Gastrointestinal stromal tumour of stomach: Feasibility of laparoscopic resection in large lesions and its long-term outcomes

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Abstract

Background: Gastric gastrointestinal stromal tumours (GISTs) are rare neoplasms that require excision for cure. Although the feasibility of laparoscopic resection of smaller gastric GIST has been established, the feasibility and long-term efficacy of these techniques are unclear in larger lesions. This study is done to assess the feasibility of the laparoscopic resection of gastric GISTs and their long-term outcomes.

Methods: Patients who underwent laparoscopic resection of gastric GISTs were identified in a prospectively collected database. Outcome measures included patient demographics, operative findings, morbidity and histopathologic characteristics of the tumour. Patient and tumour characteristics were analysed to identify risk factors for tumour recurrence.

Results: There were 42 patients with a mean age of 56.7 years and had a mean tumour size was 4.5 ± 2.7 cm. Laparoscopic wedge resection was the most common procedure done. There were no major perioperative complications or mortalities. All lesions had negative resection margins. At a mean follow-up of 48 months, 36/39 (92.3%) patients were disease free and 3/39 (7.6%) had progressive disease. Univariate analysis showed that there was a statistically significant association of disease progression with tumour size, high mitotic index, tumour ulceration and tumour necrosis. The presence of > 10 mitotic figures/50 high-power field was an independent predictor of disease progression.

Conclusion: Our study establishes laparoscopic resection is feasible and safe in treating gastric GISTs for tumours > 5 cm size. The long-term disease-free survival in our study shows acceptable oncological results in comparison to historical open resections.

Keywords: Gastric gastrointestinal stromal tumours, laparoscopic wedge resection, submucosal tumours

INTRODUCTION

Among the mesenchymal tumours of GI tract, gastric gastrointestinal stromal tumours (GIST) are the most common types, accounting to up to 60% of GI GISTs.¹ Due to improved diagnostic modalities such as widespread availability of upper GI endoscopy and...
axial imaging modalities, there have been an increase in incidence/detection of these tumours. In 2002, in landmark article, Demetri et al. showed that the molecular target therapy, such as imatinib, a tyrosine kinase inhibitor as a promising treatment for advanced GIST. However, surgery remains the only potentially curative treatment of gastric GIST when complete resection can be achieved. In the treatment of GISTs, overall survival is determined mainly by the tumour size and mitotic index and not negative microscopic surgical margins. Since GIST rarely involves lymph nodes, local resection of GIST lesions with negative margins, including both wedge and submucosal resections are well-accepted modalities of surgery. Endoscopic treatment of small gastric GIST (<3 cm) such as endoscopic submucosal dissection (ESD), although have been reported, but remains controversial because of concerns of incomplete excision, tumour spillage and tumour perforation.

Open surgical resection was the standard of treatment until two decades ago, but with advent laparoscopy and experienced gained over the years, the safety and feasibility of laparoscopic resections of gastric GISTs has been proven but for tumours <2 cm. However, with a gain of experience and skill in laparoscopic surgery, many surgeons have reported a safety and feasibility excision of tumours >5 cm.

We present here, the decade long experience of managing gastric GIST and hypothesise that complete resection of gastric GISTs using a combination of laparoscopic, endoscopic and laparoendoscopic techniques even for larger lesions results in low perioperative morbidity and an effective long-term control of the disease.

METHODS

The clinical data from patients who underwent resection of gastric GIST by a laparoscopic approach, with the intent of curative surgery, was identified in a prospectively maintained database between January 2005 and July 2015, after getting approval from Institutional Review Board (approval number: Gem/2018/1157) and written informed consent from all the patients. Data collected included patient's age, sex, location of tumour, operative procedure, operative findings, morbidity and histopathologic characteristics of the tumour. Outcome measures studied include feasibility of laparoscopic resection in lesions larger than 2 cm, which is based on intraoperative tumour rupture and rate of conversion to open surgery and various patients, and tumour-related characteristics were analysed to identify risk factors for tumour recurrence. This work has been reported in line with the PROCESS criteria. All patients underwent pre-operative endoscopy for localising the tumour and abdominal computed tomography (CT) imaging for local and distant staging. Biopsy was done in select cases such as if pre-operative imatinib therapy is being considered to downstage the scope of surgery (e.g., from laparotomy to laparoscopy), for unresectable or marginally resectable tumours or if there is diagnostic dilemma with entities (e.g., lymphoma) that would be treated differently. Many times endoscopic biopsy may be negative for GIST due to intramural nature and in such cases targeted and deeper biopsy can be attempted with endoscopic ultrasonography (EUS)-guided fine-needle aspiration. Fletcher's criteria is used to classify (based on histopathology report) the patients into four-risk groups: very low-, low-, intermediate- and high-risk group.

Surgical approach

We have previously reported on technical details of resection of benign gastric lesions. Hence, the operative procedure is explained in brief here. After the induction of general anaesthesia, the patient was placed in the supine position with legs apart and reverse Trendelenburg position. With operating surgeon standing between the patient's legs and the camera surgeon and the operative assistant on the right side of the patient, with the scrub nurse on the left side of the patient and the monitor is placed behind the patient's head, pneumoperitoneum is created by Veress needle technique. We use five port technique with 10-mm trocar was placed in the supra-umbilical midline position for camera, two 5 mm right and left working ports are placed in the hypochondriac area in midclavicular line and a 5-mm liver retraction port in the subxiphoid area. Another 5-mm trocar in the left lumbar region is helpful for providing downwards traction on the stomach. Tumour location decides the approach used for resection. Therefore, a variety of options such as local resections, wedge resections, transgastric resections, intragastric resection and partial gastrectomies were performed. The tumour specimen was extracted through a small Pfannensteil incision in an endobag to avoid tumour spillage.

Laparoscopic gastric wedge resection

Most of the gastric GISTs could be visualised or palpated with laparoscopic instruments if they are located on the anterior side of the stomach, especially in the fundal area and in such cases, wedge resection was performed. Gastrocolic omentum divided using harmonic shears and proceeds along outside of the left gastroepiploic vascular arch. Next, the short gastric vessels are coagulated and
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cut with the harmonic scalpel, and the gastric fundus is completely separated from the superior pole of the spleen. Resection of the gastric fundus containing the tumour is done by firing an endocutters stapler (ECHELON FLEX™, Ethicon, CA, US) [Figure 1] and usually 2–3 sequential firings are required for enough margin in most of the cases. For tumours near oesophagogastric (OG) junction, caution is taken when the endocutter is being fired so as to ensure that the oesophagogastric junction was not involved to avoid post-operative oesophageal stenosis. Lesions near lesser curvature were resected with a margin of normal stomach using an ultrasonic scalpel or endocutter. Seromuscular dissection was done using an ultrasonic scalpel to incise the seromuscular layer at the lower edge of the tumour, and the tumour is lifted by grasping the incised seromuscular layer with atraumatic grasper. The tumour was then excised from the mucosa using the ultrasonic scalpel or endocutter stapler, and the mucosal integrity is checked and if the mucosa was penetrated, it was repaired with absorbable sutures [Figure 2].

**Transgastric resection**

When the endogenous tumour was located onto the posterior wall, an anterior gastrotomy is made exactly above the tumour, usually assisted by endoscopy and incise the full-thickness stomach wall containing the tumour along the long axis of the stomach. After tumour resection, the stomach wall was sutured with 3–0 absorbable suture vertically to the stomach long axis and closure of the anterior wall with a continuous suture.

**Laparoscopic intragastric submucosal dissection**

After localising the tumour with endoscopic assistance, a small anterior gastrotomy is made using the ultrasonic scalpel and a 12-mm optiview trocar (ENDOPATH XCEL® Trocars, Ethicon, CA, US) in the left upper abdomen was inserted into the stomach cavity and air was delivered into the cavity. Then, 30° lens was inserted through this 12-mm cannula to determine the location of the tumour and the puncture site for other accessory ports in the stomach wall. Once ports are placed, the mucosa at the edge of the tumour was then incised, and the tumour was excised from the submucosal layer using the ultrasonic scalpel. Dissection of the tumour was performed while the oesophagogastric junction was monitored with per-oral endoscopy [Figure 3]. The mucosal incision was sutured with 3–0 absorbable suture avoiding cardia stenosis caused by the sutures. A specimen bag is taken inside the stomach through ports, and the bag containing specimen is grasped with grasper and retrieved through abdominal wall. The specimen bag could also be removed by intraoperative gastroscopy if the specimen is smaller in size. Port sites in stomach suture closed with delayed absorbable sutures.
Post-operative care and follow-up
Post-operatively, nasogastric tubes were routinely used and
were removed after gastrograffin swallow was performed in
the morning of the first post-operative day and graduated
diets are allowed. Patients were discharged home after
tolerating a regular diet. Patients are advised for follow-up
visits at approximately 7 and 30 days after the surgery and
then every 6 months during the first 2-year period, and
then every year during the next 3-year period. Endoscopy
was performed every year for the first 5 years. For the
intermediate- and high-risk groups, CT abdomen is done
every 3 months for the first 2 years and then 6 monthly
for the next 3 years, in low-risk groups annual CT is done.
Most patients underwent close follow-up. However, three
patients were lost to follow-up. Follow-up was conducted
as outpatient visits or by telephone, and follow-up data
included adjunctive therapy, survival time, recurrence and
death.

Statistical analysis
Mean (±) along with standard deviation was used for
all quantitative data. Categorical variables are compared
using Chi-square test or Fischer’s exact test. A logistic
regression model was used for multivariate analysis. Value
for significance was set at \( P \leq 0.05 \). SPSS version 23 (IBM
Corp, Armonk, NY, US) statistical software was used for
analysis.

RESULTS
Between January 2005 and July 2015, 51 patients of
gastric GIST were evaluated, out of which 42 consecutive
patients underwent laparoscopic resection of gastric
GISTs with the mean age 56.70 ± 15.1 years (range,
23–79 years). Vague abdominal pain, dyspepsia and GI
bleeding were the most common symptoms. The mean
tumour size was 4.6 ± 2.7 cm (largest size operated is
12.5 cm) with most of the lesions located in the proximal
stomach [Table 1]. Laparoscopic wedge resection was
done for 21 patients [Table 2], laparoscopic transgastric
excision with endoscopic assistance (laparoendoscopic
excision) was used in 11 patients for tumours near
OG junction at posterior stomach wall. Laparoscopic
intragastric submucosal dissection was done in five
patients. Laparoscopic subtotal gastrectomy was done
in one patient having distal stomach obstructing large
lesion. Laparoscopic proximal gastrectomy was also
done in two patients having large tumour near OG
junction. In one patient having both sigmoid colon mass
and gastric GIST, laparoscopic anterior resection with
gastric wedge resection was performed. In two patients
with locally advanced GIST involving splenic vessels and
distal pancreas, laparoscopic distal gastrectomy with distal
pancreatecto-splenectomy was done.

The mean operative time was 110 ± 59 min (range,
50–310 min), the mean blood loss was 80 mL (range,
10–600 mL), and there were no episodes of tumour
rupture or spillage. There were no major intraoperative
complications such as tumour rupture, bleeding or bowel
injury. There were no conversions to open surgery. The
mean length of hospitalisation was 4.5 days (range,
2–12 days). We had no major perioperative complications
or mortality. There were no staple-line bleed or anastomotic
leaks post-operatively. All lesions had negative resection
margins (range, 2–40 mm). Four patients had five or more
mitotic figures/50 high-power fields (HPFs). According
to Fletcher’s criteria,[14] 26/42 (61.9%) cases were in the
low- or very low-risk group, 11/42 (26.2%) were in the
intermediate-risk group and 5/42 (11.9%) cases were
in the high-risk group. Patients of intermediate- and

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### Table 1: Distribution of gastric lesions

| Tumour location                  | Number of patients (%) |
|----------------------------------|------------------------|
| Proximal stomach                 |                        |
| GE junction including cardia     | 7 (16.6)               |
| Fundus                           | 9 (21.4)               |
| Gastric body                     |                        |
| Anterior wall                    | 5 (11.9)               |
| Posterior wall                   | 4 (9.5)                |
| Greater curve                    | 8 (19)                 |
| Lesser curve                     | 5 (11.9)               |
| Distal stomach                   |                        |
| Antrum                           | 3 (7.1)                |
| Pre-pyloric                      | 1 (2.3)                |

**GE:** Gastro-oesophageal

### Table 2: Various operative approaches used

| Type of resection                  | Number of patients, \( n \) (%) |
|------------------------------------|--------------------------------|
| Laparoscopic wedge resection       | 21 (50)                        |
| Laparoscopic transgastric excision | 11 (26.2)                      |
| Laparoscopic intragastric submucosal dissection | 5 (11.9)                  |
| Laparoscopic subtotal gastrectomy | 1 (2.4)                        |
| Laparoscopic proximal gastrectomy | 2 (4.8)                        |
| Laparoscopic distal gastrectomy with distal pancreatecto-splenectomy | 2 (4.8) |

### Table 3: Assessment of patient and tumour characteristics predictive of poor prognosis (disease recurrence)

| Patient/tumour characteristics | No recurrence, \( n \) (%) | Recurrence, \( n \) (%) | \( P \) |
|---------------------------------|---------------------------|------------------------|------|
| Number of patients              | 36                         | 3                      | NA   |
| Age (year)                      | 56.1                       | 65.3                   | 0.5  |
| Tumour size (cm)                | 4.3±2.3                    | 7.8±5                  | 0.02 |
| Mitotic index (mean)            | 4.6                        | 15                     | 0.003|
| CD117, \( n \) (%)              | 35 (97.2)                  | 3 (100)                | 0.9  |
| CD34, \( n \) (%)               | 36 (100)                   | 3 (100)                | 1    |
| Ulceration, \( n \) (%)         | 11 (28.9)                  | 3 (100)                | 0.0001|
| Necrosis, \( n \) (%)           | 8 (21)                     | 3 (100)                | 0.006|

**NA:** Not available
high-risk groups received adjuvant imatinib therapy of 400 mg/day. Follow-up of 39 patients was available, and at a mean follow-up of 48 months (range, 24–60 months), 36/39 (92.3%) patients were disease-free and 3/39 (7.6%) had a recurrence of disease (two cases from high-risk group and one from intermediate-risk group). Various factors such as patient characteristics (age and sex), tumour characteristics (location, size and resection margin) and microscopic (cellular markers, mitotic index, necrosis or ulceration) features were analysed as prognostic factors of disease progression [Table 3]. Univariate analysis showed that four of tumour characteristics such as tumour size (P = 0.02), high mitotic index (P = 0.003), tumour ulceration (P = 0.0001) and tumour necrosis (P = 0.006) have statistically significant association with disease progression. Patient sex, tumour location, resection margin and positive immunohistochemical markers were not associated with adverse prognosis. Multivariate analysis showed that the presence of >10 mitotic figures/50 HPF was an independent predictor of disease progression (P = 0.006).

DISCUSSION

The stomach is the most common site for GI GIST. Most of gastric GISTs are seen in proximal two-thirds of the stomach with the body of the stomach (51.2%) and fundus (22%) as most frequent site, followed by the cardia and oesophagogastric junction (17%) and antrypylorus (10%). Most GISTs are submucosal (60%) or subserosal (30%) and rarely intramural (10%). Most common symptoms of gastric GIST are vague abdominal pain (44%), upper GI bleeding (26.8%) and dyspepsia (14.6%), although other than blood loss, other symptoms were not truly related to the tumour.[18]

The primary GISTs area appears as a submucosal lesion with or without ulceration on endoscopic examination. Definitive diagnosis on endoscopic biopsy is challenging, since these tumours are submucosal or subserosal unless mucosal ulceration is seen. For resectable neoplasm, suspicious of GIST on CT scan and endoscopy, a pre-operative biopsy (EUS guided) is not routinely necessary, unless pre-operative therapy is required, which was done in four cases, of which two cases received neoadjuvant imatinib for 6 months and underwent resections later. We do EUS only in selected patients for lesions <1 cm planned for surveillance, to look for high-risk features on EUS (irregular border, cystic spaces, ulceration, echogenic foci and heterogeneity) or in whom. If any high-risk features are present, then the lesion is excised endoscopically using ESD. Four cases in this present study underwent ESD.

The presumptive diagnosis of GIST can be confirmed on pathologic analysis of tumour specimens. GISTS arise from the interstitial cells of Cajal which are present in the submucosa or muscularis propria layer of GI tract, and this origin can be identified immunohistochemically by expression of the c-kit oncogene, which encodes the tyrosine kinase receptor. CD117 (receptor tyrosine kinase and c-kit), CD34 and DOG1 (discovered on GIST-1) are key immunohistochemical markers to diagnose GIST.[3,17] More than 95% of GISTs have activating c-KIT mutations.[7,18] About 5% of GISTS lack CD117 expression. DOG1, a calcium-dependent receptor-activated chloride channel protein, is a more sensitive marker for GIST than KIT, detecting 36% of KIT-negative GISTs.[19] We routinely do CD117 and CD34 and DOG1 have been in the use for the last 3 years. Only one case in this study was CD 117 negative, however, it was positive for DOG1.

The treatment approach varies according to the size and location of the tumour. Management of GISTs <2 cm is still debated. In an autopsy study by Kawanowa et al., microscopic GISTs are present in 35 of the 100 whole stomachs, concluding that only a few microscopic GISTs may grow into a clinical size with malignant potential[20] and another study from Japan, showed that microscopic gastric GISTs were found in 35% of patients undergoing gastrectomy for gastric cancer.[21] Few seem to become clinically relevant, thus management of these small tumours is uncertain. We excise all nodules ≥2 cm size as should any smaller GISTs that are symptomatic (e.g., GI bleeding) or increase in size on follow-up. Those submucosal lesions <1 cm in size, having no features of high risk on EUS (heterogeneity, irregular border, ulceration, cystic spaces and echogenic foci) are followed up as per the surveillance protocol. In the present study, two cases had increase in size on follow-up surveillance, which underwent excision. Although for potentially resectable GISTs, surgical excision is the treatment of choice, but sometimes, neoadjuvant therapy with imatinib may be preferred if a tumour is borderline resectable or if resection would involve multi-organ resection. Routine lymphadenectomy is not required as nodal spread is rare.[22] DeMatteo et al.[3] demonstrated that tumour size and not negative microscopic surgical margins determines survival, so therefore it is accepted that the surgical goal should be a complete resection with gross-negative margins only without any lymphadenectomy.[3,23] As a result, wedge resection has been accepted for the majority of gastric GISTs if feasible.[3,23,24] In this study, all cases underwent laparoscopic surgery, especially the tumours in the fundus, greater curvature in the body of the stomach and diagnostic intraoperative endoscopy was used when
it was difficult to localise the tumour externally. In our centre, when the tumours are located near OG junction or on posterior wall, we prefer transgastric (for larger tumour) or intragastric (for smaller tumour) approach where we dissect the tumour in the submucosal plane and use linear endocutter stapler for excision or incise the tumour in submucosal plane and suture close the gastric wall with absorbable material, and this step is assisted with endoscopic guidance to avoid narrowing of OG junction. When the tumour is in distal stomach, near the antrum or pylorus, local excision through gastric cavity can be attempted if there is a clear tumour boundary with submucosal plane; however, larger tumours usually require partial gastrectomy such as distal/subtotal gastrectomy as occurred in five patients in this study. All these resections were accomplished with minimal morbidity, no perioperative mortality and short post-operative stay. Five patients who had intermediate- and high-risk features on final histopathology report (at least one of the following: tumour diameter >10 cm, mitotic count >10/50 HPFs, tumour diameter >5 cm and mitotic count >5/50 HPFs or tumour rupture before or at surgery) were treated with adjuvant imatinib 400 mg daily for 3 years based on several trials that have evaluated the impact of duration of post-operative imatinib on recurrence-free survival. In this study, we had three recurrences of which one patient had a local recurrence with the involvement of adjacent pancreas with vascular encasement, one patient had multiple liver metastasis and one patient widespread metastatic disease (lung and peritoneal) and all three cases were given imatinib therapy. There were no port site recurrences have been reported till date.

With increasing experience in foregut surgeries such as fundoplication, gastric bypass and availability of good energy sources, aided with reliable laparoscopic staplers, widespread availability of endoscopy and the laparoscopic approach appears very appealing for gastric GISTs. However, techniques used must avoid direct handling of tumours with laparoscopic instruments to eliminate the incidence of tumour rupture, as tumour rupture or spillage is one of the poor prognostic markers associated with disease recurrence, progression and poor survival. In this study, there were no incidences of operative rupture or tumour spillage. Various studies have shown reliability and safety of laparoscopic method. Although operative time is not much longer than with open surgery, laparoscopic surgery carries all the advantage of minimally invasive surgery such as that of less post-operative pain, earlier oral feeding and shorter hospital stay. The mean duration of the post-operative hospital stay in this study was 4.5 days (range, 2–12), similar to that in many reports. Novitsky YW et al in their study performed 50 cases of laparoscopic gastric GIST resections (tumour size range, 1–8.5 cm), all having negative resection margins and at a mean follow-up of 3 years, found 92% of patients were disease free. Recent larger studies show no oncologic difference between laparoscopic versus open resection of gastric GISTs and report shorter hospital stays and low morbidity associated with laparoscopic resection. Otani et al reported a series of 35 cases of laparoscopic excision of gastric GISTs (2–5 cm) with a median follow-up of 53 months and found no local or distant recurrences. We have previously presented a series of laparoscopic resections of benign gastric tumours which had four cases of gastric GISTs with size ranges from 2 cm to 6 cm. The data demonstrated a reduction in blood loss and hospital stay in the laparoscopic group. The guidelines recommend laparoscopic surgery for small GIST <5 cm when it is in a favourable location. This current study demonstrates the feasibility of the laparoscopic approach even with tumour size range up to 12 cm; however, the subgroup analysis shows the recurrence rates are more for tumour ≥7.8 ± 5 cm, as well the high mitotic index, tumour ulceration and tumour necrosis are a statistically significant factors associated with disease progression. However, size alone is not a parameter to consider for selecting the approach (open/lap), it also requires considerable expertise for safe manipulation of the tumour. Further high-quality studies are needed to come to conclusive decisions. To our knowledge, this is the largest series on laparoscopic management of gastric GIST from the Indian subcontinent. This study has its own limitations being a retrospective nature and a relatively small sample size limit the scope of our analysis; however, the outcomes of this study would help to add some evidence to the present pool of growing literature on surgical management of gastric GIST.

**CONCLUSION**

The present study indicates that laparoscopic approach should be considered in all patients with gastric GISTs irrespective of their location, who have no contraindications to this approach. Long-term survival was mainly associated with tumour stage and type, and laparoscopic surgery did not increase the risk of tumour relapse and metastasis. The low morbidity, no conversion to open surgery and the long-term disease-free interval observed in this study indicate that laparoscopic resection is safe and effective for gastric GISTs even for larger lesions.

**Financial support and sponsorship**

Nil.
Conflicts of interest
There are no conflicts of interest.

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