

Laparoscopic management of gastric gastrointestinal stromal tumors

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Author contributions: Correa-Cote J, Morales-Uribe C and Sanabria A contributed equally to this work; Correa-Cote J and Morales-Uribe C designed the research; Correa-Cote J, Morales-Uribe C and Sanabria A performed the research, analyzed the data; and wrote the paper.

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Received: November 4, 2013 Revised: April 7, 2014

Accepted: May 28, 2014

Published online: July 16, 2014

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Correa-Cote J, Morales-Uribe C, Sanabria A. Laparoscopic management of gastric gastrointestinal stromal tumors. *World J Gastrointest Endosc* 2014; 6(7): 296-303 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v6/i7/296.htm> DOI: <http://dx.doi.org/10.4253/wjge.v6.i7.296>

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 vs 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 mesoder-

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 tumors 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 extraluminal 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 sarcomato-

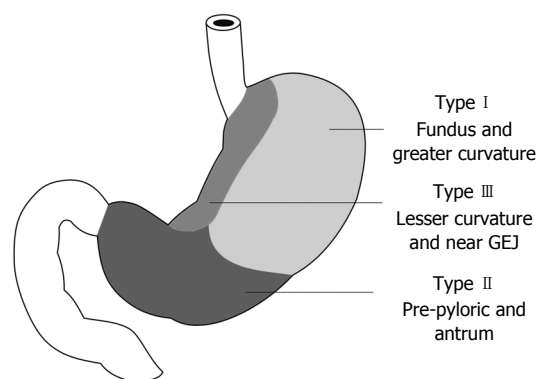


Figure 1 Surgical approach according to gastrointestinal stromal tumor localization.

sis^[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

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 <i>et al</i> ^[25] | 12 | 60.5 | 5.2 cm PG 4.6 cm TransG 5.5 cm DG | 5 Fundus or greater curvature 3 Prepyloric or antral 5 Lesser curvature | 5 PG × Lap 3 DG × Lap 5 TransG × Lap | PG 180 (122-262) DG: 322 (256-340) TransG: 236 (202-265) | 9/12 GIST 1 Schwannoma 2 Leiomiomas LOS: GP: 3.4 GD: 8.3 GT: 3.3 | 16.6% complication 1 Enterotomy 1 GI Bleeding No conversions | Only specified for 5 pts |
| Sexton <i>et al</i> ^[32] | 61 | 59.1 ± 19 | 3.8 ± 1.8 AR: 229.7 NAR 140.9 | Fundus 19 Antrum 18 Body 17 GE junction 7 Pylorus 2 | PG 52 DG 4 TotGas 3 TransG 3 | 151.9 ± 67.3 | LOS: 3.9 ± 2 LOS AR: 3.9, NAR: 4.1 | 16.4% complication No conversions 1 POP death | 15 (0-103) 3 recurrences |
| Berindoague <i>et al</i> ^[9] | 22 | 66.7 | 5.6 (2.5-12.5) | Upper third 6 Middle third 7 Lower third 10 | GP 13 1 LAP-HA TotGas 1 LAP TotGast 1 LAP-HA GD 1 TransG | NR | 18/22 GIST 1 Adenomyoma 1 Hamartoma 1 Plasmocytoma 1 Parasitic Tumor (anisakis) LOS 6 (4-32) LOS 8.5 | 18.2% complication 3 Delayed gastric emptying 1 Intestinal Obstruction 2 Conversions (9.1%) | 32 m (1-72) 1 recurrence |
| De Vogelaere <i>et al</i> ^[24] | 31 | 63.8 | 4.4 (0.4-11) | Anterior gastric wall 23 Others not specified | 31 PG | 99 | LOS 5.3 ± 1.8 41 GIST 8 Leiomyoma 4 Carcinoids 1 Liposarcoma 6 Heterotopic Pancreas 2 Hyperplastic Polyps 1 Parasitic Infection | 3.2% Complication 1 POP Bleeding | 56.3 No recurrences |
| Hwang <i>et al</i> ^[10] | 63 | 52.8 | 3.5 GE Junction 3.4 Prepyloric Size of other tumor not specified | 7 GE junction Upper third 22 Middle third 11 Lower third 19 4 Prepyloric | 3 DG 37 PG 23 TransG (5 Enucleations) | 86.1 ± 43.7 | LOS 3.8 ± 1.6 4 Minor complications | 4.7% Complication 1 Staple line bleeding 1 SSI 1 Staple line dehiscence | 14.9 (2-42) No recurrences |
| Novitsky <i>et al</i> ^[26] | 50 | 60 ± 13 | 4.4 ± 2.0 cm | GE Junction 8 Cardias 9 Anterior Wall 10 Posterior Wall 4 Greater Curvature 6 Lesser Curvature 3 Antrum 4 Prepyloric 6 | TotGas 1 DG 2 PG 40 LAP/END 4 LAP-HA 3 | 135 ± 56 | LOS 6.7 ± 1.8 3.5% conversion | 8% 4 Minor complications | 36 (4-84) 4 recurrences |
| Lai <i>et al</i> ^[2] | 28 | 56.9 ± 12.4 | 3.4 ± 1.6 | Upper third 13 Middle third 8 Lower third 7 | 28 PG | 189.6 ± 79.5 Stapled 194.3 ± 50.5 Hand-Sewn | LOS 5.2 ± 2.3 | 4.3% complication 1 Delayed gastric emptying No conversions | 43.3 ± 23.5 No recurrences |
| Choi <i>et al</i> ^[36] | 23 | 59.7 ± 8.3 | 4.2 ± 2.1 | Upper third 13 Middle third 5 Lower third 5 | 23 PG | 104.3 | LOS 5.2 ± 2.3 | 4.3% complication 1 Delayed gastric emptying No conversions | 61 (7-98) |
| Nguyen <i>et al</i> ^[22] | 28 | 65 | 4.6 (0.4-11.5) | LAP PG 22 Subtotal Gastrectomy 3 OS (Converted) : TotGas 1 Intraluminal excision 1 1 Not specified | 23 GP × LAP 3 GD × LAP 1 GT × LAP 1 TotGas × 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 conversions Mortality 1 POP death This includes Small Bowel GIST resections. No data only on gastric resections | NS |
| Huguët <i>et al</i> ^[37] | 33 | 68 | 3.9 (0.5-10.5), | GE Junction 5 Body 24 Antrum 4 | PG 29 LAP-HA PG 4 | 124 (30-253) | LOS 3 (1-40) | 9% complications 2 POP Bleeding 1 SSI 6% conversions | 13 (3-64) No recurrences |

| | | | | | | | | | |
|---|----|--------------------------|---|---|------------------|--|--|---|--|
| Ronellenfitch <i>et al</i> ^[38] | 17 | 56 (43-79) | 2.9 (0.8-6) | 11 Not specified 6 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 <i>et al</i> ^[39] | 15 | 65.3 (52-75 years) | TransG 2.9 (1.7-6.5) GP 3.9 (1.2-8) | TransG: Upper third 4 Middle third 1 Lower third 1 PG: Greater curvature 2 Lesser curvature 1 Anterior wall 2 Middle third Ant wall 1 Middle Third Post wall 1 | TransG 8 PG 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 GIST TransG 18-73 PG: 6-122 No 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.

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 submucosal 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 *vs* 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 *vs* open resection with evaluation of short and long term

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 <i>et al</i> ^[8] | 28 | 61.6 GLA 60.7 CA | 2.6 ± 1 1.8 GLA 2.5 ± 1.0 CA | Anterior fundus: 5 GLA 5 CA Posterior fundus: 6 GLA 2 CA Anterior body: 3 GLA 3 CA Posterior Body: 1 GLA 3 CA | 15 GLA 13 OS All were Wedge Resections | GLA 129 ± 36.1 CA 110.8 ± 38.1 | GLA Less POP Pain during the first 3 d Earlier oral intake Less LOS 5.8 vs 7.2 días | 7.1% complication 1 OS Ileus 1 Enterotomy during GLA corrected during LAP | NR |
| Catena <i>et al</i> ^[7] | 21 | 50.1 | 4.5 ± 2.0 | Body 16 Antrum 4 Fundus 1 | 21 PG | 151 ± 56 | LOS 4.8 ± 1.6 | No intraoperative complications | 35 (5-58) |
| | 25 | 54.6 | 6.2 ± 1.9 | Body 17 Antrum 6 Fundus 2 | 25 OS (PG) | 134 ± 33 | LOS 7.1 ± 1.2 | No differences in complications | 91 (80-136) 1 recurrence |
| Melstrom <i>et al</i> ^[31] | 46 | 62 Lap | OS 6.39 82.1-10) | Lap: Upper third 6 | 17 PG | Lap 135 | LOS: OS 6.25 | Complications OS: 13.8% | OS 59 4 |
| | 17 | 60 OS | LAP 4.27 (1.5-9.1) | Middle third 10 NS 1 | 4 DG × OS 1 TotGas × OS | OS 157 | LAP 2.68 | LAP: 11.8% 6% conversion | recurrences LAP 32 No Recurrences |
| | 29 OS | | | OS: Upper third 6 Lower third 22 NS 1 | | | I | | |
| De Vogelaere <i>et al</i> ^[11] | 53 | | Total 5.9 | | | | | LAP: 2.7% 1 Pulmonary Embolism | Lap 83 |
| | 37 | LAP 63.7 LAP ± 15.4 | LAP 5.6 | Not specified | Not specified | LAP 48.5 ± 16 | LOS Lap 7 | OS 18.7% complications: Pneumonia 1 Anastomotic Ulcer 1 Fistula 1 | No Recurrences LAP OS 71 6 recurrences CA |
| | 16 OS | OS 63.7 ± 10.7 | OS 7.5 | Not specified | Not specified | OS 155 ± 48.1 | LOS OS 14 | | |
| Karakousis <i>et al</i> ^[40] | 80 | 68 | OS 4.3 (2-9) | OS : Fundus 7 | OS 39 PG 1 DG | OS 89 | LOS: LAP 4 OS 7 | Complications OS 25% LAP 14% | LAP 28 (0.3-70 m) Recurrences 1 LAP |
| | OS 40 | | LAP 3.6 (0.7-7.8) | Body/antrum 32 Pylorus 1 Lesser curvature 12 | LAP 40 PG | LAP 96 | | 32.5% Conversions | OS 43 (0.1-139) Recurrences 1 OS |
| | LAP 40 | | | LAP: Fundus 3 Body/antrum 37 Pylorus 0 Lesser curvature 10 | | | | | |
| Kim <i>et al</i> ^[41] | 104 | 59.8 ± 10.5 | 5.1 ± 3.3 | Upper third 61 | Technique according to procedures was NS | LAP 91.1 ± 57 CA 165.8 ± 75.6 | LOS LAP 4.6 ± 2.3 CA 9.8 ± 4.1 | 1% Complications 1 Delayed Gastric Emptying | 49.3 (8.4-164.4) Recurrences 5 No Difference in recurrences between OS and LAP |
| | LAP 80 | | | Middle third 24 | 99 PG | | | | |
| | OS 24 | | | Lower third 19 | 5 TotGas | | | | |
| Silberhammer <i>et al</i> ^[21] | 63 | 62.3 ± 14.4 | CA 5.8 ± 4.0 | Body 29 Antrum 18 Fundus 10 | OS: PG 32 DG 5 | 135 ± 56 | LOS LAP 7.8 (± 3.1) LOS CA 12.8 ± 5.0 | 4.7% complications: 1 Gastrocutaneous Fistula 1 Catheter Sepsis 1 POP Ileus LAP: 18.2% conversions | 37 ± 27.9 Recurrences in 4 (7%) |
| | LAP 22 | | LAP 3.5 ± 1.4 | GE Junction 6 | RG 4 LAP 19 | | | | |
| | | | | | Tumorectomy 3 PG | | | | |
| Nishimura <i>et al</i> ^[42] | LAP 39 | 62 | LAP 3.8 (0.8-7.3) | LAP: Upper third 19 Middle third 16 Lower third 4 | LAP GP: 12 LAP-HA 17 TransG 10 | LAP: 136 min OS: 115 min | NR | No Complications Conversion Rate 2.6% | LAP: 18.9 (2.6-96.4) Recurrences 4 LAP |

| | | | | | | | | | |
|---------------------------------------|-----------|----------------------|--|--|---|---------------------------------|---------------------------|---|------------------|
| | OS 28 | OS: 4.2 (2.0-7.0) | OS Upper third 11 Middle third 11 Lower third 6 | OS PG: 19 Prox Gas: 5 TotGas: 3 DG:1 | | | | OS: 31.2 (4.4-121.9) 1 Recurrence OS 53 mo | |
| Otani <i>et al</i> ^[43] | 60 | 59 (32-86) | 4,25 (1.8-15.0) | Upper third 36 Middle third 20 Lower third 4 | LAP: PG: 35 LAP-HA: LAP-HA PG 2 LAP-HA DG 1 | LAP 141 LAP-HA 188 CA 197 | LOS LAP 7.2 vs 13.7 CA | 3.3% complications: 1 Gastric Stenosis 1 Anastomotic Leak | 2 Recurrences |
| | OS 22 | | | | OS: PG 11 ProxGas 9 DG 2 | | | | |
| | LAP 38 | | | | | | | | |

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.

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 ef-

fective 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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