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CASE REPORT

Gastric Gastrointestinal Stromal Tumors (GIST): a Case Series and Current State of the Art in the Workup and Treatment of This Rare Disease

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Background

While the annual incidence of gastrointestinal stromal tumor (GIST) is estimated at only 10–20 per million, it is the most common form of mesenchymal neoplasm of gastrointestinal (GI) tract [1, 2]. Although the majority of GISTs occur in the stomach (60–70%), they can arise anywhere along the GI tract, including the esophagus, small intestine, and colon, as well as in extravisceral locations [3]. In past medical literature, the distinction between GISTs and other non-epithelial tumors of the GI tract had been overlooked; an omission that has since become highly clinically significant.

Unlike leiomyoma's, which are benign and derive from smooth muscle, GISTs possess the potential for malignancy and are believed to develop from the pacemaker cells of the intestine, otherwise known as the interstitial cells of Cajal [4]. It is essential to differentiate the two types of intramural lesions in order to avoid unnecessary invasive treatments. The

Research Key Highlights
- Gastrointestinal stromal tumors (GISTs) are uncommon intramural tumors of the GI tract. They are most often seen in the stomach and arise from the muscular layers of the visceral wall.
- The clinical manifestations of GISTs vary depending on the tumor size and location, but are often asymptomatic.
- Advances in endosonography (EUS) and immunohistochemical staining can distinguish these lesions from other intramural and GI tract tumors and are an essential part of the diagnostic and staging workup.
- The advent of EUS-guided fine needle biopsy (FNB) allows for large core tissue acquisition. This has replaced FNA and allowed for histologic analysis of large specimens, increased IHC confirmation, and personalized medicine.
- Treatment involves surgical, endoscopic or hybrid endoscopic-laparoscopic resection. Imatinib may be given, and lesions less than 2 cm may be observed.
- The cases presented in this report represent pathology-confirmed GISTs diagnosed at a large volume, community, tertiary referral GI oncology program during July 2012 through May 2016. Follow-ups for each patient have discovered no recurrences to date.

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reported incidence of GIST has increased due to the discovery of submucosal lesions with increased use of endoscopy. Often these are incidental findings, with most lesions being 2 cm or less. Smaller lesions may not be well demonstrated on cross-sectional imaging such as CT or MRI. Because intramural tumors of the GI tract may present inconspicuously upon standard endoscopy, a confirmed diagnosis of GIST is reliant upon both endoscopic ultrasound evaluation (EUS) and pathology with immunohistochemistry techniques that detect a mutation in the proto-oncogene c-KIT (CD-117), a growth factor receptor tyrosine kinase [5]. DOG1, a cell surface protein, is expressed strongly on the cell surface of GISTs and is rarely expressed in other soft tissue tumors. Figures 1, 2, and 3 show H&E stained slides, DOG-1, and c-KIT reactivity as seen in cross-sectioned GIST. While surgical or endoscopic resection remains the first-line treatment for GISTs, the development of a pharmaceutical target for c-KIT (imatinib [Gleevec]) has markedly improved outcomes in advanced GISTs when used as an adjuvant or neoadjuvant therapy [6]. Approximately 5% of GISTs lack immunoreactivity to c-KIT, in which case mutations in platelet derived growth factor receptor alpha (PDGFR-α) are frequently detected [7].

The use of endoscopic ultrasound and EUS-guided fine needle aspiration biopsy (EUS-FNAB) was accepted as the best method to identify and diagnose lesions of the gastrointestinal tract. Recently, there have been major advancements in EUS needle technology allowing for CORE needles to obtain large histologic samples. The term "FNB" or fine needle biopsy refers to the ability of these newer needles to obtain histologic samples, which can then be placed directly in formalin similar to forceps or laparoscopic biopsies (opposed to cells and cell block which was the limitation of FNA) [8]. Cross-sectional imaging with CT or MRI allows for a global picture of the anatomy, but cannot distinguish the wall layers of the intestine with significant accuracy to distinguish the type of GI tract tumor. Endoscopic ultrasound allows for the utilization of high definition ultrasound probes, which can then distinguish the wall layers of hollow viscera. Adenocarcinomas, the most common type of malignancy of the esophagus, stomach, and colon, are readily identified on standard endoscopy because they grow from the inner mucosal layer. However, EUS allows for imaging and locoregional T and N staging by identifying layer of origin, size, and depth of the lesion, and local lymph node involvement. In the case of the stomach, there are five wall layers. From inner to outer layer: mucosa, muscularis mucosae, submucosa, muscularis propria, and serosa are readily identified via high-frequency ultrasound imaging generated by EUS. Different layers have different precursor cells which give rise to different tumors. For example, carcinoid tumors rise from the third layer. Upon EUS, GISTs are generally located in the fourth echo-poor layer (muscularis propria) and rarely in the second echo-poor layer (muscularis mucosae) and malignancy is more likely in larger tumors (> 5 cm) with irregular borders [9]. Figures 4 and 5 show the mass and fourth layer as seen by CT imaging and by EUS, respectively.

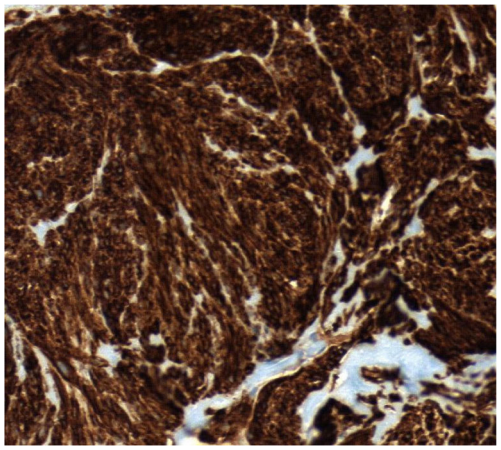

Fig. 2 DOG-1 cross-sectioned GIST

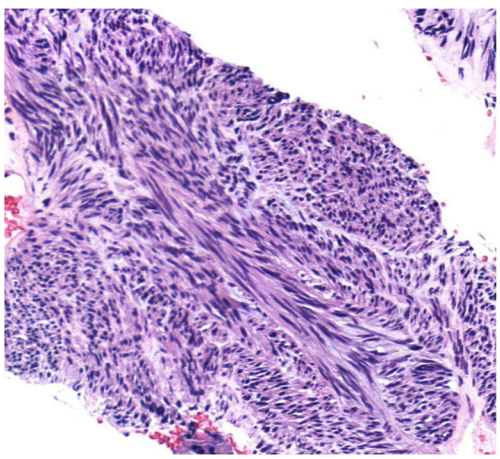

Fig. 1 H&E stain of cross-sectioned GIST

Fig. 3 Photomicrograph of cross-sectioned GIST stained for c-KIT (CD-117) reactivity

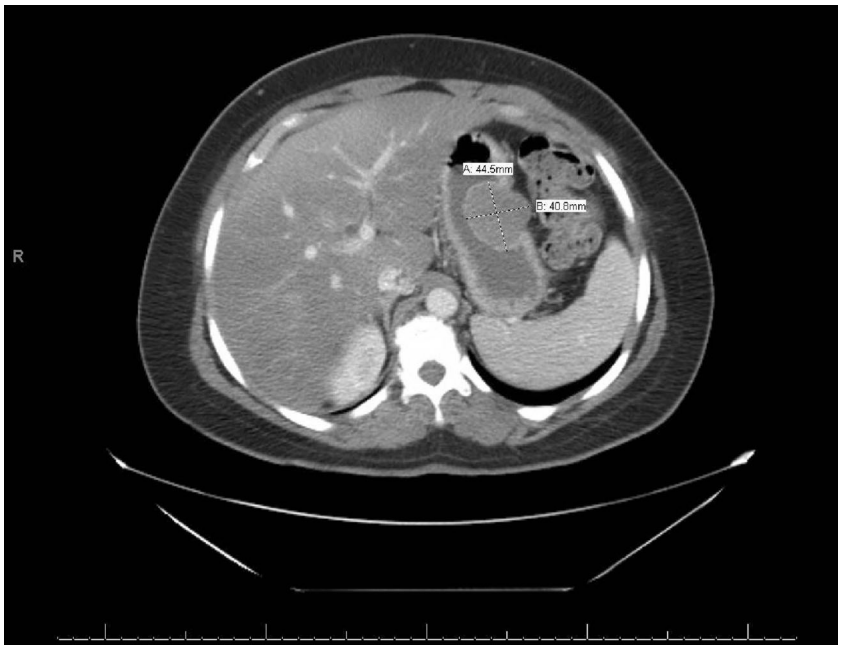

Fig. 4 Mass as seen by CT abdomen with contrast

Although some EUS findings, such as heterogeneous echo, cystic spaces, and irregular extra-luminal borders, can be used as indicators of malignancy, there are limits to imaging diagnosis predictions [8]. While EUS allows for extremely detailed imaging which can distinguish which layer the tumor originates there by distinguishing it from other types of GI tract tumors, more than one type of tumor can originate from the muscular layer of the GI tract. Leiomyoma and GIST are the most common. EUS, even in the best of hands, may not readily distinguish between leiomyoma and GIST. These lesions have very different clinical implications and treatments. Leiomyoma are benign and do not require treatment. In addition to imaging, EUS, when combined with FNB, allows for tissue collection. Cytology may be collected by fine needle aspiration (FNA). More recently, fine need biopsy (EUS-FNB) allows for the collection of large core histologic specimens to aid in diagnosis by procuring tissue for immunohistochemistry testing including DOG-1 and c-Kit (CD117) testing. EUS-FNB is a highly reliable method of diagnosis for large and small GISTs [9]. Obtaining immunohistochemistry information through EUS-FNA/FNB can indicate prognosis and assist with treatment strategies. A recent study compared FNA versus EUS-FNB for sampling of GISTs and demonstrated a significant advantage to FNB with newer fork-tip style core needle [9].

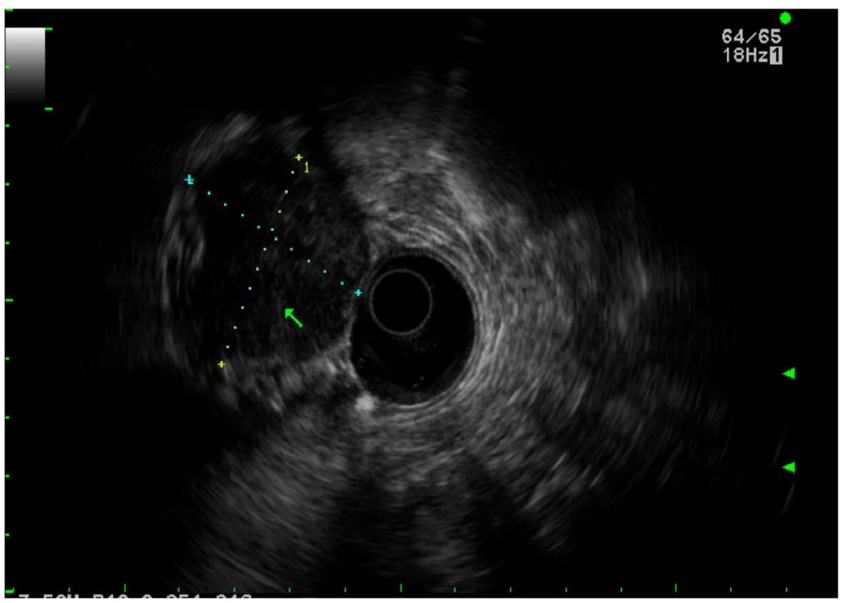

Fig. 5 Mass arising from the fourth layer (muscularis propria) of the gastric wall as seen via EUS

The clinical manifestations of GISTs vary depending on the tumor size and location, but often GISTs are asymptomatic and discovered incidentally (70%) [3]. When present, symptoms are usually vague and nonspecific, with abdominal pain and hematemesis, melena, or anemia due to bleeding being most common [10]. While lymph node metastases are uncommon, large GISTs can reseed outside their primary location, often reaching the liver or extravisceral territory [11]. The propensity of seeding and metastasis is identified by lymph node involvement, elevated mitotic rate, elevated Ki-67 index, and size greater than 10 cm.

Although a genetic component is not recognized in sporadic GISTs, several syndromes have been linked to the development of GISTs, including Carney triad syndrome and Type I-neurofibromatosis [12, 13]. Epidemiological data suggests a slight GIST predilection for men (54%), but evidence is inconclusive. The median age at diagnosis is 60–65, while diagnosis before age 40 is considered extremely rare [14–17].

Resection remains the curative treatment option for most patients with primary GIST who do not have evidence of metastasis. Goal of surgery is complete gross resection with an intact pseudocapsule and negative microscopic margins. The way in which that surgical resection is being performed continues to become less invasive. Role of laparoscopy in the resection of GISTs continues to expand with increasing evidence supporting their safety, efficacy, low recurrence rates, low morbidity, and short hospitalizations [18]. However, with a laparoscopic approach, tumor localization and determining adequate resection can often be challenging due to tumor size, location, and inherent limitation of tactile sensation [19, 20]. A combined laparoscopic-endoscopic "rendezvous" procedure with the use of intra operative EUS has been shown to be the best available approach for minimally invasive tumor localization with advantage of providing assistance with resection [19–21]. A minimally invasive laparoscopically assisted endoscopic resection (LAER) could be the ideal approach to these challenging entities [20].

The key to the least long-term morbidity is to resect the least amount of gastric tissue as possible and remove the GIST with pseudocapsule intact. This achieves the oncologic goal while reducing recovery and long-term downstream morbidity for the patient. Recently, a number of centers have begun full thickness endoscopic resection for GIST mainly those less than 5 cm [22, 23]. Using a tunneling technique or direct full thickness with endoscopic knives, the GIST can be successfully resected and the defect closed with endoscopic clips or suture. Interventional GI endoscopists have demonstrated successful resection of GIST less than 5 cm with even further decreased morbidity and good outcomes [22–24].

Resection of incidentally discovered small GISTs (< 2 cm) remains controversial as the natural history including growth rate and metastatic potential remains unclear [25]. The national comprehensive cancer network recommends conservative management follow-up for GISTs less than 2 cm. The majority of these lesions often observed with EUS and/or cross sectional imaging until they demonstrate growth or worrisome pathologic features and may never be referred for resection.

Imatinib may be added, predominantly, in the adjuvant setting if the tumor is c-kit positive and has high risk features.

Pediatric GIST represents a biologically distinct condition, as they are much less common than adult GISTs and are treated along different guidelines [26].

Methods

A cohort retrospective review was conducted at a large community tertiary referral center for all patients that were diagnosed with a gastric GIST from 2012 to May 2017. Chart analysis was performed and relevant data on epidemiology, history, tumor characteristics, treatment, and outcomes was obtained.

Inclusion criteria focused on EUS with FNA or core biopsy, and patient going for surgery with final pathology showing GIST. Exclusion criteria were patients who refused EUS and surgery and lack of access to pathology. These values are reported in Table 1.

Discussion

Estimations place the number of GISTs diagnosed annually in the USA around 5000; however, it is difficult to ascertain the true incidence of these tumors [27]. This is in part due to the number of routinely undetected sub centimeter GISTs, as well as the novelty of immunoreactive techniques that have provided more sound diagnostic criteria in recent years [28, 29]. The cases presented in this report represent pathology-confirmed GISTs diagnosed at a large community tertiary referral center from 2012 through May 2017. Patient age at diagnosis ranged from 36 to 84. Of note is that eight of the ten cases were male.

In contrast to the rare, familial form, the cases in this report classify as sporadic GISTS, developing without any known genetic predisposition. While patient #3 had been previously diagnosed with squamous cell skin carcinoma and patient #8 had a prior history of basal cell skin cancer, it is unlikely that this contributed to the development of sporadic GISTs in our patients. Patient #2 reported two first-degree relatives who had been diagnosed with an unspecified form of cancer, but any association of this fact and GIST development is unsubstantiated. The mean age at diagnosis of our cohort was 69, three of the patients were octogenarians and while the only known risk factor for sporadic GISTs is age, maintaining a healthy lifestyle (i.e., abstain from smoking, manage healthy weight) may have preventative value. Only two of our eight GIST patients reported heavy smoking, a factor that may or may not have

Table 1 Demographics

Pt #	Age at Dx	Sex	Race	Smoking	Prior hx of cancer	Location	Size per EUS	Size per surgical/ path	Mitotic rate	EUS-guided bx	Final path	Treatment	Recurrence
1	81	M	Caucasian	N	N	10 cm from GEJ along the lesser curvature	4 cm × 2.9 cm	4.5 cm × 3.4 cm	< 5/50 per HPF	Atypical spindle cells consistent with GIST	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 6 weeks
2	80	M	Caucasian	300 pack years	N	4cm from GE junction along greater curvature	3 cm × 1.9 cm	3.5 cm × 2.7 cm	< 5/50 per HPF	Atypical spindle cells consistent with GIST	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 28 months
3	61	M	Caucasian	18 pack years	Squamous cell carcinoma	11 cm from GE junction along lesser curvature	2.9 cm × 2.7 cm	3 cm × 2.8 cm	< 5/50 per HPF	Atypical spindle cells consistent with GIST	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 54 months
4	84	M	Caucasian	former	N	Antrum along the greater curvature	4.1 cm × 2.7 cn	5.3 cm × 3.0 cm	1/50 per HPF	Cellular spindle cells-GIST	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 8 months
5	72	F	Causian	N	Basal cell carcinoma of nose	3 cm distal to the GEJ	3.8 cm × 3.6 cm	4.5 cm × 4.0 cm	< 5/50 per HPF	Spindle cell	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 13 months
6	67	M	Causian	N	Dx with prostate Ca at same time	Antrum, 2.5 cm proximal to pyloric channel	3.3 × 2 cm	3.8 × 3 cm	3/50 per HPF	Spindle cell	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 1 month
7	77	M	African American	N	N	Greater curvature	3.4 × 2.9 cm	3.4 × 2.8 cm	4/50 per HPF	Spindle cell	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 3 years
8	74	F	Causian	N	Basal Cell carcinoma right leg and face	2 masses in lesser curvature, 2 cm from GEJ	2.2 × 2.7, 3.2 × 3.7 cm	4.0 × 3.4 × 3.2 cm and 2.0 × 1.8 × 1.2 cm	<5/50 per HPF	Spindle cell	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 41 months
9	58	M	Caucasian	former	N	Distal body	2.4 × 1.8 cm	4.7 × 2.8 × 2.1 cm	0/50 per HPF	Spindle cell	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 6 weeks
10	36	M	Caucasian	N	N	Anterior body	12 × 7 cm	10 × 8 cm	< 5/50 per HPF	Spindle cell	c-KIT positive GIST	Laparoscopic partial gastrectomy	None at 6 weeks

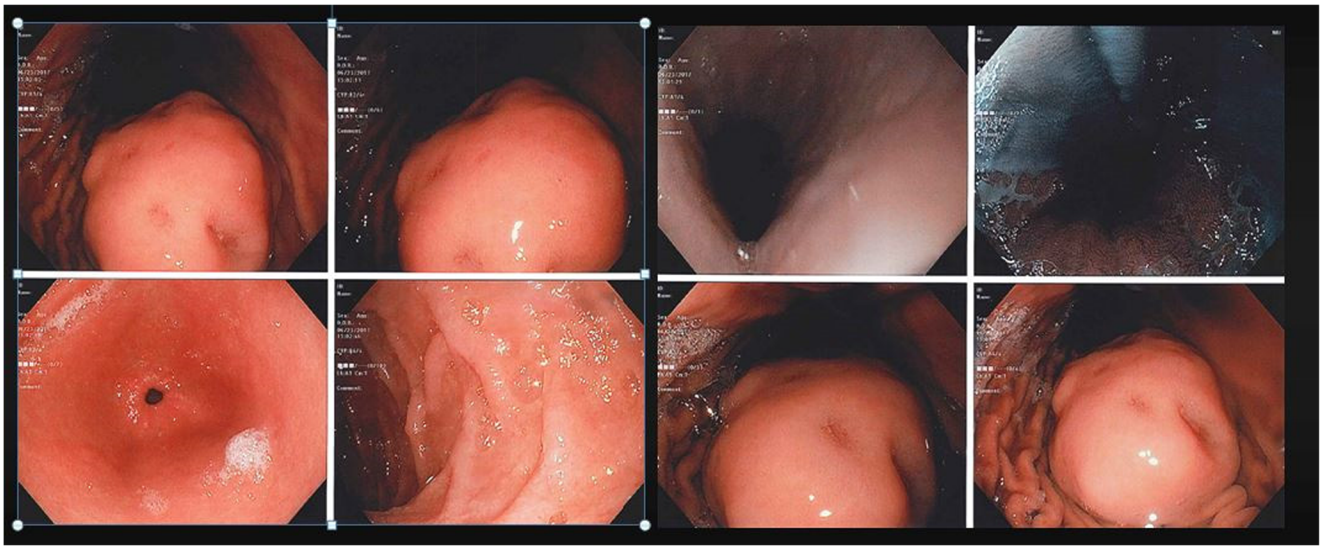

Fig. 6 GIST as seen via standard endoscopy. EUS provides definitive imaging characteristics not seen on endoscopy or high resolution CT scan

played a role in their disease, but a potential relationship cannot be excluded.

The frequently asymptomatic nature of gastric GISTs is often consequential of their insidious location in the muscularis propria and/or a diminutive tumor size upon detection [16, 17, 30]. The cases reviewed presented to our hospital with a variety of symptoms and were diagnosed by endoscopic evaluation. Four of our patients presented with a GI bleed or anemia and upon EUS, bleeding was discovered at the site of tumor. Two patients were without symptoms and the tumor was an incidental finding. Three of our cases presented with abdominal pain and one was admitted with anemia but no bleeding was found at the site. Risk assessment for GIST is stratified according to tumor origin (stomach is a favorable prognostic factor), size, and mitotic count, with tumors < 5 cm and a mitotic count of < 5 per 50 high-powered fields (HPF) defined as low risk for relapse or progression [3, 17]. Following these guidelines, all cases in our study were assessed to be either very low or low risk; however, there is a wide consensus that all GISTs, especially those greater than 1 cm, have malignant potential [3, 31, 32].

Results

In accordance with clinical standards on the treatment for localized GISTs, our patients were all recommended for surgical resection [31, 32]. Recent evidence points toward implementing laparoscopic resection for anatomically favorable GISTs, with proposed lower recurrence rates and morbidity, as well as shorter hospital stays [11, 33, 34]. All ten of our patients underwent successful laparoscopic partial gastrectomy for resection of the tumors. Each individual case proceeded without complication and yielded a final pathology report positive for the GIST biomarker c-KIT. In our cohort, one tumor was removed from the cardia of the stomach, three from the body and three each from the antrum and fundus. This distribution is somewhat curious, as a radiologic series reported a rather profound tendency for gastric GISTs to occur in the body of the stomach (75%) [35]. Although one patient has been lost to follow-up due to their relocation, follow-ups for all other patient have demonstrated no recurrences to date with the longest surveillance time at 54 months. Two patients in our cohort fit the criteria for imatinib [Gleevec]) therapy related to tumor size > 5 cm. Figure 6 shows images of a GIST as seen by standard endoscopy.

There are no published indicators for routine follow-up for those treated surgically for localized disease and routine follow-up schedules vary from institution to institution [36]. The usefulness of routine follow-up for low risk and very low risk tumors is not known but there is some risk of recurrence [36]. Patients with a low risk or very low risk classification at our institution are recommended to follow-up with scans and a clinic visit yearly.

Conclusion

While GISTs are a rare tumor, the standard of care is changing rapidly because of improvements in diagnosis and treatments. Size, mitotic rate, and other pathologic characteristics are the key to appropriate pretreatment planning. With advancements in endoscopic diagnosis and therapy and molecular directed treatment, minimally invasive techniques on appropriately selected patients can yield optimal patient outcomes with low recurrence rates. Cross-sectional imaging combined with EUS is the best method to map the extent of GIST. Staging is now facilitated by EUS-FNB which allows for precise pathologic

evaluation, and is rapidly becoming the standard of care for tissue acquisition. The advent of EUS-FNB has allowed for large core tissue for histologic confirmation of etiology and assessment of key pathologic characteristics such as mitotic index and should be performed prior to engaging in treatment. Resection remains the gold standard for treatment. This has become increasingly less invasive—progressing from laparoscopic to combined endoscopic-laparoscopic to endoscopic full thickness. This evolution is continuing and will require ongoing research and refinement in technique. Most lesions are not metastatic, and liver is the main site of metastasis. Imatinib may be added, predominantly in the adjuvant setting. Small lesions less than 2 cm may be observed. Further research needs to be done to address optimal treatment for these patients.

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