

Diagnostic and Treatment Strategy for Small Gastrointestinal Stromal Tumors

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Gastrointestinal stromal tumors (GISTs) are considered to be potentially malignant mesenchymal tumors of the gastrointestinal tract. Clinically relevant GISTs are rare; however, subclinical GISTs (mini-GISTs) (1-2 cm) and pathologic GISTs (micro-GISTs) (<1 cm) are frequently reported. Most mini-GISTs and almost all micro-GISTs of the stomach may exhibit benign clinical behavior, and only mini-GISTs with high-risk features may progress. For this review, a provisional algorithm was used to propose diagnostic and treatment strategies for patients with small GISTs. Because surgery is the only potentially curative treatment, in its application for small GISTs, the principles of sarcoma surgery should be maintained, and cost effectiveness should be considered. Indications for surgery include GISTs measuring ≥ 2 cm, symptomatic GISTs, and mini-GISTs with high-risk features (irregular borders, cystic spaces, ulceration, echogenic foci, internal heterogeneity, and tumor progression during follow-up); however, a preoperative pathologic diagnosis is infrequently obtained. For small intestinal and colorectal GISTs, surgery is indicated irrespective of size because of their greater malignant potential. Otherwise, mini-GISTs without high-risk features, micro-GISTs, and small submucosal tumors measuring <5 cm without high-risk features may be followed by periodical endoscopic ultrasonography. Although surgical approaches and operative methods are selected according to tumor size, location, growth pattern, and surgical teams, laparoscopic surgery has produced similar oncologic outcomes and is less invasiveness compared with open surgery. After resection, pathologic examination for diagnosis and risk assessment is mandatory, and genotyping is also recommended for high-risk GISTs. Endoscopic resection techniques, although feasible, are not routinely indicated for most mini-GISTs or micro-GISTs. *Cancer* 2016;122:3110-8. © 2016 The Authors. *Cancer* published by Wiley Periodicals, Inc. on behalf of *American Cancer Society*. This is an open access article under the terms of the Creative Commons Attribution-NonCommercial-NoDerivs License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

KEYWORDS: endoscopic ultrasonography (EUS), gastrointestinal stromal tumor (GIST), high-risk features, laparoscopic surgery, submucosal tumor (SMT).

INTRODUCTION

Gastrointestinal (GI) stromal tumors (GISTs) are considered potentially malignant neoplasms arising from mesenchymal cells, which may differentiate into the interstitial cells of Cajal—the pacemaker cells of the GI tract.¹ It is estimated that the clinical incidence of GIST is nearly 1 in 100,000 population per year. Most “clinically relevant” GISTs originate in the stomach (60%), followed by the small intestine (30%), and the colon/rectum (5%); however, GISTs may occur anywhere in the GI tract and abdominal cavity, including the greater omentum and mesentery.¹ Although GISTs can arise at any age, including in children and young adults aged <20 years, most GISTs are identified in middle-aged individuals. Primary GISTs rarely invade into surrounding tissues. Metastases to the lymph nodes are rare except in pediatric types of GISTs, particularly those with mutations of the gene encoding succinate dehydrogenase (*SDH*) or with *SDH* inactivation. GISTs spread mainly to the liver and peritoneal cavity. With increased malignant potential, GISTs may become more friable and hypervascular, appearing as heterogeneously enhanced lesions on contrast-enhanced computed tomography (CT) scans.

The proliferation of GISTs is most commonly driven by gain-of-function mutations in the *KIT* proto-oncogene receptor tyrosine kinase (*KIT*) (80%) or platelet-derived growth factor receptor α (*PDGFRA*) (10%) genes, both of which encode receptor tyrosine kinases. The remaining 10% usually harbor gain-of-function mutations in the B-Raf

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Correction added on 16 August 2016 after first online publication: in the second paragraph of the Conclusions section, the second sentence has been corrected to read “Indications for surgery include clinically relevant GISTs ≥ 2 cm, mini-GISTs with high-risk features or symptoms, pathologically undiagnosed SMTs with symptoms or high-risk features, and SMTs > 5 cm.”

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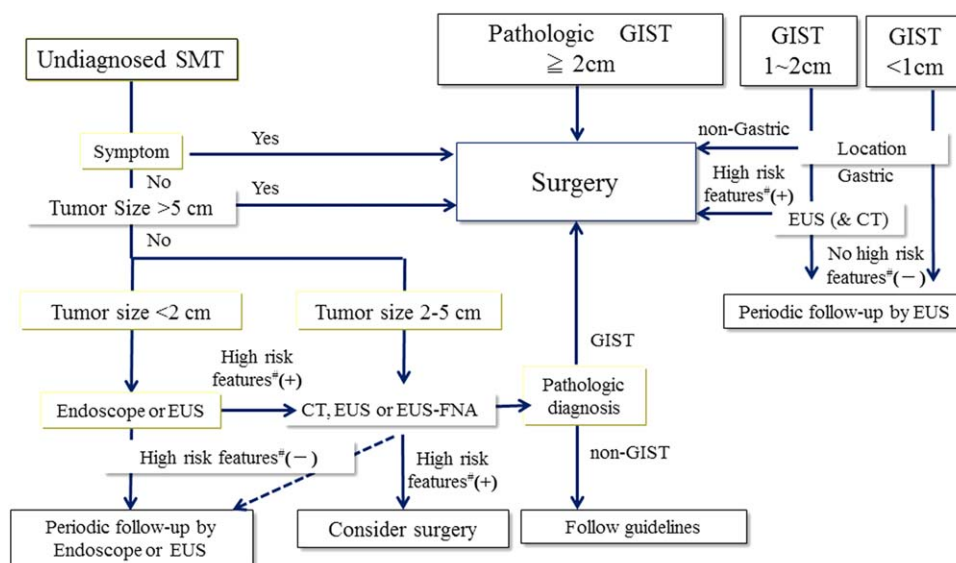


Figure 1. Approaches to pathologically undiagnosed submucosal tumors (SMTs) and pathologically confirmed gastrointestinal stromal tumors (GISTs) are illustrated. Therapeutic approaches for pathologic GISTs are divided by size (ie, ≥ 2 cm, 1-2 cm, and < 1 cm). High-risk features include irregular border, cystic spaces, ulceration, echogenic foci, heterogeneity, and progression during follow-up. CT indicates computed tomography; EUS, endoscopic ultrasonography; EUS-FNA: endoscopic ultrasonography-guided fine-needle aspiration biopsy.

proto-oncogene serine/threonine kinase (*BRAF*), Harvey rat sarcoma viral oncogene homolog (*HRAS*), or neuroblastoma rat sarcoma viral oncogene homolog (*NRAS*) genes or have loss-of-function mutations or epigenetic changes in the neurofibromin 1 (*NF1*) or *SDH* complex.^{2,3} These mutations and changes are mutually exclusive. GIST is usually diagnosed by pathologic examination. GIST morphology may demonstrate spindle (70%), epithelioid (20%), or mixed features (10%). Immunohistochemical staining for KIT is usually identified in nearly 95% of GISTs. In some patients with KIT-negative GIST (5%), genotyping may help confirm the diagnosis but is not routinely required.⁴ GIST is often diagnosed postoperatively after resection of a submucosal tumor (SMT) or abdominal mass. However, it may be diagnosed preoperatively, usually by endoscopic ultrasound (EUS)-guided fine-needle aspiration (EUS-FNA).

Surgery remains the mainstay for treatment of primary GIST and is the only potentially curative therapy. Approximately 60% of patients with clinically relevant GISTs are cured by surgery alone, whereas the remaining 40% of patients will develop recurrent disease.⁵ Tumor size (cm), mitosis (per 20 or 50 high-power fields, depending on microscope field size, or per 5-mm² field), location (gastric or nongastric), and the presence or absence of tumor rupture are independent prognostic factors after complete resection,^{1-3,5} when unresectable, metastat-

ic or recurrent, molecularly targeted agents, including imatinib, sunitinib, and regorafenib, are indicated.

In addition to the aforementioned “clinically relevant GISTs,” such as symptomatic GISTs or GISTs measuring ≥ 2 cm, several reports have confirmed that many individuals may have GISTs measuring < 2 cm (sub-2-cm GISTs) in both the stomach and the intestine.⁶⁻¹⁰ These include “mini-GISTs” (1-2 cm) and “micro-GISTs” (< 1 cm). Data regarding the natural history of these GISTs are minimal, and their diagnostic significance and optimal treatment strategy are unclear, even in various national and international guidelines.

OVERVIEW OF SMALL GISTS

In this report, mini-GISTs are defined as those measuring between 1 and 2 cm, and micro-GISTs are those measuring < 1 cm. Mini-GISTs may be identified incidentally during endoscopy, and micro-GISTs may be identified mainly during postoperative pathologic analysis of other malignancies. Clinically relevant GISTs may be defined as tumors measuring ≥ 2 cm (Fig. 1). Although no major differences are observed on immunohistochemistry between micro-GISTs and mini-GISTs, morphologic features and proliferation activity appear to be more aggressive in mini-GISTs.¹⁰ Patients with these small GISTs rarely have symptoms and seldom develop disease progression and metastasis.

Pathologic examinations at surgery or during autopsy have revealed that incidental micro-GISTs in the stomach are frequent findings in middle-aged adults (10%-35%). Similar to clinically relevant GISTs, gastric micro-GISTs, which mainly arise in the muscularis propria of the upper stomach, are usually KIT-positive on immunohistochemical staining and frequently have *KIT* or *PDGFRA* mutations.^{6,7,10} Similar to GISTs, microleiomyomas, which predominantly arise in the inner muscularis propria, are also frequent findings in the upper stomach, especially near the gastroesophageal junction. Furthermore, multiple micro-GISTs and microleiomyomas are occasionally identified in the stomach. Neoplastic SMTs measuring < 2 cm reportedly are identified in 0.15% of middle-aged adults by screening endoscopy, and nearly one-half are considered to be GISTs.¹¹ Thus, there are big differences in the incidence of GISTs among micro-GISTs, mini-GISTs, and clinically relevant GISTs, suggesting that many micro-GISTs and mini-GISTs are indolent and do not progress in a clinically significant manner. In fact, Rossi et al have suggested that the proliferation activity of small gastric GISTs is quite low and self-limiting and that features of the tumor cells appear to be benign with low cellularity and sclerosis, especially when they are micro-GISTs.^{8,10}

Micro-GISTs are less frequent in the small intestine, colon, and rectum (0.1%- 0.2%) than in the stomach.⁹ However, rectal GISTs have comparatively higher mitotic activity, and small intestinal GISTs may exhibit significant growth despite low mitotic counts, even when they measure < 2 cm.⁹ Therefore, small GISTs in the intestine may have a distinctively more aggressive biology compared with gastric GISTs. Differences between gastric and intestinal GISTs are also reported in clinically relevant GISTs with regard to gene expression, pathologic features, and clinical outcomes.^{2,12}

Most micro-GISTs appear to be less mitotically active and have different mutations compared with larger, clinically relevant GISTs.¹⁰ In an analysis that compared 101 GISTs < 2 cm with 170 GISTs ≥ 2 cm, the majority of tumors measuring ≤ 1 cm had no mitotic activity. Furthermore, in mutational analysis, the sub-2-cm GISTs typically had an excess of so-called “wild-type” mutations, a lower percentage of *KIT* exon 11 mutations, and novel mutations never previously reported in the larger, clinically relevant GISTs.

DIAGNOSIS OF SMALL GIST AND SMALL SMT

Although certain types of SMT, such as lipomas and glomus tumors, may be diagnosed endoscopically and/or ra-

diographically, most SMTs cannot be diagnosed until pathologic examination.¹³ Because SMT specimens are rarely obtained by conventional endoscopic biopsy, EUS-FNA is the best way to obtain tissue samples for subsequent pathologic diagnosis. Although endoscopy and EUS are useful in the diagnosis and follow-up of SMTs, extrinsic or exophytic growth of SMTs may be missed by such examinations, and CT scans may be required to fully characterize these tumors.¹⁴

Most small SMTs are identified incidentally by endoscopic investigation for symptoms caused by other diseases, screening endoscopy for health checks, or surveillance endoscopy after endoscopic resection (ER) or surgery for other diseases (Fig. 1).^{6,11} Otherwise, they can be identified by double-contrast barium x-ray, for instance, as in Japan, where a nationwide screening program using x-ray has been promulgated. These include neoplastic lesions (GIST, leiomyoma, schwannoma, lipoma, etc) and non-neoplastic lesions (ectopic pancreatic tumor, duplication cyst, isolated varices, etc) as well as extrinsic compression by other organs. Although it is important to differentiate potentially malignant GISTs from other benign or non-neoplastic lesions, differentiation simply by endoscopy, or even by EUS, is extremely difficult. General characteristics of small GISTs are elastic, firm, usually spindle-celled, clearly demarcated lesions within the muscularis propria or, infrequently, attached to the muscularis mucosae, which may be evaluated using various imaging modalities. During conventional endoscopy, elasticity can be estimated by gently compressing tumors with biopsy forceps or other devices. When a lesion is easily depressed (positive “cushion sign”) by forceps, it may be a lipoma or duplication cyst. EUS is an essential imaging modality for evaluating tumor shape, size, growth type, internal echo, heterogeneity, and layer of origin; thus, most mesenchymal tumors, including GISTs (which are well demarcated, hypoechoic masses), may be differentiated from other lesions by close examination with EUS.^{4,15,16} Although CT scans and magnetic resonance imaging studies are generally used to obtain information on large GI tumors,^{3,4} those modalities may miss smaller lesions, such as small SMTs and GISTs < 2 cm.¹⁷ Therefore, such studies may not be quite so helpful for the workup for small lesions compared with EUS, except for lesions that exhibit extrinsic growth.¹⁸ Positron-emission tomography (PET)-CT scanning may be an option. Because of their size and low mitotic count, however, most mini-GISTs and micro-GISTs are considered PET-negative. PET-CT is not necessarily superior to EUS for the diagnosis of

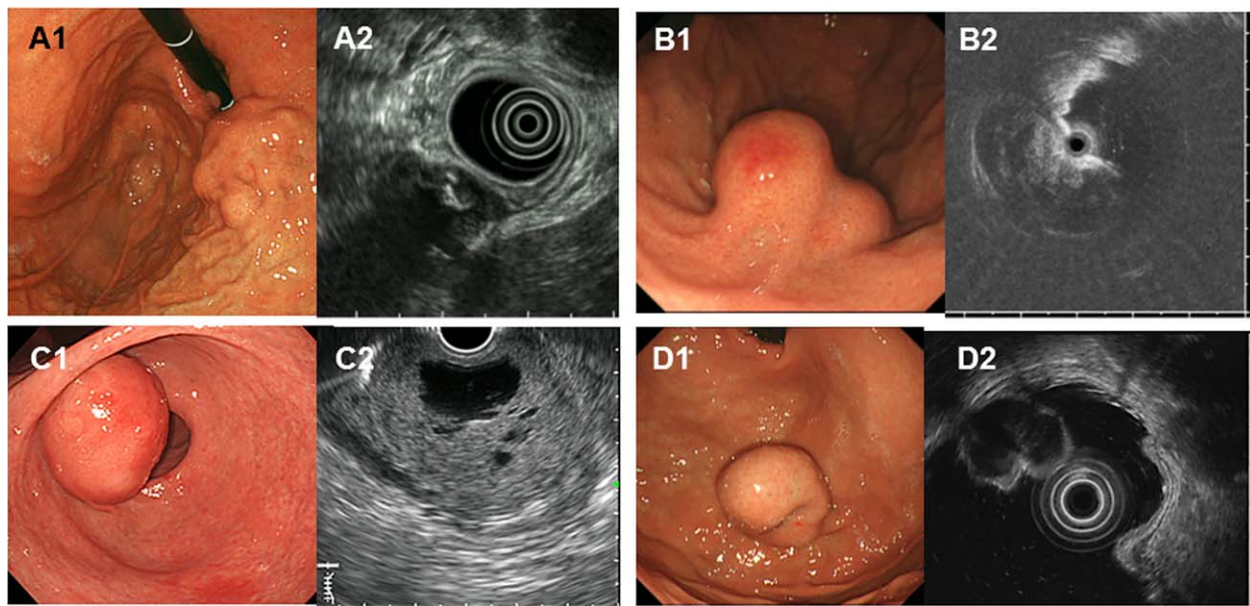


Figure 2. Representative high-risk endoscopic and endoscopic ultrasound (EUS) features of gastrointestinal stromal tumors are shown, including (A1,A2) irregular borders and echogenic foci, (B1,B2) heterogeneity, (C1,C2) cystic spaces, and (D1,D2) ulceration.

these GISTs, except in very rare tumors that have high mitotic activity.

The differentiation of GISTs from other mesenchymal tumors (eg, leiomyoma and schwannoma) simply using endoscopy is still challenging,^{19,20} whereas promising results have been reported with the use of EUS to accurately differentiate GISTs from some other SMTs.^{21,22} However, currently, a diagnosis of GIST can be only confirmed by pathologic examination with immunohistochemical staining after a suitable amount of tumor tissue is obtained. EUS might indicate potentially malignant SMTs, which would require treatment. In fact, the Japanese GIST guidelines indicate that SMTs may be potentially malignant tumors, including GISTs, when tumors have characteristics of growth during follow-up, tumor ulceration, heterogeneity of the internal echo, and/or irregular margins.⁴ National Comprehensive Cancer Network sarcoma guidelines also suggest that SMTs <2 cm with high-risk features identified on EUS, including irregular borders, cystic spaces, ulceration, echogenic foci, and internal heterogeneity, should be removed as presumed GISTs; whereas tumors without those features can be followed by EUS (Figs. 1 and 2).²

Conventional biopsy is not useful for the acquisition of a suitable amount of tumor tissues from small gastric SMTs because of the intact overlying mucosa. In contrast, EUS-FNA is feasible and more helpful for the safe and accurate histologic diagnosis of SMTs.²³⁻²⁵ The

diagnostic yield of EUS-FNA is related to size, location, layer, and tumor histology. The success rate of tissue sampling from GISTs by EUS-FNA is generally lower than that of sampling from pancreatic tumors.²⁶ This may be related to the firmness of mesenchymal tumors compared with adenocarcinoma or other epithelial neoplasms. Furthermore, tissue sampling by EUS-FNA is technically difficult when target SMTs are small, especially in tumors measuring <1 cm. Therefore, the indication for EUS-FNA may be lesions measuring >1 cm that are suspected to be potentially malignant tumors. Otherwise, periodic follow-up with EUS or endoscopy would be recommended for the other small SMTs, including micro-GISTs and mini-GISTs without high-risk features.²⁷ Indications for EUS-FNA include SMTs without a confirmed pathologic diagnosis, which may require medical or surgical treatment, depending on their histology. EUS-FNA is not recommended for patients who have tumors for which surgery is planned or for those who have apparently benign tumors on radiographic imaging and/or endoscopy.²⁸ Because the mucosa is thin in the esophagus and colon, conventional or boring biopsies may work for tissue sampling from esophageal or colorectal SMTs. Currently, the risk of metastasis cannot be estimated by histologic assessment using small samples obtained by EUS-FNA or biopsy because of the heterogeneity of GISTs and the difficulty in accurately estimating the mitotic count from aspirated

cells. Therefore, the purpose of EUS-FNA and/or biopsy is diagnostic decision making for therapeutic options, but not for risk assessment.

THERAPEUTIC APPROACHES TO SMALL GIST AND SMT

The goals of treatment for small SMTs, including GISTs, may include the control of symptoms and the potential cure of malignant lesions by surgery. Indications may include SMTs with symptoms and potentially malignant or malignant tumors confirmed by pathology. Although all clinically relevant GISTs measuring ≥ 2 cm are considered malignant, most gastric GISTs < 2 cm follow a benign clinical course and are not going to grow.² The differentiation of malignant GISTs with metastatic or recurrent potential from those that will follow an indolent course cannot always be achieved using EUS, even by pathologic examination. However, when small gastric GISTs or SMTs demonstrate an interval increase in size or have high-risk features on initial EUS, they should be resected (Figs. 1 and 2).²⁻⁴ Small gastric GISTs or SMTs without these features may be followed by periodic EUS. Most GIST guidelines for the surveillance of existing SMTs recommend an initial short-term follow-up by EUS within 6 months and subsequent annual follow-up until there is any evidence of tumor growth, high-risk features on EUS, or symptoms.^{2,4,29} A recent study indicated that periodic endoscopy within 3 years did not worsen the prognosis of patients with GISTs, suggesting that more relaxed follow-up may be acceptable in clinical practice.¹⁷ Tumor growth during follow-up is not common when gastric SMTs and GISTs measure < 2 cm. Interval growth is observed in $< 5\%$ of incidentally identified gastric SMTs over 2 years, even in histologically proven GISTs, and is estimated to be $< 20\%$ for several years.^{13,30,31} However, this applies only to gastric GISTs. We recommend surgery for small GISTs if they are located in the small intestine, colon, or rectum (Fig. 1). Decision making should be shared with patients regarding diagnostic process, histologic diagnosis, and the benefits and risks of treatment versus follow-up.

Cost effectiveness also should be considered in the treatment of small SMTs and GISTs, because asymptomatic SMTs that have a benign clinical course, such as leiomyomas, lipomas, and congenital lesions, and most micro-GISTs as well as significant numbers of gastric mini-GISTs normally do not progress and thus may not require treatment at all. Hence, we do not recommend surgery for benign SMTs, small SMTs with benign features, or micro-GISTs. We do recommend surgery for clinically relevant GISTs (> 2 cm), histologically proven

malignant SMTs, and mini-GISTs and small SMTs (< 5 cm) that have high-risk features on EUS and/or that increase in size during follow-up. Otherwise, follow-up with EUS may be acceptable for most undiagnosed small SMTs and mini-GISTs without high-risk features. When surgery is indicated for small GISTs, cost effectiveness is also a consideration in the selection of therapeutic modality. For the most part, data from retrospective reports indicate that, although laparoscopic surgery may be more expensive than open surgery, it is associated with faster recovery and shorter hospital stay, which may be more cost effective.³² The cost effectiveness of laparoscopic approaches should be evaluated in future prospective studies in addition to safety and prognostic outcomes.

SURGERY: OPEN VERSUS LAPAROSCOPIC

The objectives of surgery include macroscopically complete resection that avoids tumor rupture and injury to the pseudo-capsule with microscopically negative margins.^{2-4,29} Because prophylactic lymphadenectomy is not necessary for most GISTs, modest surgery, such as wedge resection, should be considered to preserve organ functions when tumors are resectable with negative surgical margins. For small GISTs that exhibit intraluminal growth and tumors near the gastroesophageal junction or pylorus, we recommend intraoperative use of endoscopy to identify tumors and to secure surgical margins, luminal space, deformity, and bleeding after resection. If there are enlarged lymph nodes, then limited dissection of the lymph nodes is indicated. Postoperative pathology is essential to confirm the diagnosis, and risk assessment and genotyping may be recommended for patients who have GISTs with a significant risk of recurrence.²⁹

The standard operation for GIST is complete resection with sufficient surgical margins by laparotomy, in keeping with the principles of sarcoma surgery.^{2,4,29} Several retrospective studies have suggested that laparoscopic surgery for gastric GISTs < 5 cm may be feasible and safe, with less invasiveness, better short-term cosmetic results, and long-term oncologic outcomes similar to those achieved with open surgery.³³⁻³⁶ However, the evidence for laparoscopic surgery is limited for small intestinal and colorectal GISTs. In laparoscopic surgery, staplers are used for resection, and an extraction bag is recommended to prevent potential tumor cell spillage and implantation.

Standard laparoscopic surgery or reduced-port surgery can be applied to lesions on the greater curvature, anterior wall, and posterior wall of the stomach (Fig. 3). When tumors are located on the lesser curvature, extensive resection of the curvature and injury to the vagus nerve

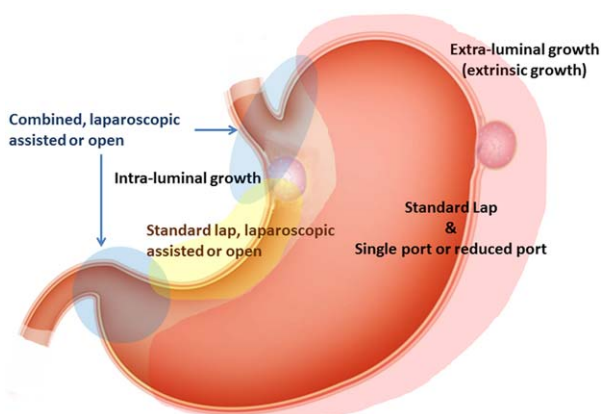


Figure 3. Several laparoscopic approaches to small gastric gastrointestinal stromal tumors that exhibit intraluminal or extrinsic growth are illustrated. Resection of a tumor on the lesser curvature appears to be challenging with a laparoscopic approach in terms of postoperative deformity and stasis. A sophisticated surgical technique is required to minimize deformity of the remnant stomach and to preserve branches of the vagal nerve.

may result in deformity of the remnant stomach and gastric stasis, respectively, and should be avoided. Laparoscopic surgery is technically demanding and sometimes challenging when tumors are located in the gastroesophageal junction, pylorus, duodenum, or lower rectum. Laparoscopic-assisted surgery may facilitate resection and reconstruction of junctional tumors. Recently, several laparoscopic approaches, including *laparoscopic and endoscopic cooperative surgery* (LECS), have been developed for small gastric GISTs near the gastroesophageal junction and pylorus to preserve junctional functions, as discussed below.³⁷ Laparoscopic approaches may be selected, depending on tumor size, location, growth pattern, and experience of the oncology team. Data on robotic resection are lacking, but oncologic principles similar to those for laparoscopic surgery should be applied.

Endoscopic and Laparoscopic Approach

A surgical approach from the outside of the stomach is sometimes difficult in small GISTs with intraluminal or intramural growth, because the identification of tumors and an unintentionally large resection may result in deformity of the remaining stomach and gastric malfunction, as mentioned above. Conversely, localization of these lesions is straightforward, and the resection area is well demarcated under endoscopic observation. Accordingly, endoscopic full-thickness resection with laparoscopic assistance may be ideal to minimize the resection area. The lesion can be isolated by an endoscopic circumferential mucosal incision under direct visualization and

resected in a full-thickness fashion by subsequent endoscopic or laparoscopic seromuscular incision. The gastric defect after tumor resection can be closed by laparoscopic linear staplers or laparoscopic suturing techniques (Fig. 4A). This is the LECS technique, and its feasibility, safety, and short-term efficacy have been reported,³⁷⁻³⁹ although data on long-term outcomes, including quality-of-life outcomes and prognosis, are awaited.

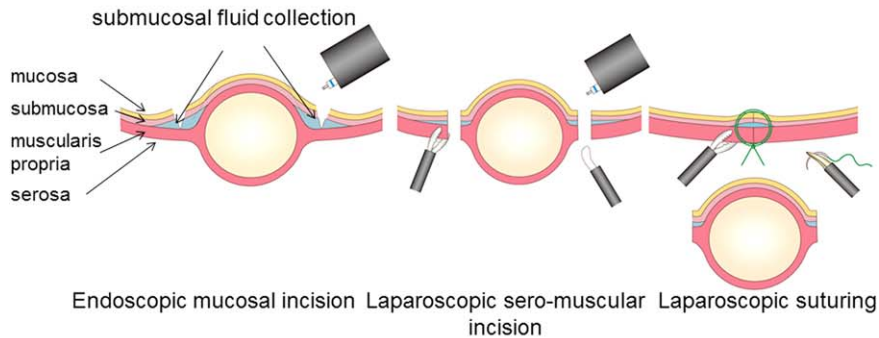
With this technique, it is important to avoid tumor cell seeding by exposure of the tumor surface. Therefore, the technique is used predominantly for gastric SMTs without tumor ulceration. SMTs and GISTs with ulceration have a potential risk of tumor dissemination into the peritoneal cavity from opening the GI tract. Recently, nonexposure techniques of collaborative surgery, such as the *combination of laparoscopic and endoscopic approaches to neoplasia with nonexposure technique* (CLEAN-NET) and *nonexposed endoscopic wall-inversion surgery* (NEWS), have been developed to prevent intraperitoneal contamination and the potential risk of tumor cell seeding, even in ulcerated tumors (Fig. 4B,C).⁴⁰⁻⁴² Although they are technically demanding, time-consuming, and even cost-ineffective, these techniques are promising and more “patient-oriented” in terms of less invasiveness and greater safety. Local resection using combined surgery with flexible endoscopy and laparoscopy is minimally invasive and may maintain subsequent quality of life. The smaller the tumor is, the more effective organ-preserving surgery will be. Therefore, surgical resection using these techniques may be recommended for mesenchymal SMTs, including GISTs, even when they are small.

Endoscopic Approaches for Small Esophageal and Gastric SMTs and GISTs

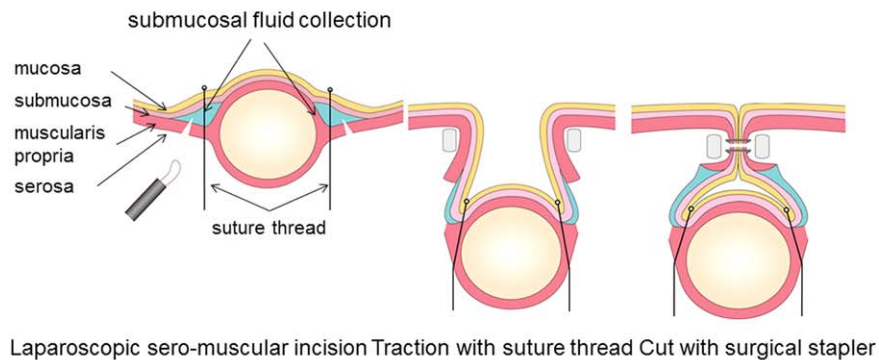
For superficial SMTs originating from the muscularis mucosae, an intraluminal approach by endoscopic resection (ER) may be an option.^{43,44} Before proceeding with ER, it should be confirmed on EUS that tumors are located in the muscularis mucosae and that the muscularis propria is intact. Indications for the removal of such tumors include symptoms, high-risk features, or an increase in size. The ER technique, including endoscopic mucosal resection and endoscopic submucosal dissection (ESD), is selected depending on the size and location of the tumor. The reported rates of negative (R0) resection range from 75% to 100% for gastric SMTs by ESD or endoscopic full-thickness resection.⁴⁵ ER may be safe, cost effective, and minimally invasive when a target lesion is sufficiently separated from the muscularis propria after submucosal injection.

Regarding SMTs arising from the muscularis propria, endoscopic full-thickness resection⁴⁶ and endoscopic

A: Classical LECS



B: CLEAN-NET



C: NEWS

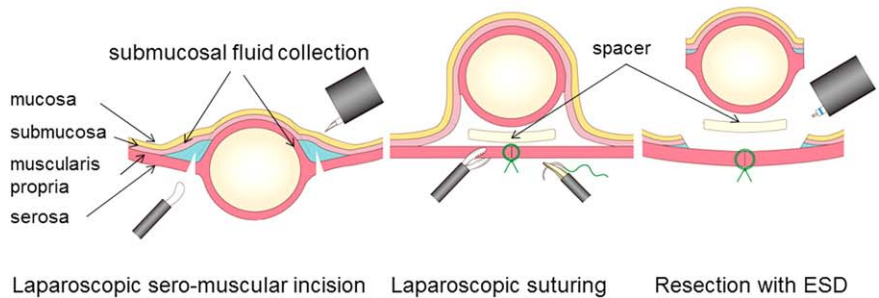


Figure 4. The laparoscopic and endoscopic combined approach is illustrated. (A) In the classical style of “laparoscopic and endoscopic cooperative surgery” (LECS), after submucosal injection, a mucosal incision and a subsequent seromuscular incision are performed endoscopically, followed by an intentional perforation of the gastric wall. The full-thickness defect is sutured laparoscopically using a linear stapler or a hand-suturing technique, and the resected tumor is laparoscopically retrieved. (B) With the “combination of laparoscopic and endoscopic approaches to neoplasia with nonexposure technique” (CLEAN-NET), after laparoscopic seromuscular incision, the full layer, including the tumor, is pulled out by dragging several suture threads. The tumor is resected with linear staplers and is laparoscopically retrieved. (C) With “nonexposed endoscopic wall-inversion surgery” (NEWS), after laparoscopic seromuscular incision, seromuscular layers are linearly sutured with a surgical sponge as a spacer, which may push the tumor into the gastrointestinal lumen. The protruded lesion is endoscopically resected using the endoscopic submucosal dissection (ESD) technique and is transorally retrieved.

muscularis excavation⁴⁷ have been reported as minimally invasive treatment. However, in the guidelines, endoscopic full-thickness resection and shelf-off resection should be avoided in GISTs and malignant SMTs, because those

techniques may be associated with some risk of tumor cell seeding upon transluminal communication and pseudo-capsule injury. Recently, submucosal tunneling ER was developed to avoid a transluminal defect. In this

technique, tumors are resected and retrieved transorally through the submucosal tunnel created from the oral side of tumors using an ESD or per-oral endoscopic myotomy technique.^{48,49} Muscular defect after the retrieval of a small tumor is not a significant problem, because the check-valve mechanism of the tunnel can avoid the collapse of the lumen, and mucosal entry is easily closed by endoclips. This rather sophisticated technique should also be avoided for GISTs and pathologically malignant SMTs, because it also has some risk for tumor cell spillage and seeding. Benign tumors, eg, leiomyomas and asymptomatic sub-2-cm GISTs without high-risk features, may not require treatment, and close monitoring once or twice a year by endoscopy would be acceptable. Thus, indications for ER may be pathologically undiagnosed, small SMTs measuring <3 cm or small SMTs with any suspected symptoms, but not suspected GISTs. When small SMTs are proven to be GISTs on postoperative pathology after ER, careful follow-up may be recommended when an R0 or R1 resection is obtained.

CONCLUSIONS

Most GISTs diagnosed in clinical practice are considered to be potentially malignant tumors, whereas there are large numbers of subclinical GISTs (mini-GISTs) and pathologic GISTs (micro-GISTs). Most mini-GISTs and almost all micro-GISTs of the stomach may exhibit good clinical behavior and, thus, do not need to be removed; and only an exceptional case may progress. Although GISTs cannot not always be identified as benign or malignant by radiographic and endoscopic imaging, in clinical practice, EUS may be used to estimate the malignant potential of practically most mini-GISTs and small SMTs measuring <5 cm. Because EUS-FNA may be safely performed for SMTs measuring >1 cm, clinical decision making by EUS and/or EUS-FNA is recommended for these tumors.

Neither surgery nor ER is indicated for tumors with a benign clinical course unless they are symptomatic. Indications for surgery include clinically relevant GISTs ≥ 2 cm, mini-GISTs with high-risk features or symptoms, pathologically undiagnosed SMTs with symptoms or high-risk features, and SMTs >5 cm. When small GISTs are located in the small intestine, colon, or rectum, surgery should be performed even when they measure <2 cm. For small gastric GISTs, open or laparoscopic surgery is standard therapy. The surgical approach and operative methods are selected according to tumor size, location, growth pattern, and an oncology team. To date,

ER still requires evidence of oncologic outcomes and remains an investigational therapy.

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AUTHOR CONTRIBUTIONS

Toshiro Nishida: Planning, conceptualization, and writing—final review and approval. **Osamu Goto:** Writing—initial draft and writing—final review and approval. **Chandrajit Premanand Raut:** Planning, supervision, and writing—final review and approval. **Naohisa Yahagi:** Conceptualization, writing—initial draft, and writing—final review and approval.

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