Clinical outcomes of laparoscopic and endoscopic cooperative surgery for submucosal tumors on the esophagogastric junction: a retrospective single-center analysis

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Abstract

Background Laparoscopic and endoscopic cooperative surgery (LECS) technique for gastric submucosal tumor (SMT) has developed, but treatment of SMT on the esophagogastric junction (EGJ) remains technically difficult because excessive resection may result in postoperative transformation of the EGJ and cause stenosis, and intervention to lower esophageal sphincter may result in gastroesophageal reflux. The study aim was to evaluate the feasibility and safety of LECS for SMT on the EGJ.

Methods Between September 2012 and December 2018, LECS was performed for 21 patients with SMTs on the EGJ. Fundoplication was performed after LECS according to the intraoperative findings for each case. The patients' backgrounds, operative outcomes, and follow-up data, including endoscopic findings of gastroesophageal reflux disease (GERD) and proton pump inhibitor (PPI) use, were reviewed.

Results In all 21 cases, LECS was completed with a mean operation time of 225 min, and a mean blood loss of 8.8 mL. All patients were alive without recurrence within the mean follow-up period of 30.5 months. Both GERD and PPI use tended to be less frequent when fundoplication was performed, although these differences were not statistically significant. (7.7% vs. 37.5%; $P=0.091$, 23.1% vs. 50.0%; $P=0.204$, respectively).

Conclusions We demonstrated the feasibility and safety of LECS for SMTs even on the EGJ. Fundoplication after LECS may be an approach for the prevention of postoperative reflux esophagitis. Future research is warranted to validate the efficacy of the addition of fundoplication.

Keywords Laparoscopic and endoscopic cooperative surgery · Submucosal tumor · Esophagogastric junction · Fundoplication

Introduction

Laparoscopic and endoscopic cooperative surgery (LECS) is a relatively new procedure for dissection of gastric submucosal tumor (SMT) that was first introduced in 2008 by Hiki et al. [1]. LECS is an excellent surgical technique that avoids excessive resection of the stomach wall by visualizing a cut line of the lesion from the inside of the lumen endoscopically. Therefore, this procedure makes it possible to maintain the function and shape of the stomach. In the

surgical treatment of gastric SMT, LECS has been shown to have the same or better surgical results than those of conventional laparoscopic resection or laparotomy [2–4]. However, treatment of SMT on the esophagogastric junction (EGJ) remains technically difficult because excessive resection may result in postoperative transformation of the EGJ and cause stenosis, and intervention to lower the esophageal sphincter may cause gastroesophageal reflux accompanied by damage to the physiological anti-reflux mechanism. Few studies have focused on resection of the tumor at the EGJ, and the actual prevalences of these complications are not known. On the other hand, some studies have reported that laparoscopy-assisted proximal gastrectomy with partial fundoplication in early gastric cancer may help prevent postoperative reflux esophagitis [5–7]. Previously, we have performed fundoplication after LECS for tumors on the EGJ according to the

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intraoperative findings for each case. The study aim was to investigate the feasibility and safety of LECS for SMT on the EGJ and to assess the efficacy of fundoplication after this procedure.

Patients and methods

Patients

A total of 21 SMTs on the EGJ in 21 patients who underwent LECS at Keio University Hospital between September 2012 and December 2018 were enrolled in this study. Patients were preoperatively evaluated by endoscopy, computed tomography (CT), and endoscopic ultrasound. Laparoscopic surgery was indicated for SMTs with a maximum diameter ≤ 5 cm that were considered to be surgical indications according to the guideline for gastrointestinal stromal tumor (GIST) in Japan [8]. In this guideline, SMTs should be treated if at least one of the following characteristics is present: having any symptoms, pathologically diagnosed as GISTs, increasing tumor size, and malignant findings by endoscopic or endosonographic findings (e.g., ulcerative change, irregular margins, and heterogeneous echo pattern). For this study, lesions were selected according to the relevant indications in the guideline [8]. We included lesions that tended to increase even if smaller than 2 cm and those of 2–5 cm where endoscopic ultrasonography-guided fine-needle aspiration biopsy had not been performed and malignant findings were not observed. The intraluminal or mixed growth-type SMTs were resected by classical LECS [1] or non-exposed endoscopic wall-inversion surgery (NEWS) [9]. NEWS was selected for the tumors with a maximum diameter ≤ 3 cm that were considered to be invertible toward the inside of the lumen [9]. The extraluminal growth-type SMTs were resected by combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET) [10]. We selected surgical approaches by preoperative imaging studies and intraoperative findings.

Only tumors on the EGJ observed by preoperative endoscopy were included in this study. Fundoplication was added after resection of the tumor according to the surgeon's judgment by the intraoperative findings for each patient before December 2016. Since January 2017, we have performed fundoplication as a standard procedure because fundoplication is considered useful for the prevention of postoperative GERD. This study was conducted with the approval of the Institutional Review Board of Keio University, and informed consent was obtained from all patients in this study.

Surgical procedures

Classical LECS

A camera port was inserted at the umbilicus using the open technique. Four trocars were inserted into the left-upper, left-lower, right-upper, and right-lower quadrants. After vessel preparation around the gastric cardia, the mucosa around the lesion was endoscopically marked, and the serosal markings were made laparoscopically. After injection of hyaluronic acid solution with a small amount of indigo carmine into the submucosal layer circumferentially around the lesion, the mucosal layer was cut circumferentially along the markings endoscopically. Subsequently, intentional perforation was made endoscopically (Fig. 1a), and full-thickness incisions along the markings about half a circumference were made using endoscopic technique. The rest of the full-thickness incisions were performed laparoscopically (Fig. 1b, c). The resected specimen was retrieved from the umbilicus site. The procedure was finished by closing the mural defect with laparoscopic hand suturing (Fig. 1d).

NEWS

Insertion of a camera port and four trocars, vessel preparation, and endoscopic and laparoscopic marking around the lesion were performed in the same manner as in the classical LECS. After injection of solution into the submucosal layer around the lesion, the seromuscular layer was cut circumferentially along the serosal markings laparoscopically (Fig. 2a, b), followed by inversion of the lesion toward the inside of the lumen and performing linear seromuscular suturing (Fig. 2c, d). Subsequently, circumferential mucosal and submucosal incisions around the mucosal markings were made endoscopically, and the full-thickness incision was completed. The resected lesion was extracted transorally. Finally, the mucosal suturing was made by clipping or endoscopic hand suturing [11].

CLEAN-NET (combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique)

Port insertion, vessel preparation, and endoscopic and laparoscopic marking around the lesion were the same as performed in other procedures. After completion of circumferential incision of the seromuscular layer with preservation of the mucosal layer along the markings laparoscopically (Fig. 3a, b), the full-layer specimen and surrounding mucosa were pulled up together. Subsequently, mucosal incision and stapling were made using a laparoscopic endostapling device for full-layer resection

Fig. 1 Classical laparoscopic and endoscopic cooperative surgery (LECS). **a** A tumor is located on the greater curvature of the esophagogastric junction. **b** and **c** Circumferential full-thickness resection is performed using endoscopic and laparoscopic technique. **d** The

mural defect is closed with laparoscopic hand suturing. **e** The gastric wall of the fundus is wrapped and fixed around the EGJ with covering of the sutured mural defect

Fig. 2 Non-exposed endoscopic wall-inversion surgery (NEWS). **a** A tumor (≤ 3 cm) is located on the greater curvature of the esophagogastric junction. **b** Circumferential seromuscular layer incision is performed laparoscopically. **c** The seromuscular layers are linearly sutured with insertion of a surgical sponge as a spacer between the

serosal surface of the inverted lesion and sutured layer. **d** Linear suturing of the seromuscular layers is completed. **e** The gastric wall of the fundus is wrapped and fixed around the EGJ with covering of the sutured mural defect

Fig. 3 Combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique (CLEAN-NET). **a** An extraluminal growth-type tumor is located on the lesser curvature of the esophagogastric junction. **b** Circumferential seromuscular layer incision is performed laparoscopically. **c** Mucosal incision and stapling are made by a laparoscopic endostapling device for full-layer resec-

tion. **d** The seromuscular defect remains after resection of the tumor. **e** Linear suturing of the seromuscular layers is completed with covering of the seromuscular defect. **f** The gastric wall of the fundus is wrapped and fixed around the EGJ with covering of the sutured seromuscular layers

(Fig. 3c, d). The resected specimen was retrieved from the umbilicus site. The seromuscular defect was closed with laparoscopic hand suturing (Fig. 3e) and then covered by the gastric wall with fundoplication (Fig. 3f).

Fundoplication

After closing the mural defect was completed, the gastric wall of the fundus was wrapped around the EGJ, including the suturing site. The stomach wall for wrapping was pulled out from the right or left side of the EGJ on a case-by-case basis. We were cautious to avoid anastomotic stenosis caused by strangling the esophagus. Finally, the wrapped gastric wall was fixed to the gastric wall or esophageal wall near the EGJ by laparoscopic hand suturing (Figs. 1e, 2e, and 3f).

Postoperative management

After discharge from the hospital, endoscopy was performed 3 and 6 months later and then every 6 months for all patients, and CT was performed every 12 months for patients diagnosed pathologically as having GIST.

Outcome measures

As short-term outcomes, operation time, estimated blood loss, perioperative adverse events, length of hospital stay, pathological results, and findings of follow-up endoscopy were examined. Postoperatively, disease-free survival, dietary conditions, and proton pump inhibitor (PPI) use were assessed.

Statistical analysis

All statistical analyses were performed using SPSS Statistics, version 24 (IBM Corp., Armonk, NY, USA). Pearson's Chi-square or Fisher's exact test was used for comparing categorical data between the two groups, and Student's *t* test was used for comparing continuous data. *P* values < 0.05 were considered to be indicative of statistical significance.

Results

LECS was performed for SMTs on EGJ in 21 patients. There were 13 intraluminal growth-type lesions, 2 extraluminal growth-type lesions, and 6 mixed growth-type lesions. The lesions were located at the greater curvature ($n = 11$),

Table 1 Characteristics of the patients

	Total (<i>n</i> = 21)
Age (years, mean $\pm$ SD)	48.2 $\pm$ 13.2
Sex: <i>n</i> (%)	
Male	10 (48%)
Female	11 (52%)
BMI (kg/m ² , mean $\pm$ SD)	22.0 $\pm$ 3.6
Circumference: <i>n</i> (%)	
Anterior wall	0 (0%)
Posterior wall	7 (33%)
Greater curvature	11 (52%)
Lesser curvature	3 (14%)
Type of tumor growth: <i>n</i> (%)	
Intraluminal	13 (62%)
Extraluminal	2 (10%)
Mixed	6 (29%)
Ulceration: <i>n</i> (%)	
Absent	21 (100%)
Tumor size (mm, mean $\pm$ SD)	32.5 $\pm$ 12.9
Preoperative endoscopic findings: <i>n</i> (%)	
GERD	1 (5%)
Hiatal hernia	2 (10%)
Atrophic gastritis	8 (38%)

SD standard deviation, BMI body mass index, GERD gastroesophageal reflux disease

lesser curvature (*n* = 3), or anterior wall (*n* = 7) of the EGJ (Table 1). None of the lesions had an ulceration. The mean tumor size was 32.5 mm.

In all patients, LECS was completed. The procedures included 14 classical LECS, 4 NEWS, and 4 CLEAN-NET. Fourteen (67%) patients underwent fundoplication. The mean operation time was 225 $\pm$ 48 min, with a mean estimated blood loss of 8.8 $\pm$ 10.7 mL (Table 2). All patients were discharged without any postoperative adverse events, with a mean time of 9.0 $\pm$ 1.9 days after the surgery.

En bloc resection with negative surgical margins was achieved in all patients. The resected SMTs were finally diagnosed as leiomyomas (*n* = 18), GISTs (*n* = 2), and ectopic pancreas (*n* = 1). All patients were alive without recurrence within the mean follow-up period of 30.5 months.

All patients underwent follow-up endoscopy, and gastroesophageal reflux disease (GERD) was observed in four patients: 1 out of 13 patients who underwent fundoplication and 3 out of 8 patients without fundoplication. The incidence of GERD was lower with fundoplication than without, although the difference was not statistically significant (7.7% vs. 37.5%, respectively; *P* = 0.091). PPI use also tended to be less with fundoplication than without (23.1% vs. 50.0%, respectively; *P* = 0.204). Of the three patients who underwent surgery without fundoplication and developed postoperative GERD, one had preoperative GERD and was taking PPI before surgery. After surgery, the mild reflux esophagitis remained unchanged and the patient continued to take oral PPI. The average tumor size was significantly

Table 2 Operative characteristics and postoperative outcomes

	Total (<i>n</i> = 21)	Fundoplication		<i>P</i> value
		+ (<i>n</i> = 13)	– (<i>n</i> = 8)	
Procedure: <i>n</i> (%)				0.221
Classical LECS	13 (62%)	10	3	
NEWS	4 (19%)	1	3	
CLEAN-NET	4 (19%)	2	2	
En bloc resection: <i>n</i> (%)	21 (100%)			
Operation time (minutes, mean $\pm$ SD)	225 $\pm$ 48	218 $\pm$ 55	237 $\pm$ 36	0.350
Blood loss (mL, mean $\pm$ SD)	8.8 $\pm$ 10.7	8.9 $\pm$ 12.4	8.8 $\pm$ 8.8	0.984
Postoperative hospital stay (days, mean $\pm$ SD)	9.0 $\pm$ 1.9	9.1 $\pm$ 2.0	8.9 $\pm$ 2.0	0.826
Pathological diagnosis: <i>n</i> (%)				0.472
GIST	2 (10%)	1	1	
Ectopic pancreas	1 (5%)	0	1	
Leiomyoma	18 (86%)	12	6	
Postoperative adverse events: <i>n</i> (%)	0 (0%)			
GERD in follow-up endoscopy: <i>n</i> (%)	4 (19%)	1	3	0.091
Stenosis in follow-up endoscopy: <i>n</i> (%)	0 (0%)			
PPI use: <i>n</i> (%)	7 (33%)	3	4	0.204

LECS laparoscopic and endoscopic cooperative surgery, NEWS non-exposed endoscopic wall-inversion surgery, CLEAN-NET combination of laparoscopic and endoscopic approaches to neoplasia with non-exposure technique, SD standard deviation, GIST gastrointestinal stromal tumor, GERD gastroesophageal reflux disease, PPI proton pump inhibitor

larger in patients with postoperative GERD compared with those without (48.3 ± 17.3 vs. 28.8 ± 9.3 mm, respectively; $P=0.005$). We found that body mass index was not significantly different between patients with or without postoperative GERD (21.4 ± 0.5 vs. 22.1 ± 4.0 kg/m², respectively; $P=0.517$). Among the four patients with postoperative GERD, there were no cases of preoperative esophageal hiatal hernia and one case of atrophic gastritis. Preoperative endoscopic findings of esophageal hiatal hernia and atrophic gastritis were not significantly related to the presence or absence of postoperative GERD.

Discussion

In this study, we investigated the feasibility and safety of LECS in 21 patients who underwent LECS for SMT on the EGJ. To the best of our knowledge, this is the first report to investigate tumors located on the EGJ. The results showed that LECS for SMT on the EGJ was safe and feasible. We also showed that fundoplication may reduce the incidence of reflux esophagitis after surgery without increasing operation time, blood loss, and other complications.

The occurrence of GIST in the stomach (60%), jejunum and ileum (30%), duodenum (4–5%), rectum (4%), colon and appendix (1–2%), and esophagus (<1%) has been reported [12]. Therefore, GISTs account for approximately 70% of gastric SMTs [3], whereas leiomyoma is the most common SMT of the esophagus and accounts for 70–80% of esophageal SMTs [13]. In this study, leiomyomas accounted for 86% of SMTs on the EGJ, of which GISTs accounted for 10% of those. This result is similar to the previous data for esophageal SMTs [13]. Although tumors on the EGJ are not GISTs in most cases, we have to determine the indication for surgical resection considering the risk that excessive resection, such as proximal gastrectomy or total gastrectomy, will be necessary if the optimal timing is missed and the tumor becomes larger. Moreover, our results suggested that even with local resection, the risk of developing postoperative reflux esophagitis increased as the tumor size increased. Therefore, we should consider surgical resection, especially for tumors with an increasing tendency while the tumor is relatively small, even if it is asymptomatic. Thus, surgery without compromising postoperative quality of life is required. Adding fundoplication to LECS for tumors on the EGJ, as performed at our institution, may be an option for preventing postoperative reflux esophagitis.

Local resection without lymphadenectomy is accepted as the standard treatment for patients with gastric SMT because the risk of nodal metastasis is considered to be low [14–16]. Therefore, laparoscopic wedge resection is widely applied for gastric SMTs [17]. However, application of a laparoscopic endostapling device is difficult for lesions located

near the EGJ or pyloric ring. In these cases, conventional surgery, such as proximal gastrectomy or distal gastrectomy, has been necessary before LECS has been proposed. An SMT near the EGJ is one of the best indications of LECS because proximal gastrectomy would be avoided and fundic function would be preserved. However, for a tumor located just above the EGJ, we have to consider the possibility of damaging the physiological backflow prevention mechanism of the cardia caused by resection of the tumor. In our institution, fundoplication was added to LECS of SMT on the EGJ according to the surgeon's judgment during the procedure for each patient. As shown in this report, because the incidence of reflux esophagitis was high in the patients without fundoplication, we have performed fundoplication in all patients since January 2017. Although a few studies have described the addition of fundoplication to laparoscopic resection for SMT on the EGJ [18], its usefulness is not clear in the literature. Our results demonstrated that the incidence rate of postoperative reflux disease decreased with the addition of fundoplication, although it was not a statistically significant difference from the rate for patients without fundoplication. However, we cannot confirm the efficacy of adding fundoplication to LECS from this study alone. The present study has a critical limitation in terms of validating fundoplication; many patients underwent surgery without fundoplication in the early part of the study period, whereas fundoplication was performed on almost all patients who underwent surgery in the later part of the study period. In the later period, our procedure had been standardized, and the indications extended to include relatively small tumors with a tendency to grow because of their potential to increase postoperative quality of life. Consequently, the operative time was shorter with fundoplication than without. Further accumulation of clinical cases and prospective randomized trials are required to validate the efficacy of adding fundoplication to LECS for the treatment of SMTs on the EGJ.

The present study had several limitations. First, this was a retrospective case series conducted at a single center in a small number of patients. Second, the heterogeneity of surgical procedures due to surgeons' preferences cannot be ignored as they may have affected surgical outcomes. In addition, the principal operators were limited to experienced laparoscopists and endoscopists. Third, the observation period was relatively short to demonstrate the significance of postoperative outcomes. Further investigation of long-term outcomes is required to clarify the role of LECS for resection of SMTs on the EGJ.

In conclusion, we demonstrated the feasibility and safety of LECS for SMTs, even those on the EGJ. Although further accumulation of clinical cases and development of techniques is required, LECS could represent a good option for the treatment of SMTs on the EGJ to avoid proximal gastrectomy and preserve fundic function. To verify the

clinical utility of fundoplication additional to this procedure for preventing postoperative reflux esophagitis, future clinical trials and multicenter, prospective, randomized trials are warranted.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All the procedures were followed 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.

Informed consent Informed consent or substitute for it was obtained from all patients for inclusion in the study.

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