

**ORIGINAL****Feasibility of laparoscopic and endoscopic cooperative surgery for gastric gastrointestinal stromal tumor with tumor diameter of >5 cm**

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**Abstract : Background :** Laparoscopic and endoscopic cooperative surgery (LECS) is an effective treatment for gastric gastrointestinal stromal tumors (GISTs). The utility of LECS for gastric GISTs of >5 cm remains controversial. This study was performed to investigate the feasibility of LECS for gastric GISTs with a tumor diameter of >5 cm. **Methods :** We analyzed 43 patients with gastric GISTs who underwent LECS or laparoscopic partial gastrectomy (Lap-Partial Gx). We compared the surgical outcomes of LECS versus Lap-Partial Gx and of LECS for a tumor diameter of >5 versus ≤5 cm. **Results :** In the comparison of LECS versus Lap-Partial Gx, there were no significant intergroup differences in the operative time or blood loss volume. The morbidity rate was similar between the groups. No postoperative mortality occurred in either group. In the comparison of LECS for a tumor diameter of >5 versus ≤5 cm, there were no significant intergroup differences in operative time, or blood loss volume. The morbidity rate was similar between the >5-cm and ≤5-cm groups (0.0% vs. 4.5%, respectively ;  $p = 0.56$ ). Additionally, no recurrence or death occurred during follow-up in either group. **Conclusion :** LECS is a feasible option for gastric GISTs with a tumor diameter of >5 cm. *J. Med. Invest.* 71:148-153, February, 2024

**Keywords :** *gastrointestinal stromal tumor, laparoscopic and endoscopic cooperative surgery, partial gastrectomy, tumor diameter*

**INTRODUCTION**

Gastrointestinal stromal tumors (GISTs) are mesenchymal tumors that originate from the interstitial cells of Cajal in the gastrointestinal tract, and their estimated incidence is 1 to 2 cases per 100,000 people each year (1). GISTs are often found as gastric submucosal tumors, and 50% to 60% of GISTs can occur in the stomach (1). About 10% to 30% of GISTs exhibit clinically malignant behavior (2, 3).

Surgical resection is the only curative management technique for gastric GISTs (4). Achievement of R0 resection to the greatest extent possible is important. Lymph node metastasis is extremely rare (5, 6). Lymph node dissection is not adopted. Therefore, partial gastrectomy is recommended because it preserves organs and organ functions and maintains a good quality of life after surgery (7). Laparoscopic partial gastrectomy (Lap-Partial Gx) has shown similar or better short-term results compared with open surgery (8-10). Lap-Partial Gx has been established as a safe and feasible surgical method. However, depending on the tumor location, Lap-Partial Gx may be difficult to perform and may result in excessive resection of the gastric mucosa or postoperative deformation (11).

In 2008, Hiki *et al.* (12) demonstrated laparoscopic and endoscopic cooperative surgery (LECS), in which endoscopic submucosal dissection (ESD) is performed to determine the resection line and the submucosal incision is made at the tumor margin. The LECS technique minimizes excessive gastric resection and

functional disorders caused by postoperative deformity of the stomach (13). Few studies have focused on the short- and long-term outcomes after LECS or partial gastrectomy (14, 15). LECS is generally recommended for GISTs with a tumor diameter of <5 cm (12). To our knowledge, only a few reports have proposed LECS for gastric GISTs with a tumor diameter of >5 cm.

In this study, we evaluated the short- and long-term outcomes of LECS versus Lap-Partial Gx for gastric GISTs. We then compared the surgical outcomes of LECS for a tumor diameter of >5 versus ≤5 cm.

**METHODS***Patient cohorts*

This retrospective analysis was based on the data of patients treated for gastric GISTs at Tokushima University Hospital from 2014 to 2021. We enrolled 43 patients with gastric GISTs who underwent laparoscopic curative resection at our hospital. The surgical strategy for gastric GISTs is shown in Figure 1. All patients were diagnosed with gastric GISTs by pathologists. These 43 patients with gastric GISTs were divided into 2 groups : those who underwent LECS ( $n = 29$ ) and those who underwent Lap-Partial Gx ( $n = 14$ ). The patients who underwent LECS were further divided into two subgroups : those with a tumor diameter of >5 cm ( $n = 7$ ) and those with a tumor diameter of ≤5 cm ( $n = 22$ ). The mean follow-up period was 29.63

**Abbreviations :**

GIST : gastrointestinal stromal tumor

LECS : laparoscopic and endoscopic cooperative surgery

ESD : endoscopic submucosal dissection

Lap-Partial Gx : laparoscopic partial gastrectomy

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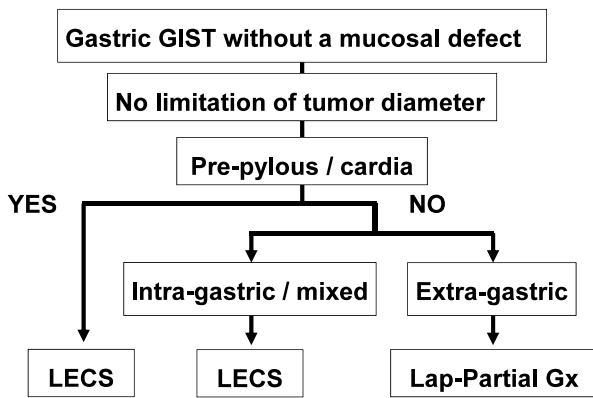


Figure 1. Surgical strategy for gastric GISTs. GIST, gastrointestinal stromal tumor; LECS, laparoscopic and endoscopic cooperative surgery; Lap-Partial Gx, laparoscopic partial gastrectomy

months. The study was conducted in accordance with the Declaration of Helsinki. This study was approved by the Institutional Review Board of the University of Tokushima Graduate School (approval ID number : 3215).

#### Procedure for LECS and Lap-Partial Gx

LECS was performed as follows. The tumor location from the serosal side was confirmed from the mucosal side by intraluminal endoscopy. After confirming the tumor location, the muco-submucosal layers around the tumor were dissected circumferentially using the ESD technique. An artificial perforation of the seromuscular layer was made using the ESD knife under the guidance of the laparoscopist. The remaining seromuscular layer was dissected along the incision line made with the ESD technique by the endoscopist and with laparoscopic ultrasonic shears by the laparoscopist. After tumor removal, the gastric wall defect was sutured using a laparoscopic linear stapler or hand-sewn suturing (16).

Lap-Partial Gx was performed as follows. Three or four operative ports and a camera port were placed for performance of laparoscopy. On entering the peritoneal cavity, the tumor location was confirmed. The tumor was dissected from the surrounding tissues. A laparoscopic linear stapler was placed at the base of the lesion. Laparoscopic wedge resection was performed for removal of the tumor, and the staple line was reinforced with 3-0 VICRYL® if necessary.

#### Statistical analysis

Data are presented as mean  $\pm$  standard deviation. All statistical analyses were performed using statistical software (JMP 8.0.1.; SAS Institute, Cary, NC, USA). Clinical variables were analyzed with the chi-squared test and Wilcoxon test. Survival curves were plotted using the Kaplan–Meier method. Statistical significance was defined as  $p < 0.05$ .

## RESULTS

#### LECS versus Lap-Partial Gx

The detailed clinicopathological characteristics of the patients in the LECS group and Lap-Partial Gx group are shown in Table 1. There were no significant differences in age, sex, body mass index, American Society of Anesthesiologists score, tumor diameter, or tumor malignancy between the two groups. However, the growth type was significantly different between the two groups.

Table 2 summarizes the port counts, operative time, blood loss volume, length of postoperative hospital stay, morbidity rate (Clavien–Dindo grade  $\geq 2$ ), and mortality rate in the two groups. There were no significant differences between the LECS and Lap-Partial Gx groups in the port count ( $4.2 \pm 0.5$  vs.  $3.2 \pm 2.0$ ,  $p = 0.16$ ), operative time ( $163.8 \pm 63.8$  vs.  $125.5 \pm 61.2$  min,  $p = 0.16$ ), blood loss volume ( $14.8 \pm 34.8$  vs.  $39.4 \pm 75.8$  mL,  $p = 0.07$ ), or length of postoperative hospital stay ( $9.5 \pm 2.9$  vs.  $8.1 \pm 2.5$  days,  $p = 0.10$ ). The morbidity rate (Clavien–Dindo grade  $\geq 2$ ) was similar between the LECS and Lap-Partial Gx groups (3.4% vs. 0.0%,  $p = 0.48$ ). No postoperative mortality occurred in either group. Additionally, no recurrence or death occurred during follow-up in either group.

#### LECS for tumor diameter of $> 5$ versus $\leq 5$ cm

Next, to evaluate the safety and feasibility of LECS for a tumor diameter of  $> 5$  cm, we divided the patients who underwent LECS into those with a tumor diameter of  $> 5$  cm ( $n = 7$ ) and  $\leq 5$  cm ( $n = 22$ ). The patients' detailed clinicopathological characteristics are shown in Table 3. There were intergroup differences in the tumor diameter and tumor malignancy between the two groups.

Table 4 summarizes the surgical outcomes. There were no significant differences between the  $> 5$ -cm and  $\leq 5$ -cm groups in the port count ( $4.4 \pm 0.5$  vs.  $4.2 \pm 0.5$ ,  $p = 0.27$ ), operative time ( $182.7 \pm 78.7$  vs.  $157.8 \pm 59.1$  min,  $p = 0.37$ ), blood loss volume ( $8.9 \pm 20.2$  vs.  $33.2 \pm 60.4$  mL,  $p = 0.26$ ), or closure method for the gastric wall defect ( $p = 0.87$ ). The postoperative hospital stay was significantly shorter in the  $\leq 5$ -cm than  $> 5$ -cm group ( $8.7 \pm 2.5$  vs.  $11.7 \pm 2.5$  days, respectively;  $p < 0.05$ ). The morbidity rate (Clavien–Dindo grade  $\geq 2$ ) was similar between the  $> 5$ -cm and  $\leq 5$ -cm groups (0.0% vs. 4.5%, respectively;  $p = 0.56$ ). No postoperative mortality occurred in either group. Additionally, no recurrence or death occurred during follow-up in either group.

## DISCUSSION

The current study demonstrated comparable surgical outcomes between LECS and Lap-Partial Gx for gastric GISTs, and LECS was shown to be safe and feasible for GISTs with a tumor diameter of  $> 5$  cm.

Lap-Partial Gx has been established as a simple and safe surgical technique that achieves R0 resection and maintenance of postoperative quality of life (17, 18). However, Lap-Partial Gx can be difficult to perform depending on the characteristics and location of the GIST. Lap-Partial Gx for GISTs exhibiting intra-gastric growth can result in excessive resection and deformity of the gastric wall (13, 19, 20). Furthermore, Lap-Partial Gx for GISTs located around the cardia, pylorus, and esophagogastric junction is also challenging (20, 21).

According to the previous report, the growth type of gastric GISTs has been classified grossly as intra-gastric, extra-gastric, intra-gastric, or mixed type (22). Our surgical strategy was shown in the Figure 1. For extra-gastric type, the main option was the Lap-Partial Gx. However, even for extra-gastric type, LECS was performed in cases which gastric resection can be minimized or surgery can be easily performed by establishing the incision line on the muco-submucosal layers based on the location of the tumor and the finding of endoscopy.

In this study, we found no significant difference in the surgical outcomes of LECS and Lap-Partial Gx. Although LECS requires the ESD technique (14, 23), it can be performed with an acceptable operation time. LECS can also minimize excessive resection and postoperative complications. Furthermore, the long-term outcomes of LECS are comparable with those of Lap-Partial Gx.

Table 1. Patients' characteristics (LECS vs. Lap-Partial Gx)

Factors	LECS (n = 29)	Lap-Partial Gx (n = 14)	p value
Age	65.3 ± 13.8	70.4 ± 8.4	0.26
Sex			
Male	17	9	
Female	12	5	0.72
BMI, kg/m <sup>2</sup>	22.9 ± 3.3	23.7 ± 3.7	0.56
ASA score			
1	15	5	
2	12	9	
3	2	0	0.29
Tumor diameter, mm	34.4 ± 12.6	45.0 ± 30.0	0.62
Localization			0.91
U	17	9	
M	8	3	
L	4	2	
Growth type			<0.05
Intragastric	11	0	
Extragastric	12	13	
Mixed	6	1	
Modified Fletcher classification			0.41
High	4	3	
Moderate	6	3	
Low	17	5	
Very low	2	3	
Miettinen classification			0.06
High	2	2	
Moderate	3	4	
Low	3	0	
Very low	19	4	
None	3	4	

Data are presented as mean ± standard deviation or number of patients.

LECS, laparoscopic and endoscopic cooperative surgery ; Lap-Partial Gx, laparoscopic partial gastrectomy ; BMI, body mass index ; ASA, American Society of Anesthesiologists ; U, upper ; M, middle ; L, lower

Table 2. Surgical outcomes (LECS vs. Lap-Partial Gx)

Factors	LECS (n = 29)	Lap-Partial Gx (n = 14)	p value
Port count	4.2 ± 0.5	3.2 ± 2.0	0.16
Operation time, min	163.8 ± 63.8	125.5 ± 61.2	0.07
Blood loss volume, mL	14.8 ± 34.8	39.4 ± 75.8	0.07
Hospital stay, days	9.5 ± 2.9	8.1 ± 2.5	0.10
Morbidity, %	3.4	0.0	0.48
Mortality, %	0.0	0.0	N.S.
Recurrence, %	0.0	0.0	N.S.

Data are presented as mean ± standard deviation unless otherwise indicated.

LECS, laparoscopic and endoscopic cooperative surgery ; Lap-Partial Gx, laparoscopic partial gastrectomy ; N.S., not significant

**Table 3.** Patients' characteristics (LECS for tumor diameter of >5 vs. ≤5 cm)

Factors	>5 cm (n = 7)	≤5 cm (n = 22)	p value
Age	66.0 ± 14.1	65.0 ± 14.1	0.98
Sex			0.06
Male	2	15	
Female	5	7	
BMI, kg/m <sup>2</sup>	23.5 ± 3.4	22.7 ± 3.3	0.61
ASA score			
1	5	10	
2	4	11	
3	1	1	0.22
Tumor diameter, mm	53.1 ± 3.7	28.5 ± 7.3	<0.05
Localization			0.11
U	2	15	
M	4	4	
L	1	3	
Growth type			0.11
Intragastric	0	15	
Extragastric	3	4	
Mixed	4	3	
Modified Fletcher classification			<0.05
High	3	1	
Moderate	4	2	
Low	0	17	
Very low	0	2	
Miettinen classification			<0.05
High	2	0	
Moderate	0	2	
Low	3	0	
Very low	1	18	
None	1	3	

Data are presented as mean ± standard deviation or number of patients.  
LECS, laparoscopic and endoscopic cooperative surgery ; BMI, body mass index ; ASA, American Society of Anesthesiologists ; U, upper ; M, middle ; L, lower

**Table 4.** Surgical outcomes (LECS for tumor diameter of >5 vs. ≤5 cm)

Factors	>5 cm (n = 7)	≤5 cm (n = 22)	p value
Port count	4.4 ± 0.5	4.2 ± 0.5	0.27
Operation time, min	182.7 ± 78.7	157.8 ± 59.1	0.37
Blood loss volume, mL	8.9 ± 20.2	33.2 ± 60.4	0.26
Closure			0.87
Hand-sewn	2	7	
Stapled	5	15	
Hospital stay, days	11.7 ± 2.5	8.7 ± 2.5	<0.05
Morbidity, %	0.0	4.5	0.56
Mortality, %	0.0	0.0	N.S.
Recurrence, %	0.0	0.0	N.S.

Data are presented as mean ± standard deviation or number of patients.  
LECS, laparoscopic and endoscopic cooperative surgery ; N.S., not significant

LECS is good option for gastric GISTs in terms of both short-term and long-term outcomes.

The general indication for LECS is a tumor diameter of  $\leq 5$  cm to avoid serosal injury and dissemination. The utility of LECS for gastric GISTs of  $> 5$  cm lacks scientific evidence. In our comparison of a tumor diameter of  $> 5$  versus  $\leq 5$  cm, we found that the postoperative hospital stay was slightly longer for patients with a tumor diameter of  $> 5$  cm. This may be attributed to our more careful postoperative management of patients with a tumor diameter of  $> 5$  cm. No patients developed serosal injury or postoperative dissemination. The long-term outcomes of LECS for a tumor diameter of  $> 5$  cm were comparable to those for a tumor diameter of  $\leq 5$  cm. The surgical outcomes of LECS for gastric GISTs with a tumor diameter of  $> 5$  cm have not been sufficiently studied; only a few case reports have been published. Di Buono *et al.* (24) safely performed LECS for a 7-cm gastric GIST. Even for lesions larger than 5 cm, laparoscopic surgery shows a recurrence rate similar to that of conventional open surgery when a curative operation is performed (25-27). Taken together, these findings indicate that LECS may be a favorable option even for a tumor diameter of  $> 5$  cm.

Our study has two main limitations. First, its retrospective and single-institute design might have resulted in selection bias. Second, the numbers of patients who underwent LECS and Lap-Partial Gx in our hospital was small. Evaluation of larger numbers of patients and performance of large-scale randomized controlled trials are needed.

In conclusion, this study showed that the short- and long-term outcomes of LECS were comparable between GISTs with a tumor diameter of  $> 5$  and  $\leq 5$  cm. No recurrence or death occurred in either group, and the postoperative prognosis was good. This study suggests that LECS is a feasible option for gastric GISTs with a tumor diameter of  $> 5$  cm.

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## DISCLOSURE OF ETHICAL STATEMENTS

The protocol for this research project was approved by the Ethics Committee of Tokushima University (approval no. 3215-1). All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964 and later versions. All informed consent was obtained from the subject(s) and/or guardian(s).

## COMPETING INTERESTS

Yosuke Iwakawa, Masaaki Nishi, Yuma Wada, Kozo Yoshikawa, Chie Takasu, Takuya Tokunaga, Toshihiro Nakao, Hideya Kashihara, Toshiaki Yoshimoto, Takayuki Noma and Mitsuo Shimada have no conflicts of interest or financial ties to disclose.

## FUNDING

None.

## AUTHORS' CONTRIBUTIONS

Masaaki Nishi is the corresponding author and carried out the revision of the manuscript. All the authors equally contributed to the conception of the study; acquisition, analysis, or interpretation of data; drafting and revision of the paper; and final approval of the paper. All authors agreed to be accountable for the integrity of the report. All authors read and approved the final manuscript.

## CONSENT TO PUBLICATION

This study was approved in advance by the Institutional Review Board of the University of Tokushima Graduate School of Medical Science (TOCMS: 3215). Written informed consent for publication was obtained from all patients.

## AVAILABILITY OF DATA AND MATERIALS

Raw data were generated at Tokushima University. Derived data supporting the findings of this study are available from the corresponding author on request.

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