Small Bowel Resection and Lymphadenectomy for Jejunoileal Neuroendocrine Tumors

19

James R. Howe

19.1 Introduction

The small bowel is one of the most common sites of origin of neuroendocrine tumors (NETs) in general, and small bowel neuroendocrine tumors (SBNETs) are the most common gastroenteropancreatic NETs. The incidence of SBNETs increased fourfold between 1973 and 2002, and has overtaken adenocarcinoma as the most common histology [1]. Whether this represents improved diagnosis, widespread use of proton pump inhibitors, or changing environmental influences is unknown.

Some patients, especially those with liver metastases, may manifest symptoms of carcinoid syndrome, which include flushing, diarrhea, wheezing, and right-sided heart disease. Others may present with symptoms of bowel obstruction or anemia, but many may be asymptomatic until they develop pain from liver metastases.

SBNET primaries are predominantly located in the ileum; they are multifocal in 25% of cases [2]. Of these, 29% are localized to the bowel at diagnosis, 41% have involved regional nodes, and 30% have metastatic disease. Nevertheless, the overall median survival is 88 months: 111 months for those with localized tumors, 105 months with regional involvement, and 56 months for patients with metastatic disease [3]. Because of this generally favorable prognosis, an aggressive approach of resecting the primary tumor and regional lymph nodes is advised, with cytoreduction of liver metastases when possible.

One of the difficulties with SBNETs is the lack of a preoperative diagnosis. Many patients present with liver lesions, which upon biopsy reveal metastatic NET of unknown primary site. In this situation, one must suspect a gastroenteropancreatic site, with SBNETs and pancreatic NETs being the most common. Pancreatic NETs are usually visible on CT scan, but SBNETs may not be. One of the best clues pointing to an SBNET primary is the presence of mesenteric lymphadenopathy as one follows the segmental branches from the superior mesenteric artery (SMA) and superior mesenteric vein (SMV). Enlarged nodes in this region, which often contain calcifications, are the telltale sign of a small bowel primary.

19.2 Operative Technique

19.2.1 Approach

Although laparoscopic surgery has gained popularity for treatment of colorectal neoplasms, its use should be strongly cautioned in SBNETs for several reasons:

- These tumors are frequently very small; palpation using the fingertips is important and cannot be substituted for by laparoscopic graspers.
- The lesions may be multiple, and additional small lesions may be missed even though larger primaries may be evident laparoscopically.
- The incision used for extracorporeal anastomosis is generally inadequate to perform extended regional node dissection, cholecystectomy, and concomitant liver cytoreduction.

For these reasons, a midline incision is preferred. If preoperative imaging shows minimal nodal disease and no liver metastases, a smaller incision beginning just below the umbilicus and extending towards the epigastrium may be used for combined small bowel resection, regional lymphadenectomy, and cholecystectomy. When the nodal disease is more substantial and if the liver is involved, a generous midline incision from the xiphoid to between the pubis and umbilicus should be used (Fig. 19.1). During the operation, if the patient has liver metastases, we will infuse octreotide at a rate of 100 μg/h to help avoid intraoperative hypotension associated with the release of vasoactive hormones. Postoperatively, the drip is decreased to 75 μg/h, and then reduced by increments of 25 μg/h every 8 h.

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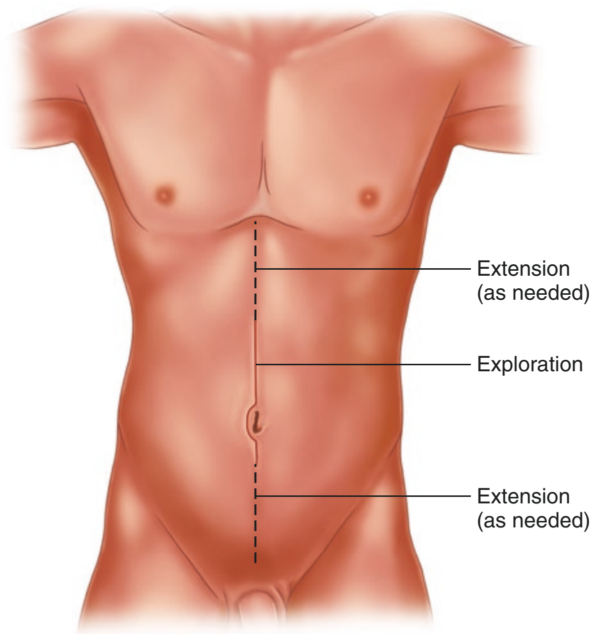
Figure 19.1

Incisions used for small bowel neuroendocrine tumor (SBNET) resection. If only the small bowel tumor, regional nodes, and gallbladder are to be resected, then a 5- to 6-inch midline incision may be used (*solid line*). If more extensive surgery is required, including extended nodal dissection, removal of peritoneal implants, or hepatic cytoreduction, then a long midline incision is preferred (*solid and dotted lines*)

Figure 19.1



19.2.2 Exploring the Abdomen

Once the peritoneal cavity is entered, a thorough exploration is carried out. This exploration begins with division of the falciform ligament, followed by careful bimanual palpation of both the right and left lobes of the liver. Liver metastases are very common, occurring in 30% of cases of SBNETs in the Surveillance, Epidemiology, and End Results (SEER) Program registries [3] and in 77% of our patients at a tertiary referral center [2]. Compare the intraoperative findings with the results of preoperative imaging, including CT scans and octreoscans, where available. Assess whether the liver disease, if present, consists of relatively few, large lesions, which may be amenable to debulking, or whether there are numerous, small lesions in both lobes, where it will be difficult to make a substantive impact on reducing the tumor burden. Also assess whether many of the lesions are peripheral and subcapsular (and therefore amenable to enucleation) or deep, requiring formal resection or ablation.

Next, palpate the gallbladder for stones, palpate the hepatoduodenal ligament for enlarged nodes, and assess for aberrant hepatic arterial anatomy. Palpate the stomach and then the duodenum for any intramural or serosal nodules. Feel the peritoneal surfaces under each diaphragm for nodularity, and then run a hand down along the anterior peritoneum and lateral peritoneal surfaces, and then to the pelvis. Feel for the catheter balloon in the bladder, and then follow the sigmoid down for lesions known as drop metastases. When the peritoneal reflection is reached, feel anteriorly for the uterus and then each ovary in female patients. Enlarged, hard ovaries are likely to represent metastases and should be removed, especially in postmenopausal women. Follow the sigmoid colon with your hand up to the splenic flexure, palpating for lesions, then across the transverse colon, then down the ascending colon to the appendix.

Locate the ligament of Treitz; then pull the jejunum upward and carefully inspect and palpate the entire small bowel to the ileocecal valve, grasping the bowel between thumb and

Figure 19.2

Palpation of the small bowel. Beginning at the ligament of Treitz, carefully pull the small bowel through thumb and forefinger to assess for lesions. Mark each lesion with a stitch, or mark the first and last lesions, if they are multiple forefinger and methodically pulling the bowel through these fingers, palpating for intramural lesions (Fig. 19.2). Lesions as small as 1–2 mm can be detected, but most tumors will be between 5 and 15 mm in size. Pull 10–15 cm of bowel through the fingers of the left hand while firmly grasping the starting point with the right hand; then re-grasp the bowel distally with the right hand adjacent to the left, and pull the next 10–15 cm through; repeat until the ileocecal valve is encountered, which is generally 300–600 cm from the ligament of Treitz. Most lesions will be in the distal jejunum to the terminal ileum; it is rare to find lesions in the proximal part of the jejunum. Multiple lesions are found in 30–40% of patients; if several lesions are encountered, place a 3-0 silk suture in the serosa of the bowel adjacent to each one. If there are many lesions (the most I have found is 139), then place a suture just proximal and distal to the first and last ones. We measure and record the total length of the small bowel and the segment of bowel affected by both the tumor(s) and lymphadenopathy, which helps in planning the resection.

Palpate the mesentery supplying the bowel adjacent to the lesions you have found, to locate grossly enlarged nodes (Fig. 19.3). Assess their size and compare them with the preoperative CT scan, which commonly shows enlarged nodes with calcification in the small bowel mesentery. Carefully follow the mesenteric vessels on the CT scan and look for enlarged nodes proximally, which can extend up to the lower border of the pancreas and may encircle the SMV and SMA. Now assess the mesentery for the most proximal extent of enlarged or firm nodes, and note their relationship to major vascular branches (such as the ileocolic) versus more central and critical vessels such as the SMV and SMA. The nodes may be matted down and pulling loops of bowel into them, as well as being heavily calcified and thick. Determine the relationship between these nodes and the lesion(s) within the bowel, and how these will be removed together. If multiple loops of bowel are adherent to the nodes in the mesentery, it may be necessary to sharply dissect them off these nodes so that the extent of nodal involvement can be better appreciated.

Figure 19.2

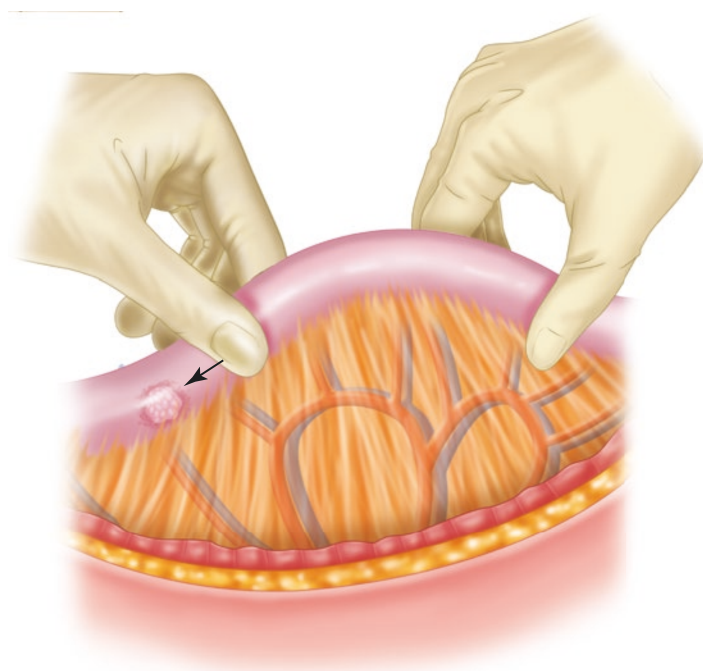
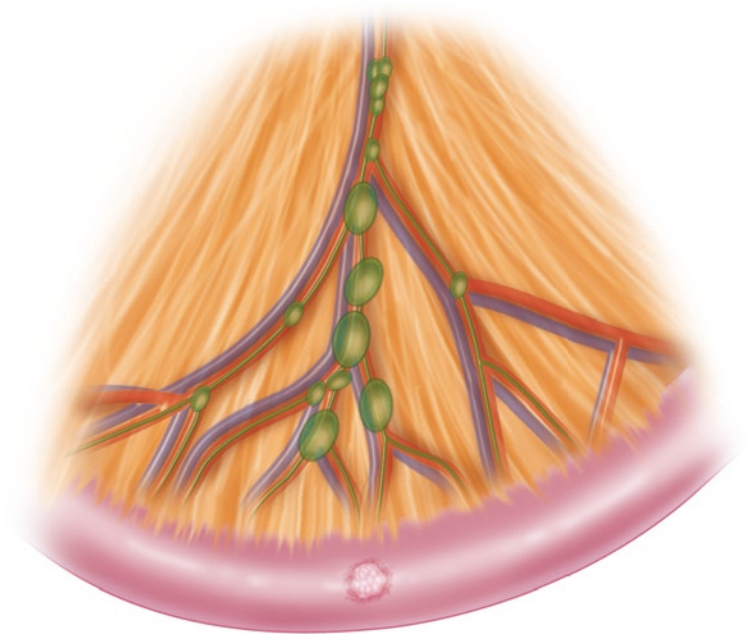


Figure 19.3

Distribution of enlarged nodes in the small bowel mesentery.

Figure 19.3



19.2.3 Small Bowel Resection and Lymphadenectomy

The extent of resection depends upon the number of lesions, the location of the lesions, and the extent of lymphadenopathy. Single lesions in the jejunum or proximal ileum require a segmental bowel resection and regional lymphadenectomy, to encompass those nodes draining along the segmental vessels supplying that portion of the small bowel (Fig. 19.4). If there is a single lesion without bulky central mesenteric lymphadenopathy, resection of approximately 30 cm of small bowel is generally required.

If there are multiple lesions, one must carefully consider how much bowel should be resected. It is generally preferable to remove one long segment and have one anastomosis, rather than removing multiple segments and having two or more anastomoses. If multiple resections and anastomoses are planned and an adequate lymphadenectomy is performed, one needs to take into account whether the blood supply to the intervening bowel segment may be compromised. Prior to resection, measure the length of bowel from the ligament of Treitz to the proposed site of transection, then from the distal resection margin to the ileocecal valve; carefully record these numbers. Also measure the length of bowel within the proposed lines of transection. Most patients will have 300–600 cm of small bowel, and even with multifocal tumor or significant involvement of the mesentery, we try to keep resections to less than 100 cm. Short-gut syndrome is a risk if one cannot preserve about 200 cm of bowel. Preservation of the ileocecal valve, if possible, can help the situation. If there are very small lesions distant from the main tumor(s), for which lymph node involvement would be unlikely (such as with lesions smaller than 2–4 mm), one might consider local excision of these lesions in order to preserve more bowel length.

Many lesions are found right at the ileocecal valve or in the terminal 30 cm of the ileum. To perform an adequate lymphadenectomy, the ileocolic artery and vein must be sacrificed (Fig. 19.4), so the terminal 20–30 cm of ileum, as well as the right colon, will be devascularized and must be removed. How much colon to remove will depend on the adequacy of flow from either the middle colic or right colic artery to the hepatic flexure. If a good pulse can be palpated in the adjacent mesentery, I try to save the hepatic flexure and perform an anastomosis of the proximal small bowel to the colon just below the right colic artery in the upper ascending colon.

Once the transection points of the bowel have been determined, create a small opening in the mesentery adjacent to the small bowel using electrocautery or a clamp. Place a GIA™-80 stapler (Medtronic–Covidien; Minneapolis, MN, USA) through this, then transect the bowel using a blue (3.5-mm) load. Repeat this procedure for the distal site of the transection in the colon or small bowel. Next, score the mesentery leading away from the point of transection, converging with a similar line from the other point of transection, carefully including the major segmental vessels and their lymph nodes.

Figure 19.4

Path of lymphatic drainage from (1) terminal ileal NET, and (2) jejunal or proximal ileal NET. *Dotted lines* designate the lines of transection of the bowel and mesentery. *Arrows* show the direction of nodal spread from the small bowel wall along segmental blood vessels to the root of the superior mesenteric artery (SMA)

Make sure to include all these nodes and any others that appear enlarged. Divide the mesentery between clamps, then suture ligate with 2-0 silk sutures, or alternatively, use a device such as the LigaSure™ Impact (Medtronic–Covidien). Continue this dissection until the point where the segmental vessel comes off the SMA. There will often be nodes at this point, which can be carefully dissected from the base of this vessel by dividing the soft tissue over the surface of the vessel. I recommend holding the nodes and segmental vessel in one hand and pulling them away from the SMA; then take small amounts of the fibrofatty tissue at a time with electrocautery or the LigaSure™. Rotate the nodes while palpating the vessel to finish dividing the tissue, until the takeoff of the artery and vein from the SMA and SMV is directly visualized. Pull the nodes toward the specimen, freeing up the area 1 cm from the surface of the SMA and SMV; then doubly clamp the artery and vein (Fig. 19.5). Divide between the clamps and pass off the specimen. Suture ligate the segmental vessels with 2-0 silk without encroaching upon the main trunk of the SMA and SMV. When hemostasis has been achieved, assess the color of the bowel at the transection sites, and try to palpate a pulse in the subsegmental artery feeding each side. Sometimes an additional 5–10 cm of small bowel (usually proximally) should be resected if it has a congested appearance and there may be questions regarding inflow. As long as there is adequate length of bowel, one should have a low threshold to resect such segments.

Once viability of the two ends of the bowel has been confirmed, it is time to perform the anastomosis. The anastomosis is performed by suturing the mesenteric edges of the two ends of the bowel limbs approximately 2 and 8 cm from the staple line using 3-0 silk sutures. Place atraumatic bowel clamps 10 cm proximally and distally to minimize spillage. Next, cut off the antimesenteric 1-cm edge of the staple line on both limbs of bowel and insert each half of a GIA™-80 blue load stapler into the lumen (Fig. 19.6). Clamp each half of the stapler together, ensuring that the mesentery is not between them, and then fire the stapler load. Remove the stapler, holding the bowel vertically with Allis clamps to avoid leakage of intestinal contents, then approximate the two sides of the enterotomy with additional Allis clamps, making sure that the GIA™ staple lines are offset from one another. Fire a TA™-60 stapler (Medtronic–Covidien) blue load (3.5 mm) under the Allis clamps to close the enterotomy. Oversewing the staple line with a running 3-0 PDS inverting suture is optional at this point. Reapproximate the edges of both sides of the mesentery using a running 3-0 Vicryl suture to obviate internal hernia and aid with hemostasis (Fig. 19.7).

At the end of resection and lymphadenectomy, it is important to carefully assess the remaining bowel. If either end appears to have compromised inflow or venous outflow, resect additional bowel at that time. It is usually better to ensure well-perfused bowel and risk some shortened length than to have a leak from the anastomosis.

Figure 19.4

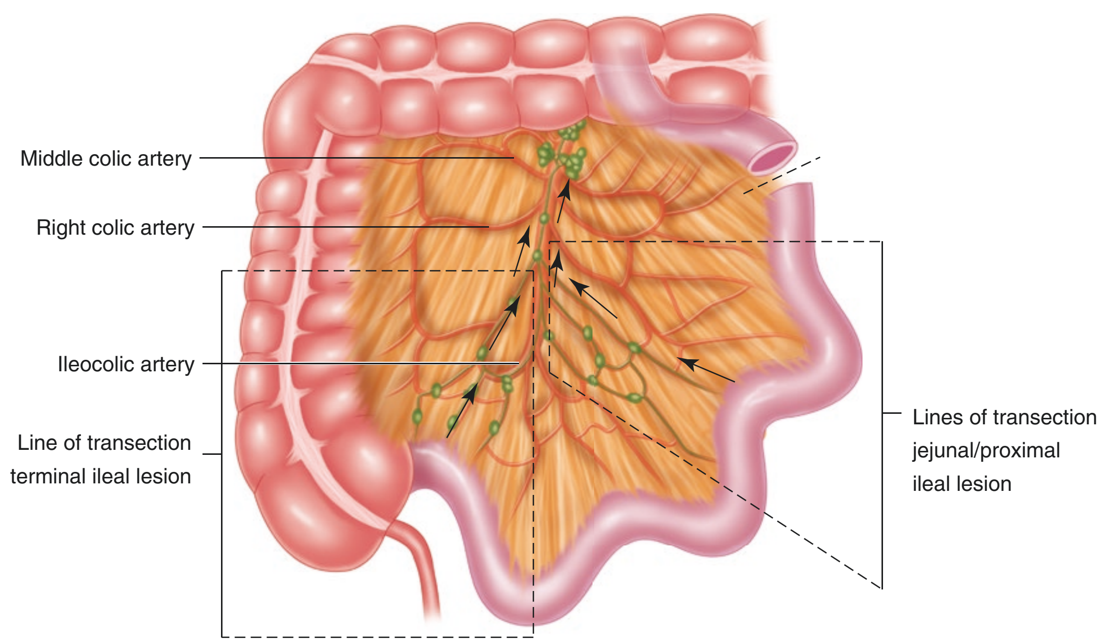


Figure 19.5

Circumferential dissection of the base of the ileocolic artery, pulling the nodes down away from the SMA and superior mesenteric vein (SMV). Once the base of the mesentery is freed of nodes (*dashed line*), doubly clamp and suture ligate the proximal subsegmental vessels

Figure 19.6

(**a**) Placement of the GIA™-80 stapler through the cut ends of the bowel at the antimesenteric side. (**b**) Closure of the enterostomy with a TA™-60 stapler

Figure 19.5

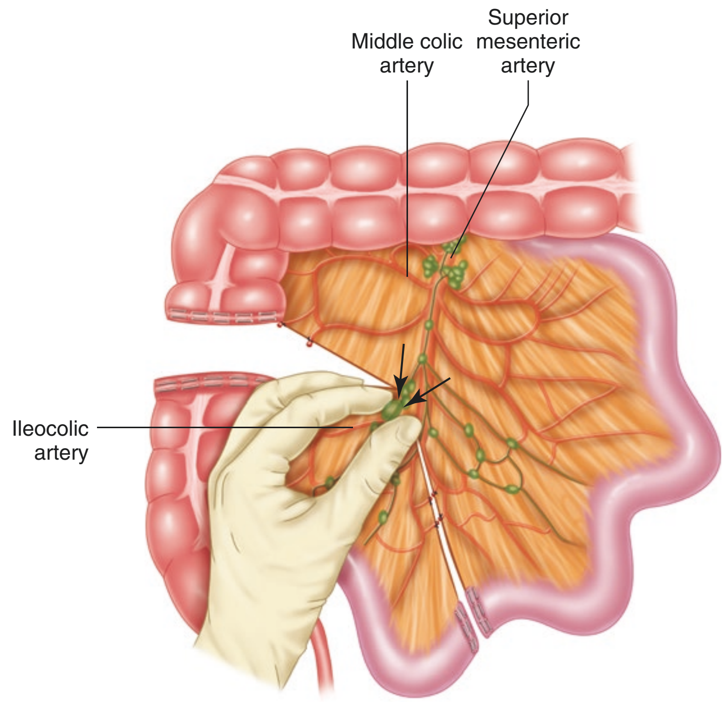


Figure 19.6

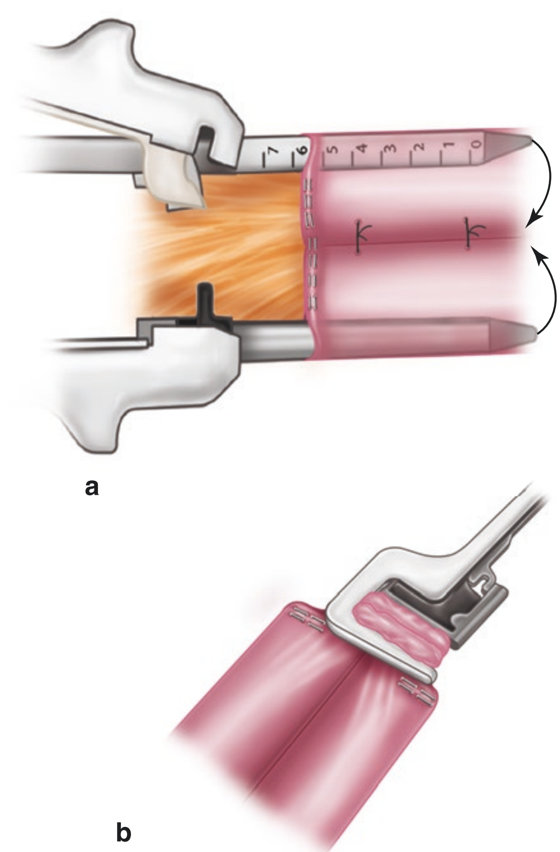
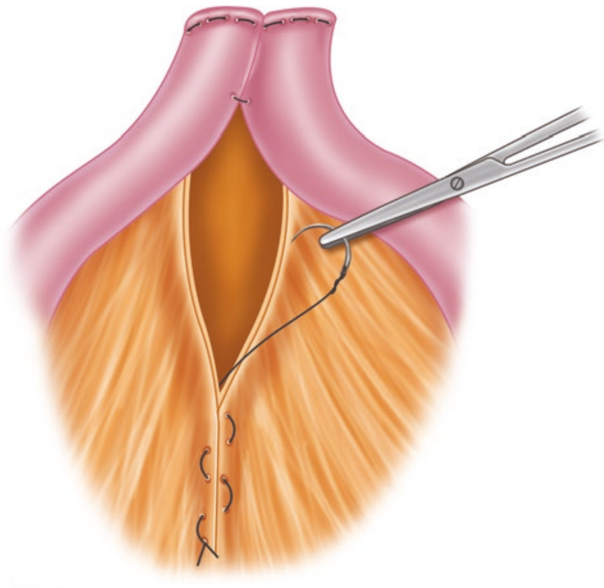


Figure 19.7

Closure of the peritoneum overlying the cut edges of the mesentery

Figure 19.7



19.2.4 Special Considerations for Lymphadenectomy

It is not uncommon for nodes to continue above the takeoff of the segmental vessels from the SMA and SMV, either as individual, enlarged nodes or a mass at the mesenteric root. Individual nodes can be removed by opening the peritoneum of the mesentery and carefully dissecting each one out circumferentially. It is important in this process not to injure the SMA or SMV, so as not to compromise inflow or outflow to the remaining bowel. On the other hand, a nodal mass extending to the root of the mesentery is often hard and flat, and encases the mesenteric vessels. In this circumstance, it is very difficult and often inadvisable to persist with the lymphadenectomy because of the risk of mesenteric vascular injury. An exception is when there are large, discrete nodes with clear boundaries rather than the more common hard, calcific mass. Leaving this kind of proximal mesenteric mass is recommended, as patients can still have extended survival, and these lesions can often remain stable in size over years. Some patients have mesenteric root masses in the absence of liver metastases, and may not develop metastases for several years.

One argument for attempted resection of a mesenteric root mass is venous insufficiency and abdominal pain, but it has been my experience that most patients develop collateral venous drainage and do not have significant abdominal pain. Some of these patients do have thickened loops of small bowel, but these are resected with the primary tumor and are the most likely affected portions of the bowel. Some surgeons have advocated splitting the nodal mass down to the mesenteric vessels, and then peeling the mass off the vessels. This is a very technically challenging endeavor, as these masses are often heavily calcified, making it very difficult to know where the vessels are. Attempting to divide the nodal mass without entering the mesenteric vessels risks significant blood loss and possible vascular compromise to the remaining bowel.

Some patients will have yet another, higher group of nodes along the mesenteric root, just below or behind the inferior margin of the pancreas. These nodes are hard to access, requiring an approach through the lesser sac. The risks of tackling these nodes are similar to the risks of tackling the nodes at the mesenteric root below the mesocolon, namely the hazard of injury to the mesenteric vessels. If the nodes are round and discrete, they may be peeled off, but beware of a flat, dense, calcified group of congruent nodes. Small bowel lesions also are occasionally accompanied by large aortocaval masses, portocaval, pararenal, or even celiac nodal lesions. Sometimes these are calcified, and preoperative CT scans or endoscopic ultrasound may even mistakenly identify them as primary pancreatic tumors. In reality, these masses represent more proximal extension of SBNET nodal disease. That is why it is very important to run the bowel and look for a small bowel tumor even when a pancreaticoduodenectomy is planned for what appears to be a primary pancreatic NET. The finding of a small bowel lesion with mesenteric lymphadenopathy at this point should make one hesitate to continue with that procedure but instead perform a small bowel resection with mesenteric lymphadenectomy, with possible extension to these peripancreatic nodes. Although these nodes may be large and adherent to nearby vascular structures, they may be freed up and removed by careful dissection. If the nodes extend into the aortocaval area near the pancreas, the nodes posterior to the portal vein should be evaluated, as they also may be involved. During these extended nodal dissections, one must keep in mind the generally favorable survival of patients with SBNETs, and weigh this against the potential risk of removing these nodes.

19.2.5 Other Considerations

Patients whose tumors have grown through the serosa of the bowel are at risk for peritoneal seeding. This seeding may manifest as plaques of tumor along the diaphragm, mesentery, small bowel, colon, and pelvic structures. Such lesions should be removed if possible, but sometimes there are so many areas that doing so becomes unrealistic. Small plaques can be treated with the argon beam coagulator to avoid the need for resection. Bulkier deposits may require omentectomy, small bowel resection, or even sigmoid resection. Again, it is important to weigh the risks and benefits of resecting bowel, but these patients will often live for many years, so areas of impending obstruction should be treated. In these cases, it is important to check for ovarian involvement, which is common.

Many patients with SBNETs (especially those with nodal and/or liver involvement) will end up receiving long-term treatment with somatostatin analogues. Over time, this will lead to cholelithiasis, and the potential for future biliary colic or acute cholecystitis. Patients undergoing embolization for unresectable liver metastases are at risk for gallbladder necrosis. For these reasons, a cholecystectomy should generally be performed at the initial operation for SBNETs, unless it is an early stage tumor.

More than 30% of patients with SBNETs will have synchronous liver metastases, and debulking of these lesions can lead to improved long-term survival. Therefore, it has been our practice to remove the SBNET primary lesion and accompanying nodal disease, then move on to cholecystectomy and debulking of liver lesions. Because of the very high recurrence rate, we favor hepatic parenchymal preservation through enucleation and targeted ablation (which usually can be accomplished through the same midline incision used for bowel resection and lymphadenectomy) rather than extended hepatic resections.

19.3 Complications

Patients do surprisingly well after these procedures, depending upon the extent of disease. Diarrhea is the most common complication of bowel resection, especially resection of the terminal ileum or greater lengths of bowel. This diarrhea can be due to malabsorption secondary to short bowel (treated with loperamide), failure of reabsorption of bile salts in the ileum (treated with cholestyramine), or fat malabsorption caused by inhibition of pancreatic enzyme secretion mediated by somatostatin analogues (treated with pancreatic enzymes).

When the involved nodes extend proximally to involve the root of the mesentery, some patients will develop mesenteric venous obstruction, which may be seen on CT scans as thickened loops of small bowel with numerous collaterals. Patients may have symptoms of abdominal pain (which may be worse after eating), but some are relatively asymptomatic. If collaterals have developed, little intervention may be needed, but when symptoms develop, one should consider either anticoagulation or resection of the involved segment of bowel. If the nodal disease is resectable, resection would be another option, but this is rarely the case.

19.4 Results

Patients with SBNETs benefit from resection of the primary, even in the presence of metastatic disease. In a retrospective review, Hellman et al. [4] looked at patients with midgut carcinoids and found a median survival of 7.4 years in those undergoing resection of their primary (n = 249) versus 4.0 years for patients with no resection or palliative procedures (n = 63; $P < 0.01$). They also found that for patients with their primaries removed, resection of involved nodes (n = 166) versus leaving them behind (n = 83) led to improved median survival of 7.9 versus 6.2 years ($P < 0.001$). Of course, there was a high potential for selection bias inherent in this study. Givi et al. [5] reviewed 84 patients with unresectable liver metastases; 60 had their primaries removed and 24 did not. They found 81% 5-year survival in those with resection of the primary tumor versus 21% in those without resection ($P < 0.001$). They believed that there was not significant selection bias in their study, and that the improved survival was due to reduced progression within the liver metastases. An international collaborative study examined patients from eight centers who had liver-directed surgeries for metastatic NETs from various sites, and found 74% 5-year survival, versus 54% in the most recent SEER data, suggesting that hepatic debulking does improve survival [6]. Most patients will develop recurrent hepatic disease, however; it occurred in 84% of patients at 5 years in the series of Sarmiento et al. [7]. Overall 5-year survival reported for patients in the SEER database is 65% for those with localized disease, 71% for those with regional disease, and 54% for those with metastatic disease [3].

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