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Consensus Guidelines for the Management and Treatment of Neuroendocrine Tumors

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Abstract

Neuroendocrine tumors (NETs) 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 degree of aggressiveness. The recent completion of several phase III 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) 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.

Keywords

Neuroendocrine tumors; carcinoid; neuroendocrine/diagnosis; neuroendocrine/treatment; neuroendocrine/pathology; pheochromocytoma

Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of tumors originating in various locations, including the 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 III 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. Though other comprehensive guidelines exist (i.e. NCCN 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 were published in 2010[1-7] 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 work-up recommendations. These tables included: I. Pathology, II. NETs of the Thorax, III. Gastric NETs, IV. Pancreatic NETs, V. NETs of the small bowel and cecum ("Midgut"), VI. NETs of the colon and rectum ("Hindgut"), VII. Pheochromocytoma, paraganglioma, and medullary thyroid cancer, and VIII. High grade neuroendocrine carcinoma. The tables include two 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 work-up, 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 RADIANT-3 study[8], published in 2011, is a randomized phase III 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 PO daily or placebo. The median progression-free survival (PFS) was 11.0 months with everolimus as compared to 4.6 months with placebo (HR 0.35; 95% CI 0.27 to 0.45; $p<0.001$). Response rate (RR) was 5% in the everolimus arm compared to 2% in the placebo arm. Median overall survival (OS) has not been reached.

In another Phase III study published in 2011, 171 patients with advanced, well-differentiated, progressive pancreatic NETs were randomized to receive sunitinib 37.5 mg PO 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. Median PFS was 11.4 months in the sunitinib arm compared with 5.5 months in the placebo arm (HR 0.42; 95% CI 0.26-0.66); p <0.001). RRs in the sunitinib and placebo arms were 9.3% and 0% respectively. Median overall survival could not be estimated given the high number of censored events in both groups.

In addition to the above treatment advances, there were two 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 prior to 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 (Table1). A few of these topics are highlighted here.

Indications for targeted therapies

Based on the aforementioned phase III clinical trials, sunitinib and everolimus are FDA approved and recommended for patients with progressive metastatic pancreatic NETs. Everolimus was also studied in metastatic functional (i.e., hormone secreting) carcinoid tumors in a large phase III clinical trial. Though this study did not meet its primary endpoint of PFS, there was a trend towards 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-FU, 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 temozolomide-based 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 pancreatic NET. There is currently no known role for cytotoxic therapies in advanced carcinoid.

Indication and dosing of somatostatin analogues

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 clinicians often increase the dose and/or frequency of somatostatin analogs in 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 analogue doses could be escalated or interval shortened in an attempt to control these symptoms but note that no prospective data exist.

The 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 analogues as antiproliferative agents in pancreatic NETs, though 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-HIAA is not as useful in patients with foregut (bronchial, gastric) or hindgut (rectal) NETs or in most patients with pancreatic NETS which do not secrete serotonin. CgA is a 49-kDa 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. Median survivals of 24-128 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 those patients in whom all hepatic metastases seem to be resectable, and in whom no (or mild non-clinically 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 two new biologic agents in this disease. There is ongoing research in biomarkers, imaging and novel agents. Below we present eight Consensus Tables summarizing available data and expert consensus in the field of NETs (Tables 2-9).

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Table 1

Controversial Topics

PANCREAS
–Use of octreotide for tumor control in patients with advanced pancreatic neuroendocrine tumors
–Indications for initiating targeted therapies or cytotoxic chemotherapy in patients with advanced pancreatic neuroendocrine tumors
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 (CVD, temozolomide, or sunitinib) in patients with advanced pheochromocytoma/paraganglioma
SURGERY
-Role of surgical debulking in asymptomatic metastatic liver predominant NET patients
-Role of surgical debulking in patients where an R0 resection cannot be achieved
EMBOLIZATION
-In absence of randomized data, which modality (bland embolization, radioembolization, chemoembolization) should be employed?
ALL
–Use and frequency of chromogranin A in following patients on or off treatment
–Use of everolimus and sunitinib in non-pNET patients
–Use of somatostatin scintigraphy imaging to follow disease

Table 2

Net Pathology

THoracic NETs

Mitotic rate should be obtained. Use of the World Health Organization (WHO) and International Association for the Study of Lung Cancer (IASLC) grading system is recommended. If specimen is inadequate, repeat biopsy is recommended.

Test or procedure	Recommendation	Comments
Grading (proliferative rate)		
Mitotic rate	Recommend	Mitoses per 10 HPF*
Ki67	Consider	
Typical carcinoid	Recommend	< 2 mitoses / 10 HPF
Atypical carcinoid	Recommend	≥ 2-10 mitoses/ 10 HPF
High grade (small cell or large cell NE carcinoma)	Recommend	> 10 mitoses/ 10 HPF
Presence of necrosis	Recommend	Absent – typical carcinoid; present – atypical carcinoid.
Immunohistochemistry		
Chromogranin A	Recommend	Marker neuroendocrine phenotype
Synaptophysin	Recommend	Marker neuroendocrine phenotype
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 non-neuroendocrine components	Recommend	Present/absent

Gastric NETS

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
Grading (proliferative rate)		
Mitotic rate	Recommend	
G1		< 2 mitoses/ 10HPF*

Gastric NETS

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
G2		2-20 mitoses/ 10 HPF
G3		>20 mitoses / 10 HPF
Ki 67	Recommend	
G1		<3%
G2		3-20%
G3		>20%
Histology differentiation		
Immunohistochemistry	Recommend	Poorly differentiated neuroendocrine carcinomas (G3) are highly aggressive and need distinguishing from other NETs
Chromogranin A	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 (pathologic metastasis) -denotes metastases location
Presence of non-neuroendocrine components	Recommend	Present/absent
Biopsies of non-tumoral gastric mucosa	Recommend	Helps differentiate types of gastric NETs
Histology/IHC		
Atrophic gastritis present		
ECL hyperplasia present		
Parietal cell hypertrophy present		

Pancreatic NETS

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 (i.e. large cell)	Recommend	

Pancreatic NETS

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
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 neuroendocrine carcinomas (G3) are highly aggressive and need to be distinguished from other NETs
Immunohistochemistry		
Chromogranin A	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 (pathologic Metastasis)-denotes metastases location
Presence of non-neuroendocrine components	Recommend	Present/absent

Midgut NETS

Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained, overall grade is defined by the highest of the two. If specimen is inadequate, repeat biopsy is recommended.

Test or procedure	Recommendation	Comment
Grading (Proliferative rate)	Recommend	
Mitotic rate		
G1		< 2 mitoses / 10 HPF*

Midgut NETS

Mitotic rate or Ki67 should be obtained. When both mitotic rate and Ki67 are obtained, overall grade is defined by the highest of the two. If specimen is inadequate, repeat biopsy is recommended.

Test or procedure	Recommendation	Comment
G2		2-20 mitoses / 10 HPF
G3		>20 mitoses / 10 HPF
Ki 67		
G1		<3%
G2		3-20%
G3		>20%
Immunohistochemistry		
Chromogranin A	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 (pathologic Metastasis) should be used to denote metastases location
Presence of non-neuroendocrine components	Recommend	Present/absent

Hindgut NETS

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, repeat 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		

Hindgut NETS

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, repeat biopsy is recommended.

Test or procedure	Recommendation	Comment
G1		<3%
G2		3-20%
G3		>20%
Immunohistochemistry		
Chromogranin A	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 (pathologic Metastasis) should be used to denote metastases location
Presence of non-neuroendocrine components	Recommend	Present/Absent

Pheochromocytoma/Paraganglioma

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
Peri-adrenal adipose tissue	Consider	
Large nests/diffuse growth	Consider	
Focal or confluent necrosis	Consider	Can be associated with malignancy
Cellularity	Consider	

Pheochromocytoma/Paraganglioma

Distinction between benign and malignant disease is difficult to ascertain pathologically

Test or procedure	Recommendation	Comment
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		
Chromogranin A	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

Poorly Differentiated NETs

Test or procedure	Recommendation	Comment
Subtype		
Small cell, Non-small cell (i.e. large cell)	Recommend	
Grading (Proliferative rate)		
Mitotic rate (G3)	Recommend	>10 mitoses/ 10 HPF* for lung >20 mitoses / 10 HPF for GEP-NET
Ki67	Recommend	>20%
Immunohistochemistry		
Chromogranin A	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	

Poorly Differentiated NETs

Test or procedure	Recommendation	Comment
Nodal metastases	Recommend	
Distant metastases	Recommend	pM (pathologic Metastasis) should be used to denote metastases location
Presence of non-neuroendocrine 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

Table 3

Nets of the Thorax

Workup and classification

Blood and urine markers (baseline)

Test or procedure	Recommendation	Comments
ACTH	Consider	As clinically indicated
Chromogranin A	Consider	Investigational in thoracic NET, check at baseline.
Urine 5-HIAA	Consider	As clinically indicated.

Imaging (baseline)

Test or procedure	Recommendation	Comments
Anatomic imaging		
Chest and abdomen (Multiphasic CT)	Recommend	
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 Chest	Consider	To determine resectability in thymic tumors.
[^{18}F]-fluorodeoxyglucose PET	Consider	May be considered in undifferentiated tumors and/or to further characterize negative/equivocal octreotide scans.
Luminal Imaging	Consider	To determine resectability, especially in lung NET
Bronchoscopy	Consider	To determine resectability, especially in lung NET
Endobronchial ultrasound	Recommend	Planar and SPECT imaging. Imaging at 4-6 hours and 24-48 hours.
Nuclear imaging		
[^{111}In-DTPA0] octreotide scintigraphy		

Treatment of Thymic NET

Generally for neuroendocrine tumors, 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 the majority (∼ 90%) of gross disease can be resected safely.

	Intervention	Recommendation
Local-regional disease	Surgical resection including mediastinal lymphadenectomy.	Recommend
Recurrent localized disease	Surgical resection of localized disease	Recommend
Metastatic/unresectable disease	Everolimus	Consider
	Interferon alpha	Consider

Treatment of Thymic NET

Generally for neuroendocrine tumors, 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 the majority (~ 90%) of gross disease can be resected safely.

	Intervention	Recommendation
	Radiation for unresectable disease	Consider
	Temozolomide	Consider

Treatment of Lung/Bronchial NET

Generally for neuroendocrine tumors, 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 the majority (~ 90%) of gross disease can be resected safely. Clinical trials should always be considered.

	Intervention	Recommendation
Local-regional disease	Surgical resection with hilar/mediastinal lymph node sampling is recommended.	Recommend
Recurrent disease, resectable	Surgical resection	Recommend
Metastatic/unresectable disease	Everolimus	Consider
	Interferon alpha	Consider
	Radiation for unresectable disease	Consider
	Temozolomide	Consider

Follow-up

Follow-up for resected disease is recommended 3-6 months after curative resection and then every 6-12 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 3-6 months; can lengthen interval to every 6 months for patient with long duration (>12 month) of stable disease.

Follow-up items	Recommendation	Comments
Blood and urine markers		
ACTH	Consider	Consider following if abnormal at baseline.
Chromogranin A	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 (see initial imaging for details).
[^{111}In-DTPA0]octreotide scintigraphy		

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Table 4

Gastric Nets

INITIAL WORKUP

Blood and Urine markers (baseline)

Test or procedure	Recommendation	Comment
Gastric pH	Recommend	Gastric pH helps differentiate Type I (gastric pH >4) from Type II gastric (gastric pH<2). Type II requires workup for 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 anti-parietal cell antibodies	Consider	Only in Type I. Consider workup for polyglandular syndrome
Chromogranin A	Consider	Recommended for Type III (normogastrinemic) gastric carcinoids; false positive with proton pump inhibitor use and renal insufficiency.

Imaging (baseline)

Test or procedure	Recommendation	Comment
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 evaluation		
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		
[^{11}In-DTPA0]octreotide scintigraphy	Consider	For types II and III only

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 that undergo major procedures, a preoperative bolus of octreotide 250 – 500 microgram IV is recommended with additional bolus doses available throughout procedure.

	Intervention	Recommendation
Type I		
[<1 cm	Surveillance or endoscopic removal.	Recommend

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 that undergo major procedures, a preoperative bolus of octreotide 250 – 500 microgram IV is recommended with additional bolus doses available throughout procedure.

	Intervention	Recommendation
[*1- 2 cm (up to 6 polyps)	Surveillance with repeat endoscopy approximately every 3 years or endoscopic resection. EUS could be used to assess depth of invasion but should be individualized. If submucosal invasion, endoscopic mucosal resection is increasingly used.	Recommend
[*> 2cm (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		Recommend
[<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.	

ADVANCED DISEASE - ONCOLOGIC CONROL GASTRIC NEUROENDOCRINE TUMORS

Advanced Disease is typically limited to Type III only. Generally for neuroendocrine tumors, 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 performed if the majority (∼ 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).

Indication	Intervention	Recommendation
Carcinoid syndrome		
Initial or non-refractory	Long acting somatostatin analogues; Octreotide LAR 20-30 mg IM is available in the US. Immediate release octreotide can be used for breakthrough symptoms.	Recommend
Refractory syndrome with stable tumor volume	Anti-diarrheal agents	Recommend
	Debulk tumor with liver directed therapy if possible	Recommend
	Escalate dose or shorten dosing interval of long acting somatostatin analogue. No prospective data exists	Recommend
	Add low dose interferon α (short acting or pegylated form)	Consider
	Referral to specialty center	Consider
	Rotate somatostatin analogue as available	Consider
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 3-6 months after curative resection and then every 6-12 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 3-6 months; can lengthen interval to every 6 months for patient with long duration (>12 month) of stable disease.

Follow-up items	Recommendation	Comments
Blood and urine markers		
Chromogranin A	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	Recommend	For Type I and II gastric carcinoid, every 1-3 years
EGD	Consider	Especially for Type II
Gastric pH		
Nuclear Imaging	Consider	As clinically indicated for suspected recurrence (see initial imaging for details).
[^{11}In-DTPA0]octreotide scintigraphy		

* Multiple lesions that are larger than 1-2 cm should be individually decided and could include local resection, surgical resection, or watchful waiting.

Table 5

Pancreatic Nets

INITIAL WORKUP

Blood and Urine markers (baseline)

Chromogranin A	Recommend	Especially useful if non-functional pancreatic NET suspected. False positive with proton pump inhibitor use and renal insufficiency.
5-HIAA	Recommend	May be useful if non-functional pancreatic NET suspected.
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[PTH-related peptide, GRF, etc]		As clinically indicated

Genetic testing

Test or procedure	Recommendation	Comment
Inherited syndromes (VHL, tuberous sclerosis, Neurofibromatosis-1)	Recommend	Genetic testing needs to be considered if clinical or family history suggestive of these syndromes (see text for details of syndromes)
MEN1	Consider	Genetic testing for MEN1 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.

Imaging (baseline)

Test or procedure	Recommendation	Comment
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	Consider	In patients suspected of gastrinoma to visualize prominent gastric folds in ZES; also with duodenal NETs (often non-functional) and in MEN-1 who have submucosal duodenal lesions
EGD	Consider	
Endoscopic ultrasound		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		

Imaging (baseline)

Test or procedure	Recommendation	Comment
[^{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 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 <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
Nonfunctional pancreatic NET		
Sporadic	Enucleation or surgical resection with lymph node dissection. Observation in elderly or comorbid conditions.	Recommend
With MEN1	If imaged tumor <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 >3cm surgical resection recommended	Recommend

ADVANCED DISEASE –ONCOLOGIC CONTROL- PANCREATIC NEUROENDOCRINE TUMORS

Generally for neuroendocrine tumors, 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 the majority(∼ 90%) of gross disease can be resected safely. Clinical trials should always be considered.

	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal syndrome	Consider
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	Everolimus	Recommend
	Sunitinib	Recommend
	Cytotoxic Chemotherapy	Consider
	Hepatic artery embolization when liver dominant disease(bland embolization, chemoembolization or radioembolization per institutional practice)	Consider

ADVANCED DISEASE –ONCOLOGIC CONTROL- PANCREATIC NEUROENDOCRINE TUMORS

Generally for neuroendocrine tumors, 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 the majority(∼ 90%) of gross disease can be resected safely. Clinical trials should always be considered.

	Intervention	Recommendation
	Octreotide LAR	Consider

HORMONAL SYNDROME CONTROL

Please also see the Section entitled, "NETs of the Jejunum, Ileum, Appendix and Colon" for control of hormonal syndromes in the carcinoid syndrome.

Indication	Intervention	Recommendation
Insulinoma		
Initial or non-refractory	Dietary modification	Recommend
	Diazoxide 200-600 mg/d	Recommend
	Everolimus	Recommend
	Medicalert bracelet	Recommend
	Glucagon Pen	Consider
	Somatostatin analogues. May worsen hypoglycemia in some cases; therefore, consider short acting octreotide trial before initiation of octreotide LAR).	Consider
	Steroids (i.e. decadron)	Consider
Gastrinoma		
Initial and long-term	Oral proton pump inhibitors	Recommend
	BID or TID dosing of PPI	Recommend
	Medicalert bracelet	Consider
	Octreotide LAR	Consider
Other Functioning PETs	Octreotide LAR	Recommend
Refractory syndrome with stable tumor volume	Non-specific anti-diarrheal 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

Follow-up

Follow-up for resected pancreatic is recommended 3-6 months after curative resection and then every 6-12 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 3-6 months; can lengthen interval to every 6 months for patient with long duration (>12 month) of stable disease.

Follow-up items	Recommendation	Comments
Blood and urine markers		
Chromogranin A	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).
[^{11}In-DTPA0]octreotide scintigraphy		

Table 6

Nets of the Jejunum, Ileum, Appendix and Cecum

INITIAL WORKUP

Blood and urine markers (baseline)

Test or procedure	Recommendation	Comment
Chromogranin A	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)

Test or procedure	Recommendation	Comment
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™)	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	Terminal ileal intubation
Deep enteroscopy	Consider	Best approached bidirectionally, tattoo location if identified
Nuclear imaging		
[^{111}In-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 that undergo major procedures, a preoperative bolus of octreotide 250 – 500 microgram IV is recommended with additional bolus doses available throughout procedure.

Primary site / size	Intervention	Recommendation
Appendix		
< 1 cm	Excision	Recommend
1 – 2 cm	Excision	Recommend

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 that undergo major procedures, a preoperative bolus of octreotide 250 – 500 microgram IV is recommended with additional bolus doses available throughout procedure.

Primary site / size	Intervention	Recommendation
	Right hemicolectomy with node dissection if high risk features present	Consider
> 2 cm	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 SMV or SMA.	Recommend

ADVANCED DISEASE - ONCOLOGIC CONROL

Generally for neuroendocrine tumors, 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 the majority (~ 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

Indication	Intervention	Recommendation
Carcinoid syndrome		
Initial or non-refractory	Long acting somatostatin analogues; Octreotide LAR 20-30 mg IM is available in the US. Immediate release octreotide can be used for breakthrough symptoms.	Recommend

Hormonal syndrome control

Indication	Intervention	Recommendation
Refractory syndrome with stable tumor volume	Anti-diarrheal agents	Recommend
	Debulk tumor with liver directed therapy if possible	Recommend
	Escalate dose or shorten dosing interval of long acting somatostatin analogue. No prospective data exist.	Recommend
	Add low dose interferon α (short acting or pegylated form)	Consider
	Referral to specialty center	Consider
	Rotate somatostatin analogue as available	Consider
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 disease is recommended 3-6 months after resection with curative intent and then every 6-12 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 3-6 months; can lengthen interval to every 6 months for patient with long duration (>12 month) of stable disease.

Follow-up items	Recommendation	Comments
Blood and urine markers		
Chromogranin A	Consider	Consider following if abnormal at baseline.
Urine 5-HIAA	Consider	Consider following if abnormal at baseline.
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 7

Nets of the Distal Colon and Rectum

INITIAL WORKUP

Blood and urine markers (baseline)

Test or procedure	Recommendation	Comment
Chromogranin A	Recommend	Often negative in those with localized tumors. False positive with proton pump inhibitor use and renal insufficiency.
Urine 5-HIAA	Consider	NETs of the colon and rectum rarely secrete serotonin. Need to follow diet during collection.

Imaging (baseline)

Test or procedure	Recommendation	Comment
Anatomic imaging		
Abdomen and pelvis (Multiphasic CT or MRI)	Recommend	Recommended for patients with tumors > 2cm, invasion beyond submucosa, or lymph node involvement. Could also consider for tumors with elevated mitotic rate or poor differentiation.
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.
Endoscopic Ultrasound (EUS)	Consider	For rectal tumors: Recommend if > 1cm or high risk features; helpful to determine depth of involvement and presence of nodes.
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 cm	Endoscopic resection (polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection) for those with mucosal or submucosal tumors.	Recommend
1 – 2 cm	Transanal excision via rigid or flexible dissection Could also consider after endoscopic resection with positive margins.	Recommend
> 2 cm	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 neuroendocrine tumors, 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 the majority (∼ 90%) of gross disease can be resected safely. Clinical trials should always be considered.

	Intervention	Recommendation
Newly diagnosed with low or intermediate tumor volume	Observation if no hormonal syndrome	Recommend
	Octreotide LAR	Consider
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 3-6 months after curative resection and then every 6-12 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 3-6 months; can lengthen interval to every 6 months for patient with long duration (>12 month) of stable disease.

Follow-up items	Recommendation	Comments
Blood and urine markers		
Chromogranin A	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)

Blood and urine markers (baseline)

Test or procedure	Recommendation	Comment
Hormonal markers		
Fractionated or free metanephrines (i.e. 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 20 min rest.
• >4X upper reference range		Diagnostic of pheochromocytoma
• 1-4X 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 complex (SDHx) related tumors

Imaging (baseline)

Test or procedure	Recommendation	Comment
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		
[^{123}I]meta-iodobenzylguanide (MIBG) scintigraphy	Consider	Should be used on all functional tumors except adrenal pheochromocytomas <5 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).
[^{18}F]-fluorodeoxyglucose PET	Consider	Obtain if 123I-MIBG scan is negative and there is concern for metastatic disease.
[^{111}In-DTPA0]octreotide scintigraphy (Octreotide Scan)	Consider	Obtain if 123I-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).

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SURGERY OF PRIMARY TUMORS (Pheochromocytoma/Paraganglioma)

For major procedures, start phenoxybenzamine at 10 mg po bid and titrate to control hypertension. May also use alpha-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 10-14 days prior to surgery. Use volume expansion through hydration before surgery. If tachycardia present, add beta adrenoceptor blocker (atenolol preferred). Only start after appropriate alpha-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
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 neuroendocrine tumors, 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 performed if the majority (~ 90%) of gross disease can be resected safely. Clinical trials should always be considered.

Indication	Intervention	Recommendation
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, dacarbazine,) if [^{123}I] – MIBG negative disease or rapidly progressing	Consider

Hormonal syndrome control (Pheochromocytoma/Paraganglioma)

Indication	Intervention	Recommendation
Treatment of catecholamine overproduction	Alpha-blockade for symptom control. May change to selective alpha-1 blockers for long-term treatment	Recommend
	Beta- blockade if necessary after adequate alpha-blockade in patients with tachycardia	Recommend
	Alpha-methyl-para-tyrosine	Consider
Treatment of catecholamine crisis	Phentolamine IV bolus 2.5 mg to 5 mg at 1 mg/min, may repeat every 5 minutes or run as an infusion (100 mg in 500 ml of D5W). Alternative is Nitroprusside infusion at 0.5 -5.0 mcg/kg/min. (do not exceed 3.0 mcg/kg/min 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 3-6 months; can lengthen interval to every 6 months for patient with long duration (>12 month) of stable disease.

Follow-up items	Recommendation	Comment
Blood markers		
Fractionated or free metanephrines	Recommend	
Chromogranin A	Consider	May be used if tumor does not produce significant levels of plasma metanephrines, especially those with SDHx 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)

Test or procedure	Recommendation	Comment
Tumor markers		
Calcitonin	Recommend	Correlates with tumor burden.
CEA	Consider	Preferentially expressed in less differentiated tumors.
Refer for genetic counseling/testing	Recommend	
Test for associated tumors (pheochromocytoma and hyperparathyroidism)		
Fractionated or free metanephrines (i.e. 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 20 min rest.
Calcium	Recommend	If abnormal obtain a PTH level.

Imaging (baseline)

Test or procedure	Recommendation	Comment
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 liver.

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SURGERY OF PRIMARY TUMORS (Medullary Thyroid Cancer)

Intervention	Recommendation	Comment
Primary tumor resection		
Local regional disease	Recommend	
Advanced disease	Consider	
Nodal disease		
Bilateral central neck dissection	Recommend	For local regional disease
	Consider	For advanced disease
Ipsilateral lateral neck dissection	Recommend	If evidence of nodal disease on pre-operative 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 pre-operative imaging.
	Consider	If bilateral tumors, or extensive lateral adenopathy on the side of the tumor.

Prophylactic surgery (Medullary Thyroid Cancer)

Test/Procedure	Recommendation	Comment
Preoperative		
Test for pheochromocytoma, hyperparathyroidism	Recommend	All patients should be tested for a pheochromocytoma (fractionated metanephrines in plasma or urine) and hyperparathyroidism (serum Calcium) pre-operatively.
Baseline tumor markers (calcitonin and CEA)	Recommend	
Neck ultrasound	Recommend	Evaluate for tumors and/or lymphadenopathy
Surgical Treatment		
Total Thyroidectomy	Recommend	Should be performed by age 1 in MEN2B and by age 5 in MEN2 and FMTC.
Bilateral central neck dissection	Consider	If elevated pre-operative calcitonin, or evidence of tumor on neck ultrasound.

Advanced disease – Oncologic Control (Medullary Thyroid Cancer)

Generally for neuroendocrine tumors, lines of therapy have not been established when multiple options are listed. Surgical resection should be performed if the majority (~ 90%) of gross disease can be resected safely. Clinical trials should always be considered.

	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

Advanced disease – Oncologic Control (Medullary Thyroid Cancer)

Generally for neuroendocrine tumors, lines of therapy have not been established when multiple options are listed. Surgical resection should be performed if the majority (~ 90%) of gross disease can be resected safely. Clinical trials should always be considered.

	Intervention	Recommendation
	Palliative regional therapy (RFA, embolization, etc)	Consider

Hormonal syndrome control (Medullary Thyroid Cancer)

	Intervention	Recommendation
Refractory symptoms due to hypercalcitonemia	Long acting somatostatin analogues.	Recommend
	Cytoreductive surgery of unresectable disease	Consider

Follow-up (Medullary Thyroid Cancer)

Follow-up for resected disease is recommended 3-6 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 3-6 months; can lengthen interval to every 6-12 months for patient with long duration (>12 month) of stable disease. Follow-up after prophylactic thyroidectomy if no tumor present or only c-cell hyperplasia found is recommended every 1-2 years.

	Recommendation	Comment
Biomarkers (calcitonin and CEA)	Recommend	
Fractionated plasma and/or urinary metanephrines	Recommend	Annually, if at risk for MEN2A or 2B
Serum calcium	Recommend	Annually, if at risk for MEN2A.
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

Table 9

Poorly Differentiated Neuroendocrine Carcinomas

INITIAL WORKUP

Generally blood and urine markers are not helpful in poorly differentiated NECs.

Imaging (baseline)

Test or procedure	Recommendation	Comment
Anatomic imaging		
CT chest, abdomen, 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 extra-pulmonary NEC is rare. Should be considered as clinically indicated.
Nuclear imaging		
Bone scan	Consider	If clinically appropriate.
[^{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.

TREATMENT OF POORLY DIFFERENTIATED NEC

Generally for neuroendocrine tumors, lines of therapy have not been established. When multiple options are listed, order of listing does not imply order of therapy.

	Intervention	Recommendation
Local-regional disease, resectable		
Clinical Stage T1-2, NO	Surgical resection, including removal of tumor with negative margins. Risk of recurrence is high, however.	Recommend
	Post-operative 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.	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 post-operative 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
Local-regional 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 can be considered.	Consider

FOLLOW-UP

Follow-up for resected disease is recommended every 3 months for one 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 6-12 weeks.

Follow-up items	Recommendation	Comment
Imaging		
Anatomic imaging (CT or MRI)	Recommend	
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 has demonstrated activity in the treatment of poorly differentiated NEC. Substitution of carboplatin for cisplatin and irinotecan for etoposide can be considered. 4-6 cycles of chemotherapy typically administered. Optimal duration of therapy is not clearly defined.