Excellent oncological outcomes besides short-term safety of laparoscopic and endoscopic cooperative surgery for gastric gastrointestinal stromal tumor

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ABSTRACT
Background and study aims Laparoscopic and endoscopic cooperative surgery (LECS) for gastric submucosal tumor was developed as a type of minimal local resection and is now widely used in Asian countries. However, the oncological safety of LECS for gastric gastrointestinal stromal tumor (GIST) remains unclear. LECS has potential oncology-related problems that may influence survival outcomes. Furthermore, the feasibility and safety of LECS have not yet been fully established.

Patients and methods Patients who were intended to undergo LECS for gastric GIST from 2006 to 2020 were retrospectively selected. The indication for LECS was determined according to the guidelines. The completion of LECS, complications, and survival outcomes of the patients were analyzed.

Results Two hundred fifty-nine patients were eligible in this study. According to intraoperative findings, 44 patients underwent local resection without luminal endoscopic procedures. Of the remaining 215 patients, 213 completely underwent LECS, which corresponds to a completion rate of 99.1%. Six patients (2.8%) had postoperative complications of Clavien-Dindo classification grade II or higher. Delayed gastric emptying was most commonly found in four patients (1.9%). Old age (P = 0.0349), female sex (P = 0.0095), tumor located in the lesser curvature (P = 0.0015), and large tumor diameter (P = 0.0232) were significantly more common in patients with complications. The 3-year overall and disease-specific survival rates were 99% and 100%, respectively, in 215 patients who were intended to undergo LECS.

Conclusions Despite several oncological concerns, LECS for gastric GIST is oncologically safe besides a feasible and safe procedure in the short-term.

Introduction
Gastrointestinal stromal tumor (GIST) is derived from Cajal-mediated cells scattered within the gastrointestinal tract walls, and has an annual incidence of 10 to 15 patients per million people [1–3]. The stomach is the most common organ in which GIST forms a submucosal tumor (SMT), and surgical resection is the main treatment modality [4, 5]. Gastric GIST is usually locally resected without lymph node dissection because it generally
has no lymph node metastasis. Many studies have reported favorable short- and long-term outcomes after such local treatment [6–9].

Laparoscopic and endoscopic cooperative surgery (LECS) was established by Hiki et al. in 2008 to minimize the area of gastric resection by laparoscopic local resection for gastric SMT including GIST [10]. In LECS for gastric SMT, both the mucosa and submucosa close to the root of the tumor protrusion is first dissected by luminal endoscopy, which is the technique of endoscopic submucosal dissection for cancer. This mucosal incision line becomes the cutting line along which the tumor is subsequently resected with the whole layer of the stomach. The defect in the stomach after resection is closed with an endoscopic linear stapler or is hand-sewn laparoscopically. LECS for gastric SMT has become common in Asian countries, and previous reports of initial experiences revealed that LECS for gastric SMT can be performed safely [11–16].

However, whether LECS is safe for GIST that has formed gastric SMT remains unclear. Only one small-sample-sized study has reported long-term results of gastric GIST resected by LECS [6]. Actually, LECS for gastric GIST which is a potential malignant tumor essentially has two surgical oncology-related problems. The first is direct tumor handling. LECS enables minimal resection of the stomach, and as a result, the tumor is handled nearly directly. In LECS, only a very short length of surgical margin is maintained and the tumor is grasped or sometimes retracted directly using endoscopic forceps to remove it from the stomach wall. Furthermore, LECS requires opening the stomach wall in the pneumo-abdominal cavity. Dissemination of tumor cells into the abdominal cavity is concerning, especially when the tumor has an ulceration called a delle, but so-called inverted-LECS was developed to prevent contamination of the gastric juice and contact of the tumor with the abdominal wall during a full-thickness incision [13]. Whether such issues influence long-term outcomes of gastric GIST treated by LECS have hardly been investigated. Moreover, even the feasibility and short-term safety of LECS for gastric GIST have not yet been established. As previous studies to evaluate these factors had small sample sizes and always included not only GIST but also other types of SMT, they did not present definitive outcomes. In fact, LECS for gastric GIST seems to be feasible, and few postoperative complications occur because it is a type of local resection. However, the rates of incomplete surgery, patient profiles, and factors related to postoperative complications were not sufficiently investigated because of the small sample sizes in previous studies.

In this study, to establish the long-term safety as well as the feasibility and short-term safety of LECS for gastric GIST more definitively, the completion rate, postoperative complications, and oncological outcomes of LECS for gastric GIST were analyzed by collecting a larger number of narrowly defined patients who were treated with the same intention at our institute. The results of this study are useful as a reference for determining indications, monitoring any complications, and determining methods of postoperative surveillance in LECS for gastric GIST.

**Patients and methods**

**Patients**

This study investigated consecutive patients who underwent surgery for gastric GIST at the Department of Gastroenterological Surgery, the Cancer Institute Hospital, Tokyo, Japan, between January 2006 and December 2020. Patients who underwent planned open surgery were excluded from the analysis set according to the flowchart in Fig. 1. In addition, patients who underwent planned laparoscopic local resection without luminal endoscopic procedures were not included in the group intended to undergo laparoscopic surgery. Data on patients who were intended to undergo LECS were collected and patients whose procedures were converted to laparoscopic local resection without luminal endoscopy according to intraoperative endoscopic findings were finally excluded (Fig. 1). The present study was approved by the ethics committee of the Cancer Institute Hospital (number 2021-CB-032).

**Selection of surgical procedure**

Selection of open or laparoscopic surgery mainly depended on tumor size (<5.0 cm or >5.0 cm) according to Japanese guidelines for GIST [17], presence or absence of combined resection of other organs, and the surgeon’s choice. In addition, indications for local resection and gastrectomy depended on tumor location and size. Gastrectomy was planned if the tumor involved more than half of the cardia or pylorus, or if the tumor attached to the stomach wall was more than half of the gastric circumferential length. In local resection, the final decision about which procedure was conducted – LECS or laparoscopic local resection without luminal endoscopic procedures – depended on the findings from intraoperative luminal endoscopy.

| Surgery for gastric GIST n = 358 |
|----------------------------------|
| Exclusion |
| Intended open surgery n = 46 |

| Intended laparoscopic surgery n = 312 |
|---------------------------------------|
| Exclusion |
| Intended |
| Gastrectomy n = 4 |
| Local resection without ESD n = 49 |

| Initially intended LECS n = 259 |
|----------------------------------|
| Conversion to |
| Local resection without ESD n = 44 |

| Finally intended LECS n = 215 |

Fig. 1 Flowchart of patient enrollment. GIST, gastrointestinal stromal tumor; ESD, endoscopic submucosal dissection; LECS, laparoscopic and endoscopic cooperative surgery.
Laparoscopic local resection without luminal endoscopic procedures was selected when intraoperative luminal endoscopy revealed that the tumor did not protrude or slightly protruded into the gastric lumen even though findings from preoperative computed tomography (CT) or luminal endoscopy indicated intraluminal growth.

Surgical procedure
LECS procedures were performed as reported previously [10]. First, a camera was inserted via a 12-mm port in the umbilicus. Under insufflation of 10 mmHg, three 5-mm ports and one 12-mm port were inserted into the upper left, lower left, upper right, and lower right quadrants. A luminal endoscope was inserted into the stomach and endoscopic dissection was performed to make a circumferential incision in both the mucosal and submucosal layers around the tumor (Fig. 2a). Next, an incision was made through all layers from the lumen of the stomach, and the tumor was removed by making an incision in the circumferential direction with the assistance of laparoscopic and luminal endoscopic procedures (Fig. 2b, Fig. 2c). The defect in the stomach wall was closed with a stapler or hand-sewn sutures (Fig. 2d).

Laparoscopic local resection without luminal endoscopic procedures is performed for extraluminal GIST. Patient positioning and port settings were prepared in the same way as for LECS. After exposing the blood vessels in the excision area around the tumor using an ultrasonic coagulation device or a vessel sealing system, the intact stomach wall attaching the tumor was clamped with a linear stapler. Then, the linear stapler was fired, and the tumor was removed.

Postoperative follow-up
According to gastric GIST treatment guidelines in Japan, postoperative surveillance using CT is performed every 6 to 12 months for patients at very low risk or low risk after complete resection, and CT is performed every 4 to 6 months for patients at intermediate risk or high risk [17].

Evaluation
Patient factors included age, sex, symptoms, performance status, and body mass index. Tumor histopathological factors included tumor diameter, tumor location, presence of mucosal defects called delles, mitotic index, and risk grade. Hematological tests included prognostic nutritional index [18], and prealbumin. The feasibility of LECS was defined as completion of LECS. The percentage of completion was calculated as the number of patients who underwent LECS among those who were finally intended to undergo LECS, excluding patients who underwent laparoscopic local resection without luminal endoscopic procedures. Surgical factors included surgical procedure, surgical time, bleeding, postoperative hospital stays, and postoperative complications. Postoperative complications were assessed in patients who completely underwent LECS according to the Clavien-Dindo classification [19]. As a principle of grading in the Clavien-Dindo classification, Grade II is defined as receiving medication for some symptoms or findings. Grade II is also applied when intravenous nutritional management is unavoidable. If treatment with local anesthesia or drain replacement is required, it is defined as Grade IIIa. Grade IIIb is defined as requiring general anesthesia, such as reoperation. Grade IV is defined as requiring Intensive Care Unit management, which is classified into two grades: Grade IVa for single organ dysfunction and Grade IVb for multiple organ dysfunction.

Follow-up data included adjuvant chemotherapy, recurrence, and 3- and 5-year overall survival (OS) and disease-specific survival (DSS) of patients who were intended to undergo LECS.

In histological evaluation, many GISTs consist of cells that exhibit a relatively single spindle-shaped morphology. GIST was defined as the presence of a positive c-kit or CD34 marker in immunohistochemistry [20]. The mitotic index was determined according to the number of mitotic images per 50 high-power fields, and the risk grade was determined according to the modified Fletcher classification [21, 22].

Statistical analysis
Continuous variables were evaluated by ANOVA or Student’s t-test and categorical variables by Fisher’s exact test or the chi-squared test, as appropriate. Clinicopathological characteristics and follow-up data were evaluated in terms of OS and DSS. Follow-up time was calculated from the date of surgery to death or endpoint. OS and DSS were estimated by the Kaplan-Meier method and compared using the log-rank test. P<0.05 was considered to indicate statistical significance. All statistical analyses were conducted using the SAS software package (JMP Pro14, SAS Institute, Cary, North Carolina, United States).
Results

Characteristics of patients who were intended to undergo LECS

During the study period, 259 of 358 patients who underwent surgery for gastric GIST were initially intended to undergo LECS. In 44 of 259 patients, an intraoperative decision was made to perform laparoscopic local resection without luminal endoscopic procedures because intraoperative luminal endoscopy confirmed that the tumors were of an extraluminal growth type and endoscopic mucosal dissection was not required. Thus, 215 patients were finally intended to undergo LECS (▶ Fig. 1) and their clinicopathological characteristics are listed in ▶ Table 1. Nearly two-thirds of the patients had tumors located in the upper third, followed by those in the middle and lower thirds. Furthermore, more than 30% of the patients had tumors involving the cardia or the fornix. Median tumor diameter was 30 mm (range 9 to 62 mm). Thirty-three patients (15%) had tumors with ulceration called delle in which SMT was exposed. Regarding the recurrence risk evaluated by the modified Fletcher classification, more than 70% of patients were classified as low or very low risk, while the remaining patients were classified as intermediate or high risk in equal proportions. Twenty-five patients (11.6%) whose tumors were not assessed in a mitotic index were not classified.

Completion of LECS

Of the 215 patients, two patients were converted to open surgery simultaneously following LECS. For one patient, reconstructive surgery was needed because of esophageal stricture. In another patient, an area in which the blood supply was insufficient appeared, and gastrectomy incorporating the area was performed by an open procedure. The completion rate of LECS was 99.1% (213/215).

Surgical data and postoperative complications of LECS

The 213 patients in whom LECS was completed were enrolled in this analysis. The procedure took approximately 3 hours to complete and the median blood loss was 5 g. R0 resection was achieved in all the patients. Six patients (2.8%) had postoperative complications of Clavien-Dindo grade II or higher. Delayed gastric emptying was most commonly found in four patients (1.9%), and anastomotic leakage and postoperative bleeding were found in one patient (0.5%). Complications of greater than grade III were found in one patient (0.5%) (▶ Table 2).

Comparing the presence or absence of postoperative complications with clinicopathological factors, old age (P=0.0349), female sex (P=0.0095), tumor located in the lesser curvature (P=0.0015), and large tumor diameter (P=0.0232) were significantly more common in patients with postoperative complications (▶ Table 3).
Survival outcomes

The median follow-up time in the 215 patients who were finally intended to undergo LECS was 43 months. One of the 215 patients experienced liver metastasis as recurrence. That patient underwent conversion to open surgery following LECS. The recurrence risk was pathologically classified as high risk. The 3-year and 5-year OS and DSS rates in the 215 patients were 99% and 100%, respectively (▶Fig.3a, ▶Fig.3b). No patient in whom LECS was completed experienced recurrence.

Discussion

At our institution, local resection using the LECS technique was performed for consecutive gastric GIST according to our own criteria based on the Japanese guidelines irrespective of tumor location. Although this was a single-institutional and retrospective study of LECS, three new findings were obtained. First, LECS for gastric GIST was a feasible procedure. We determined the surgical indication for LECS according to tumor location and size. We were able to complete LECS in more than 99% of patients who were intended to undergo LECS. Second, LECS was a very safe procedure. Fewer than 3% of the patients who underwent LECS experienced Clavien-Dindo grade II or higher postoperative complications. Several factors were associated with occurrence of complications, although the incidences were very low. Third, the patients who were finally intended to undergo LECS had favorable survival outcomes. Only one patient who was intended to undergo LECS experienced recurrence. The data clearly showed that LECS for gastric GIST was feasible and safe in the short term. Furthermore, it could achieve favorable long-term outcomes according to our patient selection criteria based on the Japanese guidelines.

There was a high rate of completion of LECS in this study, and the procedure is expected to be feasible because it is essentially a local resection. However, the feasibility of LECS may depend on tumor location and size. Gastric GIST is frequently located in the upper stomach, and more than 60% of tumors were loca-
paroscopic surgery including both laparoscopic local resection and endoscopic removal validated a previous report on the effectiveness of LECS experienced recurrence of gastric GIST. This indicates that the information may be based on the clinical backgrounds. Therefore, risk classification could not be determined in more than 10% of patients. Thus, in the future, a prospective study should be conducted at multiple institutions to assess the true short- and long-term safety of LECS for gastric GIST.

This study has several limitations. First, it is a single-institutional retrospective observational study. Gastric GIST is rare and the number of complications and recurrence events was so small at our institution that risk factors could not be analyzed sufficiently. However, such a relatively large-scale and long-observational study may be valuable because evidence regarding the short- and long-term outcomes of LECS is lacking. Furthermore, there were some patients whose tumors were not suitable for LECS as defined by the current guidelines for GIST. Patients who underwent LECS hardly experienced recurrence because LECS is an oncologically safe procedure, and gastric GIST that has indications for LECS is usually classified as high risk. Current guidelines for GIST recommend postoperative surveillance by CT once every 6 to 12 months for even very-low and low-risk tumors [17]. However, the favorable results of this study suggest that such uniform intensive surveillance may be unnecessary for patients clinically suitable for LECS. Patients who underwent LECS hardly experienced recurrence because LECS is an oncologically safe procedure, and gastric GIST that has indications for LECS is usually classified as higher risk. Further studies are required to determine adequate surveillance, considering medical costs, too.

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Conclusions

In conclusion, LECS is a feasible and perioperatively safe procedure for gastric GIST that has appropriate indications in terms of location and size. Furthermore, patients suitable for LECS have a favorable survival outcome because LECS is an oncologically safe procedure and they have lower-risk tumors. Postoperative surveillance methods recommended in the guidelines may need to be reevaluated, considering the highly curable nature of gastric GIST removed by LECS.

Competing interests

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