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Laparoscopic resection of gastrointestinal stromal tumors: Does laparoscopic surgery provide an adequate oncologic resection?

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of the GI tract. Surgical resection remains the mainstay of non-metastatic disease. However, the ability to provide an adequate oncologic resection using laparoscopic surgery is still an area of debate. This is a thorough review of the current literature, looking particularly at the use of laparoscopic surgery for larger GISTs and the long-term oncologic outcomes compared to the results of open surgery. Laparoscopic resections provide an adequate oncologic result for GISTs of all sizes, including those greater than 5 cm in size.

Key words: Gastrointestinal stromal tumors; Oncologic; Laparoscopy; Surgery

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Core tip: Laparoscopy is now increasingly being used in cases of gastrointestinal stromal tumors (GISTs). While technically possible to resect these tumors laparoscopically, there has been concern that the oncologic outcomes for these patients could be compromised for tumors greater than 5 cm in size. This review, summarizing the data from several studies, demonstrates that a proper oncologic resection can be achieved laparoscopically, even for larger GISTs.

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Abstract

Gastrointestinal stromal tumors (GISTs) are rare tumors

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are rare tu-

mors of the gastrointestinal (GI) tract but are the most common type of mesenchymal tumor found in the GI tract. They account for between 0.1% to 3% of gastrointestinal malignancies with an incidence of 14 to 20 cases per 1 million of the general population per year^[1-4]. Treatment has not been standardized; however, surgical resection remains the mainstay for non-metastatic GISTs. Furthermore, the use of minimally invasive techniques has been widely debated. Because of the low incidence of GISTs, published reports have been primarily limited to case reports and retrospective observational studies with no good randomized controlled trials encountered in the literature. This review examines the efficacy of laparoscopic surgery to achieve a proper oncologic resection for GISTs as compared to open while looking at different factors such as the biology, location and size of these tumors.

BIOLOGY OF GIST

The term GIST was originally coined by Mazur and Clark^[5] in 1983 and became more frequently diagnosed around the turn of the century. GISTs were historically classified as leiomyomas, leiomyosarcomas, or leiomyoblastomas but with advancements in immunohistochemistry and the discovery of the tyrosine kinase KIT, GIST tumors have been identified as a separate entity from leiomyomas and its diagnosis has increased 25-fold^[1].

GISTs are equally distributed between men and women. While they have been found in patients of all ages, the majority are found in patients between the ages of 40 and 70 with the median age of diagnosis between 60 and 65 years of age^[6-8]. GISTs can be found throughout the GI tract with the most common location in the stomach (60%-70%), followed by the small intestine (20%-30%), duodenum (4%-5%), rectum (4%-5%), colon (< 2%), esophagus (< 1%)^[3,7,9-11]. They are found and even more rarely outside the GI tract, including the mesentery, omentum, and retroperitoneum.

Originating from the interstitial cell of Cajal, the majority (70%-85%) of GISTs are associated with mutations in the c-KIT pathway and stain positively for CD117. The second most common mutation seen (approximately 10%) is with *PDGFRA* and the two gene mutations are mutually exclusive. Through these mutations, abnormally oncologic signaling is promoted through the mitogen-activated protein kinase (MAPK) and phosphoinositide-3-kinase (PI3K) pathways^[11]. In general, these tumors do not spread *via* submucosal invasion or lymphatics. Rather, their spread is mostly expansive and the main routes of metastasis are hematogenous. Chromosomal abnormalities in GISTs that have been associated with malignant progression include deletions on 14q, 22q, 1p, and 9p and gains on chromosomes 8q and 17q^[11]. Tumors associated with these alterations are likely to be metastatic in nature and less amenable to resection, either open or

laparoscopic at time of surgery.

DIAGNOSIS OF GISTS

The presentation of a patient with a GIST can be quite variable, based on its location and size. The most common presentation is a GI bleed followed by abdominal pain. These GI bleeds are more often chronic than acute. Other rarer symptoms and signs include anemia, a palpable mass, dysphagia, obstruction, or weight loss^[12]. However, a significant number are discovered incidentally on imaging performed for other reasons.

In a review of diagnostic modalities, Scarpa *et al.*^[12] proposed endoscopy as the first diagnostic tool in the algorithm to diagnose a GIST. On pooled analysis, endoscopy with mucosal biopsy, however, had a diagnostic yield of 33.8%. This is not surprising, given the submucosal nature of GISTs. The diagnostic yields of computed tomography (CT) and magnetic resonance imaging (MRI) were both much higher, at 73.6% and 91.7% respectively ($P = 0.07$). Between the two, CT is usually the first non-invasive imaging modality used due to its cost, ubiquity, and consistency. On CT, a GIST usually enhances with intravenous contrast and has smooth contours. While most GISTs appear solid, larger GISTs can develop areas of necrosis or hemorrhage and appear more complex. CT can also evaluate the abdomen for metastatic disease. MRI can be used as an adjunct if the mass is large and abutting other structures, as it may better demonstrate planes of dissection.

While CT and MRI have excellent diagnostic yields, the most definitive diagnosis can be obtained using an endoscopic ultrasound with fine needle aspiration (EUS-FNA). The diagnostic yield of simple EUS was 68.7%, which was significantly improved with the addition of an FNA during the procedure (84.0%) ($P = 0.01$)^[12]. If there is a high suspicion for GIST based on CT or MRI, and the lesion appears resectable, a tissue diagnosis is not required. However, a biopsy can be used to confirm the diagnosis if there appears to be metastatic disease or in large, locally advanced lesions that may benefit from preoperative treatment with imatinib.

LAPAROSCOPIC RESECTION OF GISTS

Historical perspective

The multidisciplinary management of GIST has changed over time. With further research into the molecular biology of these tumors, there has been development of better treatments for advanced GISTs, including imatinib and newer therapeutic agents such as sunitinib and regorafenib^[1,13-15]. Despite these advancements, the accepted management of non-metastatic GIST remains surgical resection.

The advent of minimally invasive surgery has affected how many procedures are being performed. With the generalized advantages of decreased pain, shorter

hospital stay and faster recovery to normal activity, laparoscopic surgery is fast becoming the standard of care for many procedures. One area of contention with minimally invasive surgery is its use in oncologic procedures. There has been extensive research in colon cancer that has shown that a laparoscopic approach can be safe and produce a safe oncologic margin. Similarly, lung cancers are routinely resected thoracoscopically. In other cases, such as low rectal cancer requiring abdominoperineal resection, the debate still continues whether a laparoscopic approach is as efficacious and provides as good an oncologic result as an open procedure. Because GISTs are a relatively newly identified entity and a rare neoplasm, there has been little consensus on the role of minimally invasive techniques in their resection.

Unresectable and metastatic GISTs are usually very aggressive and often fatal with a median survival of approximately 6-18 mo^[16]. In 2002, Fletcher *et al.*^[17] proposed a risk stratification classification for recurrence based on tumor size, mitotic rate, and tumor location. This was updated in 2006 by Miettinen *et al.*^[18] and accepted by the National Comprehensive Cancer Network (NCCN) Task Force report in 2010^[19]. Because chemotherapy and radiotherapy are ineffective in treating GISTs, imatinib is the only approved agent for unresectable/metastatic GIST at this time. With the poor prognosis of metastatic and recurrent GISTs, it is vital that a good oncologic procedure be completed at the time of resection.

The surgical management of GIST has changed significantly since Lukaszczuk and Preletz^[20] reported the first laparoscopic removal of a gastric GIST found incidentally during a cholecystectomy. Since then, others have explored the use of laparoscopy for GIST removal. Although there is still no consensus on the role of minimally invasive techniques in their resection, the biological behavior of these tumors lend themselves to laparoscopic resection. Because submucosal and lymphatic invasion is rare, local excision rather than formal organ resection has become the treatment of choice for GISTs which allows laparoscopic resection to be an attractive alternative to more invasive conventional surgery. Historically, wide resection margins were advocated but there has been no correlation with improved survival or recurrence^[21]. Therefore, wide margins and lymph node dissections are not necessary. The consensus is that a negative gross surgical margin is the important factor in decreasing the risk of local recurrence and metastatic spread of GISTs.

However, in 2004 the National Comprehensive Cancer Network and The European Society of Medical Oncology released consensus statements recommending that the use of laparoscopy be limited for GISTs less than 2 cm in size due to concerns of tumor rupture and seeding of the peritoneum and the ability to achieve an adequate oncologic margin^[19,22]. Despite these concerns, surgeons continued to resect GISTs laparoscopically with excellent results which resulted

in the NCCN updating their recommendations in their Task Force Report of 2010 to include GISTs up to 5 cm as acceptable for laparoscopic resection^[9]. The surgical management of GIST resection is based on the principles of maintaining an intact capsule to prevent tumor spillage and obtaining a negative margin to ensure complete excision of localized disease^[23].

LOCATION OF GISTs

GISTs are most frequently located in the stomach followed by the small bowel. The most frequently cited comparison studies between laparoscopic and open GIST resections were for gastric tumors. These papers identified several laparoscopic techniques for resection for these gastric tumors. They ranged from laparoscopic wedge resections, trans-gastric tumor-everting resection, and distal and proximal gastrectomies depending on the size and location of the tumors with appropriate reconstruction. Depending on the size and location of the tumor, endoscopy may be required to identify the location of the tumor intraoperatively. This is particularly true for smaller GISTs which may not be able to be easily identified grossly from outside the gastric lumen. Shu *et al.*^[24] showed that in their comparison study, operative time and complication rates between open and laparoscopic procedures were comparable while overall time to bowel function and hospital stay were significantly longer in the open group. These findings were confirmed in a more recent meta-analysis which included 17 studies and over 700 patients looking specifically at laparoscopic vs open techniques for gastric GIST resections. The study showed that complication rates and operative times were no different, but times to first flatus, oral intake and hospital stay were all significantly different in favor of the laparoscopic group. From an oncologic perspective, the recurrence rates between the laparoscopic group and the open group were not significantly different^[25]. Koh *et al.*^[26] found similar results in their meta-analysis with shorter times to flatus and oral intake and shorter hospital stays for the laparoscopic resections while finding no differences in margin positivity, local recurrence rates, recurrence free survival and overall survival when comparing laparoscopic to open resections.

GISTs located in the small bowel are less frequently identified and similarly are less frequently cited in the literature. Due to the location though, there are several techniques that can be used to resect and reconstruct the small bowel. These can range from any combination of resecting and re-anastomosing the small bowel intracorporeally or extracorporeally as well as with any combination of stapler and suture^[27]. In addition, the re-anastomosis can be performed in either a side-to-side or isoperistaltic fashion. There are many factors involved with these surgical decisions including the size of the tumor, the location of the tumor within the small bowel, body habitus of the patient, as well as technical

proficiency with intracorporeal techniques. Several studies have shown that presentation of small bowel GISTs are more likely to be gastrointestinal bleeding as compared to gastric GISTs. Although endoscopy is often unable to be performed for these small bowel tumors, it is usually unnecessary as these tumors grow outwards from the intestinal lumen and rarely cause obstruction. In one of the few studies comparing laparoscopic compared to open resection of GISTs in the small bowel, the results were similar to those seen with gastric GISTs. Operative time and complication rates were similar, yet time to bowel function and hospital stay were significantly different with shorter times in favor of the laparoscopic group^[28]. Another study comparing laparoscopic vs open resection for small bowel GISTs up to 10 cm in size indicated that operative times and length of stay were shorter for the laparoscopic group while complications rates were similar. Additionally, there was no difference found in overall survival and recurrence-free survival between the two groups, concluding that laparoscopic resection was safe for these small bowel GISTs^[29].

While the use of laparoscopy for resection for GISTs in the rectum has been limited, Fujimoto *et al.*^[30] published a series of five patient who underwent laparoscopic sphincter-preserving surgery for rectal GISTs after having received neoadjuvant imatinib. All had significant decreased in tumor size with imatinib and all were resected with negative margins. All five were recurrence free at a mean follow-up time of 36 mo, demonstrating that these cases can be performed safely laparoscopically.

SIZE OF GISTs

One of the primary benefits of laparoscopy is in using small incisions and thereby foregoing the pain and morbidity associated with a large laparotomy incision. Unfortunately, the size of the tumor dictates the length of the incision of the extraction site and as can be imagined, the larger the tumor is, the less the incision is able to be minimized. In addition, the larger the tumor, the more unwieldy it becomes to manipulate with the laparoscopic instruments and the danger of tumor capsule rupture increases. Because of these concerns, currently the NCCN guidelines advocate for the use of laparoscopy for GISTs less than 5 cm in size.

In one of the first major series of laparoscopic GIST resections, Nguyen *et al.*^[27] showed that laparoscopic resection for larger GISTs were possible. The series consisted of 43 patients with the average size of the resected gastric GIST was 4.6 cm and resected small bowel GIST was 3.7 cm. Since then, there have been several other studies that looked at tumors greater than 5 cm that were laparoscopically resected with good results including a 20 cm GIST by Sokolich^[29,31-37]. Additionally, Kim *et al.*^[38] reviewed 24 patients that underwent laparoscopic gastric resections for GISTs ranging from 5-10 cm in size. They had no incidence

of capsular rupture and had similar operative and complication rates as compared to open surgery.

ROLE OF NEOADJUVANT THERAPY

The American College of Surgical Oncology group in 2009^[13] showed that adjuvant imatinib after resection significantly improved recurrence free survival compared to placebo leading to the FDA approving imatinib for adjuvant therapy. Others studies have confirmed the effectiveness of imatinib for adjuvant therapy in certain populations^[39,40]. The use of imatinib for neoadjuvant therapy was recommended by the NCCN^[41] for patients in whom cytoreduction would be beneficial including marginally resectable tumors and tumors that would lead to significant surgical morbidity.

Studies have since shown the effectiveness of neoadjuvant therapy with imatinib, resulting in dramatic reduction in tumor size and rendering locally advanced or previously unresectable tumors to be resected with decreased morbidity for the patients^[42,43]. The use of minimally invasive techniques after neoadjuvant therapy has not been well studied. While these trials were based on open resections, there have been case reports and case series where laparoscopic resections were successful. Cavaliere *et al.*^[44] reported a patient with an approximately 10 cm × 15 cm perigastric GIST that underwent 12 mo of neoadjuvant imatinib. The treatment resulted in a greater than 50% reduction in diameter, allowing laparoscopic resection with negative margins and disease free survival at 12 mo. Pandey *et al.*^[45] reported a 5.5 cm × 4.5 cm gastric GIST the decreased in size to a 3.3 cm × 3 cm and was then resected laparoscopically with no evidence of recurrence at 18 mo. Similarly, Cao *et al.*^[46] reported a patient with a 10 cm × 15 cm gastric GIST with three liver metastases that underwent six months of neoadjuvant imatinib with a greater than 50% reduction in the tumor burden. He then had a successful laparoscopic resection of both the gastric GIST and the liver metastases with 11 mo of disease free survival. Fujimoto *et al.*^[30] reports a five-patient case series of patients with rectal GIST that underwent 4-12 mo of neoadjuvant imatinib prior to successful laparoscopic sphincter-preserving surgery. All tumors were initially thought to require an abdominoperineal resection or other extended surgery which would result in a permanent stoma. At a median follow-up of 36 mo, all diverting ostomies had been reversed with maintenance of bowel continence and no evidence of recurrence. While there is not a lot of data yet, it appears that there is a role for laparoscopic surgery after neoadjuvant imatinib therapy.

REVIEW OF LITERATURE

We reviewed 32 independent case series which were all observational studies reviewing outcomes of laparoscopic GIST resections with or without a comparison group that had undergone open resection. This

Table 1 Review of case series

	All cases included		Study period 2000 onward		Follow-up 24+ mo	
	LAP	OPEN	LAP	OPEN	LAP	OPEN
Total	1062	811	478	463	818	691
Conversion to OPEN	6.03% (64)	-	6.07% (29)	-	6.11% (50)	-
Complications	6.78% (72)	18.74% (152)	6.90% (33)	21.60% (100)	6.85% (56)	20.84% (144)
Mean/median size	2.7-6.1 cm ¹	3.15-9.2 cm	2.7-5.5 cm ¹	3.15-9.2 cm	2.7-6.1 cm ¹	3.15-9.2 cm
Follow-up	8-74 mo	18-91 mo	8-41 mo	21-91 mo	24-74 mo	36-91 mo
Margin positive	0.66% (7)	5.92% (48)	0.42% (2)	3.46% (16)	0.61% (6)	6.08% (42)
Recurrence	3.24% (31) ²	7.16% (50) ³	2.74% (11) ⁴	4.80% (19) ⁵	3.52% (25) ⁶	7.61% (44) ⁷
GIST-related mortality	0.85% (9)	3.33% (27)	0.42% (2)	0.86% (4)	0.86% (7)	3.91% (27)

¹Not including series of 4 patients and series where all tumors 2-5 cm (means not included); ²Out of 958 cases; ³Out of 698 cases; ⁴Out of 401 cases; ⁵Out of 396 cases; ⁶Out of 710 cases; ⁷Out of 578 cases. Summary of the experience of 32 independent case series: All the studies were observational studies reviewing outcomes of laparoscopic gastrointestinal stromal tumor resections, with or without a comparison group that had undergone open resection. This compilation amounted to 1873 cases, 1062 of which were laparoscopic^[4,24,26,28,29,31-38,47-49,51-67]. LAP: Laparoscopic; OPEN: Open surgery.

compilation amounted to 1873 cases, 1062 of which were laparoscopic. The analyzed data is compiled in Table 1.

Regarding size of the GISTs resected, the range of the mean/median for the laparoscopic (LAP) cases was 2.7-6.1 cm while the resections by conventional open surgery (OPEN) was 3.15-9.2 cm. These ranges did not include an observational series of 4 laparoscopic cases where the mean size was 10 cm (including a 20 cm GIST) and one laparoscopic series of 37 where only masses between 2-5 cm were resected and the mean/median size was not reported.

The conversion rate from a laparoscopic to an open procedure was 6.03% (64 cases) and the complication rate was 6.78% in the LAP group and 18.74% in the OPEN group. The margins were positive on the pathology in 0.66% of the LAP cases and 5.92% of the OPEN cases. The range of mean/median follow-up periods was 8-74 mo for the LAP group and 18-91 mo for the OPEN group with a 3.24% recurrence rate in the LAP group compared to 7.16% in the OPEN group. Overall, the GIST-related mortality was approximately 0.85% for the LAP group and 3.33% for the OPEN group.

Subgroup analysis was done on those studies that started in 2000 or later. The rationale for this was to see if there was a trend towards better laparoscopic results due to the further experience and knowledge of working with GISTs since the original laparoscopic resection in 1992. A total of 941 cases (478 LAP, 463 OPEN) were included in this subgroup. The conversion rate was similar (6.07%) as were the complication rates for the LAP (6.9%) and OPEN (21.6%) groups. The rate of positive margins was slightly lower for the LAP group (0.42%) compared to the entire LAP cohort (0.66%). Similar trend was seen in the recurrence rate (2.74%) and GIST-related mortality (0.42%) for LAP group.

A subgroup analysis was performed looking at those studies that had a mean/median follow-up of 24 mo or greater. A total of 1509 cases (818 LAP, 691 OPEN) were included in this subgroup. The conversion rate was

similar (6.11%) as were the complication rates for the LAP (6.85%) and OPEN (20.84%) groups. The rate of positive margins was approximately the same in the LAP group (0.61%) compared to the entire LAP cohort (0.66%). The recurrence rate was similar (3.52%) when compared to the entire LAP cohort (3.23%) and the GIST-related mortality was the same (0.86% vs 0.85%).

In addition, many studies have shown the benefits of laparoscopic resection over open resection with benefits including decreased operative blood loss, decreased postoperative pain, shorter length of hospital stay, and better quality of life after operation^[35,47,48]. This data shows that the complication rate is significantly lower in the LAP group (6.78%) compared to the OPEN group (18.74%). Therefore, from a recovery standpoint, laparoscopic surgery appears to be superior to open surgery.

The data demonstrated that the ability to obtain negative margins (0.66% positive margin) is not compromised with the use of laparoscopic surgery. Furthermore, the recurrence rate (3.24%) is superior compared to open cases (5.92%). However, this finding may be biased by the selection process for choosing between open and laparoscopic resection. None of the studies are randomized control trials, so the surgeons decided which tumors to resect laparoscopically. In all the series, the mean/median size of those that had undergone laparoscopic resection was smaller than those that had undergone open procedures. In many studies the size difference was not found to be significantly different, but the trend is certainly noticeable. In most studies, there was a trend towards the OPEN group having a higher risk stratification than the LAP group. This could also account for the difference in GIST-related mortality (0.85% LAP vs 3.33% OPEN). However, Karakousis *et al*^[47] and Lee *et al*^[49] reported size-matched comparisons of patients with gastric GIST and demonstrated that there was no difference in the efficacy of the oncologic resection (margin, recurrence, overall and recurrence-free survival) while showing

that these patients had decreased operative blood loss, faster return of bowel function, and shorter hospital stay. Furthermore, there were no reports of spillage of tumor during the laparoscopic resections.

Most recurrences occur within the first two years after resection and the risk stratification should determine the course of follow-up^[50]. DeMatteo *et al.*^[21] reported a recurrence rate of approximately 30% in their series of 200 patients followed out to a median of 24 mo. Lee *et al.*^[49] reported a similar size-matched series comparing laparoscopic and open resections of submucosal tumors and found that the resections were oncologically equivalent. Some of the studies reviewed did not have sufficient follow-up beyond this 24 mo period during which most recurrences were seen. For this reason, a subgroup analysis was done of the studies that had a mean/median follow-up of at least 24 mo. This analysis showed that the recurrence rate (3.52%) was similar to the overall recurrence rate (3.24%) for laparoscopic resections and lower than the recurrence rate of open cases (7.16%) and the general recurrence rate reported in the literature overall.

A further subgroup analysis looked only at those studies whose enrollment was from 2000 onward in order to see if there was an improvement in conversion rate, obtaining a negative margin, and recurrence rate, given more experience with dealing with GISTs. We found that the conversion rate was the same (6.07% vs 6.03% overall) while obtaining a negative margin was slightly better (0.42% vs 0.66% overall). Also, there was a decrease in the recurrence rate for both laparoscopic (2.74% vs 3.24% overall) and open (4.80% vs 7.16% overall) resections. The GIST-related mortality rate was lower for both laparoscopic (0.42% vs 0.85% overall) and open (0.86% vs 3.33% overall) resections. These differences could be due to improvements in surgical technique and experience, but are more likely credited to advancements in non-surgical therapy (imatinib) and slightly shorter follow-up periods.

CONCLUSION

More comparison studies need to be performed but based on retrospective data, there appears to be no difference in terms of complications between open and laparoscopic resection of GISTs in either the stomach or small bowel. Our review strongly suggests that laparoscopic resection for GISTs provides a good oncologic result with rates equal or better than would be expected for open procedures when evaluating negative margins, recurrences, and GIST-related deaths. Also, the data suggests that laparoscopic resection is associated with lower rate of complications and short hospital stay. Ultimately, to conclusively show that laparoscopy is superior, randomized control trials are needed. However, due to the low incidence of this pathology, obtaining the proper number of participants would be difficult. Despite the current NCCN recommendations of open resection for GISTs > 5 cm, many published series have shown

laparoscopic surgery is feasible and can be efficacious in larger GISTs as long as the principles of oncologic resection are followed. The limiting factor is being able to manipulate large tumors without violating the capsule and being able to remove the tumor of significant size through a laparoscopic incision. Furthermore, the role of neoadjuvant imatinib for cytoreduction prior to laparoscopic resection appears to be promising but requires further investigation. Ultimately, the decision to resect using a laparoscopic or open technique is currently based on the surgeon preference and experience. However, the data shows that laparoscopic resection of almost all GISTs does provide an oncologic result similar to conventional open resection.

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