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Laparoscopic resection for gastric GISTs: surgical and long-term outcomes of 133 cases.

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ABSTRACT

Background:
It aims to evaluate the surgical efficacy and long-term survival of different laparoscopic surgeries for gastric GISTs.

Methods:
From a prospectively collected database, 133 patients with primary gastric GISTs undergoing laparoscopic surgery were selected from January 2008 to December 2014. They were divided into three groups according to the different operations that were performed, including laparoscopic gastric wedge resection (LWR Group, n=103), laparoscopic subtotal gastrectomy (LSG Group, n=18) and laparoscopic total gastrectomy (LTG group, n=12). Clinicopathological features and short- and long-term outcomes were analyzed retrospectively.

Results:
All patients had received R0 resection. There were no differences among the three groups in age, BMI or NIH risk classification. Compared with the LSG group and LTG group, the LWR group had a shorter operative time, less blood loss, fewer operative complications and shorter time to ground activities, semi-liquid diet and hospital stay ($P<0.05$). There was no statistically significant difference in time to first flatus and liquid diet or in the rate of postoperative complications ($P<0.05$). In the patients with a large tumor (size≥5 cm), LWR was significantly associated with shorter operative time, less blood loss and shorter hospital stay compared with the laparoscopic gastric non-wedge resection (N-LWR) ($P<0.05$). The median follow-up was 30 months, with 4 cases of recurrence and 3 deaths. The 5-year cumulative survival rate was similar among the three groups ($P>0.05$).

Conclusions:
Compared with LSG and LTG, more favorable minimally invasive results can be achieved from LWR for gastric GISTs, which may be the optimal surgical procedure.

Keywords:
Stomach, gastrointestinal stromal tumors (GISTs), laparoscopic surgery, clinical outcomes.

Background:

Gastrointestinal stromal tumor (GIST) is a common mesenchymal neoplasm of the gastrointestinal (GI) tract with an annual incidence estimated to be 10–15 per million [1-2]. The majority of GISTs are found in the stomach (60%) and small intestine (30%) [3]. Complete surgical resection is the primary treatment for local gastric GISTs. Compared with open resection, laparoscopic resection for gastric GIST has advantages such as shorter operative time, less blood loss and quicker recovery [4-6]. Therefore, more and more scholars have preferred laparoscopic resection for gastric GIST in recent years. There are many controversies about the choice of laparoscopic resection for gastric GIST. The commonly used surgical methods include laparoscopic gastric wedge resection (LWR), laparoscopic subtotal gastrectomy (LSG), laparoscopic total gastrectomy (LTG), laparoscopic transgastric resection and laparoscopy endoscopic resection [7-9]. In this study, we retrospectively reviewed detailed data for patients who underwent laparoscopic resection of gastric GIST at our center from January 2008 to December 2014 and evaluated the surgical efficacy and long-term survival of different laparoscopic surgeries for gastric GIST.

Materials and methods:

Materials

From January 2008 to December 2014, 324 patients with primary gastric GISTs were treated with radical resection at the Department of Gastric Surgery, Fujian Medical University Union Hospital. A retrospective analysis was performed, using a prospectively maintained comprehensive database, to determine the technical pitfalls of the procedure. In this series, we included only patients with gastric GISTs, as confirmed by pathological examination. We excluded patients who presented with a malignant tumor (n=106); patients who underwent open surgery (n=82); and patients who underwent endoscopic excision (n=3). Finally, 133 patients were eligible for inclusion in this study. Patients were classified into three groups according to the different operations: laparoscopic gastric wedge resection (LWR Group, n=103), laparoscopic subtotal gastrectomy (LSG Group, n=18) or laparoscopic total gastrectomy (LTG group, n=12) (*Figure 1*). All patients underwent abdominal CT, endoscopy or EUS to initially assess tumor size and location and to determine whether there was distant metastasis.

Surgical procedure

Tumors were classified according to tumor location, as demonstrated in *Figure 2*. Area A is the cardia junction, area B is the fundus and body of the stomach, and area C is the antrum. Tumors were treated with LWR, LTG, laparoscopic proximal subtotal gastrectomy (LPSG), laparoscopic distal subtotal gastrectomy (LDSG) according to location of the different tumors.

The patient was placed in the reverse Trendelenburg and supine position with his or her legs spread apart. After the induction of general anesthesia, pneumoperitoneum was established at a pressure of 12 to 15 mm Hg. A 10-mm trocar for 30°telescope was inserted below the umbilicus. A 12-mm port was inserted percutaneously in the left upper quadrant as the dominant hand port. A 5-mm trocar was placed in the contralateral side. Another two 5-mm trocars were placed in the left and right lower quadrants, respectively. The surgeon stood to the left side of the patient, with the first assistant on the patient's right side and the laparoscopist between

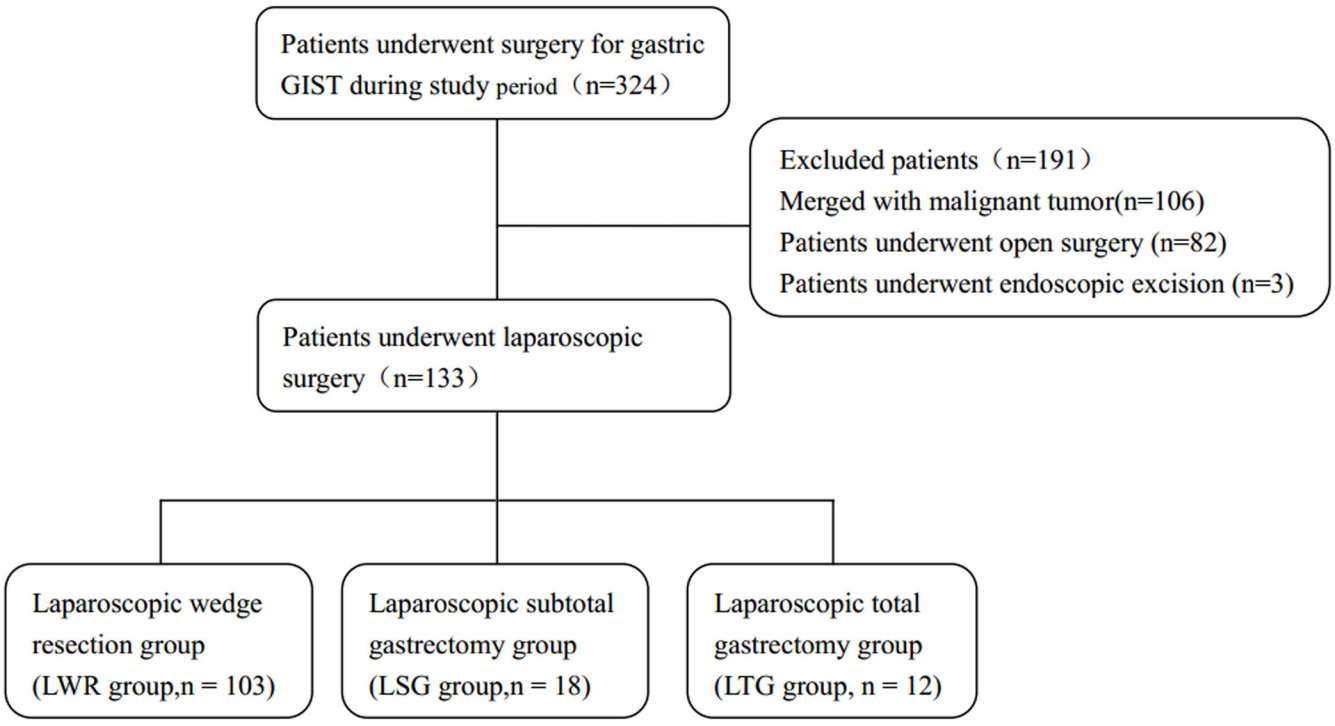

Figure 1: Patient selection flowchart

the patient's legs. Occasionally, gastroscopy was used to assist with identifying the tumor. The tumor specimen was extracted using a bag via a 6-10 cm epigastric incision. The stomach and peritoneal cavity were inspected to rule out invasion of adjacent organs and peritoneal seeding.

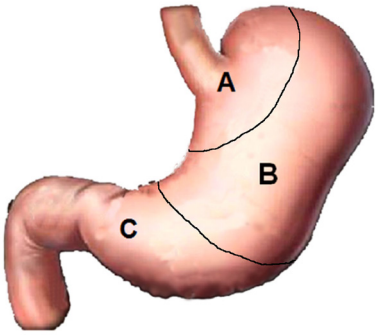

Figure 2: Anatomic classification of the gastric GIST (area A: gastroesophageal junction; area B: fundus and body of the stomach; area C: antrum)

Follow-up methods and treatment

Postoperative follow-up assessments consisted of physical examination, laboratory tests, chest radiography, abdominopelvic ultrasonography (USG) or computed tomography (CT) and an annual endoscopic examination. Survival periods were calculated from the time of surgery until death or right-censored at final follow-up.

Statistics

Continuous variables were compared using the Mann–Whitney U or Kruskal-Wallis tests, as appropriate, and categorical variables were compared using the Pearson X 2 or Fisher exact test. Total survival curves were calculated with the Kaplan–Meier method. All statistical analyses were performed using SPSS version 20 (IBM Corp., Armonk, NY).A p value<0.05 was considered statistically significant.

Results:

Patient characteristics

The LSG group had a higher proportion of male patients; the tumors of the LWR group were mostly located in the fundus and body of the stomach, and the mitotic count was lower. There was no significant difference among the three groups in age, Body Mass Index (BMI), NIH

	LSG（n=18）	LTG(n=12）	LWR(n=103)	p
Age（years）	56（45-72）	58（35-82）	59（27-80）	0.450
Gender				0.006※
Male	15（83.3%）	8（66.7%）	47（45.6%）	
Female	3（16.7%）	4（33.3%）	56（54.4%）	
BMI（kg/m2）	21.9（19.1-26.8）	21.8（18.3-26.9）	22.5（16.2-29.4）	0.724
Tumor size(cm)	4.2（1.6-8.0）	6.0（2.8-11.0）	4（0.5-11.3）	0.062
Location				0.000※
Area A	7（38.9%）	8（66.7%）	5（4.9%）	
Area B	2（11.1%）	4（33.3%）	98（95.1%）	
Area C	9（50%）	0（0%）	0（0%）	
Mitotic rate (/ 50 HPF)				0.004※
≤5	13（72.2%）	9（75%）	85（82.5%）	
>5, ≤10	3（16.7%）	0（0%）	17（16.5%）	
＞10	2（11.1%）	3（25%）	1（1.0%）	
Risk classification				0.169
Very low	1（5.6%）	0（0%）	5（4.9%）	
Low	6（33.3%）	3（25%）	54（52.4%）	
Intermediate	7（38.9%）	4（33.3%）	30（29.1%）	
High	4（22.2%）	5（41.7%）	14（13.6%）	
Pre-operative IM	1（5.6%）	1（8.3%）	1（1.0%）	0.127
Postoperative IM	5（27.7%）	3（25%）	32（31.1%）	1.000

IM: imatinib

※: p<0.05

Table 1: Comparison of clinicopathological characteristics of the patients

risk classification, pre-operative imatinib (IM) treatment or postoperative IM treatment(p>0.05)(*Table 1*).

Operative outcomes

There was no tumor rupture, and all patients successfully completed R0 resection. There was one conversion to open surgery in the LWR group due to severe adhesion with surrounding tissue. Compared with the LSG group and LTG group, the LWR group had a shorter operative time, less blood loss and fewer operative complications. The overall operative complication rate was 1.5%, with one patient in the LTG group having an injured spleen and one patient in the LSG group having an injured left gastric artery.

Postoperative outcomes

The LWR group was superior to the LSG group and LTG group in time to ground activities, semi-liquid diet and postoperative hospital stay (P<0.05). There was no statistically significant difference in time to first flatus and liquid diet or in the rate of postoperative complications (P<0.05). The overall postoperative complication rate was 6.8%; the postoperative complication rates were similar among the three groups; the rates of the LSG, LTG and LWR groups were 11.0%, 8.3%, 5.8%, respectively. The overall severe postoperative complication (≥IIIa) rate was 3.0%. One patient in the LTG group had an occurrence of an adhesive intestinal obstruction and underwent open enterolysis, and one patient in the LWR group had occurrence of bleeding that required re-exploration; both patients were discharged after recovery. Two patients developed an anastomotic stricture after LTG and LWR; both received endoscopic anastomotic dilation after one month (*Table 2*).

The efficacy of laparoscopic surgery in patients with tumor diameter ≥5 cm

We further compared the laparoscopic surgery efficacy of 55 patients with a tumor diameter ≥5 cm. Thirty-nine patients underwent LWR, and sixteen patients underwent laparoscopic gastric non-wedge resection (N-LWR, including LTG and LSG). These patients were similar in age, gender, BMI, NIH risk classification, pre-operative IM treatment and post-operative IM treatment. The LWR group was significantly associated with shorter operative time, less blood loss and shorter hospital stay compared with the N-LWR group (P<0.05).

	LSG（n=18）	LTG(n=12）	LWR(n=103)	p
Operating time（min）	120（90-315）	195（120-240）	90（30-225）	0.000※
Blood lost（ml）	50（10-100）	50（20-100）	10（5-100）	0.000※
Convert to open	0	0	1（1.0%）	1.000
Operative complication	1（5.6%）	1（8.3%）	1（0%）	0.050※
Flatus (days)	3（2-6）	3（1-14）	3（1-6）	0.079
Ground activities	2（1-5）	4（2-5）	2（1-6）	0.000※
Liquid diet (days)	4（3-6）	3（2-14）	4（1-9）	0.377
Semi-liquid diet	7（6-13）	8（4-28）	6（1-27）	0.000※
Hospital stay (days)	9（9-26）	11（10-28）	7（2-40）	0.000※
Postoperative complication	2（11.1%）	1（8.3%）	6（5.8%）	0.469＋
Pneumonia	1（5.6%）	1（8.3%）	3（2.9%）	
Anastomotic stenosis	1（5.6%）	0（0%）	1（1.0%）	
Ileus	0（0%）	1（8.3%）	0（0%）	
Wound infection	1（5.6%）	0（0%）	0（0%）	
Gastrasthenia	1（5.6%）	0（0%）	1（1.0%）	
Bleeding	0（0%）	0（0%）	1（1.0%）	

＋：two patients had two or more postoperative complications.

Table 2: Comparison of operative characteristics and perioperative outcome

	N-LWR(n=16）	LWR (n=39)	p
Age（years）	56（35-82）	56（35-82）	0.925
Gender			0.236
Male	12（75%）	22（56.4%）	
Female	4（25%）	17（43.6%）	
BMI（kg/m2）	20.7（18.3-25.5）	21.6（16.2-28.1）	0.066
Tumor size(cm)	7.3（5.1-11.0）	6.0（5.0-11.3）	0.315
Location			0.000※
Area A	8（50%）	1（2.6%）	
Area B	6（37.5%）	38（97.4%）	
Area C	2（12.5%）	0（0%）	
Mitotic rate (/ 50 HPF)			0.044※
≤5	10（62.5%）	30（76.9%）	
>5, ≤10	2（12.5%）	8（20.5%）	
＞10	4（25%）	1（2.6%）	
Risk classification			0.384
Very low	0（0%）	0（0%）	
Low	0（0%）	4（10.3%）	
Intermediate	8（50%）	21（53.8%）	
High	8（50%）	14（35.9%）	
Pre-operative IM	2（12.5%）	1（2.6%）	0.200
Postoperative IM	6（37.5%）	18（46.2%）	0.765

Table 3: Comparison of clinicopathological characteristics of the patients (tumor size≥5cm)

	N-LWR (n=16）	LWR (n=39)	p
Operating time（min）	150（90-315）	120（60-225）	0.004※
Blood lost（ml）	50（10-100）	30（5-100）	0.033※
Convert to open	0（0%）	1（2.6%）	1.000
Operative complication	1（6.3%）	1（0%）	0.291
Flatus (days)	3（1-14）	3（1-5）	0.756
Ground activities(days)	2（1-5）	2（1-5）	0.420
Liquid diet (days)	3（3-14）	4（3-9）	0.181
Semi-liquid diet(days)	7（4-28）	6（1-27）	0.106
Hospital stay (days)	10（8-28）	8（5-40）	0.001※
Postoperative complication	2（12.5%）	2（5.1%）	0.571
Pneumonia	1（6.3%）	0（0%）	
Ileus	1（6.3%）	0（0%）	
Anastomotic stenosis	1（6.3%）	1（2.6%）	
Bleeding	0（0%）	1（2.6%）	

Table 4: Comparison of operative characteristics and perioperative outcome (tumor size≥5cm)

There were no statistically significant differences in time to ground activities, first flatus, liquid diet, semi-liquid diet or operative or postoperative complications (P<0.05) (*Table 3, Table 4*).

Follow-up

One hundred thirty patients (97.7%) were followed up; the median follow-up duration for the entire cohort was 30.0 months (range, 4–78 months), with 4 cases of recurrence and 3 deaths. The 5-year cumulative survival

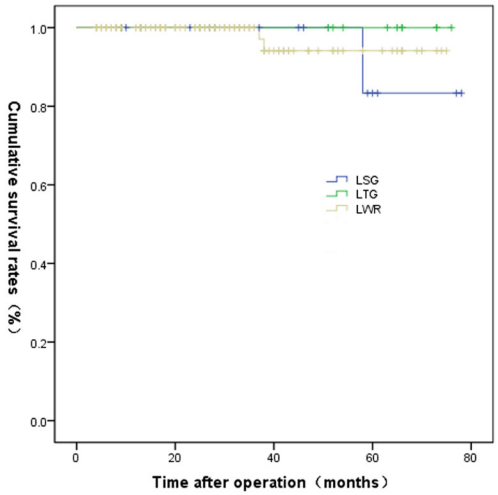

Figure 3: Total survival curve of the group LSG, group LTG and group LWR

rates of the LSG, LTG, and LWR groups were 80%, 100%, and 94.5%, respectively, which was similar among the three groups (P>0.05)(*Figure 3*). *Table 5* shows the clinicopathologic characteristics for cases of recurrence and death after resection.

Discussion:

Most GISTs are in a submucosal location and usually grow exogenously instead of diffusely infiltrating. It is generally accepted that the surgical goal should be a complete resection with negative margins. Meanwhile, extensive lymphadenectomy is not recommended because lymph node involvement is rare[10-12]. These unique growth patterns make GIST resection relatively simple and provide favorable conditions for minimally invasive surgery. A number of studies have shown the safety and feasibility of laparoscopic resection of gastric GISTs. Koh[13] et al. performed a systematic review and meta-analysis to compare the outcomes of laparoscopic gastric resection (LR) versus open gastric resection (OR) for gastric GIST. Although there was no difference in operative time, LR results in less blood loss, lower risk of minor complications, shorter time to first flatus, oral intake and a decreased postoperative hospital stay. The long-term oncological outcomes of the two groups are comparable. De Vogelaere[14] et al. considered that LR also had a similar minimally invasive effect, and the operative time of LR was significantly shorter than that of OR. In recent years, with the improvement in laparoscopic instrumentation and accumulated laparoscopic experience, an increased number of surgeons prefer laparoscopic resection of gastric GIST. Since the first laparoscopic resection for gastric GIST in 2008, our department has completed more than 100 cases with laparoscopic gastric GIST resection, and it has become the first choice for surgical treatment of gastric GIST.

There are a variety of ways for conducting a laparoscopic resection of gastric GIST, and we should determine the appropriate surgical procedures based on tumor location, tumor size and growth pattern [15-17]. The main methods of pure laparoscopic surgery contain LWR, LSG (including LPSG and LDSG) and LTG. When the tumor is located in cardia and is large enough to be involved, local resection has a high incidence of causing gastrointestinal tract stenosis. Therefore, LTG or LPSG is preferred. Meanwhile, LWR is suitable for tumors that are small or that grow exogenously with pedicle, where the digestive tract remains unobstructed. Because fundus and greater curvature are spacious, GISTs located in these areas are often removed by LWR, whereas small tumors of lesser curvature require sufficient isolation of the surrounding tissues. Large GISTs with an endogenous growth model are difficult to operate, and stenosis is a frequent outcome. In such a case, LTG or LPSG will be a safer option. For the antral GISTs, LDSG is recommended. In this study, we demonstrated that LWR had less invasiveness, faster recovery and similar long-term prognosis when compared with LTG and LSG, making it an optimal surgical approach for gastric GIST treatment.

Although the advantages of laparoscopic surgery for gastric GIST are clear, there is also the risk of intraoperative tumor rupture, especially when the tumor is large. The feasibility of laparoscopic surgery for large tumors is controversial. Because large tumors are prone to rupture during the operation and result in peritoneal spreading, laparoscopic resection of gastric GIST is mostly limited to small gastric GIST with a diameter ≤5 cm[18-19]. However, some scholars believe that laparoscopic surgery is equally applicable to large gastric GIST (≥5 cm)[20-22]. Takahashi [20] et al. suggested that laparoscopic surgery could achieve equal short- and long-term efficacy compared with

No.	gender	Age (years)	Pre-operative IM	Gastrectomy extent	Postoperative IM	Tumor size(cm)	Tumor location	Risk classification	Status	months
1	Male	56	No	LSG	No	4.0	Area B	Low	Death	37
2	Male	57	No	LWR	Yes	3.3	Area B	Medial	Death	38
3	Male	72	No	LWR	No	4.8	Area B	Low	Death	44
4	Male	35	Yes	LTG	Yes	9.0	Area A	High	Recurrent	49

Table 5: Clinicopathologic characteristics of recurrent/death cases

open surgery, which is in agreement with our previous studies [23]. In this study, 55 cases of GIST larger than 5 cm were successfully completed with laparoscopic resection except for 1 case that was converted to open due to severe adhesion to the surrounding tissue. There was no intraoperative rupture, and all cases had received R0 resection. For gastric GIST larger than 5 cm, LWR was associated with shorter operation time, less blood loss and shorter hospital stay than N-LWR was. Hence, we believe laparoscopic resection of gastric GIST with tumor diameter ≥5 cm is still feasible and safe. LWR can be a preferred surgical approach for those GISTs if conditions allow.

Conclusion:
Laparoscopic treatment of gastric GISTs is safe and feasible with satisfactory clinical efficacy. Compared with LSG and LTG, more favorable minimally invasive results can be achieved from LWR for gastric GISTs, which may be the optimal surgical procedure.

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Contributors
Jian-Xian Lin, Qian Yu and Chang-Ming Huang conceived of the study, analyzed the data, and drafted the manuscript; Mi Lin, Chao-Hui Zheng, Ping Li, Jian-Wei Xie helped revise the manuscript critically for important intellectual content; Jun Lu and Qi-Yue Chen helped collect data and design the study. All authors read and approved the final manuscript. The authors have declared no conflicts of interest.

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Competing interests
All authors declare that they have no competing interests.

Availability of data and materials
Further information is available from the corresponding author on reasonable request.

Ethics approval
Ethics Committee of Fujian Medical University Union Hospital approved this retrospective study (Approval number: 20070428). Written consent was given by the patients for their information to be stored in the hospital database and used for research. All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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