The Surgical Management of Small Bowel Neuroendocrine Tumors

Consensus Guidelines of the North American Neuroendocrine Tumor Society

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Abstract: Small bowel neuroendocrine tumors (SBNETs) have been increasing in frequency over the past decades, and are now the most common type of small bowel tumor. Consequently, general surgeons and surgical oncologists are seeing more patients with SBNETs in their practices than ever before. The management of these patients is often complex, owing to their secretion of hormones, frequent presentation with advanced disease, and difficulties with making the diagnosis of SBNETs. Despite these issues, even patients with advanced disease can have long-term survival. There are a number of scenarios which commonly arise in SBNET patients where it is difficult to determine the optimal management from the published data. To address these challenges for clinicians, a consensus conference was held assembling experts in the field to review and discuss the available literature and patterns of practice pertaining to specific management issues. This paper summarizes the important elements from these studies and the recommendations of the group for these questions regarding the management of SBNET patients.

Key Words: small bowel tumors, liver metastases, carcinoid tumors, hepatic debulking, unknown primary NET, carcinomatosis, video capsule endoscopy, DOTATATE, octreotide prophylaxis

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Neuroendocrine tumors (NETs) arise from specialized cells that are dispersed throughout the body, and one convention for categorizing these tumors is their division into foregut (bronchial, gastric, duodenal, and pancreas), midgut (jejunal, ileal, appendiceal, and ascending/transverse colon), and hindgut (distal colon and rectum) tumors. Midgut NETs of the jejunum and ileum (small bowel NETs or small bowel neuroendocrine tumors [SBNETs]) are the third most common site of NETs after the lung and rectum, but are the most common site of NETs that develop distant metastases. Their incidence has increased 4-fold between 1973 and 2004.[1] With respect to all small bowel malignancies, NETs have recently surpassed adenocarcinoma as the most frequent type,[2,3] accounting for 37% of cases. Because of their increasing incidence, now reaching 0.67 cases per 100,000 population in the United States,[1] patients with these tumors are no longer a rarity for general surgeons and surgical oncologists.

It is often difficult to make the diagnosis of midgut NETs at an early stage, because the primary tumors tend to be small and generally do not lead to symptoms until they cause partial obstruction, abdominal pain, or bleeding or become metastatic and initiate carcinoid syndrome. As a result, patients often present with metastatic disease, which has been estimated to occur in 35% of cases in large population-based studies[1] and more than 60% of cases from larger referral centers.[4,5] However, despite this advanced presentation at the time of diagnosis, patients with metastatic SBNETs have a median survival of 56 months,[1] which can be improved further by cytoreduction.[6,7] Therefore, the optimal treatment of SBNET patients is complicated by the fact that long-term survival is common, and there may be benefits to aggressive management that would not be contemplated in comparable-stage patients with other gastrointestinal (GI) malignancies.

Not surprisingly, there has been much confusion and controversy surrounding the management of patients with SBNETs, and there are no randomized studies that define their optimal surgical treatment. Therefore, in treating these patients, clinicians must rely on their experience and the results of retrospective studies, both of which are subject to bias. Furthermore, there may be significant differences in opinion among the physicians taking care of these patients, depending on whether they are surgical oncologists, medical oncologists, endocrinologists, gastroenterologists, interventional radiologists, or nuclear medicine physicians. Both the European Neuroendocrine Tumor Society (ENETS) and North American Neuroendocrine Tumor Society (NANETS) have published consensus guidelines for the diagnosis and management of SBNETs,[8,9] but there remain many clinical scenarios for which the ideal approach is unclear. The objective of this article was to assemble a group of physicians specializing in the treatment of patients with SBNETs and to specifically address many of the most frequent questions that arise regarding their surgical management.

MATERIALS AND METHODS

A list of topics was created summarizing important areas of ongoing controversy or uncertainty regarding the surgical management of SBNETs. Ten surgeons with recognized expertise in these tumors were invited to participate in the guidelines process,

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as well as a gastroenterologist, body imaging radiologist, and a nuclear medicine physician. The questions to be discussed were reviewed by the group in advance, and each participant was assigned 1 to 2 specific questions to research and present the results of the most relevant studies to the group. All references were collected and distributed to each member, and the group met on August 11 and 12, 2016. Each participant communicated his/her findings to the assembly, followed by discussion to explore consensus on each question based on the best available evidence. The broad topics included the perioperative use of octreotide, open versus laparoscopic resection of SBNETs, the management of nodal metastases, the role of surgical exploration in various situations (high-grade tumors, tumors of unknown primary site, and metastatic disease), the role of liver-directed surgery, and prophylactic cholecystectomy. The utility of cross-sectional and functional imaging and capsule endoscopy in the preoperative evaluation was also discussed. An audience response system was used to survey the opinions of the group on a series of multiple-choice questions tailored to different clinical scenarios, followed by discussion to attempt to reach consensus. After this, a joint meeting was convened with a parallel group assembled to explore issues pertaining to the medical management of SBNET patients. The information and opinions of the surgical group were presented to the medical group to gather further perspective. The responses to each question were summarized then distributed to each participant several months later for final voting. Consensus was defined as unanimous agreement, near consensus as 1 or 2 oppositional votes, and less than 80% agreement was defined as lack of consensus. The final recommendations of the surgical group were then reviewed by 2 medical oncologist members from the medical group for their perspectives and comments.

RESULTS

There were 8 broad topics and a total of 19 specific questions that were addressed concerning the surgical management of patients with SBNETs, which appear in the sections that follow. Each question is accompanied by a review of the relevant information pertaining to each subject, followed by the summary of the recommendations of the group; some questions (1a + b; 2a + b; 3a + b + c) are grouped together with a common recommendation at the end of that section. Consensus was reached with full agreement of the group on the majority of the recommendations, with the exception of near consensus (one dissent) on questions 1a/b, 5a and 5c.

Preoperative and Postoperative Delivery/Management of Octreotide

1a. When Is Perioperative Treatment With Octreotide Needed and What Is the Optimal Dose?

Carcinoid crisis is the sudden onset of hemodynamic instability that can occur during anesthesia, operations, or other invasive procedures performed on patients with SBNETs. It can have serious sequelae of organ dysfunction and may lead to complete circulatory collapse and death. It is generally believed that administration of octreotide, either before or during induction of anesthesia and/or invasive procedures, prevents carcinoid crises. Recommendations on how to administer octreotide vary widely from treating patients with long-acting octreotide prior to operation, to preoperative doses of subcutaneous octreotide, to intraoperative intravenous boluses of octreotide, to continuous intravenous infusion of octreotide. Furthermore, there is considerable variation in the recommended doses, infusion rates, and duration of infusions. Generally, prophylaxis is recommended only for patients with carcinoid syndrome, whereas some also extend this to those with asymptomatic neuroendocrine tumor liver metastases (NETLMs) and/or elevation of preoperative serotonin, chromogranin A, or urinary 5′-hydroxyindoleacetic (5′-HIAA).

However, outcome data supporting the efficacy of these various octreotide regimens are scant. The only data for effective perioperative octreotide prophylaxis come from a publication by Kinney et al.[10] In their series of 119 patients with metastatic carcinoid tumors undergoing abdominal operations, intraoperative complications were defined as flushing, dysrhythmias, bronchospasm, hypertension, acidosis (pH <7.2), hypotension (systolic blood pressure <80 mm Hg), and need for vasopressor support (systolic blood pressure <80 mm Hg for >10 minutes). The overall rate of intraoperative complications was 7%, with events occurring in 7 (10%) of 67 patients who received no octreotide and 1 (17%) of 6 patients who received only a preoperative dose. In 45 patients who received intraoperative octreotide, either alone or with a preoperative dose, no intraoperative complications occurred ($P = 0.023$, relative to those not receiving intraoperative octreotide). Carcinoid heart disease and elevated preoperative 5′-HIAA levels were significant risk factors for complications and death. Despite these findings, the authors concluded that their "study was not able to evaluate the efficacy of intraoperative octreotide therapy to prevent intraoperative carcinoid crises." Thus, the case for octreotide prophylaxis in the literature is based on these 45 patients who received intraoperative octreotide. However, the doses used in those patients ranged from 30 to 4000 μg (median, 350 μg intravenously or subcutaneously); hence, the proper prophylactic dose is unclear. Furthermore, the optimal time in the course of an operation that the dose should be given and under what circumstances remain undefined.

Massimino et al[11] studied 97 consecutive patients at Oregon Health & Science University undergoing abdominal operations for GI carcinoid tumors and used the same criteria for intraoperative events as did Kinney et al.[10] They gave patients a preoperative intravenous bolus of 500 μg of octreotide and 250- to 500-μg intravenous boluses intraoperatively as needed. The event rate was 24% in their patients, with liver metastases being the strongest predictor of events, but events also occurred in asyndromic patients. However, neither preoperative octreotide LAR nor a preoperative dose of 500 μg of octreotide significantly decreased the incidence of these events. Fifty-six patients also received intraoperative doses of octreotide, and 46% of those patients still had a subsequent event. Patients who had intraoperative events in their series were significantly more likely to have serious postoperative complications.[11]

Woltering et al[12] retrospectively reviewed the anesthesia records of 150 patients undergoing 179 cytoreductive procedures for SBNETs. Eighty-five percent of patients had some component of carcinoid syndrome preoperatively, and a similar number were treated with long-acting somatostatin analogs (SSAs) at baseline. All patients were given an octreotide infusion at 500 μg/h preoperatively, intraoperatively, and postoperatively, and they used similar criteria to define carcinoid crisis as described by Massimino et al.[11] Their review found that only 6 (3.4%) of 179 patients had carcinoid crisis, and this group felt that the continuous infusion of octreotide was better than a preoperative bolus, because the half-life of octreotide is 90 to 120 minutes.

A follow-up study from Oregon Health & Science University examined 127 patients having 150 operations for GI carcinoids.[13] All patients received a preoperative intravenous bolus of 500 μg followed by a continuous infusion at 500 μg/h. However, the rate of events in this series was still 30%. The presence of carcinoid syndrome or hepatic metastases was significantly associated with intraoperative carcinoid crises, whereas preoperative 5′-HIAA and serum chromogranin were not. Because of the association of sustained hypotension and serious postoperative complications observed in their previous series, the investigators modified their treatment protocol such that if the systolic blood pressure was less than 80 mm Hg, and the surgeon and anesthesiologist agreed that there was no other plausible explanation for the hypotension, they would declare it to be a crisis and immediately treat the hypotension with vasopressors. With earlier initiation of treatment for hypotension, events were no longer associated with complications, except when hypotension persisted for more than 10 minutes. The authors concluded that intraoperative infusion of octreotide did not prevent crises, but that prompt treatment of crisis was important to reduce postoperative complications.

Thus, the literature does not definitively support the notion that prophylactic octreotide LAR, a preoperative bolus of octreotide, intraoperative boluses of octreotide, and/or a continuous infusion of octreotide prevent carcinoid crises. On the other hand, there does not appear to be any harm in giving octreotide perioperatively. For example, despite the fact that octreotide decreases visceral perfusion, the rate of anastomotic leaks in patients who received continuous infusions is not higher than that generally reported in the literature. However, there may be danger in relying on octreotide to completely prevent or reduce crises, and therefore one must be prepared to treat them promptly should they arise. Surgeons and anesthesiologists alike should recognize that crises do occur at a significant rate in patients with SBNETs; they can occur in asyndromic patients and if prolonged are associated with increased rates of serious postoperative complications. Accordingly, they should be prepared to expeditiously treat hypotension with vasopressors (generally vasopressin and phenylephrine).

1b. Is Octreotide Needed for Procedures (Hepatic Arterial Embolization, Colonoscopy, Endoscopic Ultrasound Biopsies, or Percutaneous Liver Biopsies)?

Patients with SBNETs often require invasive procedures for tumor localization, staging, and/or therapy, which may include endoscopy, colonoscopy, endoscopic ultrasound, biopsy of liver tumors, hepatic arterial embolization, and ablation. There is an abundance of case reports of carcinoid crisis in patients with SBNETs and other NETs occurring during or soon after a variety of invasive procedures.[14–23] However, there are no clear data on the rate of these events in the literature. Furthermore, the role of preprocedural or periprocedural octreotide during invasive procedures to prevent carcinoid crisis is unclear as there are no relevant data to support this practice.

Recommendation

It has not been established that routine administration of octreotide either preoperatively or preprocedurally, during the procedure itself either as an intravenous bolus or infusion, or that weaning it perioperatively prevents carcinoid crisis. Physicians should be prepared to manage carcinoid crisis events in patients with SBNETs who undergo operations or invasive procedures. Episodes of hypotension may be treated with an octreotide infusion should they occur, but vasopressors such as vasopressin and phenylephrine should also be used as needed. Many surgeons may still elect to run an octreotide infusion intraoperatively at a rate ranging from 100 to 500 μg/h in an attempt to avoid carcinoid crisis, and although this practice does not appear to be supported by the available literature, it does not appear to increase complication rates and is generally safe.

Open Versus Laparoscopic Resections

2a. Are Open Resections of SBNETs the Best Approach?

Surgical resection of SBNETs should include a complete oncologic resection of the primary tumor(s), regional lymph nodes, and mesenteric fibrosis, if feasible. Operations should be performed optimizing safety, operative time, quality of life, and cost. Regardless of the surgical approach (open vs laparoscopic/minimally invasive), adherence to these surgical principles is paramount. Intraoperative staging should be undertaken to evaluate the extent of disease. Peritoneal metastases are found in 20% of patients with SBNETs,[4] so care should be taken to search for these in the pelvis, on the sigmoid colon, mesentery, and diaphragms. The liver surface should be examined, and intraoperative ultrasound can augment preoperative imaging tests for evaluation of liver metastases, which may occur in up to 61% of patients.[4] Both ovaries should be inspected to rule out ovarian metastases, which occur in 4% of patients and can cause carcinoid syndrome.[4] The primary tumors in the jejunum or ileum are often very small,[24] so careful palpation of the small intestine from the ligament of Treitz to the ileocecal valve is essential. In 25% to 44% of patients, there are multifocal primary tumors.[4,24–26] Many of the multifocal primary tumors are subcentimeter and can be identified only by careful digital palpation.[24] Therefore, it cannot be overemphasized that careful palpation of the entire jejunum and ileum is a critical step to identify small NETs and multifocal disease.

Most patients with SBNETs (>80%) have regional lymph node metastases.[4,27] Careful review of preoperative imaging and intraoperative appraisal should be carried out to evaluate the extent of regional lymph node metastases and the characteristic mesenteric fibrosis associated with SBNET lymph node metastases. Some use lymphatic mapping to help guide the extent of intestinal and mesenteric resection,[28] but this technique has not been widely adopted. Resection of the primary tumor(s), regional lymph nodes, and mesenteric fibrosis, when possible, should be done with extreme care to maximize the length of residual viable intestine by preserving the proximal superior mesenteric artery (SMA) and vein (SMV).[29] Based on the clinical context, additional procedures, such as cholecystectomy and resection of liver or ovarian metastases, should also be considered.

The recognized standard for SBNETs is exploratory laparotomy with careful palpation of the entire jejunum and ileum to identify small and/or multifocal NETs. In fact, guidelines from North America and Europe do not consider laparoscopic surgery or minimally invasive surgery (MIS) ideal for managing SBNETs because of their small size and multifocal nature.[8,9] Consequently, the role of laparoscopic surgery/MIS in the management of patients with SBNETs is not well defined, given the risk of missing multifocal lesions, compromising nodal resection, and limiting one's ability to perform peritoneal debulking.

2b. When Is Laparoscopic Exploration Reasonable?

There are few studies in the literature describing laparoscopic resection of SBNETs. Figueiredo et al[30] reported successful laparoscopic resections in 12 patients, and Reissman et al in 20 patients.[31] Wang et al[32] described successful laparoscopic/minimally invasive resection of ileal NETs in 6 patients who presented with NETs of unknown primary. In this article, the authors emphasized the importance of palpation as part of MIS to identify the small primary tumors, which are frequently multifocal. To do this, they used a hand-assisted laparoscopic device (Gelport; Applied Medical) or a soft tissue wound retractor (Alexis Wound Retractor; Applied Medical, Rancho Santa Margarita, Calif) to exteriorize the jejunum and ileum, which facilitates complete palpation, resection of the primary tumor(s), dissection of the mesenteric lymph nodes/fibrosis, and intestinal anastomosis.[32] A larger study by Massimino et al[33] reported 63 patients with occult primaries but biopsy-proven nodal or hepatic NET metastases. They began operations laparoscopically in 46 of these patients and successfully localized the tumors in 28 (61%). Fourteen patients had conversion to an open procedure, 2 for palpation of the bowel and 12 for debulking of liver metastases. They concluded that laparoscopic exploration was superior to preoperative imaging and endoscopy for finding these primary tumors.[33]

Regardless of the surgical approach, the surgical goals should remain the same: (1) complete oncologic resection of the primary tumor(s) and mesenteric adenopathy/fibrosis; (2) thorough staging with evaluation of the peritoneum, liver, ovaries, primary tumor (s), and mesenteric adenopathy/fibrosis; and (3) optimization of safety, operative time, quality of life, and cost. Thorough staging and palpation for multiple primaries can be achieved by a minimally invasive approach when a hand-assisted laparoscopic device or the soft tissue wound retractor is used, which also facilitates extracorporeal anastomosis. However, extensive mesenteric adenopathy/fibrosis may preclude safe resection through a small incision, and in such cases, there should be no hesitation to convert to an open procedure to more safely achieve the proper mesenteric dissection to remove proximal nodes while maximizing viable intestine.

Recommendation

The accepted surgical approach for resection of SBNETs is an open abdominal operation, to achieve the goals of careful palpation of the entire small bowel and adequate resection of mesenteric lymph nodes while preserving vascular inflow and outflow to the remainder of the intestine. Purely laparoscopic techniques are inadequate for thorough evaluation of the small bowel for diminutive tumors, as these will not be visible through the laparoscope and not necessarily palpable with metal graspers. However, if a small incision is made, and the bowel can be run from the ligament of Treitz to the ileocecal valve and carefully palpated (with the surgeon's fingers), then this may be an acceptable alternative, as long as an appropriate bowel resection and adequate lymphadenectomy (to the origin of segmental vessels) are carried out. Cases requiring extensive nodal dissection, peritoneal debulking, and hepatic cytoreduction are better treated by an open approach. For selected patients with extensive, inoperable liver metastases, application of a laparoscopic approach may be very reasonable, depending on the surgical goals. If the goals are determining whether the patient has an SBNET primary, resecting the primary SBNET, and even adding a prophylactic cholecystectomy, these can often be accomplished laparoscopically with less morbidity for the patient.

Management of Regional and More Distant Nodes

Several factors need to be considered when determining the optimal lymph node clearance in patients with SBNETs. Should the lymph node dissection be prophylactic or therapeutic? What is the appropriate extent of lymph node dissection based on the small bowel lymphatic drainage, selective (removal of only lymph nodes adjacent to the primary SBNET) or systematic (removal of lymph nodes up to the main segmental vessels off the SMA and SMV or removal of the lymph nodes from the main SMA and SMV trunks themselves)? How should other abdominal lymph nodes be handled?

3a. What Is the Optimal Removal of Regional Lymph Nodes During Segmental Bowel Resections?

The rate of lymph node metastases in patients who have SBNETs and who have had lymph node dissection ranges from 46% to 98%.[4,27,34–36] Given this, in most patients with SBNETs with or without gross lymph node involvement, routine lymph node clearance is warranted and allows for accurate staging. Furthermore, when tumors are removed with only the adjacent mesentery, recurrence in proximal lymph nodes may occur.[8] Several retrospective studies have demonstrated increased overall survival (OS) and disease-free survival in patients with SBNETs who had lymph node dissection along with removal of the primary tumor in univariate and/or multivariate analyses.[4,27,34,36] In these studies, the numbers of lymph nodes removed were defined as at least 1, 6 or more lymph nodes, and more than 7 lymph nodes.[4,27,36] In the largest cohort studied, a retrospective analysis of the Surveillance, Epidemiology and End Results database, removal of more than 7 lymph nodes and lymph node ratio (no. of positive/no. of total nodes) of less than 0.29 were associated with higher survival rates in patients who had lymph node dissection, adjusting for age and tumor size.[27] One problem with studies using node counts in this disease is the frequent presence of large mesenteric masses, which often represent a conglomeration of lymph nodes, which cannot be accurately enumerated. Some surgeons have used isosulfan blue injection into the primary small bowel tumors to better define the lymphatic drainage of the tumor(s). This approach led to selective resection of the involved lymph node basin, changing the extent of resection in 98% of the operations and preservation of the ileocecal valve in 44% of terminal ileal tumors, with no recurrences reported in 1 to 5 years of follow-up.[35] Lymphatic mapping is not a standardly performed procedure,[9] and recommendations from Uppsala and ENETS are that regional nodes should be removed along the segmental vessels up to their junction with the main trunk of the SMV (when feasible).[4,9,37]

3b. How Should Nodes Be Managed That Are Encasing the SMV/SMA?

Mesenteric nodal metastases from SBNETs are often considerably larger than the primary tumor(s) and associated with extensive mesenteric fibrosis and desmoplastic reaction. The nodal metastases often extend to the root of the mesentery, as well as into the retroperitoneum (such as para-aortic, aortocaval, or pararenal nodes), around the pancreas and hepatic artery.[37–41] These mesenteric lymph node metastases have been stratified into 4 different groups as follows: stage 1 nodes are those close to the SBNET; stage 2 nodes involve the distal branches of the mesenteric arteries; stage 3 nodes extend proximally without encasing the SMA; stage 4 encompasses a wide spectrum of cephalad regional disease progression, including retropancreatic/retroperitoneal extension and encasement of the SMV and SMA.[37] Stage 1 to 2 nodes can be adequately treated by segmental bowel resection with removal of all nodes up to the origin of the segmental vessels coming off the SMA/SMV. Stage 3 nodes are treated by segmental resection as with stage 1 to 2 nodes, but more proximal nodes are removed from alongside the proximal vessels by incising the peritoneum overlying them and dissecting them off carefully up to the root of the mesentery. In general, patients with stage 4 nodal metastasis are commonly deemed unresectable and are often treated medically.[37–39] Ohrvall et al[37] describe transecting the mesenteric mass in these cases (while preserving the more proximal vessels) in order to remove the affected intestine.

The consequences of encasement of the mesenteric vessels vary among patients. In many individuals, the development of adequate collateral circulation may avoid the life-threatening sequela of mesenteric ischemia. Nonetheless, these patients can still suffer from chronic mesenteric ischemia and bowel obstruction, and thus, segmental resection of the primary with involved nodes may be beneficial.[37,39–41] In cases of stage 4 nodes, leaving the nodes circumferentially surrounding the SMA/SMV in place may potentially avoid the complication of catastrophic vascular compromise resulting from an overly aggressive resection, especially because these patients can still have long-term survival. However, vascular encasement can cause a variety of symptoms, including intestinal ischemia and even infarction of the small intestine. Intestinal ischemia is probably due to a combination of tumoral secretion products causing fibrosis, desmoplastic mesenteric retraction, and nodal compression, which leads to elastic vascular sclerosis, predominantly affecting the adventitia of the involved mesenteric blood vessels, leading to mesenteric luminal narrowing.[37–39]

Careful dissection may allow for resection of proximal nodes in some of these patients, whereas others with encasement of the root of the mesentery by a calcified, fibrotic mass may be better served by leaving the nodal mass in place and dividing the segmental vessels at its lower edge, so as not to risk injury to the main trunks of the SMA/SMV. Patients with residual nodal disease can still have long-term survival and often adapt to SMV thrombosis by the development of collaterals over time. However, in recent years, surgeons in specialized NET centers have developed techniques to remove proximal root of the mesentery lymph node metastases in selected patients. Patients successfully treated surgically may have better quality of life because of a lower incidence of bowel obstruction, intestinal angina, and avoiding the worst consequences of mesenteric ischemia, namely, bowel perforation and/or gangrene.[37–41]

3c. How Should Nodes Beyond the Root of the Mesentery Be Managed?

Distant lymph nodes outside the typical locoregional drainage basin can be present in SBNET patients and identified on cross-sectional imaging. These include nodes in the periportal, para-aortic, aortocaval, and pararenal regions, as well as along the hepatic artery. One retrospective study identified involvement of these distant abdominal nodes in 18% of their SBNET patients and was an independent factor associated with reduced survival.[4] Management of these nodal basins should be considered when a patient is undergoing abdominal exploration and resection.

Extended lymph node dissection in the abdominal cavity has been well studied in randomized trials in both gastric and pancreatic cancers. In an effort to improve survival, these resections have included splenectomy and dissection of perihilar nodes in gastric cancer and more extensive retroperitoneal dissection in pancreatic cancer.[42,43] These experiences revealed that greater complications were observed in patients undergoing more extensive lymphadenectomy without a survival benefit. Extrapolating from these data from other tumor types suggests that in the absence of gross disease on imaging routine, prophylactic resection of these nodes is not beneficial. When gross disease in these nodes is evident by imaging, surgical resection can be considered in select circumstances, particularly if the nodes have the potential to encroach on vital structures or if resection would render the patient with no evidence of disease. Extended resections and high-risk surgical approaches should be carefully considered in the context of each patient's overall disease burden.

Recommendation

Patients with SBNETs should have regional lymph nodes removed with their segmental bowel resection. In most cases, this should include resection up to the origin of the segmental vascular branches from the SMA/SMV. Low-risk surgical patients with lymph node metastases encasing the root of the mesentery and thus the proximal SMA/SMV, whether symptomatic or not, should be considered for referral to a specialized NET center to be evaluated by experienced surgeons for possible surgical cytoreduction of the root of the mesentery nodes. Symptoms of intermittent bowel obstruction, significant weight loss, intestinal angina, or signs of bowel ischemia should alert the treating physician to more urgent referral to specialized centers. The decision to resect root of the mesentery nodes needs to be carefully considered based on the operative findings, and if compromise of the mesenteric vessels is likely with removing these nodes, then not attempting resection is advised. Distant abdominal lymph nodes outside the superior mesenteric vessels (such as para-aortic, pararenal, portocaval, aortocaval, hepatic artery) should not be routinely resected in the absence of imaging studies suggesting an imminent threat of involvement with neighboring vital structures. Resection of these nodes may be considered when they are identified on imaging, to the extent that it is feasible and will not compromise patient outcome.

The Role of Surgery in Specific Clinical Situations

4a. Should Surgical Exploration Be Considered in Patients With High-Grade Tumors?

High-grade SBNETs (grade 3, Ki-67 >20%) are typically poorly differentiated tumors, but more recently, tumors have been described with well-differentiated histology that are also high grade based on their proliferative index and/or mitotic rate. Poorly differentiated SBNETs are exceedingly rare and have an aggressive disease course, similar to their counterparts in the stomach, pancreas, and colon.[44] Metastatic disease at presentation is typical with median survival usually measured in months.[45] Well-differentiated SBNETs are rarely high grade (grade 3), but have been observed in metastases, as well as in tumors with a mixture of low- and high-grade components.[46] Often, these high-grade tumors are recognized only after resection, and the optimal treatment of patients with these SBNETs is unclear. A recent review of multiple series of high-grade gastroenteropancreatic neuroendocrine tumors/carcinomas (GEPNETs) suggests that there are 3 useful categories of grade 3 tumors, which behave differently, based on morphology and Ki-67 index: well-differentiated G3, with Ki-67 of 21% to 55% (NET G3); poorly differentiated large or small cell neuroendocrine carcinoma with Ki-67 of 21% to 55% (NEC G3); and poorly differentiated large or small cell neuroendocrine carcinoma with Ki-67 of greater than 55% (NEC G4).[47] Treatment of NET G3 tumors may be similar to that used for G2 lesions, NEC G3 tumors may benefit from treatment with oxaliplatin and/or alkylating agents, and NEC G4 tumors are commonly treated with cisplatin or carboplatin and etoposide.[47] Review of slides by an experienced pathologist is very important, and quantification of Ki-67 and/or mitotic figures is critical. Because of limited response rates of SBNETs to medical therapy and the paucity of natural history data for NET G3 lesions,[48] resection is reasonable and should be considered, particularly for patients with localized or local-regional disease.

Recommendation: Poorly differentiated, high-grade SBNETs are very rare and should be managed primarily with systemic therapy. Well-differentiated SBNETs with high-grade features (Ki-67 >20%), if identified preoperatively, can be considered for systemic therapy, especially in the setting of widespread metastases. However, resection of limited disease may also be reasonable, given the limited options for systemic treatments and the lack of knowledge regarding their natural history.

4b. What Is the Optimal Approach for Peritoneal and Diaphragmatic Metastases Found at Exploration? Is There a Role for Hyperthermic Intraperitoneal Chemotherapy?

Small bowel neuroendocrine tumors often grow through the serosal layer of the bowel, gaining access to the peritoneal cavity. This results in peritoneal carcinomatosis, which is found in approximately 20% of patients undergoing exploration for SBNETs.[4] Areas at particular risk of peritoneal metastases are so-called "drop metastases" in the pelvis, with plaques forming on the sigmoid colon, and peritoneal lining of the pelvis. The diaphragms, lateral peritoneum, omentum, small bowel, and colonic mesentery are also frequent sites of disease.

There is no good surgical or medical treatment for carcinomatosis from SBNETs, although patients treated with cytoreductive surgery can have long-term survival.[49–51] Limited areas of disease may be treated by peritoneal stripping operations that have been well described for pseudomyxoma peritonei and low-grade appendiceal tumors.[52] Other approaches are peritoneal resection limited to the areas of implants, diaphragmatic resection, sigmoid resection, or burning small lesions with electrocautery or argon beam.[53] However, because of the pattern of this spread, these procedures can never be complete, and there will always be a risk of recurrent disease. Peritoneal implants from SBNETs, like those resulting from other GI tumors, cause significant morbidity for patients. Specifically, because of the peritoneal fibrosis they cause, even small lesions can serve as a focus for bowel adhesions and obstruction. Bowel obstructions may occur at multiple locations, requiring challenging surgical procedures to relieve symptoms, and patients will be at risk of recurrence. Large plaques on the sigmoid colon may also lead to colonic obstruction. This causes morbidity for patients that is not immediately lethal, but may lead to long-term nausea and vomiting, crampy pain, and need for diverting colostomy or parenteral nutrition. The lack of effective therapies for peritoneal disease should be considered a key argument for resection of primary SBNETs, even in the face of inoperable hepatic metastases, with the goal of preventing the development of peritoneal disease. There are multiple therapies available to treat liver metastases, but minimal effective treatments for peritoneal carcinomatosis, where the most appropriate remedy is resection of the primary tumor and nodes so that this pattern of spread does not occur.

Cytoreductive surgery with hyperthermic intraperitoneal chemotherapy (HIPEC) is a regional cancer therapy for diffuse peritoneal nodules combining surgical debulking, chemotherapy, and hyperthermia.[54] This is an intracavitary treatment in which maximal surgical debulking and resection are done, including resection of the primary lesion(s), regional nodal disease, and peritoneal stripping. Because of the diffuse pattern of spread from peritoneal implants, even if all gross disease can be removed it is highly likely that small residual nodules will grow over time. The theory behind HIPEC is that it will deliver chemotherapy to the surface of residual tumor cells in the presence of heat, which augments the kinetics of the chemotherapy drugs to kill either microscopic or small nodular disease. Hyperthermic intraperitoneal chemotherapy has been most extensively utilized for pseudomyxoma peritonei and low-grade appendiceal cancers. There are still no randomized data among the practitioners of this regional therapy to definitively prove its benefit in these diseases. It has been used for ovarian carcinoma, which commonly spreads intraperitoneally, as well as colorectal cancers and gastric cancers. There are limited data available for the use of HIPEC for SBNETs that spread intraperitoneally. Elias et al[51] treated 28 SBNET patients over a 13-year interval with cytoreductive surgery and HIPEC using oxaliplatin or oxaliplatin plus irinotecan. The recurrence rate of peritoneal metastasis was 47%, but the investigators conducting the study felt that the complications of the HIPEC did not justify utilizing this treatment, and they stopped using this for the last one-third of the patients in their surgical series and showed no difference in OS for those treated with HIPEC.[51] Randle et al[55] reported a median survival of 18.4 months in 31 patients with the more aggressive goblet cell NETs of the appendix treated by cytoreduction and HIPEC, but these tumors are not directly comparable to SBNETs.

Recommendation: The best way to prevent peritoneal implants is to operate on patients with SBNETs before they grow through the bowel wall. However, when patients present with this extent of disease, removing as much disease as possible while minimizing risks is recommended. Limited areas of seeding can be resected with the underlying peritoneum or diaphragm, and smaller lesions treated with electrocautery or argon beam. At present, there is no evidence supporting the use of HIPEC as an adjunct to these local treatments for intraperitoneal metastases from SBNETs.

4c. What Is the Role for Surgical Exploration in Patients With an Unknown Primary and Metastatic Liver Disease?

Patients with SBNETs frequently present with multiple liver lesions with no radiographic imaging identifying the primary tumor. Cross-sectional imaging identifying these liver metastases is often performed for symptoms of flushing and diarrhea, nonspecific symptoms of abdominal pain, or abnormalities of hepatic function tests. Other patients may have scans done for other reasons, such as a chest computed tomography (CT), which identifies liver lesions, or CT done for renal stones, where these unexpected liver lesions are found. A core biopsy of a liver lesion will confirm the diagnosis of metastatic NET, but in many cases, the origin of the primary tumor is undetermined. The differential diagnoses include NETs originating in the small bowel, pancreas, bronchus, thymus, colon or rectum, appendix, stomach, or duodenum. Chest CT scans should identify primary thoracic NETs, and upper endoscopy will identify the type 3 gastric carcinoids most likely to present with liver metastasis. Multiphase CT scans with intravenous contrast, magnetic resonance imaging (MRI) scans, and/or endoscopic ultrasound will usually identify a pancreatic primary as the source of liver metastasis. Colorectal primaries may be seen on CT or colonoscopy. It is very unusual to have a completely occult lesion which is not seen on radiographic and endoscopic studies to originate from sites other than the small bowel.[32,56]

Small bowel neuroendocrine tumors are frequently small and have to reach a certain size to be identified radiographically or cause obstruction leading to dilated loops of small bowel. Small bowel neuroendocrine tumor lymph node metastases are frequently evident and will more commonly identify the source of the primary.[25,56] The appearance of lymph node metastases from SBNETs is classic, usually with a spiculated mass, often containing calcifications and sometimes foreshortening of the mesentery. It is important when evaluating for occult NETs metastatic to the liver to carefully follow out the branches of the superior mesenteric vessels all the way to the bowel and look for enlarged nodes, masses, or distortion of the mesentery. Wang et al[32] reviewed their experience with 71 patients presenting with NETLMs, where 79% had primaries identified by radiology or endoscopic studies. All patients with pancreatic NETs (PNETs) were identified by CT scan, and in the 15 patients with unknown primaries that were explored, tumors were found in the small bowel in 13 (and not found in 2 patients). They concluded that most occult primaries in patients with NETLMs will be SBNETs.[32] Massimino et al[33] described 63 patients presenting with NETLMs where the primary was not found by imaging in 52 (83%) of 63 patients. At surgical exploration, 79% had primaries identified, where 70% were SBNETs, 3% appendiceal, 3% pancreatic, 2% colonic, and 2% were ovarian. Bartlett et al[57] studied 61 patients presenting with NETLMs in which the primary was not found by imaging in 28 (46%). At laparotomy, 80% of primaries were identified (75% were SBNETs, and there was 1 duodenal primary). Keck et al[56] reported on 134 patients presenting with metastatic GEPNETs that were explored. The primary site was identified by preoperative imaging in 91%, with 10 patients not localized preoperatively.

Primaries were found in 6 of these 10 patients at exploration, 5 of which were in the small bowel and 1 in the pancreas. In these studies, other investigations such as double-balloon enteroscopy and capsule endoscopy added little to the workup. Because occult primaries are usually in the midgut, even if a submucosal intestinal mass is seen by capsule endoscopy, it needs to be located by the surgeon at exploration to allow for appropriate resection. A recent study demonstrated the utility of ^{68}Ga-DOTATATE positron emission tomography (PET) scans for finding the site of unknown primary GEPNETs, which successfully localized 4 of 14 lesions.[58]

The majority of SBNET primaries are identified by palpation, and these lesions are generally easily found by carefully running the small bowel from the ligament of Treitz to the ileocecal valve between the thumb and forefinger. Up to 25% to 44% of SBNETs are multifocal,[4,24–26] and therefore it is important to run the entire bowel and not stop when 1 lesion is felt, because there may be multiple lesions. Enlarged lymph nodes in the mesentery will often be evident as well. As reported in these large series from tertiary referral centers, most NETs of unknown primary (80%) can be found at exploration, and the majority of these will be of midgut origin. Several of these studies also combined treatment of liver tumors with the intraoperative identification of the primary to maximize surgical therapy at the initial procedure. Unfortunately, the finding of NETLMs with unknown primary frequently leads to medical or embolic treatment of the liver lesions, with the assumption that unless the primary can be identified, there is no role for surgical consultation. For patients who have the option of complete or significant debulking of NETLMs, referral should be made to a center with expertise in treating NETs, and surgical exploration with palpation of the bowel should be performed. If palpation of the small and large bowel does not reveal a primary lesion, kocherization of the duodenum with digital palpation and exposure and mobilization of the pancreas with palpation and intraoperative ultrasound are additional techniques that should be used to look for the unidentified primary lesion.

Alternative strategies to determine the site of unknown primaries have used a gene expression classifier to evaluate expression profiles of metastases indicative of SBNETs versus PNETs, or immunohistochemistry, where positivity for CDX2 is consistent with SBNETs (whereas PAX6/8 and islet1 staining is consistent with PNETs).[59] Elevated serum serotonin or urinary 5′-HIAA may also point strongly to an SBNET primary. Although other primary sites can occasionally secrete serotonin and its byproducts, including pancreatic carcinoid tumors, occult lesions will most commonly be in the midgut.

Recommendation: Patients with NETLMs and unknown primaries should undergo staging with multiphase abdominal, pelvis, and chest CT scans with thin cuts to evaluate the bronchi, thymus, stomach, duodenum, colorectum, appendix, pancreas, and small bowel with its mesentery. Endoscopic ultrasound can be added to evaluate for PNETs, although most of these will be identified by CT. There may also be utility in the use of ^{68}Ga-DOTATATE scans in patients with unknown primaries.[58] However, the inability to identify the primary NET preoperatively should not inhibit exploration for the primary tumor, or potential surgical debulking of metastatic liver disease. Intraoperative identification of primary tumors is highly successful, and most will be found within the small bowel.

4d. Should Primary SBNETs Be Removed in Asymptomatic Patients With Inoperable Metastatic Liver Disease?

As discussed previously, it is relatively common for SBNET patients to have a CT scan performed for some type of abdominal sign or symptom that reveals liver metastases. A biopsy of one of these lesions revealing a NET, or elevated chromogranin A or urine 5′-HIAA, in conjunction with a mesenteric mass is highly indicative of a small bowel primary.[56] Clearly, if the patient is having symptoms of bowel obstruction, diarrhea, cramping, or intestinal ischemia, then the primary tumor should be removed to improve these symptoms. However, if the patient is asymptomatic, the benefits of removing the primary tumor are not as clearly discernable.

There are several arguments for not removing the primary SBNET in asymptomatic patients with metastatic disease. First, if the patient truly does not have symptoms, is it really possible to improve upon this with surgery? Second, the patient's ultimate survival may be dictated by the presence of distant disease, and removing the primary will not change this fact. There have been 4 randomized controlled trials showing improvement of progression-free survival (PFS) in patients with metastatic SBNETs; thus, some clinicians argue that the best evidence supports treating these patients with systemic agents shown to be effective in these trials. These active agents include octreotide LAR (from the PROMID trial),[60] lanreotide (CLARINET),[61] everolimus (RADIANT4),[62] and ^{177}Lu–peptide radioreceptor therapy (NETTER-1).[63] Although most would agree that these treatments can play an important part in managing patients with metastatic SBNETs, the role of surgical resection is more controversial, principally because studies showing its advantages have all been retrospective and therefore potentially influenced by selection bias.

Objectively, there are 3 main lines of reasoning supporting removing the primary SBNETs in patients with metastatic disease. The first is that most patients are not truly asymptomatic. Their diagnosis of metastatic disease may have become evident while being worked up for some other condition or vague symptoms, but the fact that they had a CT scan for their evaluation suggests that they are not asymptomatic. Of 80 patients with SBNET NETLMs operated on at the University of Iowa, only 8 (10%) lacked symptoms of diarrhea, flushing, or abdominal pain.[64] Surgeons from Uppsala evaluated symptoms in 121 patients with SBNETs undergoing either emergent or elective laparotomy, 93% of whom had metastases (80% mesenteric and 62% liver).[65] Half of these patients had symptoms of carcinoid syndrome (such as diarrhea and flushing, plus other manifestations), which might be ascribed to having metastatic disease. The other half had symptoms that might be related to a primary tumor, with 81% of this group having abdominal pain, 52% acute abdominal episodes, 39% nausea and distention, and 37% weight loss. The majority of patients had an operation, and of those, 82% had relief of symptoms (67% complete, 15% partial). They showed that most patients had good symptom relief for 4 to 5 years and felt their results supported removal of these primaries and nodal metastases even in "asymptomatic" patients. A follow-up study from this group with 314 patients found that in patients undergoing elective operations there was a "retrospective appreciation" of symptoms beginning at a mean of 1.25 years prior to the diagnosis.[41]

A second reason for resecting the primary is to treat or avoid those situations that lead to symptoms, that is, bowel obstruction, bleeding, mesenteric fibrosis, peritoneal dissemination, or reducing the risk of further metastasis. Clearly, if these procedures are to be performed in asymptomatic patients, they should be done with minimal morbidity and mortality, which has been shown to be achievable by several groups.[64,66]

The third reason for pursuing resection of SBNETs in the setting of metastatic disease is that it may lead to a survival benefit for patients. In Hellman and colleagues'[41] series of 314 patients with SBNETs (286 with mesenteric and 249 with liver metastases), 83% of patients had an operation, and the primary tumors could be resected in 95% of cases. Patients having resection of their primaries (249 patients) had a median survival of 7.4 years versus 4.0 years for those who were not resected (65 patients; $P < 0.01$). There are a few caveats to consider when interpreting the finding of improved survival in patients having resection, because retrospective studies are prone to selection bias. One is that most of the patients without liver metastases were in the resected group, and another is that it is possible that patients who were likely to do better (with less advanced disease, fewer comorbidities) had an operation, and those with worse disease or comorbidities were not operated on. Therefore, it is hard to be certain that surgical resection itself was the major factor leading to this apparent improvement in survival.

Another study of 360 patients with midgut NETs and liver metastases from 5 institutions in the United Kingdom and Ireland reported on the results of a multivariate analysis of factors contributing to patient survival.[67] Of these 360 patients, 209 (58%) had resection of their primary, 12 (3%) had surgical bypass, and 17 (5%) were explored and found to be unresectable. The median survival of those who had their primary resected was significantly longer (9.9 years) than in those who did not undergo operation (4.7 years), or for those undergoing bypass (5.6 years), or those who were explored but did not have their lesion resected (6.7 years). This reduced survival in patients who are explored and do not have their lesion resected or not bypassed suggests that removing the primary itself, rather than just selection bias for patients having an operation, was an important contributor to the survival differences observed. A wide variety of clinical, radiological, treatment, and pathologic factors were examined statistically, but the only 3 found to be significant by multivariate analysis were (1) resection of the primary tumor; (2) the age at diagnosis; and (3) Ki-67 index. The authors felt that the low mortality in the surgical group (1.4%), higher fraction of unresected patients dying of bowel obstruction, and survival advantage in resected patients provided evidence that patients with midgut NETs and liver metastases should have their primaries resected if possible.

A recent study from Milan examined 139 patients with functional, well-differentiated NETLMs from various sites (ileal, 66; pancreas, 36; lung, 13; stomach, 5; and unknown, 19) with a median follow-up of 127 months. Resection of primary tumors was carried out in 67% of patients, and the median survival of this group was 138 versus 37 months in whom the primary tumor was not resected ($P < 0.001$ on multivariate analysis). This survival benefit of resecting the primary also held up in the 103 patients who did not have their liver metastases resected. Although this article does demonstrate a survival benefit for resecting the primary tumor when there are metastases present, it should be noted that the vast majority of patients with SBNETs in this study had their primary tumors resected (63 of 66). Likely because of this, the survival advantage for the SBNET subgroup was not specifically reported (although it was significant in those with PNETs), but it was clear that this was their preferred management of SBNET primaries.[68]

A systematic review of the literature on the question of resection of primary SBNETs in patients with unresectable liver metastases found a clear trend toward improved survival for resection.[69] One of the studies included tried to retrospectively address the issue of selection bias in carcinoid patients presenting with liver metastases that were not amenable to hepatic cytoreductive procedures.[70] There were 84 patients, of whom 60 underwent resection, and 24 were not resected. Of these, 18 were not explored (10 declined an operation, and 8 were not offered an operation by their managing physician), whereas 6 patients were explored but did not have their lesion resected. Both groups were similar in terms of Karnofsky status, chromogranin A levels, treatment with octreotide or interferon, and symptoms. Median survival of those resected was 159 months versus 47 months in those in whom the primary was not resected ($P < 0.001$). When the 6 patients explored but did not have their lesion resected were added to the resection group, survival was still improved at 108 months in the operative group versus 50 months in the nonoperative group ($P < 0.001$). The median survival of a subgroup of 28 patients with asymptomatic primary tumors that were resected was not reached and was significantly improved over nonresected patients ($P = 0.001$). The majority of patients in both groups (79%) died of liver failure, but the median time to progression of liver disease was 25 months in the nonresected group versus 56 months in the resected group. Therefore, a possible explanation for this improved survival is that resection of the primary removes the source of new liver metastases.

Recommendation: Resection of primary SBNETs in selected patients with metastatic disease should be considered when feasible to relieve existing symptoms and avoid future symptoms, and for its potential survival advantage. However, other factors need to be carefully considered, such as the patient's performance status and degree of liver replacement, with higher levels (>50%–70%) being associated with shorter survival and higher risk of significant postoperative liver dysfunction. The fact that asymptomatic patients will generally have a long survival without intervention, with or without SSAs or additional medical therapies, means that surgical procedures must be performed with minimal mortality and morbidity.

Liver-Directed Operations for Metastatic NETs

5a. What Are the Survival Advantages and Other Benefits of R0, R1, and R2 Resections for Metastatic SBNETs?

Despite the indolent nature of SBNETs, NETLMs will develop in 50% to 60% of patients.[66,71–73] These patients are at risk of developing potentially debilitating hormonal symptoms and syndromes (carcinoid syndrome and carcinoid heart disease) secondary to the hepatic tumor burden. Historically, patients with NETLMs have been reported to have a 5-year survival of approximately 30%. Although there have been recent advances in our therapeutic armamentarium in patients with advanced NETs, surgical resection remains the only potentially curative intervention for patients with NETLMs.

A study from the Mayo Clinic in 2003 evaluated the impact of surgical resection using a debulking threshold of 90% for NETLMs.[74] Of 170 patients, 90 had SBNETs, and both patients with functional and nonfunctional (ie, asymptomatic) NETLMs were included. Surgical resection was associated with a 5-year survival rate of 61% with no significant difference in survival between patients with functional or nonfunctional tumors or the site of tumor origin. Moreover, in patients with hormonal symptoms, surgical resection was associated with an improvement or complete relief of symptoms in 96% of patients.

Several subsequent studies have shown similar improvements in hormonal symptom control and survival after surgical resection of NETLMs, with 5-year survival rates between 60% and 90%.[6,64,75] One international, multi-institutional study reported on the outcome of hepatic resection in 339 patients with NETLMs, of whom 25% had SBNETs, and 72% were nonfunctional.[6] They described 5- and 10-year survival rates of 74% and 51%, respectively. Boudreaux et al[7] studied 189 patients with small bowel NETLMs that underwent hepatic cytoreduction, where they had 5- and 10-year survival rates of 87% and 77%, respectively. The majority of these patients (86%) had carcinoid symptoms.

In comparison to other liver metastases, the more indolent nature of NETLMs and the observation that they tend to push rather than infiltrate within the liver make surgical debulking (cytoreductive surgery) an option for patients with this disease.

Numerous studies have shown that when the majority of gross disease can be removed (R1 or R2 resections) the survival advantage is comparable to cases in which all disease is removed (R0 resection).[6,64,76] For example, Glazer et al[76] reported a 5-year survival of 77% for patients who underwent resection of NETLMs, and there was no survival difference in patients having R0 versus R1or R2 resections. Similarly, Graff-Baker et al[75] found no difference in disease-specific survival or liver PFS in 52 patients with NETLM who underwent an R0 versus R2 resection, with a 5-year disease-specific survival of 90%. The international, multi-institutional study of Mayo et al[6] also found no difference in survival between those having R0 or R1 versus R2 resections of NETLMs.

Recommendation: Numerous single-institution and multi-institutional studies have shown that hepatic resection is associated not only with an improvement in control of hormonal symptoms but also with an improvement in survival, with 5-year survival rates ranging between 60% to 90%. Moreover, many of these studies have shown that regardless of whether an R0, R1, or R2 resection was achieved, there was no difference in survival. Although the optimal R2 resection threshold remains to be defined, surgical cytoreduction of NETLMs should be attempted when anatomically feasible and can be performed with low morbidity and mortality.

5b. Are Major Hepatic Resections Necessary or Are Parenchymal-Sparing Procedures Reasonable?

Recurrence of NETLMs after surgical resection is common, if not universal, and has been reported to be 90% to 95% at 5 years.[6,74] Therefore, surgical strategies have continued to evolve to allow for optimal surgical resection or cytoreduction of all or the majority of disease, while preserving and maintaining adequate functional liver parenchyma. As a result, parenchymal-sparing procedures (PSPs) of the liver, such as enucleations, nonanatomic parenchymal resections (ie, wedge resections), and intraoperative ablation (radiofrequency or microwave ablation), have all been utilized in patients with NETLMs.

In the studies by Mayo et al[6] (n = 339 [83 SBNETs]) and Saxena et al[71] (n = 74 [32 SBNETs]) in which surgical resection of NETLM was associated with 5-year survival rates of 74% and 63%, respectively, PSPs were used in 55% and 66% of cases, respectively. Intraoperative ablation in combination with surgical resection was used in up to 50% of cases in the Saxena and colleagues' study. Maxwell et al[64] recently reported their experience using PSPs in combination with a 70% debulking threshold in patients with NETLMs (n = 108), of which 74% had SBNET primaries. In this study, 93% of patients underwent wedge resections in combination with enucleations and/or ablations. Major resection was undertaken in 7% of patients, but all were done in combination with some form of PSP. The reported 5-year survival rate was 76%, which is comparable to previously reported outcomes in series using primarily major hepatic resections, with no mortality.

Recommendation: Parenchymal-sparing procedures of the liver (enucleations, wedge resections, and intraoperative ablations) have been studied in patients with NETLMs and have been associated with acceptable survival outcomes. Most patients with NETLMs ultimately die of liver failure, and even R0 resections are associated with 95% recurrence rates. Therefore, PSPs allow for preservation of functional hepatic parenchyma and should be considered a reasonable option when evaluating patients with NETLMs for hepatic resection or debulking.

5c. Should Only Patients in Whom Greater Than 90% of Metastases Can Be Debulked Undergo Hepatic Cytoreduction?

Previously, liver debulking operations had been considered applicable only for patients in whom at least 90% of the grossly visible liver metastases could be removed and for those who had no extrahepatic disease. Operations usually involved formal major hepatic resections, with 5-year survival rates in excess of 60%. However, it is estimated that fewer than 20% of patients with liver metastases qualify for such operations at this 90% threshold. Recently, series with expanded eligibility criteria of using a 70% debulking threshold, allowing for extrahepatic disease, and utilizing PSPs has rendered considerably more patients eligible for liver debulking surgery, while still producing excellent survival rates.[64,66,75]

The concept of a minimum debulking threshold of 90% of grossly visible liver metastases can be traced to one of the first reports of liver debulking surgery for NETLMs by McEntee et al[77] from the Mayo Clinic. They operated on 37 patients, 23 of whom had SBNETs. This was in the era prior to the availability of SSAs, and the indication for operation was symptom relief in syndromic patients. Curiously, in this article that is widely quoted as the source of the 90% debulking threshold, no debulking threshold is mentioned. Rather, the term 90% is introduced in the discussion section where the authors noted that there was little relief of symptoms unless at least 90% of the grossly visible tumors were resected. There were no survival curves, and outcomes for individual patients were listed in text form. The authors specifically commented that they could not define factors that were predictive of survival.

The next report from the Mayo Clinic by Que et al[78] included 74 NETLM patients undergoing liver debulking, 50 of whom had SBNET primaries. The indication was still for symptom relief in syndromic patients, and the debulking threshold was set at 90%, based on McEntee and colleagues'[77] series. However, the authors commented that what was noteworthy about their study was the apparent doubling of survival compared with historical controls. In fact, their published Kaplan-Meier survival curve showed a level not very far below that of the normal population. What was also a remarkable observation was that there was no significant difference in survival rates between patients who had complete and incomplete resections, so they learned that there was no oncologic survival penalty for performing only palliative versus complete resection.

The subsequent Mayo Clinic report by Sarmiento et al[74] was quite different. It included 170 patients, 90 of whom had SBNETs. This was now well into the era of SSA therapy, so patients had a nonsurgical option for control of hormonal symptoms. Accordingly, their indication for operation changed. The authors stated that "surgical debulking of hepatic disease has been shown to improve survival," and the statement "a plea for resection to increase survival" was appended to the title of the article. Other major differences compared with their previous reports were that they included asyndromic patients for the first time, who comprised 37% of the population. Also, more than 50% of the operations were incomplete resections (not R0). Therefore, the indications for operation were evolving, as there could be no reason to perform incomplete resections on asyndromic patients other than to increase survival. However, patients chosen for attempted debulking were still limited to those in whom they believed they could remove at least 90% of their disease, based on their previous experience of trying to relieve symptoms. They obtained 5-year survival rates of approximately 60%, but the most important observation of this series was that there was no significant difference in survival rates between syndromic patients and asyndromic patients. It was at this point in the history of debulking surgery for NETLMs that the 90% debulking threshold, which was originally adopted for relief of hormonal symptoms, was transferred to all patients to be used as an oncologic threshold for increasing patient survival.

However, just because a 90% debulking threshold yields excellent survival rates does not prove that it is the optimal minimum oncologic debulking threshold. To this end, several series of liver debulking surgery for NETs were subsequently published from other centers showing equally good or better 5-year survival rates, in which no specific debulking threshold is mentioned.[6,7,66,79,80] More recently, Graff-Baker et al[75] reported 52 patients with SBNETs who underwent liver debulking surgery using expanded eligibility criteria. This included patients in which greater than 70% of the liver disease was deemed resectable, allowing for extrahepatic disease, and for positive margins using PSPs such as tumor enucleation to avoid major hepatic resections and reduce blood loss.[75] Neuroendocrine tumor liver metastases are expansile, pushing the liver parenchyma aside as they grow, not invasive like other types of metastases, and therefore can be enucleated. These patients had a mean of 22 tumors (range, 1–121) resected, ranging in size from a few millimeters to 16 cm. One-third of patients with low-grade primary tumors had at least 1 intermediate-grade metastasis. There were no significant differences in liver progression rates or survival rates based on the number of tumors resected, their size, their grade, presence of extrahepatic disease, or the percentage of tumors debulked. Median time to liver progression was 72 months, but this was age dependent. Patients younger than age 50 years had a median time to liver progression of only 39 months, compared with a time not yet reached in patients older than 50 years. The series yielded a 5-year survival rate of 90%, but this was also age dependent: patients younger than 50 years had a 5-year survival rate of 73% compared with 97% in patients older than 50 years.

The 70% oncologic liver debulking threshold was confirmed by Maxwell et al, who strongly championed a parenchyma-sparing approach.[64] They published a series of 108 NETLM patients undergoing liver-directed operations, 80 of whom had SBNETs. The median percent liver replacement was 10%, median number of liver lesions treated was 6, 84% of patients had concurrent resection of primary lesions, and the median percentage of cytoreduction on preoperative versus postoperative CT scans was 80%. Median PFS of all patients was 2.2 years, and median OS was 10.5 years. For patients with SBNETs, median OS was not reached, demonstrating good results using the PSP approach. The important point of this series is that it included patients who had a wide variety of percentage of their liver tumors debulked, ranging from less than 50% through greater than 90%. The results clearly showed that patients who had greater than 70% debulking had significantly improved survival rates compared with patients who had less than 70% (median OS not reached vs 6.5 years for all 108 patients, respectively, $P = 0.009$; median PFS 3.2 vs 1.3 years, $P < 0.001$).

Recommendation: The guidelines for liver debulking operations in patients with metastatic SBNETs may be expanded to include patients with any number or size of metastases, intermediate grade, and extrahepatic disease, provided that a 70% debulking threshold can be achieved. Furthermore, a parenchyma-sparing approach, using techniques such as tumor enucleation and ablation, may be used wherever feasible.

5d. When Is Liver Cytoreduction Not Indicated?

Although hepatic cytoreduction of NETLMs appears to benefit patients in terms of improvement of symptoms and survival, not all patients will be eligible for debulking procedures. Certainly when the threshold for obtaining 90% cytoreduction is used, 67% to 90% of patients with NETLMs will be excluded from surgical treatment.[72] When this threshold is lowered to 70%, as many as 76% of patients with NETLMs may be eligible for cytoreduction.[64] The latter study found that liver replacement of greater than 25% by NETLMs was a negative prognostic factor, as was debulking more than 5 (and >10) lesions.

Another important factor in deciding whether to perform hepatic debulking of NETLMs is the degree of liver involvement. Many patients have a large burden of disease in the liver, and resection or ablation may place the patient at high risk of liver failure. In Frilling and colleagues'[81] study of 119 patients evaluated for debulking of NETLMs, they excluded patients with greater than 70% liver replacement from consideration for cytoreduction. In addition, a study by Chamberlain et al[72] reported that patients with greater than 75% liver involvement had a poorer prognosis and that surgical resection was rarely done. Touzios et al[82] divided 60 patients with NETLMs into groups with greater than 50% and less than 50% liver involvement and found 5-year survival rates of 8% and 67%, respectively. Patients were treated "aggressively" with resection and/or ablation with or without hepatic arterial embolization or "nonaggressively" with resection of the primary but no liver-directed treatment. Of 13 patients with greater than 50% liver replacement, 7 were treated nonaggressively. These studies do not establish a clear threshold for liver replacement where an operation is absolutely contraindicated, but greater than 50% to 70% liver replacement significantly elevates the likelihood of postoperative liver dysfunction and death with surgical intervention.

Many patients present with diffuse, bilobar metastases throughout the liver, which pose significant challenges to cytoreduction. Sometimes, these are relatively small in size but 50 to 100 in number, and it is clear that no resection is possible and that even an aggressive strategy of resection, enucleations, and ablations will lead to incomplete debulking, risk significant damage to normal hepatic parenchyma, and the potential for postoperative liver failure. Frilling et al[81] divided patients referred with NETLMs (n = 119) into 3 types: (1) single metastases (19% of their patients); (2) isolated bulky metastases with smaller bilobar lesions (15% of patients); and (3) disseminated bilobar metastases with no normal liver (66%). Their approach was to perform complete resection in type 1 patients (which they did in 23 of 23 patients), whereas those with type 2 lesions were primarily treated nonsurgically (13 of 18), with only 4 having palliative cytoreduction and 1 liver transplantation. Of those with type 3 NETLMs, 16 of 78 had liver transplantation (with 4 operative mortalities), and 57 had embolization and/or peptide receptor radionuclide therapy (PRRT). The strategy used by this group appears to be more conservative than that used by others in recent series,[64,75] but it is difficult to extrapolate these definitions of types 2 and 3 metastases to other studies. Clearly, patients with diffuse metastases (some type 2 and all type 3 patients) are the most challenging and may be better served by embolization, PRRT, systemic therapy, or liver transplantation.

The Working Group on Neuroendocrine Tumor Liver Metastases reviewed the available evidence related to multiple aspects of NETLMs and came up with recommendations for when resection should be done, but did not specifically address supplementing resection with enucleation and/or ablative techniques.[83] To be a candidate for resection of NETLMs, they specified 5 criteria: (1) World Health Organization grade 1 or 2 tumors; (2) the absence of unresectable extrahepatic disease; (3) type 1 or 2 tumors where R0 or R1 resection is possible with at least a 30% liver remnant; (4) the absence of advanced carcinoid heart disease; and (5) when procedures can be done in tertiary referral centers. They also suggested that grade 3 tumors were generally not resectable because of their diffuse, bilobar nature and high rate of recurrence. They concluded that quality data addressing when to perform less than complete cytoreduction were lacking in the literature and that available studies were likely affected by selection bias. As such, they did not make a recommendation.

Unquestionably, other patient-related factors need to be taken into account when considering resection or cytoreductive procedures. As mentioned, significant carcinoid heart disease is a contraindication and leads to increased right-sided pressure and increased risk of liver surgery. Cirrhosis predicts for poor postoperative liver function and preexisting liver injury, such as that resulting from previous embolization, radioembolization, or PRRT should be carefully assessed before considering surgery. As with liver surgery for any other disease process, comorbidities such as atherosclerotic cardiovascular disease, impaired pulmonary function, and poor performance status should all be considered as potential contraindications to major operative intervention. As in hepatocellular carcinoma, other factors, such as good performance status and preserved liver function (as measured by serum bilirubin within normal limits), Child-Pugh class A or Model for End-stage Liver Disease scores of less than 9, and lack of portal hypertension, are desirable in resection candidates.[84]

Another option for SBNET patients with NETLMs who might not be candidates for hepatic cytoreduction is liver transplantation. The Milan criteria and ENETS guidelines require that tumors be low grade (Ki-67 <10% per ENETS), the primary tumor has been removed, there is no extrahepatic disease (by ^{68}Ga PET/CT), stable disease has been demonstrated in the prior 6 months, age is younger than 55 years, and there is less than 50% liver involvement (or <75% with refractory symptoms per ENETS).[85,86] Exclusion criteria are small cell or high-grade tumors, medical or surgical conditions including comorbidities, non-GI carcinoids, and tumor not drained by the portal system.[86] In a literature review of 706 patients undergoing hepatic transplantation of NETLMs, Fan et al[87] reported 5-year survival rates of 50% and 5-year disease-free survival rates of 30% in the 3 largest series (514 patients). Therefore, liver transplantation may be an option with good results for some patients, but the scarcity of organs and the requirement that patients generally have favorable tumor biology[86] (and thus may also be candidates for cytoreduction) have limited its use. This pattern of practice was confirmed in a study from Uppsala evaluating 33 SBNET patients with NETLMs meeting the Milan criteria where none were referred for transplant. They had excellent survival with standard multimodality treatment (5-year survival of 97%) which they felt were better than results from the literature for liver transplantation (76% 5-year survival).[88]

Recommendation: Patients with poor performance status, substantial comorbidities, or evidence of significant hepatic dysfunction should not be offered hepatic cytoreduction. Patients with grade 3 SBNET NETLMs are rare, but those who are found to have high-grade lesions on liver biopsy are at significant risk of rapid progression, are less likely to benefit from an operation, and should be referred for systemic medical therapy. Patients with significant liver replacement with tumor (such as that exceeding 50%–70%) are at high risk of having a compromised liver remnant and for postoperative liver failure, and therefore other strategies, such as embolization, PRRT, or medical therapy, are preferable. Those with diffuse liver metastases that are not amenable to a resection, enucleation, and ablation strategy that can effectively achieve at least 70% cytoreduction should also not be considered for an operation. The presence of extrahepatic disease itself is not an absolute contraindication to cytoreductive strategies[64,75] but needs to be carefully considered in the decision to offer these procedures with potential for patient morbidity. Liver transplantation is controversial, but may be an option for some patients if the Milan and ENETS criteria are met.[85,86]

Prophylactic Cholecystectomy in SBNET Patients

6a. Should Cholecystectomy Be Routinely Performed in SBNET Patients During Exploration? When Is Cholecystectomy Indicated in Patients Receiving SSAs (Who Still Have Their Gallbladders)?

Gallbladder disease is commonly seen as a result of long-term SSA therapy. It is well known that SSAs decrease gallbladder function and can cause gallstones in patients on chronic therapy.[89,90] In the general population, gallstone disease occurs in 10% to 20%,[91] but the majority are asymptomatic.[92] However, the prevalence of gallstones in patients on SSAs is much higher, between 52% and 63%.[93] Up to 77% of patients with SBNETs will require treatment with SSAs; therefore, the risk of developing gallbladder pathology is significantly increased.[94] Norlén et al reviewed their cases of SBNETs in which the tumor was resected and patients received SSAs and found that 63% of evaluable patients had gallstones. They reported that 22% of patients receiving SSAs required cholecystectomy or a drainage procedure, and the 5-year cumulative risk of having cholecystectomy or drainage was 19%. In 23 patients undergoing hepatic arterial embolization procedures with gallbladders left in place, 3 developed gallbladder complications (septicemia, cholecystitis, cholangitis). They concluded that cholecystectomy should be performed in patients having resection of SBNETs who are likely to receive SSAs, especially if they have liver metastases.[94] Trendle et al[93] found that 18% of patients receiving subcutaneous SSAs eventually had cholecystectomy performed, but did not feel that prophylactic cholecystectomy was indicated in all patients receiving SSAs, although it should be considered in conjunction with resection of the SBNET or cytoreductive operations.

The timing of when to perform cholecystectomy is highly dependent on the patient situation. The major influences are (1) the probability of requiring SSA therapy and (2) the risk associated with future laparoscopic cholecystectomy. For the minority group of patients with limited early-stage disease, tumor resection may be performed laparoscopically with a minilaparotomy to palpate the bowel, with minimal risks of major adhesions. However, if the patient requires major liver debulking or extended lymphadenectomy that may result in significant adhesions in the right upper quadrant, then future laparoscopic cholecystectomy may be compromised.

Recommendation: If there is a high likelihood that the patient will require long-term SSA therapy (such as those with liver metastases, peritoneal disease, or significant nodal involvement), prophylactic cholecystectomy should be performed at the time of the original operation. Patients receiving prolonged treatment with SSAs are at high risk of gallstone formation, and previous cytoreductive procedures may complicate future laparoscopic cholecystectomy. If a patient has already had their primary tumor removed, and cholecystectomy was not performed, then a prophylactic cholecystectomy is not recommended for those who are receiving SSAs and are asymptomatic.[85] Cholecystectomy can be delayed until a future abdominal procedure is planned (like hepatic cytoreduction), or until such time that the patient develops symptoms of biliary colic or complications from embolization.

Imaging: What Are the Optimal Imaging Modalities for Diagnosis, Staging, and Follow-up of SBNETs?

7a. What Is the Role of Cross-sectional Imaging Modalities for Localizing SBNETs and Following for Progression?

Imaging for NETs can be divided into anatomic and functional categories. The former includes examinations such as CT and MRI scans, which generally demonstrate masses and their relationships to other structures. Functional imaging tests take advantage of the fact that NETs take up radiolabeled somatostatin (or glucose) and help define that masses seen are NETs and are particularly useful in helping to define the extent of disease. In surgical series of patients presenting with NET metastases ultimately shown to have SBNETs on exploration, Keck et al[56] reported that 74 (82%) of 90 primary tumors were found by preoperative CT. It is important to emphasize that this study used not only the typical

CT findings of a small bowel mass or thickening, but also the presence of mesenteric lymphadenopathy for CT localization to be considered positive for localization of SBNETs. Other similar studies found lower levels of sensitivity for CT detection of SBNET primaries, which did not include mesenteric lymphadenopathy, with rates of 35% (n = 79),[32] 7% (n = 63),[33] and 38% (n = 61).[57]

These studies used a variety of CT techniques, including the frequent use of positive oral contrast agents, which makes the small bowel contents appear white, obscuring identification of small, enhancing lesions within the bowel wall. The use of negative contrast agents, such as water, milk, or polyethylene glycol improves the ability to identify small bowel lesions.[95] Computed tomography optimized to evaluate the small bowel will utilize a negative oral contrast agent along with high-spatial-resolution, multiplanar imaging. Different options include enteroclysis, where contrast is administered through a tube placed at the junction of duodenum and jejunum under fluoroscopy,[96–98] or enterography, where the patients drinks 1.5 to 2 L over 45 to 60 minutes.[95,99] A meta-analysis of CT enteroclysis for small bowel tumors reported a pooled sensitivity of 92.8% and a pooled specificity of 99.2%.[96] Computed tomography enterography can provide comparable accuracy to CT enteroclysis and has the advantage of not requiring placement of a nasojejunal tube, but does require that large volumes be consumed orally over a short period.[100,101] Computed tomography enterography may result in suboptimal bowel distension without adequate patient compliance with oral contrast consumption. Magnetic resonance imaging optimized to evaluate the small bowel has also shown good sensitivity for the detection of Crohn disease[102] and small bowel tumors.[103] One recent series of 150 patients comparing the results of CT and MRI enterography for detecting small bowel tumors found that the sensitivity of MRI (93%) was actually higher than CT (76%; $P = 0.04$).[104] The choice of modality (CT vs MRI) will vary based on local practice pattern and expertise, but as long as the correct technique is utilized (multiphase with thin cuts), the results for detection of SBNETs should be good with either method.

Cross-sectional imaging for initial staging of NETs should include a CT scan of the abdomen and pelvis with multiphase imaging of the abdomen. Although ^{68}Ga-labeled DOTA–conjugated peptide PET/CT should accurately identify the primary tumor and sites of metastatic disease, initial cross-sectional imaging is useful for planning therapy (operation or liver-directed therapy) and as a baseline for follow-up imaging. Neuroendocrine tumor metastases to the liver can have a very heterogeneous appearance, and multiphase imaging provides the best chance to detect and characterize these lesions.[105] In addition, a small proportion of NET metastases may be seen only on arterial-phase imaging, which essentially mandates multiphase imaging for accurate initial staging.[106] In cases of known SBNET, the use of enterography technique depends on the clinical scenario. Computed tomography or MRI enterography will provide the best chance of identifying all sites of small bowel tumor, but if an operation is planned, this may not be necessary because small bowel palpation to detect all tumor sites is routine practice. Computed tomography is considered the first-line imaging modality based on availability, speed, cost, and ease of use relative to MRI. However, MRI of the abdomen and pelvis is also acceptable and would be preferred in some scenarios (ie, prior adverse reaction to CT contrast, renal insufficiency, and radiation exposure) and may give more information on the tumor burden within the liver.[107] The Working Group on NETLMs suggests that MRI is the best method of imaging for NETLMs, whereas 3-dimensional CT is useful for determining the size of future liver remnant prior to resection.[83]

After resection of the primary tumor or in cases of advanced disease, earlier NANETS guidelines recommended follow-up surveillance imaging of the abdomen and pelvis with multiphase CT or MRI every 3 to 6 months, which could be extended to 6 to 12 months in those with stable disease.[107] Recent evidence suggests that an annual follow-up interval is reasonable in those having complete resection of SBNETs, then being extended to every 24 months after a few years.[108] In general, CT will be the modality of choice given its availability, speed, and lower cost relative to MRI. Computed tomography is also probably more sensitive for recurrent nodal or mesenteric disease, whereas MRI will image the liver better without ionizing radiation. Either multiphase CT or MRI is important to accurately detect all hepatic metastases and evaluate changes in enhancement, which may indicate response to therapy. For example, hepatic metastases treated with liver-directed therapy or antiangiogenic drugs may result in decreased enhancement without much change in size.[109]

Recommendation: Anatomic imaging using CT or MRI is recommended for diagnosis, staging, and follow-up of patients with SBNETs. Computed tomography scans are more readily available and less expensive, but deliver ionizing radiation, and require intravenous contrast, to which some patients have allergies and can be an issue for those with borderline renal function. Multiphase CT is very good for imaging primary tumors (which is improved further by use of negative GI contrast), the locations and extent of nodal disease, identifying peritoneal disease, and the distribution of liver metastases. Magnetic resonance imaging is excellent for imaging liver lesions and may provide improved information over multiphase CT, but this may come at the expense of reduced definition of nodal disease.

7b. What Is the Role of Nuclear Imaging for Localizing SBNETs and Following for Progression?

The previous NANETS recommendation was to perform ^{111}In-octreotide single-photon emission CT (SPECT) for nuclear imaging of SBNETs as part of the initial workup.[107] The main value of functional SSA-based imaging studies such as ^{111}In-octreotide SPECT is to confirm that the lesions that are seen on anatomic imaging have uptake and therefore are NETs, to screen for metastatic disease throughout the body (such as the bones), and gauge the potential for response to PRRT and SSAs.[25] Some also use these scans and ^{111}In-octreotide for probe-directed exploration for challenging sites of disease.[110,111] The sensitivity of ^{111}In-octreotide SPECT in surgical series looking for occult SBNETs in patients presenting with NETLMs was low, calling this into question, unless initial anatomic imaging is negative.[25,112] The range of ^{111}In-octreotide SPECT sensitivity for identifying SBNET primaries has been reported to be as low as 2%,[33] with other studies reporting higher rates of 22%,[54] 26%,[32] and 56%.[56] The image quality is generally poor unless coregistered with CT and may not significantly affect surgical decision making.[25]

More recently, ^{68}Ga-labeled DOTA–conjugated peptides have been developed for somatostatin receptor PET imaging. The 3 most commonly used ^{68}Ga-labeled somatostatin receptor PET imaging agents are ^{68}Ga-DOTATATE, ^{68}Ga-DOTATOC, and ^{68}Ga-DOTANOC. Despite the slight variation of the somatostatin receptor affinity of these agents, all of them have shown excellent sensitivity in detection of NETs. At this time, there is no evidence of significant diagnostic superiority of one agent over the others.[113–116] ^{68}Ga-DOTATATE was recently approved by the US Food and Drug Administration (FDA) in June 2016, whereas ^{68}Ga-DOTATOC and ^{68}Ga-DOTANOC are considered investigational. These agents provide significant advantages over ^{111}In-octreotide because of the higher resolution achieved with PET compared with SPECT and higher affinity of ^{68}Ga-DOTATATE for target somatostatin receptors (subtype 2; sstr2).[117,118] The radiation dose to the patient is significantly lower with ^{68}Ga-DOTA agents compared with ^{111}In-octreotide, and imaging with ^{68}Ga-DOTA agents is typically completed in 90 minutes, compared with multiple imaging sessions obtained over 24 hours with ^{111}In-octreotide.[119] A meta-analysis of 17 eligible studies with 971 patients found a high accuracy of ^{68}Ga-DOTATATE in diagnosing NETs, with a sensitivity of 90.9% (confidence interval, 81.4%–96.4%) and specificity of 90.6% (confidence interval, 77.8%–96.1%).[120] Sadowski et al[58] recently compared ^{68}Ga-DOTATATE with ^{111}In-octreotide and CT imaging in 131 patients with NETs. They found that ^{68}Ga-DOTATATE PET/CT was significantly more sensitive for detection of NET lesions, with a sensitivity of 95% compared with 31% for ^{111}In-octreotide and 45% for CT imaging.

Initial staging of SBNETs should potentially include the use of ^{68}Ga-DOTA somatostatin receptor PET/CT imaging because numerous series have shown ^{68}Ga-DOTA agents can lead to a change in management.[58,121–124] Improved accessibility is expected now that ^{68}Ga-DOTATATE imaging is FDA approved, and this will become the specific agent of choice in the United States. New-generation PET/CT scanners also allow for simultaneous diagnostic quality multiphase liver CT imaging with intravenous contrast to improve detection of hepatic disease. This provides initial whole-body imaging with sensitivity and accuracy rivaling cross-sectional imaging, with the exception that PET/MRI with gadoxetate disodium may potentially provide higher sensitivity for hepatic metastases.[125] If ^{68}Ga-DOTA PET/CT is not available, then ^{111}In-octreotide SPECT could be substituted. However, as ^{68}Ga-DOTA PET/CT becomes more widely available over the next few years, ^{111}In-octreotide SPECT will no longer be considered standard-of-care imaging for SBNET staging. Nuclear imaging may also be useful for follow-up of NETs when cross-sectional imaging is equivocal or when there is high clinical suspicion for active disease, but cross-sectional imaging is negative. Somatostatin receptor nuclear imaging is also valuable in restaging of recurrent NETs for planning therapy and is essential to determine if the patient will qualify for PRRT.

The value of fluorodeoxyglucose (^{18}F-FDG) PET/CT for NETs appears to be in patients with higher-grade tumors (Ki-67 >15%)[126] and uptake predicts for early disease progression and poorer prognosis.[127–129] In 1 study, ^{18}F-FDG uptake was seen in 60% of well-differentiated tumors and in 100% of poorly differentiated NETs, as compared with 80% and 57% for ^{111}In-octreotide SPECT, respectively. Therefore, ^{18}F-FDG PET/CT may have value for staging, prognosis, and selecting NET patients who might benefit from medical versus surgical therapy, but the utility of these scans appears to be limited to patients with higher-grade tumors.[130]

Recommendation: Functional imaging studies such as ^{111}In-octreotide SPECT and ^{68}Ga-DOTA PET/CT have utility in identification of NET primary tumors and their metastases. ^{111}In-octreotide SPECT may not add much to surgical decision making, other than confirming that suspicious lesions seen on anatomic imaging are NETs, assessing the potential for PRRT, and identifying occult sites of metastatic disease. ^{68}Ga-DOTA PET/CT imaging has several advantages over ^{111}In-octreotide SPECT in terms of resolution, sensitivity, radiation exposure, and convenience and is expected to replace ^{111}In-octreotide SPECT now that ^{68}Ga-DOTATATE has been FDA approved in the United States. ^{18}F-FDG PET/CT is not useful in the routine staging of well-differentiated NETs, but may have utility in staging of higher-grade tumors.

Should Capsule Endoscopy Play a Role in the Identification of Primary SBNETs?

In the workup of patients with NETs, physicians often attempt to elucidate the primary site, allowing clinicians to optimize the management and understanding of the clinical course and disease outcome. Small bowel neuroendocrine tumors are notoriously difficult to confirm. Despite the presence of bulky metastatic disease, the primary site may be subcentimeter, multifocal, and submucosal—all features that may present challenges in localization of the small bowel primary.

Video capsule endoscopy (VCE), double-balloon enteroscopy, and colonoscopy may all be used to endoscopically localize small bowel primaries. Video capsule endoscopy is the most frequently considered as it is noninvasive and relatively easier to perform. van Tuyl and colleagues[131] assessed the utility of VCE in the evaluation of patients with NETs of unknown primary and demonstrated a sensitivity of 60% (12 of 20 patients). The limitation of this study was the lack of histological confirmation in all patients. In an English study, VCE was performed in 10 patients with metastatic NETs of unknown primary and localized the primary in 8, the majority of which were later confirmed histopathologically.[132] Although these findings presented an impressive sensitivity of 80% for VCE, this represents the experience of a small number of patients, and the total number of patients who underwent VCE in an attempt to localize primary tumors was not reported.

In 2 surgical studies assessing the performance of presurgical imaging modalities in localizing metastatic disease of unknown primary, VCE was infrequently performed, but contributed minimally to localizing the primary site (2 of 4 in Bartlett et al,[57] 0 of 2 in Massimino et al[33]). For patients undergoing surgical resection or debulking, close inspection of the small bowel with palpation was by far the best test for localization of small bowel primaries, with a sensitivity of 75% when considering laparotomy alone and 79% to 93% when considering laparotomy with all other presurgical imaging modalities.[33,57] The strength of these studies was that all small bowel primaries were confirmed histopathologically. Limitations of capsule endoscopy include an inability to biopsy and the possibility of capsule retention. For this reason, capsule endoscopy is contraindicated in those with obstructive symptoms and in patients (particularly the elderly) with swallowing dysfunction. Other limitations of VCE include the potential nonvisualization of small submucosal tumors, incomplete detection of multifocal disease, and the possibility of false-positive results. This means that physicians need to carefully select which patients would benefit from capsule endoscopy.

Colonoscopy and double-balloon enteroscopy have other limitations related to identifying primary SBNETs. Colonoscopy with terminal ileal intubation may yield a limited view of the terminal ileum, but this is typically not sufficient to visualize enough small bowel to localize the primary site in a majority of patients. Although balloon enteroscopy allows more extensive examination of the small bowel and potentially enables histopathologic confirmation, balloon enteroscopy is a prolonged, advanced endoscopic procedure that is not widely available outside tertiary centers and is extremely operator dependent.

Recommendation: Video capsule endoscopy and double-balloon enteroscopy have limited roles in the diagnosis of SBNETs, although there may be some utility in patients with unknown primary lesions where the preoperative diagnosis is essential for referral for surgical management. Because most patients with metastatic GEPNETs and undiagnosed primaries after imaging will have SBNETs, surgical exploration is a higher-yield procedure with therapeutic benefits as well.

DISCUSSION

The incidence of SBNETs is on the rise, and surgeons will be seeing increasing numbers of these patients with these tumors in their clinical practice. The management of patients with SBNETs can be very challenging because physicians may manage only a few cases in their careers, and patients may live for a long time, despite often presenting with metastatic disease. Aggressive surgical management of SBNETs appears to be very useful in well-selected patients and may improve patient survival, but randomized clinical trials demonstrating this are lacking. Such trials will likely never be performed given the challenges of randomization in patients who are candidates for resection.

There are a variety of clinical situations in which questions frequently arise in the management of patients with SBNETs, where the answers are not clear from the literature, but physicians specializing in the care of these patients generally agree on. We assembled a group of experts in the management of patients with SBNETs, reviewed the relevant data addressing these questions, and have put forth consensus recommendations in this article. The objective of this conference was to improve the care of NET patients by increasing awareness of treatment options and providing expert recommendations based on clinical experience and careful review of the literature. Although the lack of randomized trials makes it difficult to prove the validity of these clinical recommendations, consensus or near consensus of our expert panel was reached for all of these questions. Our hope is that this article will offer guidance for physicians struggling to decide on how to deliver optimal care to their patients with SBNETs.

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