

Unusual presentations, management and outcomes of gastric stromal tumors: a single-center case series

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Abstract

Background Gastrointestinal stromal tumors (GISTs) are uncommon mesenchymal tumors of the gastrointestinal tract. This study explores the safety of laparoscopy and the long-term oncological outcome in gastroesophageal GIST treatment.

Methods A prospectively maintained single-institution database was examined. The variables collected were patient demographics and comorbidities, surgical access (laparoscopic/open), type of surgery, length of stay, and complications.

Results A total of 69 patients underwent GIST resection between January 2011 and June 2018, of whom 56.5% were male; the median age was 68 years (interquartile range 60-76). The majority of patients (78.3%, n=54/69) had a laparoscopic resection. Median length of stay was 6 days in the laparoscopic group and 9 days in the open group (P=0.003). Most patients had wedge excision (n=57/69, 82.6%), while 12 patients (17.4%) required a gastrectomy (one a Merendino type). All patients had an R0 resection and 1 patient (1.4%) had a recurrence, despite having a low-risk grade original tumor with negative margins. Patients in the open group had a significantly higher proportion of patients with a high-risk tumor (50%) compared to the laparoscopic group (3.7%, P=0.001). The mean survival was 92.7 months (95% confidence interval 86.3-99.2). Survival was better in the laparoscopic group (100.4 months) compared with the open group (55.1 months, P<0.001).

Conclusion Laparoscopic gastric GIST resection is an oncologically safe alternative to open surgery and is associated with a shorter hospital stay with no difference in complication rates or recurrence rates.

Keywords Gastrointestinal stromal tumors, GIST, surgery, laparoscopy, outcomes

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Introduction

Gastrointestinal (GI) stromal tumors (GIST) are rare tumors with an incidence of 10-20 cases per one million of the population; the highest rates are in China and northern Norway [1-5]. They arise from muscle or connective tissues of the GI tract and can occur at any GI site, but tend to

occur most frequently in the stomach and small bowel [6]. Whilst the majority are benign, they have potential for malignancy, particularly non-gastric GISTs [7]. There is considerable variability in the tendency for these tumors to turn malignant and their histological differentiation is equally heterogeneous.

Clinically, patients can present with a variety of symptoms, depending on the size and the site of the tumor. Larger tumors may exert a mass effect and cause abdominal pain, or bleeding in the GI tract, although a significant proportion may be entirely asymptomatic and their discovery incidental. Surgical resection remains the mainstay treatment of GISTs, although the use of other approaches (notably endoscopic) has been increasing [8], despite reports of potential tumor rupture during the procedure [9]. Laparoscopic resection has become increasingly attractive recently, and its short- and long-term outcomes appear favorable [10]. A recent meta-analysis deemed laparoscopy to have potentially favorable outcomes over endoscopic treatment of GIST [11]. The aim of this study was to report our short and long-term outcomes

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from a large case series of patients with gastric GIST and to highlight unusual signs and symptoms which patients may present.

Patients and methods

A single-institution dataset prospectively maintained was used for this study. All consecutive patients undergoing gastric GIST resection between January 2011 and June 2018 were included in the study. Patient demographics, comorbidities, surgical access (laparoscopic/open), length of stay and complications were all recorded.

Diagnosis and tumor assessment

Our institution receives referrals from general practice, other hospitals (via a tertiary referral system), as well as via the emergency department at the hospital itself. Upon diagnosis, patients would go through our multidisciplinary team meeting, comprising upper GI surgeons, gastroenterologists, oncologists and radiologists. All patients underwent esophagogastroduodenoscopy and computed tomography (CT) to assess the characteristics of the GIST. In a selection of patients who required further diagnostic clarity or evaluation of the tumor and obtaining pathological sample, endoscopic ultrasound was used. The risk of progression was calculated using modified National Institute of Health risk classification criteria, as set out by Joensuu *et al* and published in 2008 [12].

Treatment and operative approach

The multidisciplinary team made recommendations for treatment in line with the patient's wishes, based on patient comorbidity, tumor location, size, risk of malignancy, and previous surgical history. Laparoscopy was the preferred surgical approach in all patients with tumors up to 5 cm in size. In patients with tumors between 5 and 10 cm, laparoscopy was attempted but there was a low threshold for conversion to open. In patients who had undergone multiple previous surgeries or had large tumors (>10 cm), an open method was adopted. The surgeon's experience could play a role in the surgical approach. In case of tumors not amenable to resection because of their large size (10 cm+) or involvement of surrounding structures that mandated multi-organ resection, imatinib was given as neoadjuvant therapy.

Statistical analysis

Scale variables were reported as medians with accompanying interquartile range (IQR), groups were compared using Pearson chi-squared analysis and a P-value of <0.05 was considered statistically significant. Statistical analysis was carried out

using the Statistical Package for the Social Sciences (SPSS) IBM version 23.

Results

Population characteristics

A total of 69 patients (Table 1) underwent gastric GIST resection, of whom 56.5% (n=39/69) were male; the patients' median age was 68 years (IQR 60-76 years). The median tumor size was 5.0 cm (IQR 4.0-7.2 cm). The majority of the patients had an American Society of Anesthesiology grade II (n=47/69, 68.1%), a smaller proportion (17.4%, n=12/69) were grade III and the remainder (14.5%, n=10/69) were grade I. In 43 patients (62.3%) the GIST was in the gastric body, whilst in 19 patients (27.5%) and 6 patients (8.7%) it was in the gastric fundus or antrum, respectively. In one patient the tumor was located in the pylorus. Overall, 72.5% (n=50/69) had a GIST

Table 1 Patient demographics, tumor characteristics and outcomes

Characteristics	n	%
Sex	Male	39 56.5%
	Female	30 43.5%
Age	<60 years	17 24.6%
	60-69 years	20 29.0%
	70-79 years	19 27.5%
	80+ years	13 18.8%
Tumor site	Gastric antrum	6 8.7%
	Gastric body	43 62.3%
	Gastric fundus	19 27.5%
	Gastric pylorus	1 1.4%
Risk of progression	Low	50 72.5%
	Intermediate	9 13.0%
	High	10 14.5%
Treatment	Surgery	63 91.3%
	Surgery & adjuvant chemotherapy	1 1.4%
	Surgery & neoadjuvant chemotherapy	5 7.2%
Surgery type	Gastrectomy	12 17.4%
	GIST excision	57 82.6%
Surgical access	Laparoscopic	54 78.3%
	Open	12 17.4%
	Converted to open	3 4.3%
Postoperative complication	Yes	6 8.7%
	No	63 91.3%
Mortality status	Alive	62 89.9%
	Deceased	7 10.1%

GIST, gastrointestinal tumor

histopathologically graded as low risk of progression, whilst 14.5% (n=10/69) had a high-risk tumor.

Surgical outcomes

The majority of the patients (78.3%, n=54/69) underwent a laparoscopic resection, whilst 17.4% (n=12/69) had an open procedure. In 4.3% (n=3/69) of cases, a laparoscopic procedure was converted to open. All 3 of these latter patients had had previous major abdominal surgery. There was a higher proportion of patients undergoing gastrectomy in the open group (66.7%) compared with the laparoscopic group (8.9%, $P<0.001$, Table 2). Patients in the open group had a significantly higher proportion of patients with high-risk tumors (50%) compared with the laparoscopic group (3.7%, $P=0.001$). Most patients only required a GIST excision (82.6%, n=57/69), whilst 17.4% (n=12/69) required a gastrectomy (1 of whom had a Merendino type resection). The median length of stay was 7 days (IQR 4-10 days) across the entire population and was significantly lower in the laparoscopy group (6 days, IQR 5-10) compared with

the open group (9 days, IQR 7-13, $P=0.003$). A total of 6 complications (8.7%) occurred and complication rates by surgical approach were similar (7.4% in the laparoscopy group and 8.3% in the open group, $P=0.882$). These 6 complications included 2 patients who experienced GI bleeding/melena, probably due to the gastrojejunal anastomosis site, which resolved without any intervention. Two patients developed postoperative pneumonia and 1 elderly female patient developed a urinary tract infection postoperatively; all were treated with antibiotics. One patient developed a small subphrenic collection (also treated with antibiotics) and 1 patient developed a pyloric stricture as demonstrated on oral contrast study; however, the patient had mild symptoms and did not require intervention. There were no returns to theater from any of the above complications.

Long-term outcome

None of the patients were lost to follow up and at a median of 53 months' follow up (IQR 26-75 months), 89.9% (n=62/69) of the population were alive. One patient who underwent a

Table 2 Demographics and outcomes according to surgical access

Characteristics		Laparoscopic		Open		Converted to open		P-value
		n	%	n	%	n	%	
Sex	Male	30	55.6%	9	75.0%	0	0.0%	0.061
	Female	24	44.4%	3	25.0%	3	100.0%	
Age	<60 years	11	20.4%	6	50.0%	0	0.0%	0.247
	60-69 years	17	31.5%	2	16.7%	1	33.3%	
	70-79 years	15	27.8%	2	16.7%	2	66.7%	
	80+ years	11	20.4%	2	16.7%	0	0.0%	
Tumor site	Gastric antrum	4	7.4%	2	16.7%	0	0.0%	0.197
	Gastric body	36	66.7%	6	50.0%	1	33.3%	
	Gastric fundus	14	25.9%	3	25.0%	2	66.7%	
	Gastric pylorus	0	0.0%	1	8.3%	0	0.0%	
Risk of progression	Low	45	83.3%	4	33.3%	1	33.3%	0.001
	Intermediate	7	13.0%	2	16.7%	0	0.0%	
	High	2	3.7%	6	50.0%	2	66.7%	
Treatment	Surgery	52	96.3%	8	66.7%	3	100.0%	0.331
	Surgery & adjuvant chemotherapy	1	1.9%	0	0.0%	0	0.0%	
	Surgery & neo-adjuvant chemotherapy	1	1.9%	4	33.3%	0	0.0%	
Surgery type	Gastrectomy	3	8.9%	8	66.7%	1	33.3%	<0.001
	GIST excision	51	91.1%	4	33.3%	2	66.7%	
Complication	Yes	4	7.4%	1	8.3%	1	33.3%	0.300
	No	50	92.6%	11	91.7%	2	66.7%	
Mortality status	Alive	53	98.1%	7	58.3%	2	66.7%	<0.001
	Deceased	1	1.9%	5	41.7%	1	33.3%	

GIST, gastrointestinal tumor

laparoscopic resection had a recurrence (1.4%), despite having an R0 resection and a tumor grade deemed to have low risk for recurrence (1.9% risk of progression). Overall survival analyses were undertaken and all-cause mortality was considered. Survival analysis demonstrated an overall mean survival of 92.7 months (95% confidence Interval [CI] 86.3-99.2). This was significantly better in the laparoscopy group, who had a mean survival of 100.4 months (95%CI 97.2-103.6), compared with 55.1 months (95%CI 41.2-68.9) in the open group and 59.3 months (95%CI 11.9-106.8) in the laparoscopy converted to open group ($P<0.001$, Fig. 1). Patients in the open group had a greater proportion of patients who had high-risk tumors (50%, $n=6/12$) compared with the laparoscopic group (3.7%, $n=2/54$, $P=0.001$), and mortality was also significantly higher in the open group compared with the laparoscopic group (41.7% vs. 1.9%, $P<0.001$), reflecting the advanced tumors presented by patients in the open group.

Uncommon presentation

Three of the patients presented with unusual or uncommon findings. One female patient presented with dysphagia and epigastric pain and a mass was identified in the mediastinum on CT. Endoscopic examination of the esophagus and stomach, however, was normal. She underwent surgery and an entirely extraluminal GIST at the gastroesophageal junction was resected. The patient recovered well without any complications. Another young female patient presented with major hemorrhage requiring multiple blood transfusions and urgent laparotomy. At laparotomy, an exophytic GIST on the greater curvature was found to be actively bleeding intraperitoneally. The third patient was a 51-year-old female who presented as an emergency with sudden-onset epigastric pain. Subsequent CT imaging demonstrated a perforated mass in the gastric antrum that required immediate laparotomy and distal gastrectomy. These 3 cases highlight some of the unusual

ways which these tumors can present, ranging from unseen masses on esophagogastroduodenoscopy, causing extrinsic compression of the esophagus and dysphagia, to catastrophic bleeding and perforation.

Discussion

The main finding of this single-institution case series was that gastric GIST excision surgery was associated with a low risk of complications and good long-term survival. Laparoscopic resections were safe for selected gastric GISTs in favorable anatomic locations (greater curvature or anterior wall of the stomach), for smaller size GISTs, and when performed by surgeons with appropriate experience. They were associated with a lower risk of complications and equivalent long-term outcomes compared to open surgery. Our findings are similar to those reported by others. In one of the largest studies, involving 1057 patients across Korea and Japan, the authors found low rates of 30-day mortality (0.2%) and postoperative complications (8.1%), and only a 5% 5-year recurrence rate [13].

Much like the use of laparoscopy in other GI tumors (notably colon), the use of a minimally invasive approach was initially met with suspicion. Concerns over marginal clearance and non-disruption of the tumor itself were widespread at first. However, as laparoscopic resection for a variety of tumors, including esophageal, gastric, liver, kidney, colon and even pancreatic, have become commonplace, these concerns have largely been demonstrated to be unfounded. In our case series, the majority of patients (78.9%, $n=56$) underwent a laparoscopic resection; all had clear margins, with no recurrence at a median 4 years of follow up. The first laparoscopic excision of a GIST, carried out in 1992, was incidental [14]. Since then, a number of case series and observational studies have demonstrated that laparoscopic surgery is not only feasible and safe in GIST

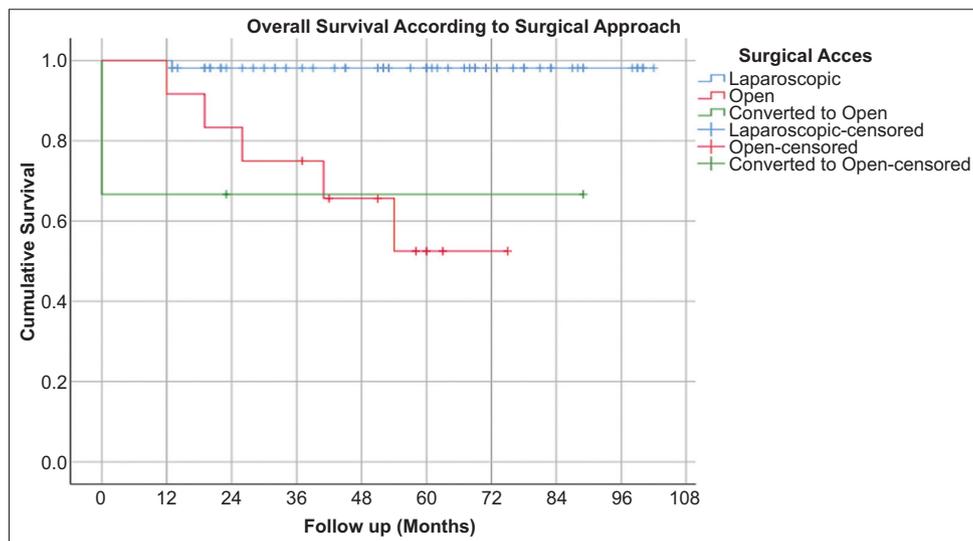


Figure 1 Survival analysis comparing the populations in the different surgical access groups

excision, but is also associated with a shorter length of stay, lower risk of postoperative ileus and quicker return to bowel function, and has long-term oncological outcomes equivalent to those of open surgery [15-20]. As yet, however, there has been no definitive trial data for laparoscopic vs. open surgery in the surgical management of GIST. In our study, patients in the laparoscopic group fared better in terms of long-term survival; however, this is most probably because the laparoscopic group had a lower rate of aggressive/advanced tumors.

Therefore, it would be erroneous to presume laparoscopic superiority over open surgery in terms of oncological outcome. However, the findings do demonstrate that it is at least not inferior to open surgery, and that laparoscopic surgery can provide clear margins and equivalent long-term results, with the benefits of decreased tissue trauma and length of stay perioperatively. Our data also demonstrated that the majority of patients could have a laparoscopic excision with a relatively low risk of having to convert to open. In this study, the conversion rate from laparoscopic to open surgery was 4.3% (3 patients), in keeping with the published literature, which quotes a conversion rate of around 6% [21]. Other concerns around laparoscopic use center on port site metastases. Resected specimens should be retrieved from the abdomen in a plastic bag to avoid rupture and intraperitoneal spillage. Whilst there are case reports of port site seeding from sampling GISTs laparoscopically [22], this is extremely rare and sampling itself has largely become a thing of the past, as modern imaging modalities such as CT or endoscopic ultrasonography are usually adequate for establishing a diagnosis without the need for sampling. In cases where there is diagnostic uncertainty, or where quantification of the risk of malignancy is required, preoperative biopsies can be useful. Furthermore, preoperative biopsies may be helpful in confirming metastatic disease and in certain institutions a preoperative biopsy is mandatory prior to the initiation of definitive treatment, although there are concerns about potential tumor seeding via a transabdominal biopsy tract [23].

A variety of factors can affect the decision to undertake laparoscopic resection in GIST patients. Previous abdominal surgery, tumor size and location, resource/equipment availability, as well as the surgeon's experience or preference, all have a role to play in the decision whether to undertake laparoscopic or open surgery. Although rare, GISTs can sometimes present as emergencies, usually with substantial intraabdominal hemorrhage and bowel obstruction [24,25]. The concern in undertaking GIST resection in the non-elective setting is potential breach of the tumor capsule, which has been associated with a significant risk of recurrence and metastases. In our study, 3 patients presented in an unusual way. One female patient presented with catastrophic internal hemorrhage requiring multiple blood transfusions and an urgent life-saving laparotomy. Another female patient had a complete exophytic tumor not detected on gastroscopy. There are several reports of atypical presentation of GISTs affecting a variety of organs, including the liver, prostate, ovaries, uterus, omentum and rectum, amongst others. Such unusual and potentially life-threatening presentations are rare; however, a high index of

suspicion is required and timely surgical treatment of known GISTs is essential to avoid their presentation acutely, as this invariably results in a poorer outcome for the patient.

Overall survival from GISTs is variable, given their vastly heterogeneous nature. Unsurprisingly, much like other tumors, survival seems to be at least in part dependent on tumor DNA, mitotic count and tumor differentiation, rather than on tumor size alone [26]. Tumors that have a high mitotic index, i.e., above 10/50 high-power field, and those greater than 5 cm in size have been demonstrated to adversely impact survival [27]. This discrepancy in the risk of progression between the open and laparoscopic groups is the likely explanation for the low recurrence and mortality rate in the laparoscopic group compared to the open group. One of the aims of this study was to demonstrate whether the laparoscopic approach is safe in the short and long term and is comparable to the open approach in terms of recurrence and subsequent survival, rather than to demonstrate superiority. Undoubtedly, open surgery continues to have a major role. Other negative prognostic indicators include advanced age, non-gastric tumors and incomplete resection of tumor (R1) or tumor rupture. Perhaps one of the biggest factors affecting survival is tumor rupture. The Oslo criteria set out a range of definitions of what constitutes tumor rupture. These include both natural and iatrogenic causes of rupture. Spontaneous rupture of tumor causing hemorrhage and peritonitis, GI organ perforation through the tumor, and blood-stained ascites are concerning features of tumor rupture. Similarly, iatrogenic causes can arise during laparoscopic surgery itself, when the tumor capsule is breached and piecemeal resection occurs. Importantly, R1 resections, tumor spillage into GI lumen, microscopic tumor penetration into the peritoneum and uncomplicated transperitoneal needle biopsy without complication do not constitute tumor rupture. Incisional biopsies, however, would qualify as tumor rupture and must therefore not be attempted in suspected GISTs [28].

A factor that positively affects survival is the administration of postoperative imatinib (Glivec) to patients with high-risk tumors, although no survival benefit was noted in patients with intermediate risk [27]. The duration of imatinib therapy is also important. An analysis of trial data of 400 patients with GIST has demonstrated a significant survival benefit in patients who have 3 years of imatinib as opposed to 1 year [29]. Imatinib has also been demonstrated to improve quality of life in GIST patients at high risk of recurrence, although the financial cost of long-term therapy may be prohibitive in certain parts of the world [30]. The efficacy of imatinib has led to it being recommended as essential adjuvant therapy in patients with GISTs that are at high-risk (and even arguably intermediate risk) of recurrence and those patients who have had a spontaneous or iatrogenic tumor rupture. However, despite the recommendations put forward by the US based National Comprehensive Cancer Network and the European Society for Medical Oncology, advocating the use of imatinib in high-risk and even intermediate risk GISTs, many institutions are not consistently offering high-risk patients adjuvant imatinib and the reasons for this are not entirely clear [31]. In our case series, 5 patients had neoadjuvant imatinib therapy and only 1 had adjuvant therapy, despite 10 patients being deemed high-risk

for disease progression. A concerted effort is required to identify patients with a high risk of disease progression and in appropriate circumstances offer imatinib therapy. The case for routinely administering imatinib to intermediate risk patients is less clear, with no convincing evidence to justify its use.

The main limitations of our study were that it was a single-center, retrospective case series, prone to certain inherent biases. Our sample size was small, making it difficult to draw definitive conclusions. Our population may also be different to that of other hospitals and our results not entirely applicable to populations of other regions of the world. Moreover, although in our series survival appeared to be better in the laparoscopic group, this was almost certainly due to a difference in the case mix of the patients undergoing open and laparoscopic surgery. Tumors in unfavorable anatomic locations (lesser curvature, posterior gastric wall or in proximity to cardia or pylorus) are more likely to have an open resection rather than a laparoscopic one. Therefore, there is still a definite role for open surgery in patients with excessively large tumors, particularly in the non-elective setting or in patients who have had multiple previous abdominal surgeries for other pathology, making laparoscopy challenging or unsafe. Additionally, in less common cases with pathologically enlarged regional lymph nodes (succinate dehydrogenase-deficient GIST), where a lymphadenectomy, is indicated open surgery constitutes a more realistic approach.

In conclusion, this single-center case series has demonstrated that, although most gastric GISTs are incidental findings or are diagnosed in a non-emergency setting, some patients can present in unusual ways. Large tumor sizes and patients at high risk of progression are important considerations when deciding upon the surgical approach. In appropriately selected patients, laparoscopy is safe, has good perioperative outcomes and is equivalent to open surgery in terms of oncological outcome. The use of adjuvant imatinib should be discussed with all patients who have GISTs deemed to be high-risk.

Summary Box

What is already known:

- Gastrointestinal tumors (GISTs) are tumors with a potential for malignancy and can present in unusual ways
- Overall survival post-surgical resection is very good provided an R0 resection is achieved

What the new findings are:

- Laparoscopic surgery is a safe alternative to open surgery in appropriately selected patients and entails a shorter length of stay
- The R1 resection rate is low, irrespective of the surgical approach taken
- Survival and complication rates are comparable between open and laparoscopic surgery

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