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Laparoscopic versus open gastric resections for primary gastrointestinal stromal tumors (GISTs): a size-matched comparison

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Abstract

Background—Laparoscopic resection of gastric GISTs appears technically feasible and associated with favorable outcomes. Tumor size however frequently plays a role in surgical approach with larger tumors tending towards laparotomy, raising concern that favorable outcomes reported for the laparoscopic approach may reflect this selection bias.

Methods—From a prospectively collected sarcoma database, 155 primary gastric GIST resections were identified (1998–2009); 40 patients underwent successful laparoscopic resection for non-GE junction GIST and were randomly matched (1:1) by tumor size (+/− 2.0 cm) to patients with open resection. Clinical, pathologic variables and surgical outcomes were associated with surgery type using conditional logistic regression analyses.

Results—The two surgical approaches were comparable for clinical and pathologic variables. Median operating room (OR) time was similar, although median length of stay post-surgery was lower in the laparoscopic versus open group (4 vs. 7 d, p=0.002), as was estimated blood loss (EBL) (25 vs. 100 mL, p=0.006). There was no operative mortality, and 30 d morbidity was similar. Oncologic outcomes were also similar with no positive microscopic margins, and 1 recurrence in each group with a median follow-up of 34 months. There were 13 conversions overall, 5 secondary to tumor location at the GE junction or lesser curve.

Conclusions—When matched for tumor size, laparoscopic resection of primary gastric GISTs ≤ 8 cm results in shorter hospital stays with similar OR time while maintaining sound oncologic outcomes compared to open resection.

Keywords

Gastric; GIST; Minimally Invasive Surgery; Laparoscopic Gastrectomy

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INTRODUCTION

Gastrointestinal tumor (GIST) is the most common mesenchymal derived tumor of the gastrointestinal (GI) tract with an estimated annual U.S. incidence of approximately 5,000 cases. While GISTs can occur throughout the GI tract, the most common location is the stomach, accounting for 60–70% of tumor location[1]. In the past decade, the management of GISTs, which harbor mutations of the KIT proto-oncogene (CD117)[2], has been revolutionized with the introduction of KIT tyrosine kinase inhibitors[3]. While this targeted therapy has shown great success in the metastatic and adjuvant setting, the mainstay of curative treatment for primary GIST remains surgical resection.

GIST in adults rarely metastasizes to lymph nodes[4], making routine lymphadenectomy during resection unnecessary. Moreover, tumor recurrence has been shown to be dominated primarily by factors of mitotic index, size and tumor location (gastric location associated with more favorable outcomes). Wide resection margins, historically advocated, have not been associated with improved oncologic outcomes when these other tumor factors are considered[5]. Simple wedge resection, when feasible, has become the recommended surgical approach. Gastric GIST resection is therefore particularly amenable to a minimally invasive technique, and an increasing number of laparoscopic experiences have been reported demonstrating the feasibility and safety of this approach[6–9]. While the size limit for laparoscopic GIST resection is continuously being modified[10], larger tumors have generally been approached through an open approach and frequently involve more extensive resections. The perceived advantages or equivalence of the laparoscopic approach when compared to the open approach may therefore be a result of this size selection bias and improved outcomes associated with laparoscopy may be surrogates for less extensive resections.

We hypothesize that, even when controlling for tumor size, the laparoscopic approach offers similar safety and oncologic outcomes as the open approach, with the added advantages associated with the minimally invasive approach. To test this, we performed a size-matched analysis comparing the open versus laparoscopic approach for gastric GIST. Since tumor location can impact upon selection of surgical approach and extent of resection, we focused the analysis on non-GE junction tumors, since there were no GE junction tumors resected by laparoscopy.

PATIENTS AND METHODS

We queried the prospectively maintained sarcoma database at Memorial Sloan-Kettering Cancer Center (MSKCC) for patients undergoing resection of primary localized gastric GIST (January 1998 to December 2009). Study approval was granted by the MSKCC Institutional Review Board (IRB) and the study was conducted in accordance with the Health Insurance Portability and Accountability Act (HIPAA) regulations. One hundred fifty-five patients were identified undergoing surgery specifically for resection of a primary gastric GIST. Patients were excluded if they underwent concomitant resection of other malignancies, e.g. patients with incidentally discovered GISTs in specimens resected for gastric, esophageal, or pancreatic carcinomas. Of the 155 included patients, forty

consecutive patients underwent gastric resection by a completely laparoscopic approach and constituted the laparoscopic group in the matched analyses. Of the remaining 115 patients, the following patients were excluded to establish greater parity between the two surgery groups: patients with GE junction tumors (N=14), patients with additional organ resection as part of the GIST resection (N=4), and patients with multifocal disease (N=2). Thirteen additional cases underwent conversion to an open approach. These cases were excluded to allow for direct comparison of the laparoscopic to open technique, leaving 82 patients in the open approach pool from which the case-matching was performed. A laparoscopic to open conversion was classified as any case in which laparoscopy was used with therapeutic intent based on the operative report with subsequent creation of a laparotomy incision, regardless of the extent of attempted resection. Hand-assisted cases were classified as conversions. Clinical and histopathologic data were obtained from patient medical records. All GISTs were pathologically confirmed by dedicated sarcoma pathologists at MSKCC. Mitotic rate was defined as number of mitoses per 50 high-power fields (HPF), and tumor size was defined as the maximal tumor dimension in the resected specimen. EBL was obtained from operative or anesthesia records; when not precisely quantified but described as negligible or minimal, it was assigned a value of 5 mL.

Open resections were typically performed through a midline incision. For the laparoscopic approach, entry into the peritoneum was achieved either through the Hasson technique or with a Veress needle. Pneumoperitoneum was established to an insufflation pressure of 15 mm Hg. Three or four port sites were generally used to facilitate the gastric resection. Occasionally, identification of the tumor and its extent was assisted with gastroscopy. The gastric wedge resection was usually achieved using an endoGIA stapler, and the tumor specimen was extracted using an endocatch bag. Post-operative care, including analgesia, timing of oral intake and discharge was at the discretion of the surgical team.

Statistical Analyses

Patients in the laparoscopic group were randomly matched to patients in the open group by tumor size (± 2.0 cm) using a 1:1 interval matching method. Patient and tumor characteristics and other clinical parameters were compared between the two groups using conditional logistic regression. Given the very low incidence of deaths and recurrence in the study for both groups, formal statistical comparisons for these outcomes were not performed. We compared the tumor size and length of hospital stay of open cases in the same time period as the laparoscopic group to the earlier open cases using the exact Wilcoxon Rank-Sum test. Statistical analyses were completed using SAS version 9.2 software (SAS Institute, Cary, NC).

RESULTS

Clinical and pathologic characteristics

Clinical and pathologic variables of patients are summarized in Table 1. The median age of all patients was 68 years and 61% were female. There was no significant difference between the laparoscopic and open group based on age or gender. Most tumors in both groups had a mitotic rate < 5/50 HPF (87% in the laparoscopic and 88% in the open group) and were of

spindle histologic subtype (87% in both the laparoscopic and open groups). The median tumor size in the laparoscopic and open groups was 3.6 cm (0.7–7.8 cm) and 4.3 cm (2.0–9.0 cm) respectively. The two groups were comparable with respect to tumor location, with the majority of patients having tumors located in the gastric body or antrum (80% in the laparoscopic and 93% in the open group).

Operative characteristics and peri-operative outcomes

All patients in the laparoscopic and most (95%) in the open group underwent wedge resection of their GIST. Two patients in the open group underwent distal gastrectomy, and one underwent a sleeve resection (classified as wedge resection). Additionally, one patient in the open group underwent pyloroplasty with wedge resection for a distal antral tumor. Median OR time was similar between the groups (96 min in laparoscopic group versus 89 min in open group, p=0.32). EBL was significantly lower in the laparoscopic versus the open group (25 mL versus 100 mL, p=0.006). The median post-surgical hospital stay also significantly differed between groups; 4 days in laparoscopic versus 7 days in open group (p=0.002).

Post-operative morbidity was not significantly different between the matched groups. Ten patients in the open group (25%) and six in the laparoscopic group (14%) had some type of complication (grade 1–3). There were two grade 3 complications in the open group which included a DVT and pneumonia. In the laparoscopic group, there were also two grade 3 complications. One patient developed a GI bleed from the staple line requiring endoscopic evaluation and treatment and a second patient returned after discharge with fever and a small collection in the surgical bed suspicious for a leak which was managed conservatively and did not require drainage. This second patient also developed an upper GI bleed from the staple line and underwent endoscopic evaluation and treatment. Operative characteristics and peri-operative morbidity are summarized in Table 2.

Five patients underwent additional procedures in the same OR setting unrelated to the treatment of their GIST. In the laparoscopic group, one patient underwent an inguinal hernia repair, and two patients underwent laparoscopic cholecystectomy, while in the open group, one patient underwent cholecystectomy and one patient underwent bilateral oophorectomies (for a pelvic mass which proved to be a fibroma).

Adjuvant treatment and oncologic outcomes

Microscopic tumor margins were negative in 79 of 80 study patients; for one patient in the laparoscopic group with the tumor at the pylorus, the margin was noted to be <0.1 cm. There were no instances of tumor rupture identified in the laparoscopic group. Three patients in each group received adjuvant imatinib treatment of variable duration (4–14 months). One patient in the open group with 9 cm tumor received neoadjuvant imatinib for 5 months.

With a median follow-up of 28 months (range: 0.3–70 months) in the laparoscopy group and 43 months (range: 0.1–139 months) in the open group (34 months for overall group), there were a total of 2 recurrences. One patient in the laparoscopic group with a 3.5 cm tumor and mitotic rate of 11/50 HPF developed recurrence in the left upper abdomen confirmed by laparoscopy which revealed a dominant mass and several smaller (multifocal) nodules. In

the open group, one patient with a 3.5 cm tumor developed metastatic disease in the liver. Both patients were alive with disease at last follow-up (10 years and 4 years post-surgery for the patients treated by open and laparoscopic approach respectively).

There were no disease-related in the study period, although six patients (3 in each surgery group) died secondary to other or unknown causes. Oncologic outcomes are summarized in table 3.

Because of possible confounding influence of time period, we compared the open study cases performed in the same period as the laparoscopic cases (N=31) to the earlier open cases (N=9) with respect to median tumor size and length of hospital stay. No significant difference was found in either variable: 4.5 vs. 4.2 cm, (p=0.59); 7 vs. 7 days (p=0.78).

Laparoscopic to Open Conversion Patients

There were 13 cases classified as conversions from laparoscopy to laparotomy; 4 were by surgeons very early in their laparoscopic learning curve, with minimal or no attempt at laparoscopic resection described in the operative report. Characteristics of the remaining 9 patients are summarized in Table 4. Median tumor size for these patients was 4.2 cm; median EBL and OR time was 100 mL and 139 min respectively. Median length of hospital stay was 4 days.

Various factors were responsible for conversion from laparoscopy to open, including tumor location, size, and technical factors. In no case was conversion performed for bleeding. Tumor location was a factor in the decision for conversion in 6 patients. Three tumors were in close proximity to the gastric cardia/GE junction and were not felt to be amenable to a laparoscopic approach. Two tumors were located in the lesser curvature; of these, one was located in the posterior wall, and although it was extracted laparoscopically, to ensure safe closure of the ensuing gastrostomy which was not amenable to staple closure, a laparotomy was performed with suture closure (additional technical reason for conversion). A 5.9 cm GIST in the posterior fundus led to a laparotomy incision based on its size and location. In two other patients, size and technical factors played a role in the decision for conversion. A 4.5 cm in size tumor located along the greater curvature was removed laparoscopically, but the large ensuing gastric defect could not be closed safely laparoscopically, and an incision was created for suture closure. In the other case, the tumor was felt to have a significant intra-gastric component which would cause significant gastric lumen narrowing with an endoGIA stapler, and therefore an incision was made. Finally, in one patient, a large ventral hernia was noted on laparoscopy and converted to open for GIST resection and ventral hernia repair.

DISCUSSION

Laparoscopy is being used with increasing frequency for gastric GIST[6–8, 11–13]. While there has been no prospective randomized trial directly comparing laparoscopic and open approaches for gastric GIST, several retrospective series have demonstrated that the laparoscopic approach is associated with low morbidity, mortality, and sound oncologic outcomes. The NCCN guidelines were modified in 2007 to reflect the increasing literature

on this approach. Under the new guidelines, tumors up to 5 cm can be safely approached laparoscopically, and even larger tumors could be considered through a laparoscopic hand-assisted approach[14].

In our review of the literature, we found four other series of gastric GIST to date with at least 30 patients who underwent successful laparoscopic resection[6–9]. None of these series reported a direct comparison to open cases, although a smaller subset of patients in one series had been published earlier with such a comparison[15]. Mean tumor size ranged from 3.8–4.4 cm, which was comparable to our experience, and only one positive margin was reported in these series of laparoscopic resections[7]. Similarly, there was only one close margin <0.1 cm in our laparoscopic series in a patient with a pre-pyloric lesion who remains recurrence free (13 months follow-up). Mean OR time for laparoscopic resection ranged from 135–151.9 min in the larger series, which is slightly higher than what we found, although these series often included a subset of patients who underwent esophagogastrectomy for GE junction tumors, antrectomy for distal lesions, or transgastric resections[9]. Mean hospital stay post-surgery was 3.8–3.9 days in the studies from the Western hemisphere[6–7], while higher in the Japanese series 7–8 days[8–9].

Since tumor size appears to be one of the dominant variables that determines surgical approach, this selection bias could impact outcomes of approach. We performed a size-matched comparison between laparoscopic and open gastric GIST resections in an effort to mitigate this potential bias. We excluded patients in the open group with tumors at the GE junction or invading adjacent organs requiring extra-gastric resections as there were no such patients in the laparoscopic group. Patients who underwent conversion from laparoscopy to laparotomy were excluded as our interest was in a pure comparison of the two approaches. We found laparoscopy to be associated with a statistically significantly lower (though not clinically significantly different) EBL when compared to the open approach and with a shorter hospital stay. Matthews et al reported similar findings with respect to hospital stay in a comparison of 21 patients undergoing laparoscopic gastric GIST resection to 12 patients undergoing an open approach[15]. Although patients were chosen consecutively, the mean tumor size between the two groups was similar (4.9 cm in open versus 4.5 in laparoscopy group). However, half of the patients in the open group underwent either an antrectomy or proximal gastrectomy versus none in the laparoscopic group. Catena et al compared 21 cases of laparoscopically resected gastric GISTs to 25 open cases[11]. Mean tumor size was 6.2 cm in the open group versus 4.5 cm in laparoscopic group (not different statistically). Although also not significantly different, the mean hospital stay was 4.8 days in the laparoscopy group versus 7.1 days in the open group.

The findings in this study are concordant with randomized prospective trials comparing open and laparoscopic approaches for other disease processes including donor nephrectomy, colorectal cancer, and gastric adenocarcinoma, which also have reported a shorter hospital stay[16] and EBL[17–18] associated with the laparoscopy. Importantly, we as others, found no difference in oncologic outcomes between surgical approaches, although the median follow-up for our patients in the laparoscopic group was shorter given the relative recent more frequent employment of this technique at our institution, and therefore more definitive conclusions about long-term oncologic outcomes should be reserved at this time.

Thirteen patients in our study were converted from a laparoscopic to open approach. While this rate (13/53 or 25%) is higher than other larger published series of exclusively gastric GISTs (0–2.2%),[6–9] it should be noted that laparoscopic hand-assisted were categorized as conversion cases in our series. Moreover, there was considerable variability in the laparoscopic experience of surgeons. Other series have reported similar conversion rates of up to 23%[19]. For five of nine cases in our experience, reason for conversion included proximity of the lesion to the gastric cardia or GE junction or lesser curve location. While there are no clear consensus guidelines for gastric GIST resection approach based on location, others have similarly noted difficulty in successful laparoscopic resection of very proximal tumors. Basu et al reported conversion of one of three patients with a GE junction tumor in a series of 21 attempted laparoscopic GIST resections, with an additional patient who underwent a planned open procedure for a GE junction tumor[20]. In 25 cases of gastric GISTs attempted laparoscopically reported by Nguyen et al, three were converted to open (12%), two because of tumor proximity to the GE junction[21].

More recently, transgastric methods have been described for removal of very proximal tumors using balloon trocars in the stomach with endoscopic assistance[22]. Privette et al reported on 12 patients who underwent tailored laparoscopic approach of suspected gastric GISTs based on tumor location[12]. Four patients with very proximal or lesser curve lesions underwent laparoscopic transgastric resection. This approach was associated with longer operative times compared to laparoscopic partial gastrectomy for tumors of the fundus and greater curvature, but similar EBL and hospital stay. Sasaki et al reported a series of 10 patients undergoing a transgastric approach, also with median OR times nearly double that of the exogastric approach[9]. As more resections are performed using this transgastric approach, its feasibility and outcomes can better be characterized.

While we have demonstrated that resection of non-GE junction gastric GISTs up to 8 cm achieved laparoscopically is associated with similar OR time, morbidity and outcomes when compared to open resection of similar size tumors but with shorter hospital stay, tumor location is clearly an important selection factor for choosing an operative approach. We recommend a relatively low threshold for conversion to open for very proximal lesions of the GE junction or distal pre-pyloric tumors to ensure sound oncologic outcomes with low morbidity. These decisions should take into account other factors including the surgeon’s experience with a variety of complex laparoscopic techniques.

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SYNOPSIS

When laparoscopic and open approaches were compared for resection of primary non-GE junction gastric GISTs matched by tumor size, laparoscopy was associated with shorter post-surgical hospital stay with similar operative time, oncologic outcomes, and morbidity.

Table 1

Clinical and pathologic variables by surgery type of primary gastric gastrointestinal stromal tumor (GIST)

Variables	Surgery Type			p-value*
	All N=80	Lap N=40 (%)	Open N=40 (%)	
Age				
Median in years (range)	68 (29 – 90)	67 (36 – 86)	70 (29 – 90)	0.25
Gender				
Female	49	26 (53%)	23 (47%)	0.49
Male	31	14 (45%)	17 (55%)	
Size				
Median cm (range)	3.9 (0.7 – 9.0)	3.6 (0.7 – 7.8)	4.3 (2.0 – 9.0)	
< 5 cm	60	31 (52%)	29 (48%)	0.48
5 –10 cm	20	9 (45%)	11 (55%)	
Mitotic Rate (per 50 HPF)				
< 5	62	34 (55%)	28 (45%)	
5 –10	7	4 (57%)	3 (43%)	0.84
>10	3	1 (33%)	2 (67%)	
Tumor sub-type				
Epitheloid	5	4 (80%)	1 (20%)	1.00
Spindle	47	27 (57%)	20 (43%)	
Mixed	2	0 (0%)	2 (100%)	
Location of primary				
Fundus	10	7 (70%)	3 (30%)	0.40
Body/Antrum	69	32 (46%)	37 (54%)	
Pylorus	1	1 (100%)	0 (0%)	
Lesser curvature	22	12 (55%)	10 (45%)	0.62

* p-value is based on conditional logistic regression

Table 2

Operative characteristics and peri-operative outcomes

Variables	Surgery Type			p-value*
	All N=80	Lap N=40	Open N=40	
Gastrectomy				
Wedge†	78	40 (51%)	38 (49%)	0.99
Distal	2	0 (0%)	2 (100%)	
OR Time				
Median minutes (range)	90 (30 – 249)	100 (48 – 200)	89 (30 – 249)	0.32
Estimated Blood Loss				
Median mL (range)	50 (5 – 400)	25 (5 – 200)	100 (5 – 400)	0.006
Length of Hospital Stay				
Median days (range)	5 (2–25)	4.0 (2 – 7)	7 (4 – 25)	0.002
Complications				
Minor (grade 1 or 2)	12	4 (33%)	8 (67%)	1.0
Major (grade 3)	4	2 (50%)	2 (50%)	

*p-value is based on conditional logistic regression

†1 sleeve gastrectomy in open group

Table 3

Adjuvant treatment and oncologic outcomes for laparoscopic versus open (GIST) resections

Variables	Surgery Type			p-value
	All (N=80)	Lap (N=40)	Open (N=40)	
Chemotherapy				
None	74	37 (93%)	37 (93%)	
Adjuvant (imatinib)	5	3 (60%)	2 (40%)	0.91
Neoadjuvant and adjuvant	1	0 (0%)	1 (100%)	
Margins Status				---
-Gross − Micro	79	39 (49%)	40 (50%)	
-Gross +Micro	0	0	0	
-Gross close (<0.1 cm) Micro	1	1 (1%)	0	
Recurrences				
Metastatic	2	1	1	---
Survival Status				
Alive and Recurrence Free	72	36	36	
Alive with Disease	2	1	1	---
Died of Other Causes	4	2	2	
Died of Unknown Causes	2	1	1	

Table 4

Pathologic, operative, and peri-operative characteristics of laparoscopic converted to open resections

Variable	N=9 patients
Size	
Median cm (range)	4.2 (3–5.9)
Tumor Location	
GE jxn/cardia	3
Fundus	2
Body/Greater Curvature	2
Lesser curve	2
OR Time	139 (78–205)
Median minutes (range)	
Estimated Blood Loss	100 (0–150)
Median mL (range)	
Length of Hospital stay	4 (4–8)
Median days (range)	
Reasons for conversion	
Location	6
Size	3
Technical factors	3
Incidental findings *	1

* In one patient, a large ventral hernia was identified on laparoscopy.