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In brief ☆,☆☆

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Neuroendocrine tumors are heterogeneous malignancies that arise from neural crest-derived cells of the diffuse neuroendocrine system. The term neuroendocrine neoplasm encompasses both poorly-differentiated neuroendocrine carcinomas (NECs) and well-differentiated neuroendocrine tumors (NETs). Small bowel neuroendocrine tumors (SBNETs) originate from enterochromaffin cells, which are enteroendocrine cells that line the epithelium of the digestive tract and secrete serotonin, the hormone responsible for carcinoid syndrome. SBNETs, which occur from the ligament of Treitz to the ileocecal valve, are increasing in incidence and prevalence, and they have overtaken adenocarcinoma as the most common primary malignancy of the small bowel. SBNETs comprise 17% of all diagnosed NETs, making the small bowel one of the most common sites for NETs. It is thus not uncommon for surgeons to encounter SBNETs during an operation for obstruction or during evaluation for abdominal pain and obstructive symptoms. This review focuses on SBNETs arising from the jejunum and ileum, which have histological and clinical manifestations distinct from duodenal and appendiceal NETs.

Compared to NETs from other sites, SBNETs have a relatively good prognosis, as evidenced by a median overall survival (OS) of 103 months and 5-year survival rate of 69%. The median OS for patients with localized disease is 14 years, while the median OS in those with distant disease is almost 6 years, the longest OS for distant metastases among in NETs from different sites. Survival for patients with distant SBNETs has improved over the previous 2 decades due to advances in imaging and treatment.

Our understanding of the molecular drivers of SBNET development has also progressed over this time. SBNETs commonly have deletion of chromosome 18 (including *SMAD* genes). Although most SBNETs have few mutations, sporadic *CDKN1B* alterations have been reported in 5%-10% of cases, and one family has been found with a germline *IPMK* mutation. Epigenetic changes, such

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as hypomethylation, occur in 70%-80% of SBNETs, suggesting these changes may be an early and important event in tumorigenesis.

SBNETs can cause carcinoid syndrome, which consists of a classic triad of flushing, diarrhea, and wheezing. These symptoms are caused by the bioactive amines that SBNETs can secrete, such as serotonin, histamine, tachykinins, and prostaglandins. The presence of carcinoid syndrome due to an SBNET suggests a very large tumor burden or hepatic metastases, as the responsible amines are often metabolized by the liver. Other less common features of carcinoid syndrome include valvular heart disease and heart failure, pellagra, telangiectasias, edema, and arthritis.

Despite its notoriety, classic carcinoid syndrome is an unusual presentation of patients with SBNETs. Patients are more likely to present with vague abdominal pain, diarrhea, or symptoms of obstruction. Due to the nonspecific nature of symptoms, patients may be misdiagnosed with functional gastrointestinal disorders and struggle with incomplete symptom relief for months or years. They may also manifest as an asymptomatic mass found incidentally on imaging or during surgery performed for bowel obstruction or an unrelated diagnosis.

Because of the varied ways in which SBNETs can manifest, diagnosis can require multiple modalities. Imaging is the most common tool for diagnosis and computed tomography (CT) is often the initial tool of choice, as it is noninvasive, widely available, and relatively quick to obtain. Primary SBNETs tend to be small and difficult to identify, but they can appear on CT as a small bowel mass or bowel wall thickening. The sensitivity of CT scans for the primary tumor can be improved if multiphase images are obtained and oral contrast is used. Other imaging findings suggestive of an SBNET include a spiculated, stellate fibrotic mass in the mesentery due to fibrosis and calcifications of mesenteric lymph nodes. Liver metastases tend to be hypervascular and appear as enhancing masses on arterial phase CT. Hepatic metastases are best seen on magnetic resonance imaging (MRI), which appear hypodense on T1-weighted MRI and hyperintense on T2-weighted MRI.

In contrast to anatomic imaging, functional imaging takes advantage of the expression of somatostatin receptors (SSTRs) by NETs. SSTR-PET imaging, such as ^{68}Ga DOTATATE, ^{68}Ga DOTATOC, and ^{68}Ga DOTANOC, have supplanted ^{111}In pentetreotide SSTR scintigraphy (Octreoscan) as the functional imaging test of choice. These PET modalities are good for demonstrating that masses or nodes seen on anatomic imaging are indeed NETs, and for evaluating the extent of disease.

In conjunction with imaging, biochemical testing is used in diagnosis and surveillance of SBNETs. In the setting of appropriate symptoms, carcinoid syndrome can be confirmed with a 24-hour urinary collection for 5-HIAA. Blood tumor biomarkers are easier to collect and more often used to monitor for treatment response, progression, or recurrence. The most commonly monitored marker is chromogranin A (CgA), and CgA is the most consistently recommended marker by expert and consensus guidelines. Chromogranin A has a sensitivity and specificity of 71% and 50%, respectively, and levels can correlate with hepatic tumor burden and recurrence after surgical resection. However, it can be falsely elevated in patients with multiple diseases, such as renal dysfunction, non-neuroendocrine malignancies, and rheumatoid arthritis. Chromogranin A may also be elevated with the use of various medications, including proton pump inhibitors.

Other tumor markers include pancreastatin, neurokinin A, substance P, and neuron-specific enolase. A multianalyte assay been developed, but is more expensive than monoanalyte tests, and is not widely used. Pancreastatin has emerged as the superior monoanalyte tumor marker, as it is more sensitive, specific, and accurate than CgA in detecting recurrence after surgical resection. Pancreastatin also provides more prognostic information regarding progression-free (PFS) and OS compared to other markers. Levels of pancreastatin are unaffected by the use of proton pump inhibitors, and recent studies suggest pancreastatin replace CgA as the tumor biomarker of choice in surveillance of surgically-resected SBNETs.

Ultimately, the diagnosis of a NET is confirmed by pathologic examination. Tissue can be obtained surgically or by needle biopsy. On hematoxylin and eosin (H&E) staining, NETs have centrally located, ovoid “salt-and-pepper” nuclei, and positive immunohistochemistry (IHC) staining for neuroendocrine markers synaptophysin and chromogranin helps confirm the diagnosis of a

NET. When the primary site is uncertain, such as in the case of biopsy of liver metastases, further IHC staining can be helpful, as midgut NETs tend to have positive CDX2 staining and negative PAX6 and ISL1 staining. Gene expression classifiers can also help determine the primary site of a metastatic NET of unknown primary.

Pathologic examination should include information regarding tumor differentiation (well vs poorly differentiated) and grade (grade 1, 2, or 3), as both are important in determining prognosis. Poorly differentiated neuroendocrine carcinomas are frequently aggressive, present with metastases, and are associated with worse survival compared to well-differentiated NETs. Grade is determined by proliferative rate, which is based on the mitotic rate or Ki-67 index. Higher-grade tumors also tend to be more aggressive with more metastatic potential and worse survival. The Ki-67 should be determined in the primary and metastatic tumors, as the highest Ki-67 from any site predicts PFS and OS. Staging is based on the TNM staging system by the American Joint Committee on Cancer.

Unlike in other malignancies, the presence of distant metastases does not preclude surgery in SBNETs. Surgical exploration is sometimes required for diagnosis and can relieve symptoms of obstruction or hormone overproduction. Although surgery may not be curative, it can improve survival and quality of life, and may delay the development of metastases.

Perioperative management involves consideration and prevention of carcinoid crisis, which is sudden hemodynamic instability or cardiovascular collapse triggered during surgery due to the release of hormones from tumor manipulation. Preoperative evaluation may include an echocardiogram if patients have high serotonin levels or a history concerning for carcinoid heart disease. Significant tricuspid or pulmonic valve disease must be corrected prior to surgery for abdominal disease. Intraoperatively, our practice is to provide a continuous infusion of octreotide at 100 mcg/hour throughout the case and to be prepared to administer additional fluids and vasopressors, if necessary. We wean the octreotide infusion by 25 mcg/hr every 8 hours, and provide standard postoperative prophylaxis for venous thromboembolism.

Surgery of the primary site may be laparoscopic or open and must involve careful palpation of the entire length of the bowel. Arising most often in the ileum, primary SBNETs can be small and multifocal. These small tumors can escape detection on imaging and may be identified only by running the bowel. Resection involves removing the affected segment of bowel and associated mesentery, including the blood supply and lymph nodes down to segmental branch vessels coming off the mesenteric root. Resection of bulky, involved nodes can require painstaking dissection from larger mesenteric vessels, which may not always be possible, but may relieve symptoms related to ischemia. Limited peritoneal stripping and ablation of small lesions can provide acceptable control of peritoneal metastasis.

Management of liver metastases focuses more on control, rather than complete elimination, of disease. Cytoreduction of hepatic metastases, which tend to be well-circumscribed and non-infiltrative, reduces hormonal symptoms and can improve survival. Superficial metastases can be resected with limited margins by partial hepatectomy, wedge resections, or enucleation. Ultrasound-guided ablations can be employed for deeper lesions, preserving normal hepatic parenchyma and minimizing the morbidity of large hepatic resections. Data suggest that debulking of at least 70% of hepatic metastases improves OS and usually results in significant reduction of hormone levels. Liver arterial embolic therapies with bland, chemo-, or radioembolization can shrink tumors, reduce hormonal symptoms, and possibly extend survival for patients with unresectable liver disease. Liver transplant is another option for highly selected patients. Cytoreductive surgery combined with heated intraperitoneal chemotherapy is not currently recommended for the management of carcinomatosis in patients with SBNETs.

For patients with unresectable disease or with residual disease or hormonal symptoms after surgery, medical treatment can reduce symptoms and slow progression. Somatostatin analogues (SSAs) are a mainstay of treatment for of carcinoid syndrome, as NETs express high levels of somatostatin receptors (SSTRs) and activation of these receptors reduces hormone secretion. The growth of SBNETs can also be stabilized or slowed by SSAs decreasing signaling in cell proliferation pathways. The SSAs octreotide and lanreotide improved PFS in the PROMID and CLARINET

trials, respectively. For patients who have hormonal symptoms refractory to SSAs, the tryptophan hydroxylase inhibitor telotristat can provide relief by reducing serotonin production.

If patients experience progression of disease on first-line SSAs, additional treatment options include everolimus, peptide receptor radionuclide therapy (PRRT), and chemotherapy. The mTOR inhibitor everolimus increased PFS in pancreatic NETs in the RADIANT-3 trial, but its role in SBNETs was less clear in 2 other randomized trials (RADIANT-2 and RADIANT-4). PRRT treats NETs with a radioisotope conjugated to an SSA, which binds to SSTRs on NET cells and is then internalized. Radioisotopes used for PRRT have included ^{111}Indium, ^{90}Yttrium, and ^{177}Lutetium. The latter agent has demonstrated improved PFS in patients with midgut NETs and is the preferred treatment for patients who have progressed on SSA therapy and whose tumors express SSTRs. For patients with higher grade or aggressive tumors, systemic chemotherapy may provide some benefit. For grade 3 neuroendocrine carcinomas, platinum-based regimens such as carboplatin/etoposide, are preferred. For G2 and well-differentiated G3 tumors, capecitabine/temozolamide are most commonly used.

The increase in prevalence of SBNETs is likely due to the increased use of abdominal imaging and recognition of these tumors. As SBNETs increase in incidence and prevalence, surgeons are more likely to come across SBNETs in their practice. The diagnosis and treatment of SBNETs is a multidisciplinary effort and providers who regularly care for patients with SBNETs should be familiar with the increasing variety of modalities for imaging, surveillance, and treatment. Improvements in imaging and treatment have improved detection and survival in patients diagnosed with SBNETs. Surgical resection remains the cornerstone of treatment, and may extend survival and decrease symptoms even in patients with metastatic disease.