

## Current clinical management of gastrointestinal stromal tumor

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### Abstract

Gastrointestinal stromal tumors (GISTs) are the most common malignant subepithelial lesions (SELs) of the gastrointestinal tract. They originate from the interstitial cells of Cajal located within the muscle layer and are characterized by over-expression of the tyrosine kinase receptor KIT. Pathologically, diagnosis of a GIST relies on morphology and immunohistochemistry [KIT and/or discovered on gastrointestinal stromal tumor 1 (DOG1) is generally positive]. The prognosis of this disease is associated with the tumor size and mitotic index. The standard treatment of a GIST without metastasis is surgical resection. A GIST with metastasis is usually only treated by tyrosine kinase inhibitors without radical cure; thus, early diagnosis is the only way to improve its prognosis. However, a GIST is usually detected as a SEL during endoscopy, and many benign and malignant conditions may manifest as SELs. Conventional endoscopic biopsy is difficult for tumors without ulceration. Most SELs have therefore been managed without a histological diagnosis. However, a favorable prognosis of a GIST is associated with early histological diagnosis and R0 resection. Endoscopic ultrasonography (EUS) and EUS-guided fine needle aspiration (EUS-FNA) are critical for an accurate diagnosis of SELs. EUS-FNA is safe and effective in enabling an early histological diagnosis and adequate treatment. This review outlines the current evidence for the diagnosis and management of GISTs, with an emphasis on early management of small SELs.

**Key words:** Gastrointestinal stromal tumor; Endoscopic ultrasonography-guided fine needle aspiration; Endoscopic ultrasonography; Diagnosis; Therapy

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**Core tip:** Potentially malignant gastrointestinal stromal tumors are the most common subepithelial lesions (SELs) of the gastrointestinal tract. SELs include a broader range of differential diagnoses from benign to malignant lesions.

The possibility of having a malignant lesion may cause anxiety and discomfort in patients and gastroenterologists. Early and accurate diagnosis of SELs using endoscopic ultrasonography (EUS) and/or EUS-guided fine needle aspiration is vital to guide selection of early appropriate management.

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## INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common malignant subepithelial lesions (SELs) of the gastrointestinal tract in the daily clinical setting<sup>[1,2]</sup>. GISTs are thought to originate from the interstitial cells of Cajal, which are the pacemaker cells of gastrointestinal movement<sup>[3]</sup>. GISTs are largely caused by oncogenic mutations in the tyrosine kinase receptor KIT<sup>[4]</sup> and/or platelet-derived growth factor receptor- $\alpha$  (PDGFR- $\alpha$ )<sup>[5]</sup>. Approximately 10% to 30% of GISTs have a malignant clinical course<sup>[1,6,7]</sup>. Additionally, it has been reported that not only large GISTs with a high mitotic index frequently exhibit a malignant clinical course, but also small GISTs with a low mitotic index rarely show a malignant course with metastasis. Thus, a GIST is considered to be a potentially malignant tumor. GISTs are not classified as either benign or malignant but are rather stratified by their clinical risk of malignancy: Very low, low, intermediate, or high<sup>[7]</sup>. Miettinen reported that the metastatic risk of GISTs increases according to the tumor size irrespective of the mitotic count<sup>[6]</sup> (Figure 1). Surgical resection is the primary approach to management of localized GISTs<sup>[8]</sup>. Despite complete resection, postoperative recurrence occurs in at least half of all patients with GISTs<sup>[2,9]</sup>. Although tyrosine kinase inhibitors have been shown to provide sustained disease management in patients with metastasis<sup>[10-16]</sup>, surgical R0 resection of small GISTs without metastasis is the only promising treatment for a permanent cure<sup>[8,17]</sup>. The best treatment strategy for GISTs is early diagnosis and early resection. However, GISTs are frequently detected as SELs during endoscopy<sup>[8,18-20]</sup>. The differential diagnoses of SELs are quite broad and can include extra-gastrointestinal tract compression, varices, an ectopic pancreas, and various tumors including GIST, SEL-like cancer, leiomyoma, schwannoma, and lipoma<sup>[8,20,21]</sup>. GISTs should be diagnosed by immunohistochemical analysis including assessment of KIT, CD34, and/or discovered on gastrointestinal stromal tumor 1 (DOG1)<sup>[8,22,23]</sup>. However, it is more difficult to obtain a conclusive histologic diagnosis of a GIST than gastrointestinal cancer by standard endoscopic forceps biopsy because a GIST is covered by normal mucosa. Although imaging tests including endoscopic

ultrasonography (EUS) and computed tomography (CT) are useful for narrowing down the differential diagnoses of SELs, these techniques are unable to provide a conclusive diagnosis. At present, EUS-guided fine needle aspiration (EUS-FNA) is the most accurate, safe, and reliable preoperative immunohistological test to secure a definitive diagnosis of SELs<sup>[8,18,19,23]</sup>. Aggressive use of EUS and EUS-FNA for SELs is the key to facilitating early intervention of GISTs<sup>[21,23]</sup>.

This paper provides an overview of the diagnosis and treatment of GISTs, with an emphasis on early diagnosis and management of GISTs using EUS-FNA.

## EPIDEMIOLOGY

In epidemiological surveys of GISTs, the estimated mean age at diagnosis is in the sixth decade of life, and the frequency of occurrence is 6.8 to 14.5 cases per million individuals per year<sup>[24-26]</sup>. GISTs most commonly occur in the stomach (51%), followed by the small intestine (36%), colon (7%), rectum (5%), and esophagus (1%)<sup>[24]</sup>.

## HISTOLOGICAL FINDINGS

The main morphologic types of GISTs are the spindle-shaped cell type (70%), epithelial cell type (20%), and mixed type (10%)<sup>[27]</sup>. It is difficult to differentiate between leiomyomas and neurinomas, two other mesenchymal tumors, using only hematoxylin and eosin staining; differentiation using immunostaining is indispensable<sup>[8,22,23]</sup>. A GIST is diagnosed in the presence of KIT or CD34 positivity. If the tumor is negative for KIT, CD34, desmin, and S-100, additional tests including DOG1 staining or a mutation search of the KIT or PDGFRA gene are useful for diagnosis of GISTs<sup>[28]</sup> (Figure 2).

## CLINICAL PRESENTATION AND INCIDENTAL GIST

The most common symptoms of GISTs are gastrointestinal bleeding, including acute melena and hematemesis with subsequent anemia; weakness; and abdominal pain, distension, and discomfort due to a tumor-induced mass effect<sup>[29]</sup>. Previous studies have shown that 15% to 30% of patients with GISTs are asymptomatic, and their GISTs are found incidentally during postmortem autopsy or surgery for treatment of other diseases<sup>[6,25,30]</sup>. Many pathological studies have highlighted the existence of subclinical microscopic or so-called mini (< 1 cm) GISTs<sup>[31-36]</sup>. Kawanowa *et al.*<sup>[31]</sup> reported that microscopic GISTs were present in 35% of patients who underwent gastrectomy for treatment of gastric adenocarcinoma. Agaimy *et al.*<sup>[32]</sup> reported that microscopic gastric GISTs were found in 22.5% of consecutive autopsies of patients aged  $\geq$  50 years. The reported incidence of mini-GISTs according to the affected organ is 3% to 10% in the stomach, 0.2% in the colon, and 0.01% in the

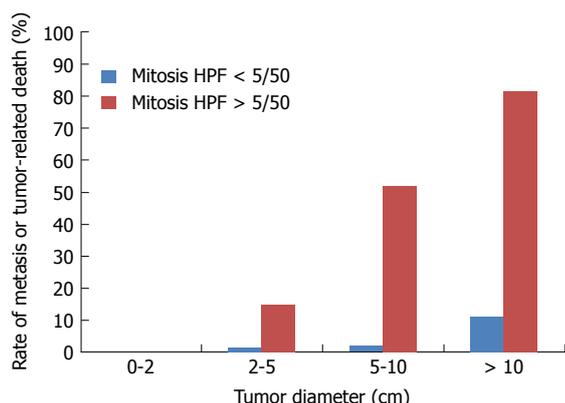


Figure 1 Rate of metastasis or tumor-related death according to tumor diameter and mitotic index. Created using reference<sup>[6]</sup>.

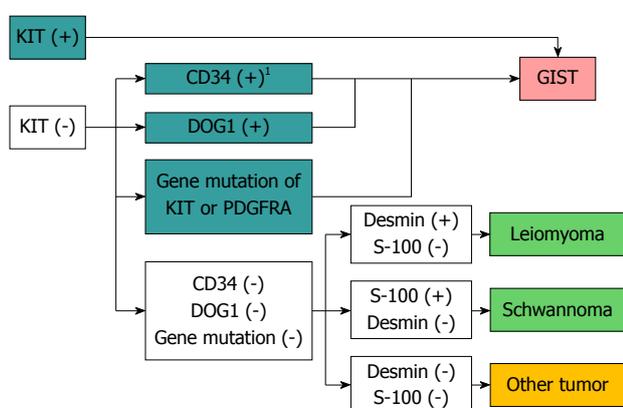


Figure 2 Flow chart of diagnosis of gastrointestinal mesenchymal tumors using immunohistochemical or genetic analysis. <sup>1</sup>Solitary fibrous tumors should be ruled out. Quoted and modified from reference<sup>[6]</sup>. GIST: Gastrointestinal stromal tumor.

rectum<sup>[31-36]</sup>. The detection of incidental SELs during gastrointestinal endoscopy has recently increased with the more widespread performance of endoscopic examinations. Gastric SELs are found in 0.36% of middle-aged adults during health examinations, and half of these tumors are considered to be neoplastic<sup>[37]</sup>. Most gastric SELs found during physical check-ups are small and asymptomatic. GISTs are considered to account for half of these incidentally found SELs in the stomach<sup>[31,34]</sup>. Based on these studies, GISTs are presumed to be much more common than previously recognized<sup>[18]</sup>.

## ENDOSCOPY

SELs are frequently found during ordinary optical endoscopy. The main endoscopic finding of GISTs is common to all SELs: A nonspecific smooth bulge covered with normal mucosa<sup>[11,21,38]</sup> (Figure 3). Therefore, endoscopic examination provides insufficient information for differential diagnosis of SELs. Irregular borders, ulceration, and/or growth during endoscopic follow-up are considered clinically malignant features on endoscopy<sup>[36]</sup>. GISTs are usually hard and the cushion sign is negative.

When GISTs increase in size, ulceration may be seen on the top of the tumor<sup>[19]</sup>.

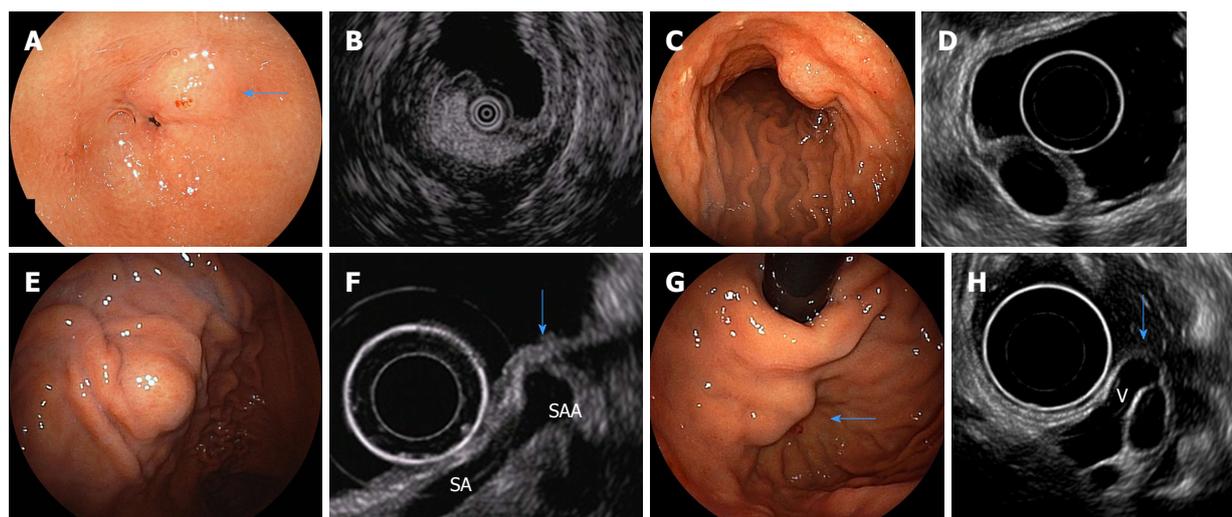
## EUS

EUS is a key test for differential diagnosis of SELs because it provides high-resolution tomographic imaging using high-frequency ultrasound. EUS provides the following information regarding SELs<sup>[39]</sup> (Figure 4): The gastrointestinal wall layer from which it originates (within the submucosal layer, in continuity with the muscularis propria, or outside the wall), the nature of the lesion (liquid, fat, solid tumor, or blood vessel), and the true size of the SEL from a cross-sectional image<sup>[39]</sup>. Thus, EUS is the safest and most useful modality for differential diagnosis and follow-up of SELs<sup>[21,40,41]</sup>. EUS allows for the conclusive diagnosis of many lesions using echo findings only, such as lipomas (highly echoic masses) (Figure 3A and B), cysts (anechoic masses) (Figure 3C and D), extraluminal compression by surrounding normal organs or lesions<sup>[42]</sup> (Figure 3E and F), and varices (Figure 3G and H)<sup>[21,38,43]</sup>. The typical EUS imaging feature of a GIST is a hypoechoic solid mass. EUS can accurately discriminate a SEL suspected to be a GIST (hypoechoic solid mass) from other SELs, including lipomas, cysts, varices, and extra-gastrointestinal compression. According to previous reports, possible high-risk EUS features for GISTs are a size of > 2 cm, irregular borders, heterogeneous echo patterns, anechoic spaces, echogenic foci, and growth during follow-up<sup>[44,45]</sup>. However, Kim *et al.*<sup>[46]</sup> reported that tumor size and EUS features cannot be used to preoperatively predict the risk of malignancy of medium-sized (2-5 cm) gastric GISTs. At present, estimation of the risk of malignancy of GISTs of < 5 cm by EUS imaging alone seems to be difficult. The finding of a hypoechoic solid mass by EUS is also seen in malignant tumors such as malignant lymphoma, metastatic cancer, neuroendocrine tumor, and SEL-like cancer and in benign conditions such as leiomyoma, neurinoma, and an aberrant pancreas<sup>[21]</sup>. It is difficult to distinguish among these lesions using EUS findings only. The accuracy of differential diagnosis of SELs by EUS is extremely poor and ranges from 45.5% to 48.0%<sup>[47,48]</sup>. Because current EUS imaging characteristics alone provide insufficient accuracy in the diagnosis of GISTs, tissue sampling for immunohistochemical analysis using EUS-FNA or biopsy is required for a definite diagnosis before surgery or chemotherapy<sup>[18-21]</sup>.

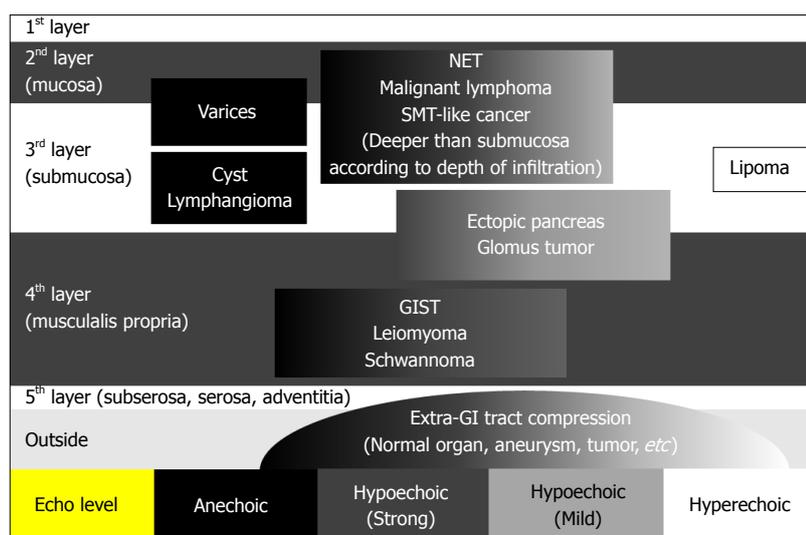
## TUMOR TISSUE SAMPLING METHODS

### Endoscopic forceps biopsy

Conventional endoscopic forceps biopsy is limited because these forceps usually cannot reach the tumor beyond the overlying normal mucosa and submucosa<sup>[49]</sup>. When ulceration is present, a biopsy within the ulcer is effective for a conclusive diagnosis<sup>[18,49,50]</sup>. Although special methods such as "jumbo" or "bite-on-bite" biopsy



**Figure 3** Endoscopic images of subepithelial lesions that can be diagnosed only with endoscopic ultrasound findings and their specific endoscopic ultrasonography images. A: Endoscopic image of a gastric lipoma (arrow); B: Endoscopic ultrasound (EUS) image of A (high-echo mass); C: Endoscopic image of a gastric cyst; D: EUS image of C (anechoic mass); E: Endoscopic image of extra-gastric compression due to splenic artery aneurysm; F: EUS image of E [normal gastric wall is compressed by a splenic artery aneurysm(SAA) (arrow). SA: splenic artery]; G: Endoscopic image of gastric varices (arrow); H: EUS image of G [varices are present in the submucosa from the outside of the wall (V) (arrow)]. Quoted and modified from reference<sup>[38]</sup> with permission.



**Figure 4** Differential diagnosis of subepithelial lesions by endoscopic ultrasound. Quoted and modified from reference<sup>[39]</sup> with permission. GIST: Gastrointestinal stromal tumor.

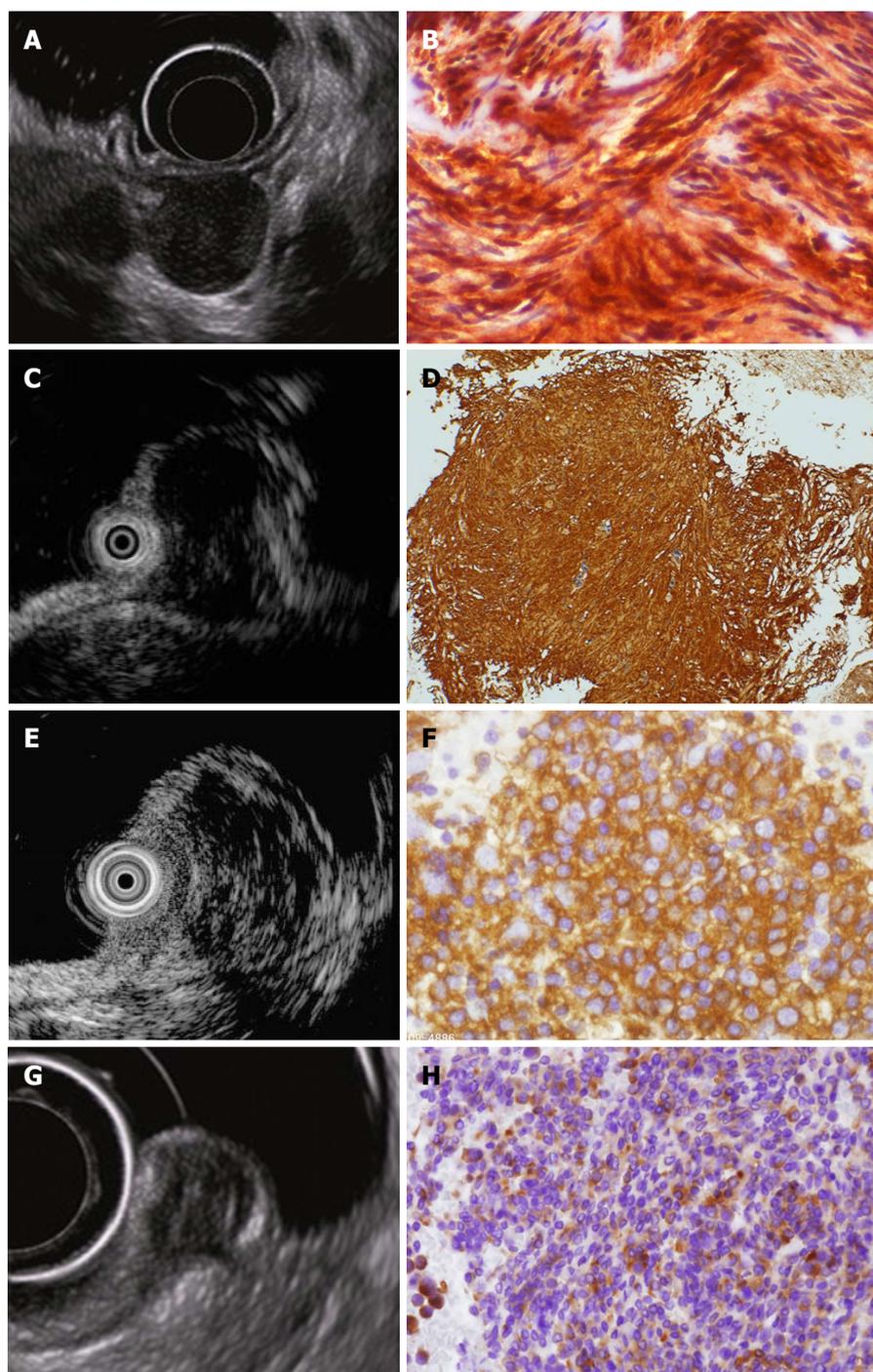
are available, the diagnostic yield of these approaches is poor, ranging from 17% to 59%<sup>[51-53]</sup>. Additionally, one study showed that significant bleeding occurred in 35.7% of patients after jumbo biopsy, and 34.9% of patients needed subsequent endoscopic hemostasis<sup>[53]</sup>.

**EUS-FNA**

EUS-FNA is the most established tissue sampling method for SELs and can provide a conclusive immunohistochemical diagnosis safely and accurately (Figure 5) (Video 1). Typical EUS-FNA findings of GISTs are KIT- or CD34-positive spindle-shaped cells or epithelial cells. The diagnostic rate of SELs using EUS-FNA ranges from 62.0% to 93.4%<sup>[23,54-56]</sup>. The diagnostic rate according to tumor diameter is 71% for 1-cm to 2-cm tumors,

86% for 2-cm to 4-cm tumors, and 100% for > 4-cm tumors<sup>[23]</sup>. The diagnostic rate tends to be higher as the tumor diameter increases. Unfortunately, EUS-FNA for a subepithelial hypoechoic solid mass of < 1 cm is technically difficult using a standard EUS-FNA scope; thus, EUS-FNA is recommended for masses of > 1 cm<sup>[56,57]</sup>. However, forward-viewing and curved linear-array echoendoscopes<sup>[58]</sup> and drill needles<sup>[59]</sup> have recently been developed and are expected to improve the diagnostic rate of small SELs. The rate of adverse events associated with EUS-FNA using a 22-gauge needle is reportedly close to 0<sup>[54-56]</sup>.

Evaluation of mitosis is important to determine the metastatic risk of GISTs. Unfortunately, the tissue sample volume obtained by EUS-FNA is usually small. Therefore,

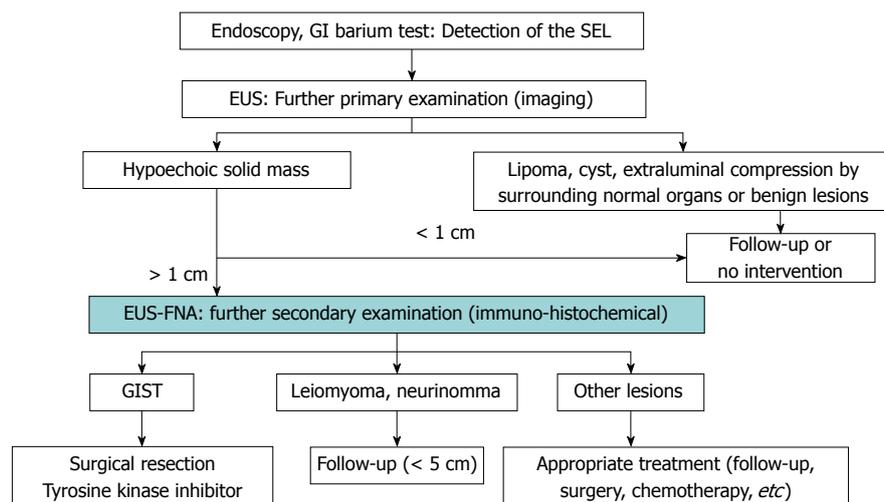


**Figure 5** Endoscopic ultrasound images and corresponding endoscopic ultrasonography-guided fine needle aspiration specimens of hypoechoic solid tumors. A: Endoscopic ultrasound (EUS) image of a gastric gastrointestinal stromal tumor; B: EUS-guided fine needle aspiration (EUS-FNA) specimen tissue image of A (KIT-positive spindle-shaped tumor cells are observed); C: EUS image of gastric leiomyoma; D: EUS-FNA specimen tissue image of C [ $\alpha$ -SMA-positive spindle-shaped tumor cells are observed; diagnosis of leiomyoma was made by immunohistochemical analysis, which revealed  $\alpha$ -SMA (+), KIT (-), CD34 (-), and S-100 (-)]; E: EUS image of gastric malignant lymphoma; F: EUS-FNA specimen image of E (diagnosis of diffuse large B-cell lymphoma was made by CD20-positive lymphoid tumor cells); G: EUS image of rectal neuroendocrine tumor (NET); H: EUS-FNA specimen image of G (diagnosis of NET was made by typical findings of irregular nest of synaptophysin-positive epithelial-like cells). Quoted and modified from reference<sup>[38]</sup> with permission.

assessment of mitosis by EUS-FNA is difficult. Ando *et al*<sup>[60]</sup> reported that the MIB-1 labeling index is accurate (100%) for diagnosis of malignant GISTs because Ki-67-positive cells can be easily recognized in the small specimens obtained by EUS-FNA.

#### **Endoscopic biopsy using endoscopic submucosal dissection or endoscopic snare resection techniques**

Invasive endoscopic tissue acquisition to obtain a higher tissue volume was recently developed and clinically applied<sup>[56-59]</sup>. Various endoscopic tissue-obtaining me-



**Figure 6 Proposed algorithm for management of subepithelial lesions.** Quoted and modified from reference<sup>[21]</sup>. GIST: Gastrointestinal stromal tumor; GI: Gastrointestinal; SEL: Subepithelial lesion; EUS: Endoscopic ultrasound; EUS-FNA: Endoscopic ultrasound-guided fine needle aspiration.

thods using endoscopic submucosal dissection (ESD) techniques or endoscopic snare resection techniques significantly increase the diagnostic yield when compared with standard forceps biopsy; the reported diagnostic rates range from 85% to 94%<sup>[61-64]</sup>. An additional advantage of these methods is the ability to evaluate the risk classification of GISTs using the mitotic count per 50 high-power fields<sup>[65,66]</sup>. However, ESD and endoscopic snare resection are invasive procedures; therefore, endoscopists should pay special attention to intra-operative bleeding and perforation while performing these techniques because such complications may cause severe hypotension or tumor cell seeding. Lee *et al*<sup>[63]</sup> reported that minor hemorrhage occurred in 56% of patients who underwent endoscopic partial removal with the unroofing technique, but hemostasis was successfully achieved in all patients with argon plasma coagulation, and no perforations occurred. Furthermore, tissue sampling of SELs with an extraluminal growth pattern is difficult<sup>[64]</sup>. A potential disadvantage of these aggressive endoscopic tissue acquisition techniques using ESD or endoscopic snare resection is the development of perilesional fibrosis, which may render subsequent attempts at submucosal tunneling endoscopic resection<sup>[67,68]</sup> difficult or even impossible<sup>[69]</sup>.

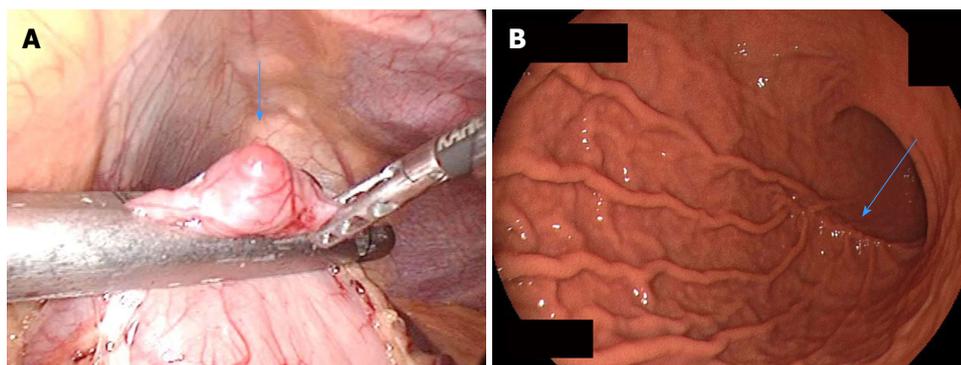
## DIAGNOSTIC PROCESS

GISTs have no specific endoscopic or EUS findings, and diagnosis is difficult to achieve by histopathological examination using hematoxylin and eosin staining alone. Immunohistochemical analysis such as that involving KIT, CD34, or DOG1 measurement is essential for a definitive diagnosis<sup>[8,21]</sup>. However, because not all SELs are GISTs, it is necessary to identify those SELs that are suspicious for GISTs and perform immunohistochemical analysis of these SELs in clinical practice. Figure 6 shows our institutional algorithm for the detection and management of SELs as discussed

herein<sup>[21]</sup>. First, all SELs are examined by EUS, and the SELs mentioned in the EUS section (Figure 3) that are conclusively diagnosed by EUS findings only are excluded. Second, EUS-FNA using immunohistochemical analysis is performed for the remaining hypoechoic solid masses to differentiate GISTs from other tumors. Narrowing down of SELs by EUS is important for efficient performance of EUS-FNA in the diagnosis of GISTs. In the Japanese clinical practice guidelines for GISTs, biopsy is recommended for exclusion of SEL-like cancer when an SEL is endoscopically diagnosed<sup>[70]</sup>. However, because SELs also include vascular diseases for which biopsy is contraindicated, such as varices (Figure 3G and H), it is desirable to perform EUS before biopsy.

## TREATMENT

The principle treatment strategy for immunohistologically confirmed GISTs is as follows: (1) Surgical resection is the first choice for resectable GISTs without metastasis; and (2) Administration of tyrosine kinase inhibitors such as imatinib is the primary approach for unresectable, metastatic, or recurrent GISTs<sup>[70-73]</sup>. The objective of surgery is to achieve R0 resection to the greatest extent possible. Lymph node dissection is not recommended except when lymph node metastasis is clinically suspected; most metastasis of GIST is liver metastasis or peritoneal seeding, and lymph node metastasis is extremely rare<sup>[74,75]</sup>. Therefore, wedge or segmental resection with preservation of organs and organ functions and maintenance of a good quality of life after surgery is recommended<sup>[76]</sup>. Previous studies have shown that laparoscopic resection is feasible and safe for gastric GISTs and is less invasive than traditional open surgery, with similar oncological outcomes (Figure 7)<sup>[77-79]</sup>. Other minimally invasive techniques such as submucosal tunneling endoscopic resection<sup>[67,68]</sup>, endoscopic fullthickness resection<sup>[80]</sup>, and laparoscopic endoscopic cooperative surgery<sup>[81]</sup> have recently shown good clinical outcomes;



**Figure 7** Laparoscopic resection of a small gastric gastrointestinal stromal tumor. A: Laparoscopic view of a small gastric gastrointestinal stromal tumor (arrow) during resection; B: Postoperative endoscopy shows mild postoperative deformity (arrow). Quoted and modified from reference<sup>[7]</sup> with permission.

Table 1 Modified Fletcher's risk classification			
Risk category	Tumor size (cm)	Mitotic index (per 50 HPFs)	Primary tumor site
Very low risk	< 2.0	≤ 5	Any
Low risk	2.1-5.0	≤ 5	Any
Intermediate risk	2.1-5.0	> 5	Gastric
	< 5	6-10	Any
High risk	5.1-10.0	≤ 5	Gastric
	Any	Any	Tumor rupture
	> 10 cm	Any	Any
	Any	> 10	Any
	> 5.0	> 5	Any
	2.1-5.0	> 5	Non-gastric
	5.1-10	≤ 5	Non-gastric

Quoted and modified from reference<sup>[7]</sup> with permission. HPF: High-power fields.

however, there are still insufficient studies concerning their long-term safety, and they are still at clinical research levels.

In contrast, the introduction of imatinib (first-line tyrosine kinase inhibitor) has dramatically improved the management of GISTs, prolonging recurrence-free survival after surgery<sup>[82]</sup> and extending overall survival in metastatic or unresectable cases<sup>[14]</sup>. Three years of adjuvant therapy with imatinib for patients with high-risk GISTs who have undergone macroscopic complete tumor resection (R0 and R1) is recommended because it improves overall survival and recurrence-free survival<sup>[82]</sup>. Sunitinib (second-line tyrosine kinase inhibitor)<sup>[83]</sup> and regorafenib (third-line multikinase inhibitor)<sup>[84]</sup> can be used in advanced GISTs after treatment failure with imatinib. However, it is difficult to obtain a permanent cure by tyrosine kinase inhibitors. Therefore, early diagnosis (early GISTs without metastasis) with early surgical resection is the only promising way to obtain complete cure of this disease<sup>[20,21,56]</sup>.

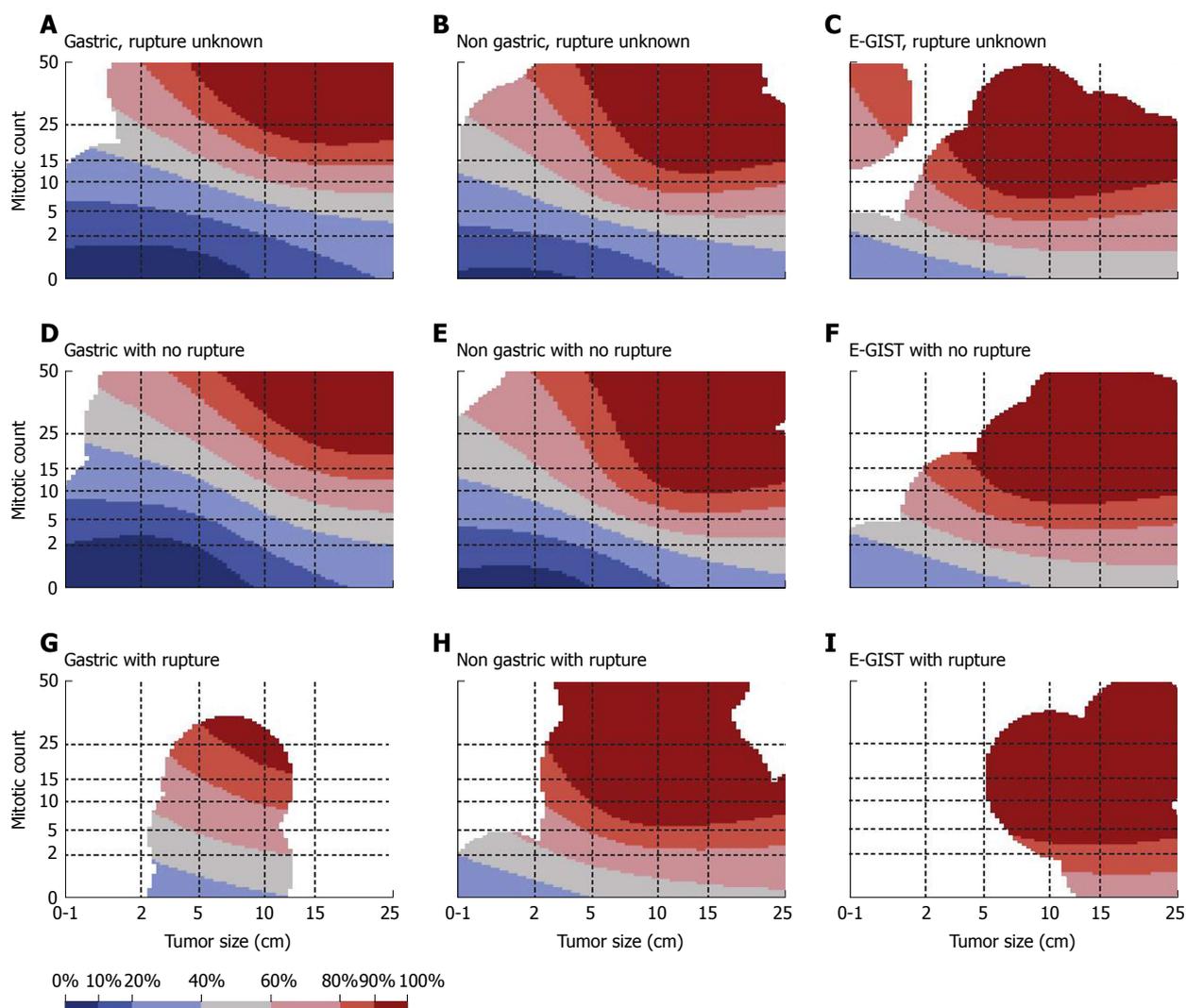
## PROGNOSIS AND RISK CLASSIFICATION

Differentiation between a benign and malignant GIST is difficult even using postoperative histopathological findings. Thus, even if the tumor diameter is small

and/or the mitotic rate is low, postoperative metastasis is possible. GISTs are currently regarded as potentially malignant tumors. Discrimination of a benign GIST from a malignant GIST by postoperative histological analysis (tumor diameter, mitotic index, and Ki67 expression level) is difficult; therefore, risk classifications to predict postoperative metastasis have been introduced<sup>[7,85,86]</sup>. Currently, the modified Fletcher classification (Joensuu classification) is widely used (Table 1)<sup>[7]</sup>. In addition, contour maps (Figure 8) can be created based on investigation of the prognosis of many cases worldwide. In these maps, the risk of recurrence at the 10<sup>th</sup> year after surgical treatment of a GIST is calculated using the maximum diameter of the tumor, the number of mitoses, the tumor site, and the presence or absence of tumor capsule rupture; continuous risk assessment is also possible<sup>[87]</sup>. Using such maps, physicians and patients can predict the probability of recurrence in the 10<sup>th</sup> postoperative year. This is useful for individual decision-making with respect to adjuvant therapy.

## POSTOPERATIVE FOLLOW-UP BY CT

The goal of postoperative follow-up is early detection and management of recurrence. Because the targets of postoperative follow-up observation are local recurrence, liver metastasis, and peritoneal dissemination, abdominal contrast CT, which can be sufficiently evaluated from the diaphragm to the inguinal region, is recommended as a follow-up examination method according to the Japanese clinical practice guideline for GISTs<sup>[70]</sup>. Based on the above-mentioned risk classification, the following observation intervals are recommended<sup>[70]</sup>: GISTs with very low, low, and moderate risks are followed up by CT every 6 mo to 1 year, and high-risk and clinically malignant GISTs (those with metastasis, injury to the pseudocapsule, peritoneal dissemination, or infiltration of other organs) are followed up by CT every 4 to 6 mo. The natural history of GISTs is unknown. Previous studies have shown that the estimated 5-year recurrence-free survival rate after surgery is 59.9%; few recurrences occurred after the first 10 years of follow-up<sup>[7,88]</sup>. Follow-up observation after surgery is considered necessary for



**Figure 8** Contour maps for estimating the risk of gastrointestinal stromal tumor recurrence after surgery. Areas of colors according to the recurrence rate at the 10<sup>th</sup> year after surgical treatment of GIST: Blue-black: 0%-10%, Blue: 10%-20%, Light blue: 20%-40%, Gray: 40%-60%, Pink: 60%-80%, Red: 80%-90%, Dark red: 90%-100%. Reprinted from reference<sup>[87]</sup> with permission. E-GIST: Extra-gastrointestinal stromal tumor (arising outside the gastrointestinal tract).

more than 10 years.

## MANAGEMENT OF SMALL SELS SUSPECTED TO BE GISTS

The detection rate of small GISTs has continuously increased with advancements in endoscopy<sup>[89,90]</sup>. However, the surveillance and management of GISTs smaller than 2 cm is controversial or lacks evidence-based approaches<sup>[41,56,89-92]</sup>. Most small GISTs are discovered incidentally and usually show a benign or indolent clinical course. Conversely, strict discrimination between benign and malignant GISTs is considered to be very difficult using both clinical and pathological examinations. Thus, the European Society for Medical Oncology<sup>[72]</sup>, Japanese<sup>[70]</sup>, and Chinese Society of Clinical Oncology<sup>[73]</sup> GIST guidelines recommend surgical resection when an SEL is immunohistochemically diagnosed as a GIST, even when smaller than 2 cm. In contrast, the National Comprehensive Cancer Network<sup>[71]</sup> guide-

lines recommend that small GISTs of < 2 cm may be periodically followed up by EUS when they lack high-risk features including an irregular border, cystic spaces, ulceration, echogenic foci, and heterogeneity. However, in the examination of 378 histologically diagnosed GISTs of < 2 cm registered in the National Cancer Institute's Surveillance Epidemiology and End Results database, which is a cancer database in the United States, 11.4% of the patients had regional/distant metastatic disease and the 5-year GIST-specific mortality rate was 12.9%<sup>[93]</sup>. In a study of 43 surgically resected small GISTs of < 2 cm with immunohistochemical analysis, 23% of lesions were classified as having intermediate risk according to the Joensuu risk stratification<sup>[56]</sup>. Although GISTs of  $\leq$  2 cm are reportedly metastatic at a low frequency (but not 0%)<sup>[89,90,93]</sup>, early tissue diagnosis and early resection with postoperative follow-up are desired. Importantly, therefore, gastroenterologists should consider early interventions such as EUS for incidentally detected small SELs. Active performance of EUS is effective even

for small SELs of  $\leq 2$  cm to ensure early detection of hypoechoic solid masses suspected to be GISTs<sup>[56]</sup>. If EUS imaging of a SEL with an endoscopically negative biopsy shows a hypoechoic solid mass of  $> 1$  cm, subsequent EUS-FNA is needed to obtain a conclusive tissue diagnosis of a GIST<sup>[21,56]</sup>. Small SELs of  $< 1$  cm are currently recommended to undergo periodic EUS follow-up (every 6 mo or 1 year)<sup>[56,91]</sup> because EUS-FNA for small SELs of  $< 1$  cm is technically difficult. These aggressive approaches for early diagnosis and early treatment of small SELs, similar to the approaches for gastrointestinal tract cancer, seem to be the only promising way to improve patients' quality of life and prognosis.

## CONCLUSION

GISTs are the most common malignant SELs of the digestive tract. According to previous studies, early histologic diagnosis and early surgical resection of small localized disease is currently the most reliable and curative treatment technique for GISTs. However, sufficient prospective studies including small GISTs have not been performed to improve the current clinical GIST management. Further studies are needed to focus on early tissue diagnosis and therapeutic approaches, especially for small SELs.

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