Clinical presentation, diagnosis, and prognosis of gastrointestinal stromal tumors

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INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare mesenchymal neoplasms of the gastrointestinal tract. GISTs that arise from the bowel wall typically present as subepithelial neoplasms in the stomach and small intestine; however, they can also arise in any portion of the gastrointestinal tract and, occasionally, the omentum, mesentery, and peritoneum [1-5]. Most GISTs harbor characteristic mutations in *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA)*, while mutations in succinate dehydrogenase (*SDH*) or other genes are less frequent.

The clinical presentation, diagnosis, and prognosis of GISTs will be discussed here. The approach to treatment for localized (algorithm 1) and advanced GISTs (algorithm 2) is discussed separately.

- (See "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract".)
- (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors".)
- (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors".)

EPIDEMIOLOGY

GISTs are rare neoplasms that represent approximately 1 to 2 percent of primary gastrointestinal (GI) cancers [2,3,6]. Despite their rarity, GISTs are the most common mesenchymal (ie, nonepithelial) neoplasms of the GI tract [2,3].

Age of presentation

- **Adults** – GISTs occur predominantly in older adults, with a median age of diagnosis between 65 and 69 years [7-11]. GISTs rarely occur in those under the age of 40 years [7]. However, the age of diagnosis can range between 10 and 100 years old.

- **Pediatric patients** – Approximately 0.4 to 2 percent of GISTs arise in children and young adults under the age of 20 years [12]. Among pediatric patients with GIST, the median age at diagnosis is 15 years [12-15]. These patients typically have an underlying genetic predisposition to these neoplasms [13]. (See 'Genetic syndromes' below.)

Geographic incidence — The incidence of GISTs varies according to geographic location. In a systematic review of 29 studies conducted in 19 countries, the most commonly reported incidence rates were between 10 and 15 cases per million population per year [7]. The highest incidence rates were seen in China (Hong Kong and Shanghai), Taiwan, Korea, and Norway (19 to 22 cases per million population per year), whereas the lowest incidence rates were seen in the Shanxi province of China (4.3 cases per million population per year) as well as the Czech Republic and Slovakia (5.2 cases per million population per year). In the United States and Canada, the incidence of GISTs ranges between approximately 7 to 8 cases per million population per year [7,8,16-18].

It is important to note that the incidence of GISTs also depends upon the availability of accurate pathologic diagnostic criteria and is subject to selection bias. As an example, in one Surveillance, Epidemiology, and End Results (SEER) analysis of 6142 cases identified using a GIST-specific histology code, the incidence of GISTs rose between 2001 and 2011 from 5.5 to 7.8 cases per million population per year [8].

In addition, most GISTs are diagnosed incidentally, so the true incidence of this disease may be difficult to determine accurately. While some autopsy data suggest that gastric GISTs are more common than previously estimated (with tumors <1 cm identified in up to 35 percent cases) [19,20], other data suggest that only a few microscopic tumors grow to a clinically relevant size with malignant potential, which is consistent with the relatively low annual incidence rate of this disease [9].

Sex — GISTs are equally common in male and female patients (1:1 ratio) [7]. However, succinate dehydrogenase (*SDH)* deficient tumors, most frequently seen in pediatric patients, are twice as

common in females than males [21,22]. (See 'SDH-deficient tumors' below and 'GIST syndromes in pediatric and AYA patients' below.)

Ethnicity — In the United States, GISTs are more common among African Americans compared with other ethnicities [16,23]. In a SEER database analysis of 7204 patients with GISTs diagnosed between 2002 and 2015, African Americans had the highest overall incidence rate (13.7 cases per million population), followed by Asians/Pacific Islanders (11 cases per million population), White Americans (6.5 cases per million population), and American Indians/Alaskan Natives (2.8 cases per million population) [23].

PATHOGENESIS

GISTs represent a distinct entity from other mesenchymal tumors of the gastrointestinal (GI) tract [24]. GISTs were initially thought to be derived from smooth muscle, based upon histologic assessment. However, their immunohistochemistry profile differs from that of leiomyomas and leiomyosarcomas arising from other sites (eg, uterus or soft tissues). GISTs have near-universal expression of the CD117 antigen (table 1) [25], whereas true leiomyosarcomas, leiomyomas, and other spindle cell tumors of the gastrointestinal tract are typically CD117 negative. The CD117 antigen is synonymous with the transmembrane KIT receptor tyrosine kinase, which is the product of the *KIT* proto-oncogene (ie, *c-KIT*; the human homolog of the viral oncogene *v-KIT* [26]). Approximately 80 percent of GISTs carry a mutation in the *KIT* gene, leading to a structural variant of the KIT protein that is abnormally activated and enables oncogenic signaling in the cell [25,27-29]. (See 'Molecular alterations' below.)

GISTs likely originate from the interstitial cells of Cajal (ICCs), sometimes referred to as the GI pacemaker cells. ICCs are located in the intramuscular layer of the bowel wall below the epithelium; they regulate peristalsis by forming the interface between the autonomic innervation of the bowel wall and the smooth muscle itself [30]. GISTs arising in the GI tract typically present as subepithelial masses, which is generally consistent with the primary location of the ICCs. (See "Endoscopic ultrasound for the characterization of subepithelial lesions of the upper gastrointestinal tract", section on 'Gastrointestinal stromal tumors'.)

ICCs have the immunophenotypic and ultrastructural features of both smooth muscle and neuronal differentiation. It is assumed that GISTs originate from CD34-positive ICC stem cells within the wall of the GI tract and differentiate toward the pacemaker cell phenotype [31-33]. Therefore, a link between GISTs and ICCs has been proposed because both cell types can express KIT protein and CD34 [34]. An exception is the extremely rare "extragastrointestinal stromal tumor" (EGIST), a primary GIST that arises outside of the GI tract. EGISTs are

phenotypically identical to true GIST lesions of GI tract origin [4,35,36]. While this finding seemingly contradicts the hypothesis of GISTs arising from ICCs within the gut wall [32,37], it is thought that these tumors arise from ICCs that were accidentally dispersed during embryogenesis.

In support of the origin of GISTs from ICCs, resected tumors have been accompanied by diffuse ICC hyperplasia in the adjacent GI tract wall (Auerbach plexus) in several kindreds with primary familial GIST [21,37-40]. These are thought to represent precursor lesions to GIST in these patients. Diffuse ICC hyperplasia may also represent a precursor lesion to sporadic GIST [20]. In these cases, they must be distinguished from syndromic ICC hyperplasia seen in hereditary syndromes characterized by the development of GISTs [41]. (See 'Genetic syndromes' below.)

Various studies have elucidated the genetic events responsible for the transformation of microscopic GIST lesions (ie, those <1 cm in diameter) into clinically relevant GISTs. For example, homozygous inactivation of the basic helix-loop-helix leucine zipper (bHLHZ) transcription factor MYC-associated factor X (MAX) leads to p16 inactivation and cell cycle perturbation [42]. The presence of MAX inactivation in both microscopic GISTs/low-risk GISTs and metastases from the same patient indicates that it is likely an early step in GIST progression. Furthermore, inactivation of dystrophin (DMD, chromosome Xp21.1), which was present in more than 90 percent of metastatic GISTs in one study, is likely a late event in GIST progression [43].

GENETIC SYNDROMES

Although a majority of GISTs are sporadic, approximately 5 percent of patients with GISTs have one of several genetic syndromes associated with the development of these tumors. These genetic syndromes include primary familial GIST syndrome, neurofibromatosis type 1 (NF1), Carney-Stratakis syndrome, and Carney triad. Familial cases of GIST are indistinguishable from sporadic cases in terms of phenotype, histology, and molecular features. [44,45]. Patients diagnosed with GISTs who also present with clinical characteristics consistent with these syndromes should be referred for genetic counseling and appropriate germline testing. (See "Genetic counseling: Family history interpretation and risk assessment".)

Primary familial GIST syndrome — Patients with primary familial gastrointestinal stromal tumor (GIST) syndrome have tumors characterized by heritable mutations in either the *KIT* or platelet-derived growth factor receptor alpha (*PDGFRA*) genes [46-54]. These families have a predisposition to the early development of GISTs in multiple primary sites, such as the stomach and small intestine. In addition, patients with germline *KIT* mutations sometimes present with skin hyperpigmentation, dysphagia, or gastrointestinal (GI) autonomic nerve tumors, such as

paragangliomas [46-50]. By contrast, patients with germline *PDGFRA* mutations often present with intestinal fibromatosis and inflammatory fibroid polyps, a diagnosis formerly classified as intestinal neurofibromatosis/neurofibromatosis 3b (INF/NF3b) [52-54].

Neurofibromatosis type 1 — Patients with NF1 have a high incidence of GISTs, which occur most frequently in the small intestine (>70 percent) [44,55]. GISTs associated with NF1 are often multifocal, have spindled histology, and have low mitotic rates. Somatic mutations in the *KIT* or *PDGFRA* genes are rare among these tumors, in contrast with sporadic cases of GISTs [44,45]. Nevertheless, KIT is often expressed in these *KIT*/*PDGFRA* wild-type tumors, but the mechanism of overexpression is not clear. Further details on the clinical features and diagnosis of NF1 are discussed separately. (See "Neurofibromatosis type 1 (NF1): Pathogenesis, clinical features, and diagnosis", section on 'Soft tissue sarcomas'.)

GIST syndromes in pediatric and AYA patients — Carney-Stratakis syndrome and Carney triad are syndromes commonly associated with the development of GISTs in pediatric, adolescent and young adult (AYA) patients [56]. These syndromes are typically characterized by succinate dehydrogenase (*SDH*) deficient tumors. Approximately 85 percent of pediatric and AYA patients with GIST lack oncogenic mutations in *KIT* and *PDGFRA*, and a majority of these are characterized by molecular alterations in the *SDH* family of genes. (See 'KIT/PDGFRA wild-type GISTs' below and 'SDH-deficient tumors' below.)

Carney-Stratakis syndrome (dyad) — Carney-Stratakis syndrome, also referred to as Carney-Stratakis dyad, is an autosomal dominant disorder with incomplete penetrance that is typically diagnosed in children and young adults at a median age of 19 to 21 years [57]. Patients with this rare, heritable condition present with the dyad of GISTs and paragangliomas. (See "Paragangliomas: Epidemiology, clinical presentation, diagnosis, and histology", section on 'Carney-Stratakis dyad'.)

GISTs in patients with Carney-Stratakis syndrome are not commonly associated with mutations in *KIT* or *PDGFRA* [58]. Rather, in many cases, they are associated with germline mutations in the *SDH* gene, which cause loss of function of an SDH family enzyme (typically SDHB, SDHC, or SDHD) [59-61]. Patients with GIST who are suspected of having Carney-Stratakis syndrome should undergo genetic testing for germline abnormalities in the *SDH* gene [62-64]. Further details on *SDH*-deficient GISTs are discussed below. (See 'SDH-deficient tumors' below.)

Carney triad — Carney triad is an extremely rare syndrome consisting of GIST, paraganglioma, and pulmonary chondromas [65]. It predominantly affects young women and is generally considered to be a nonhereditary disorder caused by hypermethylation of the SDHC promoter. This results in epigenetic inactivation of the *SDHC* gene locus with functional impairment of the

SDH complex [57,65-68]. However, almost 10 percent of patients harbor germline variants in *SDHA*, *SDHB*, or *SDHD*, suggesting that there might be a hereditary contribution to Carney triad in some cases [69]. (See 'KIT/PDGFRA wild-type GISTs' below and "Paragangliomas: Epidemiology, clinical presentation, diagnosis, and histology" and "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract".)

CLINICAL PRESENTATION

Location

- **Primary tumor** – GISTs occur throughout the gastrointestinal (GI) tract from the esophagus to the anus. Within the GI tract, primary tumor sites are most common in the stomach (40 to 60 percent) and jejunum/ileum (25 to 30 percent) [16,70-72]. Less common sites include the esophagus (≤1 percent), duodenum (5 percent), colorectum (5 to 15 percent), and anus (<0.5 percent) [73]. Extragastrointestinal stromal tumors (EGISTs) are rare tumors (<5 percent) that lack any association with the bowel wall and occur in the retroperitoneum, mesentery, and omentum [4,12,36,72]; however, these could also be metastases from an undetected primary tumor.

  The presentation of GISTs varies depending on the primary tumor location [74]. For example, GISTs involving the upper GI tract (eg, stomach, small intestine, or esophagus) could present with GI bleeding, dysphagia, or obstructive jaundice, whereas those involving the colon or rectum could present with constipation, bowel obstruction, or urinary hesitancy in men (due to a rectal tumor abutting the prostate [75]). (See "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'Presentation and management at specific sites'.)

- **Metastatic disease** – Approximately 10 to 20 percent of patients present with metastatic disease. Patients with multifocal disease are usually classified as advanced (metastatic) stage, although some (particularly those with rare hereditary conditions) are affected by multiple primaries [76]. (See 'Primary familial GIST syndrome' above.)

  The most common sites of metastases are the liver, omentum, and peritoneum, and these could present with abdominal pain or bowel obstruction. GISTs rarely metastasize to abdominal lymph nodes (except in pediatric patients) or outside the abdominal cavity. Pulmonary metastases are also uncommon with GISTs, unlike most soft tissue sarcomas. (See 'Evaluation for metastatic disease' below and "Clinical presentation, histopathology,

diagnostic evaluation, and staging of soft tissue sarcoma", section on 'Clinical presentation'.)

Presenting symptoms by age — Adult patients with GISTs typically have a different clinical presentation compared with pediatric patients, which is discussed below. (See 'Pediatric and AYA patients' below.)

Adults — Adult patients with GISTs commonly present with the following symptoms [10,12,77-79]:

- Overt or occult GI bleeding – 28 percent (small intestine) and 50 percent (gastric)
- Incidental finding (asymptomatic) – 13 to 25 percent
- Abdominal pain/discomfort – 8 to 17 percent
- Acute abdomen – 2 to 14 percent
- Asymptomatic abdominal mass – 5 percent

Patients with GISTs can present with a wide range of symptoms. Most patients with subepithelial masses are asymptomatic, and their tumors are often discovered incidentally. For example, GISTs can be detected during an endoscopic study; elective surgical procedures (eg, sleeve gastrectomy for patients with obesity [80]); or on imaging done for another purpose. Other patients with indolent endoluminal progression of the primary tumor may present with nonspecific chronic symptoms (eg, early satiety or bloating). (See "Endoscopic ultrasound for the characterization of subepithelial lesions of the upper gastrointestinal tract", section on 'Gastrointestinal stromal tumors' and "Bariatric procedures for the management of severe obesity: Descriptions", section on 'Sleeve gastrectomy'.)

However, some tumors may eventually grow large enough to ulcerate or cause pain [81,82]. In certain circumstances, such patients may present with symptoms that require urgent clinical evaluation such as tumor rupture, GI bleeding, bowel perforation, or GI obstruction [12]. (See "Approach to acute lower gastrointestinal bleeding in adults" and "Approach to acute upper gastrointestinal bleeding in adults" and "Overview of gastrointestinal tract perforation" and "Etiologies, clinical manifestations, and diagnosis of mechanical small bowel obstruction in adults".)

Paraneoplastic syndromes are rare in adult patients with GISTs; however, potential paraneoplastic syndromes have been reported in a few patients, including non-islet cell tumor hypoglycemia and consumptive hypothyroidism [83].

- **Consumptive hypothyroidism** – In treatment-naïve patients with GIST, consumptive hypothyroidism occurs due to excessive degradation of thyroid hormone caused by

overexpression of the thyroid hormone inactivating enzyme type 3 iodothyronine deiodinase (D3) within large GISTs. (See "Disorders that cause hypothyroidism", section on 'Consumptive hypothyroidism' and "Toxicity of molecularly targeted antiangiogenic agents: Non-cardiovascular effects", section on 'Thyroid dysfunction'.)

Patients with GIST who present with this condition typically require high levels of thyroid hormone supplementation. Consumptive hypothyroidism is not considered a treatment-related toxicity related to tyrosine kinase inhibitors (TKIs); nevertheless, patients with consumptive hypothyroidism who initiate TKI therapy need close monitoring of thyroid function, with adjustment of thyroid supplementation as needed. Referral to an endocrinologist is indicated in patients with consumptive hypothyroidism who are severely symptomatic and/or are having difficulty managing thyroid supplementation. Further details on the management of consumptive hypothyroidism are discussed separately. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Side effects and management' and "Treatment of primary hypothyroidism in adults", section on 'Persistent elevation in TSH'.)

Pediatric and AYA patients — Pediatric and adolescent and young adult (AYA) patients have a different clinical presentation compared with adults. In these patients, the most common presenting symptoms and signs are GI bleeding, fatigue, and anemia. These patients also have a more indolent disease course, despite the higher propensity for multifocal gastric tumors and lymph node metastases, disease recurrence, and metastatic disease [84-86]. (See 'Other risk factors' below.)

Additionally, patients with the Carney-Stratakis dyad or Carney triad can present with paragangliomas and their associated symptoms, such as catecholamine secretion or mass effect. Further details on the clinical presentation of paragangliomas are discussed separately. (See "Paragangliomas: Epidemiology, clinical presentation, diagnosis, and histology".)

Physical examination — In all patients with suspected GISTs, the physical examination should include a detailed abdominal examination. GISTs may present as palpable abdominal masses either due to the primary tumor or intra-abdominal metastases (eg, liver, omentum, or peritoneum). Signs of acute abdomen or peritonitis may indicate the presence of GI bleeding, tumor rupture, bowel perforation, or GI obstruction. However, most patients with localized GISTs may have no specific physical exam findings, as some tumors present without symptoms, and extra-abdominal metastases are rare. (See "Evaluation of the adult with abdominal pain", section on 'Diagnostic approach to acute abdominal pain'.)

DIAGNOSTIC EVALUATION

GISTs are detected either incidentally in asymptomatic patients, or during the evaluation of the symptomatic patient. As such, the diagnostic evaluation in patients with GISTs often requires attention to specific clinical findings as well as a high level of suspicion for the disease. Both imaging and endoscopic procedures are necessary to the initial diagnostic evaluation of GISTs.

Imaging the primary tumor — In patients with suspected GIST, we suggest imaging using computed tomography (CT) for initial evaluation of the primary tumor. Magnetic resonance imaging (MRI) is a reasonable alternative in patients who cannot receive CT contrast or have a rectal primary. We typically do not choose positron emission tomography (PET) scanning using fluorodeoxyglucose (FDG-PET) in combination with CT (PET-CT) to evaluate the primary tumor because it is not sufficiently specific to make a preoperative diagnosis.

- **CT** – Contrast-enhanced CT of the abdomen and pelvis is the imaging method of choice to characterize an abdominal mass suspicious for GIST. Oral as well as intravenous contrast should be administered to define the bowel margins. The usual CT appearance of a GIST is that of a solid, smoothly contoured mass that enhances brightly with intravenous contrast. Very large tumors (>15 cm) may appear more complex due to necrosis, hemorrhage, or degenerating components (image 1).

  CT imaging can also assess for the extent of the primary mass, including local invasion into adjacent structures. However, it may be difficult to identify the primary location of a large mass on CT because of exophytic growth. CT also can better visualize small intestinal thickness and the presence of bowel perforation when compared with MRI [87].

- **MRI** – Although CT remains the preferred initial diagnostic imaging study for the evaluation of a suspected GIST, MRI of the abdomen and pelvis has a comparable diagnostic yield compared with CT and lacks radiation exposure [88]. MRI may also be offered as an alternative to CT in patients who cannot receive intravenous CT contrast. (See "Radiation-related risks of imaging".)

  MRI may also be preferred over CT to evaluate primary rectal GISTs or those undergoing preoperative evaluation. Small GISTs on MRI appear round and symmetric, whereas larger GISTs are asymmetric and lobulated [74]. (See 'Rectal EUS versus MRI' below.)

- **PET-CT** – PET-CT has not replaced CT or MRI as the initial imaging modality of choice in patients suspected of having a GIST. PET-CT imaging is highly sensitive for detecting

tumors with a high glucose metabolism, including GISTs [89]; however, it is not sufficiently specific to make a preoperative diagnosis.

The approach to imaging metastatic disease in patients with a confirmed diagnosis of GIST is discussed below. (See 'Evaluation for metastatic disease' below.)

Diagnostic procedures — Procedures that lead to the diagnosis of GIST are chosen based on the sites of primary and metastatic disease.

Upper endoscopy with EUS — Upper endoscopy with endoscopic ultrasound (EUS) is the preferred diagnostic procedure to further characterize upper gastrointestinal (GI) tumors suspicious for GIST involving the stomach, small intestine, or esophagus. GISTs present with characteristic findings on both endoscopy and EUS. (See "Endoscopic ultrasound for the characterization of subepithelial lesions of the upper gastrointestinal tract", section on 'Gastrointestinal stromal tumors'.)

On endoscopy, both GISTs and leiomyomas may appear as a submucosal mass with smooth margins, with a normal overlying mucosa, and bulging into the gastric lumen. Central ulceration is occasionally seen (picture 1).

The addition of EUS to endoscopy can distinguish intramural from extramural tumors by identifying the layer of origin. On EUS, GISTs are typically hypoechoic, homogeneous lesions with well-defined margins, although they can rarely have irregular margins and ulcerations. Most GISTs originate from within the muscularis propria (fourth layer of the GI tract); small lesions may originate from the muscularis mucosa (second layer). Infrequently, the tumors are inhomogeneous, which has been attributed to liquefaction necrosis, connective tissue, and cystic and hyaline degeneration. Further details on the endosonographic findings of GISTs are discussed separately. (See "Endoscopic ultrasound for the characterization of subepithelial lesions of the upper gastrointestinal tract", section on 'Endosonographic findings in GISTs'.)

Furthermore, EUS enables guided-tissue acquisition for diagnostic studies, including immunohistochemistry (IHC), which is discussed below. (See 'Indications for preoperative biopsy' below.)

Colonoscopy — Colonoscopy is used to identify masses suspicious for GIST that present in the colon, rectum, and anus. Colorectal GISTs are extremely rare and comprise approximately 0.1 percent of all colorectal tumors [90]. Small colonic polypoid masses can be resected endoscopically. However, masses that are larger or subepithelial are more challenging to biopsy using endoscopy alone, as this approach could result in inadequate tissue sampling for a definitive diagnosis, bleeding, and/or seeding of the biopsy tract with tumor. Therefore, these

masses should either be surgically resected or (in the case of rectal GISTs) sampled using EUS-guided biopsy. (See 'Rectal EUS versus MRI' below and 'Indications for surgical resection' below.)

Rectal EUS versus MRI — Both rectal endoscopic ultrasound (EUS) and/or magnetic resonance imaging (MRI) may play a role in the diagnostic evaluation of suspected rectal GISTs. A similar imaging approach may also be used for patients with extremely rare anal GISTs.

- **Rectal EUS** – Rectal EUS may be useful to help delineate anatomy prior to EUS-guided fine needle aspiration (EUS-FNA) of rectal GISTs. However, because rectal GISTs often lack nodal involvement, it does not have as much utility in the nodal staging of these tumors as in rectal adenocarcinomas. (See "Endoscopic ultrasound for evaluating patients with rectal cancer".)

- **MRI** – MRI of the abdomen and pelvis may be offered to patients with rectal GISTs in order to delineate the anatomic extent of disease prior to surgery. Characteristic MRI findings of rectal GISTs include low to intermediate signal intensity on T1-weighted images and a heterogeneous or homogeneous high signal intensity on T2-weighted images [91]. (See "Principles of magnetic resonance imaging" and 'Indications for surgical resection' below.)

Tissue sampling

Indications for preoperative biopsy — The preoperative diagnosis of GISTs requires a high degree of suspicion and familiarity with its radiologic or endoscopic appearance. For patients with large, locally advanced lesions suspected to be GIST, we suggest preoperative biopsy rather than initial surgical resection to confirm the diagnosis, especially for patients with metastatic disease or those eligible for neoadjuvant imatinib. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Neoadjuvant therapy'.)

Approaches to biopsy

EUS-guided biopsy (primary tumor) — For patients undergoing preoperative biopsy of the primary tumor, we suggest endoscopic ultrasound (EUS)-guided tissue sampling rather than endoscopic sampling alone or percutaneous biopsy [92]. Tissue acquisition can be performed using either EUS-FNA or EUS-guided fine needle biopsy (EUS-FNB). (See "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract" and "Endoscopic ultrasound-guided fine needle biopsy in the gastrointestinal tract".)

- **EUS-guided fine needle aspiration** – The diagnosis of most GIST tumors may be obtained using EUS-FNA, along with the combined use of cytologic analysis, IHC for KIT protein expression, and genetic analysis for characteristic GIST mutations. In one study of 65

patients undergoing EUS-FNA for an upper gastrointestinal tract submucosal lesion, among the 28 lesions with a definitive pathologic diagnosis, the sensitivity for diagnosis of GIST was 82 percent and the specificity was 100 percent [93]. (See "Endoscopic ultrasound-guided fine needle aspiration in the gastrointestinal tract", section on 'Upper GI tract lesions'.)

- **EUS-guided fine needle biopsy** – Endoscopic biopsies alone using standard techniques usually do not obtain sufficient tissue for a definite diagnosis of GIST [94]. While EUS-FNB forceps also may not yield enough tissue, their main utility is to exclude other lesions that arise submucosally. Snare biopsies (in which a polypectomy snare is used to remove a large piece of tissue) can result in perforation of GISTs and generally should be avoided, except in carefully selected cases [94].

Percutaneous biopsy — For patients who are unable to undergo successful EUS-guided biopsy of the primary tumor, image-guided percutaneous biopsy is an alternative option to sample either the primary tumor or distant metastatic sites. However, percutaneous biopsy is less-preferred due to the potential risk of primary tumor rupture or spread of metastatic disease. Such patients may also be evaluated for surgical resection. (See 'Indications for surgical resection' below.)

- **Percutaneous biopsy of the primary tumor** – Image-guided percutaneous biopsy of the primary tumor carries the theoretical risk of rupture of the tumor capsule with peritoneal spread of disease. However, there is no evidence in patients receiving imatinib that individuals undergoing a percutaneous biopsy have inferior outcomes compared with those who do not [95]. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors" and "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors".)

- **Percutaneous biopsy of metastatic disease** – Image guided percutaneous biopsy may be used to biopsy distant sites of metastatic disease, such as the liver, omentum, or peritoneum. This approach may be used in patients whose primary site has been biopsied via alternative approaches (such as EUS-guided biopsy) and the pathologic diagnosis of GIST still remains in question (eg, due to inadequate tissue sampling) or if the metastatic site is more accessible for biopsy than the primary tumor site. The most common modalities include CT- or ultrasound-guided biopsy. Image guided percutaneous biopsies should be performed at institutions that specialize in such procedures, given the theoretical risk of peritoneal spread of disease or biopsy tract seeding with this procedure (See "Approach to liver biopsy".)

Indications for surgical resection — Surgical resection of the primary tumor is indicated for disease that cannot be safely biopsied, or when initial biopsy attempts have been either unsuccessful or non-diagnostic. Patients with unresectable or metastatic disease may also undergo surgical resection of a symptomatic primary tumor if it requires immediate surgical intervention (eg, due to hemorrhage, tumor rupture, bowel obstruction, or gastrointestinal perforation). (See 'Evaluation for metastatic disease' below.)

The approach to surgical resection of GISTs based on primary tumor site is discussed separately. (See "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'Presentation and management at specific sites'.)

DIAGNOSIS

The diagnosis of GISTs is established using histopathology, immunohistochemistry (IHC), and identification of disease-specific mutations characteristic to these neoplasms.

Histopathology

Cellular morphology — The cellular morphology of GISTs ranges from predominantly spindle shaped to epithelioid in character. Histologically, the appearance of these tumors usually falls into one of three relatively uniform categories:

- Spindle cell type – 70 percent
- Epithelioid type – 20 percent
- Mixed type – 10 percent

GISTs of the spindle cell type are composed of relatively uniform eosinophilic cells arranged in short fascicles or whorls (picture 2) [30]. Compared with leiomyomas, the eosinophilic cytoplasm is paler and often has a fibrillary appearance. The nuclei tend to be uniform, and there may be juxtanuclear cytoplasmic vacuoles and nuclear palisading. Stromal collagen is minimal in most cases, and stromal hemorrhage is a common feature. Marked cytologic pleomorphism is rare and should raise the possibility of an alternative diagnosis if present.

GISTs of the epithelioid type are composed of rounded cells with variably eosinophilic or clear cytoplasm (picture 2) [34]. They tend to have round to oval nuclei with vesicular chromatin, and the architecture may be nested, potentially leading to confusion with an epithelial or melanocytic neoplasm. Interestingly, epithelioid type GISTs are more often KIT-expression negative, harbor platelet-derived growth factor receptor alpha (*PDGFRA*) mutations, and are

present most often in the stomach [5]. Epithelioid GISTs are also more common in pediatric than in adult patients [88,96].

GISTs of the mixed type may have areas of abrupt transition between spindle and epithelioid areas or complex intermingling of both cell types throughout (picture 3).

Immunohistochemistry — IHC staining can help to distinguish GISTs from other subepithelial tumors that may arise in the gastrointestinal tract (table 1). (See 'Differential diagnosis' below.)

- **KIT (CD117)** – The most prominent diagnostic marker of GIST is the near universal overexpression of the receptor tyrosine kinase KIT (CD117), which is easily identified by positive IHC staining (picture 4). However, the relationship between expression of the KIT protein (CD117) and the *KIT* mutation in GISTs is not entirely straightforward. (See 'KIT mutations' below.)

  Approximately 95 percent of GISTs are positive for KIT expression on IHC, and a majority are due to known *KIT* mutations. However, some GISTs that express KIT are *KIT* mutation negative. Overexpression of KIT and presumably aberrant KIT signaling may be present even in the absence of *KIT* mutations, especially in pediatric GISTs and GISTs that arise in the setting of neurofibromatosis type 1 (NF1) [21,39,44,45,97]. These tumors typically stain on IHC for KIT but are *KIT* wild-type (ie, have no detectable mutations in the *KIT* gene), and they have a poor response to imatinib [45]. In tumors deficient of succinate dehydrogenase (*SDH*) without an identifiable *KIT* mutation, there is evidence that the mechanism of KIT overexpression is related to epigenetic changes near the *KIT* oncogene [98]. (See 'KIT/PDGFRA wild-type GISTs' below.)

  GISTs that are negative for KIT expression on IHC account for 4 to 5 percent of cases. Within this small subset tumors, many also lack *KIT* mutations, and some instead harbor activating mutations in the *PDGFRA* gene [99,100]. By contrast, in some GISTs that do not express KIT on IHC, *KIT* gene mutations have been detected, suggesting that transcriptional silencing has occurred via a different mechanism [101]. This phenomenon also tends to occur as part of a resistance mechanism during imatinib therapy [102]. In such patients and in those with an unclear diagnosis, mutational analysis is necessary to confirm the diagnosis of GIST. (See 'Molecular alterations' below.)

- **DOG-1 and PKC-theta** – DOG-1 (discovered on GIST-1) and PKC-theta (protein kinase C theta) are two immunohistochemical markers that are positive in GIST irrespective of *KIT* or *PDGFRA* mutational status. DOG-1 especially has become a widely used diagnostic marker in addition to KIT IHC [102-107].

- **Other markers** – Between 60 to 70 percent of GISTs are positive for **CD34**; 30 to 40 percent for **smooth muscle actin**; 5 percent for **S-100 protein**; and 1 to 2 percent for **desmin or keratin** [1,25,108].

Molecular alterations — Molecular alterations that are commonly identified in GISTs include mutations in *KIT*, *PDGFRA*, and the family of *SDH* genes. Other molecular aberrations can be present but are much less common. (See 'Other mutations' below.)

Approach to testing — Concurrent with initiation of first-line therapy with imatinib, an assessment of *KIT/PDGFRA* tumor mutational status using DNA sequencing techniques is advised during the initial evaluation of most patients diagnosed with GIST because clinical responses to systemic therapy (eg, imatinib and other tyrosine kinase inhibitors) correlate with tumor genotype. The approach to molecular testing varies based on institutional practices and available techniques (eg, next-generation sequencing [NGS] versus assessment of individual mutations) [109]. If pursued, at minimum, molecular testing should assess for *KIT* mutations. If no *KIT* mutation is detected, reflex testing can be obtained for *PDGFRA* mutations. If the tumor is negative for both *KIT* and *PDGFRA* mutations, extended panel testing can be sent to assess for less common mutations. SDH-deficient tumors are typically diagnosed based on expert pathology review of tumor morphology and immunohistochemistry. (See 'KIT/PDGFRA wild-type GISTs' below.)

However, molecular analysis is not required as part of initial assessment for all patients. 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. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors".)

Similarly, some UpToDate contributors do not obtain further molecular testing for patients receiving neoadjuvant imatinib whose tumor histology and immunohistochemistry are consistent with either a *KIT* or *PDGFRA* mutation. For those with insufficient tissue samples for molecular testing, repeat biopsy is not required if patients are responding to imatinib. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Neoadjuvant therapy'.)

KIT mutations — Approximately 95 percent of GISTs in adults overexpress the tyrosine kinase receptor KIT. Approximately 80 percent of GISTs have *KIT* gene mutations that lead to constitutive activation of the KIT receptor [2,25,27,28,101,110,111]. These gain-of-function mutations in *KIT* are observed in both sporadic and hereditary cases. (See 'Immunohistochemistry' above.)

The *KIT* proto-oncogene has been postulated to play an important role in tumorigenesis [2,25,27,28,37,46,101,110,111]. In normal cells, KIT receptor tyrosine kinase activity is regulated by binding of the endogenous ligand for the receptor (known as KIT ligand or stem cell factor [SCF]) [38]. *KIT* mutations, however, lead to a ligand-independent activation of KIT; this results in constitutive activation of downstream signaling pathways that stimulate cell survival, growth, and proliferation (figure 1) [112]. *KIT* mutations in GIST can occur in different exons of the gene and can be either point mutations, deletions, or insertions. There is no single mutational hotspot, although some regions are affected more often than others.

Primary *KIT* mutations in GISTs most commonly occur in exons 11 and 9 and more rarely in exons 13, 17, 14, and 18 (figure 2):

- **Exon 11** – Exon 11 is the most common *KIT* mutation and occurs in approximately 70 percent of newly diagnosed GISTs [25,112]. This mutation codes for the intracellular juxtamembrane domain of the receptor. This region usually has an autoinhibitory function on kinase activation, which is alleviated by the mutation.

- **Exon 9** – Exon 9 *KIT* mutations are detected in 12 to 15 percent of cases. This mutation affects the extracellular dimerization domain and allows receptor dimerization in the absence of ligand and subsequent kinase activation.

- **Other *KIT* mutations** – *KIT* mutations in exons 13, 14, 17, and 18 are rare and occur in approximately 1 to 2 percent of cases [113]. These mutations affect the kinase domain (exon 13 and 14 mutations alter ATP-binding; exon 17 and 18 mutations alter the activation loop) [112]. While uncommon in newly diagnosed GISTs, they are seen at a high frequency as secondary mutations in GISTs that develop imatinib resistance [112]. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors".)

- **KIT wild-type** – Approximately 15 percent of GISTs lack mutations in the *KIT* gene (ie, are *KIT* wild-type). The pathogenesis of these subsets is discussed below. (See 'PDGFRA mutations' below and 'KIT/PDGFRA wild-type GISTs' below.)

PDGFRA mutations — A subset of GISTs lacking *KIT* mutations have activating mutations in the tyrosine kinase platelet-derived growth factor receptor alpha (*PDGFRA*) gene [5,99,100,114]. *KIT* and *PDGFRA* are mutually exclusive oncogenic mutations in GISTs. Moreover, *PDGFRA* mutations are more likely to occur in GISTs that lack IHC expression of KIT. Patients with *PDGFRA* mutations have tumors that most commonly arise in the stomach and present with more indolent disease [115,116]. (See 'Clinical presentation' above.)

The frequency of *PDGFRA* mutations among patients with GIST ranges between 2 and 14 percent [117]. In one analysis, *PDGFRA* mutations was detected in approximately 7 percent of tumors (80 of 1105 GIST samples), although the study was enriched by a large number of tumors that were negative for KIT (CD117) expression on IHC [40].

Various molecular alterations in the *PDGFRA* pathway exist, including [5,40]:

- **Exon 18** – Exon 18 is the most common *PDGFRA* mutation and accounts for approximately 80 to 90 percent of PDGFRA mutations. This mutation affects the activation loop in the second tyrosine kinase domain.
  - **D842V** – D842V exon 18 mutations occur in approximately 62 percent of *PDGFRA* mutations. This mutant isoform confers significant resistance to imatinib [40,99,100] and requires the use of alternative tyrosine kinase inhibitors such as avapritinib and ripretinib. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Avapritinib for PDGFRA D842V mutant tumors' and "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Ripretinib'.)
  - **Non-D842V** – Non-D842V exon 18 mutations occur in approximately 27 percent of *PDGFRA* mutations. In general, non-D842V mutations in exon 18 confer sensitivity to imatinib [40].
- **Exon 12** – Exon 12 makes up approximately 9 percent of *PDGFRA* mutations and affects the juxtamembrane domain of the receptor.
- **Other mutations** – *PDGFRA* mutations in other exons such as those in exons 14 and 10 are relatively rare.

The influence of *PDGFRA* mutational status in the adjuvant setting, neoadjuvant setting, and as initial therapy in patients with metastatic disease is discussed separately. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Molecular subtypes and primary resistance' and "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Role of genotyping' and "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'PDGFRA mutations'.)

KIT/PDGFRA wild-type GISTs — Patients with *KIT/PDGFRA* wild-type GISTs (ie, tumors without detectable mutations in *KIT* or *PDGFRA*) comprise approximately 10 to 15 percent of all GIST cases. *KIT/PDGFRA* wild-type GISTs are seen in patients with syndromes such as Carney-Stratakis syndrome (*SDH* gene mutations), Carney triad (epigenetic changes affecting the succinate

dehydrogenase C [SDHC] promoter), and those with NF1 (*NF1* gene mutation) [118]. (See 'Genetic syndromes' above.)

One series examined the various molecular subtypes of *KIT*/*PDGFRA* wild-type GISTs in 95 patients who presented with either a GIST at age <19 or a wild-type GIST at age ≥19. Among the 84 patients with adequate tissue for analysis, three molecular subtypes were defined [14]:

- *SDHX* mutations – 66 percent
- SDHC promoter hypermethylation – 22 percent
- SDH competent – 12 percent (which included mutations in *NF1*; *BRAF* V600E; other rare mutations or fusions; or no identified abnormalities)

KIT/*PDGFRA* wild-type GISTs are often localized to the stomach, multicentric in origin, and can have an indolent clinical course [56,84]. Many of these tumors arise in younger patients. Approximately 85 percent of all GISTs diagnosed in children and adolescents are *KIT/PDGFRA* wild-type. Furthermore, many are also associated with mutations and/or functional loss of expression of an SDH enzyme. Nevertheless, these *KIT/PDGFRA* wild-type GISTs can occasionally occur in adults, with virtually identical features to those observed in pediatric patients [119]. (See 'GIST syndromes in pediatric and AYA patients' above.)

SDH-deficient tumors — SDH-deficient tumors lack mutations in *KIT* or *PDGFRA* [56]. These tumors have loss of function of a succinate dehydrogenase (SDH) family enzyme (SDHA, SDHB, SDHC, or SDHD; commonly combined under the term "SDHx"). This loss of function occurs either due to a mutation in one of the *SDHx* genes or due to epigenetic silencing [62].

Tumor immunostaining for SDHB is appropriate to diagnose SDH deficiency in *KIT/PDGFRA* wild-type GISTs, as absence of SDHB indicates deficiency of any of the *SDHx* genes. Patients with such tumors should be referred for evaluation of genetic syndromes such as Carney-Stratakis syndrome. (See 'Carney-Stratakis syndrome (dyad)' above and "Paragangliomas: Epidemiology, clinical presentation, diagnosis, and histology", section on 'Carney-Stratakis dyad' and "Pheochromocytoma and paraganglioma in children".)

KIT/*PDGFRA* mutation-negative GISTs are poorly responsive to imatinib. The approach to systemic therapy in patients with *KIT*/*PDGFRA* wild-type GISTs is discussed separately. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Molecular subtypes and primary resistance' and "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'SDH-deficient tumors and those associated with NF1'.)

Other mutations — A number of *KIT*/*PDGFRA* wild-type GISTs harbor other genetic abnormalities that are mutually exclusive with *KIT* and *PDGFRA* mutations. Some of these molecular alterations can be targeted with available systemic therapies and may have important therapeutic implications in GISTs. As examples:

- **BRAF** – Mutations in *BRAF* V600E can be detected in up to 13 percent of patients with *KIT*/*PDGFRA* wild-type GISTs [120,121], and these tumors may be amenable to treatment with BRAF plus MEK inhibitors [122]. (See "Systemic treatment of metastatic melanoma with BRAF and other molecular alterations".)

- **NF-1** – Neurofibromatosis type 1 (NF1)-associated GISTs exhibit increased signaling through the mitogen-activated protein kinase (MAPK) signaling cascade [123], raising the possibility of treatment with MEK inhibitors. (See "Neurofibromatosis type 1 (NF1): Management and prognosis".)

- **NTRK** – Gene fusions involving neurotrophic tyrosine kinase receptor type 3 (NTRK3) or fibroblast growth factor receptor 1 (FGFR1) have been identified in patients with *KIT*/*PDGFRA* wild-type GISTs. However, other studies suggest that mesenchymal tumors with *NTRK* gene fusions may represent other sarcomas and not GISTs, so this association is controversial [124]. Tumors with these molecular alterations may be targetable with TRK or FGFR inhibitors, respectively [125]. (See "TRK fusion-positive cancers and TRK inhibitor therapy".)

DIFFERENTIAL DIAGNOSIS

The differential diagnosis of a subepithelial tumor arising in the gastrointestinal (GI) tract includes both benign and malignant tumors, many of which present similarly to GISTs. The distinction between these tumors and GISTs is based upon immunohistochemistry (table 1) and molecular alterations specific to GISTs [37]. (See 'Immunohistochemistry' above and 'Molecular alterations' above.)

Benign tumors include leiomyoma, schwannoma, and desmoid tumors, and their clinical presentation is discussed separately. (See "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'GIST and leiomyoma' and "Peripheral nerve tumors", section on 'Schwannoma' and "Desmoid tumors: Epidemiology, molecular pathogenesis, clinical presentation, diagnosis, and local therapy", section on 'Clinical presentation and diagnosis'.)

Malignant tumors include leiomyosarcoma, malignant melanoma, malignant peripheral nerve sheath tumor, inflammatory myofibroblastic tumor, and metaplastic ("sarcomatoid") carcinoma [126]. The clinical presentation of these tumors is discussed separately. (See "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'Leiomyosarcoma' and "Overview of the management of advanced cutaneous melanoma" and "Peripheral nerve tumors", section on 'Malignant peripheral nerve sheath tumors' and "Uncommon sarcoma subtypes", section on 'Inflammatory myofibroblastic tumor'.)

By light microscopy alone, the distinction among GISTs and other tumors (particularly GI tract leiomyomas, leiomyosarcomas, and schwannomas) can be difficult because the histologic findings seen on hematoxylin and eosin (H&E)-stained sections do not reliably or specifically relate to the immunophenotype or the molecular genetics of the lesions [126]. Further details on the histopathology of these tumors are discussed separately. (See "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'GIST and leiomyoma' and "Local treatment for gastrointestinal stromal tumors, leiomyomas, and leiomyosarcomas of the gastrointestinal tract", section on 'Leiomyosarcoma' and "Schwannomatoses related to genetic variants other than *NF2*", section on 'Tumor pathology'.)

EVALUATION FOR METASTATIC DISEASE

For all patients with a confirmed diagnosis of GIST, we evaluate for metastatic disease using computed tomography (CT) and/or magnetic resonance imaging (MRI) of the abdomen and pelvis, if not already performed during initial diagnostic evaluation. CT can more accurately detect the presence of metastatic disease involving the mesentery, omentum, and peritoneal cavity. However, hepatic metastases may be better visualized by either positron emission tomography (PET)-CT or MRI with gadolinium enhancement, since liver metastases may be isodense on contrast-enhanced CT [127].

For primary tumors ≥2 cm in size, we obtain either a chest radiograph or CT of the chest to assess for pulmonary metastases, a rare clinical finding in patients with GIST. (See 'Clinical presentation' above.)

PET using fluorodeoxyglucose (FDG-PET) in combination with CT (PET-CT) may have a role in the evaluation of metastatic disease. Baseline PET-CT imaging may be obtained prior to initial therapy with a tyrosine kinase inhibitor in order to assess treatment response in the neoadjuvant or metastatic setting. (See "Tyrosine kinase inhibitor therapy for advanced

gastrointestinal stromal tumors", section on 'Assessing response to therapy' and "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Response assessment'.)

PET-CT imaging can be useful for detecting an unknown primary site or resolving ambiguities from CT (eg, when initial CT findings are inconclusive or inconsistent with the clinical findings) [128]. PET-CT imaging may also be useful in detecting hepatic metastases that may appear isodense on contrast-enhanced CT. The reported sensitivity of PET-CT for GISTs (including metastatic lesions) is 86 to 100 percent [89,129,130]. However, nearly all the data obtained by PET-CT imaging can be found in a good quality CT scan with intravenous contrast, with superior anatomic definition.

STAGING SYSTEM

Patients with a confirmed diagnosis of GIST are staged using the eighth edition (2017) American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) tumor, node, metastasis (TNM) staging system (table 2) [131]. In the AJCC staging system, all primary tumor sites follow the same tumor (T) and node (N) designations. However, gastric and omental primaries are staged separately from small intestine, esophageal, colorectal, mesenteric and peritoneal primaries.

RISK STRATIFICATION AND PROGNOSIS

Although GISTs can exhibit variable biologic disease behavior, all have the potential to develop into metastatic disease. Based on available clinical risk factors, prognostic models have been developed to predict the relative risks of recurrence and metastasis [108,132,133]. Some of these models can identify patients at risk for recurrence and individualize management with systemic therapy using tyrosine kinase inhibitors (TKIs). (See 'Prognostic and risk stratification models' below.)

Risk factors — Risk factors that influence prognosis in patients with GIST are mainly based on the characteristics of the primary tumor. The most clinically relevant risk factors are as follows:

Tumor size and mitotic rate — Tumor size and mitotic rate are both independent prognostic factors and are used in models to predict aggressive tumor behavior (table 3 and table 4). These factors (along with primary tumor site) were identified using data from three large retrospective studies from the Armed Forces Institute of Pathology (AFIP) on GISTs diagnosed and treated largely prior to the era of TKIs [71,81,82]. However, it is not clear how the presence

or absence of gene mutations influences these prognostic factors, particularly as the role of targeted treatments specific to tumor mutation status evolves.

Primary tumor site — In general, primary tumors arising from the stomach are associated with more favorable survival outcomes compared with those arising from the small intestine, colon, rectum, or mesentery [132].

- **Gastric and small intestinal primaries** – The prognosis of primary tumors arising from the stomach or small intestine is influenced by size and mitotic count. Based on data from the AFIP series, small tumors with a low mitotic rate have a similarly good prognosis regardless of whether the primary site is gastric or small intestine, with only 2 to 3 percent of such tumors progressing to metastatic disease [81,82]. Large tumors with a high mitotic rate have a similarly poor prognosis, regardless of the primary site, with more than 86 percent of such tumors progressing to metastatic disease. However, intermediate tumors (larger tumors with a low mitotic rate or smaller tumors with a high mitotic rate) arising from the stomach have a more favorable prognosis (metastatic rate of 11 to 15 percent) compared with those arising from the small intestine (metastatic rate >50 percent) [81,82].

- **Other primary site** – Patients with colorectal GISTs appear to have similar or slightly decreased relapse-free survival compared with those with small intestinal GISTs. Similarly, patients with GISTs outside the gastrointestinal (GI) tract appear to relapse more frequently [15,134]. However, the effect of primary location on prognosis is more difficult to determine, given the rarity of these tumors.

Other risk factors

- **Tumor rupture** – Tumor rupture (either spontaneously or at surgery) is an independent risk factor that negatively impacts disease-free survival [135-138]. Tumor rupture is included as a prognostic variable in a modified version of the National Institutes of Health consensus criteria for risk stratification (in addition to tumor size, site, and mitotic rate) (table 5) [138]. However, tumor rupture is not included in the tumor, node, metastasis (TNM) staging system of the American Joint Committee on Cancer (AJCC). (See 'Staging system' above.)

- **Imaging characteristics** – Tumor characteristics on computed tomography (CT) or endoscopic ultrasound (EUS) may not only suggest the diagnosis of a GIST but may also correlate with recurrence risk. In general, tumors with higher metastatic potential include those larger than 5 cm; those that are lobulated or enhance heterogeneously; those with mesenteric fat infiltration, ulceration, or regional lymphadenopathy; or those with an exophytic growth pattern on CT [139-143]. By contrast, GISTs with less metastatic potential

tend to enhance in a homogeneous pattern and often show an endoluminal growth pattern.

- **Lymph node involvement** – Data are limited for the prognostic impact of lymph node involvement, given the rarity of this finding in adults with GISTs. As examples, in the data from the AFIP series of gastric and small intestinal GISTs, no patients with nodal involvement were identified [81,82]. In another study from the SEER database analysis of 5138 adults with GISTs, nodal involvement was identified in approximately 5 percent of cases and was associated with decreased cancer-specific and overall survival [144].

  However, nodal involvement is common in patients with succinate dehydrogenase (*SDH*)-mutant or *SDH*-epimutant GISTs (65 and 38 percent, respectively) [14]. Such patients with nodal involvement (who tend to be children or young adults) demonstrate more indolent disease and a better prognosis, compared with adults with nodal involvement. (See 'Pediatric and AYA patients' above.)

- **Molecular alterations** – There are limited data for risk assessment based on molecular alterations associated with GISTs. Some studies obtained prior to the modern era of TKI therapy suggest that patients with *KIT* mutations have a worse prognosis than those without *KIT* mutations) [28,101,114,115,138,145,146]. Specific *KIT* mutations are associated with an aggressive phenotype, including those affecting exon 9 [138,145,147,148] and deletions involving codons 557 to 558 on exon 11 [101,114,115,145,149,150]. (See 'Molecular alterations' above.)

  However, it is not clear how the presence or absence of *KIT* gene mutations influences prognosis, particularly as the role of targeted treatments specific to tumor mutation status evolves. (See "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Influence of mutations on response to therapy'.)

Prognostic and risk stratification models — Based on the risk factors described above, various prognostic models and risk stratification schemes have been proposed to better delineate the prognosis of patients with GISTs. Molecular alterations (eg, *KIT*, platelet-derived growth factor receptor alpha [*PDGFRA*], or *SDH* mutation status) are not incorporated in these prognostic models, and their prognostic role remains to be defined.

- **AFIP prognostic model** – The prognostic model proposed by the Armed Forces Institute of Pathology (AFIP) (table 3 and table 4) is the most commonly used risk stratification scheme in the United States, although others are also available. The AFIP prognostic model is influenced by tumor size, mitotic rate, primary site [82,151,152], and the completeness of resection [70,153-158]. This model was developed by comparing

outcomes for different primary sites with long-term follow-up largely prior to the era of TKIs, including 1055 gastric, 629 jejunal/ileal, 144 duodenal, and 111 rectal GISTs [132].

- **NIH risk stratification scheme** – A modified National Institutes of Health (NIH) risk stratification scheme was developed based on tumor size, mitotic counts, and the addition of tumor rupture (table 5) [15]. This model proved better than conventional models at predicting 10-year risk for GIST recurrence and are particularly useful for discussing individual risk with patients as they are graphic and easy to explain.

- **AJCC staging** – The American Joint Committee on Cancer (AJCC; eighth edition 2017) described rates of disease progression for gastric (table 6), small intestinal (table 7), and rectal GISTs (table 8), stratified by eighth edition (2017) TNM stage at diagnosis (table 2) [132]. (See 'Staging system' above.)

- **Memorial Sloan Kettering nomogram** – The risk of disease recurrence has been quantified through the use of an online GIST nomogram from Memorial Sloan Kettering Cancer Center that predicts postoperative recurrence-free survival based on primary tumor size, disease site, and mitotic rate [159-161]. This nomogram may be used as an alternative to risk classification systems that stratify patients into discrete categories.

The implications of these prognostic models and risk stratification schemes in selecting patients for adjuvant imatinib based upon estimated recurrence risk are discussed separately. (See "Adjuvant and neoadjuvant therapy for gastrointestinal stromal tumors", section on 'Estimation of recurrence risk'.)

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

SUMMARY AND RECOMMENDATIONS

- **Epidemiology** – Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal (GI) tract. They typically present as subepithelial neoplasms in the stomach and small intestine, but can involve any portion of the GI tract. GISTs occur predominantly in older adults and are less common in children and young adults. (See 'Epidemiology' above.)

- **Molecular alterations** – 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. Other molecular alterations are less common. An assessment of mutation status is advised during the initial evaluation of most patients diagnosed with GIST because clinical responses to systemic therapy (eg, imatinib and other tyrosine kinase inhibitors [TKIs]) correlate with tumor genotype and influence treatment options. (See 'Molecular alterations' above.)

- **Clinical presentation** – Patients with GISTs can present with a wide range of symptoms based on age and location of the primary tumor. (See 'Clinical presentation' above and 'Location' above.)

  - **Adult patients** – Most adult patients with subepithelial masses are asymptomatic and their tumors are discovered incidentally. Others may present with nonspecific chronic symptoms (eg, early satiety or bloating). Some tumors may grow large enough to ulcerate, cause pain, or result in tumor rupture, GI bleeding, bowel perforation, or GI obstruction. (See 'Adults' above.)

  - **Pediatric and AYA patients** – Pediatric and adolescent and young adult (AYA) patients commonly present with GI bleeding, fatigue, and anemia. (See 'Pediatric and AYA patients' above.)

- **Diagnostic evaluation** – GISTs are detected either incidentally in asymptomatic patients, or during the evaluation of the symptomatic patient. (See 'Diagnostic evaluation' above.)
  - **Imaging and diagnostic procedures** – Both imaging (eg, computed tomography [CT] of the abdomen and pelvis) and endoscopic procedures (eg, upper endoscopy with endoscopic ultrasound [EUS]) are necessary to the initial diagnostic evaluation of GIST. (See 'Imaging the primary tumor' above and 'Diagnostic procedures' above.)
  - **Tissue sampling** – Whenever possible, we perform preoperative biopsy rather than resection to confirm the diagnosis. (See 'Tissue sampling' above.)
- **Diagnosis** – The diagnosis of GIST is established using histopathology, immunohistochemistry (IHC) (table 1), and identification of disease-specific molecular alterations. (See 'Diagnosis' above and 'Molecular alterations' above.)
  - ***KIT* mutations** – Approximately 95 percent of GISTs are positive for expression of the receptor tyrosine kinase KIT (CD117) by IHC. However, not every GIST with KIT expression carries a *KIT* mutation. (See 'KIT mutations' above.)
  - ***PDGFRA* mutations** – Mutations in *PDGFRA* are mutually exclusive with *KIT*. Tumors with the *D842V* mutation in exon 18 of *PDGFRA* are characterized by relative insensitivity to imatinib and are treated using alternative agents such as avapritinib and ripretinib. (See 'PDGFRA mutations' above and "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Avapritinib for PDGFRA D842V mutant tumors' and "Tyrosine kinase inhibitor therapy for advanced gastrointestinal stromal tumors", section on 'Ripretinib'.)
  - ***KIT* and *PDGFRA* wild-type tumors** – *KIT/PDGFRA* wild-type GISTs (eg, tumors without detectable mutations in *KIT* or *PDGFRA*) may harbor epigenetic changes in succinate dehydrogenase C (SDHC), or mutations in *SDHx*, neurofibromatosis type 1 (*NF1*), or *BRAF* V600E. (See 'KIT/PDGFRA wild-type GISTs' above.)
- **Evaluation of metastatic disease** – For all patients with a confirmed diagnosis of GIST, we evaluate for metastatic disease using CT and/or magnetic resonance imaging (MRI) of the abdomen and pelvis. Positron emission tomography (PET)-CT or MRI may be used to better visualize hepatic metastases; PET-CT may also be used to follow response to therapy. For primary tumors ≥2 cm in size, we also obtain either a chest radiograph or CT of the chest. (See 'Evaluation for metastatic disease' above.)

- **Risk stratification and prognosis** – Various prognostic models and risk stratification schemes have been developed to predict the risks of metastatic disease, identify patients at risk for recurrence, and individualize management with systemic therapy using TKIs. Risk factors that have been incorporated into these models include tumor size, mitotic rate, primary site, and tumor rupture. (See 'Risk stratification and prognosis' above.)

  - The Armed Forces Institute of Pathology (AFIP) prognostic model (table 3 and table 4) is the most commonly used risk stratification scheme in the United States, although others are available. (See 'Prognostic and risk stratification models' above.)

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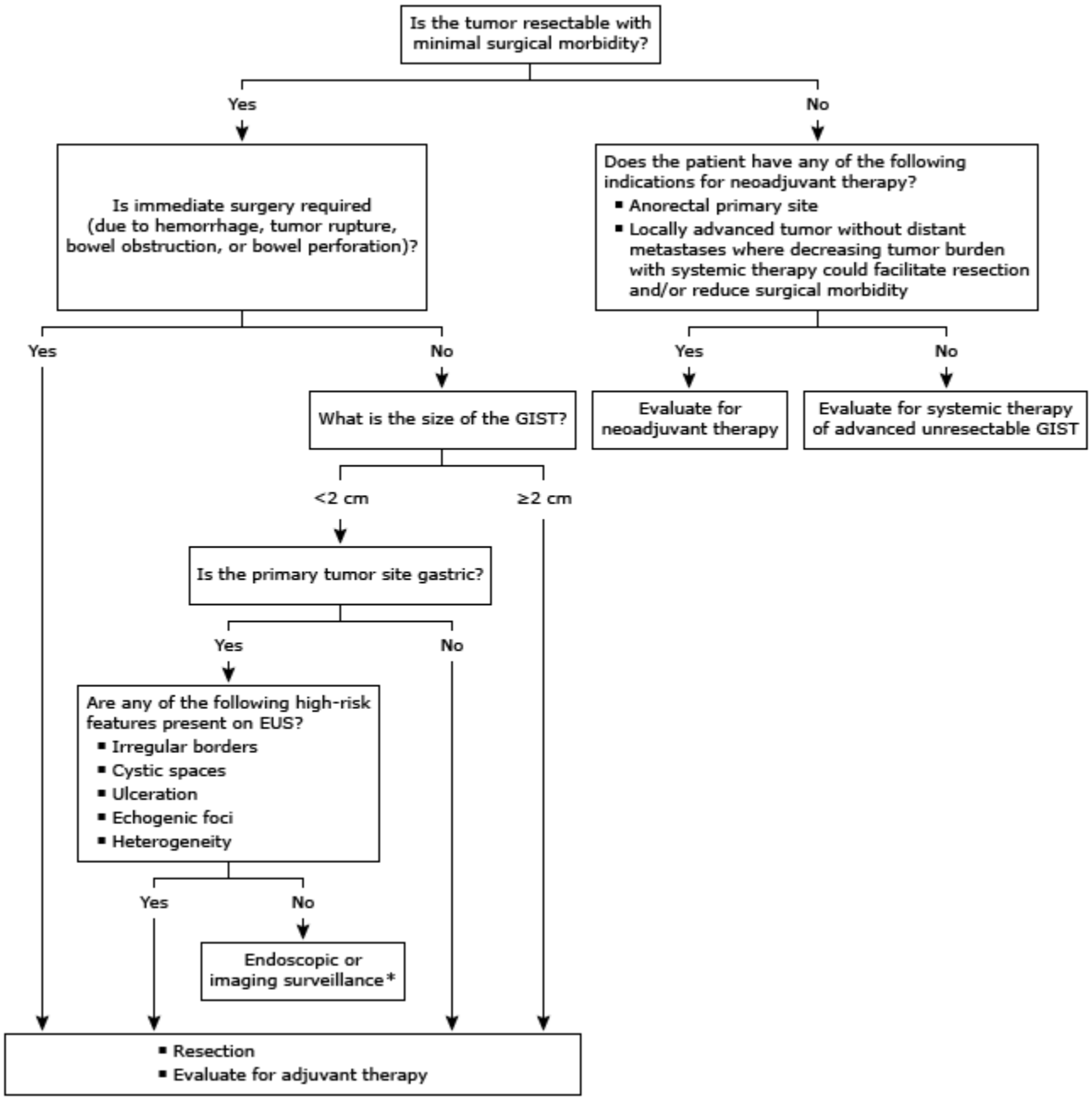
Topic 7745 Version 51.0

GRAPHICS

Initial management of localized gastrointestinal stromal tumors



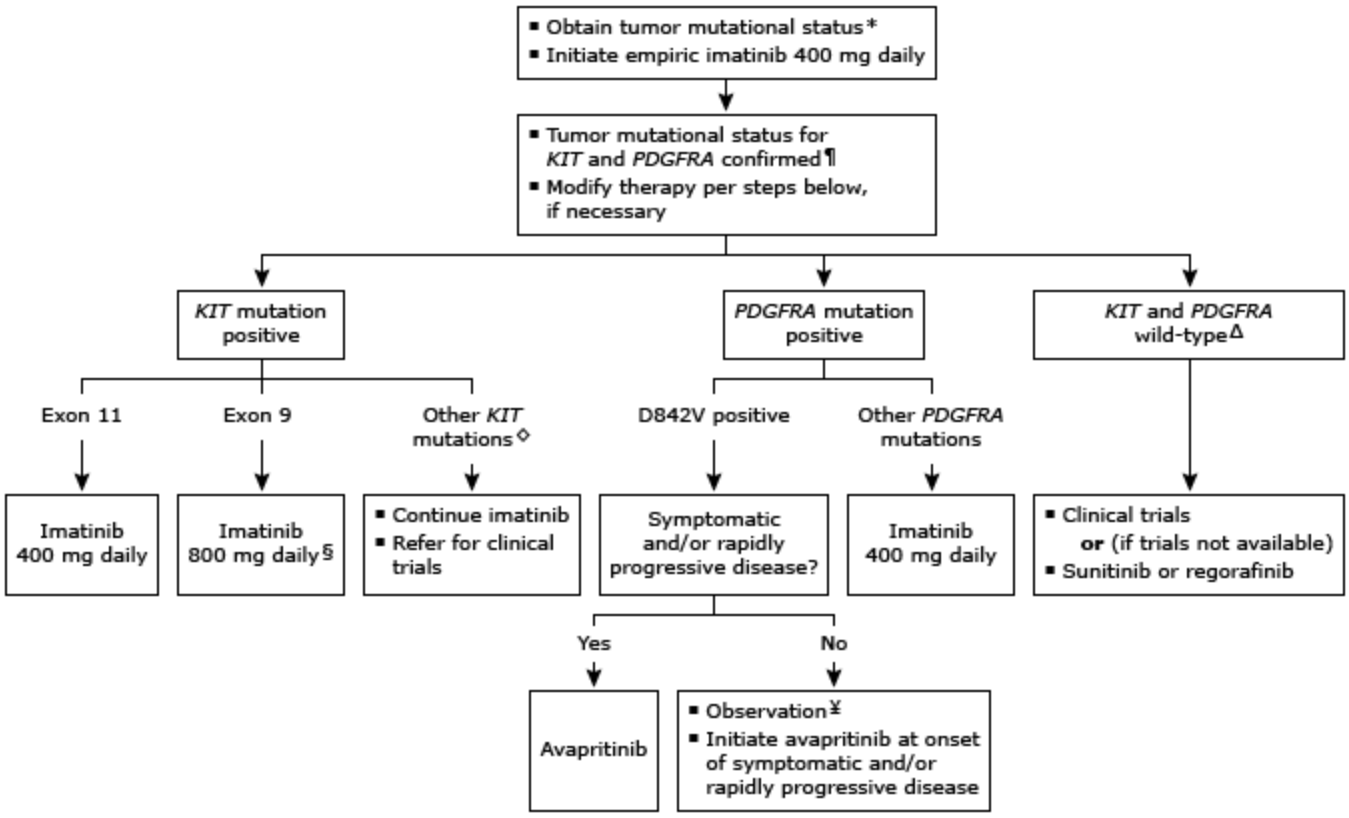
While some patients with GIST are candidates for observation, most are treated with primary surgical resection. Systemic therapy may be offered either in the adjuvant setting to decrease recurrence risk or in the neoadjuvant setting to decrease tumor burden prior to surgical resection. Refer to UpToDate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

Approach to initial therapy for advanced and metastatic gastrointestinal stromal tumors based on tumor mutational status



Patients with advanced or metastatic, unresectable GIST are typically treated with systemic targeted therapy as initial treatment. Listed treatments are preferred options, although alternative agents that are not listed may also be effective. Clinical trials are encouraged where available.

PDGFRA: platelet-derived growth factor receptor alpha; GIST: gastrointestinal stromal tumors; SDH: succinate dehydrogenase; TKIs: tyrosine kinase inhibitors; NF1: neurofibromatosis 1.

* An assessment of tumor mutational status using DNA sequencing techniques is advised during the initial evaluation of patients with advanced or metastatic disease because clinical responses to imatinib (and other TKIs) correlate with tumor genotype. However, for most patients, systemic treatment with imatinib can be initiated empirically while awaiting confirmation of tumor mutational status. Treatment may be subsequently modified once tumor mutational status becomes available. However, for those with histologies suggestive of imatinib resistance (eg, SDH deficiency or NF1-related disease), referral to a tertiary care center for clinical trials is warranted, rather than empiric imatinib. Refer to UpToDate content on diagnosis and treatment of GIST.

¶ *KIT* and *PDGFRA* are mutually exclusive oncogenic mutations in patients with GIST.

Δ Patients with tumors that are *KIT* and *PDGFRA* wild-type are typically resistant to imatinib and may harbor certain mutations (eg, SDH deficiency, NF1, and *BRAF* V600E). Refer to UpToDate content on classification of GIST.

◇ Other *KIT* mutations involving exons 13, 14, 17, or 18 are extremely rare, and the optimal treatment approach varies. Referral for clinical trials at a sarcoma center of excellence is encouraged.

§ Patients with a *KIT* exon 9 mutation demonstrate some relative resistance to imatinib, and higher doses of imatinib are preferred.

¥ For patients with a *PDGFRA* D842V mutation who exhibit asymptomatic and/or indolent disease, a period of observation is preferable to immediate treatment with avapritinib in order to avoid treatment-related toxicities, such as potential cognitive impairment.

Graphic 127116 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.

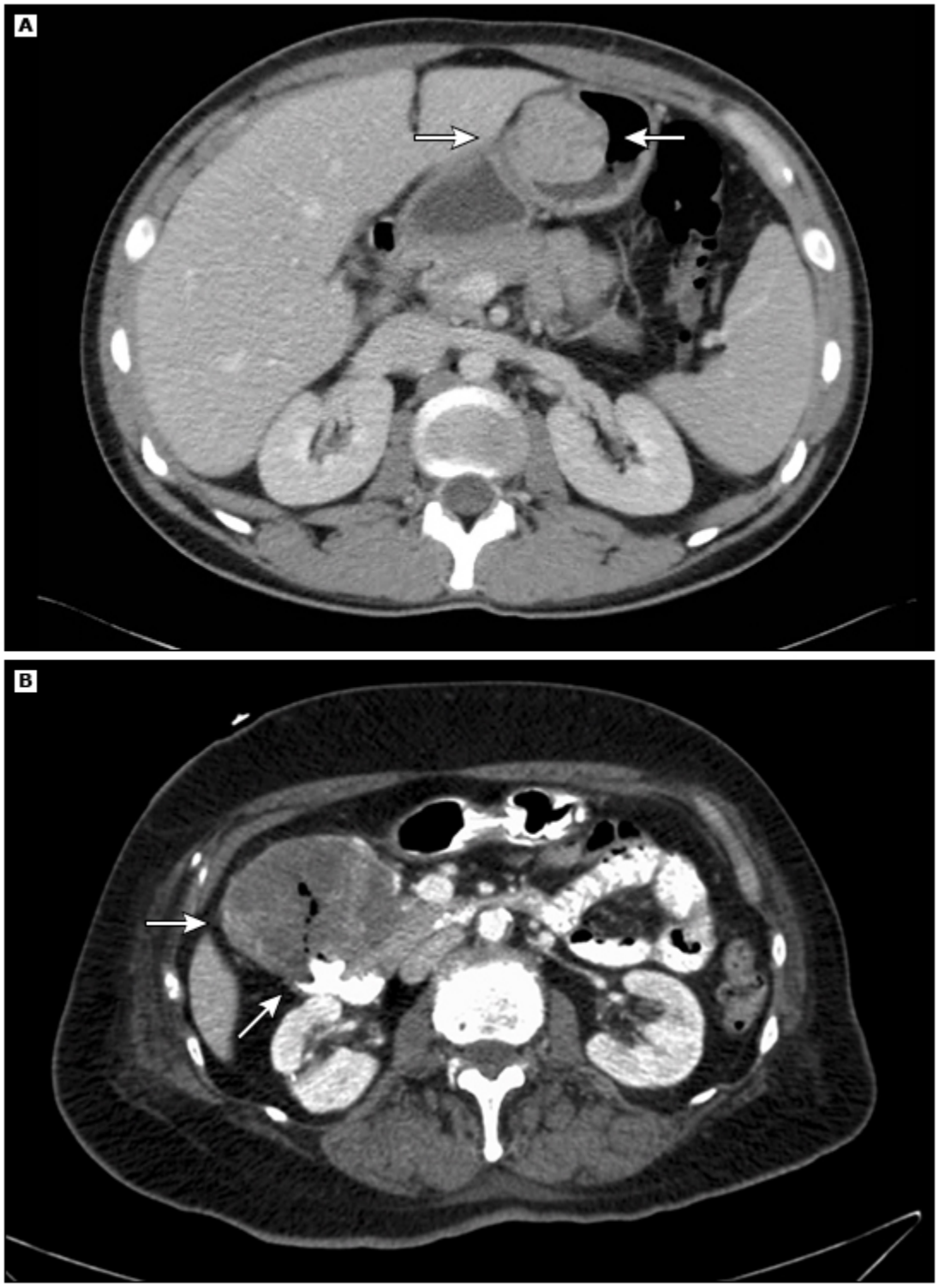
* Alpha smooth muscle actin.

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

CT of gastrointestinal stromal tumor (GIST)



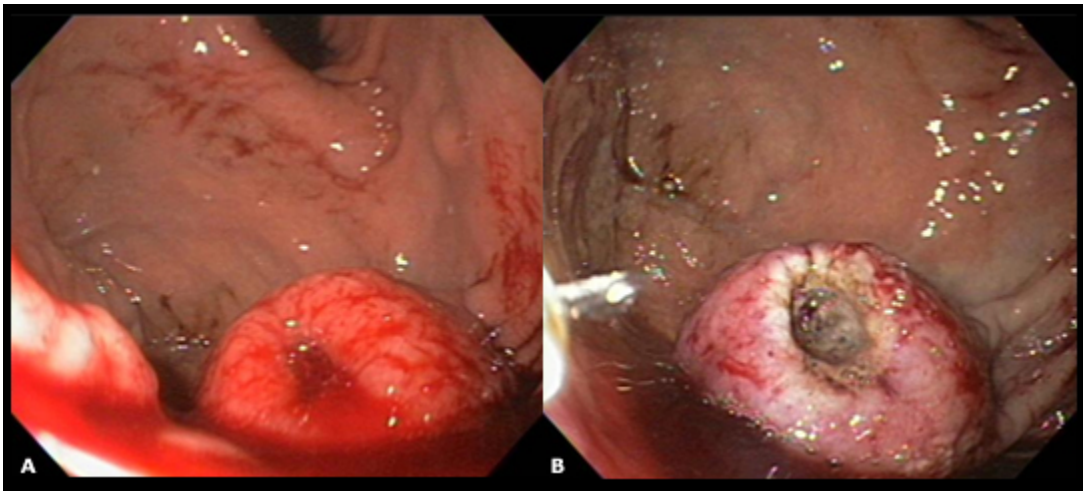
(A) Axial image of a contrast-enhanced CT scan of the abdomen, showing a 4 cm hyperenhancing mass arising from the submucosa of the body of the stomach.

(B) Axial image of a contrast-enhanced CT scan of the abdomen of a patient who presented with gastrointestinal bleeding. Exophytic GIST arising from the second portion of the duodenum, with area of ulceration along the descending duodenum into the mass.

CT: computed tomography.

Graphic 113958 Version 1.0

Gastrointestinal stromal tumor (GIST)

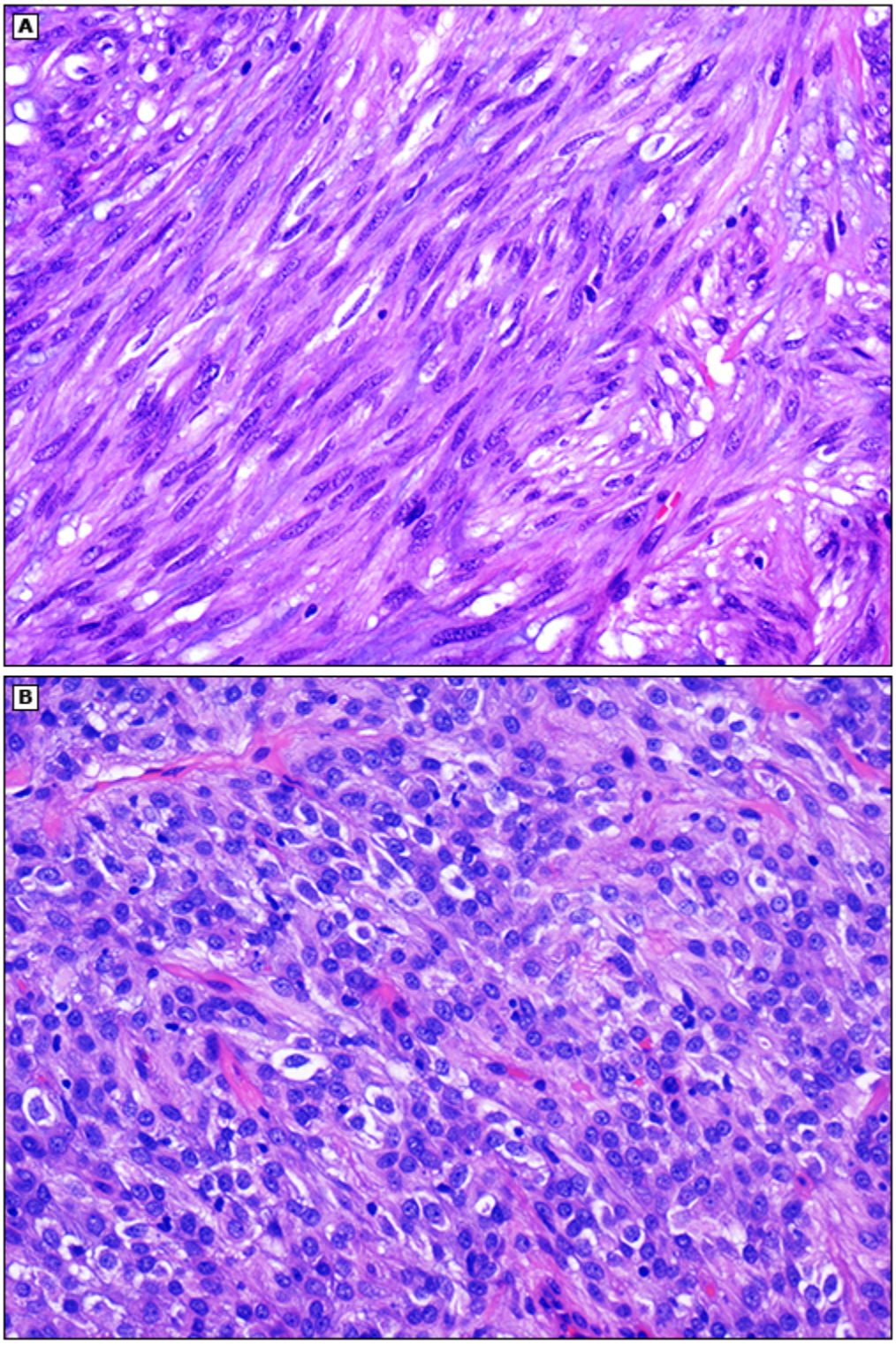


Endoscopic view of an actively oozing 20 by 30 mm submucosal mass in the stomach body (left panel). Bleeding was controlled by injection of a 1:10,000 epinephrine solution and bipolar electrocautery (right panel).

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

Graphic 52275 Version 3.0

Histology of gastrointestinal stromal tumor (GIST) with spindle cell and epithelioid morphology



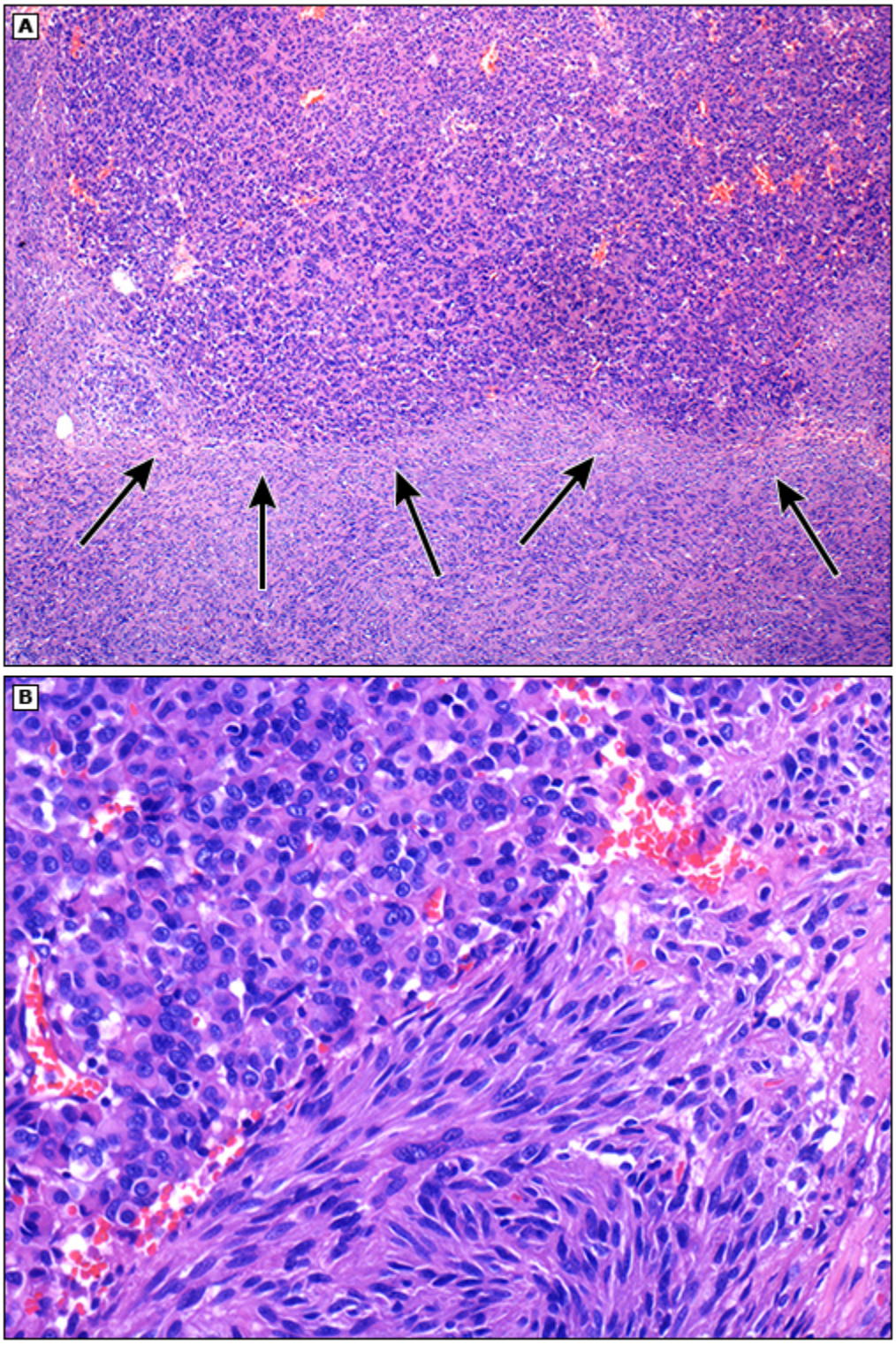
Spindle cell and epithelioid histologic patters of GIST.

(A) Biopsy specimen (20x) of a spindle cell GIST stained with hematoxylin and eosin (H&E). Histologically, the tumor is composed of fairly uniform spindle cells with elongated nuclei and eosinophilic cytoplasm, growing in fascicles.

(B) Biopsy specimen (20x) of an H&E-stained section of an epithelioid GIST with rounded cells, round central nuclei, and eosinophilic or clear cytoplasm. Note the nested morphology.

Graphic 114562 Version 1.0

Histology of gastrointestinal stromal tumor (GIST) of mixed spindle cell and epithelioid type



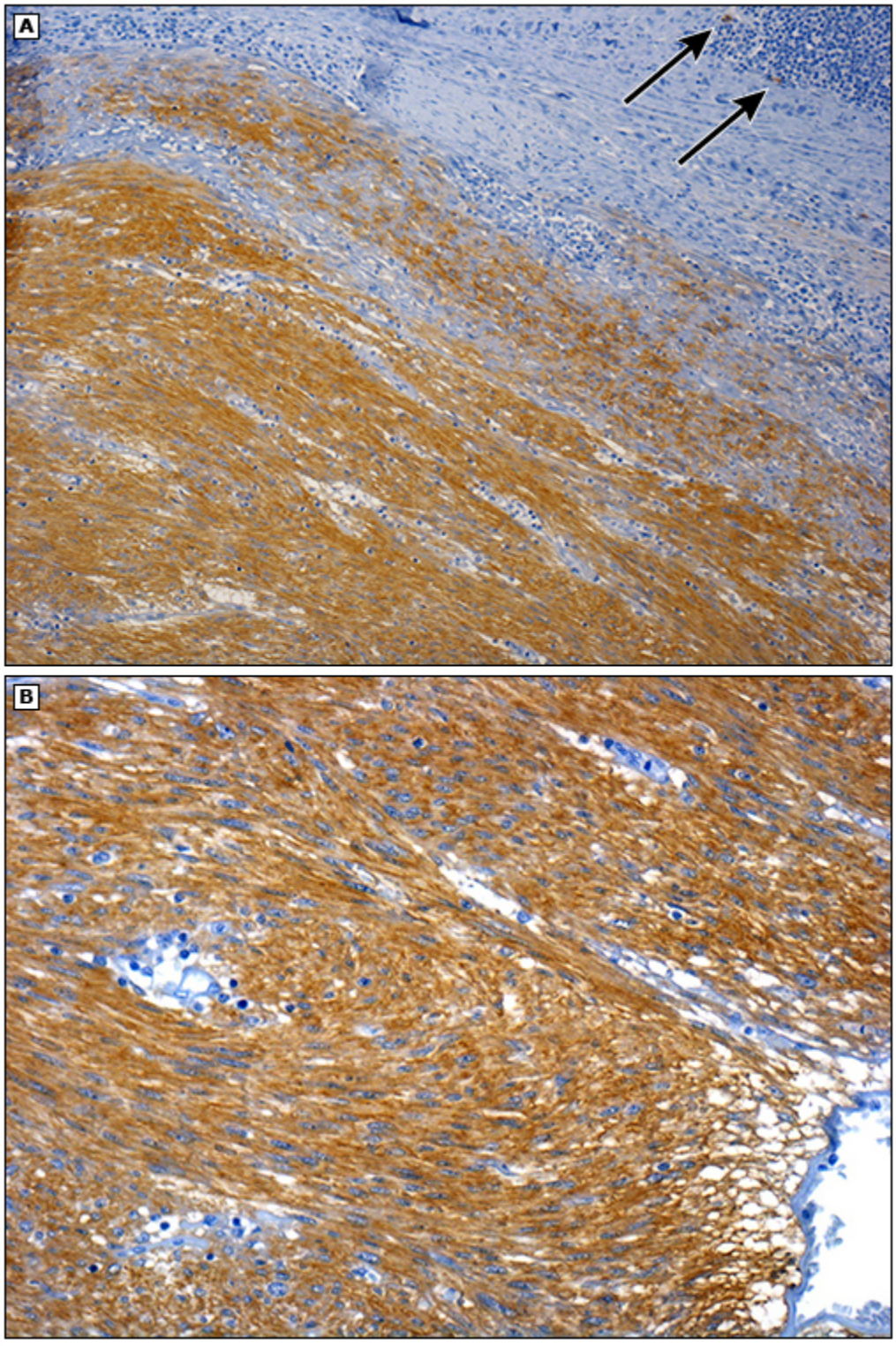
Biopsy specimen of a mixed-type GIST stained with hematoxylin and eosin (H&E).

(A) At low power (4x), note the abrupt transition between spindle and epithelioid areas, as indicated by the arrows.

(B) As shown with higher magnification (20x), the tumor is composed of elongated spindle cells as well as rounded epithelioid cells.

Graphic 114563 Version 1.0

Positive immunohistochemical staining for KIT (CD117) in a spindle cell type gastrointestinal stromal tumor (GIST)

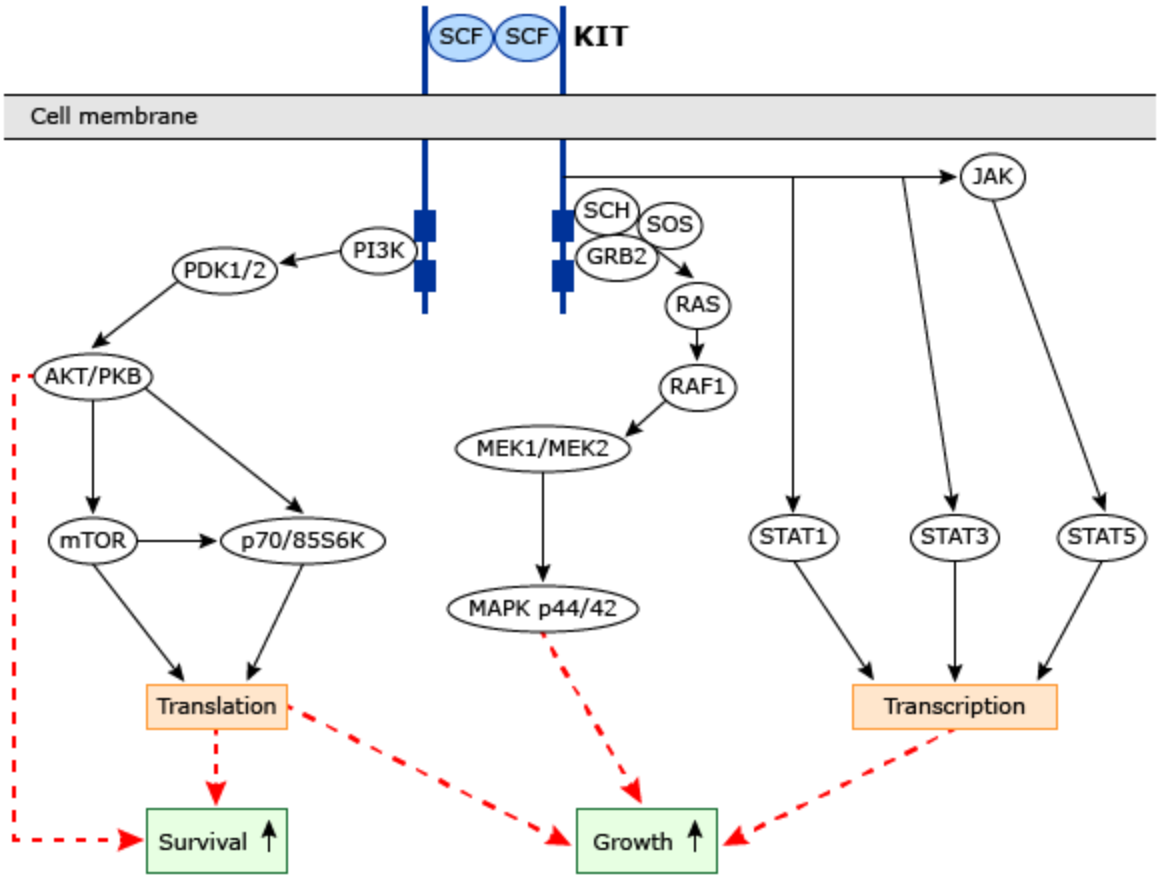


(A) Low magnification (10x) image of a section of a spindle type GIST stained for KIT expression by immunohistochemistry. The positive tumor cells are brown, and the surrounding tissue is negative. Note the KIT-positive mast cells (arrows) in a lymphoid aggregate.

(B) High magnification (20x) image shows typical membrane and cytoplasmic KIT staining with dot-like enhanced staining of the Golgi apparatus. The tumor vasculature does not stain for KIT.

Graphic 114564 Version 1.0

KIT signaling in gastrointestinal stromal tumors (GIST)

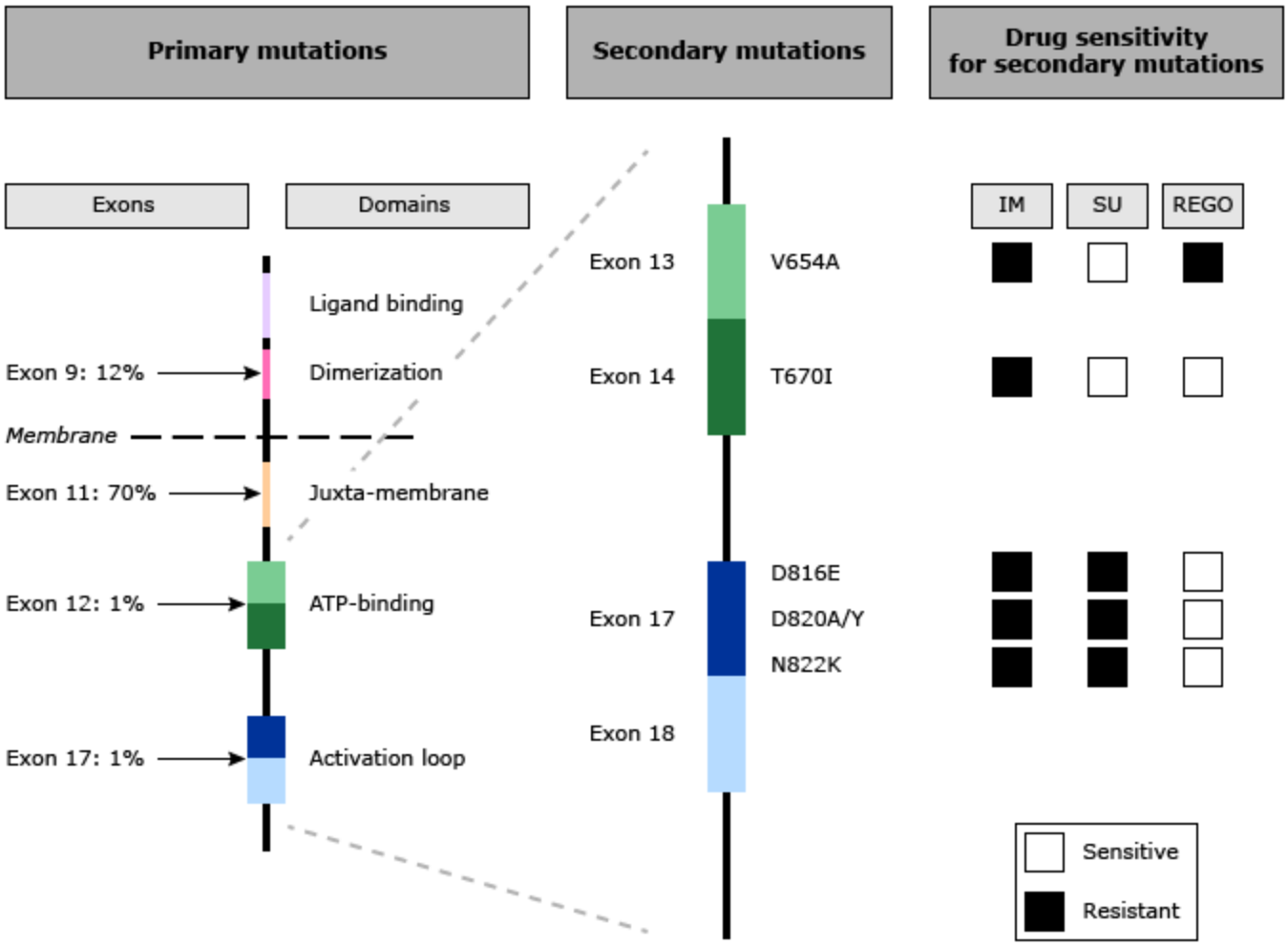


Physiologic KIT activation is triggered by binding of the dimeric KIT ligand (SCF) to the extracellular, ligand-binding domain of the KIT receptor tyrosine kinase. This in turn leads to homodimerization of two KIT molecules, which is accompanied by structural changes in the receptor and activation (autophosphorylation) of the intracellular KIT kinase domain. The phosphorylated tyrosine residues on KIT serve as binding sites for various cell signaling proteins, resulting in the activation of various signaling cascades, such as the PI3K/AKT/mTOR, RAS/RAF/MAPK, and the JAK/STAT pathways. Ultimately, the activated KIT receptor stimulates intracellular signaling pathways controlling cell proliferation, adhesion, apoptosis, survival, and differentiation.

SCF: stem cell factor; PI3K: phosphoinositide 3-kinase; PDK1/2: pyruvate dehydrogenase kinase isoenzymes 1 and 2; GRB2: growth factor receptor-bound protein 2; MEK: mitogen-activated protein kinase kinase; mTOR: mechanistic target of rapamycin; STAT: signal transducer and activator of transcription; MAPK: mitogen-activated protein kinase.

Graphic 113954 Version 3.0

Range of KIT mutations in gastrointestinal stromal tumors (GIST)



KIT is a type III receptor tyrosine kinase that is comprised of extracellular ligand-binding and dimerization domains, a transmembrane sequence, as well as an intracellular juxtamembrane domain and kinase domain, which is split by an 80 amino acid insert. Mutations in exon 11 of KIT, which encode the juxtamembrane domain and are seen in approximately 70% of GISTs, relieve its autoinhibitory function and lead to constitutive, ligand-independent activation of the receptor. Mutations in the dimerization domain, encoded by exon 9 (approximately 12% of GISTs), allow receptor dimerization in the absence of ligand and likewise lead to activation of the kinase. Mutations in the kinase domain (exons 13/14, ATP-binding, phosphotransferase region; exons 17/18, activation loop) are rare in primary, imatinib-naïve GISTs. However, because they favor the active conformation of the kinase, leading to impaired binding of imatinib, they comprise the most prominent imatinib resistance mechanism. A comparison of the relative effectiveness of IM, SU, and REGO in GIST with the most frequent KIT secondary mutations is shown on the right.

IM: imatinib; SU: sunitinib; REGO: regorafenib; ATP: adenosine 5'-triphosphate.

Adapted from: Clinical Cancer Research, 2009, Vol. 5, Issue 24, pp. 7510-7518, Gramza AW, Corless CL, Heinrich MC, Resistance

to Tyrosine Kinase Inhibitors in Gastrointestinal Stromal Tumors, with permission from AACR.

Graphic 113953 Version 10.0

GIST TNM staging AJCC UICC 8th edition

Primary tumor (T)	
T category	**T criteria**
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Tumor 2 cm or less
T2	Tumor more than 2 cm but not more than 5 cm
T3	Tumor more than 5 cm but not more than 10 cm
T4	Tumor more than 10 cm in greatest dimension
Regional lymph nodes (N)	
N category	**N criteria**
N0	No regional lymph node metastasis or unknown lymph node status
N1	Regional lymph node metastasis
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis
Mitotic rate	
Mitotic rate	**Definition**
Low	Five or fewer mitoses per 5 mm^2
High	Over five mitoses per 5 mm^2
Prognostic stage groups	
Gastric and omental GIST	

When T is…	**And N is…**	**And M is…**	**And mitotic rate is…**	**Then the stage group is…**
T1 or T2	N0	M0	Low	IA
T3	N0	M0	Low	IB
T1	N0	M0	High	II
T2	N0	M0	High	II
T4	N0	M0	Low	II

T3	N0	M0	High	IIIA
T4	N0	M0	High	IIIB
Any T	N1	M0	Any rate	IV
Any T	Any N	M1	Any rate	IV
Small intestinal, esophageal, colorectal, mesenteric, and peritoneal GIST				
When T is…	**And N is…**	**And M is…**	**And mitotic rate is…**	**Then the stage group is…**
T1 or T2	N0	M0	Low	I
T3	N0	M0	Low	II
T1	N0	M0	High	IIIA
T4	N0	M0	Low	IIIA
T2	N0	M0	High	IIIB
T3	N0	M0	High	IIIB
T4	N0	M0	High	IIIB
Any T	N1	M0	Any rate	IV
Any T	Any N	M1	Any rate	IV

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

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing. Corrected at 4th printing, 2018.

Graphic 110847 Version 8.0

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

Modified NIH risk stratification criteria for GIST with rupture included

Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	<2.0	≤5	Any
Low risk	2.1 to 5.0	≤5	Any
Intermediate risk	2.1 to 5.0	>5	Gastric
	<5.0	6 to 10	Any
	5.1 to 10.0	≤5	Gastric
High risk	Any	Any	Tumor rupture
	>10 cm	Any	Any
	Any	>10	Any
	>5.0	>5	Any
	2.1 to 5.0	>5	Nongastric
	5.1 to 10.0	≤5	Nongastric

NIH: National Institutes of Health; GIST: gastrointestinal stromal tumor; HPF: high power fields.

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Graphic 85938 Version 2.0

2017 AJCC disease progression in gastric GISTs

Stage	Tumor size (cm)	Mitotic rate	Observed rate of progressive disease
Stage IA	≤5	Low	0 to 2%
Stage IB	>5 to 10	Low	3 to 4%
Stage II	≤2	High	Insufficient data
	>2 to 5	High	16%
	>10	Low	12%
Stage IIIA	>5 to 10	High	55%
Stage IIIB	>10	High	86%

AJCC: American Joint Committee on Cancer; GISTs: gastrointestinal stromal tumors.

Original figure modified for this publication. Miettinen M, Lasota J. Gastrointestinal stromal tumors: pathology and prognosis at different sites. Semin Diagn Pathol 2006; 23:70. Table used with the permission of Elsevier Inc. All rights reserved.

Graphic 110724 Version 2.0

2017 AJCC disease progression in small intestinal GISTs

Stage	Tumor size (cm)	Mitotic rate	Observed rate of progressive disease
Stage IA	≤5	Low	0 to 4%
Stage II	>5 to 10	Low	24%
Stage IIIA	>10	Low	52%
	≤2	High	50%
Stage IIIB	>2 to 5	High	73%
	>5 to 10	High	85%
	>10	High	90%

AJCC: American Joint Committee on Cancer; GISTs: gastrointestinal stromal tumors.

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Graphic 110723 Version 2.0

Disease progression in rectal GISTs according to AJCC 2017 stage

Stage	Tumor size (cm)	Mitotic rate	Observed rate of progressive disease
Stage IA	≤2 cm	Low	0%
	>2 to 5	Low	8.5%
Stage II	>5 to 10	Low	NR
Stage IIIA	>10	Low	57%
	≤2	High	54%
Stage IIIB	>2 to 5	High	52%
	>5 to 10	High	NR
	>10	High	71%

GISTs: gastrointestinal stromal tumor; AJCC: American Joint Committee on Cancer; NR: not reported.

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Graphic 110725 Version 3.0

Contributor Disclosures

Chandrajit P Raut, MD, MSc, FACS No relevant financial relationship(s) with ineligible companies to disclose. **Anette Duensing, MD** No relevant financial relationship(s) with ineligible companies to disclose. **Vicki L Keedy, MD, MSCI** Grant/Research/Clinical Trial Support: Adaptimmune [Sarcoma]; Advenchen [Sarcoma]; Bayer [Sarcoma]; Boehringer-Ingelheim [Sarcoma]; Deciphera [GIST]; Plexxicon [PVNS]; SpringWorks [Desmoid]; Tracon [Sarcoma]. Consultant/Advisory Boards: Deciphera [GIST]. All of the relevant financial relationships listed have been mitigated. **Kenneth K Tanabe, MD** Patent Holder: EGF SNP to determine risk for HCC [Cirrhosis, hepatocellular carcinoma]; Use of EGFR inhibitors to prevent HCC [Cirrhosis, hepatocellular carcinoma]. Consultant/Advisory Boards: Cancer Expert Now [GI cancers, melanoma]; GSK [GI Cancers]; Imvax [GI cancers]; Leidos [Melanoma, GI cancers]; Teledoc [GI cancers, melanoma]. Other Financial Interest: American Cancer Society [Honoraria as editor of Cancer]. All of the relevant financial relationships listed have been mitigated. **Robert Maki, MD, PhD** No relevant financial relationship(s) with ineligible companies to disclose. **Alberto S Pappo, MD** Grant/Research/Clinical Trial Support: Bayer [Inhibitor of TRK]; LOXO [Inhibitor of TRK]; Merck [Cancer immunotherapy]. Consultant/Advisory Boards: Lilly [Treatment of solid tumors]; Pediatric DSMC Memorial Sloan Kettering [CAR T cell and GPC 3 antibodies]; Pfizer [Data safety monitoring]. All of the relevant financial relationships listed have been mitigated. **Sonali M Shah, MD** No relevant financial relationship(s) with ineligible companies to disclose.

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