Laparoscopic *vs.* open surgery for gastrointestinal stromal tumors of esophagogastric junction: A multicenter, retrospective cohort analysis with propensity score weighting

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Abstract

Objective: Laparoscopic resection is increasingly performed for gastrointestinal stromal tumors (GISTs). However, the laparoscopic approach for GISTs located in the esophagogastric junction (EGJ-GIST) is surgically challenging. This study compares the efficacy of laparoscopic surgery and the open procedure for EGJ-GIST through the propensity score weighting (PSW) method.

Methods: Between April 2006 and April 2018, 1,824 surgical patients were diagnosed with primary gastric GIST at four medical centers in South China. Of these patients, 228 were identified as EGJ-GISTs and retrospectively reviewed clinicopathological characteristics, operative information, and long-term outcomes. PSW was used to create the balanced cohorts.

Results: PSW was carried out in laparoscopic and open-surgery cohorts according to year of surgery, sex, age, body mass index (BMI), tumor size, mitotic rates and recurrence risk. After PSW, 438 patients consisting of 213 laparoscopic (L group) and 225 open surgery (O group) patients were enrolled. After PSW, the following measures in the L group were superior to those in the O group: median operative time [interquartile range (IQR)]: 100.0 (64.5−141.5) *vs.* 149.0 (104.0−197.5) min, P<0.001; median blood loss (IQR): 30.0 (10.0−50.0) *vs.* 50.0 (20.0−100.0) mL, P=0.002; median time to liquid intake (IQR): 3.0 (2.0−4.0) *vs.* 4.0 (3.0−5.0) d, P<0.001; median hospital stay (IQR): 6.0 (4.0−8.0) *vs.* 7.0 (5.0−12.0) d, P<0.001; and postoperative complications (10.3% *vs.* 22.7%, P=0.001). The median follow-up was 55 (range, 2−153) months in the entire cohort. No significant differences were detected in either relapse-free survival (RFS) [hazard ratio (HR): 0.372, 95% confidence interval (95% CI): 0.072−1.910, P=0.236) or overall survival (OS) (HR: 0.400, 95% CI: 0.119−1.343, P=0.138) between the two groups.

Conclusions: Laparoscopic surgery for EGJ-GIST is associated with the advantages of shorter operative time, reduced blood loss, shorter time to liquid intake, and shorter length of stay, all without compromising postoperative outcomes and long-term survival.

Keywords: Esophagogastric junction; gastrointestinal stromal tumor; laparoscopic surgery; open surgery; propensity score weighting

Introduction

Gastrointestinal stromal tumors (GISTs) originate from the interstitial cells of Cajal and are the most common mesenchymal tumors of the digestive tract. GISTs may occur in any part of the digestive system but gastric GISTs (gGISTs) account for 50%−70% and are the most common primary tumors (1). The body of the stomach is by far the most common location of the primary tumor (70%−82%), while tumors at the esophagogastric junction (EGJ) contribute a small percentage (5.8%−13.5%) to the overall incidence (2-4).

Surgical resection, when feasible, has become the main treatment of choice for GISTs in recent years. With the development of laparoscopic techniques and instruments, laparoscopy has rapidly become a preferred approach, especially for gGISTs (5). Recent studies have demonstrated that efficacy of laparoscopic surgery for gGISTs is comparable to that of the open approach and even better with respect to short-term outcomes (2,6,7).

The indication for a laparoscopic procedure depends on the location, shape and size of the gGIST. The latest National Comprehensive Cancer Network (NCCN) and European Society for Medical Oncology (ESMO) Guidelines suggest that a laparoscopic resection may be considered for gGISTs in favorable anatomic locations (such as the greater curvature or anterior wall of the stomach) and discourage its use in patients who have large tumors (8,9). However, tumors located in the lesser curvature or posterior wall of the stomach, at the cardia, or at the prepyloric region were classified as unfavorable locations (10). Notably, the laparoscopic approach for GISTs located in the esophagogastric junction (EGJ-GIST) is rarely reported because of the complex anatomical factors and the difficulty of preserving cardia function, which is technically challenging (11,12).

In our previous study, we carried out four types of laparoscopic resection for EGJ-GIST. Surgery in all patients was completed successfully without operative complications, and no patient experienced recurrence within the follow-up period (13). However, this single-center, small-sample report does not reflect the overall status of surgical treatment for EGJ-GIST in China. There remain limited comparative data to date on the long-term outcomes in laparoscopic resection and open surgery for EGJ-GIST.

Hence, we present a multicenter, retrospective study including patients with EGJ-GIST who underwent radical excision in four medical centers in China from April 2006 to April 2018. Selection bias was eliminated through propensity score weighting (PSW). The primary purpose of this study is to compare short-term efficacy and long-term outcomes of laparoscopic *vs.* open surgery for EGJ-GIST.

Materials and methods

Patients

This is a retrospective, multicenter, cohort study in China. From April 2006 to April 2018, there were 1,824 patients diagnosed with primary GIST who underwent resection in the Guangdong Provincial Hospital of Chinese Medicine, Guangdong General Hospital, Nanfang Hospital of Southern Medical University, and the Third Affiliated Hospital of Southern Medical University. Among them, 228 patients with primary GISTs located in the EGJ were included in this study. All operations were performed by experienced surgeons. Of these patients, 157 underwent a laparoscopic surgery (L group) and 71 underwent an open procedure (O group). Patients' age, sex, body mass index (BMI), tumor size, operative duration, blood loss, time to liquid intake, length of postoperative hospital stay, postoperative recovery and complications, and pathological results were reviewed. Risk stratification was evaluated according to the modified National Institutes of Health (NIH) risk classification scheme (14). The complications were classified according to the Clavien-Dindo classification scheme (15). Approval was obtained from the Institutional Review Board of Guangdong Provincial Hospital of Chinese Medicine and the registration number was ZE2020-298.

After PSW, 438 patients were selected for the comparison, 213 with laparoscopy (L group) and 225 with open surgeries (O group). The flow diagram for the study subject screening and group assignment is shown in *Figure 1*.
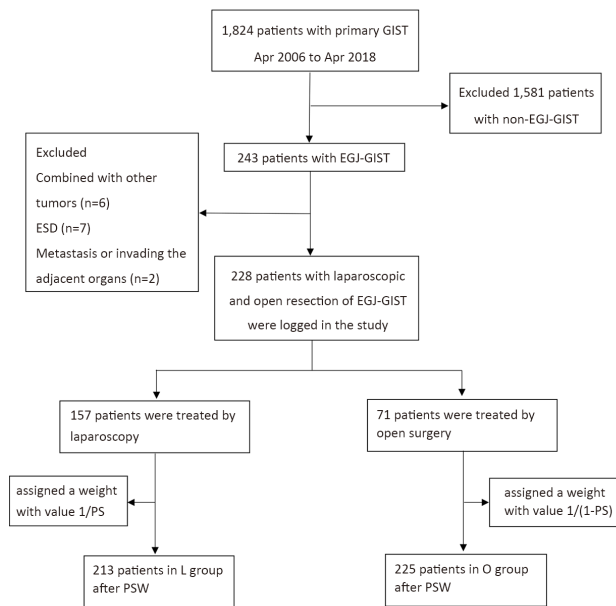
Figure 1 Flow diagram extracting eligible cases for comparison, GIST, gastrointestinal stromal tumor; EGJ-GIST, gastrointestinal stromal tumor in esophagogastric junction; ESD, endoscopic submucosal dissection; PS, propensity scores; PSW, propensity score weighting.

Definition of EGJ-GIST

EGJ-GIST is defined as a gGISTs with an upper border of less than 5 cm from the esophagogastric line (16).

Surgical procedure

Laparoscopic approach
Following general anesthesia, patients were placed in the supine position with legs separated. Pneumoperitoneum was established to an insufflation pressure of 10−15 mmHg. Five trocars were used. Before the procedure, we used a gastroscope to identify the tumor location and estimate the distance between the upper border of the tumor and the esophagogastric line before the procedure.

There are four types of laparoscopic resection for EGJ-GIST: wedge resection; resection by opening whole layers of the stomach wall and closing with sutures or a linear stapler; mucosa-preserving resection; and proximal gastrectomy with pyloroplasty. After mobilization, one of these was selected according to various criteria such as tumor location and size, distance between the upper border of the tumor and esophagogastric line, and manner of growth.

Open approach
Patients under general anesthesia were placed in the supine split-leg position. A midline incision with 8−15 cm was typically performed to expose the tumors adequately. All incisions were covered using a protective sleeve. Wedge resection, proximal gastrectomy, total gastrectomy, or multiple organ resection was performed, depending on the tumor size and location.

Follow-up

The clinical data were collected from medical records, and the survival information was obtained from telephone or outpatient visit follow-up by investigators at each medical center. The follow-up data included postoperative adjuvant therapy, survival and recurrence. The latest follow-up date for the study was in June 2018. Recurrent disease was defined as new lesions identified by postoperative endoscopy, abdominal computed tomography scan, or magnetic resonance imaging; recurrent disease was found most often in the liver and/or peritoneum. In addition, the recurrence event was confirmed by an experienced team (8,9). Relapse-free survival (RFS) was defined as the time from surgery to the first recurrence of disease and overall survival (OS) was calculated as the time from surgery to the date of death. Median follow-up time was 55 (range: 2−153) months in the entire cohort.

Statistical analysis

Data management and statistical analyses were performed usingIBM SPSS Statistics (Version 20.0; IBM Corp., New York, USA) and R software (Version 4.0.3; R Foundation for Statistical Computing, Vienna, Austria). PSW was implemented to reduce covariate confounding. Propensity scores (PS), reflecting the conditional probability of each surgical approach, were calculated by generalized linear models, in which the connecting function was logit fuction (family=binomial). Patients in the laparoscopy cohort were assigned a weight with the value 1/PS, while patients in the open cohort were assigned a weight with the value 1/(1-PS). The propensity model included variables that may have affected the distribution of patients in different operative types or outcomes including year of surgery, sex, age, BMI, tumor size, mitotic rate and recurrence risk. In propensity score matching (PSM), seven covariates (year of surgery, sex, age, BMI, tumor size, mitotic rate and recurrence risk) that may have affected the distribution of patients in different operative types or outcomes were

selected to calculate the propensity score. The reason for choosing 2010 as the cutoff point for year of surgery was that the year was when imatinib was approved in China to be effective for use as adjuvant therapy for primary GIST after complete resection (10).

Quantitative data were normally distributed and homogeneity of variance was showed as $\overline{x}\pm s$, using the *t*-test for comparison. Non-normal distribution of measurement quantitative data was represented as the median and interquartile range (IQR), using the Wilcoxon rank-sum test. Differences in categorical data between groups were determined by the Chi-square test or Fisher's exact test. Survival was calculated using the Kaplan-Meier method, and Cox regression was used for comparing the differences between the groups. The inverse probability of treatment weighting (IPTW) was used to estimate the effect value of factors. Cox regression was performed within the weighted sample to compare survival curves by study cohorts. A P<0.05 was considered to be significant.

Results

In total, 228 patients with EGJ-GIST were enrolled: 64 patients from Guangdong Provincial Hospital of Chinese Medicine, 66 from Guangdong General Hospital, 62 from Nanfang Hospital of Southern Medical University, and 36 from the Third Affiliated Hospital of Southern Medical University. Comparisons of demographic data and clinicopathological information between the two groups of patients are summarized in *Table 1*. There was no statistically significant difference between the baseline characteristics of L and O groups except for BMI. After PSW, a weighted sample of almost perfectly balanced covariates between the L and O group cohorts was created (*Table 1*), which were the same after PSM.

Tables 2, 3 show the comparison of intraoperative and postoperative outcomes. The L group was superior to the O group in most characteristics whether before or after PSW, including operative time, blood loss, time to liquid intake, hospital stay, and postoperative complications (all

Table 1 Comparison of demographic data and clinicopathological characteristics

Characteristics	Overall population (N=228)	Before PSW			After PSW			After PSM		
		L group (n=157)	O group (n=71)	P	L group (n=213)	O group (n=225)	P	L group (n=51)	O group (n=51)	P
Year of surgery [n (%)]				0.112			0.613			0.523
Before 2010	27 (11.8)	15 (9.6)	12 (16.9)		29 (13.6)	27 (12.0)		4 (7.8)	7 (13.7)	
After 2010	201 (88.2)	142 (90.4)	59 (83.1)		184 (86.4)	198 (88.0)		47 (92.2)	44 (86.3)	
Sex [n (%)]				0.138			0.826			1.000
Male	113 (49.6)	83 (52.9)	30 (42.3)		100 (46.9)	108 (48.0)		24 (47.1)	23 (45.1)	
Female	115 (50.4)	74 (47.1)	41 (57.7)		113 (53.1)	117 (52.0)		27 (52.9)	28 (54.9)	
Age ($\overline{x}\pm s$) (year)	57.9±11.9	58.2±12.1	57.3±11.4	0.602	57.9±12.5	57.6±11.2	0.806	55.0±11.9	57.4±12.4	0.331
BMI [median (IQR)] (kg/m²)	22.2 (21.0–24.3)	22.7 (21.0–24.7)	21.2 (20.2–23.7)	0.013	22.1 (20.8–23.8)	21.8 (21.0–25.0)	0.584	21.9 (20.6–23.3)	21.4 (20.8–24.0)	0.883
Tumor size [median (IQR)] (cm)	3.5 (2.0–5.0)	3.9 (2.0–5.0)	3.5 (2.0–5.5)	0.969	4.0 (2.0–5.0)	3.0 (2.3–4.5)	0.092	3.2 (2.1–5.0)	3.5 (2.3–4.5)	0.885
Mitotic rates [n (%)] (/50 HPF)				0.335			0.669			0.755
≤5	162 (71.1)	116 (73.9)	46 (64.8)		148 (69.5)	165 (73.3)		32 (62.7)	35 (68.6)	
6–10	34 (14.9)	22 (14.0)	12 (16.9)		32 (15.0)	29 (12.9)		12 (23.5)	9 (17.6)	
≥11	32 (14.0)	19 (12.1)	13 (18.3)		33 (15.5)	31 (13.8)		7 (13.7)	7 (13.7)	
Recurrence risk [n (%)]				0.130			0.508			0.870
Very low risk	50 (21.9)	35 (22.3)	15 (21.1)		49 (23.0)	46 (20.4)		8 (15.7)	10 (19.6)	
Low risk	92 (40.4)	70 (44.6)	22 (31.0)		80 (37.6)	100 (44.4)		21 (41.2)	19 (37.3)	
Intermediate risk	44 (19.3)	25 (15.9)	19 (26.8)		44 (20.7)	44 (19.6)		13 (25.5)	15 (29.4)	
High risk	42 (18.4)	27 (17.2)	15 (21.1)		40 (18.8)	35 (15.6)		9 (17.6)	7 (13.7)	

IQR, interquartile range; PSW, propensity score weighting; PSM, propensity score matching.

Table 2 Comparison of intraoperative and postoperative outcomes

Characteristics	Overall population [median (IQR)] (N=228)	Before PSW [median (IQR)]			After PSW [median (IQR)]			After PSM [median (IQR)]		
		L group (n=157)	O group (n=71)	P	L group (n=213)	O group (n=225)	P	L group (n=51)	O group (n=51)	P
Operative time (min)	117.0 (69.0–170.0)	100.0 (62.0–144.0)	155.0 (117.5–218.8)	<0.001	100.0 (64.5–141.5)	149.0 (104.0–197.5)	<0.001	100.0 (59.3–146.3)	150.0 (112.5–236.0)	<0.001
Blood loss (mL)	30.0 (10.0–50.0)	20.0 (10.0–50.0)	50.0 (20.0–100.0)	0.001	30.0 (10.0–50.0)	50.0 (20.0–100.0)	0.002	20.0 (10.0–50.0)	50.0 (20.0–100.0)	0.051
Distance of upper border of tumor to esophagogastric-line (cm)	3.0 (2.0–4.0)	3.0 (2.0–4.0)	3.5 (2.0–4.0)	0.140	3.0 (2.0–4.0)	3.6 (3.0–4.0)	0.002	3.1 (2.1–4.0)	3.5 (2.0–4.0)	0.765
Time to leave bed (d)	2.0 (1.0–2.0)	2.0 (1.0–2.0)	2.0 (2.0–3.0)	0.189	2.0 (1.0–2.0)	2.0 (1.0–3.0)	0.500	2.0 (1.0–2.0)	2.0 (1.0–3.0)	0.166
Time to first flatus (d)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	3.0 (2.0–3.0)	0.733	3.0 (2.0–3.0)	3.0 (2.0–3.0)	0.584	2.0 (1.0–3.0)	3.0 (2.0–3.0)	0.092
Time to liquid intake (d)	3.0 (2.0–5.0)	3.0 (2.0–4.0)	4.0 (3.0–5.0)	<0.001	3.0 (2.0–4.0)	4.0 (3.0–5.0)	<0.001	3.0 (2.0–4.0)	4.0 (3.0–5.0)	0.001
Hospital stay (d)	6.0 (5.0–9.0)	6.0 (4.0–8.0)	7.0 (5.0–12.0)	0.001	6.0 (4.0–8.0)	7.0 (5.0–12.0)	<0.001	5.0 (4.0–8.0)	7.0 (5.0–12.0)	0.001
Type of gastrectomy [n (%)]				0.003			<0.001			0.057
Local excision	192 (84.2)	136 (86.6)	56 (78.9)		181 (85.0)	186 (82.7)		42 (82.4)	39 (76.5)	
Proximal	30 (13.2)	21 (13.4)	9 (12.7)		32 (15.0)	21 (9.3)		9 (17.6)	6 (11.8)	
Total	5 (2.2)	0 (0)	5 (7.0)		0 (0)	16 (7.1)		0 (0)	5 (9.8)	
Other	1 (0.4)	0 (0)	1 (1.4)		0 (0)	2 (0.9)		0 (0)	1 (2.0)	
Rate of receiving adjuvant therapy (%)	19.8	16.6	27.4	0.072	18.4	23.8	0.187	20.8	20.0	0.921

IQR, interquartile range; PSW, propensity score weighting; PSM, propensity score matching.

Table 3 Comparison of postoperative complication

Postoperative complications	Overall population (N=228)	Before PSW			After PSW			After PSM		
		L group (n=157)	O group (n=71)	P	L group (n=213)	O group (n=225)	P	L group (n=51)	O group (n=51)	P
Total [n (%)]	29 (12.7)	14 (8.9)	15 (21.1)	0.010	22 (10.3)	51 (22.7)	0.001	1 (2.0)	13 (25.5)	<0.001
Type [n (%)]				0.115			0.006			0.004
Hemorrhage	2 (0.9)	1 (0.6)	1 (1.4)		1 (0.5)	6 (2.7)		0 (0)	1 (2.0)	
Anastomotic leakage	2 (0.9)	1 (0.6)	1 (1.4)		2 (0.9)	4 (1.8)		0 (0)	1 (2.0)	
Abdominal incision site or intraabdominal infection	5 (2.2)	3 (1.9)	2 (2.8)		3 (1.4)	6 (2.7)		0 (0)	2 (3.9)	
Urinary tract or pulmonary infections	10 (4.4)	5 (3.2)	5 (7.0)		9 (4.2)	11 (4.9)		1 (2.0)	4 (7.8)	
Gastrointestinal dysfunctions	10 (4.4)	4 (2.5)	6 (8.5)		7 (3.3)	24 (10.7)		0 (0)	5 (9.8)	
Clavien-Dindo [n (%)]				0.001			<0.001			0.001
Grade I	12 (5.3)	4 (2.5)	8 (11.3)		8 (3.8)	30 (13.3)		0 (0)	7 (13.7)	
Grade II	13 (5.7)	10 (6.4)	3 (4.2)		14 (6.6)	10 (4.4)		1 (2.0)	2 (3.9)	
Grade IIIa	4 (1.8)	0 (0)	4 (5.6)		0 (0)	11 (4.9)		0 (0)	4 (7.8)	

PSW, propensity score weighting; PSM, propensity score matching.

P<0.05), which were the same after PSM except for blood loss (P=0.051). By contrast, after PSW, the distance between the upper border of the tumor to the esophagogastric line was significant (P=0.002). In addition, four patients in the L group were converted to laparotomy because of a particular tumor location, difficulty in visual field exposure, or technical issues with laparoscopy.

In this study, there were 14 patients in the L group that had postoperative complications: hemorrhage in 1 case, anastomotic leakage in 1 case, abdominal incision site or intra-abdominal infection in 3 cases, urinary tract or pulmonary infections in 5 cases, and gastrointestinal dysfunction in 4 cases. According to the Clavien-Dindo classification of surgical complications (15), 10 cases were grade II and 4 cases were grade I. There were 15 instances of complications in the O group, including one case of hemorrhage, one case of anastomotic leakage, two cases of abdominal incision site or intra-abdominal infection, five cases of urinary tract or pulmonary infection, and six cases

of gastrointestinal dysfunction. According to the Clavien-Dindo classification of surgical complications (15), four cases were grade IIIa, three cases were grade II, and eight cases were grade I. The comparison was statistically significant whether before (P=0.010) or after PSW (P=0.001), which was the same after PSM (*Table 3*).

Before PSW, the rate of receiving adjuvant therapy was 16.6% for the L group and 27.4% for the O group (P=0.072, *Table 2*). The 1-, 3- and 5-year RFS rates were 100%, 98.2% and 98.2% in L group and 100%, 92.8% and 92.8% in the O group, respectively. The 1-, 3- and 5-year OS rates were 99.3%, 98.4% and 97.0% in the L group and 100.0%, 96.1% and 88.5% in the O Group, respectively. There were insignificant differences in RFS (HR: 0.366, 95% CI: 0.074−1.816, P=0.219, *Table 4*, *Figure 2A*) and OS (HR: 0.294, 95% CI: 0.082−1.050, P=0.059, *Table 4*, *Figure 2B*).

After PSW, the rate of receiving adjuvant therapy was 18.4% for the L group and 23.8% for the O group

Table 4 Comparison of long-term survival

Factor	Before PSW			After PSW			After PSM		
	HR	95% CI	P	HR	95% CI	P	HR	95% CI	P
RFS	0.366	0.074−1.816	0.219	0.372	0.072−1.910	0.236	1.075	0.151−7.653	0.942
OS	0.294	0.082−1.050	0.059	0.400	0.119−1.343	0.138	5.018	0.553−45.540	0.152

RFS, relapse-free survival; OS, overall survival; PSW, propensity score weighting; PSM, propensity score matching; HR, hazard ratio; 95% CI, 95% confidence interval.
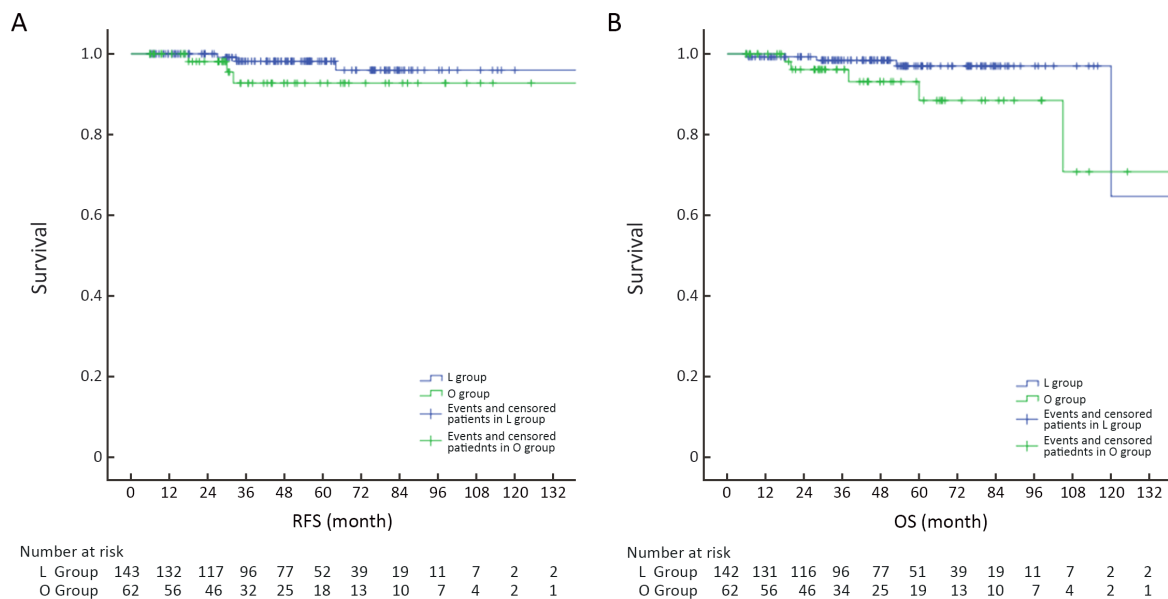
Figure 2 Comparison of RFS and OS. (A) RFS before PSW (P=0.219); (B) OS before PSW (P=0.059). RFS, relapse-free survival; OS, overall survival; PSW, propensity score weighting.

(P=0.187, *Table 2*). There were insignificant differences in either RFS (HR: 0.372, 95% CI: 0.072−1.910, P=0.236) or OS (HR: 0.400, 95% CI: 0.119−1.343, P=0.138) between the two groups (*Table 4*).

After PSM, the rate of receiving adjuvant therapy was 20.8% for the L group and 20.0% for the O group (P=0.921, *Table 2*). There were insignificant differences in either RFS (HR: 1.075, 95% CI: 0.151−7.653, P=0.942) or OS (HR: 5.018, 95% CI: 0.553−45.540, P=0.152) between the two groups (*Table 4*).

Discussion

In the current study, we evaluated the efficacy and safety of laparoscopic surgery for regional and resectable EGJ-GIST and accumulated long-term follow-up data from multiple institutions for comparison with open surgery. Since the first laparoscopic resection was reported by Lukaszczyk *et al.* in 1992 (17), laparoscopic surgery has become the main treatment for GIST patients in recent years. More patients with localized or potentially resectable GISTs prefer laparoscopic to open surgery because it is less traumatic and has a more rapid recovery. Nevertheless, because of the higher risk of tumor rupture and the difficulty of preserving function, the laparoscopic approach for EGJ-GIST is considered technically challenging and is controversial. As is stated in ESMO and NCCN guidelines (8,9), laparoscopic surgery is not encouraged for GISTs located in certain anatomic sites such as the EGJ. In 2018, we reported four types of laparoscopic surgery for EGJ-GIST. Complications and recurrence within the follow-up period had not been reported in patients who underwent laparoscopic reaction for EGJ-GIST (13), which indicated the safety and feasibility of the technique.

In this retrospective cohort study using laparoscopic resection, we found a median operation time of 100.0 min, median intraoperative blood loss of 20.0 mL, median time to oral intake of 3.0 d, median length of hospital stay of 6.0 d, and a postoperative complication rate of 8.9%. Comparatively, the open reaction was associated with longer operative time, more blood loss, longer time to liquid intake, slower hospital discharge, and higher postoperative complications regardless of whether PSW was performed or not. This might suggest that laparoscopic surgery induces less trauma and facilitates quicker recovery with improved short-term effects, as has been reported in previous studies (2,6,10).

Although there have been advances in laparoscopic technique as well as in minimally invasive surgical instruments, it is still hard to expose the EGJ field in the laparoscopic approach, especially in cases of digestive tract reconstruction. In our study, there were four cases of conversion to laparotomy in the L group. In one case, the tumor was located in the posterior gastric wall and it was difficult to expose the anatomical area via laparoscopy because of extensive abdominal adhesions. Among the

others, two tumors were hard to excise laparoscopically because of extensive intra-peritoneal adhesions, and in one case the tumor was estimated to have a high risk of rupture. In addition, intraoperative tumor rupture is a worse prognostic factor than a positive margin because patients with a ruptured GIST have a nearly 100% risk of recurrence (18,19). Consequently, we recommend that the laparoscopic treatment of EGJ-GIST should be carried out only in a medical unit with a strong laparoscopic technology foundation.

Our study shows that operative time in laparoscopic surgery is significantly shorter than in open surgery. Although some studies have reported that laparoscopic resection takes longer operative time than open resection, this might be related to tumor size and location (5,20). In this study, EGJ-GIST tumor size was treated as a covariate, and PSW was used to reduce selection bias. Unlike the findings in Goh's study and Lee's study of tumors of similar size and location, operative time in laparoscopic resection was significantly shorter than in open resection in this research (5,20). We considered that might be a result of the abundant laparoscopic experience with GIST resection in this unit. In addition, the distance from the upper border of the tumor to the esophagogastric line became statistically significant after PSW, which might suggest this factor is meaningful in choosing the surgical approach.

It is important for the surgeon to identify EGJ-GIST accurately during laparoscopic resection, and therefore intraoperative endoscopy plays an increasingly important role. In recent years, with the application of intraoperative endoscopy and the development of minimally invasive instruments, laparoscopic endoscopic cooperative surgery is getting more attention. A multicenter study in Japan showed that laparoscopic and luminal endoscopic cooperative surgery was a safe and feasible procedure (4). In this study there were 17 tumors located at the EGJ, but no patient experienced local or distant tumor recurrence during the follow-up period. Additionally, many new laparoscopic methods with endoscopy assistance were investigated, showing that using intraoperative endoscopy provides a safe and effective method of examination for complete resection of EGJ-GIST and the integrity of the cardia (21-23).

With the rapid advances in the development of endoscopic skill and endoscopic instruments, endoscopic resection has been used for treatment of local GISTs (24). There are a number of research studies showing that compared with surgical resection, endoscopic resection is safe and feasible and has a certain advantage in small gastric GISTs, although perforation and postoperative bleeding could not be totally avoided during and after resection (25-27). However, comparative long-term safety studies of endoscopic resection of GIST are lacking, especially for EGJ-GIST. The reason is that it is hard to preserve cardia function and avoid complications such as cardia stenosis and dysfunction of the cardia sphincter in achieving complete resection of the tumor using endoscopy. Consequently, endoscopic resection is not commonly recommended for EGJ-GIST.

Unlike surgery for other solid tumors, lymphadenectomy is not conventionally performed during GIST surgery because nodal involvement is rare in these patients (i.e., 1.1%−3.4% of cases), which not only decreases the surgical trauma but also relates to the quality of long-term survival (28,29). On the other hand, there are few reports and long-term prognosis data on GIST near the EGJ because of this complex anatomical relationship. Furthermore, studies have shown that most of GISTs carry a mutation in the *KIT* gene (9,30-32), which has led to development of imatinib and other successful drugs. Since imatinib was approved in China in 2010 (10) as effective for use as adjuvant therapy for primary GIST after complete resection, it has greatly prolonged the survival time and improved the quality of life of GIST patients (33-35). The latest NCCN and ESMO guidelines recommend imatinib adjuvant therapy for high-risk GIST patients (8,9), while the Chinese consensus guidelines (2017) advocate that patients with moderate and high risk of recurrence as the adaptive population (36). In the current study, before PSW, the rate of receiving adjuvant therapy was 16.6% for the L group and 27.4% for the O group, which was not a statistically significant difference (P=0.054). After PSW, the rate of receiving adjuvant therapy was 18.4% for the L group and was similar when compared to the O group (23.8%) (P=0.187). In addition, one patient received a neoadjuvant therapy. Based on Choi criteria (37), he was assessed at 6 months as having a partial response (PR). He then had laparoscopic resection and was alive during the follow-up period.

At present, the use of laparoscopic treatment compared with that of laparotomy for GIST still remains controversial. Some studies report the oncological outcome of GIST as based on tumor biology rather than resection type (34,35,38), whereas some studies have found the long-term outcome in the laparoscopic approach superior to that of open surgery for tumors in favorable locations (2,10). In

addition, some randomized control trials comparing open and laparoscopic approaches for colorectal or esophageal cancer have already observed the positive impact of a laparoscopic approach on OS (39,40). However, few studies have compared the long-term outcome between laparoscopic resection and open resection for EGJ-GIST.

In the present report, we use PSW to overcome the different distributions of covariates in the study, achieving the goals of reducing selection bias and increasing credibility. There was no statistical difference in the RFS and OS between the L and O groups whether before or after PSW, but it has been shown preliminarily that laparoscopy has some advantages for long-term prognosis and survival, especially OS. The advantages of laparoscopic surgery might be shown more definitively with a large enough sample size.

In EGJ-GIST, to determine whether laparoscopic surgery can improve the survival rate and long-term prognosis of patients better than open surgery, we need larger samples and more multicenter and randomized controlled clinical trials.

Conclusions

Laparoscopic resection is a safe and efficacious treatment for EGJ-GIST, providing the advantages of shorter operative time, reduced blood loss, earlier time to liquid intake, and quicker hospital discharge, all without compromising postoperative outcomes and survival.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

References

1. Huang Y, Chen G, Lin L, et al. Resection of GIST in the duodenum and proximal jejunum: A retrospective analysis of outcomes. Eur J Surg Oncol 2019;45:1950-6.

2. Piessen G, Lefèvre JH, Cabau M, et al. Laparoscopic versus open surgery for gastric gastrointestinal stromal tumors: What is the impact on postoperative outcome and oncologic results? Ann Surg 2015;

262:831-9; discussion 829-40.

3. Feng X, Li R, Zhang P, et al. Current status of surgical treatment of gastric gastrointestinal tumors: a national multi-center retrospective study. Zhonghua Wei Chang Wai Ke Za Zhi (in Chinese) 2016; 19:1258-64.

4. Matsuda T, Nunobe S, Kosuga T, et al. Laparoscopic and luminal endoscopic cooperative surgery can be a standard treatment for submucosal tumors of the stomach: a retrospective multicenter study. Endoscopy 2017;49:476-83.

5. Goh BK, Goh YC, Eng AK, et al. Outcome after laparoscopic versus open wedge resection for suspected gastric gastrointestinal stromal tumors: A matched-pair case-control study. Eur J Surg Oncol 2015;41:905-10.

6. Xiong H, Wang J, Jia Y, et al. Laparoscopic surgery versus open resection in patients with gastrointestinal stromal tumors: An updated systematic review and meta-analysis. Am J Surg 2017;214:538-46.

7. Chen K, Zhou YC, Mou YP, et al. Systematic review and meta-analysis of safety and efficacy of laparoscopic resection for gastrointestinal stromal tumors of the stomach. Surg Endosc 2015;29:355-67.

8. National Comprehensive Cancer Network (NCCN): Clinical Practice Guidelines in Oncology. Gastrointestinal stromal tumor (GIST). 2019. Version 2. Available online: www.nccn.org/patients

9. Casali PG, Abecassis N, Aro HT, et al. Gastro-intestinal stromal tumours: ESMO-EURACAN clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2018;29(4 Suppl):iv267.

10. Xiong Z, Wan W, Zeng X, et al. Laparoscopic versus open surgery for gastric gastrointestinal stromal tumors: a propensity score matching analysis. J Gastrointest Surg 2020;24:1785-94.

11. Sakamoto Y, Sakaguchi Y, Akimoto H, et al. Safe laparoscopic resection of a gastric gastrointestinal stromal tumor close to the esophagogastric junction. Surg Today 2012;42:708-11.

12. Privette A, McCahill L, Borrazzo E, et al. Laparoscopic approaches to resection of suspected gastric gastrointestinal stromal tumors based on tumor location. Surg Endosc 2008;22:487-94.

13. Xiong W, Zhu J, Zheng Y, et al. Laparoscopic resection for gastrointestinal stromal tumors in

esophagogastric junction (EGJ): how to protect the EGJ. Surg Endosc 2018;32:983-9.

14. Joensuu H. Risk stratification of patients diagnosed with gastrointestinal stromal tumor. Hum Pathol 2008;39:1411-9.

15. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg 2004;240:205-13.

16. Siewert JR, Hölscher AH, Becker K, et al. Cardia cancer: attempt at a therapeutically relevant classification. Chirurg (in German) 1987;58:25-32.

17. Lukaszczyk JJ, Preletz JR Jr. Laparoscopic resection of benign stromal tumor of the stomach. J Laparoendosc Surg 1992;2:331-4.

18. McCarter MD, Antonescu CR, Ballman KV, et al. Microscopically positive margins for primary gastrointestinal stromal tumors: analysis of risk factors and tumor recurrence. J Am Col Surg 2012;215:53-9.

19. Hohenberger P, Ronellenfitsch U, Oladeji O, et al. Pattern of recurrence in patients with ruptured primary gastrointestinal stromal tumour. Br J Surg 2010;97:1854-9.

20. Lee HH, Hur H, Jung H, et al. Laparoscopic wedge resection for gastric submucosal tumors: a size-location matched case-control study. J Am Col Surg 2011;212:195-9.

21. Ye X, Yu J, Kang W, et al. Short- and long-term outcomes of endoscope-assisted laparoscopic wedge resection for gastric submucosal tumors adjacent to esophagogastric junction. J Gastrointestinal Surg 2018;22:402-13.

22. Katsuyama S, Nakajima K, Kurokawa Y, et al. Single-incision laparoscopic intragastric surgery for gastric submucosal tumor located adjacent to esophagogastric junction: report of four cases. J Laparoendosc Adv Surg Tech A 2018;28:78-82.

23. Siow SL, Mahendran HA, Wong CM. Laparoscopic transgastric resection for intraluminal gastric gastrointestinal stromal tumors located at the posterior wall and near the gastroesophageal junction. Asian J Surg 2017;40:407-14.

24. Serrano C, George S. Recent advances in the treatment of gastrointestinal stromal tumors. Ther Adv Med Oncol 2014;6:115-27.

25. Kim GH, Choi KD, Gong CS, et al. Comparison of the treatment outcomes of endoscopic and surgical resection of GI stromal tumors in the stomach: a propensity score–matched case-control study. Gastrointest Endosc 2020;91:527-36.

26. Chen L, Zhang Q, Li F, et al. Comparison of treatment outcomes between laparoscopic and endoscopic surgeries for relatively small gastric gastrointestinal stromal tumors. Surg Oncol 2018; 27:737-42.

27. Feng F, Liu Z, Zhang X, et al. Comparison of endoscopic and open resection for small gastric gastrointestinal stromal tumor. Transl Oncol 2015; 8:504-8.

28. Agaimy A, Wünsch PH. Lymph node metastasis in gastrointestinal stromal tumours (GIST) occurs preferentially in young patients < or = 40 years: an overview based on our case material and the literature. Langenbecks Arch Surg 2009;394:375-81.

29. Li C, Su D, Xie C, et al. Lymphadenectomy is associated with poor survival in patients with gastrointestinal stromal tumors. Ann Transl Med 2019;7:558.

30. Hirota S, Nishida T, Isozaki K, et al. Gain-of-function mutation at the extracellular domain of KIT in gastrointestinal stromal tumours. J Pathol 2001;193:505-10.

31. Rubin BP, Singer S, Tsao C, et al. KIT activation is a ubiquitous feature of gastrointestinal stromal tumors. Cancer Res 2001;61:8118-21.

32. Ganjoo KN, Villalobos VM, Kamaya A, et al. A multicenter phase II study of pazopanib in patients with advanced gastrointestinal stromal tumors (GIST) following failure of at least imatinib and sunitinib. Ann Oncol 2014;25:236-40.

33. Joensuu H, Eriksson M, Sundby Hall K, et al. Adjuvant imatinib for high-risk GI stromal tumor: Analysis of a randomized trial. J Clin Oncol 2016;34:244-50.

34. Joensuu H, Eriksson M, Sundby Hall K, et al. One vs three years of adjuvant imatinib for operable gastrointestinal stromal tumor: a randomized trial. JAMA 2012;307:1265-72.

35. Chok AY, Goh BK, Koh YX, et al. Validation of the MSKCC gastrointestinal stromal tumor nomogram and comparison with other prognostication systems: Single-institution experience with 289 patients. Ann

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Surg Oncol 2015;22:3597-605.

36. Li J, Ye Y, Wang J, et al. Chinese consensus guidelines for diagnosis and management of gastrointestinal stromal tumor. Chin J Cancer Res 2017;29:281-93.

37. Choi H. Response evaluation of gastrointestinal stromal tumors. Oncologist 2008;13(2 suppl):4-7.

38. DeMatteo RP, Ballman KV, Antonescu CR, et al. Adjuvant imatinib mesylate after resection of localised, primary gastrointestinal stromal tumour: a randomised, double-blind, placebo-controlled trial. Lancet 2009;373:1097-104.

39. Lacy AM, García-Valdecasas JC, Delgado S, et al. Laparoscopy-assisted colectomy versus open colectomy for treatment of non-metastatic colon cancer: a randomised trial. Lancet 2002;359:2224-9.

40. Rinieri P, Ouattara M, Brioude G, et al. Long-term outcome of open versus hybrid minimally invasive Ivor Lewis oesophagectomy: a propensity score matched studydagger. Eur J Cardiothorac Surg 2017;51:223-9.