

Neuroendocrine Tumors: Current Recommendations for Diagnosis and Surgical Management

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The diverse clinical and histologic nature of neuroendocrine tumors (NETs) and the relative paucity of adequately powered studies make it difficult to formulate a consistent diagnosis and treatment strategy. In addition, the rapid emergence and incorporation of new technologies into the clinical arena makes defining a “static” gold standard for diagnosis or treatment difficult.

Based on the expertise of the Inter-Science Institute’s GI council and the expertise of the Louisiana State University Neuroendocrine tumor group’s extensive experience, the authors compiled recommendations for the diagnostic work-up of patients with suspected NETs. These recommendations are presented in tabular form to make it easier for clinical reference. The guidelines help serve as an aggregate of the available consensus reports and reflect a practical, but academically oriented, approach to these tumors. These recommendations are from diverse areas of clinical practice including surgery, endocrinology, oncology, and gastroenterology.

TUMOR CLASSIFICATION

The most recent World Health Organization classification described three general categories of NETs: (1) well-differentiated NETs, which exhibit uncertain malignant potential; (2) well-differentiated NE carcinomas, which are low-grade malignancies; and (3) poorly differentiated NE carcinomas, which are high-grade malignancies.¹ Currently, the term “carcinoid” is commonly used to refer to well-differentiated tumors of the bronchus, thymus, ovary, or gut. The term “islet cell tumor” commonly refers to well-differentiated adenoma-like lesions that behave in a benign fashion. Likewise, the term “islet cell carcinoma” commonly refers to a well-differentiated neuroendocrine carcinoma that arises from the pancreas or periampullary region.² In all of these tumors, therapeutic decisions are influenced by the degree of cellular differentiation. The standard criteria for classifying these tumors are based on the histologic characteristics of the tumor. The microscopic assessment of tumor differentiation is commonly supplemented by immunohistochemical stains, such as Ki-67, chromogranin A (CgA), and synaptophysin. Other stains, such as neuron-specific enolase and specific stains for multiple peptides in pancreatic or duodenal tumors, are commonly used in the classification of NETs. Ultimately, the rationale for classification of these tumors is to provide the clinician with a framework for the prediction of a tumor’s behavior. These “islet” cell tumors commonly stain positively for gastrin, glucagon, somatostatin, vasoactive intestinal peptide, pancreatic polypeptide, insulin, and C-peptide. It is critical to note that the presence of a positive peptide or amine stain in these pancreatic-duodenal tumors often leads to the mistaken diagnosis of a specific functional tumor type. The ultimate diagnosis of the functionality of these tumors is solely dependent on hypersecretion of peptide being documented in the serum, plasma, or urine. All NETs should undergo histologic evaluation by an experienced pathologist with extensive experience in NETs. These pathologists should determine the tumor’s degree of differentiation. This should be determined by visual examination of the tumor and the selective use of stains, such as Ki-67, CgA, synaptophysin, and others as needed to assist the pathologist in determination of the proper classification.¹

More recently, within the appendiceal carcinoid specimens, the terms “adenocarcinoid” or “mucinous carcinoid” have been used. It is the authors’ opinion that these tumors represent a subset of carcinoid tumors that exhibit macroscopic similarities to carcinoids but morphologically also possess glandular structures that produce mucin. Their behavior mimics that of a classic adenocarcinoma rather than an NET.

BIOCHEMICAL MARKERS

Clinically suspicious symptoms or radiographic findings suggestive of an NET necessitate biochemical testing for hypersecreted peptides or amines or their metabolic by-products. Determination of peptide-amine levels requires attention to pre-blood draw (fasting) requirements and the cessation of specific foods or medications to yield optimal sensitivity and accuracy. Specific blood drawing techniques, such as the use of a tourniquet, tubes with special preservatives, specific specimen handling, and strict adherence to proper transportation requirements, are critical to ensure that the reported values are as accurate as possible.³

It is important to use laboratories that have specific expertise in the determination of peptide levels. Not all laboratories "normal" value ranges for a peptide or amine are the same and results from various laboratories' are not directly comparable. Split sample testing is the only way to ensure that two laboratory's normal values are identical or at least comparable (parallel values but consistently higher or lower by a given fraction).

Serotonin (5-HT) is commonly secreted by mid-gut NETs. This amine is costored with CgA in secretory granules in NET cells. Both are released on stimulation.⁴ Common stimuli for the release of serotonin is the 5 "E's": (1) epinephrine, (2) exercise, (3) emotions, (4) ethanol, and (5) eating. Determination of plasma levels of 5-HT has not been generally useful in clinical practice, unlike its by-product, 5-hydroxy indole acetic acid (5-HIAA).⁴

The rate-limiting step for the synthesis of serotonin is the conversion of tryptophan into 5-HTP, catalyzed by the enzyme tryptophan hydroxylase. In midgut NETs, 5-HTP is rapidly converted to 5-HT by the enzyme dopa-decarboxylase. 5-HT is either stored in the neurosecretory granules or may be secreted directly into the vascular compartment. Most of the secreted 5-HT is taken up by platelets and stored in secretory granules. The rest remains free in the plasma, and circulating 5-HT is then largely converted into the urinary metabolite 5-HIAA by the enzyme monoamine oxidase and by aldehyde dehydrogenase. These enzymes are abundant in the kidney, and the urine of a patient with a symptomatic midgut carcinoid typically contains large amounts of 5-HIAA. In contrast, in patients with foregut tumors, the urine contains relatively little 5-HIAA but can contain large amounts of 5-HTP. It is presumed that these tumors are deficient in dopa-decarboxylase, which impairs the conversion of 5-HTP into 5-HT, leading to 5-HTP secretion into the vascular compartment. Some 5-HTP, however, is converted to 5-HT and 5-HIAA, resulting in the modest increase in these metabolites.

The normal range for 5-HIAA secretion is 2 to 8 mg per 24 hours, and the quantitation of serotonin and all of its metabolites usually permit the detection of 84% of patients with carcinoid tumors. No single marker measurement detects all cases of carcinoid syndrome, although the urine 5-HIAA seems to be the best screening procedure for patients suspected of having a mid-gut carcinoid.

In addition to specific peptides, secretory granules of neuroendocrine cells typically contain CgA-secretogranin (Sg) proteins.^{5,6} These acidic peptides belong to a unique family of secretory proteins that share biochemical properties and are exclusively localized in neuronal and neuroendocrine secretory granules.⁷ The name is derived from its original identification in the catecholamine-containing chromaffin granules of the adrenal medulla.⁸

The three major Cg-Sg proteins are currently designated as CgA and CgB and Sg11. CgA is the predominant protein in this family used as a biochemical marker. The levels of CgA are significantly elevated in most types of NETs, but particularly high levels are encountered in classical midgut NETs where levels of CgA may

increase 100- to 1000-fold.⁷ Because it does not rely on serotonin secretion, serum CgA is a more sensitive and broadly applicable marker than urinary 5-HIAA and may be used not only in patients with foregut and midgut NETs, but also in patients with bronchial and rectal carcinoid tumors in whom urinary 5-HIAA levels are less likely to be elevated.

The widespread use of proton pump inhibitors limits the usefulness of CgA as a screening tool for NETs. Chronic proton pump inhibitors use elevates CgA levels to similar levels as seen with patients with NETs, thus making it hard to interpret results.

Pancreastatin, a fragment of CgA, useful in several studies, is believed by some authors to be a more sensitive marker of tumor volume than the intact CgA molecule.^{9,10} This is caused by intracellular and extracellular processing of CgA by prohormone convertase 1.¹⁰ The authors recommend that any patient with a suspected NET have CgA and pancreastatin blood levels checked after cessation of proton pump inhibitors. They also suggest that all patients have a 24-hour urine collection for 5-HIAA. Furthermore, depending on history the location and symptomatology of most patients NETs can be identified. This can assist in the decision of what other tumor markers should be checked at the time of blood testing (**Tables 1 and 2**).

IMAGING

The preliminary work-up of an NET often includes plain abdominal radiographs and CT. These tests are often used nonspecifically because of the presence of vague symptom complexes. Once the NETs diagnosis is suspected, more specific means of imaging are typically used. For detecting the primary NET tumor, a multimodality approach is best and may include CT, MRI, somatostatin receptor scintigraphy (SRS), endoscopic ultrasound (EUS), endoscopy, digital selective angiography, and venous sampling. There is little difference in sensitivity between CT and MRI, although CT is probably superior for localizing the primary tumor, mesenteric invasion, and thoracic lesions, whereas MRI may be superior in characterizing liver lesions.¹¹ EUS combined with biopsy is the most sensitive method to detect pancreatic NETs.¹²

The most sensitive imaging modality for detecting metastatic disease in NETs is SRS (OctreoScan). This technique is based on the tumor's expression of somatostatin receptor type 2 (sst2). Five somatostatin receptor subtypes exist; however, tumors may not express all types of this receptor. Thus, some NETs are not visualized because of the lack of sst2 receptor.

The use of positron emission tomography scanning in undifferentiated tumors or small cell-like lesions of the bronchus or thymus is highly effective. The role of positron emission tomography scanning for well-differentiated NETs is less well delineated. Results suggest that these well-differentiated tumors are seen by ¹⁸F positron emission tomography scans in about 10% to 20% of patients.¹³

After a gut-based NETs is suspected, barium studies or endoscopy may be helpful to localize the primary tumor. Capsule endoscopy and double-balloon push-pull enteroscopy have been useful in some cases of midgut-based NETs. The authors currently use a multimodality approach to the imaging of NET patients. Visualization of the primary tumor can be done with endoscopy, EUS, or barium studies; however, these do not provide information about the nodal or organ metastasis status. They routinely use CT scanning for the evaluation of mesenteric and mediastinal nodal basins and to search for metastatic disease. All patients should undergo SRS imaging to document if the tumor has the sst2 receptors and to help identify occult disease that can be missed by other imaging techniques. The authors reserve

MRI with gadolinium contrast administration for patients found to have liver metastasis that may be amenable to surgical excision. Newer contrast agents for liver imaging may be helpful for identification of occult metastasis; however, this is still experimental (**Tables 3 and 4**).

SYMPTOMATIC TREATMENT

Long-acting somatostatin analogs have been proved to provide reliable control of peptide and amine-mediated symptoms. The current generation of approved somatostatin analogs predominantly recognizes sst2 and sst5. These somatostatin analogs bind to membrane-bound somatostatin receptors, turn on the inhibitory subunit of the G-protein, and subsequently trigger the activation of a number of postreceptor signal transduction pathways, such as IP-3, c-AMP, and adenylate cyclase. The result of somatostatin analog therapy is the inhibition of amine and peptide hypersecretion.²

The two commercially available somatostatin analogs are octreotide and lanreotide. Aqueous octreotide has a 90- to 120-minute half-life and requires subcutaneous injection three times per day. Currently, it is limited to use as “rescue medication” for breakthrough symptoms of carcinoid syndrome, as intravenous infusion to prevent carcinoid crisis in patients undergoing operative or stressful medical examinations, or as a continuous subcutaneous infusion in patients who wish to avoid monthly injection of octreotide LAR. Typical starting doses for the aqueous form of octreotide are 150 to 500 μg three times a day. When used as a continuous infusion, common doses of aqueous octreotide range from 1000 to 2000 μg per day (30–60 mg/month).¹⁴ Finally, to prevent carcinoid crisis during operation, the authors recommend a 500- μg intravenous bolus 2 hours before the surgical procedure followed by a 500- μg per hour intravenous infusion. This infusion is tapered off in the immediate postoperative period. In cases where carcinoid crisis still occurs, 1- to 5-mg boluses of octreotide may be useful.

Several experts have advocated use of higher monthly doses of octreotide LAR in patients with breakthrough symptoms. Most clinicians prefer to use 30-mg doses at shorter dosing intervals rather than using multiple injections once a month. Trough plasma octreotide levels can be used to evaluate the circulating octreotide levels in patients with poorly controlled symptoms, rising biomarker values, or progressive tumor growth.^{15,16} The authors believe that the optimum saturation of the sst2 receptor should occur at plasma levels of approximately 10,000 pg/mL (1×10^{-8} M). These plasma levels are approximately 10 times the K_d for octreotide and the sst2 receptor. These measurements may become increasingly important because it has been shown that the optimum antiproliferative effects of somatostatin analogs occur in similar concentration ranges.^{17,18}

Traditionally, somatostatin analog therapy has been considered to be useful only for the control of symptoms and was thought not to have a proved benefit on survival. Recently, a randomized prospective multiinstitutional trial has shown a survival benefit for the use of octreotide LAR. In this study the authors showed a significant increase in progression-free survival in those patients who used LAR.¹⁹

Lanreotide (Somatuline Depot Ipsen, Brisbane, CA) is a long-acting somatostatin analog that is available in 60-, 90-, and 120-mg doses. These doses can be administered by deep subcutaneous injection. Currently, Somatuline Depot is available in the United States for the treatment of acromegly; however, it can be used as an “out of indication” medication by physicians wishing to offer their patients an alternative to octreotide LAR.

The use of long-acting somatostatin analog therapy varies by the disease process. Doses of octreotide LAR (30 mg/every 2–4 weeks) are commonly associated with

Table 1
Recommendations of the Inter Science Institute Gastrointestinal Council on the use of biomarkers for diagnosis and treatment of neuroendocrine tumors (carcinoid and islet cell)

Marker	Consensus Recommendation		Individual Recommendations: Physician/Specialty							
	Tumor Type	Rec	EAW Surgery		TMO Endocrinology		AIV Endocrinology		WG Gastroenterology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec
5-HIAA	C	M	C	M	C	M	C	M	B	M
CGA	B	M	B	M	B	M	B	M	B	M
Substance P	C	P	C	P	C	M	C	P	N	P
Neurokinin A	C	P	C	P	C	P	C	P	N	P
Secretin	N	NR	N	NR	N	NR	N	NR	N	NR
Gastrin	B	P	B	P	B	P	IC	M	IC	P
Parietal cell Ab	C	P	C	P	C	P	C	P	IC	P
PP	IC	P	IC	P	IC	P	IC	P	IC	P
Blood glucose	B	M	B	M	B	M	B	M	B	M
Fasting insulin	IC	M	IC	M	IC	M	IC	M	IC	M
Proinsulin	IC	M	IC	M	IC	M	IC	M	IC	M
C-peptide	IC	M	IC	M	IC	M	IC	M	IC	M
VIP	IC	R	IC	M	IC	P	B	M	IC	P
Glucagon	IC	R	IC	M	IC	R	IC	M	IC	P

Somatostatin	IC	P	IC	M	IC	P	B	M	N	NR
PTH	IC	R	B	R	IC	R	IC	M	IC	P
Ca++	B	M	B	R	B	R	B	M	B	M
Calcitonin	B	P	B	P	B	P	B	M	B	P
Prolactin	IC	P	IC	P	IC	R	IC	P	IC	P
ACTH	B	P	B	P	B	R	B	P	B	P
PSA	N	NR	N	NR	N	NR	N	NR	N	NR
AFP	N	NR	N	NR	N	NR	N	NR	N	NR
CEA	N	NR	N	NR	N	NR	N	NR	N	NR
Chemistry	B	M	B	M	B	R	B	M	B	M
CBC	B	M	B	M	B	R	B	M	B	M

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: AIV, Aaron Vinik; EAW, Eugene Woltering; TMO, Thomas O'Dorisio; WG, Vay Liang (Bill) Go.

Abbreviations: Ab, antibody (parietal cell antibody); ACTH, adrenocorticotrophic hormone; AFP, alpha-fetoprotein; Ca++, calcium ion; CBC, complete blood count; CEA, carcinoembryonic antigen; CGA, chromogranin A; 5-HIAA, 5-hydroxyindoleacetic acid; PP, pancreatic polypeptide; PSA, prostate-specific antigen; PTH, parathyroid hormone; VIP, vasoactive intestinal peptide.

Table 2
Recommendations of the New Orleans Louisiana Neuroendocrine Tumor group on the use of biomarkers for diagnosis and treatment of neuroendocrine tumors (carcinoid and islet cell)

Markers	Consensus Recommendation		Individual Recommendations: Physician/Specialty									
	Tumor Type	Rec	EAW Surgery/ Oncology		JPB Transplant Surgery		YZW General Surgery		SJ HPB Surgery		LA Medicine/ Oncology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec	Type	Rec
5-HIAA	C	M	C	M	C	M	C	M	C	M	B	M
CGA	B	M	B	M	B	M	B	M	B	M	B	M
Substance P	B	P	C	P	B	P	B	M	C	P	C	P
Neurokinin A	B	R	C	P	B	R	B	P	C	P	B	M
Secretin	N	NR	N	NR	IC	P	IC	P	N	NR	N	NR
Gastrin	B	P	B	NR	B	P	IC	R	B	P	B	R
Parietal cell Ab	C	R	C	P	C	R	C	P	C	P	B	R
PP	IC	R	IC	P	IC	R	IC	R	IC	P	IC	R
Blood glucose	B	M	B	M	B	M	IC	M	B	M	IC	M
Fasting insulin	IC	R	IC	M	IC	R	IC	M	IC	R	IC	P
Pro-insulin	IC	R	IC	M	IC	R	IC	M	IC	R	IC	P
C-peptide	IC	R	IC	M	IC	P	IC	M	IC	R	IC	P

VIP	IC	R	IC	M	IC	P	IC	R	IC	R	IC	P
Glucagon	IC	R	IC	M	IC	P	IC	R	IC	R	IC	P
Somatostatin	IC	R	IC	M	IC	P	IC	R	IC	R	IC	P
PTH	B	P	B	R	B	P	C	P	B	P	B	P
Ca++	B	P	B	R	B	P	C	P	B	P	B	P
Calcitonin	B	P	B	P	B	P	N	NR	B	P	IC	P
Prolactin	IC	P	IC	P	IC	P	N	NR	IC	P	N	NR
ACTH	N	NR	B	P	N	NR	N	NR	N	NR	C	P
PSA	N	NR	N	NR	C	P	N	NR	N	NR	N	NR
AFP	N	NR	N	NR	N	NR	N	NR	N	NR	N	NR
CEA	N	NR	N	NR	N	NR	N	NR	N	NR	N	NR
Chemistry	B	R	B	M	C	P	IC	P	B	R	B	M
CBC	B	M	B	M	B	M	B	R	B	R	B	M

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; JPB, J. Philip Boudreau; YZW, Yi-Zarn Wang; SJ, Saju Joseph; LA, Lowell Anthony.

Abbreviations: Ab, antibody (parietal cell antibody); ACTH, adrenocorticotrophic hormone; AFP, alpha-fetoprotein; Ca++, calcium ion; CBC, complete blood count; CEA, carcinoembryonic antigen; CGA, chromogranin A; 5-HIAA, 5-hydroxyindoleacetic acid; PP, pancreatic polypeptide; PSA, prostate-specific antigen; PTH, parathyroid hormone; VIP, vasoactive intestinal peptide.

Table 3

Recommendations of the Inter Science Institute Gastrointestinal Council on the use of imaging for diagnosis and treatment of neuroendocrine tumors (carcinoid and islet cell)

Imaging Study	Consensus Recommendation		Individual Recommendations: Physician/Specialty							
	Tumor Type	Rec	EAW Surgery		TMO Endocrinology		AIV Endocrinology		WG Gastroenterology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec
CT	B	M	B	R	B	R	B	M	B	M
MRI/MRA	B	P	B	P	B	P	B	P	B	R
Octreoscan	B	M	B	R	B	M	B	M	B	R
Ultrasound	B	R	B	R	B	R	B	P	IC	M
EUS	IC	P	IC	P	IC	R	IC	P	IC	M
Endoscopy	B	P	B	P	B	R	B	P	B	P
Barium studies	N	NR	N	NR	N	NR	N	NR	N	NR
Angiography	B	P	B	P	B	P	B	P	B	P
Multimodality approach	B	M	B	M	B	M	B	M	B	M
Imaging for metastasis	B	M	B	M	B	M	B	M	B	M
MIBG	B	P	B	P	C	P	B	P	B	P
Bone scan	B	P	B	P	B	P	B	P	B	P
FDG-PET	B	P	B	P	B	P	B	P	B	P
Transthoracic echo	N	NR	NR	NR	NR	NR	NR	NR	NR	NR

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; TMO, Thomas O'Dorisio; AIV, Aaron Vinik; WG, Vay Liang (Bill) Go.

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FDG-PET, fluorodeoxyglucose-positron emission tomography; MIBG, meta-iodobenzyl-guanidine; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

Table 4

Represents the recommendations of the New Orleans Louisiana Neuroendocrine Tumor group on the use of imaging for diagnosis and treatment of neuroendocrine tumors (carcinoid and islet cell)

Imaging Study	Consensus Recommendation		Individual Recommendations: Physician/Specialty									
	Tumor Type	Rec	EAW Surgery		JPB Transplant Surgery		YZW General Surgery		SJ HPB Surgery		LA Medicine/Oncology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec	Type	Rec
CT	B	M	B	R	B	M	B	M	B	M	B	M
MRI/MRA	B	P	B	P	B	R	B	P	B	P	B	P
Octreoscan	B	M	B	R	B	M	C	M	B	M	B	M
Ultrasound	B	R	B	R	B	P	B	M	B	R	B	P
EUS	IC	P	IC	P	IC	R	B	P	IC	P	IC	P
Endoscopy	B	P	B	P	C	P	C	P	B	P	B	P
Barium studies	N	NR	N	NR	N	NR	N	NR	N	NR	B	P
Angiography	B	P	B	P	B	P	IC	P	B	P	B	P
Multimodality approach	B	M	B	M	B	R	B	R	B	M	B	M
Imaging for metastasis	B	M	B	M	B	M	B	M	B	M	B	M
MIBG	B	R	B	P	B	R	B	M	B	R	B	R
Bone scan	B	P	B	P	B	R	B	P	B	P	B	P
FDG-PET	B	P	B	P	N	NR	B	P	B	P	B	P
Trans-thoracic Echo	C	R	N	NR	C	M	C	P	C	R	C	R

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

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Physicians making recommendations: EAW, Eugene Woltering; JPB, J. Philip Boudreaux; YZW, Yi-Zarn Wang; SJ, Saju Joseph; LA- Lowell Anthony.

Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FDG-PET, fluorodeoxyglucose-positron emission tomography; MIBG, meta-iodobenzylguanidine; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging.

excellent symptom control in patients with carcinoid syndrome. Similar results have been seen with Somatuline Depot (120 mg every 2 weeks).

Long-acting somatostatin analogs are less effective in the control of hypoglycemia in insulinoma caused by the lack of sst2 receptors on the tumor. Use of somatostatin analogs in patients with insulinomas may actually worsen hypoglycemia because of the relative higher efficacy of these analogs to inhibit glucagon and growth hormone secretion versus insulin secretion.

The control of gastric acid hypersecretion in gastrinoma (Zollinger-Ellison syndrome) is easy to achieve with higher-dose oral proton-pump inhibitors than for treatment of ulcer disease. Proton pump inhibitors effectively control acid, but leave gastrin levels unchanged. Recent studies advocate the early use of somatostatin analogs in patients with metastatic gastrinomas to help control excessive gastrin release and gastric acid secretion.^{20,21} Jensen and colleagues,²² from the National Cancer Institute, believe that somatostatin analog therapy now should be the “front line” therapy rather than chemotherapy in the treatment of patients with metastatic gastrinoma.

Octreotide has been shown to be effective in the control of watery diarrhea for patients with Verner-Morrison syndrome (vasoactive intestinal peptideoma) and for the control of necrolytic migratory erythema in patients with glucagonoma syndrome.⁷

All patients with NETs, except insulinomas, should receive octreotide therapy either with LAR injections or subcutaneous pumps. The goal of this therapy is to control symptoms and keep sst2 receptors saturated to inhibit proliferation of tumor cells. Any patient with worsening symptoms on a stable dose, increasing tumor marker levels, or new patients on treatment should undergo plasma testing for octreotide trough level to ensure the use of appropriate doses. Furthermore, for asymptomatic patients occasional trough levels and tumor marker levels should be checked as part of routine surveillance (**Tables 5 and 6**).

CHEMOTHERAPY

Tumor growth leading to liver failure has emerged as the leading cause of death in patients with NETs, underscoring the need for new systemic therapies. Approximately two thirds of patients present with metastatic disease that is not amenable to surgical resection or biotherapy. In those patients who are not surgical candidates and who do not respond to biotherapy with somatostatin analogs, or in those whose symptoms recur following careful adjustment of analog dosing, chemotherapy should be considered. Cytotoxic therapy is also used in patients with atypical carcinoids that exhibit high proliferation rates, as evidenced by a proliferation index greater than 10% to 20%, determined by Ki-67 staining (MEB-1 antibody). In general, patients with pancreatic or duodenal malignant islet cell tumors respond better to systemic chemotherapy than those who suffer from gut-based carcinoid tumors. Recent work by Drs Warner and Woltering suggest that well-differentiated midgut carcinoids with low proliferative indices may still be candidates for chemotherapy.²³

Responses to single-agent chemotherapy have been disappointing. In patients with pancreatic NETs tumors streptozotocin, chlorozotocin, doxorubicin, 5-fluorouracil, taxol, and dacarbazine have been tested individually and are relatively ineffective. Such monotherapies not only result in poor response rates, but more importantly all induced significant toxicity.²⁴ Streptozotocin has demonstrated the most activity in pancreatic NETs, with response rates between 36% and 42%.^{24,25} Recently, single-agent studies of irinotecan and high-dose paclitaxel have been evaluated but responses continue to be disappointing.^{26,27} Combination therapy for pancreatic

Table 5
Recommendations of the Inter Science Institute Gastrointestinal Council on symptomatic treatment of neuroendocrine tumors (carcinoid and islet cell)

Treatment	Consensus Recommendation		Individual Recommendations: Physician/Specialty							
	Tumor Type	Rec	EAW Surgery		TMO Endocrinology		AIV Endocrinology		WG Gastroenterology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec
Somatostatin analog	B	M	B	M	B	M	B	M	B	M
Octreotide	B	M	B	M	B	M	B	M	B	M
Lanreotide	B	M	B	M	B	M	B	M	B	M
Long-acting release	B	M	B	M	B	R	B	M	B	M
Octreotide LAR dose	B	R	B	R	B	R	B	R	C	R
Lanreotide Autogel	B	R	B	R	B	R	B	R	C	R
SSA for symptom control	B	M	B	M	B	M	B	M	B	M
SSA to control tumor progression	B	R	B	R	B	R	B	P	B	R
Interferon	B	P	C	P	IC	R	C	P	B	P
Combination interferon and octreotide	C	P	C	P	IC	R	C	P	C	P
Proton pump inhibitors	IC	R	IC	R	IC	M	IC	R	IC	P
Diazoxide	I	R	IC	R	IC	M	IC	R	N	NR

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; TMO, Thomas O'Dorisio; AIV, Aaron Vinik; WG, Vay Liang (Bill) Go.

Abbreviations: LAR, long-acting release; SSA, somatostatin analog.

Table 6**Recommendations of the New Orleans Louisiana Neuroendocrine Tumor group on symptomatic treatment of neuroendocrine tumors (carcinoid and islet cell)**

Treatment	Consensus Recommendation		Individual Recommendations: Physician/Specialty									
	Tumor Type	Rec	EAW Surgery/ Oncology		JPB Transplant Surgery		YZW General Surgery		SJ HPB Surgery		LA Medicine/ Oncology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec	Type	Rec
Somatostatin analog	B	M	B	M	B	P	B	M	B	M	B	R
Octreotide	B	M	B	M	B	P	B	M	B	M	B	R
Lanreotide	B	M	B	M	B	P	B	M	B	M	B	P
Long-acting release	B	R	B	M	B	P	C	M	B	R	B	R
Octreotide LAR dose	B	R	B	R	B	P	C	M	B	R	B	R
Lanreotide Autogel	B	R	B	R	B	P	C	M	B	M	B	P
SSA for symptom control	B	M	B	M	B	M	B	R	B	M	B	M
SSA to control tumor progression	B	R	B	R	B	P	C	P	B	R	B	R
Interferon	C	P	C	P	B	P	N	NR	C	P	C	P
Combination Interferon & Octreotide	C	P	C	P	B	P	N	NR	C	P	C	P
Proton pump inhibitors	IC	R	IC	R	B	NR	N	NR	IC	R	IC	M
Diazoxide	IC	R	IC	R	IC	P	IC	R	IC	P	IC	P

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; JPB, J. Philip Boudreaux; YZW, Yi-Zarn Wang; SJ, Saju Joseph; LA, Lowell Anthony.

Abbreviations: LAR, long-acting release; SSA, somatostatin analog.

NETs most commonly use streptozotocin and 5-fluorouracil, with higher response rates reported than with monotherapy alone. Doxorubicin used in combination with streptozotocin has also been used, but conflicting interpretation of studies has made determination of the efficacy of these regimens difficult. Doxorubicin-streptozotocin combinations have been more effective in patients with metastatic insulinoma and vasoactive intestinal peptideoma than in carcinoid-related tumors. Another indication for chemotherapy is in patients with anaplastic small-cell neuroendocrine carcinomas (atypical carcinoids). These tumors often respond to treatment with etoposide and cisplatin.²⁴

Although a two-drug regimen may be more effective than a single-agent regimen, there is no evidence that a three-drug combination, such as streptozotocin, 5-fluorouracil, and doxorubicin, is better than a two-drug regimen, and three-drug combinations should not be considered as standard therapy.²⁸

Interferon- α , an anticancer therapeutic agent, is active as an immunomodulator secondary to up-regulation of natural killer cells. In addition, interferon demonstrates a cytostatic effect by stalling the (G1-S) phase of the cell cycle and down-regulating genes coding for nuclear proteins involved in cell proliferation. Because of its severe side effects this drug is not commonly used in the United States to treat metastatic NETs. The combined use of interferon and somatostatin has not shown a greater anti-tumor effect than the individual agents alone and the combination is associated with significant side effects.²⁹

All patients who require chemotherapy for NETs should be evaluated for clinical trials at expert centers. Although the treatment regimens are quite standard, the rarity of these cases makes it imperative that all eligible patients be involved in clinical trials or tracked for further study (**Tables 7** and **8**).

RADIONUCLIDE THERAPIES AND CHEMOEMBOLIZATION

Radiolabeled Somatostatin Analog Therapy

After somatostatin-receptor binding, a fraction of the ligand-receptor complexes (endosomes) internalize. This internalization process is an effective means of delivering cytotoxic treatments, especially those emitting short-range decay particles, such as Auger or conversion electrons, to the neoplastic cell nucleus. Such short-range therapies include ¹²⁵I- and ¹¹¹Indium-labeled somatostatin analogs. Unfortunately, these short-range agents lack significant ability to kill adjacent non-receptor expressing cells, which has led to the use of higher-energy radionuclides.³⁰

In contrast, ¹⁷⁷Lu- and ⁹⁰Y-labeled somatostatin analogs have significant advantages over the short-range therapies because they have significantly higher energy and thus a wider radius of action. Peptide receptor radiotherapy has developed into a critical component of the overall therapeutic strategy in patients with NETs. Even though the more energetic therapies (¹⁷⁷Lu and ⁹⁰Y) are not currently available in the United States, the European nuclear medicine community has been actively treating patients with these agents.³¹

Treatment with radiolabeled somatostatin analogs is a promising new tool in the management of patients who have inoperable or widely metastatic NETs, especially because these treatments are associated with minimal severe side effects. Review of the available literature revealed partial tumor response rates ranging from 9% to 38%.³¹ The results obtained with ⁹⁰Y and ¹⁷⁷Lu are encouraging, although a direct, randomized comparison between the various isotopic treatments is unlikely to occur. Tumor remission has been positively correlated with high uptake by tumors during SRS, limited number of metastases, and size of liver metastases. Interestingly,

Table 7
Recommendations of the Inter Science Institute Gastrointestinal Council on the use of chemotherapy for treatment of neuroendocrine tumors (carcinoid and islet cell)

Chemotherapeutic Agent	Consensus Recommendation		Individual Recommendations: Physician/Specialty							
	Tumor Type	Rec	EAW Surgery		TMO Endocrinology		AIV Endocrinology		WG Gastroenterology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec
Cisplatin	B	R	C	R	B	R	C	R	B	M
Etoposide	B	R	C	R	B	R	C	R	B	R
Cisplatin + etoposide	B	R	C	R	B	R	C	R	B	P
5-Fluorouracil	B	R	B	R	B	R	B	R	IC	P
Streptozotocin	IC	P	IC	R	IC	P	IC	R	B	R
5-FU + STZ	IC	P	IC	R	IC	P	IC	R	B	P
Adriamycin	B	P	B	P	N	NR	B	P	N	P
Dacarbazine	N	NR	N	NR	N	NR	N	NR	N	P
Carboplatin	B	P	C	P	B	P	B	P	N	P
Doxorubicin	N	NR	C	P	N	NR	N	NR	N	P
Other combinations	B	P	B	P	B	P	B	P	B	P
5-FU/STZ/Dox	IC	R	IC	R	IC	R	IC	R	N	P

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; TMO, Thomas O'Dorisio; AIV, Aaron Vinik; WG, Vay Liang (Bill) Go.

Abbreviations: 5-FU, 5-fluorouracil; Dox, doxorubicin; STZ, streptozotocin.

Table 8
Recommendations of the New Orleans Louisiana Neuroendocrine Tumor group on the use of chemotherapy for treatment of neuroendocrine tumors (carcinoid and islet cell)

Chemotherapeutic Agent	Consensus Recommendation		Individual Recommendations: Physician/Specialty					
	Tumor Type	Rec	EAW Surgery/ Oncology		SJ HPB Surgery		LA Medicine/ Oncology	
			Type	Rec	Type	Rec	Type	Rec
Cisplatin	C	R	C	R	C	P	N	NR
Etoposide	C	R	C	R	C	P	N	NR
Cisplatin + etoposide	C	R	C	R	C	P	N	NR
5-FU	B	P	B	R	B	P	B	P
STZ	IC	P	IC	R	IC	P	IC	P
5-FU + STZ	IC	P	IC	R	IC	R	IC	P
Adriamycin	B	P	B	P	B	P	I	P
Dacarbazine	N	NR	N	NR	N	NR	IC	P
Carboplatin	C	P	C	P	C	P	N	NR
Doxorubicin	B	P	C	P	B	P	IC	P
Other combinations	B	P	B	P	B	P	B	P
5FU/STZ/Dox	IC	P	IC	R	IC	P	IC	P

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; SJ, Saju Joseph; LA, Lowell Anthony.

Abbreviations: 5-FU, 5-fluorouracil; Dox, doxorubicin; STZ, streptozotocin.

metastatic gastrinomas often exhibit extremely intense ^{111}In uptake, but have a significantly reduced survival compared with other NETs patients.

In general the “Krenning” scale is used to evaluate the potential for response to these therapies. A “Krenning” Grade II tumor uptake is isodense with the liver, whereas a Grade III tumor uptake is greater than the liver but less than the kidney. A grade IV tumor has equal uptake to the kidney on octreotide scanning.³⁰ Responses to radiolabeled somatostatin analog therapy are generally proportional to the Krenning scale uptake.

^{131}I MIBG Therapy

One of the newest treatment modalities available in the United States is the use of I-MIBG for scanning and treatment for those individuals who exhibit intense tumor uptake. Long-term studies of this therapy are underway and seem to have a reasonable risk–benefit ratio. The newest addition to this therapy is the availability of high specific activity ^{131}I . The ability to treat patients with higher specific activity iodine should enhance response rates.³²

Chemoembolization

Early in our clinical experience, chemoembolization was used before surgery to shrink tumors and it was hoped to enhance the effectiveness of resection. It was quickly discovered, however, that subsequent cytoreduction was significantly hindered by the extensive scarring induced by the chemoembolization. Thus, chemoembolization is reserved for patients with advanced NETs involving the liver that are no longer amenable to curative surgery or ablation.^{33,34}

On occasion, alternating chemoembolization with systemic chemotherapy may offer an improvement over chemotherapy alone, even when the tumor is not confined to the liver.³² Because liver disease is often a major source of symptoms and is generally the life-limiting aspect of the disease, aggressive liver-targeted treatment is indicated.

In chemoembolization, doxorubicin, mitomycin C, or cisplatin is combined with iodized oil (lipiodol) or gelatin foam. When Gelfoam (Pfizer Injectables, Pharmacia & Upjohn Co, New York, NY, USA) is used as the embolic material, the chemotherapies are admixed with the Gelfoam until a maple-syrup–like consistency is achieved. Using highly selective hepatic arterial catheterization, the emulsion is injected into the arterial blood supply of the liver metastases. Alternatively, the injection of a lipiodol drug mixture is followed by embolization of the vessels using a gelatin-containing slurry. The process of embolization is continued until a marked degree of vascular occlusion has been obtained. If arterial spasm occurs during embolization the angiographer waits until the spasm clears to ensure that the maximum amount of the embolic agent has been injected.

It has been speculated that the ischemia and resulting hypoxia induced by the embolization component may actually enhance the cytotoxic action of the chemotherapy. The mechanism for this is unclear but may revolve around the metabolic changes induced in tumor cells under hypoxic conditions.

The M.D. Anderson experience suggests that carcinoid tumors have improved outcomes following chemoembolization compared with pancreatic islet cell tumors. The addition of systemic chemotherapy to embolization did not alter treatment effects in patients who had carcinoid tumors but did result in higher response rates in the patients who had pancreatic islet cell tumors. In each tumor type neither chemoembolization nor simple embolization conferred a significant overall survival or progression-free survival advantage over the other.³⁴

New techniques for chemoembolization have also enhanced treatment techniques. With the development of microsphere technology, chemoembolization is capable of

delivering not only chemotherapeutics but also radiation to the tumor sites. This may represent a new treatment modality that enhances the ability to treat hepatic NETs metastasis.

All patients with metastatic NETs should be evaluated for a multimodality approach. The authors use radiolabeled octreotide for most patients with unresectable metastatic disease. Also, early aggressive treatment of unresectable liver metastasis with chemoembolization and microsphere techniques is recommended. This often allows for symptom reduction, which is a significant morbidity in this patient population. The authors have now begun an aggressive MIBG treatment protocol that is reserved for patients with no surgical options. Any patient with metastatic NETs should be referred to a center with experience in advanced NET treatment techniques including MIBG, microsphere, and chemoembolization procedures. Finally, patients with previous biliary manipulation or reconstruction have a significantly higher incidence of liver abscess after intervention by either chemoembolization or MIBG and these patients should be treated empirically with antibiotics and watched for signs of abscess formation (**Tables 9** and **10**).

SURGERY

NETs are often biologically inert, slow-growing tumors with a prolonged disease course. Their indolent nature makes surgical resection of primary disease, nodal involvement, and metastatic lesions an integral part of both curative and palliative treatment regimens. The slow growth of most NETs and the high incidence of nonfunctional tumors often allow extensive disease to develop undetected. These tumors often manifest themselves by secondary symptoms, such as bowel obstruction or hepatic dysfunction. In general, an aggressive approach should be used to clear the primary tumor, to cytoreduce regional lymph nodes, and to resect or treat appropriate distant metastases, including liver tumors.

Radiofrequency ablation has increased the surgeon's ability to render the liver free of tumor. In addition, for those lesions previously treated with resection or Transarterial chemoembolization, radiofrequency ablation may provide adjunctive treatment after regrowth or recurrence. However, there is still a great deal of controversy as to whether radiofrequency ablation should be used as a primary treatment technique.

The decision to undertake liver cytoreduction is made easier when symptoms of hormone excess are not well controlled medically. Surgical resection of NET liver metastases has, on occasion, seemed to provide a long-term cure and 5-year survival rates have been reported to be 71% to 85%.³⁵ Resection of the primary tumor and the mesenteric lymph nodes can lead to a significant reduction in tumor-related symptoms and result in a survival advantage.³⁶

Cytoreductive surgery, commonly defined as resection of 90% of the tumor, attempts to reduce symptoms and facilitate the effect of nonoperative strategies.³⁷ Que and colleagues³⁷ reported a successful control of symptoms in 90% of patients after a debulking of 90% or more of liver-based tumor burden. Givi and colleagues³⁸ recently showed improved survival in patients whose primary tumors were resected at the time of cytoreductive surgery, despite their having metastatic disease.

In a recent study, mesenteric encasement leading to intestinal ischemia was successfully relieved in 10 of 12 patients.³⁸ Bowel obstruction secondary to peritoneal carcinomatosis is a major cause of mortality in these patients. Carcinoid tumors of the small intestine typically cause a severe desmoplastic reaction and deeply infiltrate lymph nodes around major vessels of the root of the small bowel. In these circumstances, complete resection is seldom achieved; however, cytoreduction should be

Table 9

Recommendations of the Inter Science Institute Gastrointestinal Council on the use of radionuclide and embolic therapy for the treatment of neuroendocrine tumors (carcinoid and islet cell)

Radionuclide or Embolic Therapy	Consensus Recommendation		Individual Recommendations: Physician/Specialty							
	Tumor Type	Rec	EAW Surgery		TMO Endocrinology		AIV Endocrinology		WG Gastroenterology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec
¹³¹ I-MIBG	C	P	IC	P	C	P	C	P	C	P
⁹⁰ Y Octreotide	B	P	B	P	B	P	B	P	B	P
⁹⁰ Y Lanreotide	B	P	B	P	B	P	B	P	B	P
¹⁷⁷ Lu-DOTA Try3 Octreotide	B	P	B	P	B	P	B	P	B	P
RFA	B	R	B	R	B	R	B	P	B	P
Chemoembolization	B	R	B	R	B	R	B	R	B	P
CE + doxorubicin	B	R	B	R	B	R	B	R	B	P
CE + cisplatin	B	R	B	R	B	R	B	R	B	P
CE + 5-FU	B	P	B	R	B	R	B	R	N	NR
CE + mitomycin C	B	P	B	R	B	R	B	R	B	NR
Bland HA embolization	N	NR	N	NR	N	NR	B	NR	B	P
CE + IV chemo	N	NR	N	NR	N	NR	N	NR	N	NR
Bisphosphonates	B	P	B	R	B	R	B	R	N	NR
Alcohol injection	B	P	B	P	B	NR	B	P	B	P
Cryotherapy	N	NR	N	NR	N	NR	N	NR	B	P
Laser	N	NR	N	NR	N	NR	N	NR	B	P
External beam XRT	B	P	B	P	B	R	B	P	B	P
Imatinib	N	NR	N	NR	N	R	N	NR	N	NR

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; TMO, Thomas O'Dorisio; AIV, Aaron Vinik; WG, Vay Liang (Bill) Go.

Abbreviations: CE, chemoembolization; HA, hepatic artery; IV, intravenous; ¹³¹I-MIBG, iodine-131-meta-iodobenzylguanidine; ¹⁷⁷Lu-DOTA Tyr3, Lutecium-177 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; RFA, radiofrequency ablation; XRT, radiation therapy; ⁹⁰Y, Yttrium isotope with 90 neutrons.

Table 10

Recommendations of the New Orleans Louisiana Neuroendocrine Tumor group on the use of radionuclide and embolic therapy for the treatment of neuroendocrine tumors (carcinoid and islet cell)

Radionuclide or Embolic Therapy	Consensus Recommendation		Individual Recommendations: Physician/Specialty									
	Tumor Type	Rec	EAW Surgery		JPB Transplant Surgery		YZW General Surgery		SJ HPB Surgery		LA Medicine/Oncology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec	Type	Rec
¹³¹ I-MIBG	B	P	IC	P	B	P	B	P	B	P	C	P
⁹⁰ Y octreotide	B	P	B	P	B	P	B	P	B	P	B	P
⁹⁰ Y lanreotide	B	P	B	P	B	P	B	P	B	P	B	P
¹⁷⁷ Lu-DOTA Try3 Octreotide	B	P	B	P	B	P	B	P	B	P	B	P
RFA	B	R	B	R	B	P	B	R	B	R	B	R
Chemoembolization	B	R	B	R	B	R	B	R	B	R	B	R
CE doxorubicin	B	R	B	R	B	R	B	P	B	R	B	P
CE cisplatin	B	R	B	R	B	R	B	P	B	R	B	P
CE 5-FU	B	R	B	R	B	R	B	P	B	R	B	P
CE mitomycin C	B	R	B	R	B	R	N	NR	B	R	B	P
Bland HA embolization	N	NR	N/	NR	B	NR	N	NR	N	NR	B	P
Combination CE w/IV chemotherapy	N	NR	N	NR	B	P	B	P	N	NR	B	P
Bisphosphonates	B	P	B	R	B	P	IC	P	B	P	B	P
Alcohol injection	B	P	B	P	B	P	N	NR	B	P	B	P
Cryotherapy	N	NR	N	NR	B	P	N	NR	N	NR	N	NR
Laser	N	NR	N	NR	N	NR	B	P	N	NR	N	NR
External beam XRT	B	P	B	P	B	P	N	NR	B	P	C	P
Imatinib	N	NR	N	NR	B	P	IC	P	N	NR	N	NR

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; JPB, J. Philip Boudreaux; YZW, Yi-Zarn Wang; SJ, Saju Joseph; LA, Lowell Anthony.

Abbreviations: CE, chemoembolization; HA, hepatic artery; IV, intravenous; ¹³¹I-MIBG, iodine-131-meta-iodobenzylguanidine; ¹⁷⁷Lu-DOTA Tyr3, Lutecium-177 1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid; RFA, radiofrequency ablation; XRT, radiation therapy; ⁹⁰Y, Yttrium isotope with 90 neutrons.

attempted by surgical teams with extensive experience in these procedures. Boudreaux and colleagues³⁹ observed a 50% decrease in 5-HIAA levels during postoperative follow-up and found aggressive surgical exploration and tumor debulking to significantly improve symptomatic outcome with relatively few complications.

The increased incidence of cholelithiasis following chronic administration of somatostatin analog and gallbladder wall necrosis caused by chemoembolization of the liver dictate the routine performance of prophylactic cholecystectomy during the resection of the primary tumor or metastatic lesions. In selected patients, liver transplantation for unresectable neuroendocrine hepatic metastases may provide not only long-term palliation but even cure. There is a severe shortage of donor organs, however, and thus liver transplantation for neuroendocrine metastases should only be considered in patients without evidence of extrahepatic tumor and in whom all other treatment methods are no longer effective. The use of living-related liver transplantation may allow more widespread use of this aggressive approach in patients with extensive liver metastasis.

Patient's tumors are often deemed "unresectable" by clinicians who are not surgeons, or even more disconcerting by physicians who are not familiar with the clinical course and the current array of treatments that have been developed for NETs. In all cases, a surgeon comfortable with advanced surgical techniques, such as repeat liver resection and skeletonizing the mesenteric vasculature at the base of the small bowel mesentery, should view the pertinent radiographs to help the attending physician determine the resectability of primary, nodal, and metastatic disease.

There are multiple techniques that have been developed to assist surgeons in the operating room dealing with complex NET patients. The authors currently use methylene blue dye injected subserosally to help identify surgical resection margins for midgut carcinoids.⁴⁰ They also use radiolabeled octreotide as a guide to identify tumor deposits that are not readily evident on CT or MRI. These lesions are often active on SRS imaging but not visible by standard techniques. By using a gamma-detecting probe similar to that used in sentinel lymph node resection, metastatic deposits can be found in the absence of palpable disease. Furthermore, the authors often use intraoperative chemotherapy-infused Gelfoam for areas of unresected disease. This theoretically provides much higher doses of chemotherapeutic agent in the area of significant disease. They guard against anastomotic leakage or poor healing by protecting the anastomosis using omentum and tacking the Gelfoam to the area of interest to inhibit its movement. Finally, the authors often use multiple operations to address specific areas of metastatic disease after a short healing interval. This allows for better planning and execution on subsequent operations and allows time to assess the biologic behavior of the tumor (**Tables 11** and **12**).

RECOMMENDATIONS

Any patient with suspected NETs either because of symptoms or radiologic findings should undergo a complete history and physical examination. From this the clinician can often discern the location and functionality of the primary tumor.

Patients with NETs should undergo full tumor analysis based on tumor markers. CgA, pancreastatin, and 24-hour urine for 5-HIAA should be checked for all patients with NETs and depending on location other tumor markers should be checked and help guide clinical decision-making.

Imaging of patients with NETs should include attempted visualization of the primary tumor with endoscopy or EUS, evaluation of the lymphatic basins and liver using CT

Table 11
Recommendations of the Inter Science Institute Gastrointestinal Council on the use of surgery for the treatment of neuroendocrine tumors (carcinoid and islet cell)

Surgery	Consensus Recommendation		Individual Recommendations: Physician/Specialty							
	Tumor Type	Rec	EAW Surgery		TMO Endocrinology		AIV Endocrinology		WG Gastroenterology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec
Preop/periop octreotide to prevent carcinoid crisis	B	M	B	M	B	M	B	M	B	M
Primary resection	B	M	B	M	B	M	B	M	B	M
Debulking of metastasis	B	M	B	M	B	M	B	M	B	M
Resection of metastasis	B	M	B	M	B	M	B	R	B	M
Resection of simultaneous primary and liver metastasis	B	R	B	M	B	R	B	M	B	R
Liver transplantation	B	P	B	R	B	P	B	P	B	P

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; TMO, Thomas O'Dorisio; AIV, Aaron Vinik; WG, Vay Liang (Bill) Go.

Table 12
Recommendations of the New Orleans Louisiana Neuroendocrine Tumor group on the use of surgery for the treatment of neuroendocrine tumors (carcinoid and islet cell)

Surgery	Consensus Recommendation		Individual Recommendations: Physician/Specialty									
	Tumor Type	Rec	EAW Surgery		JPB Transplant Surgery		YZW General Surgery		SJ HPB Surgery		LA Medicine/Oncology	
			Type	Rec	Type	Rec	Type	Rec	Type	Rec	Type	Rec
Preop/Periop octreotide to prevent carcinoid crisis	B	M	B	M	B	M	C	M	B	M	B	M
Primary resection	B	M	B	M	B	M	B	M	B	M	B	P
Debulking of metastasis	B	M	B	M	B	M	B	M	B	M	B	P
Resection of liver metastasis	B	M	B	M	B	M	B	R	B	M	B	P
Resection of simultaneous primary and liver metastasis	B	R	B	M	B	M	B	R	B	R	B	P
Liver transplantation	B	P	B	R	C	M	B	P	B	P	N	NR

Tumor type: B, both; C, carcinoid; IC, islet cell; N, neither.

Recommendation: M, mandatory; NR, not recommended; P, potentially useful; R, recommended.

Physicians making recommendations: EAW, Eugene Woltering; JPB, J. Philip Boudreaux; YZW, Yi-Zarn Wang; SJ, Saju Joseph; LA, Lowell Anthony.

and MRI, and investigation for metastatic disease not otherwise visible using SRS. SRS should be performed on all patients because this allows for identification of occult disease and evaluation of the receptor status of the tumor for subsequent treatment options.

All patients with NETs, whether or not functional, should be treated with octreotide, initially with short-acting octreotide and then transitioned to a longer-acting agent. Patients should have routine tumor surveillance and any change in symptom control, tumor size, or tumor marker levels, should necessitate trough levels to ensure adequate treatment with somatostatin analogs.

Surgery should be considered for all patients with NETs. Advanced surgical techniques have made large numbers of patients candidates for cytoreductive surgery. These surgical procedures should not be delayed until symptoms occur or tumor causes obstructive symptoms, because this often makes cytoreduction much more difficult. Furthermore, advanced treatment techniques, such as methylene blue lymphatic mapping for surgical margins, gamma probe-guided tumor debulking, and intraoperative chemotherapy, have all been shown to be effective in treatment of these patients.

For patients with unresectable disease, peptide receptor radiotherapy, chemoembolization, microsphere-guided radiation techniques, and MIBG can all be used to reduce tumor burden and help with symptoms. These patients should be evaluated by clinicians with expertise in the advanced treatment of NETs and with a multidisciplinary approach. These patients should be considered for chemotherapy regimens that address the root cause of symptoms and help reduce the chance of death from these tumors. Also, these patients should be considered for clinical trials that might change the future management of such patients.

NETs have become a more common malignancy in recent years. Although the incidence is rising, the treatment of these complex patients has not changed dramatically. However, with better understanding of tumor biology, more aggressive surgical techniques, and significant advances in radiologic techniques, the treatment of patients with NETs has become even more confusing. It is hoped that this article helps clinicians with the decision-making process and surgical management of patients with NETs.

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