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Minimally Invasive Resection of Large Gastric Gastrointestinal Stromal Tumors

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Keywords
Gastrointestinal stromal tumors · Laparoscopic surgery · Morbidity · Cohort study

Abstract
Introduction: Gastrointestinal stromal tumors (GISTs) frequently present as a large exophytically growing mass in the stomach, for which open partial gastrectomy is standard of care. The aim of this study was to evaluate the safety and feasibility of minimally invasive gastric resection (MIG) of large (>5 cm) GIST. ***Methods:*** All patients who underwent MIG for a GIST in the University Medical Center Utrecht between 2011 and 2019 were included. Postoperative course and oncological outcomes were analyzed. ***Results:*** Twenty-two patients with gastric GIST, median size 53 mm [20–175 mm], underwent MIG. In 4 patients, preoperative imatinib was given, aiming for tumor regression. Conversion from laparoscopic to open surgery occurred once (5%). An additional resection was performed in 3 patients (14%). In 2 patients (9%), an intraoperative complication occurred, consisting of tumor rupture in 1 patient (5%), and 6 patients (27%) developed postoperative complications. Median hospital stay was 5 days [3–7 days]. R0 resection was achieved in 96%. In 4 patients, adjuvant treatment was indicated. The median follow-up was 31 months, and 1-, 3- and 5-year disease-free survival were 94, 74 and 74%, respectively. One patient presented with local recurrence 2 years after the index resection. ***Conclusion:*** MIG for large GIST up to 17.5 cm in diameter is safe, feasible, and oncologically sound, allowing for a controlled resection and reduced patient morbidity.

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common type of mesenchymal tumors in the gastrointestinal tract [1] and most frequently occur in the stomach (50–60%), followed by the small intestines (20–30%) and rectum (10%) [2]. In the Netherlands, gastric GIST has had an annual incidence of 130 cases for the entire population (17 million) but appears to be increasing [3]. Radical surgical resection with prevention of rupture is the cornerstone of curative treatment for GIST ≥2 cm [4, 5].

Minimally invasive gastric surgery (MIG) has gained popularity in surgical oncology since it embraces benefits such as reduced postoperative morbidity and shorter length of hospital stay [6, 7]. In addition, since MIG appears to cause less operative trauma compared to traditional open surgery, more frail patients may be considered for resection. However, previously reported contraindications for MIG are tumor size, invasion into adjacent organs, and a tumor near the gastroesophageal

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junction [1, 8]. Opinions differ on whether MIG is feasible and safe for "large" GIST (those exceeding 5 cm in size). To date, guidelines advise that GIST exceeding 5 cm in size should only be treated by open resection [5]. Few studies report on laparoscopic resection being superior to open surgery for gastric GIST [1, 9–11]. However, most of these studies were conducted in an Asian population with different patient and tumor characteristics, such as lower BMI and smaller sized tumors, compared to the Western population. Consequently, the aim of this study was to evaluate the safety and feasibility of MIG for large gastric GIST in a Western population.

Materials and Methods

Study Population

This descriptive, single-center, retrospective study included all patients who underwent MIG for a GIST between January 2011 and December 2019 from the University Medical Center Utrecht (UMC Utrecht). In the regional Comprehensive Cancer Network Utrecht (population: 1.2 million), surgical treatment of upper gastrointestinal tumors is centralized in the UMC Utrecht, and approximately 130 upper gastrointestinal cancer patients are operated annually, varying from wedge resections of GIST to robot-assisted minimally invasive thoracolaparoscopic esophagectomy. Since 2006, MIG is the standard procedure for gastric GIST in the UMC Utrecht.

Patients were diagnosed via gastroscopy with biopsies or EUS with fine needle aspiration and CT of the thorax and abdomen. If indicated, preoperative treatment with imatinib was given, and surgical wedge resection or partial gastrectomy was performed. No lymphadenectomy was performed, since gastric GISTs have a very low risk of dissemination to the lymph nodes [1, 5, 8, 9]. Data on all upper gastrointestinal procedures were prospectively registered in the Upper-GI database of the Department of Surgery. The resection specimens were collected from the pathology archives and re-evaluated by an experienced gastrointestinal pathologist (L.A.A.B.) to reassess pathological characteristics. In case of a high-grade tumors with high risk of progressive disease according to the NCCN Guidelines, adjuvant imatinib was given [5]. According to the Medical Ethical Committee and the Medical Research Involving Human Subjects Act (WMO), informed consent requirement was waived.

Surgical Techniques

All patients were positioned in the supine position. A 12-mm balloon trocar was placed and 4 additional ports were used: 2 working ports (each 5 mm), an assisting port (5 mm), and a port through which the liver retractor could be introduced (12 mm). The lesser omentum was opened. Then, the tumor was located and approached carefully, and in case of a dorsally located tumor, the bursa was opened through the gastrocolic ligament. As preservation of the vagus nerve is important to achieve good functional outcome, these were preserved. If a wedge excision was sufficient, a local resection of the tumor was performed, using a barbed suture to close the defect anatomically. In case no hand-sewn anatomical reconstruction could be performed (e.g., in case of a tumor near the gastroesophageal junction), the EndoGIA (60 mm) was used to perform the wedge resection. In case of a tumor location near the gastroesophageal junction, a gastroduodenoscopy was used intraoperatively to assess the patency and diameter of the lumen. If a partial gastrectomy was necessary, this was performed laparoscopically as described previously [12]. The resected specimen was removed through a mini-laparotomy, which was intraoperatively infiltrated with bupivacaine and located according to the surgeon's insight. A ring wound retractor that enlarges the wound was used to extract large tumors. If required, a Roux-en-Y gastroenterostomy was created. Supplementary file (see online suppl. 1; see www.karger.com/doi/10.1159/000510386 for all online suppl. material) demonstrates a video of a minimally invasive partial gastrectomy for a large GIST (13.9 × 8.6 cm).

Study Outcomes

Patient and tumor characteristics, intraoperative surgical parameters, postoperative outcomes, histopathological characteristics, and follow-up were prospectively collected and assessed (Tables 1–5).

Table 1. Baseline characteristics of the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor

	GIST n = 22 (%)
Age, years (mean±SD)	70.4±10.0
BMI, kg/m^2 (mean±SD)	27.9±5.5
Gender (female, %)	13 (59)
ASA classification	
I	0 (0)
II	13 (62)
III	7 (33)
IV	1 (5)
Comorbidities	
Cardiac	9 (41)
Vascular	11 (50)
Diabetes	3 (14)
Pulmonary	3 (14)
c-KIT expression	19 (86)
Neoadjuvant treatment	
Yes (imatinib)	4 (18)

Percentages may not add up to 100% due to rounding. ASA, American Society of Anesthesiologists.

Results

Study Population

Between 2011 and 2019, 22 consecutive patients underwent surgical gastric resection for a GIST. The mean age was 70.4 years, and mean BMI was 27.9 kg/m^2 (Table 1). Most of the patients were female (59%) and had an ASA II classification, where cardiac and vascular comor-

Table 2. Surgical characteristics of the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor

	GIST $n = 22$ (%)
Conversion	1 (5)
Type of resection	
Partial gastrectomy[a]	3 (14)
Wedge	19 (86)
Additional resection	3 (14)
Diaphragm + spleen	1 (5)
Spleen + pancreas	1 (5)
(Meso)Colon	1 (5)
Cruroplasty	2 (9)
Operation time (min; mean±SD)	107 (48)
Operation time (min; median, IQR)	103 [72–138]
Intraoperative complication	3 (14)
Bowel injury	2 (9)
Spill due to tumor rupture	1 (5)

Percentages may not add up to 100% due to rounding. [a] In all patients, a gastroenterostomy was created.

Table 3. Postoperative outcomes of the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor

	GIST $n = 22$ (%)
Morbidity	6 (27)
Intra-abdominal complications	
Anastomotic leakage[a]	0 (0)
Perforation at suturing site	1 (5)
Abscess	0 (0)
Bleeding	0 (0)
Pancreatitis, leakage or fistula	0 (0)
Chyle leakage	0 (0)
Trauma of the gut	0 (0)
Gastroparesis	0 (0)
Wound complications	0 (0)
Non-surgical complications	
Pulmonary[b]	2 (9)
Cardiac[c]	1[g] (5)
Thromboembolic[d]	0 (0)
Neurologic[e]	0 (0)
Urologic[f]	1 (5)
Other	1 (5)
Re-interventions	1 (5)
Mortality	0 (0)
Recovery	
ICU stay (median, IQR)	0 [0–0]
Hospital stay (median, IQR)	5 [3–7]
Readmissions	0 (0)

Percentages may not add up to 100% due to rounding. ICU, Intensive Care Unit; IQR, interquartile range. [a] Any clinically or radiologically proven anastomotic leakage. [b] Pneumonia, pleural effusion, respiratory failure, pneumothorax, and/or acute respiratory distress syndrome (ARDS). [c] Supraventricular arrhythmia, myocardial infarction, and/or heart failure. [d] Pulmonary embolism, deep venous thrombosis, and/or cerebrovascular accident. [e] Acute delirium. [f] Acute renal insufficiency, acute kidney failure requiring dialysis, urinary tract infection, and/or urine retention. [g] Patient in whom conversion from minimally invasive to open surgery took place.

bidities were most common (both accounting for almost 50%). c-KIT expression was found in the biopsies of 19 patients (86%), and 4 patients received preoperative imatinib. In 2 patients, the effect of preoperative imatinib on the tumor was objectively assessed by a re-staging CT abdomen, which showed a size reduction to 9.2 cm in 1 patient (original size 13.9 cm) and to 2.0 cm in another patient (original size 7.0 cm). In the other 2 patients, persistent bleedings occurred during imatinib treatment, resulting in resection before completion of the imatinib.

Intraoperative Parameters

Intraoperative parameters are shown in Table 2. The majority of patients underwent a wedge resection (86%). In case of partial gastrectomy (3 patients, 14%), a gastrojejunostomy was created. Conversion from laparoscopic to open surgery occurred in 1 patient, due to invasion of the GIST in the pancreas and spleen, resulting in an additional partial resection of the pancreas and splenectomy. In another 2 patients, an additional resection was performed beyond the GIST to ensure en bloc oncological resection: resection of diaphragm and an edge of the spleen and resection of part of the transverse mesocolon. All additional resections took place during the index operation. A cruroplasty was performed intraoperatively in 2 patients (9%). In 3 patients (14%), an intraoperative complication occurred: in 2 patients, a bowel injury occurred (requiring suturing), and in 1 patient, who was operated in an emergency setting because of bleeding, a small tumor perforation occurred at extraction, without spill (macroscopically no tumor was left behind). The mean overall operating time was 107 min.

Postoperative Outcomes

In total, 6 patients (27%) developed postoperative complications (Table 3). In 1 patient, a re-operation was needed with surgical drainage and repair of a leakage at the sutured defect following a wedge resection. In this patient, the defect was located near the pylorus at the lesser curve and closed with a barbed suture. Two patients developed a hospital-acquired pneumonia, 1 patient had cardiac complications (supraventricular fibrillation combined with a troponin

Table 4. Histopathological characteristics of the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor

	GIST $n = 22$ (%)
Size (mm; mean±SD)	57 (35)
Size (mm; median, ranges)	53 (20–175)
Size >5 cm	12 (55)
Mitotic rate ≤5/5 mm^2[a]	17 (77)
Risk of progressive disease[b]	
Low risk (WHO I, II, IIIa–IV)	15 (68)
Moderate risk (WHO IIIb, V)	2 (9)
High risk (WHO VIa–VIb)	5 (23)
c-Kit mutation analysis	9 (41)
Radicality of the resection	
R0	21 (96)
R1	1 (5)
Lymph node resection (yes, %)[c]	5 (23)
Lymph node yield (median, IQR)	2 [2–11]
Positive lymph nodes (median, IQR)	0 [0–0]

IQR, interquartile range. [a] If a patient received preoperative treatment with Imatinib, it is questionable whether or not MAI count is reliable due to therapeutic changes (e.g., fibrosis) of the tumor. [b] According to the NCCN Guidelines. [c] The lymph nodes resected during the procedures were taken as part of the gastric resection. In none of the patients it was intentionally decided that lymphadenectomy was required.

Table 5. Follow-up data on the patients who underwent minimally invasive surgery for gastrointestinal stromal cell tumor

	GIST $n = 22$ (%)
Stenosis	0 (0)
Adjuvant treatment	4 (18)
Follow-up (months; median, IQR)	31 [1–75]
Overall survival	
1 year	94%
3 year	86%
5 year	86%
Recurrence[a]	1 (5)
Disease-free survival	
1 year	94%
3 year	76%
5 year	76%

IQR, interquartile range. [a] Two years after surgery, patient presented with local recurrence with hepatogenic and peritoneal metastases.

rise), and 1 patient had a urologic complication (replacement of a bladder catheter due to retention). There was no postoperative mortality. Median ICU stay was 0 [0–0] days and hospital stay was 5 days [3–7 days].

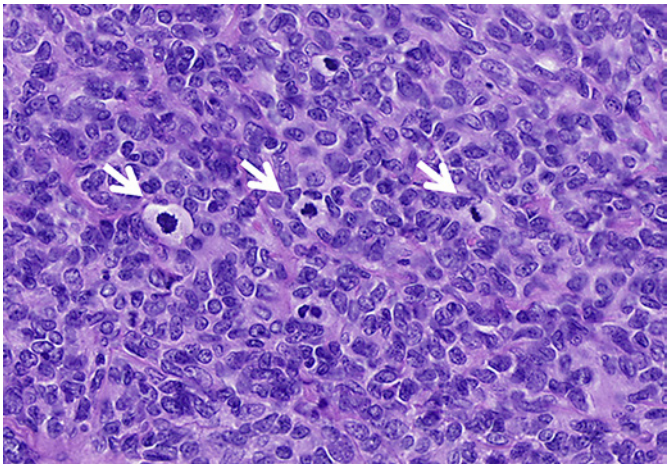

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Fig. 1. Three mitoses per HPF in a patient with a high-grade GIST.

Histopathological Outcomes

Table 4 shows histopathological outcomes. The median size of the GIST was 53 mm (range 20–175 mm), and mitotic rate was ≤5 per 5 mm^2 in the majority of patients (Fig. 1). Based on the WHO classification and Risk Stratification of Primary GIST by Mitotic Index, Size and Site table [5, 13], 15 patients (68%) had a low risk of progressive disease, 2 patients (9%) had a moderate risk, and 5 patients (23%) had a high risk of progressive disease. R0 resection was performed in all but 1 patient (96%). In 1 patient with a dorsally located GIST, the tumor had a close relationship with the mesocolon and retroperitoneum. In this patient, tumor cells were found in the stapler edge, resulting in R1 resection. c-KIT expression was found in 19 patients (86%) by immunohistochemistry. c-KIT mutation analysis was performed in 9 patients (41%), of whom 4 patients were treated with preoperative imatinib.

Follow-Up

Table 5 summarizes follow-up data. Postoperative therapy with imatinib was administered in 4 patients (18%, of whom 3 patients also received preoperative imatinib), as soon as this was permitted by the physical condition and postoperative recovery of the patient. The median follow-up was 31 months, and 1-, 3- and 5-year disease-free survival were 94, 76, and 76%, respectively. Overall survival rates were 94, 86, and 86% (1, 3, and 5 years, respectively). To date, the patient in whom an R1 resection was performed did not present with recurrence. Two years after surgery, another patient presented with local recurrence with hepatogenic and peritoneal metastases. In this patient, with an initial tumor of 5.5 cm, mitotic index of >5 mitoses per HPF, WHO risk category 6a

and R0 resection, postoperative imatinib was stopped after 2 months due to toxicity. As yet, there are no patients with postoperative gastric stenosis.

Discussion/Conclusion

This study demonstrates that minimally invasive surgery for gastric GIST up to 17.5 cm in diameter can be performed safely and oncologically effective with excellent long-term results. In patients in whom an irresectable tumor with c-KIT expression is suspected, preoperative imatinib resulted in adequate tumor regression, allowing for MIG.

GISTs are the most common type of mesenchymal tumors in the gastrointestinal tract and require surgical resection once over 2 cm, with clear margins because of its malignant potential. No lymphadenectomy is necessary due to the very low risk of dissemination to the lymph nodes [1, 5, 8, 9]. Since the reports on improved patient outcomes following laparoscopic gastrectomy, MIG for GIST has gained popularity [2, 13, 14]. Several studies have reported on safety and feasibility of MIG for small gastric GIST [1, 8, 9, 15–19]. In addition to the safety and feasibility, MIG has many other benefits, as reviewed by Chen et al. [9]. In their systematic review and meta-analysis, 1,166 gastric GISTs were included, and benefits such as reduced blood loss, earlier first flatus day and oral intake, fewer postoperative complications, shorter hospitalization, and lower recurrence risk were described. Koh et al. [1] performed a similar study a year before with roughly the same results; however, the larger tumor size was mostly approached by open surgery.

Unfortunately, no systematic reviews or meta-analyses have been conducted for a Western population. De Vogelaere et al. [8] were one of the first to describe MIG for GIST in a Western population (31 patients) with a mean tumor size of 4.4 cm and range 0.4–11.0 cm. A low morbidity rate was reported (1 patient [3.2%] suffered from hemorrhage postoperatively) and no spill was reported [8]. Bischof et al. [19] performed a propensity score matched analysis on 248 Western patients with a mean tumor size of 3.9 cm (range 2.3–5.2 cm) in the MIG group and found a postoperative grade 3+ (Clavien-Dindo) morbidity rate of 3.2% in the MIG group and 13.7% in the open surgery group. They reported a spill rate of 1.6% during minimally invasive surgery and 0.8% during open surgery. A study by Melstrom et al. [17] also comparing laparoscopic versus open surgery for GIST in 17 patients with a mean tumor size of 4.3 cm (range 1.5–9.1 cm) reported 100% radical resections and 11.8% postoperative complications. In the current study, much larger tumors (mean 5.7 cm, range up to 17.5 cm) in patients with less favorable characteristics (higher age and high BMI) could be treated laparoscopically. In this study, a higher number of patients required subtotal gastrectomy, which may explain the higher overall morbidity rate (27%) and possibly higher rate of spill (5%). Other Western studies report similar overall postoperative morbidity rates of 33%, despite including younger patients with smaller tumors: 3.6 cm (0.7–7.8 cm) and 5.5 cm (2.5–12 cm) [16, 20].

In comparison with results from DeMatteo et al. [2], a higher R0 resection rate was found (81 vs. 96%). Compared to De Vogelaere et al. [8], a shorter hospital stay (8.4 vs. 5 days) was found in the current study. Bischof et al. [19] and Melstrom et al. [17] reported a longer operation time (157 vs. 135 vs. 108 min in the current study). These differences might be caused by centralization of gastric cancer care in the Netherlands, starting of 2009, which results in more experienced surgeons in high-volume centers (>20 gastrectomies per year per center required in the Netherlands).

The literature is scarce regarding long-term survival after MIG for large GIST. In the study of Karakousis et al., disease-free survival was 90%, whereas Bischof et al. [19] reported a recurrence-free survival of 79.5% at the 5-year follow-up. Likewise, the current study demonstrated a 5-year disease-free survival of 76%.

Although this study has several strengths, such as the prospective data collection with complete data registry of patient and tumor characteristics, intra- and postoperative parameters (including recovery and follow-up data), and the preference for MIG regardless of the tumor size, a few limitations should be addressed. The current results are based on an observational study design and data of 2 experienced surgeons in a single university hospital; generalization of these results might therefore not be possible. In addition, the small sample size is potentially limiting.

In conclusion, MIG for large gastric GIST up to 17.5 cm in diameter is safe and feasible in a Western population with advanced GIST. The laparoscopic approach could be considered the standard of care for gastric GIST regardless of tumor size.

Statement of Ethics

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. This study does not fall within the Medical Research Involving Human Subjects Act (WMO), and informed consent requirement was waived.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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E.C.G., G.I.B., L.A.A.B., J.P.R., and R.H. declare that they have no financial ties to disclose.

Author Contributions

All authors have made substantial contributions to conceptualization, methodology, validation, formal analysis, investigation, resources, writing – original draft, writing – review and editing, visualization, and project administration. All authors have approved the submitted versions and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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