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Clinicopathological Features and Surgical Management of Gastrointestinal Stromal Tumors: State-of-the-Art

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Abstract: Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors, thought to arise from the interstitial cells of Cajal. Almost all GISTs have mutations in the oncogenic tyrosine protein kinase KIT or platelet-derived growth factor receptor-alfa. GISTs are mostly formed in the stomach and the small intestine.

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GISTs are often asymptomatic, but when symptoms occur, they most commonly include gastrointestinal bleeding, early satiety, and abdominal pain. These tumors do not have specific endoscopic or radiological features. The treatment for confirmed GISTs is surgery if the lesion is resectable with no metastases, or therapy with tyrosine kinase inhibitors if the lesion is unresectable, metastatic, or recurrent. The prognostic factors are tumor location, tumor size, mitotic index, and type of mutation. All surgical techniques can be performed laparoscopically using five trocars for wedge resection, subtotal gastrectomy or total gastrectomy based on tumor location. In case of intragastric resection with a single port under laparoscopic control, intraoperative endoscopy is used to identify the exact location of the lesion, and to guide single port device placement inside the stomach after gastrotomy. During subtotal and total gastrectomy, indocyanine green fluorescence angiography is performed to assess the vascular supply. This chapter discusses the clinicopathological features of gastric GISTs and describes the standard minimally invasive management techniques.

Keywords: gastrointestinal stromal tumor; minimally invasive surgery for GIST; prognostic factors of gastrointestinal stromal tumor; risk classification of gastrointestinal stromal tumor; surgical management of gastric GISTs

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors with a variable clinical behavior, arising from the interstitial cells of Cajal (1). GISTs belong to soft tissue sarcomas family (STSs) but are considered separately due to their peculiar histogenesis, clinical behavior, and specific therapy (2). The estimated global incidence of GISTs is 1–1.5 per 100,000 persons per year, and the prevalence is 13 per 100,000 persons per year (3). The median age at diagnosis is 62.5 years (3). GISTs in children and adolescents are very rare, but represent a distinct, often syndromic, subset (4). The etiology of GISTs is unknown in most cases, and the co-existence of another cancer is more common in GISTs patients than in the general population (5). The most common sites of GISTs are the stomach (50–60%) and small intestine (20–30%), but they may also be located in the colon, rectum, esophagus, mesentery, omentum, and retroperitoneum (6).

Almost all GISTs contain mutations in the oncogenic tyrosine kinase (KIT) or platelet-derived growth factor receptor-alpha (PDGFRA) genes (7, 8); however, KIT/PDGFRA mutations are mostly absent in children and young patients (4). Other mutations in GISTs patients may include loss of function of neurofibromatosis type 1 (NF1) or gain of function in the proto-oncogene BRAF (9). Several genetic syndromes that are linked to GISTs has been reported:

- *The Carney triad syndrome*: Gastric GISTs, paraganglioma, and pulmonary chondroma can occur at any age (10).
- *Familial GIST*: This syndrome is rare, occurs in families with autosomal dominant mutation of KIT and shows multiple GISTs in pediatric age (11).
- *Carney–Stratakis syndrome*: Germ-line mutations of one of the succinate dehydrogenases (SDH) subunits with development of GISTs and paragangliomas (12, 13).

- *Type-1 neurofibromatosis:* Localization is in the small bowel, often multifocal, loss of function of NF1 and absence of mutations in KIT and PDGFRA (14).

The diagnosis and treatment of GISTs have rapidly improved after the discovery of mutations in KIT and PDGFRA genes and the subsequent introduction of tyrosine kinase inhibitors (TKIs) (15).

CLINICAL PRESENTATION

The most common symptoms of GISTs are gastrointestinal bleeding, anemia, early satiety, abdominal distension, pain or discomfort, and a palpable mass (16). Based on location, the clinical presentation may change: small bowel GISTs may present with acute events like hemorrhage or rupture, after a long silent period; colorectal GISTs can occur with abdominal pain, obstruction or bleeding; and dysphagia can appear in esophageal and gastro-esophageal junction GISTs. Gastrointestinal bleeding is more frequently observed in gastric GISTs than in other locations. Symptoms can change from chronic microcytic anemia to acute hematemesis or melena, and at diagnostic endoscopy they may be wrongly diagnosed as peptic ulcer. Non-specific systemic symptoms, which are common in some patients, like weight loss and night sweating, may be misleading and may delay the diagnosis. Often GISTs are asymptomatic until advanced stages but may be found incidentally during endoscopy, especially in the stomach, or at postmortem autopsy (17, 18). Metastasis to lymph nodes or extra-abdominal spread of GISTs is rare, except for the succinate dehydrogenase (SDH)-deficient GIST (19). Recently, the observation of so-called mini GISTs (<1cm) as an incidental microscopic diagnosis in the stomach resected from patients with gastric cancer, and at autopsy, has been reported (20–22).

The natural history of GISTs remains mostly unknown, and microscopic subclinical gastric GISTs have an unexpectedly high incidence in clinicopathologic studies (20, 23). In patients over 50 years of age, small GISTs (up to 10mm in diameter) are commonly found, especially in the proximal stomach (22). However, these mini/small GISTs are often biologically inert at medium- and long-term follow-up, except in cases with high-risk features (like irregular margins or ulceration) (24). Even though the gold standard treatment for symptomatic GISTs is surgical resection, the indication of surgery for incidentally discovered mini GISTs is still debated (25).

DIAGNOSIS

GISTs do not have specific endoscopic or endoscopic ultrasound (EUS) features, and often they are identified during endoscopy like a submucosal tumor (SMT), with pathological diagnosis only after surgery. In SMTs that are smaller than 2 cm with no high-risk features, and also in cases where histological diagnosis of GISTs was made after biopsy, only endoscopic follow up can be carried out until the patient becomes symptomatic or the tumor grows in size (24).

The decision-making process may also include a histological diagnosis by EUS-guided fine-needle aspiration (EUS-FNA) biopsy. The optimal follow-up timing for these lesions is still debated in the literature, so an initial short-term follow-up at six months with EUS is recommended, which may then be deferred in time if high-risk features do not appear. This prolonged follow-up does not worsen the prognosis of patients with gastric GIST, as confirmed by a recent retrospective study (26). Endoscopic resection of SMTs is not considered oncologically safe, due to the risk of positive margins and high risk of cells dissemination. EUS-FNA biopsy can provide a histological diagnosis before surgery and set the indications for neoadjuvant therapy on the basis of the histological characteristics. EUS-FNA biopsy is to be preferred instead of conventional endoscopic forceps biopsy, because standard biopsy forceps do not reach the lesion beyond the normal mucosa and submucosa (27). However, EUS-FNA biopsy is not necessary for tumors measuring less than 2 cm, for undoubtedly benign tumors and for tumors which have already been planned for surgical resection (28). Instead, contrast enhanced computed tomography (CT) is recommended for initial diagnosis of tumors larger than 2 cm in diameter (Figure 1), to evaluate for the presence of high-risk features (25, 26). Furthermore, the Japanese guidelines recommend surgical resection for all GISTs that are larger than 5 cm in diameter (29). Finally, in metastatic disease, a biopsy of an easily accessible metastatic site can be performed, followed by a local and/or systemic treatment.

PATHOLOGY

Immunohistochemistry plays a central role in the pathologic assessment of GISTs, with CD117 (KIT) immunopositivity (30) and more recently with the inclusion of

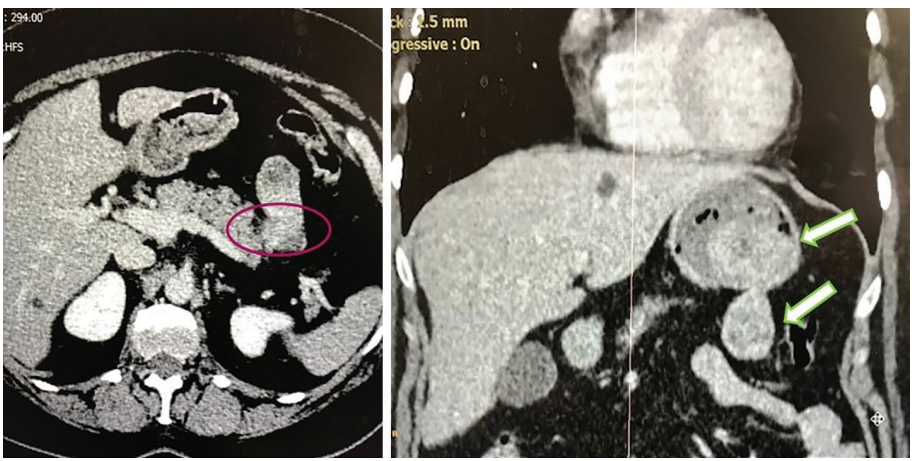

Figure 1. CT Scans. Abdominal CT scans showing an intraluminal and extraluminal gastric GIST. On the left, the extraluminal portion of the lesion is in close contact with the tail of the pancreas with no signs of infiltration. On the right, the two portions of the lesion, in continuity with each other, are shown by the arrows.

DOG1 (Discovered on GIST-1) protein as tumor marker (31). However, a small number of GISTs are immunonegative: 5% are negative for CD117, 5% are negative for DOG1 and about 1% for both (32). In case of diagnostic doubt in strongly suspected GISTs, but with CD 117 and DOG1 negativity, the analysis for activating mutations in KIT or PDGFRA may be of help (32). Another prognostic factor for risk stratification is the mitotic count (33): an index of less than 5 mitoses per 50 high-power fields classifies the GIST as at low risk; an index of mitoses between 6 and 10 per 50 high-power fields classifies the GIST as at intermediate risk; an index of mitoses more than 10 per 50 high-power fields classifies the GIST as at high risk (33).

Analysis of the mutational state is fundamental to predict the sensitivity to molecular-targeted therapy, especially for treatment with imatinib, and for overall prognostic value. In the diagnostic process of GISTs, the analysis of the mutational state should be carried out routinely as standard practice in all patients. Furthermore, in KIT or PDGFRA negative GISTs the recommendation is to perform immunohistochemistry for succinate dehydrogenase B (SDH-B), and, if negative, for SDH-A (32). In case of KIT or PDGFRA negativity, mutations in BRAF should also be searched, since BRAF inhibitors (Dabrafenib) may be included in the therapeutic strategy in these patients (33). A special focus is for patients with neurofibromatosis and a germline mutation in NF1, because of the increased risk of GISTs' development and recurrence (33).

STAGING

For staging and follow-up of GISTs, the main investigation is contrast enhanced abdominal and pelvic CT scan, because disease recurrence is almost exclusively located in the liver and/or in the peritoneum. Magnetic resonance imaging may be considered as an alternative investigation only in very selected young patients in order to limit exposure to radiation. The chest should be investigated with CT scan only in the staging process, but this is not considered a routine exam during follow-up. The 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) scan can be used in patients treated with neo-adjuvant imatinib therapy in order to evaluate the response.

TREATMENT

For small GISTs measuring less than 2 cm in diameter, when the diagnosis by endoscopic biopsy may be difficult, the only way to make a histological diagnosis is by surgical excision, though most of these nodules are at very low risk. In these patients, a standard approach would include diagnosis by EUS-FNA biopsy and annual follow-up. Surgical excision is recommended only for patients who become symptomatic or for tumors increasing in size. In GISTs that are larger than 2 cm in diameter, the gold standard treatment is surgical excision. Only in selected cases, like low-risk GISTs and in patients with major morbidity at high risk for surgery, a follow-up strategy without surgery may be an option after in-depth discussion with the patient. A multidisciplinary approach is always mandatory,

including oncologist, surgeon, radiologist, and histopathologist. The optimal strategy would be to refer the patient to a high-volume center, like highly specialized centers for the management of sarcomas and GISTs with highly experienced surgeons.

When the surgical indication is set by the multidisciplinary team, in case of localized GISTs, the gold standard is complete surgical excision without lymphadenectomy if lymph nodes are clinically negative, but always respecting the principles of oncological surgery. In case of involvement of adjacent organs, in bloc resection is required. When the risk of tumor rupture is high, as in the case of large tumors, the laparoscopic approach should be avoided because of the high risk of cell dissemination.

The aim of surgery should be an R0 excision, meaning absence of residual tumor. If this is envisioned to be not possible, because of major functional sequelae, a neoadjuvant therapy is indicated (34, 35). After cyto-reduction therapy, lasting between 6 and 12 months, surgical excision is performed. Prior analysis of KIT or PDGFRA mutations is mandatory in order not to delay surgery, in case of non-responding tumors. An early radiological re-evaluation after a few weeks is possible to study tumor response to imatinib. In case of failure of neoadjuvant therapy, an R1 resection with microscopically positive margins may be proposed by the multidisciplinary team, especially for low-risk tumors (36). In case of histologically unexpected R1 margins, a surgical strategy with re-excision should be considered.

Imatinib is the gold standard treatment in patients with metastatic disease or with inoperable tumors because a surgical approach as primary treatment is not recommended in these patients. The MetaGIST group (37) reported that a standard dose of imatinib (400 mg daily) should be doubled in patients with KIT exon 9 mutations for a better progression-free survival rate.

In case of progressive disease during imatinib treatment, surgical treatment is not recommended. In case of limited local or distant recurrence, the indication for surgery may be discussed with the patient, to possibly achieve better progression-free interval as compared to a second-line treatment with sunitinib. In case of liver metastases, interventional radiology procedures may be considered. In case of disease progression after therapy, or in case of intolerance to imatinib, the approved second line treatment is tyrosine kinase inhibitor (TKI) sunitinib (38) with benefits in progression-free survival, possibly also with a continuous lower daily dose (39). However, a small number of patients do not respond even to sunitinib, and this is suggestive of special mutations in loop domain of KIT or in exon 18 of PDGFRA. Figure 2 shows a proposed algorithm for the management of SMT.

PROGNOSTIC FACTORS AND RISK CLASSIFICATION

Prognostic factors for GISTs are tumor location, tumor size, mitotic index, type of mutation, and the presence of tumor rupture (29). However, discrimination between benign and malignant GISTs is difficult. The occurrence of postoperative metastases is possible in case of small tumors with low mitotic index. The Miettinen and Lasota (32), and the modified Fletcher classification (33), are the two most utilized risk-classification methods; both incorporate tumor size, mitotic index, and tumor site.

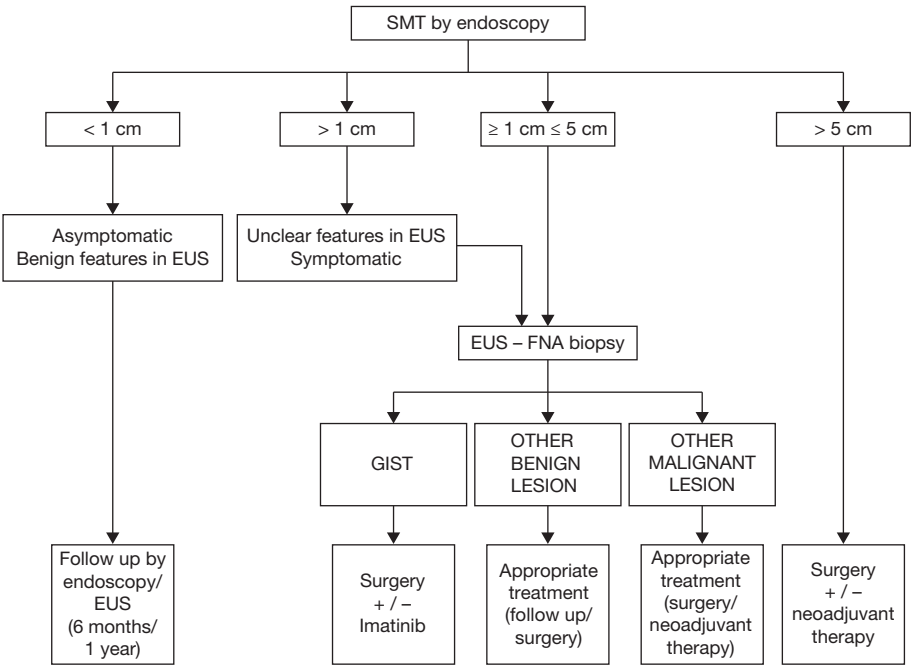

Figure 2. **Proposed strategies for management of submucosal tumor (SMT).**

SURGICAL TECHNIQUES

GIST resection may be performed by open, laparoscopic, or robotic surgery (40–43) but the surgical approach that is most frequently reported in the literature is the laparoscopic one (40–43). In fact, minimally invasive surgery is associated with better intra- and post-operative outcomes as compared to open surgery in term of intraoperative blood loss, hospital stay, postoperative pain and return to daily activities, with the same oncological results of open surgery (40–43). However, the open approach still has a rationale, in case of large masses infiltrating adjacent structures, which may be technically difficult to remove by minimally invasive surgery (40–43). On the other hand, the role of the robotic approach in comparison to laparoscopy has not been clarified yet, due to the lack of comparative studies between the two approaches (41). The laparoscopic approach for the management of GIST is briefly described below.

The patient is under general anesthesia, placed in supine position with abducted legs and the surgeon stands between the patient's legs. The operating table is placed in anti-Trendelenburg position. Pneumoperitoneum at 14mmHg is established with a Veress needle in the left hypochondrium (Palmer's point), and a 30°, 10 mm optic is used. During subtotal and total gastrectomy, indocyanine green (ICG) fluorescence angiography (FA) may be employed to assess the vascular supply. ICG powder 25 mg (Verdye, Diagnostic Green, Aschheim-Dornach,

Germany) is diluted in 5 cc of sterile water and 3 cc of the solution are intravenously administered to evaluate the vascular organ perfusion by FA during surgery (total of 15 mg per patient). The camera is positioned approximately 5 cm away from the tissue in zooming modality and fluorescence evaluation is performed in real time.

Laparoscopic gastric wedge resection

Five trocars are used: one 11 mm trocar is placed in the supraumbilical position; two 12 mm trocars are placed along the right and left midclavicular lines, two cm above the transverse umbilical line; and two 5 mm trocars are placed, one in subxiphoid position and the other one along the right anterior axillary line. The first step of the procedure is to identify the lesion. It can be located on the anterior or on the posterior wall of the stomach. In case of posterior location, it is necessary to gain access to the lesser sac. Gastric mobilization is performed using an advanced energy device (LigaSure™, Medtronic, Minneapolis, Minnesota, USA or Ultracision, Harmonic Scalpel, Ethicon Endo Surgery, Cincinnati, Ohio, USA). Next, wedge resection of the tumor is performed using a linear stapler with two or three 60 mm gold or blue cartridges (Echelon Flex Powered Endopath, Ethicon Endo-Surgery, Johnson & Johnson, Cincinnati, Ohio, USA), based on the gastric tumor location and on surgeon's preference, buttressed with absorbable material (polyglycolic acid and trimethylene carbonate, Seam-guard® Gore & Associates, Inc. Newark, Delaware, USA). Intraoperative endoscopic control is recommended in order to ensure that tumor margins are free (R0 resection) and to avoid stenosis. The specimen is removed by an endobag through a Pfannenstiel incision or by enlarging one of the 12 mm trocar incisions.

Intragastric resection with single port under laparoscopic control

After establishing pneumoperitoneum, one 11 mm trocar is placed in supraumbilical position, and two 5 mm trocars are placed laterally to the previous one along the midclavicular line on the left and on the right. Another 5 mm trocar is placed in a subxiphoid position to retract the liver. Intraoperative endoscopy is used to identify the exact location of the lesion and to define the best position to insert the single port device. Next, a single port (TriPort Plus, Advanced Surgical Concepts, Bray, Ireland) replaces one of the 5 mm trocars and it is placed inside the stomach after creation of a 12–15 mm gastrotomy. Full thickness resection of the gastric wall harbouring the tumor is performed by using the ultrasonic device (Ultracision, Harmonic Scalpel, Ethicon Endo Surgery, Cincinnati, Ohio, USA), and then closing the residual defect by means of running 3–0 absorbable barbed suture (V-Loc™, Medtronic, Minneapolis, Minnesota, USA). The specimen is removed using an endobag. The single port is then removed from the stomach, but it is left in the abdominal cavity to be used as a trocar. The gastrotomy is closed by using a linear stapler with 60 mm blue cartridges (Echelon Flex Powered Endopath, Ethicon Endo-Surgery, Johnson & Johnson, Cincinnati, Ohio, USA) and the stomach is then insufflated by the endoscopist in order to evaluate the presence of leakage by performing an air leak test (44).

Laparoscopic subtotal gastrectomy

Five trocars are used. One 11 mm trocar is placed in supraumbilical position, two 12 mm trocars are placed along the right and left midclavicular lines two cm above the transverse umbilical line, and two 5 mm trocars are placed, one in a subxiphoid position and the other one along the right anterior axillary line. The liver is retracted with a grasper introduced from the subxiphoid trocar. Gastric mobilization is performed by using an advanced energy device (LigaSure™, Medtronic, Minneapolis, Minnesota, USA or Ultracision, Harmonic Scalpel, Ethicon Endo Surgery, Cincinnati, Ohio, USA).

The first step of the procedure is to mobilize the greater omentum. The lesser sac is opened by dividing the short gastric vessels along the greater curvature and right gastroepiploic artery, taking down any retrogastric adhesions (Figure 3). The duodenum is prepared 2 cm beyond the pylorus, paying attention not to injure the gastroduodenal artery, and it is divided by linear stapler with a 60 mm blue cartridge (Echelon Flex Powered Endopath, Ethicon Endo-Surgery, Johnson & Johnson, Cincinnati, Ohio, USA) buttressed with absorbable material (polyglycolic acid and trimethylene carbonate, Seam-guard® Gore & Associates, Inc. Newark, Delaware, USA). After opening the *pars flaccida* of the lesser omentum along the lesser curvature of the stomach, the right gastric artery near the antrum, the descending branch of the left gastric artery and the coronary vein are divided using the energy device. The stomach is then divided above the tumor using the linear stapler with 60 mm blue cartridges. Before the anastomosis is created, ICG-FA is performed in order to assess the vascular supply of the gastric stump and jejunum.

A double-loop Roux-en-Y reconstruction technique is used to restore bowel continuity, as reported for gastric bypass in bariatric surgery. The greater omentum is divided and a side-to-side mechanical antecolic gastro-jejunal anastomosis is created on the posterior wall of the stomach (biliary limb, measured at 60 cm from the Treitz ligament). The enterotomy is closed using a running suture with a 3–0 reabsorbable barbed suture (V-Loc™, Medtronic, Minneapolis, Minnesota, USA). A mechanical side-to-side jejuno-jejunal anastomosis is then created (alimentary limb, measured 80–100 cm from the first anastomosis), with a similar technique as previously described, by using a linear stapler with white cartridge, followed by enterotomy closure with a running suture. The two anastomoses are checked by the methylene blue test. After that, the small bowel between the gastro-jejunal and the jejuno-jejunal anastomosis is divided by a linear stapler with 60 mm white cartridge. The specimen is removed using an endobag through a Pfannesteil incision.

Laparoscopic total gastrectomy

Five trocars are used. One 11 mm trocar is placed in supraumbilical position, two 12 mm trocars are placed along the right and left midclavicular line two cm above the transverse umbilical line, and two 5 mm trocars are placed, one in a subxiphoid position and the other one along the right anterior axillary line. The liver is retracted with a grasper introduced from the subxiphoid trocar. Gastric mobilization is performed using an advanced energy device (LigaSure™, Medtronic,

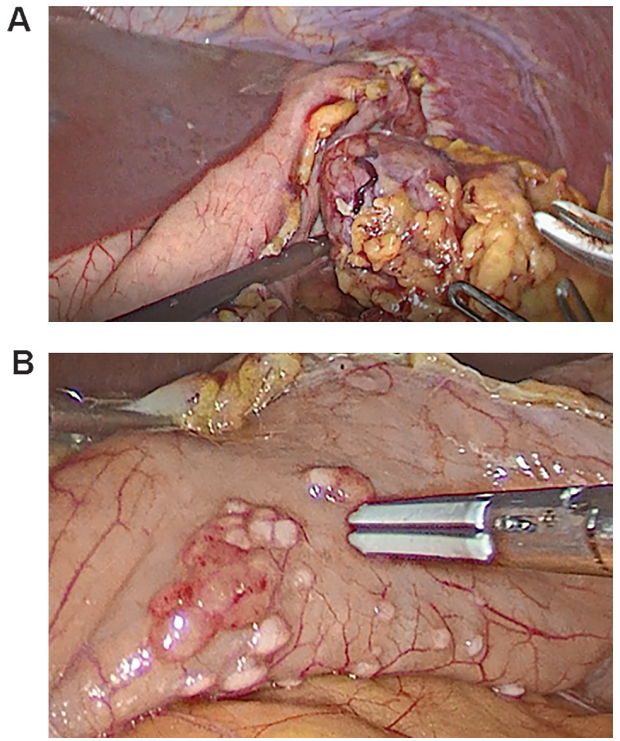

Figure 3. Extraluminal portion of gastric GIST. A, Laparoscopic resection. After division of the short gastric vessels on the greater curvature and along the right gastroepiploic artery, the lesser sac is opened showing a large extraluminal portion of a gastric GIST in continuity with the intraluminal portion, both located along the posterior wall of the gastric fundus and body. **B,** After division of the short gastric vessels on the greater curvature and along the right gastroepiploic artery, the lesser sac is opened showing multiple synchronous satellite nodules of gastric GIST located in the antrum of the same patient displayed in Figure A.

Minneapolis, Minnesota, USA or Ultracision, Harmonic Scalpel, Ethicon Endo Surgery, Cincinnati, Ohio, USA). The first step of the procedure is to mobilize the greater omentum. The lesser sac is opened by dividing the short gastric vessels on the greater curvature and along the right gastroepiploic artery (Figure 3). The dissection proceeds cranially along the greater curvature up to the angle of His and with exposure of the left crus of the esophageal hiatus.

The duodenum is prepared beyond the pylorus, and it is divided by a linear stapler with 60 mm blue cartridge (Echelon Flex Powered Endopath, Ethicon Endo-Surgery, Johnson & Johnson, Cincinnati, Ohio, USA) buttressed with absorbable material (polyglycolic acid and trimethylene carbonate, Seam-guard® Gore & Associates, Inc. Newark, Delaware, USA). The lesser omentum is opened, and the right and left gastric arteries are divided, as well as the left gastric vein.

Esophageal hiatus dissection continues from the left crus towards the right one and posteriorly until the aorta is visualized. Next, the abdominal esophagus is divided by using a linear stapler with 60 mm blue cartridge. Before creation of the anastomosis, ICG-FA is performed in order to assess the vascular supply of the esophageal stump and jejunum. A double-loop Roux-en-Y reconstruction

technique is used, as reported for gastric bypass in bariatric surgery. In this case, the jejunal loop runs posteriorly to the colon after creating a retrocolic window through the transverse mesocolon on the left of the middle colic vessels. The greater epiploon is divided and a side-to-side mechanical esophago-jejunal anastomosis on the posterior wall of the esophagus is performed (biliary limb, measured 60 cm from the Treitz ligament), followed by closure of the residual enterotomy with a 3-0 absorbable barbed suture (V-Loc™, Medtronic, Minneapolis, Minnesota, USA). A mechanical side-to-side jejuno-jejunal anastomosis is created (alimentary limb, measured 80–100 cm from the first anastomosis), following a similar technique as previously described, using a linear stapler with white cartridge. Both anastomoses are checked by the methylene blue test to detect any leakage. The small bowel is then divided between the esophago-jejunal and the jejuno-jejunal anastomosis using the linear stapler with 60 mm white cartridge. The specimen is then removed by endobag through a Pfannenstiel incision.

OPEN vs LAPAROSCOPIC SURGERY

Inaba et al. reported data obtained from the National Cancer Database (NCDB) of 5096 patients who underwent open and laparoscopic surgery for GIST between 2010 and 2014 (42). The study included 2910 (57%) stage I, 954 (19%) stage II, and 1232 (24%) stage III patients. Patients' characteristics were similar between the two groups, with no statistically significant differences (42). Laparoscopy, in comparison to the open approach, showed decreased 90-day mortality and 30-day readmission rates, in all stages, even though a statistically significant difference was observed only in stage I (42). Moreover, laparoscopy was associated with shorter hospital stay in comparison to open surgery in all stages (42). Regarding follow-up, the Kaplan-Meier long-term survival curves showed better results for the laparoscopic approach in stages I and II, with no significant differences in stage III (42).

In the meta-analysis by Chen et al., 19 observational studies comparing laparoscopic and open surgery were included (45). They reported significantly lower intraoperative blood loss, shorter time of first flatus and first oral intake days in the laparoscopic group, indicating quicker recovery of the bowel function (45). Furthermore, a lower dose of postoperative analgesics consumption and a shorter hospital stay in the laparoscopic group were observed (45). The postoperative complication rate was also statistically significantly lower in the laparoscopic group (45). During follow up, the recurrence rate in the laparoscopic group was lower and the difference was statistically significant ($p = 0.03$). However, it should be considered that in the open surgery group the tumors were larger and had a higher mitoses rate, both being negative prognostic risk factors (45).

CONCLUSION

GISTs are mesenchymal tumors marked by differentiation towards the interstitial cells of Cajal, and almost all contain mutations in oncogenic KIT or PDGFRA. The most common localizations of GISTs are the stomach and the small intestine.

The treatment for confirmed GISTs is surgery if the lesion is resectable with no metastases, or therapy with tyrosine kinase inhibitors if the lesion is unresectable, metastatic, or in case of recurrent disease. The prognostic factors are tumor location, tumor size, mitotic index, and type of mutation. When feasible, laparoscopic surgery is the recommended option for management of GISTs because it is associated with more favorable outcomes in terms of complications, length of hospital stay, postoperative pain and recurrence rates, as compared to the open approach.

Conflict of Interest: The authors declare no potential conflict of interest with respect to research, authorship and/or publication of this chapter.

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