cytokeratin	Consider	Marker for epithelial carcinoma
CDX2	Consider	Marker for bowel origin
CD56	Consider	Less specific marker for neuroendocrine phenotype
Resection of primary tumor		
Size	Recommend	In 3 dimensions
Depth of invasion	Recommend	
Nodal metastases	Recommend	
Distant metastases	Recommend	pM should be used to denote metastases location
Presence of nonneuroendocrine components	Recommend	Present/Absent

*Based on a 0.5-mm field diameter at high power, which yields a total area of 2 mm2 for 10 high power fields. ECL indicates enterochromaffin-like; GEP, gastroenteropancreatic.

Table 3: Neuroendocrine Tumors of the Thora

Initial workup		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
Adrenocorticotropic hormone	Consider	As clinically indicated
CgA	Consider	Investigational in thoracic NET, check at baseline
Urine 5-hydroxyindoleacetic acid (5-HIAA)	Consider	As clinically indicated
Imaging (baseline)		
Anatomic imaging		
Chest and abdomen (multiphasic computed tomography [CT])	Recommend	
Magnetic resonance imaging (MRI) with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly, when CT shows indeterminate lesions in the liver that need characterizing
MRI of the chest	Consider	To determine resectability in thymic tumors
[^{18}F]-fluorodeoxyglucose positron emission tomography (PET)	Consider	May be considered in undifferentiated tumors and/or to further characterize negative/equivocal octreotide scans
Luminal imaging		
Bronchoscopy	Consider	
Endobronchial ultrasound	Consider	
Nuclear imaging	Recommend	Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours
[^{111}In-DTPA0] octreotide scintigraphy		

Treatment of Thymic NET		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely.		
Disease Stage	Intervention	Recommendation
Locoregional disease	Surgical resection including mediastinal lymphadenectomy	Recommend
Recurrent localized disease	Surgical resection of localized disease	Recommend
Metastatic/unresectable disease	Everolimus	Consider
	Interferon α	Consider
	Radiation for unresectable disease	Consider
	Temozolomide	Consider

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Table 3: Neuroendocrine Tumors of the Thora (Continued)

Treatment of Lung/Bronchial NET		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Disease Stage	Intervention	Recommendation
Locoregional disease	Surgical resection with hilar/mediastinal lymph node sampling is recommended	Recommend
Recurrent disease, resectable	Surgical resection	Recommend
Metastatic/unresectable disease	Everolimus	
	Interferon α	Consider
	Radiation for unresectable disease	Consider
	Temozolomide	Consider
Follow-Up		
Follow-up for resected disease is recommended 3 to 6 months after curative resection and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (912 month) of stable disease.		
Test or Procedure	Recommendation	Comment
Blood and urine markers		
Adrenocorticotropic hormone	Consider	Consider following if abnormal at baseline
CgA	Consider	Consider following if abnormal at baseline
Urine 5-HIAA	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated for suspected recurrence
[^{111}In-DTPA0]octreotide scintigraphy		(see initial imaging for details)

Table 4: Gastric NETs

Initial workup		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
Gastric pH	Recommend	Gastric pH helps differentiate type I (gastric pH >4) from type II (gastric pH <2). Type II requires workup for Multiple Endocrine Neoplasia (MEN) 1 syndrome. Type III gastric pH <4
Gastrin	Recommend	Should be fasting and off PPI when feasible (types I and II will have elevated gastrin levels; type III will have normal gastrin level)
5-HIAA	Consider	As indicated for atypical type III foregut tumors or if symptoms suggestive of carcinoid syndrome. Need to follow diet during collection.
Anti-intrinsic factor and antiparietal cell antibodies	Consider	Only in type I. Consider workup for polyglandular syndrome
CgA	Consider	Recommended for type III (normogastrinemic) gastric carcinoids; false positive with proton pump inhibitor use and renal insufficiency
Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	For types II and III only
MRI with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly, when CT shows indeterminate lesions in the liver that need characterizing
Luminal imaging		
Esophagogastroduodenoscopy (EGD)	Recommend	Permits sampling of gastric mucosa and determination of disease extent
Endoscopic ultrasound (EUS)	Consider	Best procedure to determine tumor size/infiltration and to identify possible lymph node metastases
Nuclear imaging		
[^{111}In-DTPA0] octreotide scintigraphy	Consider	

Table 4: Gastric NETs (Continued)

Surgery of Primary Tumors		
In general, resection is recommended for local regional disease and in setting of impending obstruction and should still be considered for patients with advanced disease. Ability to resect primary tumors depends on the number, size, depth of invasion, and institutional expertise. In patients with suspected carcinoid syndrome who undergo major procedures, a preoperative bolus of octreotide, 250 to 500 Hg intravenous, is recommended with additional bolus doses available throughout the procedure.		
Tumor Type	Intervention	Recommendation
Type I		
<1 cm	Surveillance or endoscopic removal	Recommend
1–2* cm (up to 6 polyps)	Surveillance with repeat endoscopy approximately every 3 years or endoscopic resection. Endoscopic US could be used to assess depth of invasion but should be individualized. If submucosal invasion, endoscopic mucosal resection is increasingly used.	Recommend
>2* cm (up to 6 polyps)	Endoscopic resection (if possible) or surgical resection	Recommend
>2* cm (>6 polyps)	Must be individualized and could include surveillance, endoscopic resection or surgical resection	Recommend
Type II		
<1 cm	Surveillance or endoscopic removal	Recommend
1–2 cm	Endoscopic resection. EUS should be used to assess depth of invasion. If submucosal invasion, endoscopic mucosal resection is increasingly used.	Recommend
>2 cm	Surgical resection or endoscopic resection (if possible)	Recommend
Type III	Partial gastrectomy and lymph node dissection	Recommend

Table 4: Gastric NETs (Continued)

Advanced Disease—Oncologic Control of Gastric NETs		
Advanced disease is typically limited to type III only. Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal symptoms present	Recommend
	Octreotide LAR	Consider
Newly diagnosed with high-volume disease	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
Stable disease	Observation if no hormonal symptoms	Consider
Progressive disease	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
	Refer to specialty center	Consider
Hormonal Syndrome Control		
Carcinoid syndrome is rarely found in gastric NETs (type III only).		
Carcinoid syndrome		
Initial or nonrefractory	Long-acting somatostatin analogs; octreotide LAR, 20–30 mg IM is available in the United States. Immediate release octreotide can be used for breakthrough symptoms.	Recommend
Refractory syndrome with stable tumor volume	Antidiarrheal agents	Recommend
	Debulk tumor with liver-directed therapy if possible	Recommend
	Escalate dose or shorten dosing interval of long-acting somatostatin analog. No prospective data exist.	Recommend
	Add low-dose interferon α (short-acting or pegylated form)	Consider
	Referral to specialty center	Consider
	Rotate somatostatin analog as available	Consider

Table 4: Gastric NETs (Continued)

Indication	Intervention	Recommendation
Refractory syndrome with increasing tumor volume	Measures for refractory syndrome	Recommend
	Measures for oncologic control See Oncologic control section.	Recommend
	Refer to specialty center	Consider
Follow-Up		
Follow-up for resected gastric NET disease is recommended 3 to 6 months after curative resection and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (>12 months) of stable disease.		
Test or Procedure	Recommendation	Comment
Blood and urine markers		
CgA	Consider	Consider following if abnormal at baseline
Specific hormone marker	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	See initial imaging for details
Luminal Imaging		
EGD		
Gastric pH		
Nuclear imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details)
[^{111}In-DTPA0]octreotide scintigraphy		

*Multiple lesions that are larger than 1 to 2 cm should be individually decided and could include local resection, surgical resection, or watchful waiting. EGD indicates esophagogastroduodenoscopy; MEN, multiple endocrine neoplasia.

Table 5: Pancreatic NETs

Initial workup		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
CgA	Recommend	Especially useful if nonfunctional pancreatic NET suspected. False positive with proton pump inhibitor use and renal insufficiency
5-HIAA	Recommend	As clinically indicated
Gastrin	Recommend	As clinically indicated; need to follow diet during collection
Glucagon	Recommend	As clinically indicated; should be fasting
Insulin/proinsulin	Recommend	As clinically indicated; should be fasting with concurrent glucose
Pancreatic polypeptide	Recommend	As clinically indicated
VIP	Recommend	As clinically indicated
Other [Parathyroid hormone-related peptide, growth hormone releasing factor, etc]	Recommend	As clinically indicated
Genetic testing		
Inherited syndromes (Von-Hippel Lindau, tuberous sclerosis, neurofibromatosis-1)	Recommend	Genetic testing needs to be considered if clinical or family history is suggestive of these syndromes (see text for details of syndromes)
(Von-Hippel Lindau, tuberous sclerosis, neurofibromatosis-1)		
Multiple Endocrine Neoplasia Type 1 (MEN1)	Consider	Genetic testing for MEN 1 is recommended in all young patients with gastrinomas or insulinomas, any patient with a family or personal history of other endocrinopathies (especially hyperparathyroidism) or multiple pancreatic NETs.

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Table 5: Pancreatic NETs (Continued)

Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	Thin sections
MRI with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly, when CT shows indeterminate lesions in the liver that need characterizing
Additional sites	Consider	As clinically indicated
Luminal imaging		
EGD	Consider	In patients suspected of gastrinoma to visualize prominent gastric folds in Zollinger Ellison Syndrome; also with duodenal NETs (often nonfunctional) and in MEN 1 who have submucosal duodenal lesions
EUS	Consider	Should be performed for diagnostic purposes if pancreatic NET is suspected and no primary identified on cross-sectional imaging; helps identify small pancreatic NET lesions
Nuclear imaging		
[^{111}In-DTPA0] octreotide scintigraphy	Recommend	Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours
Surgery of Primary Tumors		
In general, resection is recommended for local regional disease and should still be considered for patients with advanced disease. Optimize nutritional status and control of hormone excess state medically preoperatively as outlined in the functional pancreatic NET section.		
Functional Status	Intervention	Recommendation
Functional pancreatic NET		
Gastrinoma		
Sporadic	Surgical removal with enucleation, resection, or occasionally a pancreaticoduodenectomy. Routine duodenotomy and periduodenal/ tumoral nodal dissection required	Recommend
With MEN1	If imaged tumor is <2–2.5 cm, most observe, although some recommend enucleation or resection. Pancreaticoduodenectomy rarely indicated	Recommend
Other functional tumor (sporadic or with MEN1)	Enucleation or surgical resection/ enucleation	Recommend

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Table 5: Pancreatic NETs (Continued)

Functional Status	Intervention	Recommendation
Nonfunctional pancreatic NET		
Sporadic	Enucleation or surgical resection with lymph node dissection. Observation in elderly or comorbid conditions	Recommend
With MEN1	If imaged tumor is <2–2.5 cm, most observe, although some recommend enucleation or resection. Pancreaticoduodenectomy rarely indicated. If >2–2.5 cm, enucleation or surgical resection with adjacent lymph node dissection.	Recommend
With VHL	If imaged tumor is >3 cm, surgical resection is recommended.	Recommend
Advanced Disease—Oncologic Control of Pancreatic NETs		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal syndrome	Recommend
Newly diagnosed with high-volume disease	Observation for a brief 3-month period if no hormonal syndrome	Recommend
	Everolimus	Consider
	Hepatic artery embolization when liver dominant disease (bland embolization, chemoembolization, or radioembolization per institutional practice)	Consider
	Sunitinib	Consider
Stable disease	Observation if no hormonal syndrome	Recommend
Progressive disease	Sunitinib	Recommend
	Everolimus	Recommend
	Cytotoxic chemotherapy	Consider
	Hepatic artery embolization when liver dominant disease (bland embolization, chemoembolization, or radioembolization per institutional practice)	Consider
	Octreotide LAR	Consider

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Table 5: Pancreatic NETs (Continued)

Hormonal Syndrome Control		
Please also see the section entitled, ''Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Colon'' for control of hormonal syndromes in the carcinoid syndrome.		
Indication	Intervention	Recommendation
Insulinoma		
Initial or nonrefractory	Dietary modification	Recommend
	Diazoxide 200–600 mg/d	Recommend
	Everolimus	Recommend
	Medicalert bracelet	Recommend
	Glucagon pen	Consider
	Somatostatin analogs. May worsen hypoglycemia in some cases; therefore, consider short-acting octreotide trial before initiation of octreotide LAR).	Consider
	Steroids (ie, decadron)	Consider
Gastrinoma	Oral proton pump inhibitors	Recommend
Initial and long-term	BID or TID dosing of Proton Pump Inhibitor	Recommend
	Medicalert bracelet	Consider
	Octreotide LAR	Consider
Other functioning PETs	Octreotide LAR	Recommend
Refractory syndrome with stable tumor volume	Nonspecific antidiarrheal agents as clinically indicated	Recommend
	Escalate dose or shorten dosing interval of octreotide LAR	Consider
	Liver-directed therapy if possible	Consider
	Surgical debulking	Consider
Refractory syndrome with increasing tumor volume	Measures for refractory syndrome	Recommend
	Measures for oncologic control (see Oncologic control section).	Recommend
	Referral to specialty center	Recommend

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Table 5: Pancreatic NETs (Continued)

Follow-Up		
Follow-up for resected pancreatic is recommended 3 to 6 months after curative resection and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (>12 months) of stable disease.		
Test or Procedure	Recommendation	Comment
Blood and urine markers		
CgA	Consider	Consider following if abnormal at baseline
Specific hormone marker	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details)
[^{111}In-DTPA0]octreotide scintigraphy		

GRF indicates growth hormone releasing factor; PPI, proton pump inhibitor; PTH, parathyroid hormone; VHL, Von-Hippel Lindau; ZES, Zollinger Ellison syndrome.

Table 6: Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum

Initial workup		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
CgA	Recommend	Often negative in those with localized tumors. False positive with proton pump inhibitor use and renal insufficiency
Urine 5-HIAA	Recommend	Need to follow diet during collection
Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	Thin section with negative bowel contrast if attempting to identify primary tumor. Consider MRI if unable to give iodine-based contrast. Consider specific enterography protocols if available.
MRI with gadoxetate (Eovist)	Recommend	In patients where surgery is being considered to get a better sense of liver disease burden, particularly when CT shows indeterminate lesions in the liver that need characterizing
Additional sites	Recommend	As clinically indicated

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Table 6: Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum (Continued)

Test or Procedure	Recommendation	Comment
Luminal Imaging		
Colonoscopy	Recommend	Terminal ileal intubation
Deep enteroscopy	Consider	Best approached bidirectionally; tattoo location if identified
Nuclear imaging		
[111In-DTPA0]octreotide scintigraphy	Recommend	Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours
Cardiac imaging		
Echocardiogram	Consider	If symptoms of carcinoid heart are suspected or as clinically indicated

Surgery of Primary Tumors
In general, resection is recommended for local regional disease and in setting of impending obstruction and should still be considered for patients with advanced disease. Ability to resect primary depends on size, depth of invasion, and institutional expertise. In patients with suspected carcinoid syndrome who undergo major procedures, a preoperative bolus of octreotide 250 to 500 µg IV is recommended with additional bolus doses available throughout procedure.

Primary Site/Size	Intervention	Recommendation
Appendix, cm		
<1	Excision	Recommend
1–2	Excision	Recommend
	Right hemicolectomy with node dissection if high risk features present	Consider
>2	Right hemicolectomy with node dissection	Recommend
Cecum	Right hemicolectomy with node dissection	Recommend
Ileum	Resection with node dissection. Ileocecal valve and right colon can be preserved for more proximal tumors. Full bowel examination required at time of surgery in case of lateral metastases.	Recommend
Jejunum	Resection with node dissection. Full bowel examination required at time of surgery in case of lateral metastases.	Recommend
Root of mesentery disease	Refer to expert center for assessment when nodal disease approaches branches of Superior Mesenteric Vein or Superior Mesenteric Artery.	Recommend

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Table 6: Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum (Continued)

Advanced Disease—Oncologic Control		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal symptoms present	Recommend
	Octreotide LAR	Consider
Newly diagnosed with high-volume disease	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
Stable disease	Observation if no hormonal symptoms	Consider
Progressive disease	Refer to specialty center	Recommend
	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
Hormonal Syndrome Control		
Carcinoid syndrome		
Initial or nonrefractory	Long-acting somatostatin analogs; octreotide LAR 20–30 mg IM is available in the United States. Immediate release octreotide can be used for breakthrough symptoms.	Recommend
Refractory syndrome		
Stable tumor volume	Antidiarrheal agents	Recommend
	Debulk tumor with liver-directed therapy if possible	Recommend
	Escalate dose or shorten dosing interval of long-acting somatostatin analog. No prospective data exist.	Recommend
	Add low-dose interferon α (short-acting or pegylated form)	Consider
	Referral to specialty center	Consider
	Rotate somatostatin analog as available	Consider

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Table 6: Neuroendocrine Tumors of the Jejunum, Ileum, Appendix, and Cecum (Continued)

Increasing tumor volume	Measures for refractory syndrome	Recommend
	Measures for oncologic control (see Oncologic control section)	Recommend
	Refer to specialty center	Consider
Follow-Up		
Follow-up for resected disease is recommended 3 to 6 months after resection with curative intent and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (>12 months) of stable disease.		
Test or Procedure	**Recommendation**	**Comment**
Blood and urine markers		
CgA	Consider	Consider following if abnormal at baseline
Urine 5-HIAA	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details)
[^{111}In-DTPA0]octreotide scintigraphy		

SMA indicates superior mesenteric artery; SMV, superior mesenteric vein.

Table 7: Neuroendocrine Tumors of the Distal Colon and Rectum

Initial workup		
Test or Procedure	**Recommendation**	**Comment**
Blood and urine markers (Baseline)		
CgA	Recommend	Often negative in those with localized tumors. False positive with proton pump inhibitor use and renal insufficiency
Urine 5-HIAA	Consider	Need to follow diet during collection
Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	Recommended for patients with tumors 92 cm, invasion beyond submucosa, or lymph node involvement. Could also consider for tumors with elevated mitotic rate or poor differentiation.

Table 7: Neuroendocrine Tumors of the Distal Colon and Rectum (Continued)

MRI with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly when CT shows indeterminate lesions in the liver that need characterizing.
Additional sites	Consider	As clinically indicated
Luminal imaging		
Colonoscopy	Recommend	Often detected incidentally on colonoscopy; consider tattoo for localization.
EUS		
Nuclear imaging		
[^{111}In-DTPA0]octreotide scintigraphy	Recommend	Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours

Surgery of Primary Tumors		
In general, resection is recommended for local regional disease and in setting of impending obstruction and should still be considered for patients with advanced disease. Ability to resect primary depends on size, depth of invasion, and institutional expertise.		
Primary Site/Size	Intervention	Recommendation
<1	Endoscopic resection (polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection) for those with mucosal or submucosal tumors	Recommend
1–2	Transanal excision via rigid or flexible dissection. Could also consider after endoscopic resection with positive margins	Recommend
>2	Surgical resection (low anterior resection or abdominoperineal resection) for larger tumors, tumors invading muscularis propria, or those with lymphadenopathy	Recommend
Incidentally discovered	Tattoo location if polyp has unusual features suggestive of carcinoid at screening colonoscopy.	Consider

Advanced Disease—Oncologic Control		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal syndrome	Recommend
	Octreotide LAR	Consider

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Table 7: Neuroendocrine Tumors of the Distal Colon and Rectum (Continued)

Newly diagnosed with high-volume disease	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider
Stable disease	Observation if no hormonal syndrome	Consider
Progressive disease	Refer to specialty center	Recommend
	Everolimus	Consider
	Liver-directed therapies when liver-dominant disease	Consider
	Octreotide LAR	Consider

Follow-Up
Intensity and duration of surveillance depends on stage of disease. Stage I tumors require no surveillance. Stage II or III should be followed 3 to 6 months after curative resection and then every 6 to 12 months for at least 7 years. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patients with long duration (>12 months) of stable disease.

Test or Procedure	Recommendation	Comment
Blood and urine markers		
CgA	Consider	Consider following if abnormal at baseline
Urine 5-HIAA	Consider	Consider following if abnormal at baseline
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details)
[^{111}In-DTPA0]octreotide scintigraphy		

Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer

Initial workup (Pheochromocytoma/Paraganglioma)		
Test or Procedure	Recommendation	Comment
Blood and urine markers (Baseline)		
Hormonal markers		
Fractionated or free metanephrines (ie, normetanephrine and metanephrines) in urine or plasma, respectively, or both	Recommend	It is preferred to measure fractionated or free metanephrines versus the parent catecholamines. Blood sampling should be done in the supine position after a 20-minute rest.
>4 upper reference range		Diagnostic of pheochromocytoma
1–4 upper reference range		Needs further evaluation. First, exclude drug effect, and then use clonidine suppression test coupled with the measurement of plasma normetanephrine (does not work if coupled with the measurement of plasma metanephrine).
Genetic counseling/genetic testing when appropriate	Recommend	To choose the proper genetic testing sequence, consider the biochemical profile of catecholamine secretion, age of the patient, localization of the primary tumor, and previous family history.
Methoxytyramine	Consider	Marker of dopamine secreting tumors, associated with malignancy and mutations in the succinate dehydrogenase complexYrelated tumors
Imaging (baseline)		
Anatomic imaging		
Abdomen and pelvis (multiphasic CT or MRI)	Recommend	Both modalities are effective for localizing and characterizing adrenal masses.
MRI with gadoxetate (Eovist)	Consider	In patients where surgery is being considered to get a better sense of liver disease burden, particularly, when CT shows indeterminate lesions in the liver that need characterizing
Additional sites	Consider	As clinically indicated, if no lesion is seen on abdomen and pelvis imaging
Nuclear imaging		Planar and SPECT imaging. Imaging at 4–6 hours and 24–48 hours
Iodine 123		
[^{123}I]-metaiodobenzylguanide (MIBG) ([^{123}]I-MIBG) scintigraphy	Consider	Should be used on all functional tumors except adrenal pheochromocytomas G5 cm that are associated with elevations of plasma and urine metanephrine (rarely metastatic). Also to be used when treatment with 131I-MIBG is considered (metastatic disease already proven by anatomic imaging)

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

[^{18}F]-fluorodeoxyglucose PET	Consider	Obtain if [^{123}]I-MIBG scan is negative and there is concern for metastatic disease.
[^{111}In-DTPA0]octreotide scintigraphy (octreotide scan)	Consider	Obtain if [^{123}]-MIBG scan is negative and there is concern for metastatic disease as well as when treatment with octreotide is considered (metastatic disease already proven by anatomic imaging).
Surgery of Primary Tumors (Pheochromocytoma/Paraganglioma)		
For major procedures, start phenoxybenzamine at 10 mg oral 2 times a day and titrate to control hypertension. May also use α-1 adrenoceptor blockers. Also consider calcium channel blocker or angiotensin receptor blockers, especially in patients with mild hypertension, and treatment should be for at least 10 to 14 days before surgery. Use volume expansion through hydration before surgery. If tachycardia is present, add β-adrenoceptor blocker (atenolol preferred). Only start after appropriate α-blockade has started.		
Surgical Approach	Intervention	Recommendation
Laparoscopic resection	Procedure of choice if no evidence of local invasion or malignancy. Consider cortical sparing adrenalectomy if familial or bilateral disease.	Recommend
Test or Procedure	Recommendation	Comment
Open resection	Procedure of choice if evidence of local invasion or malignancy or recurrent disease.	Recommend
Cytoreductive resection when locally unresectable or distant metastases present	Cytoreductive surgery should be considered in all patients to help aid in symptom control.	Consider
Advanced Disease–Oncologic Control (Pheochromocytoma/Paraganglioma)		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Indication	Intervention	Recommend
Locally unresectable	Cytoreductive surgery, if feasible	Recommend
	External beam radiation therapy	Consider
Distant Disease	Cytoreductive surgery, if feasible	Recommend
	[^{131}I]-MIBG treatment if [^{123}I]-MIBG–positive disease	Consider
	Radiofrequency ablation	Consider
	Systemic chemotherapy (cyclophosphamide, vincristine, and dacarbazine,) if [^{123}I]-MIBG–negative disease or rapidly progressing	Consider

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

Hormonal Syndrome Control (Pheochromocytoma/Paraganglioma)		
Indication	Intervention	Recommendation
Treatment of catecholamine overproduction	Alpha-blockade for symptom control. May change to selective α-1 blockers for long-term treatment	Recommend
	Beta-blockade if necessary after adequate α-blockade in patients with tachycardia	Recommend
Treatment of catecholamine crisis	Alpha-methyl-para-tyrosine	
	Phentolamine IV bolus 2.5–5 mg at 1 mg/min, may repeat every 5 minutes or run as an infusion (100 mg in 500 mL of Dextrose 5% water). Alternative is nitroprusside infusion at 0.5–5.0 µg/kg per minute. (do not exceed 3.0 µg/kg per minute for long-term use)	Recommend

Follow-up (Pheochromocytoma/Paraganglioma)		
Follow-up for resected disease is recommended 6 and 12 months after curative resection and then annually. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 months for patient with long duration (>12 months) of stable disease.		
Test or Procedure	Recommendation	Comment
Blood and urine markers		
Fractionated or free metanephrines	Recommend	
CgA	Consider	May be used if tumor does not produce significant levels of plasma metanephrines, especially those with succinate dehydrogenase complex gene mutations
Imaging		
Anatomic imaging (multiphasic CT or MRI)	Recommend	As clinically indicated for suspected recurrence.
PET scan, octreotide scan, MIBG scan	Consider	As clinically indicated for suspected recurrence.
Initial workup (Medullary Thyroid Cancer)		
Blood and urine markers (baseline)		
Tumor markers		
Calcitonin	Recommend	Correlates with tumor burden
Carcinoembryonic antigen (CEA)	Consider	Preferentially expressed in less differentiated tumors
Refer for genetic counseling/testing	Recommend	

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

Test or Procedure	Recommendation	Comment
Test for associated tumors (pheochromocytoma and hyperparathyroidism)		
Fractionated or free metanephrines (ie, normetanephrine and metanephrines) in urine or plasma, respectively, or both	Recommend	Fractionated or free metanephrines preferred over the parent catecholamines. Blood sampling should be done in the supine position after a 20-minute rest.
Calcium	Recommend	If abnormal, obtain a PTH level.
Imaging (baseline)		
Anatomic imaging		
CT of chest, mediastinum, and abdomen	Recommend	Evaluate for metastatic disease, especially if evidence of nodal disease on neck ultrasound or calcitonin is significantly elevated.
Neck ultrasound	Recommend	To assess for additional thyroid masses and neck lymphadenopathy
Laparoscopy of liver	Consider	As clinically indicated if concerned about micrometastatic disease in the liv
Surgery of Primary Tumors (Medullary Thyroid Cancer)		
Intervention	Recommendation	Comment
Primary tumor resection		
Locoregional disease	Recommend	
Advanced disease	Consider	
Nodal disease		
Bilateral central neck dissection	Recommend	For locoregional disease
	Consider	For advanced disease
Ipsilateral lateral neck dissection	Recommend	If evidence of nodal disease on preoperative imaging
	Consider	If tumor is >1 cm or there is evidence of positive nodes in the central neck
Contralateral lateral neck dissection	Recommend	If evidence of nodal disease on preoperative imaging
	Consider	If bilateral tumors, or extensive lateral adenopathy on the side of the tumor
Prophylactic surgery (medullary thyroid cancer)		
Preoperative		
Test for pheochromocytoma, hyperparathyroidism	Recommend	All patients should be tested for a pheochromocytoma (fractionated metanephrines in plasma or urine) and hyperparathyroidism (serum calcium) preoperatively.
Baseline tumor markers (calcitonin and CEA)	Recommend	
Neck ultrasound	Recommend	Evaluate for tumors and/or lymphadenopathy

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

Intervention	Recommendation	Comment
Surgical treatment		
Total thyroidectomy	Recommend	Should be performed by age 1 in MEN 2B and by age 5 in MEN 2 and Familial Medullary Thyroid Carcinoma.
Bilateral central neck dissection	Consider	If elevated preoperative calcitonin or evidence of tumor on neck ultrasound
Advanced Disease–Oncologic Control (Medullary Thyroid Cancer)		
Generally for NETs, lines of therapy have not been established when multiple options are listed. Surgical resection should be considered if most (approximately 90%) of gross disease can be resected safely. Clinical trials should always be considered.		
Disease Stage	**Intervention**	**Recommendation**
Locally unresectable	Cytoreductive surgery, if feasible	Recommend
	Vandetanib	Recommend
	External beam radiation therapy should be used only if surgical resection is not feasible or surgical resection is incomplete	Consider
Distant disease	Cytoreductive surgery, if patient is symptomatic and resection is feasible	Recommend
	Vandetanib	Recommend
	Palliative regional therapy (RFA, embolization, etc.)e	Consider
Hormonal Syndrome Control (Medullary Thyroid Cancer)		
Indication	**Intervention**	**Recommendation**
Refractory symptoms due to hypercalcitonemia	Long-acting somatostatin analogs	Recommend
	Cytoreductive surgery of unresectable disease	Consider
Follow-up (Medullary Thyroid Cancer)		
Follow-up for resected disease is recommended 3 to 6 months after curative resection and then annually; maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 3 to 6 months; may lengthen interval to every 6 to 12 months for patient with long duration (>12 months) of stable disease. Follow-up after prophylactic thyroidectomy if no tumor present or only c-cell hyperplasia found is recommended every 1 to 2 years.		
Test or Procedure	**Recommendation**	**Comment**
Biomarkers (calcitonin and CEA)	Recommend	
Fractionated plasma and/or urinary metanephrines	Recommend	Annually, if at risk for MEN 2A or 2B
Serum calcium	Recommend	Annually, if at risk for MEN2A

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Table 8: Pheochromocytoma/paraganglioma, Medullary Thyroid Cancer (Continued)

Imaging		
Neck ultrasound	Recommend	May discontinue if calcitonin and CEA are stable and previous ultrasound was negative. Consider in advanced disease.
Anatomic imaging		
CT or MRI	Consider	As clinically indicated for suspected recurrence
Additional imaging	Consider	As clinically indicated for rising calcitonin and/or CEA

CEA indicates carcinoembryonic antigen; D5W, dextrose 5% water; FMTC, familial medullary thyroid carcinoma; PTH, parathyroid hormone.

Table 9: Poorly Differentiated NECs

Generally, blood and urine markers are not helpful in poorly differentiated NECs.		
Initial workup (Medullary Thyroid Cancer)		
Test or Procedure	Recommendation	Comment
Imaging (baseline)		
Anatomic imaging		
CT chest, abdomen, and pelvis	Recommend	Used for baseline imaging and to monitor for response to treatment
Brain MRI	Consider	MRI of brain is recommended for poorly differentiated NEC of lung origin. Risk of brain metastases for extrapulmonary NEC is rare. Should be considered as clinically indicated.
Nuclear imaging		
Bone scan	Consider	
[^{18}F]-fluorodeoxyglucose PET	Consider	If clinically appropriate. Poorly differentiated NEC can be strongly hypermetabolic on FDG-PET CT scan, which may be helpful to stage disease and monitor response to treatment.
[^{111}In-DTPA0]octreotide scintigraphy	Consider	Consider only if disease is not avid on FDG-PET scan.

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Table 9: Poorly Differentiated NECs (Continued)

Treatment of Poorly Differentiated NEC		
Generally for NETs, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy.		
Disease Stage	Intervention	Recommendation
Locoregional disease, resectable		
Clinical stage T1-2, NO	Surgical resection, including removal of tumor with negative margins. Risk of recurrence is high, however.	Recommend
	Postoperative therapy with 4Y6 cycles of cisplatin or carboplatin and etoposide. Radiation should only be considered in cases where risk of local recurrence is considered high and morbidity is low.	Recommend
Clinical stage in excess of T1-2, N0	Chemotherapy with or without concurrent radiotherapy	Recommend
	Surgery where morbidity is low, particularly where risk of obstruction is high. Risk of recurrence is high, however. Consider postoperative therapy with 4–6 cycles of cisplatin or carboplatin and etoposide. Radiation should only be considered in cases where risk of local recurrence is considered high and morbidity is low.	Consider
Locoregional disease, unresectable	Platinum-based chemotherapy regimen (cisplatin or carboplatin and etoposide) for 4–6 cycles with concurrent or sequential radiation	Recommend
Metastatic: initial therapy	Platinum-based chemotherapy*	Recommend
Metastatic: progressive or relapsed disease	For relapse >6 months after termination of first-line therapy: original chemotherapy regimen	Recommend
	For relapse <3–6 months: irinotecan or topotecan, paclitaxel, docetaxel, vinorelbine, gemcitabine, temozolomide may be considered.	Consider

Continued on next page

Table 9: Poorly Differentiated NECs (Continued)

Follow-Up		
Follow-up for resected disease is recommended every 3 months for 1 year, followed by every 6 months. Maximum duration of follow-up is not defined; late recurrence can occur in some patients. Follow-up for advanced disease is recommended every 6 to 12 weeks.		
Test or Procedure	Recommendation	Comment
Imaging		
Anatomic imaging (CT or MRI)	Recommend	See initial imaging for details
Nuclear imaging	Consider	As clinically indicated. Poorly differentiated NEC can be strongly hypermetabolic on FDG-PET CT scan, which may be helpful to stage disease and monitor response to treatment.
[^{18}F]-fluorodeoxyglucose PET		

*Chemotherapy regimens active against small-cell lung cancer are recommended. Cisplatin and etoposide have demonstrated activity in the treatment of poorly differentiated NEC. Substitution of carboplatin for cisplatin and irinotecan for etoposide can be considered. Four to 6 cycles of chemotherapy typically administered. Optimal duration of therapy is not clearly defined.

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