Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract

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INTRODUCTION

Stromal or mesenchymal neoplasms affecting the gastrointestinal (GI) tract are divided into two groups. The most common are neoplasms that are collectively referred to as gastrointestinal stromal tumors (GISTs). They are most often located in the stomach and proximal small intestine, but can occur in any portion of the alimentary tract and occasionally in the omentum, mesentery, and peritoneum [1-5].

A far less common group of mesenchymal GI tract neoplasms is comprised of a spectrum of tumors that are identical to those that might arise in the soft tissues throughout the rest of the body. These include lipomas, liposarcomas, leiomyomas, leiomyosarcomas, desmoid tumors, schwannomas, and peripheral nerve sheath tumors [6].

Local treatment options for GIST, leiomyomas, and leiomyosarcomas of the GI tract will be discussed here. The clinical presentation, diagnosis, and prognosis of GISTs, and the use of tyrosine kinase inhibitors (TKIs), both in the adjuvant and neoadjuvant setting, and for patients with metastatic GIST, are discussed separately.

- (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors".)
- (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors".)

- (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors".)

GENERAL SURGICAL PRINCIPLES

The management of GISTs, leiomyomas, and leiomyosarcomas involving the gastrointestinal (GI) tract depends upon the confidence in the preoperative diagnosis, tumor location and size, extent of spread, and clinical presentation (eg, whether there is evidence of tumor obstruction, perforation, or uncontrolled hemorrhage). (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Clinical presentation'.)

Some general surgical principles apply to these tumors regardless of location:

- **Preoperative biopsy** – In most patients, a preoperative biopsy is obtained to distinguish a suspected GIST, leiomyoma, or leiomyosarcoma from other GI tumors, since the diagnosis impacts the extent of surgical margins and need for lymphadenectomy. A biopsy is preferred to confirm the diagnosis, especially for patients with large, locally advanced lesions suspected to be GIST who have metastatic disease or are eligible for neoadjuvant therapy (algorithm 1). However, a biopsy may not be necessary in patients if a mesenchymal GI tumor is strongly suspected, the tumor is resectable, and there is no safe approach for a biopsy. Available preoperative biopsy techniques for GIST are discussed separately. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Indications for preoperative biopsy'.)

- **Surgical resection for GIST ≥2 cm** – All GISTs ≥2 cm in size should be resected. However, there is no consensus on the management of smaller GISTs ; guidelines from the National Comprehensive Cancer Network (NCCN) [7], European Society for Medical Oncology (ESMO) [8], and the Canadian advisory Committee on GIST [9] differ.

  The natural history of GISTs <2 cm, including their growth rate and metastatic potential, remains unknown. Although these small GISTs may be followed endoscopically until they grow or become symptomatic, the optimal frequency of follow-up and specific risks of this strategy is uncertain. Successful endoscopic resection is reported, but it remains controversial because of the risk of incomplete resection, tumor spillage, and perforation [10]. Because GISTs are submucosal, standard techniques of endoscopic mucosal resection do not necessarily extend deep enough into the submucosal tissue to guarantee removal of all the deep tissue.

  An algorithmic approach to management of gastric GISTs based upon size and EUS appearance has been proposed (algorithm 2) [11]. This approach has been adopted by

the NCCN [7] for gastric GISTs but not those at other sites in the GI tract. When endoscopic assessment is not possible, excision is the standard approach. (See 'GIST and leiomyoma' below.)

- **Neoadjuvant therapy for GIST** – Surgery is the treatment of choice for potentially resectable tumors. However, initial neoadjuvant therapy (algorithm 1) may be preferred for some patients with GIST to facilitate resection and/or reduce surgical morbidity. Neoadjuvant therapy may allow patients to switch from an open to a minimally invasive (ie, laparoscopic or robotic) surgical approach, avoid complex multivisceral resection, or preserve the affected organ in those with disease involving the esophagus, esophagogastric junction, duodenum, or rectum. The approach to neoadjuvant therapy for GIST are discussed separately. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Neoadjuvant therapy'.)

- **Surgical approach** - The goal of surgery is macroscopically complete resection with an intact capsule, if possible.

  - Segmental resection of the stomach or intestine should be performed with the goal of achieving negative resection margins. Wider resection of uninvolved tissue is of no additional benefit. However, peritumoral as opposed to segmental resection should be avoided, as there is a higher risk of local recurrence, particularly with leiomyosarcoma [12]. Routine lymphadenectomy is unnecessary because nodal metastases are rare [13].

    Although they may appear ominous on CT, GISTs often project extraluminally from the stomach or small intestine and displace rather than invade adjacent organs. They can often be lifted away from surrounding structures, although in some cases, en bloc resection is necessary because of dense adhesions.

  - At laparotomy, the abdomen should be thoroughly explored, with particular attention to the peritoneal surfaces and liver to exclude metastatic spread. The tumor should be handled carefully to avoid rupture, which markedly increases the risk of a disease recurrence. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Estimation of recurrence risk'.)

  - The necessity of achieving negative microscopic margins is uncertain with large (>10 cm) GISTs. The management of a positive margin according to the final pathology report is not well defined and depends on whether the surgeon believes the finding accurately reflects the surgical procedure that was undertaken [10,14]. Positive microscopic margins (R1 resection) have not been associated with higher rates of

recurrence compared with margin negative resections, with or without the use of adjuvant imatinib. The risks and benefits of reexcision versus initiation of adjuvant therapy must be carefully evaluated [10]. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors".)

- **Adjuvant therapy for GIST** - Patients who undergo complete resection of localized GIST should be evaluated for adjuvant therapy based on the risk of disease recurrence (algorithm 3). The approach to adjuvant therapy for resected GIST is discussed separately. . (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Adjuvant therapy'.)

STAGING AND PROGNOSIS

GIST — The staging and prognosis of patients with a confirmed diagnosis of GIST is discussed separately. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Staging system' and "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Risk stratification and prognosis'.)

Leiomyosarcoma — The current staging system for soft tissue sarcomas (eighth edition, 2017) uses a specific tumor, node, metastasis (TNM) classification system for soft tissue sarcomas of the abdominal and thoracic viscera for leiomyosarcomas arising in the GI tract (table 1); there are no AJCC prognostic stage groupings [15].

In general, outcomes for leiomyosarcomas at specific segments of the GI tract are less favorable than for GISTs arising in those segments. (See 'Presentation and management at specific sites' below.)

PRESENTATION AND MANAGEMENT AT SPECIFIC SITES

Esophagus — Mesenchymal tumors are most common in the mid to distal third of the esophagus. They are usually small and asymptomatic, but occasionally grow to enormous size and produce dysphagia.

Leiomyomas and leiomyosarcomas — Although rare elsewhere in the gastrointestinal (GI) tract, the majority of mesenchymal tumors affecting the esophagus are leiomyomas [16]. Leiomyosarcomas are far less common [16].

Leiomyomas are more common in men, and often detected incidentally on a barium swallow or endoscopy performed for other reasons [16,17]. The tumors appear as rounded submucosal lesions with intact overlying mucosa and feel rubbery when gently palpated with the endoscope. Ulceration or bleeding is uncommon.

The histologic distinction between well-differentiated leiomyosarcoma and leiomyoma can be difficult. Endoscopic resection of all small submucosal tumors has been suggested to firmly establish their benignity. In one series of 62 patients with submucosal tumors of the esophagus, tumors less than 2 cm that were polypoid or had at least a round protrusion with moderate elevation were selected for endoscopic snare polypectomy [17]. Larger tumors, or those having only mild elevation, were treated by complete stripping of the overlying mucosa followed by enucleation using an electrocautery snare and a coagulation electrode. Tumors were completely resected in all but one patient, and there were no serious complications. Histologically, there were 56 leiomyomas, four granular cell tumors, one neurogenic tumor, and one cyst.

Despite these encouraging results, no malignant tumors were encountered in this series (with the exception of the granular cell tumors, which can be malignant), and the risk of complications is uncertain. The safety of this technique depends upon the endoscopist's experience.

A more conservative approach for small asymptomatic lesions that lack features suggesting malignancy is to perform follow-up examinations using endoscopic ultrasound (EUS). Follow-up studies consist of repeat EUS at six and 12 months. If no changes occur within one year, the follow-up intervals can be lengthened. Surgery should be performed if the tumor becomes symptomatic, enlarges to >1 cm, or shows structural changes. Snare polypectomy should be reserved for lesions with mucosal elevations that meet the previously described criteria. Surgery is also indicated in any case in which a malignancy is suspected. (See "Surgical management of resectable esophageal and esophagogastric junction cancers".)

Stable lesions that are >2 cm or that produce dysphagia should be treated with appropriate surgical resection:

- Complete resection of a small leiomyosarcoma can often be accomplished through local excision [18]. However, based upon the size of the tumor, resection may require a total or partial esophagectomy.

- Esophagectomy may also be needed for adequate treatment of giant esophageal leiomyomas [19].

Five-year survival rates of approximately 30 to 40 percent are reported in patients with resected leiomyosarcoma [20], although less favorable results are reported by others [16]. Individual survival is strongly influenced by tumor differentiation and size.

GIST — Esophageal GISTs are rare; this site accounts for only 1 percent of all GISTs reported in the Surveillance, Epidemiology and End Results (SEER) registry [21]. Esophageal GISTs have a similar clinical, endoscopic and radiographic appearance as leiomyomas, although they tend to be more enhancing on contrast-enhanced CT, are fludeoxyglucose (FDG)-avid on FDG-PET scanning, and can be reliably identified preoperatively by EUS-guided FNA, especially if immunohistochemical staining for KIT can be performed [22,23]. All well-circumscribed submucosal esophageal lesions that are >2 cm, enlarging, or FDG-avid should undergo preoperative EUS with FNA, as these are not typical features of a leiomyoma. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Diagnostic evaluation'.)

Esophageal GISTs are more difficult to manage than are GISTs arising in serosa-lined intraabdominal organs because of the lack of tumor confinement by a serosal layer, and the relative contraindication to segmental resection given the blood supply of the esophagus. Although local resection of small tumors confined to the wall of the distal esophagus is reasonable if negative resection margins can be achieved [22,24], an open en bloc esophagectomy may be required for tumors ≥2 cm and for those involving the GE junction. (See "Surgical management of resectable esophageal and esophagogastric junction cancers".)

Neoadjuvant therapy should be considered to downstage the potential scope of the operation, and the patient should be referred to a center with experience in the multimodality approaches to esophageal GISTs. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors".)

While successful enucleation has been reported in smaller esophageal GIST with apparently favorable outcomes [25], the oncologic appropriateness of this limited surgery has not been evaluated in a prospective multicenter trial and cannot be routinely recommended as the best approach.

The optimal management of esophageal GISTs <2 cm in size is controversial. European Society for Medical Oncology (ESMO) guidelines recommend endoscopic ultrasound and follow-up, reserving excision only for those esophageal nodules that increase in size [8]. Canadian guidelines suggest that all GISTs, even those <1 cm, be excised because of the risk of metastases [9]. An algorithmic approach to management of GISTs ≤2 cm based upon size and EUS appearance has been proposed (algorithm 2) [11]; however, this approach has not been

prospectively validated. It has been adopted by the NCCN [7] for small gastric GISTs but not those at other sites. (See 'Stomach' below.)

Stomach — The majority of soft tissue tumors arising in the stomach are GISTs, followed by leiomyomas; leiomyosarcomas are rare [26]. The stomach is the most frequent site for GISTs, which account for 1 to 3 percent of all stomach neoplasms (picture 1). GIST may arise anywhere in the stomach, but are most common in the fundus (figure 1). Further details on the clinical presentation of GISTs are discussed separately. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors".)

GIST and leiomyoma — On histopathology, leiomyomas are formed of fascicles of benign-appearing spindle cells without nuclear atypia, mitoses are sparse or absent, and necrosis virtually never occurs (picture 2). The nucleus is centrally located and oval, but it may be displaced to one side by distinct vacuoles, suggesting signet-ring cells. These vacuoles do not contain fat or mucosubstances, which differentiates them from liposarcomas and carcinomas.

The pathologic features of GISTs are discussed separately. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Histopathology'.)

Both leiomyomas and gastric GISTs may be ≤0.5 cm or as large as 20 to 30 cm. Both tumors may grow both inwardly (intraluminal), outwardly (extraluminal), or a combination of both directions to form a dumbbell shape. Leiomyomas typically arise from the muscularis propria, are usually small and well-circumscribed and more likely to grow intraluminally (endogastric) (picture 3). By contrast, GISTs (and leiomyosarcomas) grow and expand in a predominantly extragastric fashion [27]. Multiple small leiomyomas (microleiomyomas) are found in 16 to 38 percent of resected stomachs.

Leiomyomas are typically asymptomatic, even when large in size. While most small GISTs are asymptomatic, large lesions ulcerate, and up to 60 percent present with bleeding [28,29]. Other symptoms include anorexia, weight loss, nausea, vomiting, and pain; gastric perforation is uncommon.

EUS-guided fine needle aspiration biopsy has emerged as an important method to secure the diagnosis of a gastric GIST. However, a preoperative diagnosis may not be possible if there is insufficient material to perform immunohistochemistry.

The treatment approach varies according to size. All nodules ≥2 cm should be excised. Submucosal lesions <1 cm with EUS findings suggestive of benignity may be followed conservatively, using a similar protocol as for esophageal leiomyomas. (See 'Leiomyomas and leiomyosarcomas' above.)

The management of lesions between 1 and 2 cm is controversial, and guidelines from expert groups differ in their recommendations [7-9]. Some clinicians will resect tumors between 0.5 and 1.0 cm in size by endoscopic snare polypectomy, but there is a risk of perforation. If the decision is made to remove them, we prefer that these and other larger tumors be surgically resected (preferably by a laparoscopic approach, if feasible), because of the increased frequency of complications and the difficulty in excluding malignancy preoperatively. Even 1 cm GISTs are likely to have a KIT mutation, and the risk of growth and progression to malignancy is unknown [30] (see 'General surgical principles' above). Furthermore, these tumors are submucosal, so an endoscopic snare polypectomy may conceivably leave tumor tissue behind.

Whether all gastric GISTs <2 cm need to be removed is controversial. The prognosis of gastric GISTs is better than those arising elsewhere in the intestinal tract [31]. (See 'General surgical principles' above.)

Larger tumor size and high mitotic rate correlate with a relative rather than absolute risk of malignant behavior (table 2 and table 3). Nevertheless, even lesions <2 cm in diameter with <1 mitosis per 10 high-power fields (HPFs) occasionally metastasize to the liver, peritoneum, or lung [28,29]. Canadian guidelines suggest that even small GISTs <1 cm should be excised because of the risk of metastases [9].

An algorithmic approach to management of gastric GIST based upon size and EUS appearance has been proposed (algorithm 2) [11]. Although not prospectively validated, this approach was adopted by the NCCN [7] for management of gastric GISTs (but not those at other GI sites). Complete surgical resection is recommended for small gastric GISTs <2 cm at high risk of recurrence based upon EUS appearance (irregular borders, cystic spaces, ulceration, echogenic foci, or heterogeneity in appearance).

For tumors that lack these features, surveillance using endoscopic ultrasound is an option. EUS surveillance may be offered after a risk-benefit discussion with the patient. However, many clinicians limit endoscopic resection and/or surveillance to patients who are at higher risk for surgical complications. Data are limited for the optimal interval between surveillance studies. One approach is to have a short-term initial assessment (eg, within three to six months). If the tumor remains stable, then the follow-up interval can be lengthened. The tumor should be resected if it cannot be assessed endoscopically, becomes symptomatic (eg, dysphagia), increases in size, or shows structural changes or high-risk endoscopic features on EUS. Imaging surveillance is discussed separately. (See 'Posttreatment follow-up' below.)

Minimally invasive (laparoscopic or robotic) resection of gastric GISTs is safe and effective but should only be performed by surgeons with expertise in the laparoscopic or robotic

management of upper GI cancers or sarcomas [32-36]. (See "Partial gastrectomy and gastrointestinal reconstruction".)

Leiomyosarcoma — On histopathology, the cells of a true leiomyosarcoma are characteristically elongated with an abundance of cytoplasm. Multinucleated giant cells are common (picture 4). Most are histologically high grade, and by immunohistochemistry, they express smooth muscle actin, desmin, or both (table 4) [37]. Epithelioid changes, in which the cells become rounded or polygonal cells with a clear perinuclear space lacking smooth muscle myofibrils, may occur in an otherwise typical leiomyosarcoma.

Gastric leiomyosarcomas are rare. Symptoms include nausea, vomiting, pain, weight loss, bleeding, or a palpable mass [38,39]. These tumors may be large at presentation (median 10 cm in one report of 15 cases [38]), and there may be local invasion of adjacent organs. Leiomyosarcomas have varying degrees of internal necrosis which produce an inhomogeneous pattern on EUS and heterogeneous contrast enhancement on CT. Dystrophic calcification may also be present [39-41]. Ninety percent of tumors are located in the fundus and body. Hematogenous dissemination may occur to liver and lungs [39].

Local resection with an adequate margin is the treatment of choice in the absence of invasion to adjacent structures [38,40]. En bloc resection is needed if adjacent organs are invaded. Nodal dissection is unnecessary since nodal metastases are rare [40]. (See "Partial gastrectomy and gastrointestinal reconstruction".)

In general, outcomes are less favorable than for gastric GIST. In a report of 15 cases of gastric leiomyosarcoma treated between 1981 and 1998 (median tumor size 10 cm), the three- and five-year survival rates following resection were 53 and 22 percent, respectively [38]. Others report markedly better outcomes in patients with gastric "leiomyosarcoma" (five-year disease-specific survival 93 percent), but it is likely that many of the patients included in this series would likely be classified as GIST by modern methods [40].

Small intestine — The small intestine is the second most frequent site for smooth muscle tumors. Tumors are most commonly found in the jejunum, followed by the ileum and then duodenum [42-45].

The most common type of intestinal sarcoma is a GIST, accounting for 83 to 86 percent of cases [46,47]. The majority of previously classified leiomyosarcomas in older studies are in fact GISTs [47]. (See "Epidemiology, clinical features, and types of small bowel neoplasms", section on 'Sarcoma'.)

Small intestinal mesenchymal tumors are often large at diagnosis, and they commonly present with ulceration and bleeding, which can be massive (image 1). On CT, small bowel leiomyomas may appear as a smoothly contoured, hypodense lesion immediately adjacent to the gut lumen, and may have internal foci of hemorrhage or necrosis (image 1). Diagnostic imaging findings for GISTs are discussed separately. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Imaging the primary tumor'.)

Other common presenting symptoms of small bowel sarcomas include pain, weight loss, perforation, or a palpable mass [19]. Because they tend to enlarge extraluminally, obstruction is rare and typically a late presenting symptom. By contrast, small bowel leiomyomas may obstruct the bowel as these tumors typically grow into the lumen (picture 5).

Surgical treatment for a localized, potentially resectable GIST and a leiomyosarcoma of the small bowel is similar and consists of en bloc segmental resection with tumor-free margins. Peritumoral as opposed to segmental resection should be avoided, as it is associated with a high risk of local recurrence [48]. Unlike adenocarcinoma and carcinoid, sarcomas such as GIST infrequently metastasize to regional mesenteric lymph nodes (5 percent on one database series of 1848 small intestinal GISTs [13], and mesenteric lymphadenectomy is neither necessary nor beneficial. There is less experience with laparoscopic resection of small bowel GISTs than with gastric GISTs [49,50]. (See "Bowel resection techniques".)

For duodenal GISTs, local resection is appropriate when feasible, and pancreaticoduodenectomy should be reserved for lesions that are not amenable to local resection (eg, involvement of the papilla of Vater) [51-55]. The use of neoadjuvant therapy in patients with a locally advanced duodenal GIST may potentially allow some patients who would otherwise require pancreaticoduodenectomy to undergo local resection instead, although the frequency with which this occurs is unclear [53]. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Neoadjuvant therapy'.)

The prognosis of small intestine GISTs depends upon the adequacy of resection, tumor size, mitotic activity, and, in some (but not all [56]) series, location within the small bowel (table 2 and table 3) [42,44,45,57]. In one series of 70 patients, five-year disease-free and overall survival rates were 67 and 87 percent, respectively [44]. There were no recurrences or deaths in patients with tumor size less than 5 cm, and no deaths in patients with a tumor mitotic rate less than 5 per 50 HPFs.

Colon and rectum — Smooth muscle tumors are uncommon overall in the colon and rectum, and especially rare in the appendix [58]. In the rectum, the great majority of smooth muscle tumors are GISTs [59], and they usually present as small, hard nodules <1 cm in diameter found

incidentally during a clinical examination. Large tumors can ulcerate and mimic a rectal adenocarcinoma, with rectal bleeding, constipation, and abdominal discomfort [60]. In the colon, GISTs are more common than leiomyosarcomas, and they are typically transmural, with frequent intramural and outward bulging components [37].

Lesions in which a malignancy cannot be excluded should be resected surgically, regardless of size. Although leiomyomas could theoretically be enucleated, a standard colectomy based on the blood supply to the bowel, as is done for adenocarcinomas, is technically easier, and the complication rate should be comparable. However, because lymphatic metastases are rare for GIST, resection of the adjacent mesentery (and the performance of a mesorectal resection for rectal GISTs) is not necessary [61,62]. On the other hand, locally advanced colorectal GISTs can be large, bulky tumors. Rectal GISTs are a particular challenge for the surgeon because of the confined pelvic space and often dense adherence to the pelvic floor [62]. As a consequence, rectal GIST may require extensive surgery to achieve a surgically complete resection. Such cases should be evaluated for neoadjuvant therapy to reduce tumor size [63]. (See "Overview of colon resection" and "Radical resection of rectal cancer", section on 'Total mesorectal excision' and "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Rectal GISTs'.)

Outcomes with surgery alone are poor, and a tumor site in the colon or rectum is recognized to confer a worse prognosis than location in the stomach (table 2 and table 3). Outcomes appear to be better in patients treated with perioperative imatinib [61,63-65]. In particular, positive resection margins are an important risk factor for poor survival in patients with rectal GIST. Especially for patients with high-risk tumors (>5 cm or mitotic rate >5 per 50 HPF), preoperative imatinib may increase the chance of a margin-negative resection [63,65] and for less radical sphincter-sparing surgery [65,66], and might improve survival over resection alone [65,67]. We prefer initial imatinib for most patients with a rectal GIST, unless the tumor is small and sphincter-preserving surgery is possible upfront. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Rectal GISTs'.)

LOCALLY ADVANCED OR BORDERLINE RESECTABLE GIST

KIT or PDGFRA mutated GIST — For most patients with a nonmetastatic locally advanced or borderline resectable GIST that are *KIT* or non-D842V *PDGFRA* mutated, we offer neoadjuvant therapy (algorithm 1) prior to surgery to facilitate resection and reduce surgical morbidity. Indications for neoadjuvant therapy for GIST are discussed separately. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Indications for neoadjuvant therapy'.)

Neoadjuvant therapy may allow patients to switch from an open to a minimally invasive (ie, laparoscopic or robotic) surgical approach, avoid complex multivisceral resection, or preserve the affected organ, such as the esophagus, esophagogastric junction, duodenum, or distal rectum. Surgery may be offered to patients whose disease is stable or responding to tyrosine kinase inhibitor (TKI) therapy, followed by a period of postoperative systemic therapy. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Postoperative management'.)

For patients with a *PDGFRA* D842V mutated tumor, we do not use neoadjuvant therapy and, instead, proceed directly to surgery. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Neoadjuvant therapy'.)

KIT/PDGFRA wild-type GIST — Approximately 10 to 15 percent of GISTs do not have a detectable *KIT* or platelet-derived growth factor receptor A (*PDGFRA*) mutation. *KIT*/*PDGFRA* wild-type GISTs are often localized to the stomach and multicentric in origin. Further details on the clinical presentation of patients with *KIT/PDGFRA* wild-type GISTs are discussed separately. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'KIT/PDGFRA wild-type GISTs'.)

In such patients, disease progression/recurrence is frequent, but the natural history is indolent [68,69]. Although repeated resection tends to be associated with progressively decreasing event-free survival, there are no approved drug therapies for this cohort of GIST patients. Therefore, surgery for subsequent recurrences is a reasonable option for symptomatic patients and those with progressive growth. As an example, in one report of 76 individuals with wild-type GIST who underwent initial resection, event-free survival (defined as freedom from disease progression or recurrence) rates were 73, 58, 24, and 16 percent at 1, 2, 5, and 10 years, respectively [70]. However, at a median follow-up of 4.1 years, only five patients died.

METASTATIC GIST WITH POTENTIALLY RESECTABLE DISEASE

Neoadjuvant therapy followed by surgery — For patients with potentially resectable metastatic GIST (including liver and peritoneal metastases), we suggest neoadjuvant systemic therapy rather than initial surgery. Surgery may be offered to patients who become resectable after neoadjuvant imatinib and for those with primary imatinib resistance who become resectable after therapy with sunitinib. For patients who develop extensive disease progression while on neoadjuvant therapy, we do not pursue further surgery.

Cytoreductive surgery in this setting often requires extensive, potentially morbid procedures, such as gastrectomy, hepatectomy, and pancreatic resection, and should be carried out in centers of excellence.

All patients should resume systemic therapy indefinitely after resection of metastatic disease. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors".)

Although therapy with tyrosine kinase inhibitors (TKIs) has become the first-line treatment for metastatic GIST, there are several reasons integrate surgical resection into the treatment patients who are receiving these drugs for metastatic disease but have potentially resectable disease:

- While TKIs control tumor growth in over 80 percent of patients, complete responses are only rarely achieved [71-73]. Even tumor masses that appear nonviable by metabolic imaging (eg, with PET scans) usually contain viable cancer cells [73,74].
- Most patients who initially respond to imatinib eventually acquire resistance via additional mutations in the KIT gene. The median time to progression is approximately two years. Response rates to second-line sunitinib and third-line regorafenib are low, and responses are less durable. The goal of metastasectomy is to remove disease before secondary resistance develops and stop disease progression by eliminating resistant clones.
- The liver and peritoneum are the most common metastatic sites, and approximately 25 to 30 percent of patients who present with recurrent/metastatic disease have potentially resectable disease.

The critical question of whether surgery provides additional benefit over remaining on TKI therapy alone without surgery is unanswered. Two trials addressing this question were begun in Europe and in China, but both failed to recruit quickly enough to meet target accrual. In the absence of randomized trials, single-institution and multi-institutional retrospective studies document long-term disease control and longer overall survival (OS) for selected patients with limited metastatic disease who undergo metastasectomy [75-87].

In general, resection appears to benefit responding patients (ie, those who have a partial response, stable disease, or focal progression, and possibly those with isolated sites of progression) but has little to offer those who experience generalized or multifocal disease progression while receiving a TKI [77,79,87].

As an example, one review of the experience from two institutions included 400 consecutive operations on 323 patients with metastatic GIST who were receiving a TKI [87]. As expected,

patients who underwent surgery while receiving imatinib had a significantly longer progression-free survival (PFS) from the date of metastasectomy compared with those on sunitinib (16 versus 7 months). Among the patients receiving imatinib, radiographic response at the time of surgery was predictive of both PFS and OS after surgery:

- Responsive disease – Median PFS 36 months, median OS not reached
- Stable disease – Median PFS 30 months, OS 110 months
- Unifocal progressive disease – 11 months, OS 59 months
- Multifocal progressive disease – 6 months, OS 24 months

Radiographic response was not predictive of PFS or OS in patients on sunitinib prior to surgery. On multivariate analysis, a metastatic mitotic index >5 per 50 high-power fields (HPFs), multifocal progressive disease, and a grossly incomplete (R2) resection were prognostic of worse PFS and OS after surgery.

Resection, even if complete, does not eliminate the need for continued treatment with TKI therapy. PFS is significantly shorter in patients who discontinue treatment as compared with those who continue the drug after resection [77,79].

Thus, surgery may be considered as the imatinib response permits. If there are signs of isolated progression (ie, one or two lesions growing out of proportion to other sites of responding disease), resection of such lesions is a reasonable approach, although it is not clear if survival is prolonged compared with a change in systemic therapy. For patients with more generalized progression of disease, surgery is not helpful, and other systemic options should be pursued. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Treatment of disease refractory to imatinib'.)

Timing of surgery — The appropriate timing of surgical intervention for patients with metastatic GIST is unknown. Some propose that patients be treated for six to nine months with neoadjuvant systemic therapy and subsequently evaluated for surgery if the disease appears completely grossly resectable [79]. While it has been shown that tumor load continues to decrease even after one year of imatinib, the median time to best response is 3.5 months, and there is little incremental tumor shrinkage after nine months [88].

All patients treated with presurgical imatinib should resume TKI therapy postoperatively, typically with the same agent and dose. In theory, this maximizes the potential benefit derived from the TK inhibitor by extending the time each patient is on that drug prior to proceeding to the next line of therapy. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Treatment of disease refractory to imatinib'.)

Surgery for liver metastases — The liver is the site of recurrence in as many as 67 percent of patients with relapsed GIST [89]. Prior to the imatinib era, these patients were treated like other soft tissue sarcomas metastatic to the liver, with resection when technically feasible [90,91]. The available data on GIST liver metastases suggest five-year survival rates from 27 to 34 percent in patients undergoing resection alone [92-94].

For patients with isolated liver metastases, hepatic resection combined with imatinib provides the greatest opportunity for long-term disease control [93,95-97].

A course of preoperative therapy (ie, three to nine months) is preferred in most cases, as it not only has the potential to reduce the extent of needed surgery, but it also permits the "biologic selection" of the best candidates for surgery, particularly if extensive procedures are planned. As an example, in the setting of multiple bilateral lesions (which are common with GIST), a two-staged approach may be needed, with or without portal vein embolization to increase the volume of the future liver remnant prior to hepatic resection [90]. (See "Surgical management of potentially resectable hepatocellular carcinoma", section on 'Portal vein embolization'.)

An important component of periodic response assessment during neoadjuvant imatinib is the understanding that a response to therapy consists less often of a change in tumor size or diameter, and more often of changes in density (ie, the development of cystic structures) and vascularity. This renders size-based tumor response criteria such as the Response Evaluation Criteria in Solid Tumors (RECIST) (table 5) less useful. This subject is addressed in detail separately. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Assessing response to therapy'.)

As with other sites of metastatic disease, resection following neoadjuvant imatinib appears to benefit responding patients (ie, those who have a partial response, stable disease, or focal progression) but has little to offer those who experience generalized disease progression while receiving imatinib [77]. The optimal timing of attempted surgical resection (ie, at the time of maximal response to imatinib or at the first suggestion of local progression) is unclear, but the best response to imatinib is observed with three to nine months of therapy, with little change thereafter, suggesting this is a reasonable time to consider resection.

As with other sites of metastatic disease, hepatic resection, even if complete, does not eliminate the need for continued treatment with a TKI. PFS is significantly shorter in patients who discontinue imatinib as compared with those who continue the drug after resection [93].

Existing clinical practice guidelines from the National Comprehensive Cancer Network (NCCN) [7] and European Society for Medical Oncology (ESMO) [8] recommend the indefinite administration of imatinib for patients with resected metastases in the liver or peritoneum,

even if the resection was complete. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors".)

Other local therapies for liver metastases — There may be some therapeutic benefit for hepatic arterial embolization in patients with unresectable but isolated hepatic metastases, and from radiofrequency ablation (RFA) in patients with limited discordant progression of liver metastases during therapy with a TKI for advanced disease who are not candidates for hepatic resection. However, the place of embolization and RFA in the therapeutic armamentarium remains uncertain, particularly in view of the approval of sunitinib and regorafenib, multitargeted TKIs, for second- and third-line treatment, respectively, of imatinib-resistant disease.

Hepatic arterial embolization and chemoembolization — For patients with isolated liver metastases, hepatic resection combined with imatinib provides the greatest opportunity for long-term disease control, but many patients are ineligible because they have multifocal bilobar disease. Few data are available on the long-term benefit of hepatic artery embolization, chemoembolization, or radioembolization using yttrium-90 tagged microspheres for patients with isolated unresectable liver metastases [98-102]. The largest series consisted of 110 patients who underwent the chemoembolization (using cisplatin with or without an embolic agent) for liver metastases from GIST, 38 of whom had extrahepatic involvement [98]. Sixty-two were treated in the pre-imatinib era. The number of sessions per patient ranged from one to seven; 62 percent had two or more treatments. Most patients developed a temporary postembolization syndrome (abdominal pain, fever, nausea, vomiting), which was effectively managed with supportive care alone. Moderate to severe adverse events (death, respiratory distress, myelosuppression, cholecystitis, sepsis, pulmonary embolism, symptomatic pleural effusion, and hyponatremia-induced seizures) developed in 25 (12 percent).

Among the 85 patients who could be assessed, 12 had a partial radiologic response (14 percent, according to RECIST) and 74 percent had stable disease. The median liver PFS was 8.2 months, a value which is comparable to that reported in other smaller series (8 and 10 months, respectively) [99,100]. Median OS was 17.2 months, but the contribution of chemoembolization to this value could not be ascertained because of the use of other therapies, including imatinib, after disease progression. Concomitant imatinib prolonged survival time.

In a later analysis by this group of 14 patients who underwent hepatic artery embolization or chemoembolization for imatinib-refractory disease, the PFS in the liver were 31 percent at both one and three years, and the median PFS and OS times were 7 and 9.7 months, respectively [101].

These data suggest a possible therapeutic role for hepatic arterial embolization in patients with unresectable but isolated liver metastases from GISTs. However, the benefit of chemoembolization or radioembolization over bland embolization alone is unclear; there are no comparative trials. Furthermore, the place of any type of embolization in the therapeutic armamentarium remains uncertain, particularly in view of the approval of sunitinib and regorafenib, as second- and third-line multitargeted TK inhibitors, for imatinib-resistant disease. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Sunitinib'.)

Our general practice is to consider embolization if there is multifocal disease progression in liver despite use of available systemic therapeutic options, although each patient must be considered individually.

Radiofrequency ablation — The use of thermal ablation to produce necrosis in focal hepatic malignancies has been established in patients who are not otherwise candidates for surgery. (See "Localized hepatocellular carcinoma: Liver-directed therapies for nonsurgical candidates who are eligible for local ablation" and "Nonsurgical local treatment strategies for colorectal cancer liver metastases".)

Few studies have explored the efficacy of RFA in patients with liver metastases from GIST [91,93]:

- One report included nine patients with metastatic GIST who had RFA for a single or limited number of sites of progressive disease after a median 25 months of imatinib (eight for liver metastases) [91]. In a preliminary report (median 4.2 months), all lesions were completely ablated, and four remained stable on continued imatinib. Longer-term follow-up of this cohort has not been reported.

- A second series included 31 patients who underwent intraoperative RFA for sarcoma metastatic to liver (36 of the entire series of 66 patients had GIST) [93]. For 13 patients, RFA was the sole modality for tumors in unresectable locations, the remainder had resection of large lesions combined with RFA of smaller lesions deemed unresectable [93]. Patients who were treated with RFA alone or as a combined modality with resection had a significantly shorter disease-free interval than did those undergoing resection alone. The contribution of adjuvant imatinib to RFA outcomes was not addressed.

These data suggest a possible therapeutic role for RFA in patients with advanced GIST who develop focal progression of liver metastases during imatinib therapy and who are not otherwise candidates for surgery. Both lesion size and proximity to large blood vessels (which serve as a heat sink) impact on the feasibility of RFA as a therapeutic option.

However, as with hepatic arterial embolization, the place of RFA in the therapeutic armamentarium remains uncertain, particularly in view of the approval of sunitinib, a multitargeted TK inhibitor, for imatinib-resistant disease. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Sunitinib'.)

POSTTREATMENT FOLLOW-UP

Posttreatment follow-up is not required for a leiomyoma. For GIST and leiomyosarcoma, while there are no trials that have established the optimal duration, frequency, or components of follow-up, posttreatment surveillance is usually carried out for early detection of recurrent disease that may be amenable to additional treatment. For GIST and leiomyosarcoma, the recommendations differ slightly.

GIST — The approach to follow-up after treatment of a GIST is discussed separately. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Posttreatment follow-up'.)

Leiomyosarcoma — Consensus-based guidelines for posttreatment follow-up for intraabdominal or retroperitoneal sarcomas are available from the NCCN [7] and include the following (see "Management of locally recurrent retroperitoneal sarcoma", section on 'Posttreatment follow-up' and "Clinical features, evaluation, and treatment of retroperitoneal soft tissue sarcoma", section on 'Posttreatment follow-up'):

- For completely resected tumors: physical examination with abdominal/pelvic imaging every three to six months for two to three years, and then annually; "consider" chest imaging.
- For sarcomas resected with positive margins: physical examination with abdominal/pelvic imaging every three to six months for two to three years, then every six months for the next two years, and then annually; "consider" chest imaging.
- In either case, no specific recommendation is made for periodic chest imaging. However, given the higher rate of lung metastases with retroperitoneal and visceral leiomyosarcomas (as compared with other histologies), we recommend imaging of the chest in addition to the abdomen and pelvis on a regular schedule in these cases. Some clinicians routinely perform surveillance chest imaging for all patients with large, high-grade tumors, regardless of histology.

We agree with these guidelines.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Gastrointestinal stromal tumors".)

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topic (see "Patient education: Soft tissue sarcoma (The Basics)")

SUMMARY AND RECOMMENDATIONS

- **Types of gastrointestinal mesenchymal neoplasms** – Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal neoplasm affecting the gastrointestinal (GI) tract. The clinical presentation of GIST is discussed separately. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors".)
    - GISTs differ clinically and pathogenetically from true leiomyosarcomas (which are very rare in the GI tract and are predominantly found in the stomach) and leiomyomas (which occur predominantly in the esophagus, colon, and rectum).
    - The majority of mesenchymal tumors of the stomach are GISTs, while the majority of smooth muscle tumors in the esophagus are leiomyomas.

- **Molecular alterations in GIST** – Molecular alterations that are commonly identified in GISTs include mutations in *KIT*, platelet-derived growth factor receptor alpha (*PDGFRA*), and the family of succinate dehydrogenase (*SDH*) genes. (See "Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors", section on 'Molecular alterations'.)

- **Treatment for GIST**

  - **Resectable GIST** – We recommend resection for all localized GISTs ≥2 cm in size (algorithm 2) (**Grade 1A**). There is no consensus on the management of incidentally encountered smaller GISTs, and their management must be individualized. Guidelines for treatment of intraabdominal sarcomas from the National Comprehensive Cancer Network (NCCN) [7] do not differentiate between tumors that are ≥2 cm and smaller ones. (See 'General surgical principles' above.)

    For potentially resectable gastric and intestinal GISTs, segmental (rather than peritumoral) visceral resection is preferred; regional lymphadenectomy is unnecessary. (See 'Presentation and management at specific sites' above.)

  - **Locally advanced or borderline resectable GIST**

    - ***KIT* or non-D842V *PDGFRA* mutated GIST** - For most patients with a nonmetastatic locally advanced or borderline resectable GIST that are *KIT* or non-D842V *PDGFRA* mutated, we offer neoadjuvant therapy (algorithm 1) prior to surgery to facilitate resection and reduce surgical morbidity. (See 'KIT or PDGFRA mutated GIST' above and "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Neoadjuvant therapy'.)

    - **Other GIST tumors** – For patients with a *PDGFRA* D842V mutation or those with wildtype tumors (neither *KIT* nor *PDGFRA* mutations), we do not use neoadjuvant therapy and, instead, proceed directly to surgery. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Neoadjuvant therapy' and 'KIT/PDGFRA wild-type GIST' above.)

  - **Metastatic GIST, potentially resectable** – For patients with potentially resectable metastatic GIST (including liver and peritoneal metastases), we suggest neoadjuvant systemic therapy rather than initial surgery (**Grade 2B**). Surgery may be offered to patients who become resectable after neoadjuvant imatinib and for those with primary imatinib resistance who become resectable after therapy with sunitinib. For patients who develop extensive disease progression while on neoadjuvant therapy, we do not

pursue further surgery. (See 'Metastatic GIST with potentially resectable disease' above.)

- Cytoreductive surgery in this setting often requires extensive, potentially morbid procedures, such as gastrectomy, hepatectomy, and pancreatic resection, and should be carried out in centers of excellence.

- All patients should resume tyrosine kinase inhibitors (TKI) therapy indefinitely after resection of metastatic disease. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors".)

- **Patients with isolated liver metastases** – There may be some therapeutic benefit from hepatic arterial embolization in patients with unresectable but isolated liver metastases from GISTs, and from radiofrequency ablation (RFA) in patients with limited discordant progression of liver metastases during TKI therapy who are not candidates for surgical resection. However, the place of embolization and RFA in the therapeutic armamentarium remains uncertain, particularly in view of the targeted therapies available, for imatinib-resistant disease. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Treatment of disease refractory to imatinib'.)

- **Posttreatment surveillance of GIST** – The posttreatment surveillance of GIST is discussed separately. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Posttreatment follow-up'.)

- **Leiomyosarcoma** – Leiomyosarcomas are very rare in the GI tract and are predominantly found in the stomach. We recommend local resection with an adequate margin in the absence of invasion to adjacent structures (**Grade 1A**). En bloc resection is needed if adjacent organs are invaded. As with GISTs, nodal dissection is not necessary because of the rarity of nodal metastases. (See 'Stomach' above.)

- **Posttreatment surveillance of leiomyosarcoma** – Following treatment, we suggest the following surveillance strategy (see 'Leiomyosarcoma' above):

  - For completely resected tumors, physical examination with abdominal/pelvic imaging every three to six months for two to three years, then annually.

  - For sarcomas resected with positive margins, physical examination with abdominal/pelvic imaging every three to six months for two to three years, then every six months for the next two years, and then annually.

- Given the higher rate of lung metastases with retroperitoneal and visceral leiomyosarcomas (as compared with other histologies), we recommend imaging of the chest, in addition to the abdomen and pelvis, on a regular schedule in these cases. Some clinicians also routinely perform surveillance chest imaging for all patients with large, high-grade tumors, regardless of histology.

- **Leiomyoma** – Leiomyomas are benign smooth muscle tumors that occur predominantly in the esophagus, colon, and rectum. (See 'Leiomyomas and leiomyosarcomas' above.)

  - All well-circumscribed submucosal esophageal lesions that are >2 cm, enlarging, or fludeoxyglucose (FDG) avid should undergo preoperative endoscopic ultrasound (EUS) with fine needle aspiration (FNA), as these are not typical features of a leiomyoma.

  - Surgical removal is indicated if the tumor becomes symptomatic, enlarges to >1 cm or shows structural changes during surveillance, or malignancy is suspected.

  - Posttreatment follow-up is not required for leiomyomas.

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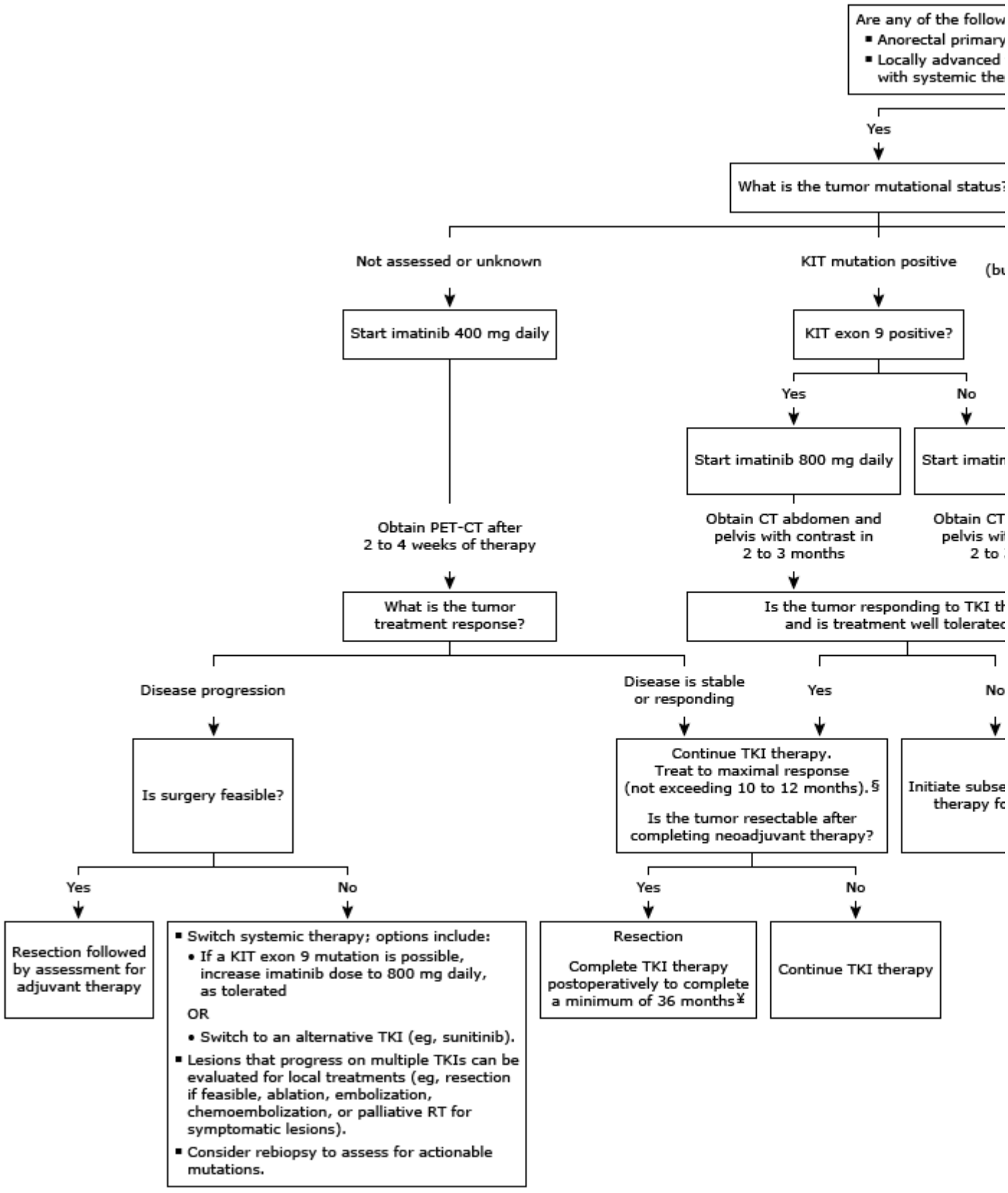
Topic 7727 Version 61.0

GRAPHICS

Neoadjuvant therapy for locally advanced gastrointestinal stromal tumors



The approach to neoadjuvant therapy in patients with a confirmed diagnosis of localized GIST is presented h
minimal surgical morbidity do not need neoadjuvant therapy. However, some patients with disease that is re
require neoadjuvant therapy prior to resection of the primary tumor. Multidisciplinary input is necessary fro
Clinical trials investigating neoadjuvant approaches are encouraged, where available.

The approach to adjuvant therapy for patients with localized GIST and systemic therapy for advanced and m

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GIST: gastrointestinal stromal tumor; TKI: tyrosine kinase inhibitor; RT: radiation therapy; CT: computed tom

* Neoadjuvant therapy may allow patients to switch from an open to a minimally invasive surgical approach
preserve the affected organ in those with disease involving the esophagus, esophagogastric junction, duod

¶ Tumor mutational status can be used to guide selection and dosing of neoadjuvant therapy, but it may no
practice or limited tissue availability. Some UpToDate contributors do not obtain further molecular testing fo
tumor histology and immunohistochemistry are consistent with either a KIT or PDGFRA mutation. For those
testing, repeat biopsy is not required if patients are responding to imatinib.

Δ We do not suggest the use of neoadjuvant avapritinib for PDGFRA D842V positive tumors. There are limite
setting, and there is a risk of long-term cognitive toxicity.

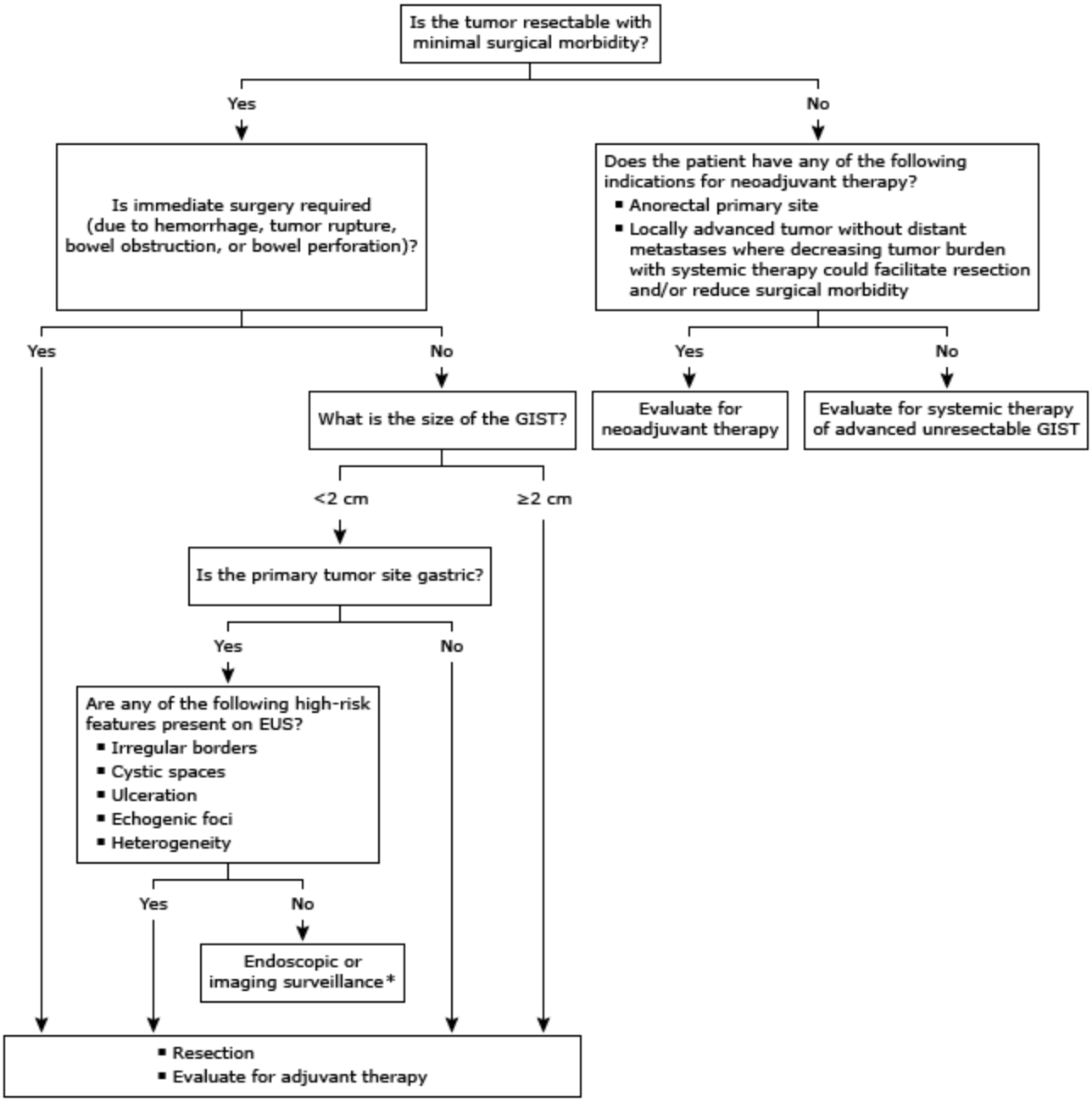
◇ For most patients on neoadjuvant therapy, we obtain a CT abdomen and pelvis with contrast to assess tre
months after initiating TKI therapy. Since GIST may increase in size during early treatment due to intratumo
treatment response is defined as the absence of progression at the time of first imaging disease re-evaluati

§ For most patients whose GIST is responding to neoadjuvant therapy, we obtain CT abdomen and pelvis wit
two to three months. In patients with stable disease at initial evaluation, maximal responses may be seen at

¥ Patients with high-risk tumors who are tolerating treatment well may elect to remain on imatinib for a tota
adjuvant imatinib for up to three years who discontinue therapy, disease recurrence has been reported with
suggesting that imatinib may maintain tumor dormancy rather than eradicate microdeposits.

Graphic 139727 Version 1.0

Initial management of localized gastrointestinal stromal tumors



While some patients with GIST are candidates for observation, most are treated with primary surgical resection. Systemic therapy may be offered either in the adjuvant setting to decrease recurrence risk or in the neoadjuvant setting to decrease tumor burden prior to surgical resection. Refer to UpToDate content on neoadjuvant and systemic therapy for GIST, which are discussed separately.

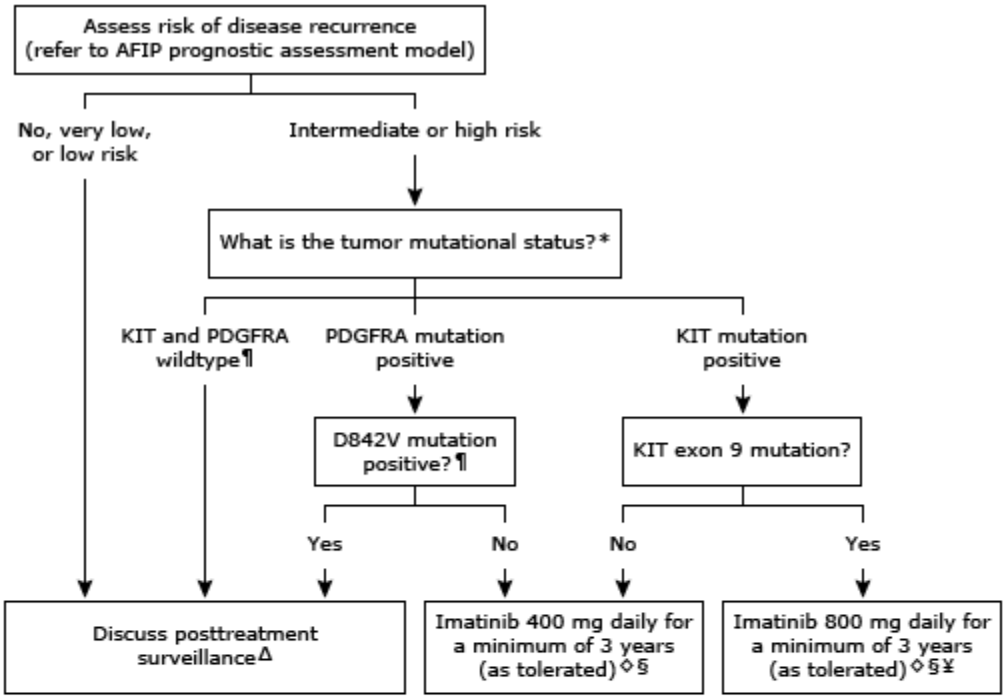
EUS: endoscopic ultrasound; GIST: gastrointestinal stromal tumor.

* EUS surveillance may be offered after a risk-benefit discussion with the patient. Data are limited for the optimal interval between surveillance studies. One approach is to have a short-term initial assessment (eg, within three to six months). If the tumor remains stable, then the follow-up

interval can be lengthened. The tumor should be resected if it cannot be assessed endoscopically, becomes symptomatic (eg, dysphagia), increases in size, or shows structural changes or high-risk endoscopic features on EUS. Refer to UpToDate content on local treatment for GIST.

Graphic 139723 Version 1.0

Adjuvant therapy for localized, resected gastrointestinal stromal tumors



AFIP prognostic model: Recurrence risk for gastrointestinal stromal tumors (GISTs) of the stomach, small intestine, and rectum by mitotic rate and tumor size

Tumor size (cm)	Risk of disease progression during long-term follow-up by primary site			
	Gastric	Jejunum/ ileum‡	Duodenum	Rectum
Mitotic rate† (HPF): ≤5/50				
≤2	No risk	No risk	No risk	No risk
2 to 5	Very low	Low	Low	Low
5 to 10	Low	Intermediate	Limited data	Limited data
>10	Intermediate	High	High	High
Mitotic rate† (HPF): >5/50				
≤2	No risk**	High**	Limited data	High
2 to 5	Intermediate	High	High	High
>5	High	High	High¶¶	High¶¶

Based on long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal cancers. Recurrence risk is based on clinical characteristics including tumor size, mitotic rate, and primary tumor site, among others. The AFIP prognostic model is most commonly used in the United States, although others are available. In this model, tumors are generally classified as no, low, intermediate, or high risk for recurrence. Refer to UpToDate content on adjuvant therapy for GIST.

The approach to adjuvant therapy for patients with resected GIST and no prior neoadjuvant therapy is presented here. Patients whose tumors are treated

with primary surgery and have completely resected disease should be evaluated for adjuvant therapy, which reduces the risk of disease recurrence.

GIST: gastrointestinal stromal tumor; EUS: endoscopic ultrasound; AFIP: Armed Forces Institute of Pathology; HPF: high-power fields.

* Assessment of tumor mutational status is advised for all patients with GIST who are being evaluated for adjuvant therapy. However, we often do not obtain mutational testing in patients with smaller GISTs (eg, 0.5 mm to 2 cm) and low mitotic rate who undergo complete resection; these patients are typically observed and mutational testing does not alter management. Refer to UpToDate content on clinical presentation and diagnosis of GIST.

¶ Surveillance is preferred over adjuvant therapy for patients with tumors that are PDGFRA D842V positive and those that are KIT and PDGFRA wildtype; these are typically resistant to imatinib and may harbor certain mutations (eg, SDH deficiency, *NF1*, *BRAF V600E*, *NTRK*, and *FGFR*).

Δ Patients with no-, very low-, or low-risk tumors do not require follow-up, although they should be informed that recurrences are still possible and surveillance imaging is available. Posttreatment surveillance is appropriate for most other groups.

◇ Patients with high-risk tumors who tolerate treatment may choose to remain on imatinib for a total of five years or longer. In patients treated with adjuvant imatinib for up to three years, disease recurrence has been reported within 6 to 12 months of stopping treatment, suggesting that imatinib may maintain tumor dormancy rather than eradicate microdeposits.

§ For patients with intermediate-risk disease, we suggest adjuvant therapy for a minimum of three years, after an informed discussion about the benefits and risks of this approach. Those who decline or are ineligible for adjuvant therapy are offered posttreatment surveillance.

¥ Patients with a KIT exon 9 mutation demonstrate some relative resistance to imatinib, and we suggest higher doses of imatinib (800 mg daily rather than 400 mg daily), although data are limited for this approach in the adjuvant setting.

‡ Patients with other anatomic primary sites (esophagus, mesentery, peritoneum) or those with limited data follow the risk stratification of jejunum/ileum tumors.

† Mitotic rate is counted in an area of 5 square millimeters (mm^2) on the glass slide section. For older microscopes with traditional field size optics, 50 HPF is equivalent to 5 mm^2. For modern microscopes with wider 40× lenses/fields, 20 HPF is equivalent to 5 mm^2. If necessary, the field of view should be measured to determine the actual number of HPF required to cover a 5 mm^2 area.[1]

** Small number of cases.

¶¶ Data are combined for tumors >5 cm. There are limited data for duodenal and rectal tumors between 5 and 10 cm in size.

Reference:

1. *Rubin BP, Blanke CD, Demetri GD, et al. Protocol for the examination of specimens from patients with gastrointestinal stromal tumor (GIST): Based on AJCC/UICC TNM, 7th edition, College of American Pathologists (CAP), Washington 2013.*

Inset table adapted from: Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23:70.

Graphic 139777 Version 2.0

Soft tissue sarcomas arising in the abdominal and thoracic viscera TNM staging AJCC UICC 8th edition*

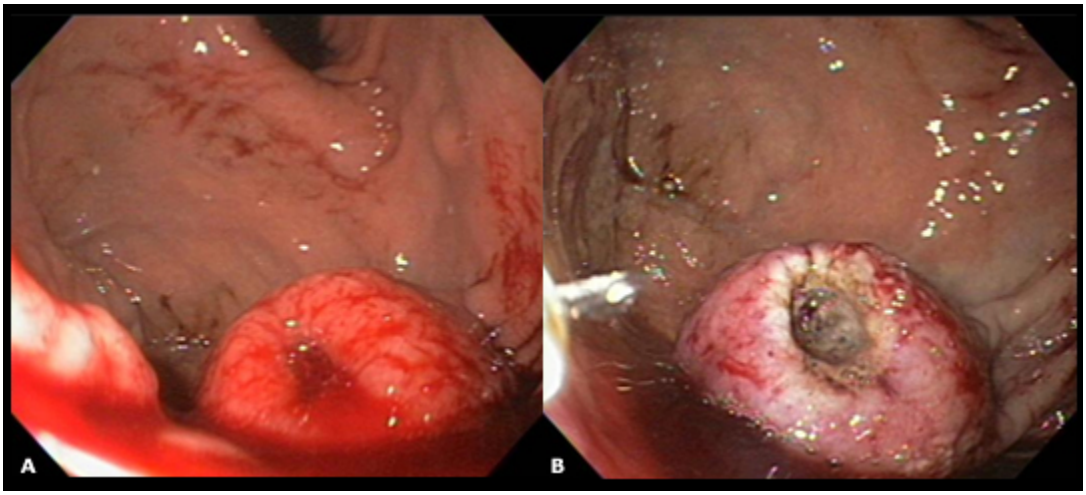
Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T1	Organ confined
T2	Tumor extension into tissue beyond organ
T2a	Invades serosa or visceral peritoneum
T2b	Extension beyond serosa (mesentery)
T3	Invades another organ
T4	Multifocal involvement
T4a	Multifocal (two sites)
T4b	Multifocal (three to five sites)
T4c	Multifocal (>5 sites)
Regional lymph nodes (N)	
N category	**N criteria**
N0	No lymph node involvement or unknown lymph node status
N1	Lymph node involvement present
Distant metastasis (M)	
M category	**M criteria**
M0	No metastases
M1	Metastases present

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

* There is no recommended prognostic stage grouping at this time.

Graphic 110739 Version 9.0

Gastrointestinal stromal tumor (GIST)

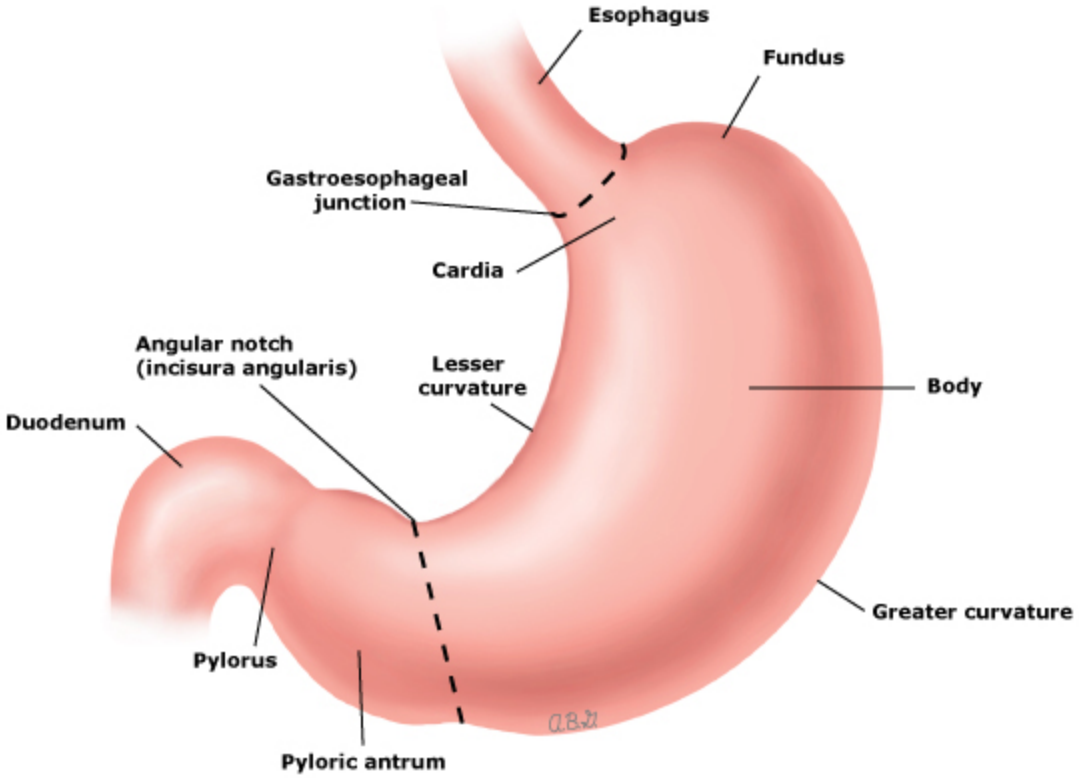


Endoscopic view of an actively oozing 20 by 30 mm submucosal mass in the stomach body (left panel). Bleeding was controlled by injection of a 1:10,000 epinephrine solution and bipolar electrocautery (right panel).

Courtesy of Kenneth Falchuk, MD and Andres Gelrud, MD.

Graphic 52275 Version 3.0

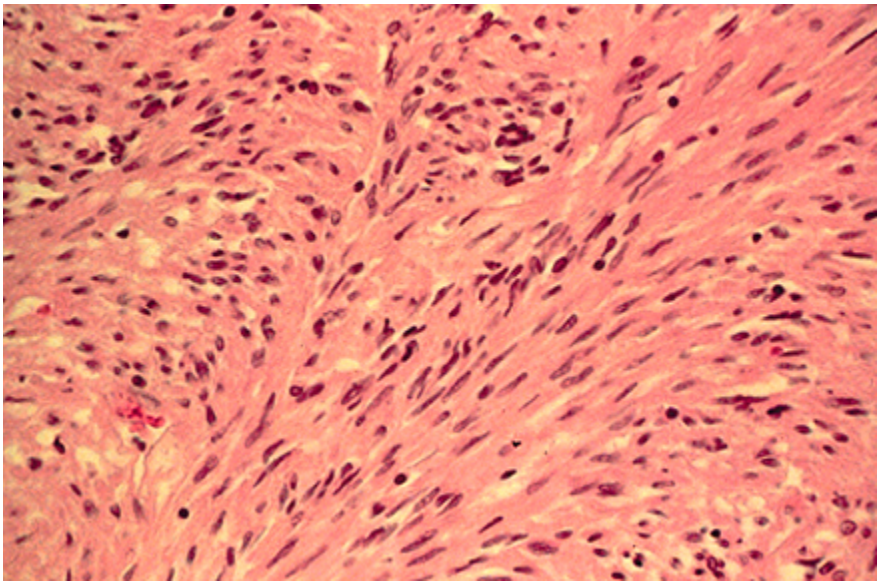
Parts of the stomach



This drawing shows the parts of the anterior surface of the stomach. The body of the stomach is separated from the pyloric part by an oblique line that extends from the angular notch (incisura angularis) on the lesser curvature to the greater curvature.

Graphic 79793 Version 4.0

Jejunal leiomyoma

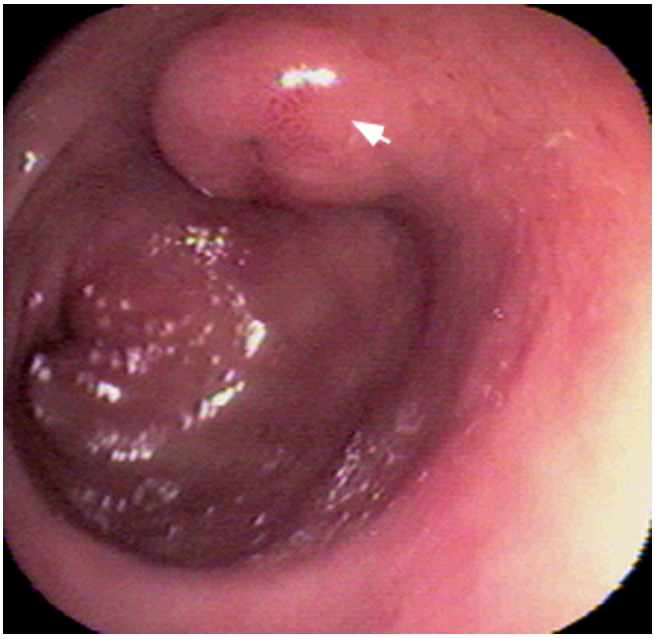


Medium power view of a jejunal leiomyoma shows sheets of short, spindled, and round cells.

Courtesy of Robert Odze, MD

Graphic 74175 Version 1.0

Gastric leiomyoma



Endoscopy shows a protuberance in the antrum with overlying normal appearing mucosa (arrow). The diagnosis of a gastric leiomyoma was made during a subsequent endoscopic ultrasound.

Courtesy of Laurence Bailen, MD.

Graphic 58068 Version 1.0

AFIP prognostic model: Recurrence risk for gastrointestinal stromal tumors (GISTs) of the stomach, small intestine, and rectum by mitotic rate and tumor size

Tumor size (cm)	Risk of disease progression during long-term follow-up by primary site			
	Gastric	Jejunum/ileum*	Duodenum	Rectum
Mitotic rate¶ (HPF): ≤5/50				
≤2	No risk	No risk	No risk	No risk
2 to 5	Very low	Low	Low	Low
5 to 10	Low	Intermediate	Limited data	Limited data
>10	Intermediate	High	High	High
Mitotic rate¶ (HPF): >5/50				
≤2	No risk[Δ]	High[Δ]	Limited data	High
2 to 5	Intermediate	High	High	High
>5	High	High	High[◇]	High[◇]

Based on long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal cancers.

AFIP: Armed Forces Institute of Pathology; HPF: high-power fields.

* Patients with other anatomic primary sites (esophagus, mesentery, peritoneum) or those with limited data follow the risk stratification of jejunum/ileum tumors.

¶ Mitotic rate is counted in an area of 5 square millimeters (mm^2) on the glass slide section. For older microscopes with traditional field size optics, 50 HPF is equivalent to 5 mm^2. For modern microscopes with wider 40× lenses/fields, 20 HPF is equivalent to 5 mm^2. If necessary, the field of view should be measured to determine the actual number of HPF required to cover a 5 mm^2 area.[1]

Δ Small number of cases.

◇ Data are combined for tumors >5 cm. There are limited data for duodenal and rectal tumors between 5 and 10 cm in size.

Reference:

1. *Rubin BP, Blanke CD, Demetri GD, et al. Protocol for the examination of specimens from patients with gastrointestinal stromal tumor (GIST): Based on AJCC/UICC TNM, 7th edition, College of American Pathologists (CAP), Washington 2013.*

Adapted from: Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23:70.

Graphic 139776 Version 4.0

AFIP prognostic model: progression-free survival for gastrointestinal stromal tumors (GISTs) of the stomach, small intestine, and rectum by mitotic rate and tumor size*

Tumor size (cm)	Percent of patients progression free during long-term follow-up by primary site			
	Gastric	Jejunum/ileum	Duodenum	Rectum
Mitotic rate¶ (HPF): ≤5/50				
≤2	100	100	100	100
2 to 5	98.1	95.7	91.7	91.5
5 to 10	96.4	76	66*	43*
>10	88	48		
Mitotic rate¶ (HPF): >5/50				
≤2	100Δ	50Δ	–	46
2 to 5	84	27	50	48
5 to 10	45	15	14*	29*
>10	14	10		

Based on long-term follow-up studies on 1055 gastric, 629 small intestinal, 144 duodenal, and 111 rectal cancers.

AFIP: Armed Forces Institute of Pathology; HPF: high-power fields.

* Data are combined for tumors >5 cm.

¶ Mitotic rate is counted in an area of 5 square millimeters (mm^2) on the glass slide section. For older microscopes with traditional field size optics, 50 HPF is equivalent to 5 mm^2. For modern microscopes with wider 40× lenses/fields, 20 HPF is equivalent to 5 mm^2. If necessary, the field of view should be measured to determine the actual number of HPF required to cover a 5 mm^2 area.[1]

Δ Small number of cases.

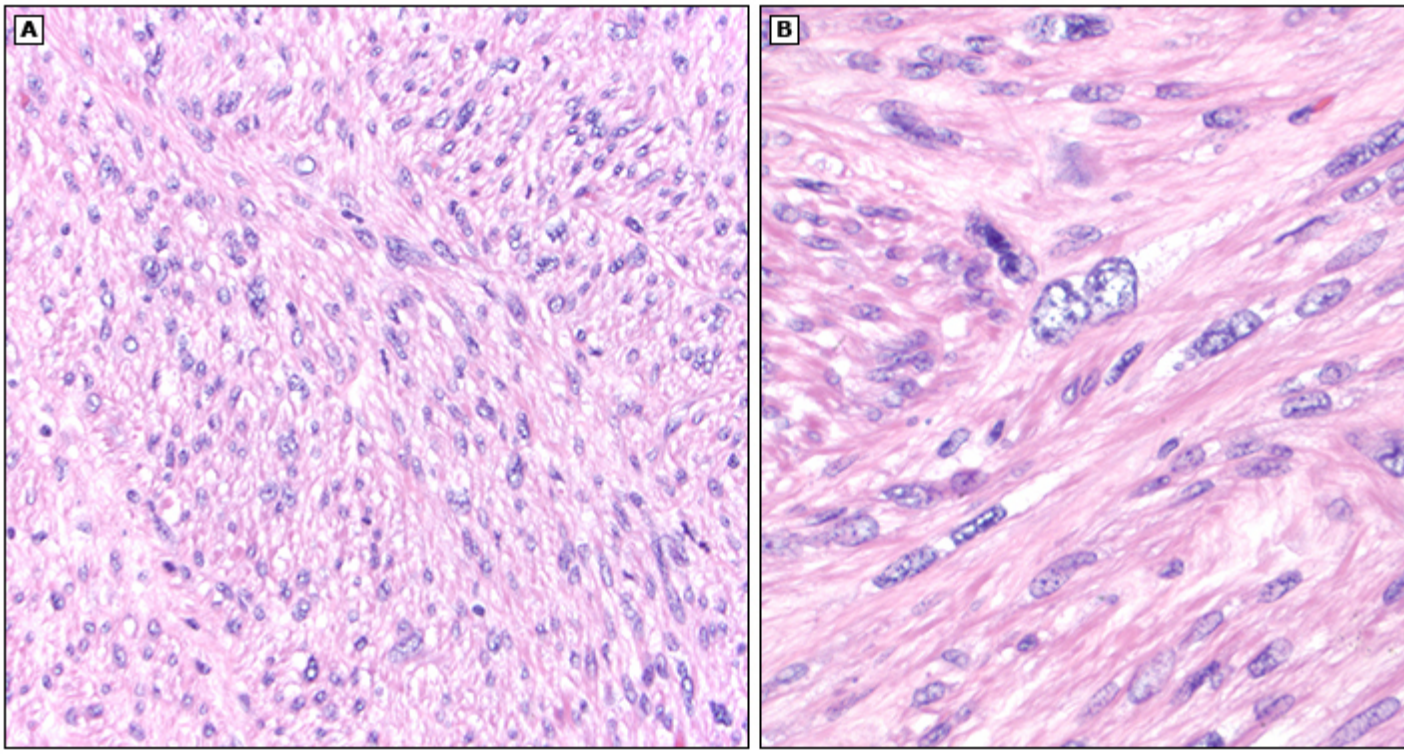
Reference:

1. *Rubin BP, Blanke CD, Demetri GD, et al. Protocol for the examination of specimens from patients with gastrointestinal stromal tumor (GIST): Based on AJCC/UICC TNM, 7th edition, College of American Pathologists (CAP), Washington 2013.*

Adapted from: Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23:70.

Graphic 60930 Version 9.0

Small bowel leiomyosarcoma



(A) Low power view of a small bowel leiomyosarcoma. Spindle cells are characteristically elongated and have abundant eosinophilic cytoplasm with well-defined cell borders and prominent perinuclear vacuoles. The tu cells are immunoreactive for desmin and actin as well as negative for *KIT* and *DOG1* (not shown), distinguish them from a gastrointestinal stromal tumor (GIST).

(B) The high power view reveals pleiomorphic spindle cells with nuclear pleomorphism and atypia.

Courtesy of Uma N. M. Rao, MD.

Graphic 114812 Version 2.0

Immunohistochemical schema for the differential diagnosis of spindle cell tumors of the gastrointestinal tract

Type	CD117	DOG-1	PKC-theta	CD34	SMA*	S100 protein	Desmin
GISTs	+ (>95%)	+ (97%)	+ (72%)	+ (60 to 70%)	+/– (30 to 40%)	– (5% +)	Very rare
Leiomyoma	–	–		+ (10 to 15%)	+	–	+
Leiomyosarcoma	–	–	+ (10%)	–	+	–	+
Schwannoma	–	–	+ (10%)	–	–	+	–

DOG-1: discovered on GIST-1; PKC-theta: protein kinase C theta; GISTs: gastrointestinal stromal tumors.

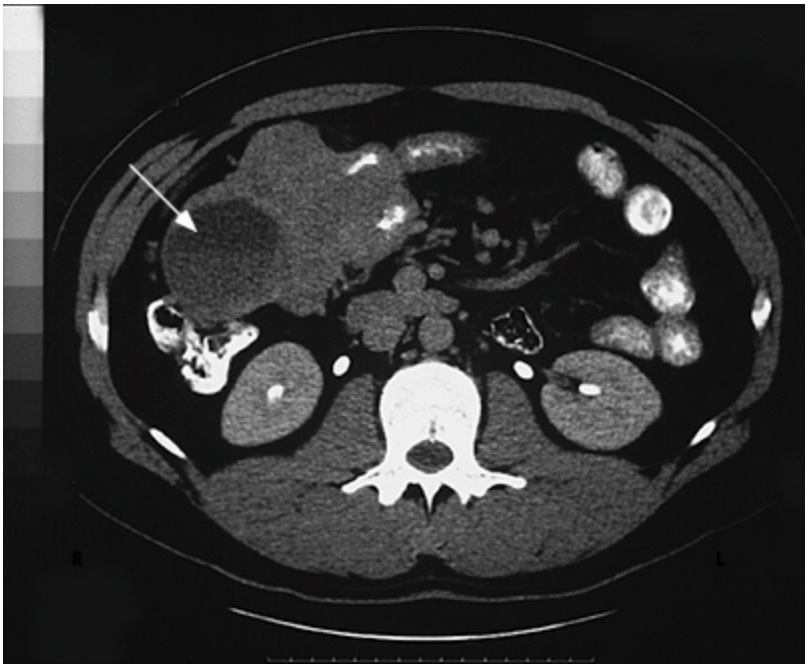
* Alpha smooth muscle actin.

Adapted from:

1. *Fletcher CD, Berman JJ, Corless C, et al. Diagnosis of gastrointestinal stromal tumors: a consensus approach. Int J Surg Pathol 2002; 10:81.*
2. *Miettinen M, Sobin LH, Sarlomo-Rikala M. Immunohistochemical spectrum of GISTs at different sites and their differential diagnosis with a reference to CD117 (KIT). Mod Pathol 2000; 10:1134.*
3. *Miettinen M, Wang ZF, Lasota J. DOG1 antibody in the differential diagnosis of gastrointestinal stromal tumors: a study of 1840 cases. Am J Surg Pathol 2009; 33:1401.*
4. *Duensing A, Joseph NE, Medeiros F, et al. Protein Kinase C theta (PKCtheta) expression and constitutive activation in gastrointestinal stromal tumors (GISTs). Cancer Res 2004; 64:5127.*

Graphic 79128 Version 5.0

Small bowel leiomyoma

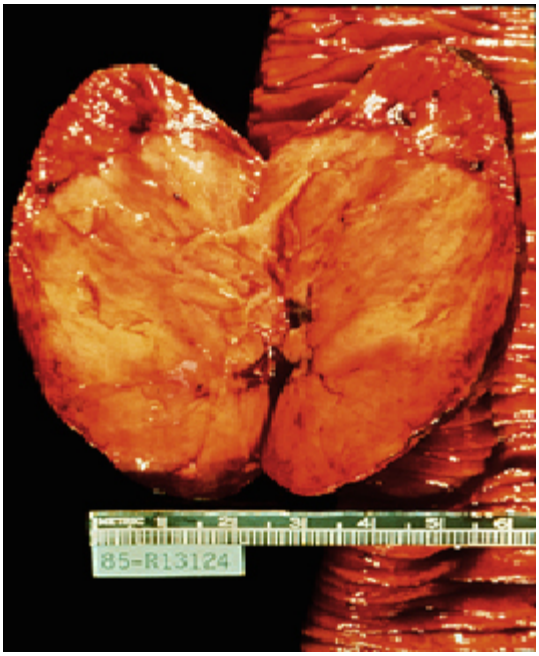


Preoperative CT scan shows a lobulated and cystic mass related to a loop of ileum. The small bowel leiomyoma has a focus of hemorrhage and necrosis (arrow).

CT: computed tomography.

Graphic 53060 Version 3.0

Jejunal leiomyoma



Surgical specimen of a large jejunal leiomyoma that caused a small bowel obstruction.

Courtesy of Robert Odze, MD.

Graphic 60327 Version 1.0

Response Evaluation Criteria in Solid Tumors (RECIST)

Response assessment	RECIST guideline, version 1.0[1]	RECIST guideline, version 1.1[2]
Target lesions		
CR	Disappearance of all target lesions	Disappearance of all target lesions and reduction in the short axis measurement of all pathologic lymph nodes to ≤10 mm
PR	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline	≥30% decrease in the sum of the longest diameter of the target lesions compared with baseline
PD	≥20% increase in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded since treatment started **OR** The appearance of 1 or more new lesions	≥20% increase of at least 5 mm in the sum of the longest diameter of the target lesions compared with the smallest sum of the longest diameter recorded **OR** The appearance of new lesions, including those detected by FDG-PET
SD	Neither PR nor PD	Neither PR nor PD
Non-target lesions		
CR	Disappearance of all non-target lesions and normalization of tumor marker levels	Disappearance of all non-target lesions and normalization of tumor marker levels
IR, SD	Persistence of 1 or more non-target lesions and/or the maintenance of tumor marker levels above normal limits	Persistence of 1 or more non-target lesions and/or the maintenance of tumor marker levels above normal limits
PD	Appearance of 1 or more new lesions and/or unequivocal progression of existing non-target lesions	The appearance of 1 or more new lesions or unequivocal progression If patient has measurable disease, an increase in the overall level or substantial worsening in non-target lesions, such that tumor burden has increased, even if there is SD or PR in target lesions If no measurable disease, an increase in the overall tumor burden comparable in

		magnitude with the increase that would be required to declare PD in measurable disease (eg, an increase in pleural effusions from trace to large, or an increase in lymphangitic disease from localized to widespread)

CR: complete response; PR: partial response; PD: progressive disease; FDG-PET: fludeoxyglucose positron emission tomography; SD: stable disease; IR: incomplete response.

References:

1. *Therasse P, Arbuck SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. J Natl Cancer Inst 2000; 92:205.*
2. *Eisenhauer E, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009; 45:228.*

Graphic 74693 Version 13.0

Contributor Disclosures

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Conflict of interest policy

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