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**Laparoscopic management of gastric gastrointestinal stromal tumors**

Correa-Cote J *et al*. GIST laparoscopic resection

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**Abstract**

Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin. Gastric GISTs represent approximately 70% of all gastrointestinal GISTs. The only curative option is surgical resection. Many surgical groups have shown good results with the laparoscopic approach. There have not been any randomized controlled trials comparing the open versus laparoscopic approach, and all recommendations have been based on observational studies.The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach.

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**Key words**: Gastrointestinal stromal tumors; Laparoscopy; surgery; Stomach; Gastrectomy

**Core tip:** Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin. Gastric GISTs represent approximately 70% of all gastrointestinal GISTs. The only curative option is surgical resection. Many surgical groups have shown good results with the laparoscopic approach. There have not been any randomized controlled trials comparing the open versus laparoscopic approach, and all recommendations have been based on observational studies. The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach.

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**INTRODUCTION**

Gastrointestinal stromal tumors (GISTs) are the most frequent gastrointestinal tumors of mesodermal origin[1], and gastric GISTs represent approximately 70% of all gastrointestinal GISTs[2]. These tumors are derived from the interstitial cells of Cajal[3], and have been shown to harbor gain of function mutations in the cell-surface KIT receptor in approximately 90% or in the Platelet-Derived Growth Factor Receptor α (PDGFRA) in 8%[4].

Most tumors are limited to the primary organ, and less than 2% of tumors present lymph node metastasis. GISTs can also metastasize to the peritoneum and infrequently present hematogenous metastasis to other intra-abdominal viscera, lung, pleura, bone and brain[5].

Most patients are asymptomatic; the tumors are usually found as an incidental finding in 4%-39% of cases[6-11]. In most surgical series, the most frequent symptoms are gastrointestinal bleeding (14%-68%), abdominal pain (16.1-45%), abdominal mass (3.3%-21%), early satiety (36%), anemia (19.4%-77%), weight loss (11%), bowel obstruction (3.6%), liver metastasis (3.6%), dyspeptic symptoms (9.7%) and dysphagia (9%)[6-10]. There is a clear relationship between tumor size and symptoms, smaller tumores are generally asymptomatic[4].

The diagnosis is usually made by endoscopy or abdominal imaging. During endoscopy, it is possible to see gastric lumen narrowing associated with normal protruded mucosa, although in larger tumors, the mucosa can show ulcers due to local ischemia[12,13]. The ideal method for diagnosis is endoscopic ultrasonography (EUS), which can define the size, vascular pattern and form of the tumor and differentiate between an extra-luminal compression and a submucous growth. GISTs are hypoechoic tumors located at the fourth layer, although some reports have shown tumors located at the third layer. However, the imaging of these tumors is not sensitive (43%), which necessitates histologic evaluation. EUS also helps guide fine needle aspiration biopsies, showing better performance than biopsies under normal endoscopy[12]. The sensitivity of FNAB guided by EUS increases by 10% if a pathologist makes an immediate examination of the adequacy of the sample[13]. In some series, preoperative diagnosis was only possible 52.3%[7].

Computed tomography (CT) is necessary for preoperative stratification. CT can usually show intra- or extraluminal tumors with different morphologic patterns according to size. Larger tumors can show irregular margins and heterogeneous internal density, and if the diameter is larger than 6 cm, the tumors are usually accompanied by central necrosis. Magnetic resonance imaging (MRI) is recommended in cases of simultaneous liver metastasis because of the possibility of conducting a combined resection. PET-CT can be useful in patients with undetermined findings on CT or MRI[14]. However, there is not a good correlation between imaging findings and malignancy[15].

A differential diagnosis with other submucous tumors such as leiomyoma, leiomyosarcoma, schwannoma, granular cell tumors, heterotopic pancreatic tissue, lipoma, neurofibroma, Kaposi tumors and non-functional adrenal tumors should be performed[16,17]. Immunohistochemistry for GIST detection is very useful and shows positivity for CD117 (95% of GISTs)[16]. Only 2% are usually related to PDGFRA mutations[16,18]. Other helpful tests are CD34 that is positive in 70% of the cases and vimentin[16].

**SURGICAL TREATMENT**

The only curative option is surgical resection, which can be offered to patients with good functional status and non-metastatic resectable tumors, although in some cases, a metastasis resection surgery can be performed in association with resection of the primary tumor[19]. Surgical principles for resection include total extracapsular resection, avoiding tumor fracture or bleeding, which are associated with recurrence and peritoneal sarcomatosis[20]. There are no recommended margins, because microscopic margins status doesn´t correlate with survival as does the mitotic count and tumor size. Wedge resection is a good option for tumors located in the anterior wall or greater curve. For tumors located at the antrum wedge resection can produce a stenosis, so formal gastric resections are favored. Wider margins have not shown any oncologic advantage[21], and lymph node dissection has not been indicated[22]. The National Comprehensive Cancer Network (NCCN) guidelines suggest that tumors smaller than 1 cm that do not fulfill high risk endosonographic criteria (irregular borders, cystic spaces, ulcer of echogenic heterogeneous focus) can be observed during endoscopic follow-up at each 6-12-mo interval[23]. Most larger tumors need adjuvant treatment with imatinib mesylate to avoid recurrence[2].

**LAPAROSCOPIC TREATMENT**

Open surgical resection was the standard of treatment until two decades ago. Many surgical groups have shown good results with the laparoscopic approach. Although NCCN guidelines suggest that laparoscopic resection is indicated in tumors less than 2 cm, many surgeons have reported a safe excision of tumors > 5 cm and other up to 10 cm[24-26]. Lukaszczry and Pretez in 1992 were the first to report a successful laparoscopic resection of a gastric GIST [27].

The laparoscopic techniques can be divided into different subtypes: transgastric resections, endoscopy-assisted laparoscopic resections, wedge resections, partial gastrectomy and hand-assisted laparoscopic resections[24]. The surgical approach depends on tumor size and location (Figure 1). Privette *et al*[25] proposed a classification system based on tumor location as a guideline to choose the best surgical approach. Trocars and operating tables are organized in a similar manner to any other hiatus procedures, with the surgeon located between the legs. A 12-15 mmHg pneumoperitoneum is established, and a 30° camera and a liver retractor are useful. Before resection, it is mandatory to review the abdominal cavity to rule out peritoneum or liver metastasis. If the surgeons suspect solid organ metastasis, the use of intraoperative ultrasound with biopsy can help in the operative decision. Assistance by endoscopy during the surgical procedure is useful for locating the tumor and guiding resection, and staining with ink could help delineate the resection margins.

Tumors located at the fundus and at the anterior and posterior walls can be resected by partial gastrectomy or wedge resection. In cases of small tumors, the greater curve is mobilized, ligating the gastroepiploic vessels with an ultrasonic scalpel or a thermal device. The gastric wall is elevated with sutures placed in the seromuscular layer around the tumor to obtain a complete resection with a linear mechanical stapler, guaranteeing macroscopic margins. In cases of larger tumors, the gastric wall is directly opened and the tumor is resected, maintaining a free margin with a late direct closure using a continuous suture. In cases where tumors are located in the posterior wall, an anterior gastrotomy is made exactly above the tumor, usually assisted by endoscopy. The tumor is resected by the techniques described, with a late closure of the anterior wall with a continuous suture[11,26].

For tumors located at the antrum or at the prepyloric area, partial gastrectomy is recommended due to the high risk of stenosis and delayed stomach emptying when wedge resections are used. In these cases, the greater and lesser curves are dissected to obtain retrogastric access. The duodenum is sectioned just distal to the pylorus with a linear mechanical stapler, and the proximal section is also made with a mechanical stapler; this is usually assisted by endoscopy. Finally, a Roux-en-Y anastomosis is made[25].

Tumors located at the esophagogastric junction are infrequent and represent less than 5% of all tumors. Some authors have recommended enucleation of these tumors based on the high morbidity (6%-24%) and mortality (0-1.5%) with classical resections and due to the lack of advantage in prognosis and survival[28]. However, the best surgical approach is still debated[29]. The enucleation is made through an anterior gastrotomy, and in these cases, a submucous infiltration with epinephrine is recommended to avoid bleeding and perforation. The use of devices such as an ultrasonic scalpel or an electrocautery has been recommended[10, 28].

Some authors have varied the surgical technique using transgastric trocars and endoscopy-assisted insufflation. In these cases, smaller tumors can even be extracted by the mouth using endoscopy[25]. For larger tumors, other authors have suggested a hand –assisted technique because it allows for better exploration and easier handling and dissection of the tumor[12,13]. Others have also shown good results with the single-port approach or dissections without insufflation[8]. In all cases, the use of a bag is recommended for the extraction of the tumor to avoid recurrence and metastasis at the port insertion sites[30,31].

Until now, there have not been any randomized controlled trials comparing the open versus laparoscopic approach, and all recommendations have been based on observational studies. Actual recommendations are based on outcomes related to surgical technique (intact specimen, free margins) and prognosis (operative complications, recurrence, cancer free survival)[32] reported from these observational studies. Tables 1 and 2 show the results of comparative and non-comparative published series.

Recently, Koh *et al*[33] published a systematic review of eleven observational studies comparing laparoscopic versus open resection with evaluation of short and long term outcomes. In their study, which included 381 patients in the laparoscopic group and 384 patients in the open group, the laparoscopic approach showed a lower frequency of minor complications (OR = 0.517; 95%CI: 0.277–0.965), lower length of stay [mean difference -3.421 d (-4.737 to -2.104)], shorter time to the initiation of oral diet [mean difference -1.887 d (-2.785 to -0.989)] and lower intraoperative bleeding [mean difference -86.508 mL (-141.184 to -31.831 mL)]. They could not find any statistically significant differences in reoperation rate, operative time, positive margins, local recurrence, cancer free survival and overall survival. However, comparisons showed that most high risk tumors were treated with open gastrectomy, introducing a selection bias.

The rate of conversion to open surgery is 0-31%[11], and this cannot be considered a complication but rather an intraoperative decision to obtain better tumor control when the surgeon is faced with adverse intraoperative conditions.

***Follow up***

Follow-up is mandatory in all patients, even in the absence of malignancy. Patients should be reviewed every 3-6 mo during the first 5 years. An annual endoscopy and CT are recommended to rule out local recurrence[20]. The survival rate of patients with early tumors is greater than 90%[34]. A size larger than 10 cm, a high mitotic rate and intraoperative rupture are risk factors for recurrence[35].

**CONCLUSION**

The experience obtained from gastric laparoscopic surgery during recent decades and the development of specific devices have allowed the treatment of most gastric GISTs through the laparoscopic approach. As with all surgical techniques, the laparoscopic approach must be applied in select patients with particular characteristics based on functional status, tumor size, location and surgeons’ experience. The case series presented in this review support laparoscopic resection as a safe and effective alternative, with similar rates of complications, but with lower pain and an early recovery. It is important to realize that tumor size by itself is not an adequate factor to contraindicate the laparoscopic approach and that other factors should be considered in the decision.

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**Figure 1 Surgical approach according to gastrointestinal stromal tumor localization.**

**Table 1 Non-comparative series of laparoscopic resection of gastric gastrointestinal stromal tumor**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | ***n*** | **Age (yr)** | **Tumor size** | **Tumor localization** | **Type of surgery** | **OR time (min)** | **Notes** | **Complications/ conversions** | **Follow-up (mo)** |
| Privette *et al*[25] | 12 | 60.5 | 5.2 cm PG4.6 cm TransG5.5 cm DG | 5 Fundus or greater curvature3 Prepyloric or antral5 Lesser curvature  | 5 PG x Lap3 DG x Lap5 TransG x Lap | PG 180 (122-262)DG: 322 (256-340)TransG: 236 (202-265) | 9/12 GIST1 Schwannoma2 LeiomiomasLOS:GP: 3.4GD: 8.3GT: 3.3 | 16.6% complication1 Enterotomy1 GI Bleeding No conversions | Only specified for 5 pts |
| Sexton *et al*[32] | 61  | 59.1 ± 19 | 3.8 ± 1.8 AR: 229.7NAR 140.9 | Fundus 19Antrum 18Body 17GE junction 7Pylorus 2 | PG 52DG 4TotGas 3TransG 3 | 151.9 ± 67.3 | LOS:3.9 ±2 LOS AR: 3.9, NAR: 4.1 | 16.4% complicationNo conversions1 POP death | 15 (0-103)3 Recurrences |
| Berindoague *et al*[9] | 22 | 66.7 | 5.6 (2.5-12.5) | Upper third 6Middle third 7Lower third 10 | GP 131 LAP-HA TotGas 1 LAP TotGast1 LAP- HA GD 1 TransG | NR | 18/22 GIST1 Adenomyoma1 Hamartoma1 Plasmocytoma1 Parasitic Tumor (anisakis)LOS 6 (4-32) | 18.2% complication3 Delayed gastric emptying 1 Intestinal Obstruction 2 Conversions (9.1%) | 32 m (1 – 72)1 Recurrence |
| De Vogelaere *et al*[24] | 31  | 63.8  | 4.4 (0.4-11) | Anterior gastric wall 23Others not specified | 31 PG | 99 | LOS 8.5 | 3.2% Complication1 POP Bleeding | 56.3No recurrences |
| Hwang *et al*[10] | 63 | 52.8 | 3.5 GE Junction3.4 PrepyloricSize of other tumor not specified | 7 GE junctionUpper third 22 middle third 11 lower third 19 4 Prepyloric | 3 DG37 PG23 TransG (5 Enucleations) | 86.1 ± 43.7 | LOS 5.3 ±1 1.841 GIST8 Leiomyoma4 Carcinoids1 Liposarcoma6 Heterotopic Pancreas2 Hyperplastic Polyps 1 Parasitic Infection  | 4.7% Complication1 Staple line bleeding1 SSI1 Staple line dehiscence | 14.9 (2-42)No recurrences |
| Novitsky *et al*[26] | 50 | 60 ± 13 | 4.4 ±2.0 cm | GE Junction 8Cardias 9Anterior Wall 10Posterior Wall 4Greater Curvature 6Lesser Curvature 3Antrum 4Prepyloric 6 | TotGas 1DG 2PG 40LAP/END 4LAP-HA 3 | 135 ± 56 | LOS 3.8 ± 1.6 | 8% 4 Minor complications  | 36 (4-84)4 Recurrences  |
| Lai *et al*[2] | 28  | 56.9 ± 12.4 | 3.4 ± 1.6 | Upper third 13Middle third 8Lower third 7 | 28 PG  | 189.6 ± 79.5 Stapled194.3 ±50.5 Hand-Sewn | LOS 6.7 ± 1.8 | 3.5% conversion  | 43.3± 23.5No recurrences |
| Choi *et al*[36] | 23 | 59.7 ±8.3 | 4.2 ±2.1 | Upper third 13Middle third 5Lower third 5 | 23 PG | 104.3 | LOS 5.2 ± 2.3 | 4.3% complication1 Delayed gastric emptyingNo conversions | 61 (7**-**98) |
| Nguyen *et al*[22] | 28 | 65 | 4.6 (0.4–11.5) | LAP PG 22Subtotal Gastrectomy 3OS (Converted) :TotGas 1Intraluminal excision 11 Not Specified | 23 GP x LAP3 GD x LAP1 GT x LAP1 TotGas x CA (converted) | 143 (46-336)This includes Small Bowel GIST resections. No data only on Gastric Resections | LOS 4 (1-50 d) | 9% complications 11% 3 conversionsMortality 1 POP deathThis includes Small Bowel GIST resections. No data only on Gastric Resections |  NS |
| Huguet *et al*[37] | 33 | 68 | 3.9 (0.5-10.5), | GE Junction 5Body 24Antrum 4 | PG 29LAP-HA PG 4 | 124 (30-253) | LOS 3 (1-40) | 9% complications 2 POP Bleeding 1 SSI 6% conversions | 13 (3-64)No recurrences |
| Ronellenfitsch *et al*[38] | 17 | 56 (43–79) | 2.9 (0.8-6) | 11 Not Specified6 Antrum | 17 PG | 130 (80–201) | LOS 7 (5-95) | 11.8% Complications:Staple leaks 5% conversion (peritoneal adhesions)  | 18 (1–53)No recurrences |
| Tagaya *et al*[39] | 15 | 65.3 (52–75 years) | TransG 2.9 (1.7–6.5)GP 3.9 (1.2-8) | TransG:Upper third 4Middle third 1Lower third 1PG:Greater curvature 2 Lesser Curvature 1Anterior Wall 2Middle Third Ant Wal 1Middle Third Post Wall 1 | TransG 8PG 7 | TransG:168 (132–211)PG: 121 (60-190) | LOS TransG: 8.8 ( 7–12) LOS PG: 9.6 (7–14) | No complications | After final Pathology only 9 tumors were GISTTransG 18 – 73 PG: 6 -122No recurrences |

GLA: Gasless laparoscopy-assisted; PG: Wedge Resection or Partial Gastrectomy; DG: Distal Gastrectomy; TransG: Transgastric Gastrectomies; TotGas: Total Gastrectomy; OS: Open surgery; AR: Anatomic resections; NAR: Non- anatomic resections; LOS: Length of stay; NS: Not specified; LAP/END: Laparoendoscopic resection; LAP-HA: Laparoscopic hand-assisted; RG: Remnant Gastrectomy; Prox Gas: Proximal Gastrectomy; SSI: Surgical site infection.

**Table 2 Comparative series of laparoscopic resection of gastric gastrointestinal stromal tumor**

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | ***n*** | **Age** | **Tumor size** | **Tumor localization** | **Type of surgery** | **OR time (min)** | **Notes** | **Complications/ conversions** | **Follow-up (mo)** |
| Wu *et al*[8] | 28 | 61.6 GLA60.7 CA | 2.6 ± 1 1.8 GLA2.5 ± 1.0 CA | Anterior Fundus:5 GLA 5 CAPosterior Fundus:6 GLA 2 CAAnterior Body:3 GLA 3 CAPosterior Body:1 GLA 3 CA | 15 GLA13 OSAll were Wedge Resections | GLA 129 ± 36.1CA 110.8 ± 38.1 |  GLALess POP Pain during the first 3 dEarlier oral intakeLess LOS 5.8 vs 7.2 días | 7.1% complication 1 OS Ileus1 Enterotomy during GLA correctered during LAP | NR |
| Catena *et al*[7] | 2125  | 50.154.6 | 4.5 ± 2.06.2 ± 1.9 | Body 16 Antrum 4 Fundus 1 Body 17 Antrum 6 Fundus 2 | 21 PG25 OS (PG) | 151±56134±33 | LOS 4.8 ± 1.6LOS 7.1±1.2 | No intraoperative complicationsNo differences in complications | 35 (5-58)91 (80**–**136)1 Recurrence |
| Melstrom *et al*[31] | 4617 LAP29 OS | 62 Lap60 OS | OS 6.39 82.1-10)LAP 4.27 (1.5-9.1) | Lap:Upper third 6Middle third 10NS 1OS:Upper third 6Lower third 22NS 1. | 17 PG24 PG x OS4 DG x OS1 TotGas x OS | Lap 135OS 157 | LOS:OS 6.25LAP 2.68I | ComplicationsOS: 13.8% LAP: 11.8%  6% conversion   | OS 594 recurrencesLAP 32No Recurrences |
| De Vogelaere *et al*[11] | 5337 LAP16 OS | LAP 63.7 ± 15.4 OS 63.7 ± 10.7 | Total 5.9LAP 5.6OS 7.5 | Not specifiedNot specified | Not specifiedNot specified | LAP 48.5 ± 16OS 155 ± 48.1 | LOS Lap 7LOS OS 14 | LAP :2.7% 1 Pulmonary Embolism OS 18.7% complications:Pneumonia 1Anastomotic Ulcer 1Fistula 1 | Lap 83 No Recurrences LAPOS 71 6 Recurrences CA  |
| Karakousis *et al*[40] | 80OS 40 LAP 40 | 68 | OS 4.3 (2-9)LAP 3.6 (0-7-7.8) | OS :Fundus 7Body/Antrum 32 Pylorus 1Lesser Curvature 12LAP:Fundus 3Body/Antrum 37Pylorus 0Lesser Curvature 10 | OS39 PG1 DGLAP 40 PG | OS 89LAP 96 | LOS:LAP 4OS 7 | ComplicationsOS 25%LAP 14%32.5% Conversions  | LAP 28 (0.3-70 m)Recurrences 1 LAPOS 43 (0.1-139)Recurrences 1 OS  |
| Kim *et al*[41] | 104LAP 80OS 24 | 59.8 ± 10.5 | 5.1 ± 3.3 | Upper third 61Middle third 24Lower third 19 | Technique according to procedures was NS99 PG5 TotGas | LAP 91.1 ± 57CA 165.8 ± 75.6 | LOSLAP 4.6 ± 2.3CA 9.8 ± 4.1 | 1% Complications1 Delayed Gastric Emptying | 49.3 (8.4-164.4)Recurrences 5 No Difference in recurrences between OS and LAP |
| Silberhummer *et al*[21] | 63OS 41LAP 22 | 62.3 ± 14.4 | CA 5.8 ± 4.0LAP 3.5±1.4 | Body 29Antrum 18Fundus 10GE Junction 6 | OS:PG 32DG 5RG 4LAP19 Tumorectomy3 PG | 135 ± 56 | LOS LAP 7.8 (± 3.1)LOS CA 12.8 ± 5.0 | 4.7% complications:1 Gastrocutaneous Fistula1 Catheter Sepsis1 POP Ileus LAP:18.2% conversions | 37 ± 27.9 Recurrences in 4 (7%) |
| Nishimura *et al*[42] | LAP 39OS28 | 62 | LAP 3.8 (0.8–7.3)OS: 4.2 (2.0–7.0) | LAP:Upper third 19Middle third 16Lower third 4OSUpper third 11Middle third 11Lower third 6 | LAPGP: 12LAP-HA 17TransG 10OSPG: 19Prox Gas: 5TotGas: 3DG:1 | LAP: 136 minOS: 115 min | NR | No Complications Conversion Rate 2.6% | LAP: 18.9 (2.6–96.4)Recurrences 4 LAPOS: 31.2 (4.4–121.9)1 Recurrence OS |
| Otani *et al*[43] | 60OS 22LAP 38 | 59 (32-86) | 4,25 (1.8 – 15.0) | Upper third 36Middle third 20Lower third 4 | LAP:PG: 35LAP-HA:LAP-HA PG 2LAP-HA DG 1OS:PG 11ProxGas 9DG 2 | LAP 141LAP-HA 188CA 197 | LOS LAP 7.2 *vs* 13.7 CA | 3.3% complications:1 Gastric Stenosis 1 Anastomotic Leak | 53 mo2 Recurrences |

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