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Small Bowel Neuroendocrine Tumors ☆

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Introduction

Neuroendocrine tumors (NETs) are a heterogeneous group of malignancies arising from neural crest-derived cells throughout the body. The presentation and natural history of NETs reflect their site of origin and secreted hormones. The first description of a neuroendocrine tumor was in 1867 when Theodor Langhans described a polyp of the small intestine that appeared poorly differentiated on histology but without evidence of invasion.[1] Otto Lubarsch described similar ileal polyps in 1888[2] and William Ransom wrote the first report of carcinoid syndrome, a woman with abdominal pain, diarrhea, wheezing, and ileal polyps.[3] Siegfried Oberndorfer coined the term "karzinoide," meaning carcinoma-like, in 1907 to describe these tumors of the small intestine that appeared histologically malignant but acted clinically benign.[4] In 1963, Williams and Sandler broadened the term carcinoid to include other functional tumors with similar clinical and biochemical findings, and they categorized carcinoid tumors by embryologic origin.[5] By their schema, foregut carcinoid tumors include those arising from the bronchus, stomach, pancreas, and proximal to the mid-duodenum. Midgut carcinoids arise in the mid-duodenum, jejunum, ileum, and mid-transverse colon. Hindgut carcinoids arise from the descending colon and rectum.

The World Health Organization used this broader understanding of the term carcinoid in its 1980 histological classification of tumors of the diffuse endocrine system.[6] As time went on, the term carcinoid seemed increasingly imprecise as immunohistochemistry and molecular biologic techniques revealed the heterogeneity of these tumors.[7] Furthermore, the majority of patients with carcinoid tumors did not have carcinoid syndrome. Therefore, Capella and colleagues recommended replacing the term "carcinoid" with "neuroendocrine tumor" to describe tumors deriving from neuroendocrine cells, which exist at the neuronal and endocrine inter-

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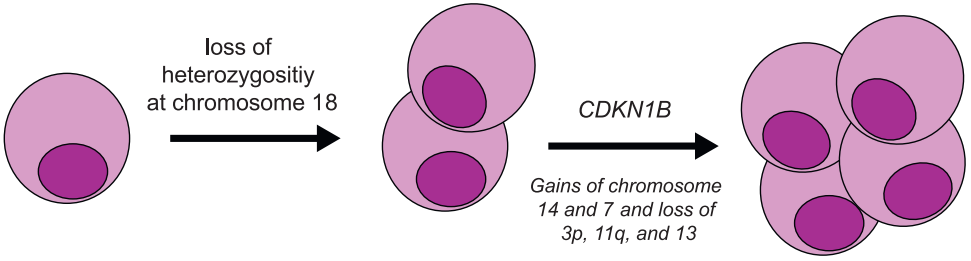

Fig. 1. Proposed mechanism for development of SBNETs. Loss of heterozygosity at chromosome 18 occurs in more than 60% of SBNETs, suggesting it is an early event in tumorigenesis.[12] More than 7% of SBNETs have mutations in *CDKN1B*,[15,17,137] but recurring mutations are uncommon, while gains of chromosome 14 and 7 and losses of 3p, 11q, and 13 are common.[10]

face and are defined by their secretory products.[7] The term neuroendocrine neoplasm includes well-differentiated NETs and poorly-differentiated neuroendocrine carcinomas (NECs).[8]

In this monograph, we discuss the presentation and management of patients with small bowel neuroendocrine tumors (SBNETs), which occur from the ligament of Treitz to the ileocecal valve. We focus on jejunal and ileal SBNETs, which have a distinct clinical presentation from duodenal and appendiceal NETs. Small bowel NETs arise from enterochromaffin cells, which are enteroendocrine cells that line the epithelium of the digestive tract and secrete the majority of the body's serotonin.[9]

Molecular Genetics

The molecular basis of SBNETs is not well understood. SBNETs harbor fewer mutations than other cancers; 1 series found SBNETs have only 0.1 somatic single-nucleotide variants per 10^6 nucleotides, whereas colon cancer can have more than 80 times that many mutations.[10,11] The most common somatic copy number alteration (SCNA) in SBNETs is a loss of heterozygosity of chromosome 18, seen in more than 60% of SBNETs.[12,13] Losses on chromosome 18 are believed to precede subsequent losses on chromosomes 3p, 11q, and 13, while maintenance of an intact chromosome 18 is associated with gains on chromosomes 14 and 7.[12,14] SBNETs have also been found to have mutations in *SMAD* genes (particularly *SMAD2* and *SMAD4*)[10], *CDKN1B*[15-17], and *IPMK* (Fig. 1).[18]

Epigenetic mutations, such as global hypomethylation, may play an important role in SBNET tumorigenesis, as 70% to 80% of SBNETs are epigenetically dysregulated.[19] Epigenetic changes can be reversible and are therefore possible targets for treatment. Demethylating agents have been approved for use in leukemia, but have had disappointing results in solid tumors and are not being clinically studied in NETs at this time. Although recent work has expanded knowledge of SBNET molecular genetics, for the majority of tumors, precise driver mutations and events leading to oncogenesis remain unknown, and this remains a rich area of investigation.

Epidemiology

Although considered rare, SBNETs have been increasing in incidence and prevalence, likely due to increased imaging leading to detection of early-stage disease and improved survival (Fig. 2).[20-22] This reflects the larger trend of increasing NET incidence, which rose 6.4-fold from 1973 to 2012 according to data from the Surveillance, Epidemiology, and End Results (SEER) program.[22] In 2000, SBNETs surpassed adenocarcinomas as the most common tumor of the small bowel[23] and the incidence is estimated to be approximately 1.2 per 100,000 persons, a 6-fold

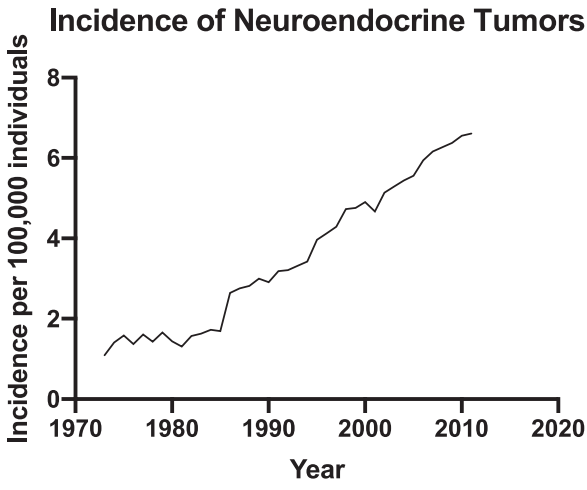

Fig. 2. Age-adjusted yearly incidence of NETs from all sites. The incidence of NETs has increased 6.4-fold from 1973 to 2012. Data from the National Cancer Institute Surveillance, Epidemiology, and End Results (SEER) database.[22]

increase from the 1970s.[22] Small bowel NETs make up approximately 17% of all diagnosed NETs and the small bowel is the second most common gastroenteropancreatic primary site of NETs after the rectum.[21] The median overall survival (OS) is 103 months and the 5-year survival rate is 69%, although survival decreases with extent of disease.[22] The median OS for patients with localized disease is 14 years, while the median OS in those with distant disease is 5.83 years, which is the highest for distant NETs of any site.[22] The incidence of SBNETs increases with age, with a median age at diagnosis of 66 years and peak incidence at 80 years of age.[21,23]

Thirty percent of patients with SBNETs will present with metastatic disease.[20] The proportion of patients presenting with distant metastases can be 60% to 80% at tertiary referral centers, possibly because early-stage lesions are removed in the community at operations for bowel obstructions, while more advanced disease is concentrated in larger hospitals.[24,25]

Presentation and Clinical Features

The classic triad of carcinoid syndrome consists of flushing (Fig. 3), diarrhea, and wheezing.[26,27] Right-sided valvular heart disease is less common but can cause significant morbidity. This syndrome results from the tumor secretion of bioactive amines, such as serotonin, histamine, tachykinins, and prostaglandins. Serotonin increases gut motility, causing diarrhea,[28] while other vasoactive substances cause flushing and wheezing through vasodilation and bronchoconstriction, respectively. Serotonin and bradykinin are thought to cause carcinoid heart disease through the development of fibrotic plaques causing tricuspid and pulmonary valve distortion and dysfunction.[29] Other less common symptoms include pellagra, telangiectasias, peripheral edema, and arthritis (Table 1).[30] Pellagra results from niacin deficiency since the essential amino acid tryptophan is shunted from the niacin synthesis pathway to serotonin synthesis.[31] The amines responsible for carcinoid symptoms are often hepatically inactivated, and the presence of carcinoid symptoms suggests a large tumor burden and/or the presence of liver metastasis.[32]

One older series related that only 0.5% of patients with NETs experienced carcinoid syndrome.[33] However, in a more recent survey of patients with SBNETs, 36% reported pain as their initial presenting symptom, 26% reported flushing, and 24% reported diarrhea as their first symptom.[34] Patients may also present with an asymptomatic mass incidentally seen on imaging.[35]

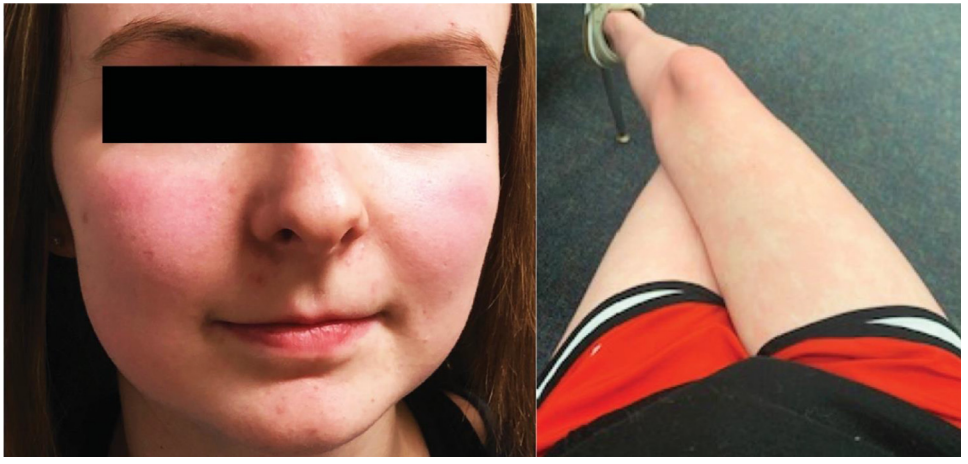

Fig. 3. Image demonstrating flushing in a patient's face (left) and legs (right) due to carcinoid syndrome secondary to an SBNET. The patient is a young woman who initially presented with postprandial flushing, nausea, vomiting, tachycardia, and diarrhea. She was determined to have a mid-ileal neuroendocrine tumor and multiple hepatic metastases.

Table 1
Symptoms of carcinoid syndrome

Organ System	Symptom
Skin	Flushing
	Telangiectasia
	Cyanosis
	Pellagra
Gastrointestinal tract	Diarrhea
	Cramping
Heart	Valvular lesions
Respiratory tract	Wheezing
Renal	Peripheral edema
Joints	Arthritis

Occasionally, an SBNET is discovered intraoperatively during surgery performed for bowel obstruction.

The abdominal pain experienced from an SBNET can be the result of multiple factors. The mass effect of the tumor can cause obstruction, intussusception, or mesenteric ischemia. Primary SBNETs and nodal metastases can cause a local desmoplastic response, resulting in dense fibrosis and calcifications. Up to 50% of patients with SBNETs can develop fibrosis of mesenteric lymph nodes, potentially causing tethering and kinking of the mesentery, leading to obstruction, pain, and mesenteric ischemia (Fig. 4).[36,37]

Because of the vague nature of their symptoms, patients with SBNETs may go an extended period of time before diagnosis. One study from the United Kingdom found the median age of diagnosis is 50.8 years and the mean time from symptom onset to diagnosis is 53.8 months.[34] Patients are sometimes misdiagnosed with functional gastrointestinal disorders for months or years with inadequate symptom control before being diagnosed with an SBNET.

Diagnosis

Diagnostic strategy depends on patient presentation. When patients present with classic carcinoid syndrome, biochemical testing can help confirm the diagnosis of carcinoid syndrome and

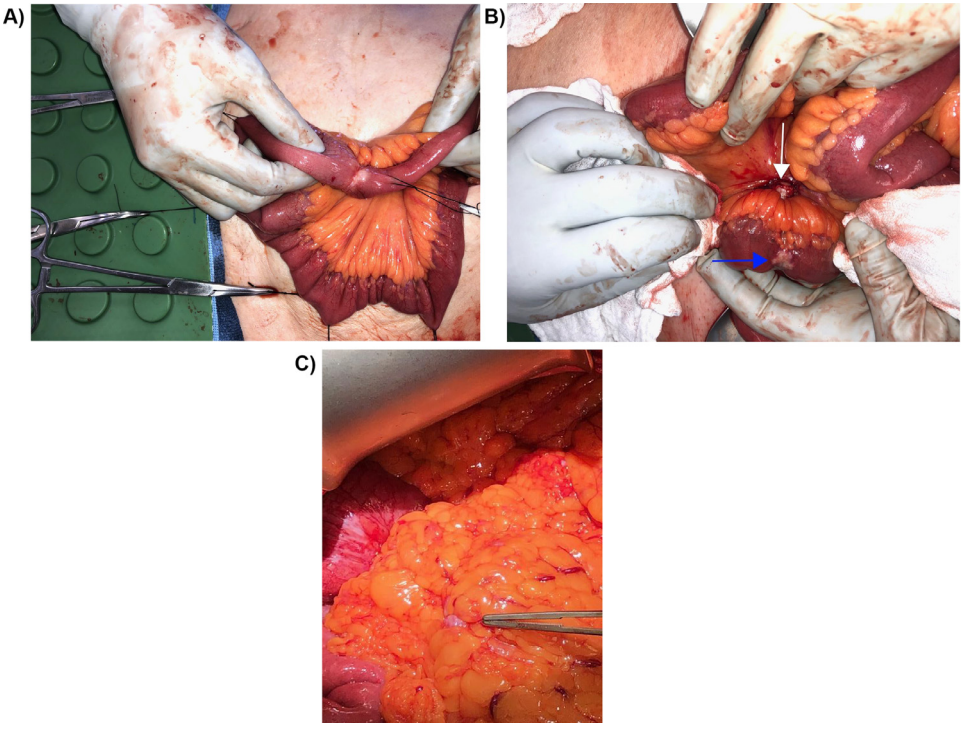

Fig. 4. A) Primary SBNET with dilated proximal bowel (held in surgeon's right hand) and multifocal lesions (each black suture designates a different primary tumor). B) Primary SBNET (blue arrow) and adjacent nodal metastasis (white arrow). C) Peritoneal metastasis from an SBNET (tip of forceps).

provide baseline hormone levels. Anatomic and possibly functional imaging should then be undertaken to determine extent of disease and feasibility of biopsy. Imaging may identify the site of primary tumor, involvement of nodes, and presence of metastatic disease, which will aid in surgical planning and provide a baseline for monitoring of disease progression. Biopsy may be helpful to confirm that a tumor is a NET, but is not always possible or necessary. Uptake on functional imaging tests, such as ^{68}Ga-DOTAPET-CT can also aid in the diagnosis.

Biochemical testing

In the setting of symptoms of carcinoid syndrome, a 24-hour collection for urinary 5-hydroxyindoleacetic acid (5-HIAA) can confirm the diagnosis of carcinoid syndrome. 5-HIAA is a metabolite of serotonin and is measured as a proxy for serotonin (Fig. 5). A 24-hour urinary 5-HIAA is more informative than a random measurement, as blood levels of serotonin change throughout the day.[31] The test has a sensitivity of 85% and specificity of 90% for detecting carcinoid syndrome.[38,39] However, it is difficult to collect, and levels can be affected by drugs and foods. A number of foods including avocados, pineapples, bananas, kiwi fruit, walnuts, and pecans can increase urinary 5-HIAA levels and should be avoided when levels are measured.[40]

Compared to urinary tests, blood biomarkers are simpler for monitoring for disease progression or recurrence. One of the most consistently checked markers is chromogranin A (CgA), a protein of the granin family secreted by SBNETs with autocrine, paracrine, and endocrine activities.[41] Chromogranin A remains the only tumor marker recommended by consensus guide-

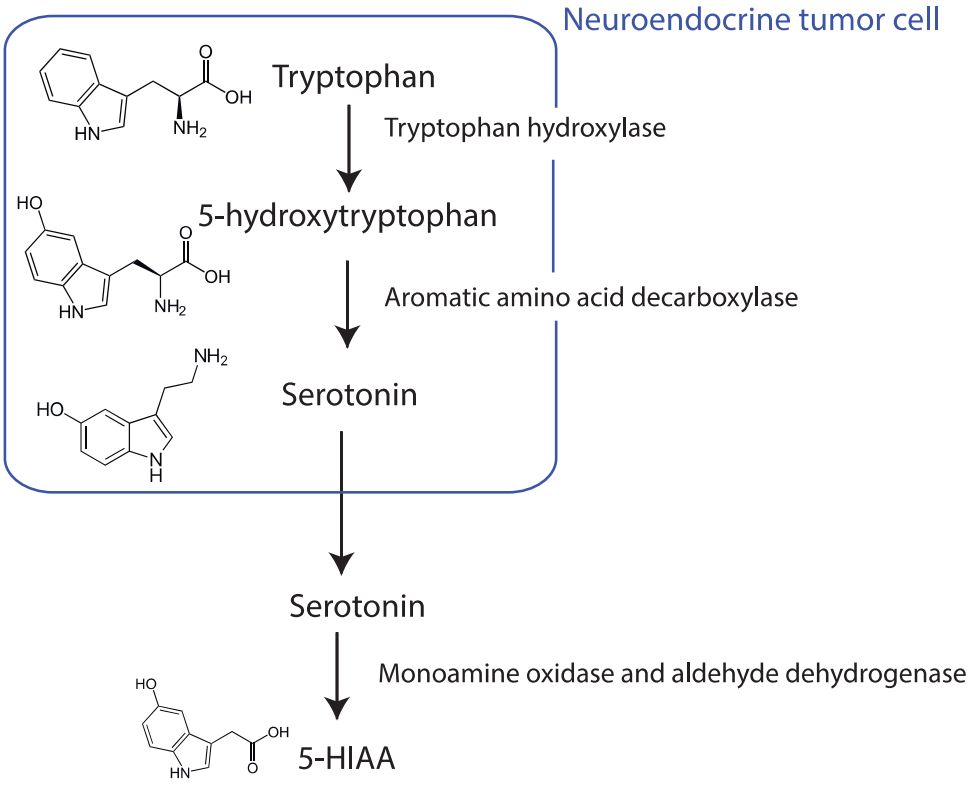

Fig. 5. Synthesis and excretion of serotonin by neuroendocrine tumor cells. Serotonin is stored in secretory vesicles in the cell and then released into the blood, where it is stored in platelets. Serotonin is converted to 5-hydroxyindoleacetic acid (5-HIAA), which is excreted in the urine. Serotonin is thought to be responsible for the symptoms of carcinoid syndrome.

lines,[35,42] despite several shortcomings. It has a limited sensitivity and specificity of 71% and 50%, respectively, for identifying imaging-confirmed progression of well-differentiated gastroenteropancreatic NETS.[43] Some studies have found that CgA levels can correlate with hepatic tumor burden[44] and a rise in CgA may correspond with tumor recurrence after surgical resection.[45] However, CgA levels can be falsely elevated in renal dysfunction, inflammatory diseases like rheumatoid arthritis, and malignancies of the pancreas, lung, prostate, ovary, and breast.[46,47] Notably, CgA levels can be falsely elevated due to the use of medications like proton pump inhibitors (PPIs).[42,48]

Other monoanalyte serum markers include pancreastatin, neurokinin A, substance P, pancreatic polypeptide, and neuron-specific enolase.[46,49] A multianalyte assay, the NETest, measures circulating tumor mRNA, but is not widely used and has not been recommended in expert guidelines. Pancreastatin is a post-translational cleavage fragment of CgA that is more specific and sensitive than CgA in detecting progression and predicting survival.[50-52] It is also unaffected by PPI use. In a study of 218 surgically resected SBNETs, pancreastatin provided more information regarding progression-free and OS than CgA.[53] Pancreastatin was more sensitive, specific, and accurate for detecting progression than CgA. Serotonin did not provide prognostic information, and neurokinin A was too infrequently elevated to be practically useful in most patients. The findings of this study and others suggest that pancreastatin should replace CgA as the tumor marker of choice for the surveillance of patients with surgically treated SBNETs.

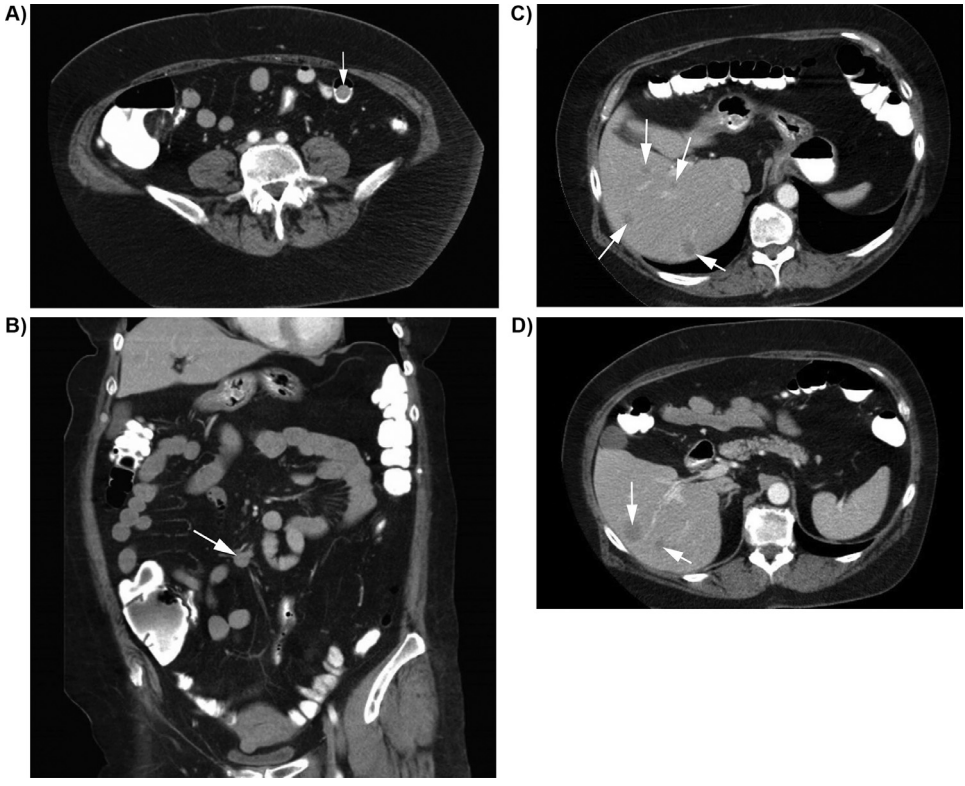

Fig. 6. A) CT scan showing a primary SBNET (white arrow). The patient is a 67 year old woman who presented with abdominal pain, diarrhea, and flushing. She was determined to have an ileal NET with numerous hepatic metastases. She underwent laparotomy, small bowel resection, and enucleation and ablation of multiple (>30) liver lesions. B) Coronal CT scan with nodal metastases (white arrow) from the same patient. Nodal metastases can cause a local desmoplastic response, causing calcifications and fibrosis that result in a characteristic stellate pattern with spiculations on CT (not present here). C) CT scan from this patient demonstrating multiple hypodense liver metastases on the venous phase (C, arrows), which on arterial phase D) tend to be hypervascular and appear as enhancing masses.

Imaging

Imaging modalities for SBNETs can be divided into anatomic and functional imaging. Anatomic imaging provides information regarding the location of tumors relative to nearby structures, blood vessels, lymph nodes, and the liver. Anatomic modalities include ultrasound (US), computed tomography (CT), and magnetic resonance imaging (MRI). In comparison, functional imaging uses radiolabeled somatostatin analogs, such as ^{111}Indium pentetreotide (OctreoScan) and ^{68}Gallium DOTA PET-CT (DOTATATE, DOTATOC, or DOTANOC), which show the location of lesions by uptake of somatostatin analogues through cell-surface receptors. These studies are useful for determining the extent of disease throughout the body and to confirm that lesions seen on anatomic imaging are NETs.

CT is often used as the initial diagnostic tool because it is noninvasive and widely available. Primary SBNETs tend to be small and can be difficult to identify on CT, but visualization can be improved with multi-phase imaging and neutral oral contrast (Fig. 6).[54-56] SBNETs result in a desmoplastic response in the mesenteric lymph nodes, which can be seen on CT as a mesenteric mass with a characteristic stellate pattern with spiculations.[56] The sensitivity of CT for identifying the primary SBNET ranges from 7% to 38%,[57-59] but sensitivity can be improved to 77%

if mesenteric lymphadenopathy is included with small bowel mass or thickening as a positive localization sign.[60] SBNETs and their metastases tend to be hypervascular, so liver metastases appear as enhancing masses on arterial phase with IV contrast.[56] Occasionally, the liver metastases are hypovascular and seen better on the venous phase, so it is important that CT scans contain both arterial and venous phases.

In comparison to CT, MRI provides greater sensitivity (sensitivity of 95%) in detecting liver metastases, with the hepatic arterial phase and fast spin-echo T2-weighted imaging allowing the best detection of metastases.[56,61] Hepatic metastases appear hypointense on T1-weighted MRI and hyperintense on T2-weighted MRI (Fig. 7). Additional advantages of MRI are that it provides no ionizing radiation and is an alternative if patients are allergic to CT contrast. However, MRIs are time-consuming to obtain, less widely available than CT, more expensive, and can still underestimate tumor burden.[61] MRI is also less sensitive than CT for detecting recurrent nodal or mesenteric disease.[62] Use of gadoxetate (Eovist), a hepatocyte-specific contrast, and hepatocellular phase MRI may improve the precision of metastasis detection and measurement.[63] However, no imaging modality will be able to visualize numerous hepatic micrometastases, which can only be seen on pathologic examination.[64]

In contrast to anatomic imaging, functional imaging takes advantage of the expression of somatostatin receptors (SSTRs) and uptake of radiolabeled somatostatin analogues by SBNETs.[62] These modalities can be useful in identifying disease when patients are symptomatic, but anatomic imaging and endoscopy are negative. The first functional imaging for NETs to be widely used was somatostatin receptor scintigraphy (Octreoscan), which utilized ^{111}Indium pentetreotide uptake to visualize NETs. The anatomic localization of tumor was enhanced when planar ^{111}In scintigraphy was combined with single-photon emission CT.[65,66] In recent years, somatostatin receptor-positive emission tomography (PET), using ^{68}Ga DOTATATE, ^{68}Ga DOTATOC, or ^{68}Ga DOTANOC has largely supplanted ^{111}In pentetreotide as the preferred functional imaging method of choice, as these PET modalities are more sensitive in detecting NETs and provide improved spatial resolution.[67,68] Furthermore, ^{68}Ga-DOTATATE is faster to acquire, less expensive, and provides less radiation exposure than ^{111}In pentetreotide scintigraphy.[69]

Another functional imaging modality is PET imaging using ^{18}fluoro-deoxy-glucose (FDG; a glucose analog), which is used to stage and monitor many types of cancers. FDG-PET takes advantage of the tendency of malignant tumors to accumulate more FDG compared to benign tissue.[70] FDG-PET has limited value in NETs, as it has low sensitivity in well-differentiated, slower-growing NETs.[71,72] FDG tends to be taken up by poorly-differentiated NETs with high proliferative activity, so FDG-PET may be useful in identifying poorly-differentiated, aggressive NETs associated with worse prognosis.[73]

Other Modalities

Despite advancements in imaging, primary SBNETs can be difficult to identify on both anatomic and functional imaging. Endoscopy is occasionally helpful when a patient has a NET and the primary site cannot be identified. However, a thorough investigation of the distal small bowel is not always possible, even with intubation of the terminal ileum on colonoscopy. The majority of SBNETs occur in the distal ileum and more than 50% of patients with SBNETs have multifocal tumors.[24] Capsule endoscopy and double-balloon enteroscopy offer improved visualization of the entire small bowel, although in the former, the capsule may become lodged if the bowel is narrowed by the primary. Double-balloon enteroscopy is labor-intensive and not widely available. More data are needed regarding the role of endoscopy in routine evaluation, staging, and post-treatment monitoring, but many authorities consider it to be unnecessary if a CT scan is highly suggestive of an SBNET.[62,74]

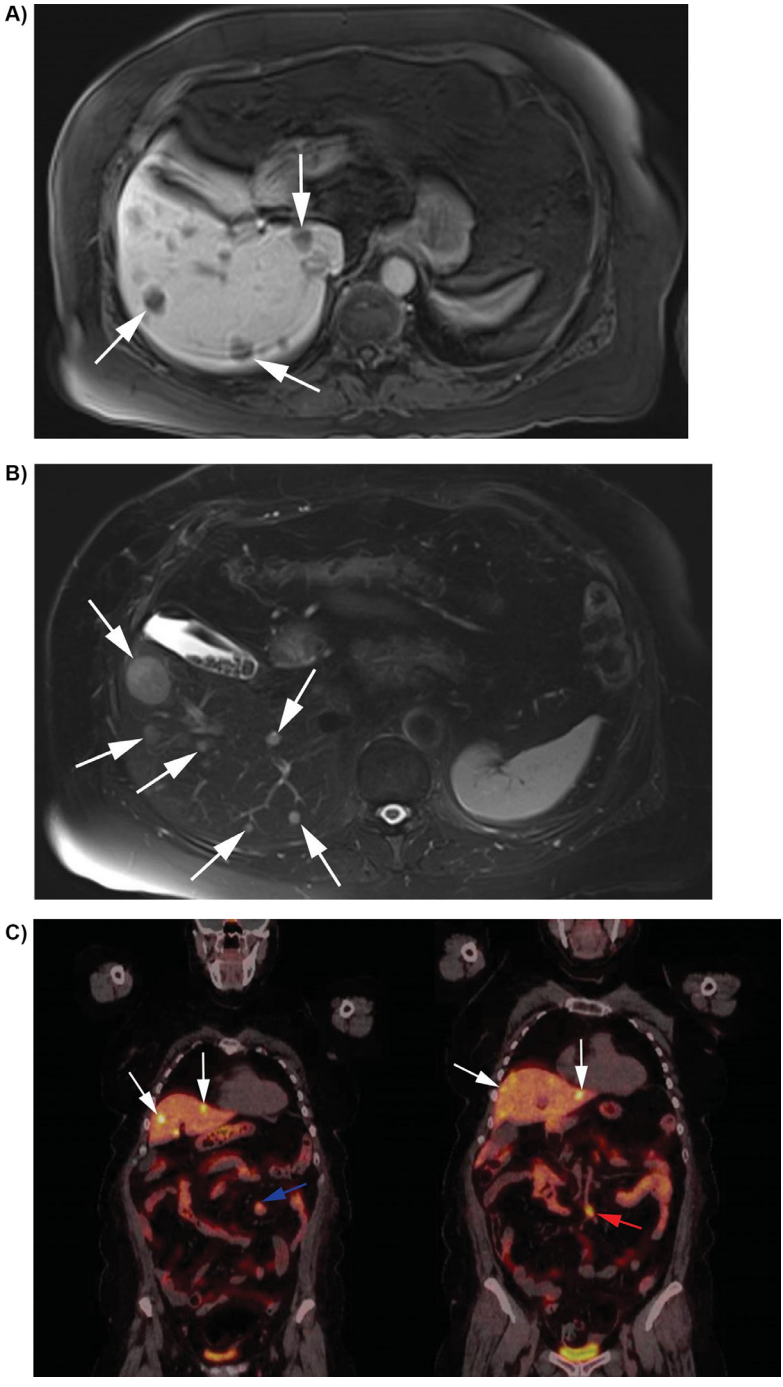

Fig. 7. Axial MRI of hepatic metastases (arrows) from an SBNET in the same patient shown in Fig. 6. Metastases appear hypointense on T1-weighed MRI (A) and hyperintense on T2-weighted MRI (B). C) ^{68}Ga-DOTATATE scan showing primary SBNET (blue arrow), nodal metastasis (red arrow), and liver metastases (white arrows) in the same patient.

Table 2
Classification and Staging of Small Bowel Neuroendocrine Tumors

Terminology	Differentiation	Grade	Mitotic rate (mitoses/2 mm^2)	Ki-67 index
NET, G1	Well-differentiated	Low	<2	<3%
NET, G2	Well-differentiated	Intermediate	2-20	3-20%
NET, G3	Well-differentiated	High	>20	>20%
NEC, small-cell type	Poorly differentiated	High	>20	>20%
NEC, large-cell type	Poorly differentiated	High	>20	>20%
mixed neuroendocrine-non-neuroendocrine neoplasm	Well or poorly differentiated	Variable	Variable	Variable
	Stage	**Definition**		
Primary Tumor	Tx	Primary tumor cannot be assessed		
	T0	No evidence of primary tumor		
	T1	Tumor invades lamina propria or submucosa and size ≤1 cm		
	T2	Tumor invades muscularis propria or size >1 cm		
	T3	Tumor invades through the muscularis propria into subserosal tissue without penetration of overlying serosa or into non-peritonealized tissues		
	T4	Tumor invades visceral peritoneum (serosa) or invades other organs		
Regional Lymph Nodes	NX	Regional lymph nodes cannot be assessed		
	N0	No regional lymph node metastasis		
	N1	Regional lymph node metastasis		
Distant Metastases	M0	No distant metastases		
	M1	Distant metastasis		

G: grade, NET: neuroendocrine tumor, NEC: neuroendocrine carcinoma
Adapted from World Health Organization 2019 neuroendocrine neoplasms and American Joint Commission on Cancer Staging of SBNETs 2018[8,86]

Pathology

The above methods can suggest the presence of an SBNET, but pathologic diagnosis is necessary for confirmation.[35] Tissue can be obtained by needle biopsy or surgically, and core needle biopsy is preferred to fine needle aspiration.[35] Positive immunohistochemical (IHC) staining for neuroendocrine markers synaptophysin and chromogranin will help confirm the diagnosis of a NET.[75] Small bowel NETs tend to have a nested architecture and centrally located, oval nuclei with a "salt-and-pepper" appearance on H&E staining (Fig. 8).[76] Cells can have eosinophilic cytoplasmic granules, which represent intracellular serotonin.

When the primary site is uncertain, especially in the biopsy of liver metastases, further IHC staining can be helpful. Positive caudal type homeobox 2 (CDX2) staining suggests a midgut primary, whereas positive paired box gene 6 (PAX6) and/or insulin gene enhancer-binding protein (ISL1) staining suggests a pancreatic primary.[77] Expanded IHC panels can determine SBNET as the primary site with greater than 85% accuracy.[78] Beyond IHC, several gene expression classifiers, both specific to NETs and for the general case of cancers of unknown primary, have been proposed for NET primary site determination, but have not entered widespread use.[79-81]

Pathologic examination should also include tumor differentiation (well vs poorly differentiated) and grade (grade 1, 2, or 3), as both provide important prognostic information (Table 2). Poorly differentiated NECs are distinct from well-differentiated NETs. NECs, which can be small or large-cell type, are also high-grade with high proliferative indices (Ki-67 >20% or mitotic rate >20 per 2 mm^2). Compared to NETs, NECs are associated with a more aggressive phenotype, more frequent metastasis, and shorter survival.[82] The median survival in patients

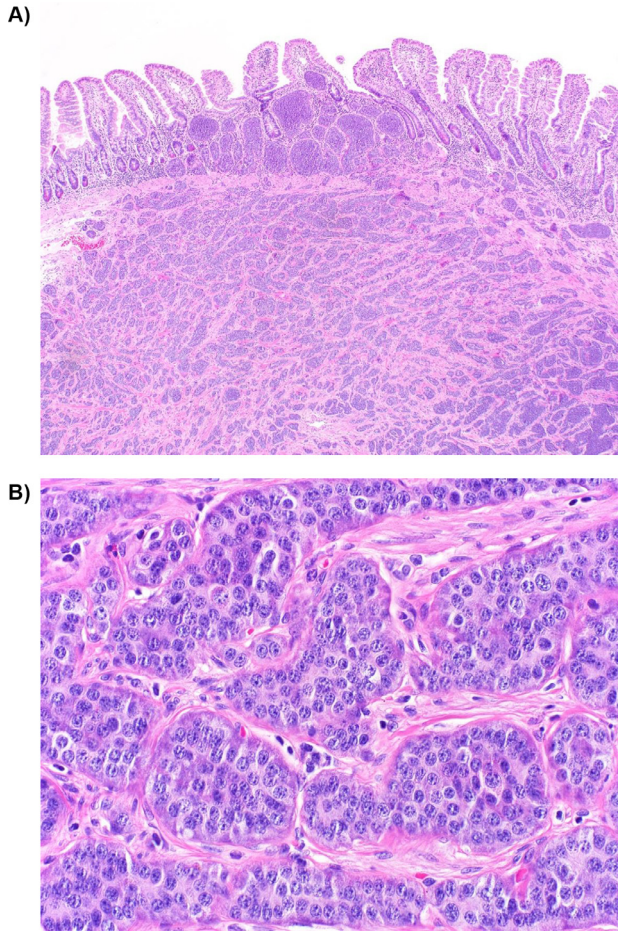

Fig. 8. A: Low (A) and high-power (B) images of hematoxylin and eosin (H&E) staining of SBNET demonstrating nested architecture and ovoid, centrally located "salt-and-pepper" nuclei. Images courtesy of Andrew Bellizzi, MD. C) Immunohistochemistry results for H&E, CDX2, PAX6, and ISL1 staining. Small bowel NETs stain positive for CDX2 and negative for PAX6, ISL1 (top panel). Pancreatic NETs stain negative for CDX2 and positive for PAX6 and ISL1 (bottom panel). Image reprinted with permission from *Surgery*, 156(6), Maxwell JE, Sherman SK, Stashek KM, O'Dorisio TM, Bellizzi AM, Howe JR, A practical method to determine the site of unknown primary in metastatic neuroendocrine tumors, 1359-1365, copyright (2014), with permission from Elsevier.[78] D) Images comparing H&E (left panels) and corresponding Ki-67 (right panels) staining of a metastatic, grade 3 neuroendocrine tumor with well- and "less well"-differentiated components. Panels A and B demonstrate a lower power view. Panels C and D demonstrate a higher power image of the well-differentiated component with Ki-67 of 0.75%. Panels E and F demonstrate a higher power image of the "less well"-differentiated component with a Ki-67 of 35%. Reprinted with permission from *Human Pathology*, Bellizzi AM, Immunohistochemistry in the diagnosis and classification of neuroendocrine neoplasms: what can brown do for you?, copyright (2019) with permission from Elsevier.[76]

with advanced gastrointestinal NECs is 1 month with best supportive care and 11 months with palliative platinum-based chemotherapy.[83]

The grade is based on proliferative rate, which is determined by mitotic rate (mitotic count per 2 mm^2) and/or Ki-67 index (percentage of cells that stain positively for Ki-67).[75] The 2019 World Health Organization (WHO) classification of tumors of the digestive system provides guidelines for grading SBNETs (Table 2).[8] Higher grade is associated with larger primary tumor size, increased regional and distant metastasis, and shorter survival times in gastroenteropancre-

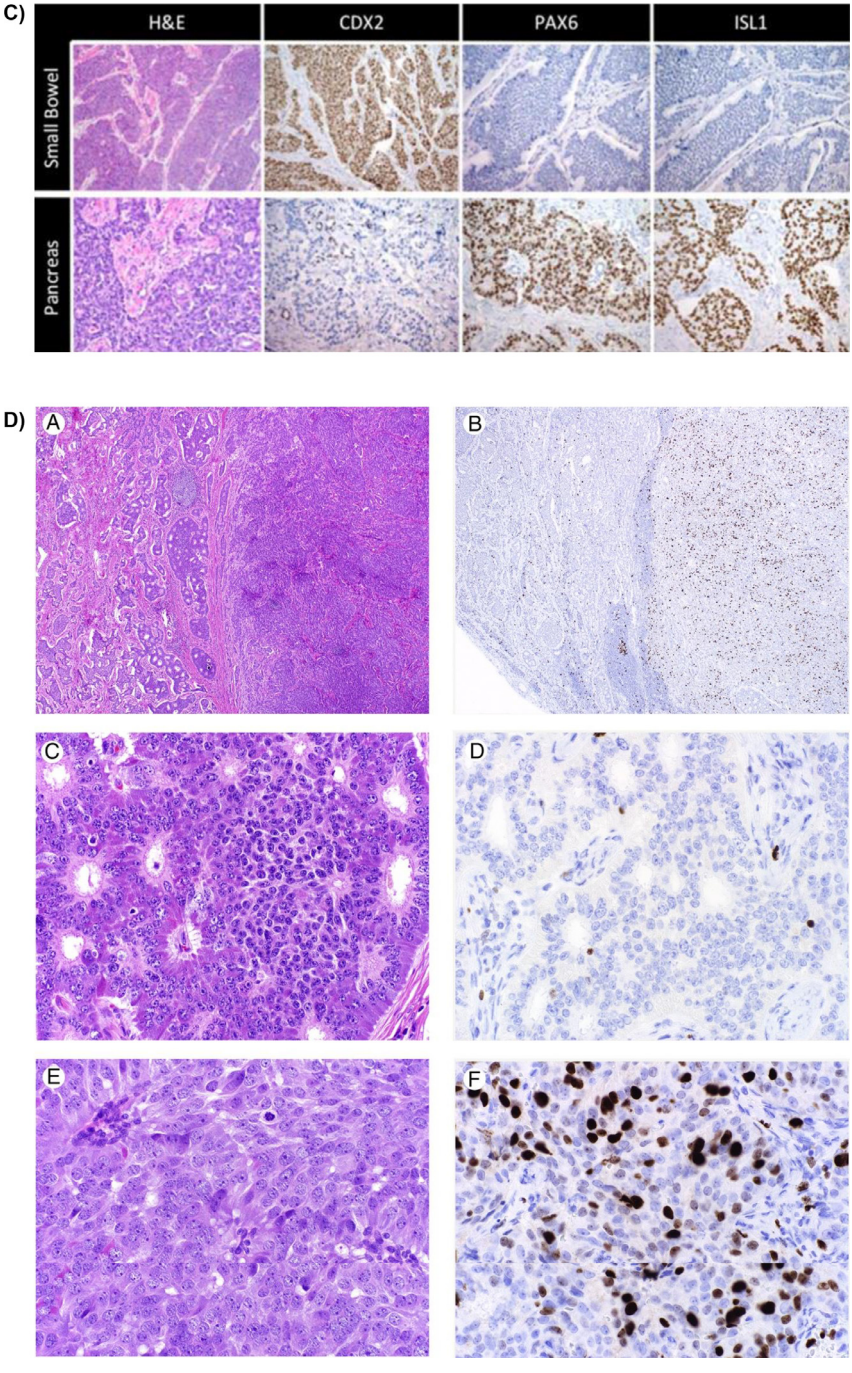

Fig. 8. Continued

atic NETs.[84] The Ki-67 should be determined for primary and metastatic tumors, as the highest grade from any site predicts both progression-free (PFS) and overall survival (OS).[85] Staging is based on the TNM staging system by the American Joint Committee on Cancer (Table 2).[86]

Surgical Treatment

Surgery plays a foremost role in SBNET management, providing diagnosis, prevention of mechanical obstruction, and improvement of symptoms due to the overproduction of hormones. The following section covers the surgical approach to SBNETs. Although discussed separately, operations for SBNETs should address both primary and metastatic tumor sites whenever possible. As most patients either have metastases at diagnosis or subsequently develop them, patients are only infrequently cured with surgery, yet a careful application of SBNET surgical principles can substantially prolong survival and improve patients' quality of life.

Perioperative Considerations

Perioperative management of SBNET patients requires preparation for the possibility of carcinoid crisis. Surgeons should maintain a low threshold for obtaining a preoperative echocardiogram in any SBNET patient with high serotonin levels or history concerning for carcinoid heart disease. Those with significant tricuspid or pulmonic valve disease must have this corrected prior to treatment of abdominal disease.[62] Even without carcinoid heart disease, sudden hemodynamic instability or cardiovascular collapse due to carcinoid syndrome can occur, even in patients without clear symptoms of hormonal overproduction.[87] Reported rates of perioperative carcinoid crisis range widely from 3% to 35%.[88-91] Prospective support for intraoperative octreotide to prevent carcinoid crisis is lacking and some have questioned its efficacy.[62,88] However, since it may ameliorate carcinoid crisis symptoms,[90,91] our practice has been to provide octreotide at 100 mcg/hr throughout the case in addition to remaining ready to give additional fluids and vasopressors if necessary (preferably vasopressin or phenylephrine rather than epinephrine). Octreotide infusions are then weaned postsurgically by 25 mcg/hr every 8 hours. Postoperative venous thromboembolism prophylaxis follows standard treatment after major surgery. Extended homegoing prophylaxis may not be required, as rates of deep vein thrombosis and pulmonary embolism were lower for SBNET resections than those for other abdominal malignancies in a national retrospective database (1.7 vs 2.4%, $P < 0.05$).[92]

Operative Technique

Surgery of the primary site, whether laparoscopic or open, must include thorough and careful palpation of the entire bowel length (Fig. 9). Primary SBNETs occur most commonly in the ileum and are often small. Although nodal metastases visible in the mesentery on CT or SSTR-imaging often exist and point to its probable location, the primary tumor frequently escapes radiologic detection and can be identified only by running the bowel. In a study of 123 resected primary SBNETs employing detailed measurement of the small bowel length and location of tumors, 72% of primary tumors arose within 100 cm of the ileocecal valve, and the mean tumor size was 2 cm.[24] As 56% were multifocal, palpation for tumors must not stop upon identification of a single lesion. After identifying all tumors, segmental resection of the affected bowel includes adequate margins to include the associated mesentery. Randomized studies establishing whether resection of primary NETs reduces subsequent metastases do not exist. Retrospective data, however, support this hypothesis in pancreatic, small bowel, and other NETs, and patients undergoing resection of the primary tumor demonstrate improved survival compared to those not receiving operations (median, 91.3 months among 4,252 resected patients vs 44.2 months

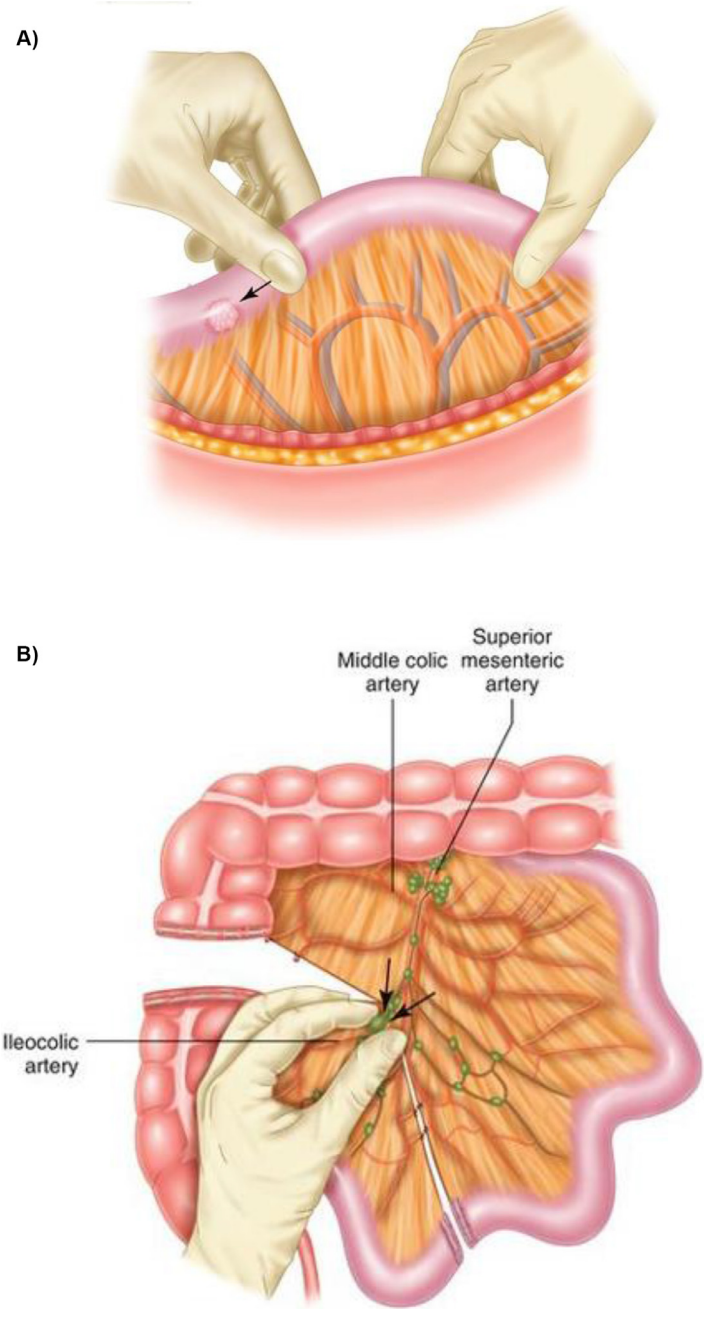

Fig. 9. A) Palpation of the small bowel beginning from the ligament of Treitz. The small bowel should be carefully pulled through the thumb and forefinger to palpate for lesions. B) Dissection of the base of the ileocolic artery. The nodes are pulled away from the superior mesenteric artery and vein. Once the nodes are freed from the base of the mesentery, the proximal subsegmental vessels are doubly clamped and suture ligated.
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in 2,526 unresected patients).[93,94] Selection biases clearly affect these retrospective data, yet as SBNET resection treats or prevents hormonal symptoms and mechanical obstruction, and may reduce metastases and improve survival, we support resection of low and intermediate-grade SBNET primaries in all surgically fit patients.

Mesenteric resection includes the blood supply and associated lymph nodes up to the level of where the segmental branch vessels come off the superior mesenteric artery (SMA) and vein (SMV). Bulky involved nodes are carefully dissected from larger mesenteric vessels when possible without endangering the SMV/SMA (Fig. 9). Large nodal metastases frequently produce fibrosis and foreshortening of the mesentery.[95] Although this adds difficulty to the dissection, fibrosis and bulky nodal disease also contribute to obstructive or intestinal ischemic symptoms if left in place.[62,96] Hormonal overproduction symptoms also may fail to improve without adequate resection of large-burden nodal disease. However, removal of these nodes is not always possible, and patients can still have long-term survival if left in place. Peritoneal implants along the mesentery or abdominal wall occur in up to 20% of patients.[62] Complete peritoneal stripping to the extent used in cytoreductive surgery for other histologies is not necessary for SBNETs, but these metastases should be addressed when possible with acceptable surgical risk. A combination of limited peritoneal stripping and ablation using electrocautery or argon beam coagulation provides excellent control in most cases.[62]

Although primary tumors likely account for most symptoms of obstruction and pain, death from SBNETs most commonly occurs due to liver metastases.[97,98] Controlling the burden of liver metastatic disease therefore not only reduces hormonal symptoms, but may prolong survival.[99] When planning operations for SBNET liver disease, the techniques used differ from those used for other cancers, with a focus on preservation of healthy parenchyma.[62] SBNET metastases tend to be well-circumscribed and non-infiltrative. More superficial metastases can therefore be resected adequately with limited margins through partial hepatectomy wedge resections or enucleation of surface lesions. Ultrasound-guided radiofrequency or microwave ablation can be used to treat deeper lesions, avoiding the morbidity and loss of healthy liver associated with larger hepatic resections.[96] Although formal hepatic lobectomies may sometimes be required, limited oligometastases, such as those encountered in resections for colorectal cancer, are less common. More often, multiple, bilobar metastases, including unrecognized micrometastases exist, necessitating a strategy seeking to control, rather than definitively eliminate, disease.[62,64]

Often with SBNETs, extensive metastases preclude complete liver clearance, even with combined resection/ablation techniques. The degree of anticipated cytoreduction necessary to justify a liver-directed operation has been subject to debate. Some authorities advocate a 90% threshold, based on favorable results when using this criterion.[99,100] More recently, it has been shown that aiming for 70% cytoreduction yields substantial clinical benefit, with reported 5-year survival of 70% to 90% and median OS in excess of 10 years.[98,101] In 1 series of 108 operations undertaken with a goal of achieving at least 70% debulking, more than 75% of patients saw “biochemical response,” defined as a 50% or greater reduction in tumor markers.[101] The average percent liver replacement was 10% and median SBNET metastatic liver lesions treated was 6 (range 0-36).[101] Although 64% of SBNET patients saw at least 70% debulking on postoperative scans, only 40% had 90% debulking. Based on these data, although patients in whom 90% debulking can be achieved have excellent outcomes, limiting liver intervention to patients with more limited liver disease potentially excludes a large number of those who could benefit. Guidelines therefore recommend liver-directed surgery for SBNET metastases when at least 70% debulking appears possible.[62]

Other Surgical Options

Beyond resection/ablation for metastases, additional surgical modalities have been investigated for SBNET treatment. Complete cytoreductive surgery combined with heated intraperitoneal chemotherapy (CRS/HIPEC) has been reported to improve outcomes in tumors of appendiceal, colorectal, and mesothelial origin with peritoneal metastases.[102-104] A leading French center investigated CRS/HIPEC (mainly fluorouracil/oxaliplatin) for NETs by retrospectively com-

paring patients treated with CRS/HIPEC between 1994 and 2007 with those treated in 2008-2012 with CRS alone.[105] Of 50 total patients, 76% were small-bowel or appendiceal in origin. Patients treated with HIPEC in addition to CRS had improved disease-free survival (49% vs 17% at 2 years, $P = 0.018$), but retrospective design, unbalanced baseline characteristics, shorter follow-up in the latter group, and changing diagnostic technology limited the authors' ability to draw meaningful conclusions about the efficacy of HIPEC for neuroendocrine metastases.[105] The fact that these authors stopped treating their NET patients with HIPEC speaks for itself, and currently HIPEC is not recommended for patients with SBNETs.[62]

Liver transplantation has also been used for NET liver metastases. A review of 706 transplanted NET patients found 5-year survival from time of liver metastasis diagnosis of 70% compared to 34% among patients from the same reviewed studies who did not receive transplants.[106] A different analysis of 33 patients treated at a Swedish center who met Milan transplant criteria but were not transplanted found 5-year survival of 97%, suggesting inferiority of liver transplant results.[107] Defining survival without a transplant remains challenging, as patients considering transplantation may represent a population not eligible for other treatments due to underlying liver disease, tumor burden, or other factors. Transplantation stands as an option in highly select patients, with alternative surgical or interventional therapies preferred in most situations.[62]

Medical Treatment

In addition to surgical treatment to remove primary and metastatic tumors, SBNET care includes several medical therapies for which randomized data support efficacy in delaying progression or death. Medical therapy is generally not indicated for patients with no evidence of disease, however, for patients with residual or unresectable disease remaining following surgery, patients with hormonal symptoms refractory to surgery, or in patients whose comorbidities or disease burdens (particularly in the liver) preclude surgical treatment, medical therapy can reduce symptoms and delay progression.[35]

Somatostatin Analogues

Somatostatin analogues (SSAs) have been used for decades to control NET hormonal symptoms.[108] Small bowel and other NETs express high levels of somatostatin receptors,[109-112] and activation of these receptors by synthetic somatostatin peptide mimetics decreases signaling in cell proliferation pathways while reducing hormone secretion.[113] First-line SSA treatment improves hormonal symptoms in 70% to 80% of patients.[114] In addition to their efficacy in controlling symptoms, the PROMID study provided level-I evidence of SSA's ability to slow midgut NET growth. This study randomized 85 patients with advanced low-grade midgut NETs to placebo or treatment with long-acting octreotide 30 mg every 28 days. In treated patients, time to progression was 14.3 months vs 6.0 months in the placebo group (HR 0.33, $P < 0.001$). Tumor regression was rare, but stable disease occurred in two thirds of treated patients with no differences in quality of life between groups.[115] Long-term follow-up at a median of 96 months revealed 5- and 10-year survival rates of 67% and 45%, with no difference in OS between octreotide and placebo-treated groups, however a high rate of crossover upon progression in the placebo group (38/43 patients) limited the study's ability to detect a survival difference.[116]

The CLARINET trial investigated the effect of another SSA, lanreotide, on PFS in advanced pancreatic, midgut, and hindgut NETs with Ki-67 of <10%. In this trial, 204 patients randomly received 120 mg of long-acting lanreotide or placebo every 28 days for 96 weeks. Patients treated with lanreotide had significantly longer PFS (median not reached vs 18.0 months, HR 0.47, $P<0.001$), with 2-year PFS of 65% vs 33%. Subgroup analyses found this effect to be independent of primary site, grade, and liver tumor burden, and no OS difference was seen.[117] Based on these studies, SSAs represent highly-effective first-line medical treatment for preventing tu-

mor progression and controlling symptoms of carcinoid syndrome in advanced gastroenteropancreatic NETs.[35]

Everolimus

Following progression on first-line SSAs, additional medical options include everolimus, peptide receptor radionuclide therapy (PRRT), and chemotherapy. Everolimus inhibits the mammalian target of rapamycin (mTOR) protein, which acts as a downstream kinase effector of the phosphoinositol-3-kinase/Akt pathway and promotes tumor cell survival, angiogenesis, and growth.[118,119] In the RADIANT-3 trial, everolimus prolonged PFS vs placebo in pancreatic NETs; however its role in SBNETs has been less clear.[120] The RADIANT-2 trial included 429 patients with advanced low or intermediate grade NETs with carcinoid syndrome and progression.[119] Randomized subjects received long-acting octreotide plus everolimus 10 mg daily or placebo with a primary endpoint of PFS. Small bowel NETs comprised approximately half of included patients, with lung the next most common primary tumor site. At a median follow-up of 28 months, PFS in the everolimus plus octreotide group was 16.4 vs 11.3 months in the octreotide only group, representing a hazard ratio of 0.77. The P-value for PFS was 0.026, which fell short of the prespecified significance bound of 0.0246, making RADIANT-2 a negative trial. Biochemical response, defined as a 50% decrease in chromogranin A, occurred in 46% of everolimus+octreotide-treated patients compared to 36% of octreotide patients. Long-term follow-up of RADIANT-2 showed numerically worse OS in the everolimus+octreotide group compared to placebo+octreotide (median 29.2 vs 35.2 months), which was not statistically significant (HR for death 1.17, 95% confidence interval 0.92-1.49, $P > 0.05$).[121] This result did not change after multivariable adjustment for unbalanced covariates between the groups. Notably, OS was a secondary endpoint for which the trial was not designed or powered to detect a difference, but the cumulative interpretation of these studies was to suggest a limited role for everolimus in SBNETs with carcinoid syndrome.

The usefulness of everolimus in SBNETs was further investigated in the RADIANT-4 trial.[122] This trial randomized the 302 included patients with advanced, unresectable grade 1-2, well-differentiated NETs of the lung or GI tract with progression and without carcinoid syndrome to treatment with either everolimus 10 mg daily or placebo. Treatment with SSAs was not permitted. RADIANT-4 had a higher proportion of lung carcinoids and fewer SBNETs than RADIANT-2 (30% lung, 31% SBNET compared to 10% lung and 52% SBNET in RADIANT-2).[119,122] The primary endpoint of PFS favored the everolimus group (median 11.0 vs 3.9 months; HR 0.48, $P< 0.001$), but objective radiologic responses occurred in only 2% of treated patients. Subgroup analyses suggested a potentially greater benefit for everolimus in lung, stomach, and colon-primary tumors than SBNETs, with confidence intervals crossing 1.00 (HR 0.63, CI 0.40-1.02) for the duodenal, jejunal, ileal, and unknown-primary subgroup.[122] An additional post-hoc subgroup analysis of RADIANT-4 identified a significant PFS advantage for combined "GI-origin" NETs (stomach, SBNETs, colon, rectum, and other; HR 0.56), but found that this result was driven by better results in stomach and rectal NETs, with confidence intervals for jejunal and ileal SBNETs both crossing 1.00 (HR 0.37, CI 0.08-1.64; HR 1.22, CI 0.56-2.65 for jejunal and ileal, respectively).[123] Despite small event numbers in subgroups and the unplanned nature of the analysis limiting conclusions from these results, taken together, the data for everolimus in SBNETs are less robust than for PNETs. In consensus guidelines, many experts favor other treatments over everolimus for progressive unresectable SBNETs.[35]

Peptide Receptor Radionuclide Therapy

PRRT represents another alternative therapy. PRRT exploits the high density of SSTRs on NETs by using a radioisotope conjugated to an SSA. The SSA concentrates the drug selectively in tu-

mor cells, where after binding to the receptor, the isotope is internalized.[113,118] European institutional series since the 1990s reported objective response rates of approximately 15% to 30% and favorable survival for patients with advanced unresectable NETs treated initially using the isotope ^{90}Yttrium and later ^{177}Lutetium.[124] In 2017, the NETTER-1 trial provided level-I evidence supporting ^{177}Lu-Dotatate PRRT for midgut NETs, demonstrating an advantage in both PFS and OS.[125]

NETTER-1 randomized 229 patients with advanced, inoperable grade 1 or 2 midgut NETs that progressed on octreotide to treatment with long-acting octreotide 30 mg every 28 days plus PRRT vs higher-dose long-acting octreotide alone at 60 mg every 28 days. Small bowel NETs comprised 90% of total patients. At the time of analysis, 20-month PFS was 65% in the PRRT group and 11% in the octreotide-only group, with a hazard ratio for progression or death of 0.21 (CI 0.13-0.33, $P < 0.001$). OS was also improved in the PRRT group, with the HR for death of 0.40 ($P = 0.004$), but the data were not mature enough to estimate median OS. Radiologic responses occurred in 18% of PRRT patients.[126] Although risks including radiation-induced renal toxicity, liver fibrosis, and long-term risk of myelodysplastic syndrome exist with PRRT, these data established ^{177}Lu-Dotatate as a principal therapy for unresectable SBNETs that express SSTRs and have progressed during SSA treatment.[35,96] Ongoing and future studies seek to further define the role of PRRT, including questions of optimal dosing, treatment sequencing (neoadjuvant, adjuvant, or progressive disease treatment), and whether additional isotopes or receptor targets might increase efficacy.[126-128] Although several treatments show efficacy in the 2nd-line setting, head-to-head comparative studies identifying the best option do not yet exist.[126]

Liver-Directed Therapies

As most SBNET patients have liver-dominant disease, those with progressive disease who are unable to undergo surgery, or whose disease burden exceeds what surgery could effectively treat, often receive liver arterial embolic therapies. Whether by bland, chemo-, or radio-embolization, retrospective data demonstrate these procedures' ability to shrink tumors, reduce hormonal symptoms, and possibly extend survival.[35,62,96,126,129,130] Unfortunately, randomized trials of embolic therapies do not exist, leaving many questions concerning which type of embolization and optimal treatment sequencing in relation to other options unanswered.[35,126,131]

Telotristat

Patients experiencing carcinoid syndrome symptoms refractory to other management can benefit from the tryptophan hydroxylase inhibitor telotristat. Tryptophan hydroxylase converts tryptophan to 5-hydroxy-tryptophan, which represents the rate-limiting step in serotonin synthesis.[132] By inhibiting this enzyme, telotristat reduces serotonin production, which can reduce carcinoid syndrome diarrhea. Whether reducing serotonin production impacts tumor growth or development of carcinoid heart disease remains under investigation.[114] In the TELESTAR trial, 135 patients with metastatic well-differentiated NETs, carcinoid syndrome, and diarrhea despite SSA treatment were randomized to placebo or telotristat at either 250 mg or 500 mg daily doses.[132] The primary endpoint of reduction in bowel movements was achieved in 44% and 42% of low and high-dose telotristat patients compared to 20% of those receiving placebo. Urinary 5-HIAA decreased by at least 30% in 78% and 87% of low and high-dose treated patients compared to 10% of placebo patients. The companion TELECAST trial randomized patients without significant diarrhea, but with elevated urinary 5-HIAA, and found that telotristat significantly reduced hormone production in this population as well.[133] On the basis of these studies, telotristat was FDA-approved for treatment of refractory carcinoid syndrome.[35,96,132]

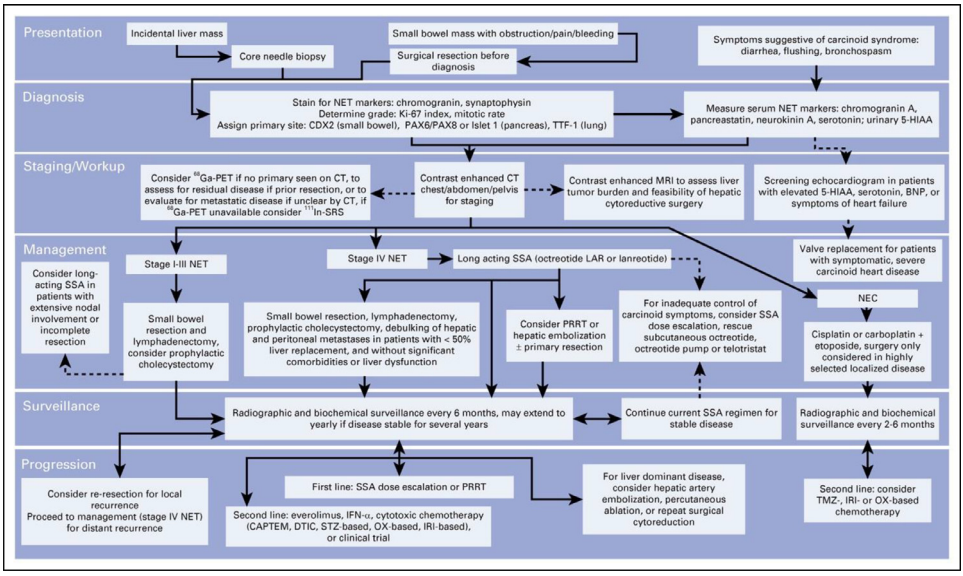

Fig. 10. An algorithmic approach to the diagnosis and treatment of small bowel neuroendocrine tumors (NETs). BNP, brain natriuretic peptide; CAPTEM, capecitabine and temozolomide; CT, computed tomography; DTIC, dacarbazine; Ga-PET, gallium positron emission tomography; IFN, interferon; In-SRS, indium somatostatin receptor scintigraphy; IRI, irinotecan; LAR, long-acting repeatable; NEC, neuroendocrine carcinoma; OX, oxaliplatin; PRRT, peptide receptor radionuclide therapy; SSA, somatostatin analog; STZ, streptozocin; TMZ, temozolomide.
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Chemotherapy

For tumors with higher grade or aggressive growth, several chemotherapeutics may be of value (see algorithm in Fig. 10).[134] Here again, no randomized studies exist to determine optimal treatment or relative outcomes.[96] High-grade, poorly-differentiated NECs arising from the small bowel are extremely rare.[96] When present, treatment for G3-NEC follows platinum-based regimens used for small-cell tumors of other origins, such as carboplatin/etoposide.[134,135] For G2 and well-differentiated G3 tumors, capecitabine/temozolomide (CAP-TEM) can be administered orally, is well tolerated, and is commonly employed, although more support exists for efficacy in pancreatic rather than SBNETs.[134] In a retrospective, propensity-matched analysis of 247 PNET and SBNET patients at French referral centers treated with chemotherapy, median progression-free survival was 20.1 months with dacarbazine regimens, vs 14.1 months with CAP-TEM (P = 0.01), with most of the difference seen in PNET patients.[136] Response rates for both regimens were lower in SBNETs compared to PNETs. The authors observed similar rates of response or stable disease in SBNETs with either dacarbazine or CAP-TEM (79 vs 87%, P= 0.2), although the series included a smaller number of SBNETs than PNETs.[136] Despite the lack of level-I evidence, CAP-TEM represents a reasonable choice in the progressive unresectable G2 population.[134]

Conclusion

Although rare, SBNETs are increasing in incidence and prevalence. Surgeons are increasingly likely to encounter SBNETs in their clinical practice, as patients can present with vague abdominal symptoms, asymptomatic masses found incidentally on imaging, or with symptoms of ob-

struction. If a diagnosis of an SBNET is suspected, patients should undergo evaluation with imaging, biochemical testing, and biopsy.

Diagnosis and treatment are multidisciplinary efforts, and patients benefit from referral to a center with experience treating NETs. In our practice, patients with localized disease undergo surgical resection, then surveillance with biomarkers and imaging every 6 to 12 months. Patients with metastatic disease are treated with somatostatin analogues and evaluated for resection of the primary tumor and cytoreduction. If these patients undergo resection, they are maintained on SSAs and undergo surveillance every 6 months. If patients experience progression of disease, PRRT is increasingly the treatment of choice. Other treatment options include increasing the dose of SSA, molecularly targeted therapies like everolimus, or chemotherapy. Liver-directed therapies can be considered for patients with primarily hepatic disease. Practitioners who treat SBNETs should be familiar with the evolving modalities available for imaging and treatment (Fig. 10), which have improved the quality of life and survival for patients with SBNETs.

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