

# Surgical Option for Intestinal Gastrointestinal Stromal Tumors – Perioperative and Oncological Outcomes of Laparoscopic Surgery

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**Abstract.** *Background/Aim: Laparoscopic surgery (LS) is being adopted for gastrointestinal stromal tumors (GISTs) of the stomach. Few studies have examined the outcome of LS for intestinal GISTs. In the present study, we evaluated the outcomes of LS for intestinal GISTs. Patients and Methods: This study was a prospective-collecting retrospective review of 85 patients with intestinal GISTs who underwent LS or laparotomy in 102 months. The demographic data and oncological outcomes were compared. Results: The cohort included 85 patients (26 LS and 59 laparotomy patients). The LS group presented earlier oral resumption and a shorter hospital stay. The recurrence rate, recurrence-free and overall survival were comparable. Tumor size greater than 7 cm [risk ratio (RR)=4.148; p=0.022] and mitotic index of greater than 5/50 high-power fields (RR=5.500; p=0.002) were two predictors for tumor recurrence. Conclusion: The study demonstrated that LS for intestinal GISTs leads to oncological outcomes comparable to those of laparotomy. Moreover, LS was associated with favorable perioperative recovery and a shorter hospital stay. With strict precautions, LS is a safe and effective procedure for intestinal GISTs.*

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors arising within the gastrointestinal (GI) tract. GISTs are thought to arise from the interstitial cells of Cajal (1, 2). These tumors most

frequently occur in the stomach (60%) or intestine (30%) (3, 4). Lymphatic spread is rare; thus, the treatment of choice for localized primary GISTs is complete surgical resection with clear margins (5, 6). For this reason, GISTs are often removed by limited resection when technically feasible, rather than by formal *en bloc* resection. Surgical resection of GISTs has been traditionally performed by laparotomy (4). Currently, laparoscopic surgery (LS) is being increasingly adopted as a minimally-invasive approach to treatment of GISTs (7, 8). Immediate outcomes of LS are comparable to those of laparotomy in terms of blood loss, operative time, and postoperative recovery (9, 10). More recently, research has demonstrated that long-term oncological outcomes after LS to remove gastric GISTs are comparable to those after laparotomy (11, 12).

Intestinal GISTs are thought to have a more aggressive malignant potential than gastric GISTs (4, 13, 14), and adopting LS as a treatment for intestinal GISTs requires further investigation. Only a few studies have examined the applicability of LS for intestinal GISTs (15-18). Furthermore, LS has only been used for small-sized intestinal GISTs; for medium-sized GISTs, there is no clear evidence that LS is safe or feasible.

In the present study, we sought to determine the feasibility of LS for removal of intestinal GISTs and examined the impact of this surgical option on perioperative and oncological outcomes.

## Patients and Methods

**Study design.** We prospectively collected data from all patients who underwent surgical resection of intestinal GISTs between January 2005 and June 2013 at Chang Gung Memorial Hospital (CGMH) in Linkou, Taiwan, and retrospectively reviewed these data. The Internal Review Board of CGMH approved this study No.102-4798B. We included patients with GISTs in the jejunum and ileum in this study. Demographic information and medical, operative, postoperative, and pathological records were prospectively collected

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**Key Words:** Laparoscopic surgery, gastrointestinal stromal tumor, intestinal GIST, overall survival, recurrence-free survival, small bowel GIST.

in a computerized database. In this study, we performed both LS and laparotomy to remove intestinal GISTs. Demographic information was collected, along with the results of physiological and clinical analyses. Additionally, perioperative findings, operative time, amount of blood loss, and conversion to laparotomy were recorded. Relevant postoperative outcomes were also recorded, including time to resumption of oral intake, duration of use of parenteral or epidural analgesics, and postoperative length of hospital stay (LOS). The follow-up time was defined as the time from the operation until recurrence or until December 2013. We excluded patients with tumors greater than 10 cm in size. Patients with tumors located in the duodenum were excluded because of the complexity of the surgical procedure. Patients who concurrently had other types of malignancies were also excluded (Figure 1).

Nasogastric tubes were routinely used and were removed on postoperative day 2 unless the drainage volume exceeded 200 ml. Oral intake was resumed when bowel movement began. During follow-up, the patients underwent a physical examination and an abdominal computed tomography (CT) scan every 3 to 6 months. Tumor recurrence and metastasis were documented during the follow-up period. When tumor recurrence was observed, patients were given imatinib mesylate (Gleevec®, 400 mg daily; Novartis, Basel, Switzerland).

**Histological classification.** Tumor pathology was reviewed to determine the size, anatomic location, mitotic index [number of mitoses per 50 high-power field (HPFs)], and resection margins. The risk assessment was described according to the National Comprehensive Cancer Network (NCCN) criteria (5); tumor spillage was defined during the operation, and microscopic rupture was defined as a break in the intact GIST pseudocapsule, as observed under a microscope.

**Surgical technique.** Various surgeons experienced in minimally-invasive surgery performed the laparoscopic resections. For the operation, the patients were placed in a lithotomy position under general anesthesia, and a nasogastric tube and a Foley tube were inserted. After the insertion of ports and establishment of the pneumoperitoneum, we identified the tumor before proceeding and avoided direct tumor manipulation (Figure 2A). We grasped the neighboring bowel or mesentery during manipulation and evaluation (Figure 2B). The GI tract and mesentery were evaluated from the ileocecal valve to the Treitz ligament to exclude the possibility of concurrent lesions. The peritoneal cavity was checked for possible seeding nodules. For exophytic tumors, we covered the lesion with a sterilized bag to protect against laceration of the capsule. Intracorporeal bowel resection was performed using linear staples, and the mesentery was divided using an ultrasonic instrument. The specimen was protected in a sealed, sterilized bag (Figure 2C). The umbilical incision was extended, and we inserted a wound retractor (Applied Medical, Rancho Santa Margarita, CA, USA) to make the incision as wide as possible. The specimens were removed from this incision with double protection (sterilized bag and wound retractor). For tumors that were difficult to remove, the incision was extended to a maximum of 6 cm to prevent crushing of the tumor. Next, we performed intracorporeal side-to-side anastomosis with linear staples or end-to-end handsaw anastomosis *via* the umbilical incision (Figure 2D). No drain was left after the operation. We switched to laparotomy if the incisions needed to be expanded to more than 6 cm.

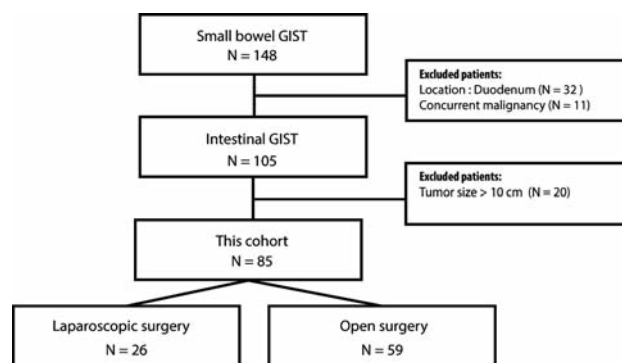


Figure 1. Diagram describing cohort identification. GIST: Gastrointestinal stromal tumor.

## Results

**Study population.** The cohort included 85 patients: 26 in the LS group and 59 in the laparotomy group. The mean age was 58.9 years for the LS group and 59.9 years for the laparotomy group (Table I). Eighty patients (94.1%) were symptomatic. The most common symptoms in both groups were GI bleeding (52.9%), abdominal pain (22.9%), and anemia (18.6%). Between the LS and laparotomy groups, there were no significant differences in age ( $p=0.576$ ), gender ( $p=0.799$ ) or clinical symptoms ( $p=0.639$ ).

**Perioperative aspects.** The American Society of Anesthesiology scores of patients in the LS and laparotomy groups were comparable ( $p=0.271$ ). The overall operating time was significantly shorter in the LS group than in the laparotomy group ( $p=0.001$ ). There was less blood loss in the LS group than in the laparotomy group ( $p=0.051$ ). There were two conversions to laparotomy in the LS group due to the presence of a large tumor that needed to be resected. Patients in the LS group resumed oral intake earlier than patients in the laparotomy group ( $p<0.001$ ). The laparoscopic approach was associated with a significantly earlier return of bowel function and resumption of diet. The duration of parenteral and epidural analgesic was significantly shorter in the LS group than in the laparotomy group ( $p<0.001$ ), as was the average length of postoperative hospital stay ( $p=0.025$ ). There was one postoperative complication (intra-abdominal abscess) in the LS group, and there were two patients (3.4%) with complications in the laparotomy group (one pneumonia and one intra-abdominal abscess). There were no perioperative mortalities in the LS group within 30 days after the operation, while one patient died due to profound sepsis in the laparotomy group during this period (Table I).

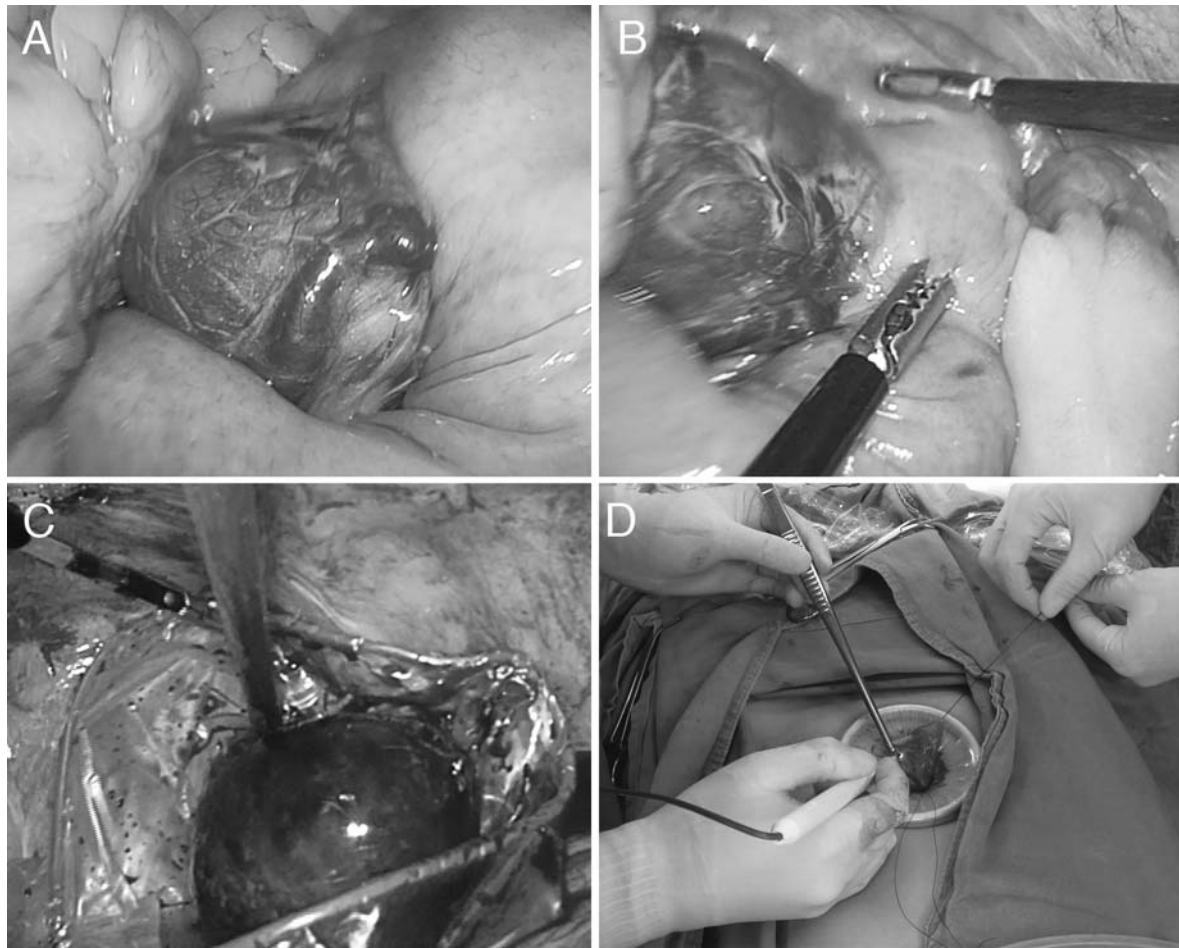


Figure 2. A: An intestinal gastrointestinal stromal tumor was identified. B: Grasping the neighboring bowel or mesentery to avoid of direct manipulation of the tumor. C: The specimen was protected in a sterilized bag. D: Handsaw anastomosis can be performed via the umbilical incision.

**Tumor characteristics.** The pathological characteristics of the patients are summarized in Table II. There was no significant difference in tumor size between the LS and laparotomy groups ( $p=0.155$ ). There was no tumor spillage during operation in the LS group, but two tumors had spillage in the laparotomy group. There were two microscopic tumor ruptures in the LS group and six microscopic ruptures in the laparotomy group.

Regarding anatomic distribution, there were 19 tumors located at the jejunum in the LS group and 41 in the laparotomy group. There were seven tumors located at the ileum in the LS group and 18 in the laparotomy group. According to NCCN criteria, only five tumors (5.9%) were classified as having no risk, while 28 (32.9%) as having high risk for recurrence. There was no statistically significant difference in NCCN classification between the LS and laparotomy groups ( $p=0.229$ ).

**Follow-up.** The median follow-up time was longer in the laparotomy group than the LS group but not significantly different (44.9 months vs. 24.3 months, respectively;  $p=0.137$ ). Four patients (17.4%) in the LS group and 13 patients (22.4%) in the laparotomy group experienced recurrence ( $p=0.316$ ). There was no difference in recurrence-free survival (RFS) between the LS and laparotomy groups ( $p=0.871$ , Figure 3).

Patients with recurrent disease were then treated with imatinib. Thus far, seven patients with GIST in the laparotomy group have died, while there have been no mortality in the LS group. However, there is no difference in the Kaplan–Meier curves for overall survival (OS) between the laparotomy and LS groups for intestinal GISTs ( $p=0.208$ ) (Figure 4).

**Risk analysis.** The significant univariate predictors of tumor recurrence were tumor size greater than 7 cm [risk ratio

Table I. Comparison of demographic and perioperative data between patients who underwent laparoscopic surgery (LS) and laparotomy for intestinal gastrointestinal stromal tumor.

	LS group N=26	Laparotomy group N=59	p-Value
Mean±SD age (years)	58.0±13.4	59.9±14.9	0.576
Male gender, n (%)	14 (53.8%)	30 (50.8%)	0.799
Symptoms, n (%)	24 (92.3%)	56 (94.9%)	0.639
ASA score, n (%)			
I	0 (0%)	4 (6.8%)	0.271
II	12 (53.8%)	31 (52.5%)	
III	14 (46.2%)	24 (40.7%)	
Mean±SD operative time (min)	107.3±49.2	175.3±89.8	0.001
Conversion, n (%)	2 (7.7%)		
Mean blood loss (ml)	31.9±54.6	93.2±222.0	0.051
Mean time to oral intake (days)	3.5±1.2	5.6±1.8	<0.001
Duration of analgesia (days)	3.2±1.6	5.8±2.3	<0.001
Hospital stay (days)	8.0±2.8	10.1±5.1	0.025
Perioperative morbidity, n (%)	1 (3.8%)	2 (3.4%)	0.369
Perioperative 30-day mortality, n (%)	0 (0%)	1 (1.7%)	1.000

ASA: American Society of Anesthesia risk score.

Table II. Comparison of tumor characteristics and oncological outcomes between patients who underwent laparoscopic surgery (LS) and laparotomy for intestinal gastrointestinal stromal tumors.

	LS group N=26	Laparotomy group N=59	p-Value
Median tumor size, cm (interquartile range)	4.2 (2.7)	4.7 (4.0)	0.155
Tumor location, n (%)			
Jejunum	19 (73.1%)	41 (69.5%)	0.738
Ileum	7 (26.9%)	18 (30.5%)	
Mitotic index, n (%)			
≤5/50 HPF	19 (73.1%)	38 (69.5%)	0.433
>5/50 HPF	7 (26.9%)	21 (35.6%)	
NCCN risk, n (%)			
None	0 (0%)	5 (8.5%)	0.229
Low	13 (50.0%)	19 (32.2%)	
Moderate	4 (15.4%)	14 (23.7%)	
High	9 (34.6%)	21 (35.6%)	
Tumor spillage, n (%)	0 (0%)	2 (3.4%)	0.550
Microscopic rupture, n (%)	2 (8.7%)	6 (13.6%)	0.718
Recurrence, n (%)	4 (15.4%)	13 (22.0%)	0.568
Alive without recurrence	22 (84.6%)	42 (71.2%)	
Alive with recurrence	4 (15.4%)	10 (16.9%)	
Overall mortality, n (%)	0 (0%)	7 (11.8%)	0.095
Due to GIST	0	3 (5.1%)	
Due to other causes	0	4 (6.7%)	

HPF: High-power field; NCCN: National Comprehensive Cancer Network.

(RR)=4.148;  $p=0.022$ ], mitotic index greater than 5/50 HPF (RR=5.500;  $p=0.002$ ), and NCCN moderate/high risk (RR=4.667;  $p=0.016$ ). Multivariate analysis identified tumor

size greater than 7 cm ( $p=0.046$ ) and mitotic index greater than 5/50 ( $p=0.015$ ) as independent predictors of tumor recurrence (Table III).

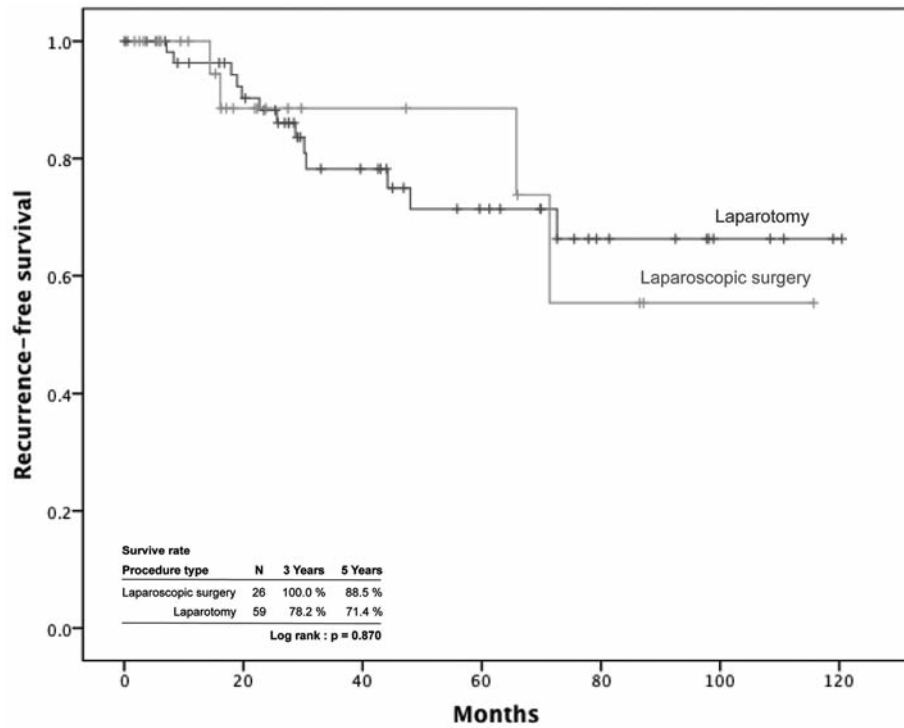


Figure 3. Kaplan-Meier survival curve of recurrence-free survival for patients with intestinal gastrointestinal stromal tumors with laparoscopic surgery versus traditional laparotomy.

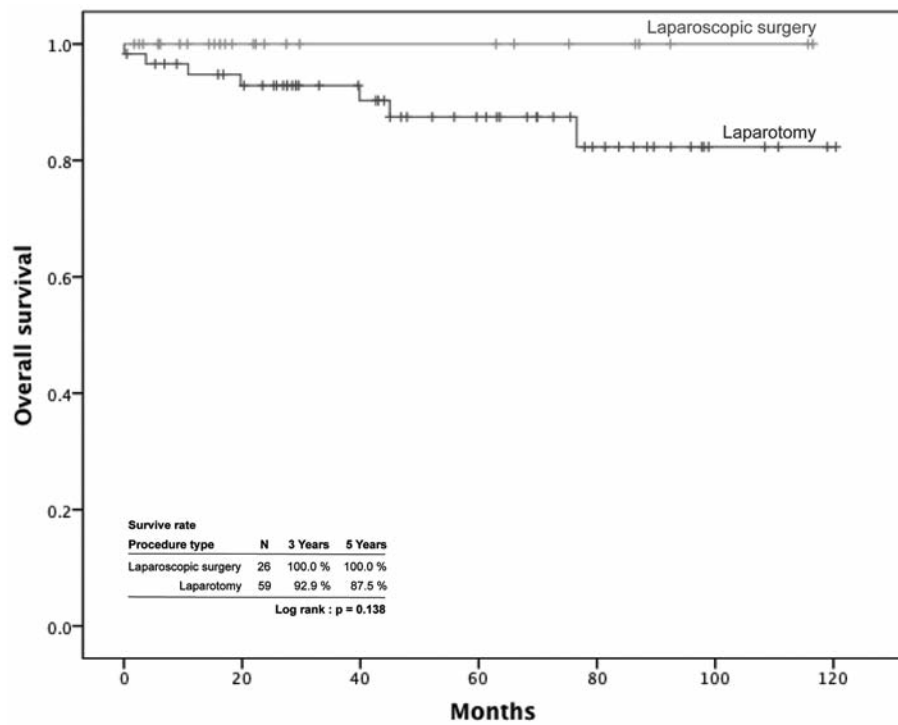


Figure 4. Kaplan-Meier survival curve of overall survival for patients with intestinal gastrointestinal stromal tumors with laparoscopic surgery versus traditional laparotomy.



Table III. Risk analysis of intestinal gastrointestinal stromal tumor recurrence.

Variable	N (%)	Univariate		Multivariate
		Risk ratio (95% CI)	p-Value	p-Value
Tumor size				
>7 cm	8 (40.0%)	4.148 (1.329-12.948)	0.022	0.046
≤7 cm	9 (13.8%)	1		
Mitotic index				
>5/50 HPF	11 (39.3%)	5.500 (1.766-17.131)	0.002	0.015
≤5/50 HPF	6 (10.5%)	1		
Location				
Jejunum	11 (18.3%)	0.711 (0.230-2.194)	0.552	-
Ileum	6 (24.0%)	1		
NCCN risk				
None/low	3 (8.1%)	1	0.016	0.713
Moderate/high	14 (29.2%)	4.667 (1.229-17.724)		
Operative procedure				
Laparoscopic surgery	4 (15.4%)	0.643 (0.188-2.202)	0.480	-
Laparotomy	13 (22.0%)	1		

CI: Confidence interval, HPF: high-power field, NCCN: National Comprehensive Cancer Network.

## Discussion

This study demonstrates that LS for intestinal GISTs may be a safe surgical option for small- to medium-sized tumors. The demographic and tumor characteristics were similar between the LS and laparotomy groups, indicating that LS is as safe and feasible as laparotomy as a treatment option for intestinal GISTs. However, LS had advantages over laparotomy for intestinal GISTs, namely, a shorter operative time, a lower rate of tumor rupture, an earlier return of bowel function, less postoperative pain, and a shorter LOS. Similar to previous studies focusing on gastric GISTs (11, 19), we postulated that LS for intestinal GISTs might be feasible and superior to laparotomy with regard to short-term results. A distinguishing feature of our study is that it successfully demonstrated the advantages of LS over laparotomy in terms of postoperative recovery time and shorter LOS.

GISTs larger than 2 cm have malignant potential; therefore, the oncological outcome is important when examining a new technique. The development of imatinib has led to modifications in the standard care for GISTs in many places around the world (20, 21). If technically possible, limited resection of GISTs is the ideal procedure from an oncological point of view (19, 22). The goal of surgery is complete resection of the tumor without large margins or lymphadenectomy. LS might be regarded as a treatment of choice if it offered a similar oncological outcome as laparotomy and better immediate results. In the past decade, there has been an increased trend toward the use of LS for gastric GISTs, but few reports have examined the use of LS for intestinal GISTs (16, 18, 23). In this study, the 3-year

RFS of patients who underwent LS and laparotomy was 100.0% and 78.2%, respectively, and the 5-year RFS was 88.5% and 71.4%, respectively. Once patients had recurrence, they were treated with imatinib, and the prognosis remained good. The 3-year OS and 5-year OS of patients who underwent LS and laparotomy were similar (3-year OS: 100% vs. 92.9%, respectively; 5-year OS: 100% vs. 87.5%, respectively). This finding indicates that the oncological outcomes are comparable between LS and laparotomy procedures.

As a surgical technique, we first started performing LS for small-sized GISTs (12, 23). As we gained experience, we extended the use of LS to larger-sized tumors. Although the NCCN guidelines recommend LS for GISTs smaller than 5 cm (5), this study demonstrated that the oncological outcomes of LS for intestinal GISTs smaller than 10 cm were comparable to those of laparotomy, with similar rates of tumor-free margins, tumor recurrence, RFS, and OS. The oncological outcomes in our study justify LS for intestinal GISTs when tumors are no larger than 10 cm.

Compared to gastric GISTs, the intestine is free in the peritoneal cavity, and the tumor can be mobilized and resected properly. Thus, intestinal GISTs have several characteristics that make them appealing candidates for a laparoscopic approach. Intestinal GISTs can be manipulated without any direct contact with the tumor by grasping the mesentery or nearby normal small bowel segment, which eliminates the risk of rupture. With this mobility, most intestinal GISTs can be treated by simple segmental resection. In the present study, we also covered the lesion with a sterilized bag before manipulation, which enhanced

the protection of tumor integrity. The 'no-touch' concept is another way to reduce tumor rupture during bowel manipulation (24, 25). In most cases, GISTs are oval, so specimens can be delivered through an incision that is slightly smaller than the shortest diameter of the mass. Therefore, even a mass that is 10 cm in diameter can be delivered through an incision smaller than 6 cm (18). A drawback of LS for intestinal GISTs is the requirement for alimentary tract anastomosis, which may not always be encountered in gastric GISTs. Surgeons who perform LS for intestinal GISTs must be skilled and familiar with intracorporeal sutures, which limits this procedure to experienced laparoscopic surgeons. To overcome this problem, we applied a wound protector, which not only prevented tumor contamination but also stretched the umbilical incision to a larger size. Due to the mobility of the bowel, we were able to position the intestine under the umbilical incision and perform the bowel anastomosis intracorporeally or *via* the umbilical incision under direct vision. Under certain circumstances, the surgeon can apply conventional instruments to bring the bowel lesion under the umbilical incision. This approach can reduce the operative time and lower the learning curve of this procedure, making it accessible to novice laparoscopic surgeons (26). Another potential benefit of LS is the decreased possibility of adhesion and incisional herniation, which is proportional to the length of the incision (27). This theoretically explains the lower possibility of adhesion and ventral herniation. Additionally, the high possibility of recurrence means that additional operations may be necessary. Minimally invasive procedures lead to fewer postoperative adhesions, thereby making subsequent operations easier (27, 28).

Based on univariate analysis, tumor size, NCCN risk, and mitotic index were identified as indicators for recurrence. The type of procedure and tumor location had a limited effect on recurrence risk. Based on multivariate analysis, the only independent factor that predicted early recurrence was a mitotic index of more than 5/50 HPF. For intestinal GISTs, the pathological presentation of the tumor was a critical factor that influenced recurrence, rather than the operative technique. Therefore, if patients have no contraindications for LS, then LS may be a therapeutic option for patients with small- to medium-sized intestinal GISTs.

Although our results may support the safety and feasibility of LS for intestinal GISTs, there were several limitations inherent to this study. Firstly, this was a retrospective study, so the selection of patients could not be randomized. Although all data were collected prospectively and the characteristics of the two groups were similar and homogeneous, selective and recall bias could not be completely prevented.

The laparoscopic operation techniques for intestinal GISTs are diverse and are dependent on the location of the tumor.

The operation became complex for tumors located at the duodenum; thus, we excluded this group of patients from the study to enhance the cohort homogeneity and to allow for a better comparison between LS and laparotomy. This exclusion may have reduced the total case number and statistical power.

Another limitation of this study is that it was not double-blinded. Therefore, biases due to patient and surgeon attitudes are likely to arise. In the LS group, the unblinded patients may have had more motivation to reduce analgesic usage and to begin early ambulation because they had undergone minimally invasive surgery. Unblinded surgeons may have been more aggressive in facilitating early feeding and discharge after the operation. Hence, the placebo effect could not be completely avoided in this study. To overcome these limitations, our results should be confirmed by further prospective randomized controlled trials that compare the open *versus* laparoscopic approach for the surgical removal of intestinal GISTs.

In conclusion, this study demonstrated that LS for intestinal GISTs led to oncological outcomes that were comparable to those of laparotomy after a long-term follow-up. Moreover, LS was associated with favorable perioperative outcomes and a shorter hospital stay compared to laparotomy. With strict oncological precautions and protection, laparoscopic treatment may be a safe and effective procedure for small- and medium-sized intestinal GISTs.

## Acknowledgements

The Authors thank Su-Fang Huang as the member of GIST databank registry who made a great contribution to data collection for this research. They also acknowledge the involvement of the participants, without whom this research could not have been conducted.

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Received September 25, 2014

Revised October 20, 2014

Accepted October 27, 2014