Malignant Tumors of the Small Intestine: A Case Series and Review of the Literature


Daniel Kurtz


Sharon Slomovich


Mahnoor Khan


Neal Shah


Frank G. Gress

Small bowel neoplasms are uncommon gastrointestinal malignancies, but their incidence has risen in recent years. The main subtypes include adenocarcinoma and neuroendocrine tumors, each accounting for approximately 40% of cases, with sarcomas and lymphomas making up the remaining 20%. These neoplasms often present with nonspecific symptoms, complicating diagnosis. While chemotherapy may be used in some cases, surgical resection often remains the primary treatment. We present a case series that underscores the nonspecific nature of these malignancies and highlights the importance of advanced endoscopic techniques for diagnosis. We also propose an actionable approach to aid clinicians in diagnosing these malignancies, while reviewing the current literature for etiology, epidemiology, clinical presentation, diagnosis, and treatment of the various subtypes.

INTRODUCTION

Small bowel neoplasms constitute less than 3% of all gastrointestinal malignancies and 0.6% of all cancers in the United States.[1–3] Their incidence has steadily increased in the last 20 years.[3] The most common histologic subtypes are adenocarcinoma and neuroendocrine tumors, each accounting for approximately 40%. Stromal tumors, sarcomas, and lymphomas comprise the remaining 20%.[4–8] Symptoms are non-specific and include abdominal pain, weight loss, nausea, vomiting, obstruction, and occult bleeding.[9,10] Clinical signs are vague, the physical exam is frequently unremarkable, and

Daniel Kurtz, DO, Resident Physician[1] Sharon Slomovich, MD, Fellow Physician[2] Mahnoor Khan, DO, Fellow Physician[2] Neal Shah, DO, Fellow Physician[2] Frank G. Gress, MD, Chief[2] [1]Icahn School of Medicine at Mount Sinai, Department of Medicine, Mount Sinai South Nassau, Oceanside, NY, USA [2]Icahn School of Medicine at Mount Sinai, Division of Gastroenterology & Hepatology, Department of Medicine, Mount Sinai South Nassau, Oceanside, NY, USA

visualization on radiological imaging is limited by motion artifacts, making it a challenging diagnosis.[2,11] Endoscopic techniques, video capsule endoscopy, and push enteroscopy have improved our ability to identify these uncommon tumors. Unclear clinical signs and symptoms can lead to late diagnosis and treatment. We present a case series of five patients with vague clinical presentations that underwent extensive workup with advanced imaging modalities and were eventually diagnosed with a small bowel malignancy.

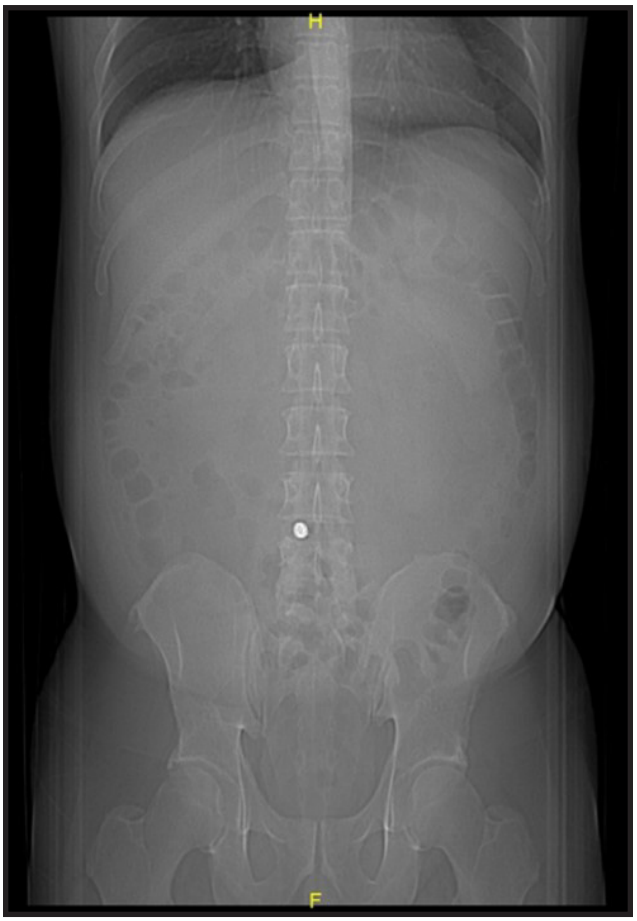


Figure 1. Endoscopic Capsule on Scout View of CT

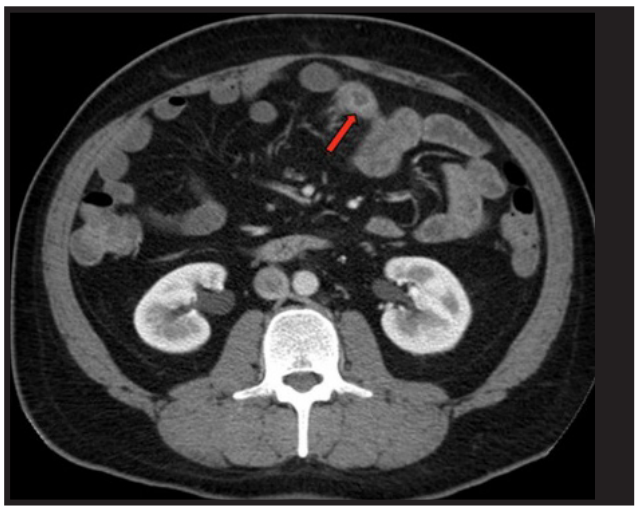


Figure 2. CT Enterography with Mild Hyperenhancement in Narrowed Region

CASE REPORT

Patient 1: A 43-year-old male with a past medical history of sarcoidosis presented with three months of worsening periumbilical pain and a 14-kilogram weight loss. Infectious workup, esophagogastroduodenoscopy (EGD), and colonoscopy was unrevealing. Video capsule endoscopy (VCE) demonstrated localized inflammation in the ileum, however, the capsule was unable to pass beyond this point (Figure 1). CT abdomen and pelvis revealed a partial small bowel obstruction. Small bowel enteroscopy demonstrated nonspecific inflammation of the ileum. CT enterography disclosed the presence of a stricture in the mid-ileum (Figure 2). Given the unclear etiology and persistent symptoms, three months following initial presentation, small bowel resection with side-to-side anastomosis was performed. Operative findings included an ileal stricture but otherwise normal bowel. Pathology revealed diffuse large B-cell lymphoma (DLBCL) of the small intestine (Figure 3) and the patient was treated with R-CHOP chemotherapy.[12]

Patient 2: A 55-year-old female with a past medical history of Lynch syndrome and a family history of colon cancer presented with abdominal pain, nausea, vomiting and a 2.3-kilogram unintentional weight loss for one month. The physical examination and laboratory investigation were unremarkable. Magnetic resonance enterography showed a 6 centimeter (cm) proximal ileal segment with evidence of irregular concentric wall thickening. Small bowel enteroscopy revealed a white nodular ileal mucosa with areas of ulceration in the mid-ileum (Figure 4). Biopsies demonstrated low-grade follicular lymphoma four months after initial presentation.

Patient 3: A 68-year-old-female with a past medical history of breast cancer presented with one month of abdominal pain, bloating and diarrhea. The physical examination and laboratory investigation work

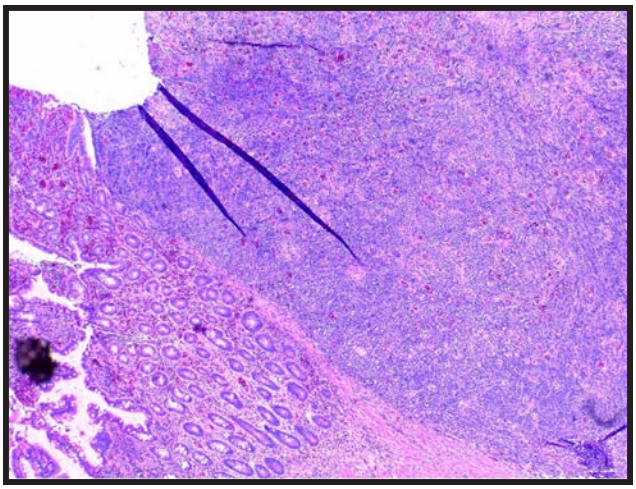


Figure 3a. Lymphoma Involving the Bowel Wall

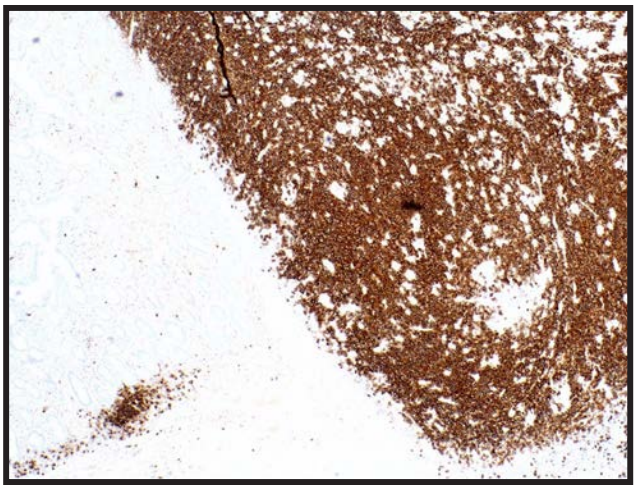


Figure 3b. Lymphoma CD20 Positive Immunostain

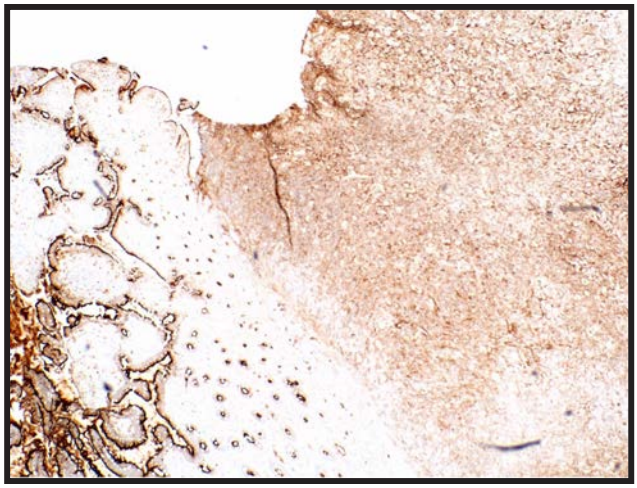


Figure 3c. Lymphoma CD10 Positive Immunostain

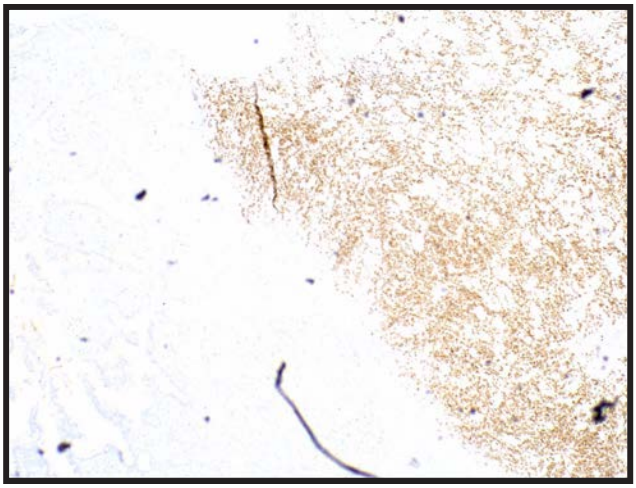


Figure 3d. Large B-Cell, Ki-67 Stain (more than 70%)

were unremarkable. Upper endoscopy revealed an antral nodule with regenerative changes and a hyperplastic duodenal bulb nodule with preserved villous architecture. Initial pathology revealed reactive gastropathy in the antrum and a benign hyperplastic/inflammatory polyp in the duodenum. Further evaluation with EGD and endoscopic ultrasound (EUS) indicated a 10 millimeter (mm) by 12 mm intramural lesion in the antrum of the stomach that was most consistent with a lipoma. Additionally, a hypoechoic 13 mm x 12 mm round mass in the duodenal bulb was seen confined to the mucosa (Figure 5). Endoscopic mucosal resection of the duodenal lesion was performed. A well-differentiated neuroendocrine tumor, low-grade World Health Organization (WHO) Grade 1 and 3, with tumor involvement of the muscularis mucosa was confirmed on biopsy six months following initial presentation.

Patient 4: A 53-year-old-male without significant medical history presented following one month of vomiting and epigastric pain. A gastric emptying study showed 60% food residual with a prolonged gastric emptying half-time. Laboratory investigation, CT abdomen and pelvis, EGD and colonoscopy were unremarkable. His symptoms were initially attributed to gastroparesis and was treated with domperidone. He presented six months after initial presentation with a 23-kilogram weight loss and treated for refractory gastroparesis with metoclopramide and erythromycin. He was scheduled to undergo a gastric peroral endoscopic myotomy procedure, however EGD

(continued on page 38)

(continued from page 36)

demonstrated 5 liters of fluid in a severely dilated duodenum suggesting an obstruction (Figure 6). Diagnostic laparoscopy revealed a nearly obstructing mass. A small bowel resection was performed, and moderately differentiated, invasive adenocarcinoma, invading through muscularis propria into nonperitonealized perimuscular tissue (mesentery and retroperitoneum) without serosal penetration, was confirmed on pathology (Figure 7).

Patient 5: A 71-year-old female with a past medical history of osteopenia and mitral regurgitation presented with intermittent abdominal pain for a few weeks and iron deficiency anemia (IDA) found on routine lab work. Colonoscopy at that time was unremarkable, however EGD at that time revealed moderate gastritis with scattered erosions and two superficial non-bleeding ulcers. She was started on a proton pump inhibitor with the assumption that gastritis was the source of her IDA. The abdominal pain persisted and resulted in loss of appetite due to the pain along with weight loss of 4.5 kilograms. Three months later she was found to have persistent IDA along with continued episodic abdominal pain and a VCE was performed. It demonstrated up to seven distinct areas of erythema, edema, and stricture in the small bowel, most of which were oozing blood, and a few lymph nodes in the proximal small bowel, one with central depression. Small bowel enteroscopy was performed and localized nodular mucosa was found in the second and fourth portion of the duodenum. Biopsies were taken and the pathology revealed low grade extranodal follicular lymphoma about four months after initial presentation. She is currently undergoing treatment with rituximab.

DISCUSSION

Small bowel cancer is uncommon; however, the incidence is on the rise, with an estimated 12,070 new cases and 2,070 deaths in the United States in 2023.[3] Adenocarcinoma and neuroendocrine tumors are the most common histological subtypes of small bowel malignancies.

Primary lymphoma of the gastrointestinal tract comprises 1%-4% of all gastrointestinal malignancies.[13] The ileocecal region is one of the most involved areas for primary intestinal lymphoma and thus, it can mimic IBD and other colonic etiologies further delaying treatment due to its initial ambiguity. Typically, on radiographic imaging, small bowel lymphoma can present as a polypoid mass, multiple nodules, infiltrative form, an extraluminal mass, mucosal thickening or in the form of strictures as seen in our patient with DLBCL (Figure 2).[13] However, CT imaging has a low sensitivity and specificity for detecting small bowel lymphomas. Thus, endoscopic evaluation can aid in the diagnosis of these tumors. In Figure 4, a white nodular ileal mucosa is seen in our patient diagnosed with follicular lymphoma on small bowel enteroscopy (SBE). A similar finding was seen in our patient with follicular lymphoma in the duodenal mucosa. The white nodular mucosa, which can include whitish polyps and white aggregates with or without ulceration of the mucosal layer, is consistent with the typical findings of follicular lymphoma seen on endoscopy.[14–16] Furthermore, EUS has enhanced our ability to visualize lesions of the gastrointestinal tract. As seen in Figure 5, a hyperechoic duodenal bulb lesion was identified and subsequently diagnosed as a neuroendocrine tumor. While several studies evaluated the role of EUS in detecting pancreatic neuroendocrine tumors, specific characteristics regarding lesions of the small bowel have yet to be established.[17] Given the rise in small bowel tumors, further studies are warranted to investigate the role of EUS in diagnoses of these malignancies. Additionally, intestinal ultrasound has been shown to accurately detect disease activity in the small bowel in patients with Crohn's disease. However, this inexpensive and non-invasive imaging modality has yet to be described for the specific detection of small bowel tumors.[18,19]

Small bowel tumors are difficult to identify and there are no established guidelines on an initial testing strategy for diagnosis. We propose the following diagnostic approach for patients presenting with symptoms of intestinal disease such as abdominal pain, gastrointestinal bleeding, symptoms of small bowel obstruction with nausea and vomiting, weight loss or bowel perforation and there is a concern for a small bowel malignancy. Initial testing should include a non-invasive modality, abdominal imaging, either with CT or MRI to evaluate for any lesions. If no lesions are

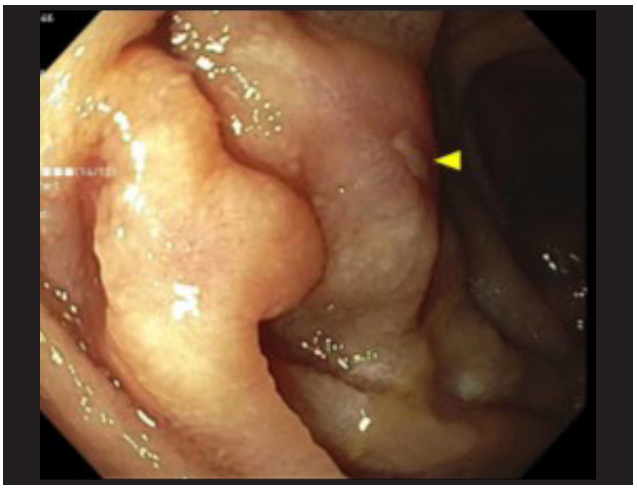


Figure 4. Small Bowel Enteroscopy with White Ulcerated Nodular Mucosa in the Ileum

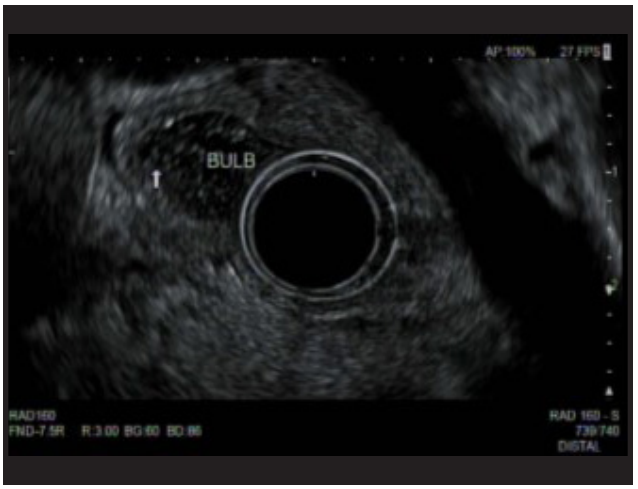
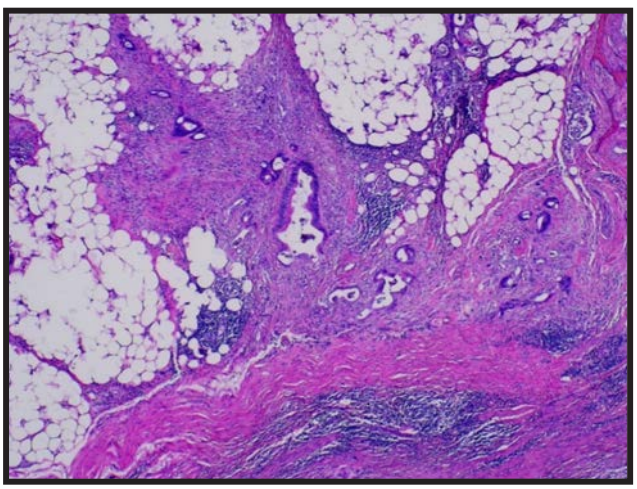
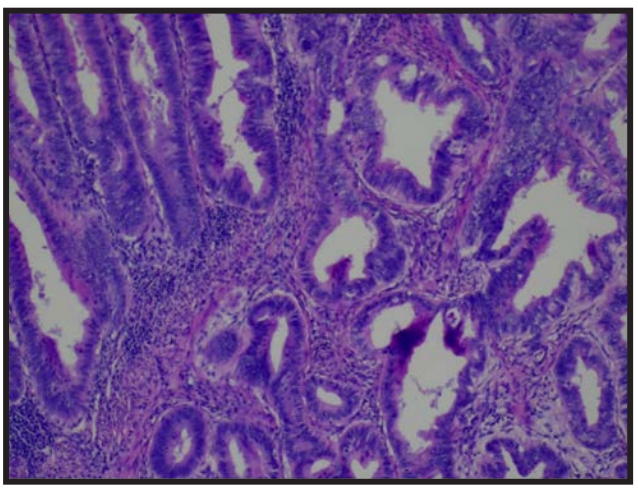


Figure 5. EUS with Hypoechoic Lobulated Mass in Duodenal Bulb 13mm x 12mm Extending from Mucosa to Submucosa



7a. Invasive Adenocarcinoma Invading Pericolonic Fat, Low Power View



7b. Adenocarcinoma Invasion into Submucosa and Muscularis Propria

identified, but a high clinical suspicion remains, endoscopic evaluation may be performed to evaluate for a tumor and tissue biopsy if possible. Choice of endoscopic evaluation includes esophagogastroduodenoscopy, push enteroscopy, device assisted endoscopy, illeocolonoscopy and VCE. Modality should be chosen based on the individual patient's presenting symptoms. For example, VCE should be avoided in patients presenting with signs and symptoms of a bowel obstruction.[20] While several of these modalities were shown to assist in the diagnosis of localized small bowel adenocarcinoma, no single modality proved adequate for definitive diagnosis.[21] If no lesion was identified and there remains a high level of suspicion for a small bowel tumor, further imaging maybe considered with CT enterography, fluorodeoxyglucose-positron emission tomography/CT (FDG PET/CT), or somatostatin receptor-based imaging if there is a concern for a neuroendocrine tumor.[22–24] If workup is nonconclusive, surgical evaluation may be considered.

LITERATURE REVIEW

Adenocarcinoma

Small bowel adenocarcinoma (SBA) is a rare tumor but comprises about 40% of all small bowel malignancies.[25] It is most often diagnosed in the sixth decade of life with a slight male predominance. The duodenum is the most common

location (55%–82%), followed by the jejunum (11%–25%) and ileum (7%–17%).[26]

The carcinogenesis of SBA is poorly understood. Nearly 20% of cases are associated with predisposing diseases such as Crohn's disease, Lynch syndrome, familial adenomatous polyposis (FAP), Peutz–Jeghers syndrome and celiac disease.[27]

Specific genetic mutations have been linked to SBA. The KRAS mutation is one of the more commonly identified mutations and accounts for nearly 50% of cases.[27–31] Mutations to TP53 are also relatively common[27–31] and often confer a poor prognosis.[32] However, they are less commonly found in duodenal lesions and those from mutations related to the deficient DNA mismatch repair abnormality (dMMR phenotype).[31] The TP53 mutation is also more frequently reported in patients with Crohn's disease.[29] The prevalence of APC mutations accounts for a lower percentage of SBA, with a range from 13%-27%,[28–31] in contrast to colorectal cancer where APC mutations make up approximately 80% of cases.[27] APC mutations are also more common in tumors located in the duodenum.[31] Alterations or amplifications of the ERBB2 gene have been reported in 7%-14% of tumors[27–31] and are more frequently found in patients with Lynch syndrome.[29] Other genetic mutations, such as the SMAD4 mutation account for 9%-17% of cases,[28–31] but SMAD4 is associated with Crohn's disease.[33] Less commonly, the BRAF mutation has been seen with a lower frequency of 4%-11%[27–31] and a mutation of BRCA2 has been reported at as low as 5% of SBA.[28] A dMMR phenotype was found with a variable frequency in 5%-35% of cases[26] and is more common in duodenal or jejunal tumors than ileal lesions.[34] SBA with dMMR mutation is associated with a better prognosis.[29]

Lynch syndrome is an autosomal dominant inherited mutation in DNA mismatch repair genes, MLH1 and MSH2, leading to microsatellite instability that most often progresses to malignancy. It is associated with colorectal, endometrial, ovarian, skin, and small bowel malignancies among others. The association with small bowel malignancy is specifically seen in adenocarcinoma. The lifetime risk of Lynch syndrome patients developing SBA remains low, however, and is estimated at around 4%.[35] During routine endoscopy, it is recommended to thoroughly evaluate the entire duodenum and distal ileum to identify these tumors.[36]

Systemic exploration of the entire small bowel with video capsule endoscopy (VCE) is not recommended unless there are suspicious symptoms including anemia, bleeding, or unexplained abdominal pain.[36] Additionally, since SBA can reveal an underlying diagnosis of Lynch syndrome,[37] MMR phenotyping must be carried out for all patients with SBA.[38]

Familial adenomatous polyposis (FAP) is an autosomal dominant inherited mutation of the APC gene resulting in numerous colonic polyps and colorectal carcinoma. Adenocarcinoma of the ampulla of Vater and duodenal adenocarcinoma are the second most common tumor localizations and the main cause of death.[39] It is reported that 4.5% of patients with FAP develop upper gastrointestinal adenocarcinoma with 50% of cases found in the duodenum, 18%, in the ampulla of Vater, 12% in the stomach, 8.5% in the jejunum, and 1.7% in the ileum.[40]

Endoscopic evaluation for screening of the duodenum is recommended in all patients with FAP.[41] Exploration of the rest of the small bowel is only indicated in the setting of a normal esophagogastroduodenoscopy (EGD) and relevant symptoms as previously described.[27]

Peutz-Jeghers syndrome is an autosomal dominant inherited mutation in the tumor suppression gene STK11, with an increased risk of colorectal, stomach, pancreatic, small bowel, and breast cancers. This mutation leads to a lifetime incidence of small bowel adenocarcinoma of 1.7%-13%.[42] Given the rarity of this disease, it is an overall uncommon etiology of SBA.

Juvenile polyposis syndrome is an autosomal dominant inherited syndrome with numerous hamartomatous polyps that can develop into cancer most commonly in the colon and stomach. There have also been reported cases of SBA in these patients related to a mutation in SMAD4.[42]

Crohn's disease is an autoimmune disease characterized by chronic inflammation of potentially any segment of the digestive tract mucosa. It most commonly affects the colon and distal ileum. Inflammation leads to an increased

(continued on page 42)

(continued from page 40)

risk of developing a malignancy. Therefore, in the case of patients with Crohn's disease, SBA is more commonly found in the ileum, as opposed to sporadic SBA as discussed above. Most SBA cases in patients with Crohn's disease are found in the ileum, followed by the jejunum, and duodenum.[43] It also tends to be diagnosed in younger patients.[43] In a large cohort study, the standardized incidence ratio of Crohn's patients developing SBA ranged from 34.9 (95% CI, 11.3–81.5) -46 (95% CI, 12.5–117.8).[44] Patients who have had a small bowel resection or who have been treated with salicylate for a prolonged time are at lower risk of developing SBA.[45] The SBA associated with Crohn's disease is often associated with an aggressive phenotype and frequently metastasizes.[43]

Celiac disease is associated with a higher risk of developing SBA when compared to the general population, however, the reported lifetime risk of patients with celiac disease developing SBA is less than 1%.[42] Patients diagnosed with SBA should be systematically screened for celiac disease, as the presence of SBA can reveal an underlying mild disease.[27]

Given the rarity of SBA and the nonspecific symptom presentation, there is no clear screening guideline for SBA. Often, the most common presenting symptom is abdominal pain, which carries an extremely broad differential diagnosis. Some other symptoms reported are bleeding from the gastrointestinal tract and obstruction. Duodenal SBA is less likely to cause obstruction when compared to jejunal and ileal tumors.[27] According to one study, the diagnosis is most often made by upper endoscopy (28%), followed by surgery (26%), small bowel barium transit (22%), computed tomography (CT) scan (18%), and ultrasound examination (3%).[4,27] While upper endoscopy is helpful for the diagnosis of duodenal lesions, colonoscopies are utilized for diagnosing ileal lesions, and video capsule endoscopy (VCE) and CT enterography (CTE) for jejunal lesions.[43]

Video capsule endoscopy should not be used if there is a suspicion of occlusion or sub-occlusive disease.[43] Video capsule endoscopy may miss lesions of the duodenum and proximal jejunum given the fast transit of gastric contents in those areas.[46]

When compared to VCE, magnetic resonance enterography (MRE) was found to be superior at identifying large polyps.[47] MRE was also found to be more accurate in identifying small bowel tumors when compared to CTE.[48]

Double balloon enteroscopy (DBE) can be used to obtain preoperative histological diagnosis.[49] Device-assisted enteroscopy can be used to remove polyps to prevent malignant transformation, bleeding or obstruction, or tattoo lesions before surgery.[27,50] Despite these newer endoscopic tools, there has been no reported improvement in early diagnosis.[51]

Histologically, SBA is characterized by glandular formation, like colorectal adenocarcinomas. In well-differentiated adenocarcinoma, greater than 95% of the tumor is gland-forming, whereas in moderately differentiated adenocarcinoma between 50-95% is gland-forming. Poorly differentiated adenocarcinoma is mostly solid with less than 50% gland formation.[52]

Duodenal adenocarcinomas distal from the ampulla are broken down into two major histologic phenotypes, intestinal-type and gastric-type. The intestinal type is morphologically like colorectal adenocarcinoma, whereas the gastric type is associated with gastric foveolar metaplasia or Brunner gland hyperplasia. The intestinal type is associated with a longer survival[27] and generally expresses proteins; CDX-2, MUC2 and CD10, while the gastric-type adenocarcinomas express MUC5AC and MUC6.[53] Immunohistochemical staining is not generally needed to differentiate between the types but may be helpful for challenging cases.[27] Tumors that arise near the ampulla have intestinal or pancreaticobiliary differentiation, however, it is often a mix of the two. Immunohistochemical staining can help differentiate the two.[54]

Once diagnosed, the initial workup includes a contrast-enhanced thoracic-abdominal-pelvic CT scan to evaluate local and metastatic extension.[43] Staging is based on standard intestinal TNM and it is recommended to assess a minimum of eight lymph nodes if surgery is necessary.[38] A positron emission tomography (PET) scan is not indicated but may be considered if there is doubt about whether metastases are visualized on CT. Endoscopy and colonoscopy are indicated if there is concern for or

evidence of an underlying genetic predisposition. For duodenal adenocarcinoma, an endoscopic ultrasound should be performed to assess the depth of invasion and to differentiate duodenal lesions from pancreatic, biliary, and ampullary lesions.[27] A CEA and CA 19-9 level should also be obtained. Additionally, anti-transglutaminase antibodies and duodenal biopsies should be performed to detect possible underlying celiac disease. Screening for microsatellite instability or loss of expression of one of the MMR proteins should be performed to screen for Lynch syndrome.[27]

The first-line treatment for localized SBA is resection of the lesion.[55] Patients should be screened for 5 years after a curative resection for clinical exam, imaging, and tumor marker levels.[27,56]

If, however, there is an advanced disease, including an unresectable tumor or metastases, systemic chemotherapy should be administered.[55] The retrospective series reported the best results in terms of response, survival, and toxicity with the use of 5-fluorouracil/leucovorin along with oxaliplatin (FOLFOX).[57–60] There is also some evidence that capecitabine plus oxaliplatin (CAPOX) can be used as a first-line treatment.[61] If patients fail platinum-based therapy, the folinic acid (leucovorin), fluorouracil, and irinotecan (FOLFIRI) regimen has shown some success in a series of patients.[62]

Neuroendocrine tumors

Neuroendocrine neoplasia (NEN) is described as a heterogeneous group of cancers derived from neuroendocrine cells found throughout the body.[63] After the lung, the small bowel is the next most common location of NENs.[64] They can be found throughout the GI tract but are specifically seen in the small intestine (45%), rectum (20%), appendix (16%), colon (11%), stomach (7%), and pancreas (5%-10%).[63, 65] About 40% of all small bowel malignancies are neuroendocrine tumors.[27] Neuroendocrine tumors of the small bowel (SB-NEN) mainly involve the ileum.[8] Approximately 30% of patients with SB-NEN will have metastatic disease at the time of diagnosis[8] most often with spread to the liver.[63]

Risk factors associated with the development of NEN include smoking, family history of cancer, and prior cholecystectomy.[66]

The development of SB-NEN is associated with a mutation of the MutY human homologue gene.[67] The most common genetic predisposition is multiple endocrine neoplasia type 1 (MEN1), making up 5%-10% of these tumors.[8]

Early in the disease process, there are usually few or no symptoms, and the late symptoms are a result of mass effect or liver metastasis.[63,68–70] Of patients with SB-NEN, 15%-20% are without symptoms and lesions are found incidentally.[64] The most common symptom is abdominal pain, but these patients can also present with gastrointestinal bleeding or anemia. The SB-NENs are typically small lesions, but they can cause an extensive fibrotic reaction. This can result in narrowing or twisting of the bowel leading to obstruction and possible mesenteric ischemia. Occasionally, they grow large enough to cause obstruction.[63]

About 10% of patients with metastatic disease develop carcinoid syndrome, especially if the liver is the site of metastases. There are several hormones produced by the NEN cells, including serotonin, neurokinin A, and histamine, but when the disease is localized to the small bowel, the liver can inactivate the hormones. Once the disease metastasizes the hormones can bypass portal circulation and lead to symptomatic carcinoid. The most common symptoms are facial flushing, diarrhea, abdominal cramps, heart valvular disease, telangiectasias, edema, and wheezing.[63] About 20% of patients have cardiac involvement, primarily affecting the right side of the heart leading to valve fibrosis patients with metastatic disease, which is associated with a poor prognosis.[64]

Given the nonspecific presentation of most NEN, laboratory investigation and imaging obtained for the diagnosis will often vary, but both can aid in making the diagnosis. Those who present with carcinoid symptoms will likely undergo biochemical testing first, while those with abdominal pain will begin with imaging.

NENs produce many hormones, as mentioned above, including 5-hydroxyindoleacetic acid (5-HIAA) and chromogranin A (CgA), both of which can be helpful when attempting to diagnose SB-NEN.[71] A 24-hour urine 5-HIAA is highly specific for SB-NEN. Chromogranin A is a sensitive and specific test for NEN, however, renal failure, severe hypertension, vitamin B12 deficiency and proton

pump inhibitor therapy can cause false elevations. Chromogranin A has also been correlated with disease burden survival rates.[63,72]

NENs also produce pancreastatin, and serial pancreastatin levels can be useful to predict and monitor responses to therapy and may be a good alternative to chromogranin A.[72]

Imaging studies can include CT, MRI, and ultrasound. SB-NENs, however, are rarely visualized on CT, but CT can be helpful as it can reveal lymph node and other metastases. CT angiography can sometimes visualize valvular involvement.[63]

Octreotide scans, DBE, and VCE are used as additional modalities with a reported diagnostic yield of 85%, 83%, and 10% respectively.[63] In occult disease, VCE appears to be superior to DBE, but may underestimate the tumor burden.[73] DBE and VCE are most helpful for diagnosing jejunal and ileal SB-NENs.[63] Positron emission tomography scans are useful for detecting small SB-NEN tumors as well as metastases of all sizes, including small lymph node metastases.[74] Diagnosis is sometimes only made after surgical resection of an obstructed bowel. If surgery has not yet been performed, endoscopic guided biopsy is needed for histological confirmation.[63]

To classify the NENs, protein markers, either the Ki67 index or number of mitoses per 10 high power field (HPF) is used. Grade 1 NENs show a Ki67 of less than 3%, or less than 2 mitoses per 10 HPF. Grade 2 NENs have a Ki67 index from 3%-20%, or 2 - 20 mitoses per 10 HPF. Grade 3 NENs have a Ki67 index of greater than 20%, or greater than 20 mitoses per 10 HPF.[63] Grade three lesions are further subclassified into G3 NENs and G3 neuroendocrine carcinomas (NEC) and is based on their differentiation. Grade 3 NENs are well differentiated while G3 NECs are poorly differentiated.[75]

Treatment is challenging due to difficulty in diagnosis and advanced disease at the time of presentation. Management depends on whether the tumor is local or metastatic. However, survival time can be long, even in those with advanced disease.[63] Patients with localized tumors with or without regional mesentery metastasis should undergo curative resection. During surgery, manual palpation of the small bowel is recommended, as it was found to catch up to 70% of lesions missed by imaging, thus laparoscopy is not recommended.[63,75] To prevent locoregional recurrence, an extensive lymphadenectomy is required and removing at least 12 nodes was related to better overall survival.[63] In cases where there is peritoneal involvement leading to peritoneal carcinomatosis (up to 30%), the peritoneal tumors should also be resected given the risk of fatal obstruction.[63] If the primary tumor is in the terminal ileum, a right hemicolectomy is indicated.[76]

Patients with small bowel NENs that have metastasized can still benefit from surgical resection as it has been shown to provide symptomatic relief and increased overall survival but it is rarely curative.[63,77] At the time of surgery in a patient who will be treated with a somatostatin analog (SSA), a prophylactic cholecystectomy should be performed due to the high presence of gallstones in patients on SSAs.[77]

First-line treatment in advanced or metastatic NENs, or the case of carcinoid syndrome, is with somatostatin analogs.[77] Injections of long-acting octreotide LAR or lanreotide are received every four weeks. Short-acting octreotide may be given more frequently to improve symptoms or rescue therapy.[63] Giving long-acting octreotide LAR along with interferon-alpha was shown to be beneficial for inhibiting hormone secretion and proliferation of the NENs.[78]

Everolimus, a rapamycin inhibitor, has been studied for use on advanced NENs. It is only approved for use in progressive non-functional NENs, however, in practice it is commonly used in all patients with progressive disease.[63,79]

Peptide receptor radionuclide therapy (PRRT), including radionuclides such as Yttrium-90 (90Y) and Lutetium-177 (177Lu), can be used in well-differentiated metastatic disease.[63,80]

While cytotoxic chemotherapy is regularly used for pancreatic NENs, it was shown to have an inferior role in SB-NENs. Nonetheless, due to a low adverse effect profile and easy administration, capecitabine and temozolomide are good second and third-line treatments for progressive SB NENs.[63]

In contrast to NENs, neuroendocrine carcinomas (NECs) are extremely rare and carry

(continued on page 46)

(continued from page 44)

a poor prognosis. Therefore, surgical resection is not recommended. Cisplatin or carboplatin along with etoposide are, however, used as first-line treatment. It should be noted though that high-grade (Ki-67 index between 20% and 55%) NECs have shown low response rates to platinum-based chemotherapy.[81]

Lymphoma

The gastrointestinal tract is the most common site for lymphoma second only to the lymph nodes themselves.[13] The small intestine is the second most common gastrointestinal site to be affected by lymphoma.[13,82] There are several types of small bowel lymphoma including diffuse large B cell lymphoma (DLBCL), mucosa-associated lymphoid tissue (MALT) lymphoma, follicular lymphoma, mantle cell lymphoma (MCL), Burkitt lymphoma, and T-cell lymphoma.

Lymphoma makes up to 15%-20% of small intestinal tumors. The most common site is the ileum (60%-65%) followed by jejunum (20%-25%), and duodenum (6%-8%).[13] The age at diagnosis of small intestinal lymphoma is variable depending on the histological subtype and has a male predominance.[13,83] Most often small intestine lymphomas need to be surgically resected for both diagnosis and treatment. In the presence of advanced disease, systemic therapy is often needed.

Diffuse large B cell lymphoma, is the most common intestinal lymphoma[13, 83] and is most often found in the ileocecal region with rare duodenal involvement.[84] Most DLBCLs occur in the sixth decade of life, with a male predominance. They can arise on their own or as a result of a transformation of indolent lymphoma, most prominently MALT, but cases have also been seen with immunoproliferative small intestinal disease (IPSID). De novo DLBCLs are BCL2 and CD10 positive, as opposed to DLBCL originating from MALT which are BCL2 and CD10 negative. Chromosomal rearrangements of the C-myc gene are responsible for 10%-45% of cases.[83] On esophagogastroduodenoscopy (EGD), DLBCL appears as ulcerative or protruded lesions and characteristically can be seen as an auriculate ulcer mound.[84] Biopsy will consist of diffuse proliferation of large b cells and a Ki-67 positivity usually greater than 40%.[84] DLBCL is aggressive, however, it responds well to chemotherapy.[84]

Mucosa-associated lymphoid tissue lymphoma can occur as polyps in the small bowel[83] and can arise in locations throughout the intestines. Often nodular lesions are the predominant feature (58.3%), followed by ulcers (16.7%), flat depression (16.7%), and subepithelial tumors (8.3%).[85] Neoplastic cells are positive for protein CD20, but negative for CD3, CD5, and cyclin D1, differentiating it from other forms of lymphoma. It carries a higher risk of transforming to DLBCL than gastric MALT.[84]

A variant of MALT lymphoma, IPSID, formerly known as alpha chain disease, is caused by infection with *Campylobacter jejuni*.[86] The median age at diagnosis is 20-30.[83] It mainly affects older children and young adults from low socioeconomic status in developing countries. The majority of reported cases are from the Middle East, the Far East, and North and South Africa.[86] It is characterized by mucosal infiltration with plasma cells that secrete immunoglobulins that only have a heavy chain but lack a light chain, and it mainly affects the proximal small bowel.[13,86] The common presenting symptoms are abdominal pain and diarrhea.[86]

Follicular lymphoma of the small bowel is common in the duodenum but can arise in locations throughout the intestines, similar to MALT.[13] It predominantly affects middle-aged women.[83] It is most commonly diagnosed incidentally in patients undergoing EGD for other indications.[84] It is visualized as polyps in the small bowel, typically as small white granules.[83,84] The t(14;18) translocation of the immunoglobulin heavy chain and BCL2 is characteristic in most cases. Follicular lymphoma cells express CD10 and BCL2 in about 90% of cases.[13] Immunostaining is essential for definitive diagnosis and often positive for CD10, BCL2, and BCL6.[84] Notably, follicular lymphoma is negative for cyclin D1 and CD5, differentiating it from MCL.[13]

Mantle cell lymphoma primarily affects individuals over the age of 50. It is most often found in the terminal ileum and jejunum.[13] It occurs as polyps in the small bowel and can present with numerous polyps, also known as multiple lymphomatous polyposis.[83] It should be noted, however, that this feature is also seen with follicular lymphoma and MALT, albeit with much

less frequency.[13] MCL is caused by a rearrangement of the BCL1 locus through a translocation of cyclin D1 and heavy chain immunoglobulin via t(11;14) leading to upregulation of cyclin D1. There have been reported cases of cyclin D1 negative MCL, which instead have upregulation of cyclin D2 and D3.[87] Some cases are CD5-positive.[13,87] Immunostaining is again essential for definitive diagnosis and may be positive for CD5, cyclin D1, and SOX11.[84]

Burkitt lymphoma primarily affects children and is associated with EBV and HIV/AIDS.[13] It occurs as a firm mass most commonly in the ileocecal region.[83]

Histopathologically, about 90% of primary gastrointestinal lymphomas are from B cells, with very few T cell lymphomas and Hodgkin lymphomas.[13] When T cell lymphomas occur in the small bowel, they occur as enteropathy-associated T cell lymphoma (EATL), monomorphic epitheliotropic intestinal T-cell lymphoma, or intestinal T cell lymphoma not otherwise specified.[84]

EATL, formerly known as EATL I, is most commonly located in the jejunum and presents as multiple ulcers, tumors, and strictures. It is most often diagnosed in the sixth decade of life, affecting men and women with similar frequency. Refractory celiac disease that does not improve with a gluten-free diet accounts for 0.5% -1% of cases. EATL is frequently CD30 positive. A reactive inflammatory infiltrate is commonly seen, and necrosis may be present in some cases.[83]

Monomorphic epitheliotropic intestinal T cell lymphoma, formerly EATL II, is usually not associated with celiac disease.[84] It is CD30-negative and has no associated inflammation or necrosis of the cells.[83]

Aggressive t-cell lymphomas that lack the clinical and pathological features of one of the other categories of T cell lymphomas are categorized as T cell lymphoma not otherwise specified.[84]

There are currently no guidelines for the treatment of MALT lymphoma of the small intestine. Localized MALT can be surgically or endoscopically resected or treated with radiation therapy. Advanced disease with lesions in multiple locations throughout the small intestine warrants multi-agent chemotherapy.[13] Helicobacter pylori eradication therapy showed a slower response rate when compared to its use for treatment of gastric MALT.[84]

Clinical presentation small bowel lymphomas are nonspecific and can include abdominal pain, nausea, vomiting, and weight loss. Rarely, it may present as obstruction, intussusception, perforation, or diarrhea.[88]

Radiologic findings of lymphoma in the small intestine are not specific, making it difficult to distinguish from other lesions, and not an appropriate method to determine the subtype. Some common features found in barium studies and CT include polypoid form, infiltrative form, and multiple nodules. IPSID often has a disseminated nodular pattern, causing a mucosal fold irregularity, speculation, and thickening most often in the proximal small bowel. Burkitt lymphoma will usually present with a mass found in the right lower quadrant. EATL usually presents with nodules, ulcers, or strictures.[13]

On VCE small intestinal lymphomas appear as a mass, polyp, or ulcer, indistinguishable from other lesions.[89] Double balloon push enteroscopy can be used to diagnose and biopsy the lesions.[13]

EUS helps diagnose lesions and is superior to CT when it comes to the tumor and node aspects of staging as it can provide details regarding invasion of mucosa, submucosa, muscularis propria, or further that CT cannot provide.[13]

CT of the chest, abdomen, and pelvis is still used to assist in staging. 18F-fluorodeoxyglucose positron emission tomography (FDG-PET) scans have been particularly helpful in staging DLBCL, follicular lymphoma, and MCL, but has not shown benefit for the MALT lymphomas.[13]

In the early stages, IPSID can be treated with antibiotics such as tetracycline or a combination of metronidazole and ampicillin, however, remission within 6-12 months is common. Once it reaches intermediate or advanced stage disease antibiotics, such as tetracycline, along with anthracycline-based chemotherapy are effective. Surgery as a treatment method has a limited role given the diffuse involvement found in most cases, but it is sometimes needed for making an accurate diagnosis.[13]

For low-grade indolent follicular lymphoma, waiting until the patient becomes symptomatic to therapeutically intervene is acceptable.[13,84]

If patients become symptomatic or in cases of advanced disease, surgery, chemotherapy consisting of cyclophosphamide, doxorubicin, vincristine and prednisolone (CHOP), and/or radiation are needed.[13] Rituximab appears to be beneficial, however, its true value has not been confirmed.[13] Recent data suggests that some predictive factors include if the lesion is located through more than half of the circumference of the intestinal lumen and if there are dense granular elevations without distinct boundaries.[90] These factors can influence progression, stage, and possible transformation into DLBCL, and may require surveillance in the short term.[84,90]

MCL has a poor prognosis and has shown poor response to treatment with short remission after chemotherapy. Ideally, patients should receive a stem cell transplant, which is generally preceded by the administration of rituximab and CHOP or rituximab and cyclophosphamide, vincristine, doxorubicin and dexamethasone. Rituximab alone or in combination with a purine nucleoside analog can be used in patients not eligible for stem cell transplant.[13]

Burkitt lymphoma often requires an aggressive approach including high-intensity chemotherapy with agents such as rituximab, cyclophosphamide, vincristine, doxorubicin, methotrexate and cytarabine.[13,83] High-dose chemoradiation and hematopoietic stem cell transplants are also beneficial.[13,91]

There are no guidelines for the management of EATL, and it generally carries a poor prognosis.[13,84] Anthracycline-based chemotherapy is the mainstay treatment, although it has a poor response.[13] Curative or debulking surgery is recommended to remove the gross EATL and to prevent obstruction or perforation in high-risk cases before initiation of chemotherapy if the patient can undergo surgery.[92] It has been reported that surgical resection followed by intense combination of chemotherapy and autologous stem cell transplant can achieve a good response,[93] but EATL remains an aggressive form of lymphoma with a poor prognosis.

Sarcoma/GIST

Gastrointestinal stromal tumors (GISTs) arise from the interstitial cells of Cajal, which are cells that electrically mediate peristalsis throughout the GI tract.[94] GISTs are largely caused by a mutation that leads to the overexpression of the tyrosine kinase receptor KIT.[95] They can also be caused by a mutation to the platelet-derived growth factor receptor-α (PDGFR-α).[96] About 10%-30% will become malignant and can develop into aggressive sarcomas.[94,97]

They are most often diagnosed in the sixth decade of life, with a frequency of about 7-14 cases per million per year.[94,98–100] There is a slight male predominance.[101,102] GISTs most commonly occur in the stomach (51%), followed by the small intestine (36%), colon (7%), rectum (5%), and esophagus (1%).[98]

Presenting symptoms are nonspecific and can include melena, hematemesis, abdominal pain, abdominal distension.[94,103] It is reported that a significant number of patients are asymptomatic, and in those patients the GIST is often found incidentally either after surgery for other reasons or postmortem on endoscopy.[94,99]

Gastrointestinal stromal tumors are usually detected as subepithelial lesions (SEL) on endoscopy, sometimes incidentally.[94] Numerous types of lesions, however, can present as SLEs including leiomyomas, schwannomas, lipomas, gastrointestinal tract compression, varices, and an ectopic pancreas, among other lesions.[104] SELs are not frequently biopsied using regular endoscopic forceps biopsy, as it cannot reach the tumor beyond the overlying mucosa and submucosa.[94,105] This makes GISTs hard to histologically diagnose as the tumor cells may be covered by normal mucosa. Additionally, while jumbo biopsy, which uses a forceps able to obtain larger tissue samples than a regular forceps, or bite-on-bite biopsy, which is when the endoscopist takes multiple sequential biopsies from the same location, may sound promising, the diagnostic yield was found to be relatively weak, ranging from 17%-59%.[106,107] There was also an increased risk for major bleed requiring hemostasis with jumbo biopsy.[107] Therefore EUS-guided fine needle aspiration is key for allowing a safe and effective method of biopsy.[104,108,109] It is also important for earlier and more accurate histological identification of the lesions, with a success rate ranging from 62%-93.4%.[94,110] On EUS a GIST will appear as a hypoechoic solid mass but

(continued on page 50)

(continued from page 48)

cannot alone be used to diagnose a GIST.[94] A fine needle aspiration is technically difficult on SELs less than 1 cm and is therefore only recommended for lesions larger than 1cm.[94,111] Lesions less than 1cm are recommended to undergo periodic EUS follow-ups every 6 months to 1 year.[94]

Definitive diagnosis relies on immunohistochemical staining. A diagnosis of GIST can be made if the cells are positive for KIT, CD34, gastrointestinal stromal tumor 1 (DOG1), and/or PDGFR-α.[112] Typically, GISTs will be KIT or CD34-positive.[94]

The standard treatment of localized GISTs without metastasis is surgical resection, and it is the only potential treatment for permanent cure. Despite complete resection, recurrence occurs in 40%-50% of patients.[94,112]

If the GIST has already developed metastases, is unresectable, or is recurrent, it is treated with a tyrosine kinase inhibitor.[113] Tyrosine kinase inhibitors often do not completely cure the disease, making early detection and early surgical resection of utmost importance.[94,104]

Even for those who underwent complete surgical resection, an abdominal CT with contrast is recommended for surveillance to detect possible local recurrence, liver metastases, and peritoneal dissemination. National Comprehensive Cancer Network (NCCN) guidelines recommend a CT every 3-6 months for the first 3-5 years post-surgery, with an annual CT in the following years. The European Society for Clinical Oncology (ESMO) guidelines recommend high-risk patients get a CT every 3-6 months while on adjuvant therapy, and then every 3 months once adjuvant therapy has been completed. Then it is recommended annually for the next 5 years. For low-risk patients, the recommendation is for CT or MRI every 6-12 months for 5 years.[114] Few recurrences occurred after 10 years of follow up,[114] and although the exact duration of surveillance is not defined it is still recommended to continue observation beyond 10 years.[94]

CONCLUSION

Small bowel malignancies are uncommon with increasing incidence in the last decade. The main histological types are adenocarcinomas, neuroendocrine tumors, stromal tumors/sarcomas and lymphomas. The clinical presentation is often nonspecific, making it a challenging diagnosis that results in delayed treatment. In our series, presenting symptoms among all patients were consistent with non-specific gastrointestinal symptoms, an unremarkable physical examination and normal laboratory investigation. While advanced endoscopic techniques have improved our ability to identify these uncommon tumors, in our case series, definitive diagnosis was delayed up to six months from the initial presentation due to the unclear etiology and treatments varied based on histologic subtype. Initial testing strategy in patients suspected of having a small bowel tumor should begin with non-invasive imaging and subsequently endoscopic evaluation, choice of procedure chosen based on the patient's presenting symptoms. Larger and more powerful studies are needed to provide further insight on a more targeted diagnostic and treatment approach for improved clinical outcomes. ■

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016 Jan 7;66(1):7–30.
2. Jasti R, Carucci LR. Small Bowel Neoplasms: A Pictorial Review. Radiographics. 2020;40(4):1020–38.
3. Small Intestine Cancer — Cancer Stat Facts [Internet]. [cited 2024 Oct 22]. Available from: https://seer.cancer.gov/statfacts/html/smint.html
4. Dabaja BS, Suki D, Pro B, et al. Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients. Cancer. 2004 Aug 1;101(3):518–26.
5. Lepage C, Bouvier AM, Manfredi S, et al. Incidence and Management of Primary Malignant Small Bowel Cancers: A Well-defined French Population Study. Am J Gastroenterol. 2006 Dec;101(12):2826–32.
6. Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg. 2009 Jan;249(1):63–71.
7. Neugut AI, Jacobson JS, Suh S, et al. The epidemiology of cancer of the small bowel. Cancer Epidemiol Biomarkers Prev. 1998 Mar;7(3):243–51.
8. Barsouk A, Rawla P, Barsouk A, et al. Epidemiology of Cancers of the Small Intestine: Trends, Risk Factors, and Prevention. Med Sci (Basel). 2019 Mar 17;7(3).
9. Ojha A, Zacherl J, Scheuba C, et al. Primary Small Bowel Malignancies. J Clin Gastroenterol. 2000 Apr;30(3):289–93.
10. Schwartz GD, Barkin JS. Small bowel tumors. Gastrointest Endosc Clin N Am. 2006 Apr;16(2):267–75.
11. Ciresi DL, Scholten DJ. The continuing clinical dilemma of primary tumors of the small intestine. Am Surg. 1995 Aug;61(8):698–702; discussion 702-3.
12. Slomovich S, Gress F, Steiner A. A Small Bowel Stricture Revealing Intestinal Lymphoma: A Rare Presentation. The American Journal of Gastroenterology The American College of Gastroenterology 2022 Annual Scientific Meeting: Oct 24, 2022, Charlotte, North Carolina. 2022;
13. Ghimire P, Wu G, Zhu L. Primary gastrointestinal lymphoma. World J Gastroenterol. 2011;17(6):697–707.
14. Yamamoto S, Nakase H, Yamashita K, et al. Gastrointestinal follicular lymphoma: review of the literature. J Gastroenterol. 2010 Apr;45(4):370–88.
15. Shia J, Teruya-Feldstein J, Pan D, et al. Primary follicular lymphoma of the

(continued on page 52)

(continued from page 50)

gastrointestinal tract: a clinical and pathologic study of 26 cases. Am J Surg Pathol. 2002 Feb;26(2):216–24.
16. Matsumoto H, Haruma K, Akiyama T. An unusual case of multiple small ulcerations throughout the GI tract. Gastroenterology. 2011 Nov;141(5):e11-2.
17. Puli SR, Kalva N, Bechtold ML, et al. Diagnostic accuracy of endoscopic ultrasound in pancreatic neuroendocrine tumors: A systematic review and meta analysis. World J Gastroenterol. 2013;19(23):3678.
18. Kucharzik T, Wittig BM, Helwig U, et al. Use of Intestinal Ultrasound to Monitor Crohn's Disease Activity. Clin Gastroenterol Hepatol. 2017 Apr;15(4):535-542.e2.
19. Pruijt MJ, de Voogd FAE, Montazeri NSM, et al. Diagnostic Accuracy of Intestinal Ultrasound in the Detection of Intra-Abdominal Complications in Crohn's Disease: A Systematic Review and Meta-Analysis. J Crohns Colitis. 2024 Jun 3;18(6):958–72.
20. Cheifetz AS, Sachar DB, Lewis BS. Small bowel obstruction—indication or contraindication for capsule endoscopy. Gastrointest Endosc. 2004 Apr 1;59(5):102.
21. Colina A, Hwang H, Wang H, et al. Natural history and prognostic factors for localised small bowel adenocarcinoma. ESMO Open. 2020 Nov;5(6):e000960.
22. Hakim FA, Alexander JA, Huprich JE, et al. CT-enterography may identify small bowel tumors not detected by capsule endoscopy: eight years experience at Mayo Clinic Rochester. Dig Dis Sci. 2011 Oct;56(10):2914–9.
23. Cronin CG, Scott J, Kambadakone A, et al. Utility of positron emission tomography/CT in the evaluation of small bowel pathology. Br J Radiol. 2012 Sep;85(1017):1211–21.
24. Maxwell JE, Howe JR. Imaging in neuroendocrine tumors: an update for the clinician. Int J Endocr Oncol. 2015;2(2):159–68.
25. Bouvier AM, Robaszkiewicz M, Jooste V, et al. Trends in incidence of small bowel cancer according to histology: a population-based study. J Gastroenterol. 2020 Feb 19;55(2):181–8.
26. Aparicio T, Zaanan A, Svrcek M, et al. Small bowel adenocarcinoma: Epidemiology, risk factors, diagnosis and treatment. Digestive and Liver Disease. 2014 Feb;46(2):97–104.
27. Aparicio T, Pachev A, Laurent-Puig P, et al. Epidemiology, Risk Factors and Diagnosis of Small Bowel Adenocarcinoma. Cancers (Basel). 2022 May 2;14(9):2268.
28. Hänninen UA, Katainen R, Tanskanen T, et al. Exome-wide somatic mutation characterization of small bowel adenocarcinoma. PLoS Genet. 2018 Mar 9;14(3):e1007200.
29. Aparicio T, Svrcek M, Henriques J, et al. Panel gene profiling of small bowel adenocarcinoma: Results from the NADEGE prospective cohort. Int J Cancer. 2021 Apr 4;148(7):1731–42.
30. Schrock AB, Devoe CE, McWilliams R, et al. Genomic Profiling of Small-Bowel Adenocarcinoma. JAMA Oncol. 2017 Nov 1;3(11):1546.
31. Laforest A, Aparicio T, Zaanan A, et al. ERBB2 gene as a potential therapeutic target in small bowel adenocarcinoma. Eur J Cancer. 2014 Jul;50(10):1740–6.
32. Alvi MA, McArt DG, Kelly P, et al. Comprehensive molecular pathology analysis of small bowel adenocarcinoma reveals novel targets with potential for clinical utility. Oncotarget. 2015 Aug 28;6(25):20863–74.
33. Liao X, Li G, McBride R, et al. Clinicopathological and Molecular Characterisation of Crohn's Disease-associated Small Bowel Adenocarcinomas. J Crohns Colitis. 2020 Mar 13;14(3):287–94.
34. Aparicio T, Svrcek M, Zaanan A, et al. Small bowel adenocarcinoma phenotyping, a clinicobiological prognostic study. Br J Cancer. 2013 Dec 5;109(12):3057–66.
35. Koornstra JJ, Kleibeuker JH, Vasen HF. Small-bowel cancer in Lynch syndrome: is it time for surveillance? Lancet Oncol. 2008 Sep;9(9):901–5.
36. Vasen HFA, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut. 2013 Jun;62(6):812–23.
37. Babba T, Schischmanoff O, Lagorce C, et al. Small bowel carcinoma revealing HNPCC syndrome. Gastroenterol Clin Biol. 2010 Apr;34(4–5):325–8.
38. Benson AB, Venook AP, Al-Hawary MM, et al. Small Bowel Adenocarcinoma, Version 1.2020, NCCN Clinical Practice Guidelines in Oncology. Journal of the National Comprehensive Cancer Network. 2019 Sep;17(9):1109–33.
39. Gallagher MC, Phillips RKS, Bulow S. Surveillance and management of upper gastrointestinal disease in Familial Adenomatous Polyposis. Fam Cancer. 2006 Sep;5(3):263–73.
40. JAGELMAN D, DeCosse J, Bussey H. UPPER GASTROINTESTINAL CANCER IN FAMILIAL ADENOMATOUS POLYPOSIS. The Lancet. 1988 May;331(8595):1149–51.
41. Bulow S, Björk J, Christensen I, et al. Duodenal adenomatosis in familial adenomatous polyposis. Gut. 2004 Mar 1;53(3):381–6.
42. Shenoy S. Genetic risks and familial associations of small bowel carcinoma. World J Gastrointest Oncol. 2016;8(6):509.
43. Aparicio T, Henriques J, Manfredi S, et al. Small bowel adenocarcinoma: Results from a nationwide prospective ARCAD-NADEGE cohort study of 347 patients. Int J Cancer. 2020 Aug 15;147(4):967–77.
44. Elriz K, Carrat F, Carbonnel F, et al. Incidence, Presentation, and Prognosis of Small Bowel Adenocarcinoma in Patients with Small Bowel Crohn's Disease. Inflamm Bowel Dis. 2013 May;1.
45. Piton G, Cosnes J, Monnet E, et al. Risk Factors Associated With Small Bowel Adenocarcinoma in Crohn's Disease: A CaseControl Study. Am J Gastroenterol. 2008 Jul;103(7):1730–6.
46. Cheung DY, Kim JS, Shim KN, et al. The Usefulness of Capsule Endoscopy for Small Bowel Tumors. Clin Endosc. 2016 Jan 30;49(1):21–5.
47. Gupta A, Postgate AJ, Burling D, et al. A Prospective Study of MR Enterography Versus Capsule Endoscopy for the Surveillance of Adult Patients With Peutz-Jeghers Syndrome. American Journal of Roentgenology. 2010 Jul;195(1):108–16.
48. Masselli G, Di Tola M, Casciani E, et al. Diagnosis of Small-Bowel Diseases: Prospective Comparison of Multi–Detector Row CT Enterography with MR Enterography. Radiology. 2016 May;279(2):420–31.
49. Hadithi M, Heine GDN, Jacobs MAJM, et al. A Prospective Study Comparing Video Capsule Endoscopy with Double-Balloon Enteroscopy in Patients with Obscure Gastrointestinal Bleeding. Am J Gastroenterol. 2006 Jan;101(1):52–7.
50. Kim ER. Roles of Capsule Endoscopy and Device-Assisted Enteroscopy in the Diagnosis and Treatment of Small-Bowel Tumors. Clin Endosc. 2020 Jul 30;53(4):410–6.
51. Legué LM, Bernards N, Gerritse SL, et al. Trends in incidence, treatment and survival of small bowel adenocarcinomas between 1999 and 2013: a population-based study in The Netherlands. Acta Oncol (Madr). 2016 Oct 2;55(9–10):1183–9.
52. Fleming M, Ravula S, Tatishchev SF, et al. Colorectal carcinoma: Pathologic aspects. J Gastrointest Oncol. 2012 Sep;3(3):153–73.
53. Ushiku T, Arnason T, Fukayama M, et al. Extra-ampullary Duodenal Adenocarcinoma. American Journal of Surgical Pathology. 2014 Nov;38(11):1484–93.
54. Perkins G, Svrcek M, Bouchet-Doumenq C, et al. Can we classify ampullary tumours better? Clinical, pathological and molecular features. Results of an AGEO study. Br J Cancer. 2019 Apr 6;120(7):697–702.
55. Puccini A, Battaglin F, Lenz HJ. Management of Advanced Small Bowel Cancer. Curr Treat Options Oncol. 2018 Dec 5;19(12):69.
56. Locher C, Batumona B, Afchain P, et al. Small bowel adenocarcinoma: French intergroup clinical practice guidelines for diagnosis, treatments and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO). Digestive and Liver Disease. 2018 Jan;50(1):15–9.
57. Zaanan A, Costes L, Gauthier M, et al. Chemotherapy of advanced small-bowel adenocarcinoma: a multicenter AGEO study. Annals of Oncology. 2010 Sep;21(9):1786–93.
58. Locher C, Malka D, Boige V, et al. Combination chemotherapy in advanced small bowel adenocarcinoma. Oncology. 2005;69(4):290–4.
59. Overman MJ, Kopetz S, Wen S, et al. Chemotherapy with 5-fluorouracil and a platinum compound improves outcomes in metastatic small bowel adenocarcinoma. Cancer. 2008 Oct 15;113(8):2038–45.
60. Tsushima T, Taguri M, Honma Y, et al. Multicenter retrospective study of 132 patients with unresectable small bowel adenocarcinoma treated with chemotherapy. Oncologist. 2012;17(9):1163–70.
61. Overman MJ, Varadhachary GR, Kopetz S, et al. Phase II study of capecitabine and oxaliplatin for advanced adenocarcinoma of the small bowel and ampulla of Vater. J Clin Oncol. 2009 Jun 1;27(16):2598–603.
62. Zaanan A, Gauthier M, Malka D, et al. Second-line chemotherapy with fluorouracil, leucovorin, and irinotecan (FOLFIRI regimen) in patients with advanced small bowel adenocarcinoma after failure of first-line platinum-based chemotherapy: a multicenter AGEO study. Cancer. 2011 Apr 1;117(7):1422–8.
63. Gonzáles-Yovera JG, Roseboom PJ, Concepción-Zavaleta M, et al. Diagnosis and management of small bowel neuroendocrine tumors: A state-of-the-art. World J Methodol. 2022 Sep 20;12(5):381–91.
64. Modlin IM, Shapiro MD, Kidd M. Siegfried Oberndorfer: origins and perspectives of carcinoid tumors. Hum Pathol. 2004 Dec;35(12):1440–51.
65. Ahmed M. Gastrointestinal neuroendocrine tumors in 2020. World J Gastrointest Oncol. 2020 Aug 15;12(8):791–807.
66. Rinzivillo M, Capurso G, Campana D, et al. Risk and Protective Factors for Small Intestine Neuroendocrine Tumors: A Prospective Case-Control Study. Neuroendocrinology. 2016;103(5):531–7.
67. Dumanski JP, Rasi C, Björklund P, et al. A MUTYH germline mutation is associated with small intestinal neuroendocrine tumors. Endocr Relat Cancer. 2017 Aug;24(8):427–43.
68. Zhang M, Zhao P, Shi X, et al. Clinicopathological features and prognosis of gastroenteropancreatic neuroendocrine neoplasms in a Chinese population: a large, retrospective single-centre study. BMC Endocr Disord. 2017 Jul 13;17(1):39.

(continued on page 54)

(continued from page 52)

69. Kaltsas GA, Besser GM, Grossman AB. The diagnosis and medical management of advanced neuroendocrine tumors. Endocr Rev. 2004 Jun;25(3):458–511.
70. Modlin IM, Kidd M, Latich I, et al. Current status of gastrointestinal carcinoids. Gastroenterology. 2005 May;128(6):1717–51.
71. Canakis A, Lee LS. Current updates and future directions in diagnosis and management of gastroenteropancreatic neuroendocrine neoplasms. World J Gastrointest Endosc. 2022 May 16;14(5):267–90.
72. Tran CG, Sherman SK, Howe JR. Small Bowel Neuroendocrine Tumors. Curr Probl Surg. 2020 Dec;57(12):100823.
73. Ethun CG, Postlewait LM, Baptiste GG, et al. Small bowel neuroendocrine tumors: A critical analysis of diagnostic work-up and operative approach. J Surg Oncol. 2016 Nov;114(6):671–6.
74. Clift AK, Kidd M, Bodei L, et al. Neuroendocrine Neoplasms of the Small Bowel and Pancreas. Neuroendocrinology. 2020;110(6):444–76.
75. Scott AT, Howe JR. Management of Small Bowel Neuroendocrine Tumors. J Oncol Pract. 2018 Aug;14(8):471–82.
76. Selberherr A, Niederle MB, Niederle B. Surgical Treatment of Small Intestinal Neuroendocrine Tumors G1/G2. Visc Med. 2017 Oct;33(5):340–3.
77. Larouche V, Akirov A, Alshehri S, et al. Management of Small Bowel Neuroendocrine Tumors. Cancers (Basel). 2019 Sep 18;11(9):1395.
78. Dai M, Mullins CS, Lu L, et al. Recent advances in diagnosis and treatment of gastroenteropancreatic neuroendocrine neoplasms. World J Gastrointest Surg. 2022 May 27;14(5):383–96.
79. Strosberg JR, Halfdanarson TR, Bellizzi AM, et al. The North American Neuroendocrine Tumor Society Consensus Guidelines for Surveillance and Medical Management of Midgut Neuroendocrine Tumors. Pancreas. 2017 Jul;46(6):707–14.
80. Strosberg J, El-Haddad G, Wolin E, et al. Phase 3 Trial of 177 Lu-Dotatate for Midgut Neuroendocrine Tumors. New England Journal of Medicine. 2017 Jan 12;376(2):125–35.
81. Ilett EE, Langer SW, Olsen IH, et al. Neuroendocrine Carcinomas of the Gastroenteropancreatic System: A Comprehensive Review. Diagnostics (Basel). 2015 Apr 8;5(2):119–76.
82. Herrmann R, Panahon AM, Barcos MP, et al. Gastrointestinal involvement in non-Hodgkin's lymphoma. Cancer. 1980 Jul 1;46(1):215–22.
83. Olszewska-Szopa M, Wróbel T. Gastrointestinal non-Hodgkin lymphomas. Advances in Clinical and Experimental Medicine. 2019 Aug 13;28(8):1119–24.
84. Iwamuro M, Tanaka T, Okada H. Review of lymphoma in the duodenum: An update of diagnosis and management. World J Gastroenterol. 2023 Mar 28;29(12):1852–62.
85. Na HK, Won SH, Ahn JY, et al. Clinical course of duodenal mucosa-associated lymphoid tissue lymphoma: Comparison with gastric mucosa-associated lymphoid tissue lymphoma. J Gastroenterol Hepatol. 2021 Feb 21;36(2):406–12.
86. Al-Saleem T, Al-Mondhiry H. Immunoproliferative small intestinal disease (IPSID): a model for mature B-cell neoplasms. Blood. 2005 Mar 15;105(6):2274–80.
87. Fu K, Weisenburger DD, Greiner TC, et al. Cyclin D1-negative mantle cell lymphoma: a clinicopathologic study based on gene expression profiling. Blood. 2005 Dec 15;106(13):4315–21.
88. Li B, Shi Y kai, He X hui, et al. Primary non-Hodgkin lymphomas in the small and large intestine: clinicopathological characteristics and management of 40 patients. Int J Hematol. 2008 May 15;87(4):375–81.
89. Pennazio M. Small-intestinal pathology on capsule endoscopy: spectrum of vascular lesions. Endoscopy. 2005 Sep;37(9):864–9.
90. Sumioka A, Oka S, Hirata I, et al. Predictive factors for the progression of primary localized stage small-bowel follicular lymphoma. J Gastroenterol. 2022 Sep 13;57(9):667–75.
91. Song KW, Barnett MJ, Gascoyne RD, et al. Haematopoietic stem cell transplantation as primary therapy of sporadic adult Burkitt lymphoma*. Br J Haematol. 2006 Jun 16;133(6):634–7.
92. Babel N, Paragi P, Chamberlain RS. Management of Enteropathy-Associated T-Cell Lymphoma: An Algorithmic Approach. Case Rep Oncol. 2009 Feb 28;2(1):36–43.
93. Bishton MJ, Haynes AP. Combination chemotherapy followed by autologous stem cell transplant for enteropathy-associated T cell lymphoma. Br J Haematol. 2007 Jan;136(1):111–3.
94. Akahoshi K, Oya M, Koga T, et al. Current clinical management of gastrointestinal stromal tumor. World J Gastroenterol. 2018 Jul 14;24(26):2806–17.
95. Hirota S, Isozaki K, Moriyama Y, et al. Gain-of-function mutations of c-kit in human gastrointestinal stromal tumors. Science. 1998 Jan 23;279(5350):577–80.
96. Heinrich MC, Corless CL, Duensing A, et al. PDGFRA activating mutations in gastrointestinal stromal tumors. Science. 2003 Jan 31;299(5607):708–10.
97. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol. 2008 Oct;39(10):1411–9.
98. Tran T, Davila JA, El-Serag HB. The Epidemiology of Malignant Gastrointestinal Stromal Tumors: An Analysis of 1,458 Cases from 1992 to 2000. Am J Gastroenterol. 2005 Jan;100(1):162–8.
99. Nilsson B, Bümming P, Meis-Kindblom JM, et al. Gastrointestinal stromal tumors: The incidence, prevalence, clinical course, and prognostication in the preimatinib mesylate era. Cancer. 2005 Feb 15;103(4):821–9.
100. Tzen CY, Wang JH, Huang YJ, et al. Incidence of Gastrointestinal Stromal Tumor: A Retrospective Study Based on Immunohistochemical and Mutational Analyses. Dig Dis Sci. 2007 Mar 26;52(3):792–7.
101. Miettinen M, Lasota J. Gastrointestinal stromal tumors: review on morphology, molecular pathology, prognosis, and differential diagnosis. Arch Pathol Lab Med. 2006 Oct;130(10):1466–78.
102. Miettinen M, Sobin LH, Lasota J. Gastrointestinal Stromal Tumors of the Stomach. Am J Surg Pathol. 2005 Jan;29(1):52–68.
103. Joensuu H, Hohenberger P, Corless CL. Gastrointestinal stromal tumour. The Lancet. 2013 Sep;382(9896):973–83.
104. Akahoshi K, Oya M. Gastrointestinal stromal tumor of the stomach: How to manage? World J Gastrointest Endosc. 2010 Aug 16;2(8):271–7.
105. Kaneko E, Kumagai J, Honda N, et al. Evaluation of the New Giant-biopsy Forceps in the Diagnosis of Mucosal and Submucosal Gastric Lesions. Endoscopy. 1983 Sep 17;15(05):322–6.
106. Cantor MJ, Davila RE, Faigel DO. Yield of tissue sampling for subepithelial lesions evaluated by EUS: a comparison between forceps biopsies and endoscopic submucosal resection. Gastrointest Endosc. 2006 Jul;64(1):29–34.
107. Buscaglia JM, Nagula S, Jayaraman V, et al. Diagnostic yield and safety of jumbo biopsy forceps in patients with subepithelial lesions of the upper and lower GI tract. Gastrointest Endosc. 2012 Jun;75(6):1147–52.
108. Sepe PS, Brugge WR. A guide for the diagnosis and management of gastrointestinal stromal cell tumors. Nat Rev Gastroenterol Hepatol. 2009 Jun;6(6):363–71.
109. Mullady DK, Tan BR. A Multidisciplinary Approach to the Diagnosis and Treatment of Gastrointestinal Stromal Tumor. J Clin Gastroenterol. 2013 Aug;47(7):578–85.
110. Larghi A, Fuccio L, Chiarello G, et al. Fine-needle tissue acquisition from subepithelial lesions using a forward-viewing linear echoendoscope. Endoscopy. 2014 Jan;46(1):39–45.
111. Akahoshi K, Oya M, Koga T, et al. Clinical Usefulness of Endoscopic Ultrasound-Guided Fine Needle Aspiration for Gastric Subepithelial Lesions Smaller than 2 cm. Journal of Gastrointestinal and Liver Diseases. 2014 Dec 1;23(4):405–12.
112. Nishida T, Blay JY, Hirota S, et al. The standard diagnosis, treatment, and follow-up of gastrointestinal stromal tumors based on guidelines. Gastric Cancer. 2016 Jan;19(1):3–14.
113. ESMO/European Sarcoma Network Working Group. Gastrointestinal stromal tumours: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014 Sep;25 Suppl 3:iii21-6.
114. Joensuu H, Martin-Broto J, Nishida T, et al. Follow-up strategies for patients with gastrointestinal stromal tumour treated with or without adjuvant imatinib after surgery. Eur J Cancer. 2015 Aug;51(12):1611–7.

Answers to this month's crossword puzzle: