Comparison of laparoscopic and open resections for gastric gastrointestinal stromal tumors (GISTs)

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Emir Çapkınoğlu*, Evren Durak*/**, Nihan Acar**, Turan Acar**, Erdinç Kamer**, Mehmet Haciyanlı**

Department of General Surgery, Bakirkoy Acibadem Hospital, Bakirkoy, Istanbul, Turkey
Department of General Surgery, Katip Çelebi University Atatürk Training and Research Hospital, Izmir, Turkey

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BACKGROUND: *Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors of the gastrointestinal tract. Today surgical resection is still the treatment of choice for primary gastric GISTs. This study compares the laparoscopic versus open surgical resection approaches of gastric GISTs.*
METHODS: *A retrospective chart review was conducted from our database, and 68 primary gastric GIST resections were found to be performed in our center between 2008- 2020. Of these 68 patients, 57 were included for the study. Open resection was performed in 32 patients, and laparoscopic resection was performed in 25 patients. The medical records were examined and compared for clinical, pathologic and surgical results according to preferred surgical method of choice.*
RESULTS: *Fifty-seven patients were qualified for the study. The average diameter of the tumor was 4.8 ± 1.91 cm in the laparoscopic group, and 6,8 ± 4,27 cm in open group. Estimated blood loss during the surgery was significantly lower in laparoscopic group patients (100.7 ml vs 287.5 ml) ($p< 0.001$) and also length of stay was shorter compared with open at 4.4 versus 11.9 days ($p < 0.001$). Laparoscopic group patients needed less pain medication, and they had quicker return to daily life.*
CONCLUSIONS: *Laparoscopic approach is safe and feasible with acceptable oncologic outcomes and certain benefits like decreased length of stay, less complication rates and better comfort. The preference of laparoscopic resection should be decided not only on tumor location or diameter but also surgeon's laparoscopic surgical experience.*

KEY WORDS: Laparoscopic, Gastric resection, GISTs

Introduction

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumor of the gastrointestinal tract [1, 2]. They are frequently located in the stomach (50%) followed by the small bowel (25%), colon (10%), omentum –mesentery and esophagus [3]. The clinical presentation of GISTs may vary with broad spectrum findings. The most common symptoms are GI bleeding and non-specific abdominal pain, and interestingly mostly not related to the location of the tumor [4-8]. Some GISTs may be asymptomatic and are discovered incidentally [9]. Tumor size, tumor location, number of mitoses (per 50 high-power fields) and proper surgical technique are the significant factors affecting the prognosis [8,10,11]. Complete surgical resection is the standard treatment for primary/non-metastatic GISTs. Negative margins and (since they are fragile lesions) pseudo-capsule integrity are the essentials regardless of the surgical fashion [12]. A meticulous effort should be put for the integrity of pseudo-capsule during surgical resection to avoid peritoneal seeding [10,13].
The advantages of laparoscopic resection for GISTs have been defined in many comparative studies [2,4,14]. It has been demonstrated that laparoscopic resection of the gastric GISTs is feasible and safe when surgeon has strict

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Correspondence to: Emir Çapkınoğlu, MD, Department of General Surgery, Bakirkoy Acibadem Hospital, Bakirkoy, Istanbul, Turkey (e-mail: emircapkinoglu@gmail.com)

adherence to oncologic surgical principles [8]. Today, laparoscopic partial or wedge resection with negative margins is adequate for most of the gastric GISTs. On the other hand, open resection or wider gastrectomies are still in use according to the surgeons experience, the tumor size and location [2,7,13].

In this study, we aimed to assess the feasibility and safety of laparoscopic fashion for gastric GISTs, and to compare the results of open and laparoscopic surgery. We hypothesized that laparoscopic approach offers excellent benefits in terms of classical advantages of minimal invasive surgery and oncological principles even for gastric GISTs larger than 5 cm in experienced hands of minimal invasive surgeons.

Materials and Methods

The study consisted of 57 patients who underwent surgery due to a primary gastric GIST between September 2008 and June 2020, and was conducted under the institutional review board approval in Katip Celebi University Ataturk Training and Research Hospital, Izmir, Turkey (Approval no: 1135/ Date: 24.12.2020). Medical records were reviewed retrospectively on the institutional database. Patients were divided into two groups according to the surgical approach (open vs laparoscopic).

Eleven patients with inconsistencies in their chart records, patients with non-gastric GISTs, and patients with diffuse metastatic disease, multifocal tumors or incidental tumors were excluded.

Patient demographics and clinical presentation were analyzed by using chart review. Following parameters were recorded: Tumor size, tumor location, negative margin status, mitotic index, CD 117, desmin and SMA stainings, operative time, intraoperative and postoperative complications, blood loss, any sign or evaluation of leak, length of hospital stay (LOS), return of gastrointestinal function. Surgical site infection, intraabdominal abscess, infectious complications including urinary tract infection and pneumonia, postoperative bleeding, deep vein thrombosis, pulmonary embolism, cardiac complications and any re-hospitalization were reviewed for early postoperative period (first 30 days). Presence of recurrence and hernia formation were also documented as long-term data. The patients were followed every 3 months with physical exam, abdominal computed tomography (CT) scan every 6 months, and a PET-CT scan every year. Upper GI endoscopy was scheduled in the presence of symptoms.

Different surgical teams performed the procedures, and the surgeons experienced in advanced laparoscopy fulfilled the laparoscopic resections. In the laparoscopic group, procedures were performed with three-trocar technique. Anterior and posterior lesions of the stomach were resected through opening the whole layers of the stomach wall and closing with preferably sutures. Endoscopic linear staplers were only preferred for pedunculated lesions. Posterior wall lesions were either resected both opening anterior wall and directly through the mobilizing and resecting posterior wall or direct mobilizing and resecting posterior wall as well. All specimens resected laparoscopically were taken to the pathology department fixed on foam base by the operating surgeon immediately after the operation to eliminate the misevaluations regarding the margins and orientation. In open group, the procedures were performed with midline laparotomy. Wedge resections, partial resections, subtotal or total gastrectomies were employed.

Selection criteria for the laparoscopic approach was defined by the surgeon often depending on the technical resources of the facility. Location or size of the tumor was not an exclusion criterion for laparoscopic approach.

Statistical Analysis

For discrete and continuous variables, descriptive statistics (mean, standard deviation, median, minimum value, maximum value, and percentile) were given. In addition, the homogeneity of the variances, which is one of the prerequisites of parametric tests, was checked through Levene's test. The assumption of normality was tested via the Shapiro-Wilk test. To compare the differences between the two groups, the Student's t test was used when the parametric test prerequisites were fulfilled, and the Mann Whitney–U test was used when such prerequisites were not fulfilled. Chi-square test was used for determining the relationships between two discrete variables. When the expected sources were less than 20%, values were determined through the Monte Carlo Simulation Method in order to include such sources in analysis. Also age and body mass index (BMI) variables were determined as covariance (to be excluded) and groups were compared with covariance analysis.

In the study, Binary Logistic Regression analysis was used to reveal the model of the relationship between independent variables and dependent variables. In addition, the Surival life time were estimated according to the Kaplan-Meier estimator. While comparing the survival times of the groups, evaluation was made with the Log Rank test. For the significance level of the tests, $p < 0.05$ and $p < 0.01$ values were accepted.

The data were evaluated via SPPS 25 (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.). $p<0.05$ and $p<0.01$ were taken as significance levels.

Results

Of the 57 patients with gastric GİST, 32 (56%) underwent open and 25 (44%) underwent laparoscopic resec-

Table I - *Demographics and clinical features of the patients.*

Variables	Total group (n=57)	Open group (n=32)	Laparoscopic group (n=25)	p value
Age				
Mean±SD	59.32±12.48	58.97±13.06	59.76±11.94	0.81
Median	60.80 (32-89)	59.40 (33-89)	62 (32-76)	
Sex				
Female	32 (56.1)	18 (56.2)	14 (56)	
Male	25 (43.9)	14 (43.8)	11 (44)	
Operation(%)				
Wedge	43 (75.4)	21 (65.7)	22 (88)	0.032
Gastrectomy	14 (24.6)	11 (34.3)	3 (12)	
Tumor Localization(%)				
Proximal	17 (29.8)	2 (9.5)	2 (15.4)	0.527
Mid-Distal	40 (71.2)	19 (90.5)	11 (84.6)	
Tumor Size(cm)				
Mean ± SD	5.82±5.09	6.59±4.27	4.84±1.91	0.040
Operation Time(min)				
Mean±SD	126.60 ± 52.32	142,38±61.06	106.4±28.56	0.010
Median	117.75 (30-400)	121.50 (80-400)	108.33 (30-145)	
Hospital Stay				
Mean±SD	8.5±6.4	11.8±6.9	4.4±1.4	0.001
Median	7 (3-35)	9 (3-35)	4 (3-8)	
Postop analgezic use (hour)				
Mean±SD	55.7±24.4	68.2±21.2	39.8±18.8	0.001
Median	52.5 (24-96)	66.5 (48-96)	36 (24-96)	
Intraop Bleeding(cc)				
Mean±SD	205.2±196.2	287.5±223.6	100±69.2	0.001
Median	222.2 (100-1200)	150 (0-500)	82.5 (50-200)	
Realimentation(day)				
Mean±SD	2.8±1.6	3.5±1.8	2.0±1.0	0.001
Median	2.6 (1-12)	3.2 (2-12)	1.9 (1-4)	

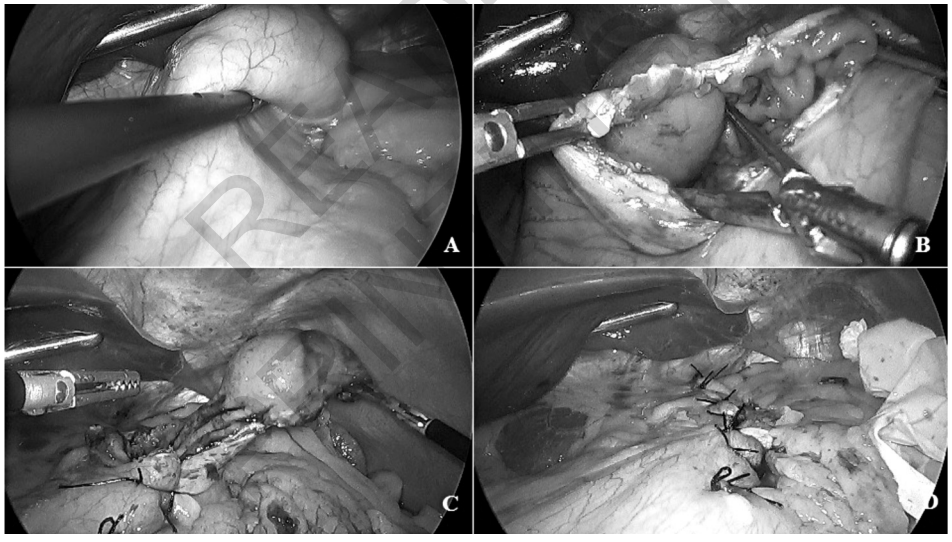

Fig. 1: Step by step laparoscopic resestion; A)GIST located in greater curvature; B) Opening the gastric wall with energy device; C) Resection of the tumor; D) Suturing the gastric wall intracorporeally.

tion. Mean ages were 59.7 years (range: 40-82) and 58.9 years (range: 43-76) in open and laparoscopic groups, respectively. Majority of the patients in both groups were female. Eighteen patients in open group and fourteen in laparoscopic group were female. There was no significant difference between laparoscopic and open group based on age and gender (Table I).

The mean BMI score was 26.89 ±6.33 in open group and 27.33 ± 2.53 in laparoscopic group, and there was no statistical significant difference. Although presence of previous abdominal operation was slightly more frequent in open group, the difference was not statistically significant.

Twenty-three of the laparoscopic group patients under-

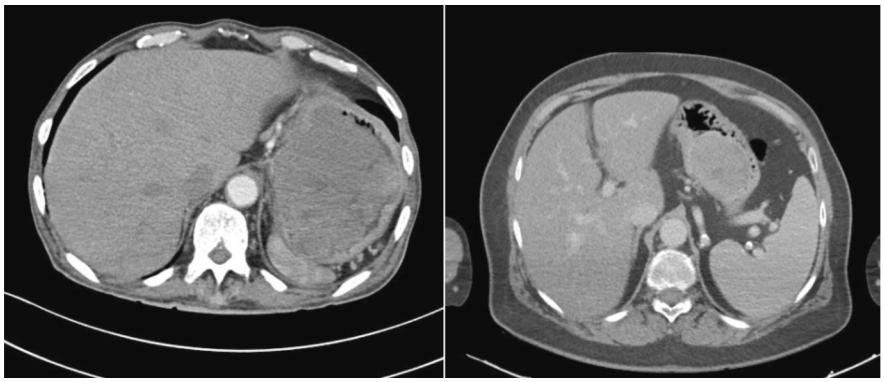

Fig. 2: CT images of two patients'.

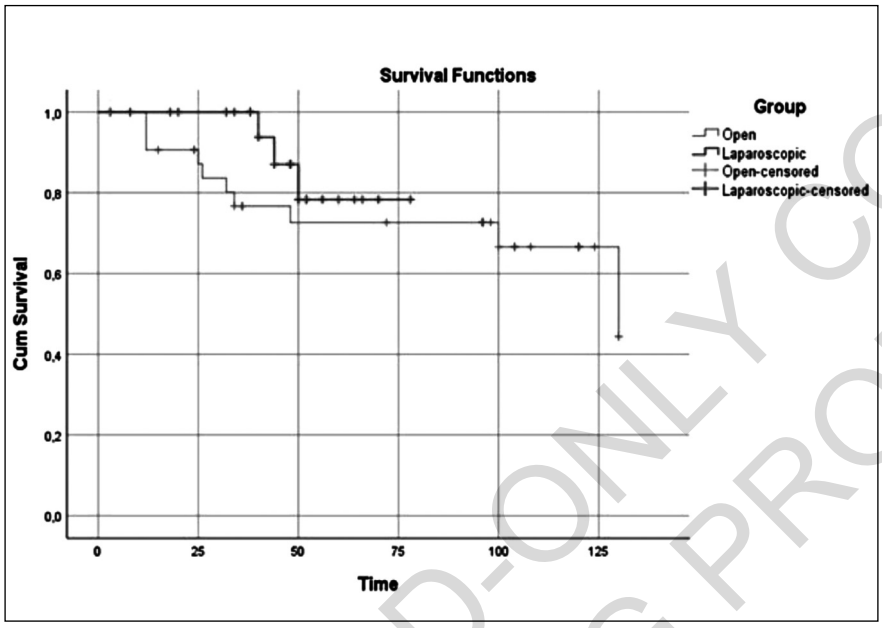

Fig. 3: Kaplan-Meier survival analyses of all patients.

went resection by either opening stomach wall with an adequate surgical margin followed by the closure with laparoscopic intracorporeal sutures (Fig. 1).

Remaining two patients underwent laparoscopic distal gastrectomy. In the open group, type of the procedures were non-anatomic wedge resection in 21 patients, distal gastrectomy in five patients and total gastrectomy in six patients.

The mean operative time, which was not statistically different in open and laparoscopic groups, was 127±32.6 minutes vs 91± 47.8 minutes, respectively. The average blood loss was significantly less in laparoscopic group, 100 ml vs 287 ml ($p < 0.001$).

The mean tumor size was 4.8 cm for laparoscopic group, and 6.5 cm for open group patients. The difference between open and laparoscopic groups in terms of tumor size was not statistically significant (Fig. 2).

In the laparoscopic group, one patient underwent concomitant laparoscopic anterior resection due to synchronous adenocarcinoma of the colon, one patient underwent cholecystectomy (gallstone disease), and one patient underwent epigastric hernia repair. In one patient from laparoscopic group, following the positivity of intraoperative frozen section evaluation of margins, resection site was enlarged and repeated histologic exam cleared margin positivity.

All tumors in both groups were resected with negative margins and pseudo-capsule integrity was complete after the pathologic review of the specimens. Histopathologic investigation demonstrated that c-KIT (CD117) positivity was 46.57% and 34% in open and laparoscopic groups, respectively. The number of patients in both groups with fewer or more mitotic rate than 5 mitoses per 50 high-power field are shown in Table II. Twelve patients had less than 5 mitoses in laparoscopic group and 17 patients in open group. Thirteen of the patients had more than 5-10 mitoses in laparoscopic group thus 15 patients in open group. The difference between two groups in terms of mitotic rate was not statistically significant. According to well-accepted Fletcher's classification, our patients were allocated into low, intermediate and high risk during postoperative consultations.

Length of hospital stay for the laparoscopic group was 4.4±1.4 days compared with 11.8±6.9 days for the open group patients, and the difference between two groups was significant ($p <0.001$).

Table II - *Histopathologic features of the tumors.*

Variables	Total group (n=57)	Open group (n=32)	Laparoscopic group (n=25)	p value
CD117				0.110
Positivity	41.0544±29.13	46.57±26,59	34±31,22	
	37.5 (0-100)	42.1 (1-100)	20 (0-100)	
Ki67				0.190
(% Proliferation Index)	4.89 ± 7.12	5.94±8.42	3.56±4.84	
	1.97 (0-35)	2.33 (0-35)	1.73 (0-20)	
RISK				0.724
Low	25 (44.0)	17 (3.1)	12 (48)	
Middle, High	32 (56.0)	15 (46.8)	13 (52)	
Mitotic rate (per 50 HPF)	14.59±32.07	20.5±39.86	7.04±15.56	0.090

Oral intake was restored in 2.04±0.93 days for laparoscopic group and 3.53±1.87days in open group patients and the difference between two groups was statistically significant. Laparoscopic group patients also needed less pain medicine during postoperative follow-up. In open group, surgical site infection (n:3), wound dehiscence (n:2), pneumonia (n:2), deep vein thrombosis (n:1) and bleeding (n:3) developed. Bleeding was managed conservatively in two patients, while the remaining one required reoperation. Four patients had urinary tract infection, two had trocar site hematoma, and one had partial pneumothorax in laparoscopic group. None of these patients required additional invasive intervention.

The median follow- up period in laparoscopic and open groups was 44.12±18.48 and 72.31±43.34 months, respectively. Local recurrence and/or metastasis was detected in 10 patients from open group and three patients from laparoscopic group. This may be explained by their low mitotic index, meticulous dissection and care during surgery, since smaller diameter lesions were enrolled for laparoscopic approach and other patient factors but we do not have statistically meaningful data to support this.

The median follow up period was significantly longer in open group and recurrence rate was also greater in this group of patients. In the open group, seven patients had radiologic uptakes during PET CT investigatons and three patients had multiple liver and peritoneal metastases. Of these, one patient was lost with metastatic disease related complications.. During the follow-up, incisional hernia was recorded in three patients from open group, and trocar site hernia was detected in one patient from laparoscopic group. Kaplan-Meier survival analyses is given in Fig. 3. Although patients from open group had longer follow-up period and better survival, the outcomes of laparoscopic group was statistically more promising.

Discussion

GISTs are relatively rare mesenchymal tumors of the GI system [1,2]. According to NCCN guidelines, surgery is the standard first-line therapy for gastric GISTs [15]. The resection with negative microscopic margins with an intact pseudo-capsule is the main goal of surgery [1,2,4]. Wide excision with lymphadenectomy is not indicated since gastric GISTs do not have tendency to invade through the gastric wall [5,7,8]. Wedge resection for gastric GISTs is the preferred procedure with acceptable oncologic principles [14].

There has been reports in the literature demonstrated the safety of the laparoscopic resection of the gastric GISTs [6-7,10]. Today, even GISTs located at esophagogastric junction and also at posterior gastric wall could be resected successfully with acceptable short and long-term results compared to open surgery [16]. We represent in our series comparing the open versus laparoscopic approach for the gastric GISTs. Laparoscopic resections have been performed widely recently with well-known advantages of minimal invasive surgery such as more comfortable perioperative period, less blood loss, shorter operative times, earlier return to daily life and work [2,4,7,17]. Among them, laparoscopic wedge resections, mucosa preserving resections, resection through opening the whole layers of stomach and laparoscopic gastrectomies have been described according to location and size of the tumor and experience of surgeon on minimally invasive surgical techniques [5,8,14].

Whatever the technique, the ultimate goal was accepted by all guidelines as providing microscopically negative margins and preserving tumor pseudo-capsule integrity [5,14]. Not only negative margin and pseudo-capsule integrity but the tumor size, mitotic index of the lesion, CD 117 and CD 34 status and also other histopathologic markers may play a role on the overall survival [2,4,7,8]. CD 117 expression is one of the most important diagnostic markers for the evaluation of GISTs. And also Wild-type GISTs(neither KIT nor PDGFRA have mutations) are deficient in succinate dehydrogenase [18].

The difference in tumor size between open and laparoscopic groups was not statistically significant in our series. We performed successful laparoscopic resections for GISTs up to 10 cm with intact pseudo-capsule.

Laparoscopic group patients even with the tumors larger than 5 cm had low morbidity and similar long term

recurrence-free follow-up to other group of patients in our series (Fig. 3).

There was no significant difference with respect to age during the operation, gender and clinical presentation. Although the tumor size was larger in open group patients, the mitotic rate was slightly lower in laparoscopic group patients. There were no significant differences in CD 117 and CD 34 status between two groups. The number of mitoses per high-power is one of the significant markers for recurrence of GISTs [6,8,13]. It has been shown that the tumors with more than 5 mitoses and larger than 5cm in size have higher risk for recurrence [7,11].

The laparoscopic group patients in our series had an obvious advantages of minimal invasive approach: earlier return of bowel function, less need for pain medicine and shorter LOS.

The best approach to resect gastric GISTs mostly based on tumor size and location. The number of patients in studies comparing minimally invasive approaches versus open surgery is still limited but we believe the successful laparoscopic resection for gastric GIST s largely depends on the minimal invasive skills of the surgeon. We also suggest that laparoscopic surgery can be considered for all gastric GISTs if the operating surgeon has reliable intracorporeal suturing skills. In our laparoscopic group, six patients had tumors located at the posterior wall of the stomach and these tumors were larger than 5 cm. Of these, two were attached to the pancreatic capsule, and resection was completed with intact pancreatic capsule tissue. None of these patients developed pancreatic leak during the postoperative follow-up. Laparoscopic resections were performed in our series with our unique technique which consist of opening gastric wall with energy devices with acceptable margins (generally at least 1.5-2 cm from the tumor edge) and suturing gastric wall intracorporeally step by step. By using this technique, adequate surgical margins were confirmed under direct vision, and also eliminated the need for intraoperative endoscopic confirmation. We recommend the use of hot jaw of the energy device upward, since the thermal damage of the jaw may cause invert contraction of the stomach wall and this phenomena may endanger the surgical margin safety. Although this technique demands high laparoscopic skills in order to perform intracorporeal suturing in difficult angles, we also recommend single layer interrupted stitches for gastric wall closure. This intracorporeal suturing technique has advantages like retracting suture line with gentle maneuvers and observing suture line cautiously for possible hemorrhagic foci. We utilized reusable laparoscopic needle holders Ethicon E 705 R (Ethicon, J&J,Connecticut, USA) and were able to finish laparoscopic resections with cost effective operating theatre expenditures. All specimens were placed in to the endo-bags to prevent peritoneal spillage during the intracorporeal suturing. There were no trocar site metastases in our laparoscopic group patients and this can be attributed to meticulous attention was employed during manipulation and resection of the tumor. Two patients had tumors located in the lesser curvature, and in these patients laparoscopic resection was started from medial to left lateral since this approach enabled the surgeon put the stay stitches to a reliable distance from the tumor also to maintain pseudocapsule integrity during the resection.

All specimens in laparoscopic group were taken to pathology department by operating surgeon right after the operation to minimize misunderstanding and misinterpretation for the tumor orientation. Resected tumor was fixed with pins on the white foam and lesions were brought to pathology department as fresh tissue.

Although not applicable for our laparoscopic cases we also suggest that all specimens resected by using Endo GIA should be brought by surgeon to pathology department and staple line close to surgical margin should be removed before the specimen is given to pathologist. This prevents wrong tissue sampling for surgical margin examination. Endoscopic staplers also may cause tumor rupture once they closed and fired, and reduce secure negative margin distance in some cases. These are the main reasons why we prefer open and suture step –by-step technique during laparoscopic resection. Today total number of our laparoscopic cases is increasing and we are still collecting follow up data from the rest of our patients. There are some limitations regarding this study. First, this is a retrospective and a single-center study. However, it does not seem easy to establish prospective randomized multicenter studies due to the rarity of these tumors. Second, we have 57 patients in this study. Further studies with more patients are required for better outcomes.

In conclusion, laparoscopic resection is safe and effective surgical procedure for gastric GISTs in terms of feasibility and oncologic outcomes. Laparoscopic approach provides obvious benefits over open resections including less operative blood loss, shorter length of stay and faster recovery. Our findings indicate that laparoscopic approach can be the operation of choice in patients with gastric GISTs regardless of location and size of the tumor. Advanced laparoscopic experience and intracorporeal suturing skills are required to perform entirely laparoscopic resections with strict oncologic surgical principles. Extreme caution should be taken on providing appropriate margins and avoiding rupture of the pseudo-capsule during laparoscopic resection of gastric GISTs. This technique provides excellent margins and operative reliability although laparoscopic suturing in difficult angles is technically.

Riassunto

I tumori stromali gastrointestinali (GIST) sono i tumori mesenchimali più comuni del tratto gastrointestinale. A

tutt'oggi per i GIST gastrici primitivi la resezione chirurgica è il trattamento di scelta. Questo studio confronta la resezione chirurgica laparoscopica dei GIST gastrici rispetto a quella della chirurgia ad addome aperta.
Per lo studio è stata effettuata una revisione retrospettiva sulle cartelle cliniche dal nostro archivio, individuando 68 resezioni gastriche per GIST primitivo tra il 2008 e il 2020. Di questi 68 pazienti, 57 sono stati inclusi nello studio. La resezione ad addome aperto è stata eseguita in 32 pazienti e quella con tecnica laparoscopica in 25 pazienti. Le cartelle cliniche sono state esaminate e confrontate per i risultati clinici, anatomo-patologici e chirurgici rispetto alla tecnica chirurgica adottata.
Risultati – Tra i 57 pazienti inclusi nello studio, il diametro medio del tumore era di 4,8 ± 1,91 cm nel gruppo laparoscopico e di 6,8 ± 4,27 cm nel gruppo ad addome aperto. La perdita di sangue stimata durante l'intervento è stata significativamente inferiore nei pazienti del gruppo laparoscopico (100,7 ml vs 287,5 ml) (p <0,001) e anche la durata della degenza postoperatoria è stata più breve rispetto a quella degli operati con laparatomia: 4,4 rispetto a 11,9 giorni (p <0,001).
I pazienti del gruppo laparoscopico hanno richiesto minore uso di farmaci antidolorifici con un ritorno più rapido alla vita quotidiana.
Conclusioni: L'approccio laparoscopico è sicuro e fattibile con esiti oncologici accettabili e alcuni benefici come una riduzione della durata della degenza, minori tassi di complicanze e un miglior comfort. La preferenza per la resezione laparoscopica dovrebbe essere decisa non solo sulla posizione o sul diametro del tumore, ma anche sull'esperienza chirurgica laparoscopica del chirurgo.

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