(Table 1). Their mean body mass index (BMI) was 22.5 kg/m^2 (range, 16.8–30.8 kg/m^2). The tumors were in the middle third of the stomach for 170 of the patients (90.4%). Six patients had a history of cholecystectomy, and 13 patients underwent laparoscopic cholecystectomy during LAPPG. Postoperative pathologic data confirmed T1 (mucosal or submucosal) tumors in 174 patients (92.6%). Although the preoperative diagnosis was stage IA (T1, N0) for all the patients, the pathologic diagnosis was lymph node metastasis for 14 patients (7.4%), and the final diagnosis was stage IB for 15 patients, stage II for 8 patients, and stage IIIA for 1 patient. The mean tumor size was 2.8 cm (range, 0.6–9 cm). Differentiated tumors were found in 65 patients and undifferentiated tumors in 123 patients.

The mean operation time was 234.4 min (range, 140–407 min), and the mean blood loss was 53.6 ml (range, 2–420 ml) (Table 2). There was no conversion to open surgery. Modified D2 lymph node dissection (D1 + β or D1 + β + 11p) was performed for 185 patients (98.4%), and the mean number of resected lymph nodes was 35.7 (range, 14–70).

Early postoperative complications developed in 29 patients (15.4%). The complications for most patients were not severe and could be managed by nonoperative therapy. Only two patients underwent reoperation because of pancreatic leakage and postoperative ileus, respectively. Gastric stasis was the most frequent complication, occurring in 14 patients (7.4%) who had severe symptoms requiring fasting and intravenous fluid. The mean postoperative hospital stay was 13.4 days (range, 7–106 days).

Table 3 summarizes the long-term follow-up outcome and survival data. The follow-up rate was 100%, and the median follow-up time was 38 months (range, 2–63 months). One patient underwent partial small bowel resection because of adhesive intestinal obstruction 8 months after LAPPG. Gallstones developed in two patients (1.1%). The one patient received laparoscopic cholecystectomy 38 months after LAPPG, and the other patient with asymptotic gallstone was still under observation. There was no evidence of bile duct stones in the 19 patients who had undergone cholecystectomy. Three patients experienced a second primary EGC, and all were treated by endoscopic submucosal dissection.

Overall, the 3-year cumulative survival rate was 97.8%. Five patients died. One of these patients with T3N0 gastric cancer died of peritoneal metastasis 27 months after surgery. Three patients died of cancers other than gastric cancer. The cause of death was unclear for the remaining patient. The disease-specific 3-year survival rate was 99.3%. No patients with a final diagnosis of EGC died.

Table 2 Surgical and early postoperative outcomes

Variable	Value
Operation time (min)[a]	234.4 ± 47.0 (140–407)
Blood loss (ml)[a]	53.6 ± 68.0 (2–420)
Lymph node dissection (D1 + α/D1 + β/ D1 + β + 11p)	3/8/177
Total number of resected lymph nodes[a]	35.7 ± 10.3 (14–70)
Early postoperative complication: *n* (%)	29 (15.4)
Stasis	14 (7.4)
Ileus	1 (0.5)
Pancreatic leak	8 (4.3)
Abdominal abscess	9 (4.8)
Wound infection	2 (1.1)
Postoperative stay (days)[a]	13.4 ± 9.5 (7–106)

[a] Values are mean ± standard deviation (range)

Table 3 Long-term outcome and survival

Variable	Value
Median follow-up period: months (range)	38 (2–63)
Intestinal obstruction: *n* (%)	1 (0.5)
Gallstone: *n* (%)	2 (1.1)
Remnant stomach cancer: *n* (%)	3 (1.6)
Cause of death: *n* (%)	
Gastric cancer metastasis	1 (0.5)
Other cause	4 (2.1)
Overall 3-year survival rate (%)	97.8
Disease-specific 3-year survival rate (%)	99.3

Discussion

Currently, PPG is indicated as a function-preserving operation for EGC in the middle third of stomach. The early and long-term outcome has proved its safety, better postoperative quality of life, and excellent long-term survival compared with CDG [5, 6, 17].

Recently, PPG was performed laparoscopically (LAPPG) as a minimally invasive technique. We and other groups have reported the safety and feasibility of LAPPG in terms of intraoperative and early postoperative outcomes [11, 17, 18]. The demonstrated benefits of LAPPG are less intraoperative blood loss, less postoperative pain, faster recovery of bowel function, and shorter hospital stay than patients experience with conventional PPG.

The intraoperative and early postoperative outcomes in the current study were in accordance with previous reports. However, as a new therapeutic method, LAPPG should meet the basic surgico-oncologic principles for maintaining curability. To this end, LAPPG should be proved safe in terms of long-term outcome. In this study, we report 188

consecutive cases of LAPPG with long-term surgical and oncologic outcomes.

Adhesive intestinal obstruction is a major concern after abdominal surgery. Studies have shown that laparoscopic surgery may reduce the incidence of intestinal obstruction. A study comparing the outcomes between laparoscopic and open surgery for patients with right-sided colon cancer showed less postoperative intestinal obstruction with laparoscopic surgery [19].

We previously performed a retrospective analysis comparing 72 patients who underwent LAPPG and 37 patients who had conventional PPG for EGC and found that the incidence of early postoperative ileus in the LAPPG group was significantly lower than in the conventional PPG group (1 vs. 14%) [11]. In the current study, only two patients (1.1%) experienced intestinal obstruction. The one patient had early positive ileus, and the other patient had adhesive intestinal obstruction 8 months after the operation. Although this was not a case–controlled study, the low incidence of intestinal adhesion showed the benefit of PPG performed by laparoscopy.

Gallstone formation is a common complication after gastrectomy for patients with gastric cancer. Fukagawa et al. [20] reported gallstones in 25.7% (173/672) of patients who had undergone gastrectomy with lymph node dissection for gastric cancer. Nunobe et al. [7] reported that gallstone incidence after conventional PPG was 10.8% (21/194). In the current study, the overall incidence of gallstone after LAPPG was 1.1%, and only one patient underwent laparoscopic cholecystectomy because of cholecystolithiasis. We performed LAPPG by routinely preserving the hepatic branch of the vagus nerve.

Denervation of the hepatic branch of the vagus nerve may play an important role in the formation of gallstone after gastrectomy. Kojima et al. [21] compared the effect of vagus nerve preservation on the incidence of gallstone after LADG and found that vagus nerve-sparing LADG had a lower incidence of gallstone than LADG. Findings have proved that PPG is less likely to cause stasis of the bile flow associated with disturbance of biliary motility [22] and that gallbladder function in patients who had PPG is better than in patients who had CDG [6].

The long-term outcome and survival after PPG is excellent. Morita et al. [23] reported their results from conventional PPG for 611 patients with EGC. The 5-year survival rate was 96.3%. Five patients experienced a second primary gastric carcinoma in the remnant stomach, and six patients experienced recurrence.

Our previous study retrospectively summarized the results of PPG for 305 patients with EGC. The overall 5-year survival probability was 98%, and the gastric cancer-related death rate was 0% during a median follow-up period of 60 months [14]. Although that study included 94 patients who underwent LAPPG, the long-term outcome for the pure LAPPG group was not estimated.

The current study is the first to report the long-term survival outcome of LAPPG itself. The median follow-up period was 38 months (range, 2–63 months). The overall 3-year survival rate was 97.8%, and the disease-specific 3-year survival rate was 99.3%. Only one patient with T3N0 gastric cancer died of peritoneal metastasis. No patients with pathologically confirmed EGC experienced death. The results of this study indicated that LAPPG may be performed safely with excellent long-term outcome for patients with EGC, and a preoperative accurate diagnosis of EGC may ensure the safety of this procedure.

Although Shimoyama et al. [24] thought PPG was optimal for serosal negative gastric tumors less than or equal to cT2 cN0 and less than or equal to 2 cm in maximum diameter, we do not suggest expanding the indication of LAPPG to advanced gastric cancer. Because EGC may recur even 5 years after treatment [25], the follow-up evaluation of these patients is continued, and the longer follow-up outcome is worth expecting.

In summary, we report the long-term outcome and survival with LAPPG for 188 consecutive patients. The satisfactory long-term surgical and oncologic outcomes showed LAPPG to be a safe surgical procedure for patients with EGC in the middle third of the stomach.

Disclosures

Drs. Xiaohua Jiang, Naoki Hiki, Souya Nunobe, Tetsu Fukunaga, Koshi Kumagai, Kyoko Nohara, Hiroshi Katayama, Shigekazu Ohyama, Takeshi Sano, and Toshiharu Yamaguchi have no conflicts of interest or financial ties to disclose.

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Original article

Laparoscopy-assisted gastrectomy in patients with previous endoscopic resection for early gastric cancer

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Background: Some patients undergoing endoscopic resection for early gastric cancer need further surgical treatment to achieve cure. However, the influence of endoscopic resection on subsequent laparoscopy-assisted gastrectomy (LAG) remains unclear.

Methods: A total of 711 patients who underwent LAG were analysed retrospectively; 111 patients had undergone endoscopic resection previously and the remaining 600 had no history of endoscopic resection. Patient characteristics, operative and postoperative outcomes were compared between the two groups. Risk factors associated with postoperative complications were analysed.

Results: Duration of operation and blood loss were comparable between the two groups. Patients who had undergone endoscopic resection had fewer dissected lymph nodes and a lower rate of preservation of the coeliac branch of the vagus nerve, especially those who had LAG within 2 months after endoscopic resection. Early postoperative outcomes, including complications, gastrointestinal recovery and length of postoperative hospital stay, were not significantly different between the two groups. Previous endoscopic resection was not a risk factor for postoperative complications.

Conclusion: LAG can be performed safely even after endoscopic resection. Endoscopic resection might increase the difficulty of subsequent LAG, including lymph node dissection and preservation of the coeliac branch of the vagus nerve; however, it has little influence on early postoperative outcome.

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Introduction

As a result of advances in diagnostic techniques and the increasing prevalence of screening programmes, early gastric cancer (EGC) accounts for over 50 per cent of gastric cancers in Japan[1,2]. Currently, EGC with a very low or no risk of nodal metastasis is first treated by endoscopic resection, either endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD)[3,4]. Endoscopic resection, however, causes iatrogenic ulcers in the resected area during the healing process, which induce inflammation and subsequent fibrosis and even adhesions in the outer gastric wall[5,6]. Such changes are more obvious in patients experiencing gastric perforation as a result of endoscopic resection[7].

Endoscopic resection is not adequate for EGC if there is a risk of nodal metastasis. Laparoscopy-assisted gastrectomy (LAG) with lymphadenectomy is a good minimally invasive therapeutic option for EGC[8]. Laparoscopy-assisted distal gastrectomy is the most common procedure, and has proven feasibility and safety in the treatment of EGC[9,10]. If the endoscopic resection specimen contains tumour residue or indicates a risk of lymph node metastasis, further operation is needed and in Japan LAG will probably be the first choice[11]. The inflammation and adhesion caused by endoscopic resection might increase the difficulty of the subsequent LAG and the risk of complications, but there are few data available on the influence of previous endoscopic resection on LAG.

This study compared surgical data and postoperative outcomes in patients who had LAG after endoscopic resection with those of patients undergoing LAG without previous endoscopic resection.

Methods

From April 2006 to December 2009, 711 patients with EGC diagnosed before surgery underwent laparoscopy-assisted distal gastrectomy or pylorus-preserving gastrectomy in the Department of Gastroenterological Surgery, Cancer Institute Hospital, Tokyo, Japan. The diagnosis of EGC was based on the preoperative assessment of depth of wall invasion by upper gastrointestinal tract endoscopy, barium radiology and endoscopic ultrasonography, with nodal involvement determined by preoperative computed tomography. Some patients had undergone endoscopic resection previously. The criteria for endoscopic resection were in accordance with gastric cancer treatment guidelines in Japan[12].

Laparoscopy-assisted gastrectomy

LAG was performed by experienced surgeons using standard procedures as described previously[13–15]. Lymph node stations corresponded to specific lymph node tiers according to the Japanese Classification of Gastric Carcinoma[16]. Lymph node dissection of D1 + α indicated dissection of the perigastric lymph nodes and nodes along the left gastric artery (station 7). D1 + β lymph node dissection indicated dissection of the perigastric lymph nodes and stations 7 and 8a (anterosuperior group of the common hepatic artery), and 9 (coeliac artery) nodes. D1 + β + 11p dissection involved stations 7, 8a, 9 and 11p (proximal splenic artery) lymph nodes. D2 lymph node dissection indicated dissection of the perigastric nodes and all second-tier nodes, depending on the tumour location.

Distal gastrectomy was indicated for neoplasms located in the middle or lower part of the stomach. Billroth I anastomosis was performed using a hemi-double stapling technique. If the proximal remnant stomach was too small to perform a Billroth I anastomosis, Roux-en-Y reconstruction was performed. Pylorus-preserving gastrectomy was carried out for tumours located in the middle third of the stomach, with a maximum diameter of 5 cm, and at least 5 cm proximal to the pyloric ring[15].

Clinicopathological and surgical outcome data

Patients were divided into two groups for analysis: those who had endoscopic resection before LAG and those who did not. Clinicopathological and surgical outcome data were compared between the two groups.

Preoperative clinical data obtained included sex, age, body mass index, preoperative co-morbidity, tumour location and clinical stage. Operative data included duration of operation, estimated blood loss, degree of lymph node dissection, whether the coeliac branch of the vagus was preserved, type of surgery and conversion to open surgery. Pathological data included depth of tumour invasion, number of harvested lymph nodes, and presence or absence of lymph node metastasis. Early postoperative outcome data comprised postoperative complications, including bleeding, anastomotic leakage, stasis, ileus, pancreatic leakage, abdominal abscess and wound infection. Time until first passage of flatus, time to resumption of eating and length of postoperative hospital stay were also recorded.

Statistical analysis

Continuous data were expressed as mean(s.d.) and compared using the Student's t test. Relationships between categorical variables were analysed using the χ^2 test or Fisher's exact test. Risk factors that might affect postoperative complications were evaluated by univariable analysis; risk factors with $P < 0{\cdot}100$ in univariable analysis were included in multivariable logistic regression analysis. $P < 0{\cdot}050$ was considered significant. Statistical analyses were performed using SPSS® version 13.0 (SPSS, Chicago, Illinois, USA).

Results

Of the 711 patients who had LAG, 111 had undergone endoscopic resection previously, including 13 EMRs and 98 ESDs. Five patients experienced gastric perforation during endoscopic resection and all underwent non-surgical treatment. Reasons for further LAG were: submucosal tumour invasion (84 patients), residual tumour (19), undifferentiated tumour (6) and tumour recurrence (2).

Patient demographics and clinical background of the 111 patients who had endoscopic resection before LAG and the 600 who did not are compared in *Table 1*. There were no significant differences in body mass index, previous upper abdominal surgery, circular location of the lesion or clinical stage between the two groups. The group that had undergone endoscopic resection had a higher percentage of men (71·2 *versus* 61·0 per cent; $P = 0{\cdot}042$) and patients with co-morbidity (43·2 *versus* 30·3 per cent; $P = 0{\cdot}044$), older patients (68·1(8·4) *versus* 60·3(11·8) years; $P < 0{\cdot}001$) and a greater proportion of tumours in the lower third of the stomach (50·5 *versus* 34·2 per cent; $P = 0{\cdot}004$).

Operative and pathological data

There were no significant differences in duration of operation or estimated blood loss between the two groups

Table 1 Characteristics of patients who did or did not undergo endoscopic resection

	Endoscopic resection ($n = 111$)	No endoscopic resection ($n = 600$)	P†
Age (years)*	68·1(8·4)	60·3(11·8)	< 0·001‡
Sex ratio (M : F)	79 : 32	366 : 234	0·042
Body mass index (kg/m^2)*	23·0(3·8)	22·6(3·2)	0·215‡
Co-morbidity	48 (43·2)	182 (30·3)	0·044
Diabetes	17 (15·3)	43 (7·2)	0·005
Hypertension	37 (33·3)	143 (23·8)	0·034
Heart disease	6 (5·4)	19 (3·2)	0·288§
Pulmonary disease	6 (5·4)	27 (4·8)	0·826§
Previous upper abdominal surgery	7 (6·3)	25 (4·5)	0·430§
Location of lesion (third of stomach)			0·004
Upper	2 (1·8)	26 (4·3)	
Middle	53 (47·7)	369 (61·5)	
Lower	56 (50·5)	205 (34·2)	
Location of lesion			0·496
Lesser curvature	35 (31·5)	230 (38·3)	
Greater curvature	26 (23·4)	131 (21·8)	
Anterior wall	20 (18·0)	108 (18·0)	
Posterior wall	30 (27·0)	131 (21·8)	
Clinical stage			0·402
IA	109 (98·2)	573 (95·5)	
IB	2 (1·8)	25 (4·2)	
II	0 (0)	2 (0·3)	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †χ^2 test, except ‡Student's t test and §Fisher's exact test.

(*Table 2*). D2 lymph node dissection was less common (5·4 *versus* 12·7 per cent; $P = 0·048$) and the rate of preservation of the coeliac branch of the vagus nerve was lower (41·4 *versus* 57·2 per cent; $P = 0·002$) in the endoscopic resection group. In accordance with the higher percentage of tumours in the lower stomach, distal gastrectomy with Billroth I reconstruction was performed more frequently in this group (62·2 *versus* 45·7 per cent; $P < 0·001$). No conversion to open surgery was needed in the endoscopic resection group, but conversion was necessary in nine patients who had not undergone endoscopic resection ($P = 0·368$). The total number of dissected lymph nodes was smaller in the endoscopic resection group (28·4(11·1) *versus* 31·5(10·1); $P = 0·003$). Depth of tumour invasion was not significantly different between the two groups, whereas the endoscopic resection group had a lower incidence of lymph node metastasis (6·3 *versus* 13·5 per cent; $P = 0·041$).

Early postoperative outcome

The early postoperative complication rate was similar in the groups with and without endoscopic resection (14·4 *versus* 10·8 per cent; $P = 0·275$) (*Table 3*). The most common

Table 2 Operative and pathological data

	Endoscopic resection ($n = 111$)	No endoscopic resection ($n = 600$)	P†
Duration of operation (min)*	230·1(60·6)	229·2(52·4)	0·876‡
Blood loss (ml)*	54·7(85·4)	56·3(109·5)	0·881‡
Lymph node dissection			0·048
D1 + α	0 (0)	2 (0·3)	
D1 + β	3 (2·7)	6 (1·0)	
D1 + β + 11p	102 (91·9)	516 (86·0)	
D2	6 (5·4)	76 (12·7)	
Coeliac branch of vagus nerve preserved			0·002
No	65 (58·6)	257 (42·8)	
Yes	46 (41·4)	343 (57·2)	
Type of surgery			< 0·001
LADG (Billroth I)	69 (62·2)	274 (45·7)	
LADG (Roux-en-Y)	11 (9·9)	95 (15·8)	
LAPPG	31 (27·9)	231 (38·5)	
Conversion to open surgery	0 (0)	9 (1·5)	0·368§
No. of harvested lymph nodes*	28·4(11·1)	31·5(10·1)	0·003‡
Depth of cancer invasion			0·096
Mucosa	24 (21·6)	283 (47·2)	
Submucosa	61 (55·0)	228 (38·0)	
Muscle	24 (21·6)	46 (7·7)	
Subserosa	2 (1·8)	34 (5·7)	
Serosa	0 (0)	9 (1·5)	
Lymph node metastasis			0·041
N0	104 (93·7)	519 (86·5)	
N1	6 (5·4)	56 (9·3)	
N2	1 (0·9)	25 (4·2)	

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). LADG, laparoscopy-assisted distal gastrectomy; LAPPG, laparoscopy-assisted pylorus-preserving gastrectomy. †χ^2 test, except ‡Student's t test and §Fisher's exact test.

complication in endoscopic resection group was abdominal infection (4·5 per cent), whereas it was pancreatic leakage (3·0 per cent) in the group that had not undergone endoscopic resection. One patient (0·9 per cent) needed reoperation because of duodenal stump leakage in endoscopic resection group. Five patients (0·8 per cent) had reoperation in the group without endoscopic resection. There were no significant differences in time until start of flatus, time to resumption of oral intake and length of postoperative hospital stay between the groups.

Effect of the interval between endoscopic resection and subsequent surgery on clinical outcome

To evaluate the effect of the interval between endoscopic resection and subsequent surgery on clinical outcome, the 111 patients who had undergone endoscopic resection were divided into two groups: 61 patients who received

Table 3 Early postoperative outcome

	Endoscopic resection ($n = 111$)	No endoscopic resection ($n = 600$)	P†
No. with postoperative complications	16 (14·4)	65 (10·8)	0·275
Intra-abdominal bleeding	0 (0)	1 (0·2)	1·000‡
Anastomotic bleeding	0 (0)	2 (0·3)	1·000‡
Anastomotic or duodenal leakage	2 (1·8)	6 (1·0)	0·359‡
Pancreatic leakage	2 (1·8)	18 (3·0)	0·755‡
Gastric stasis	2 (1·8)	15 (2·5)	1·000‡
Ileus	2 (1·8)	3 (0·5)	0·176‡
Abdominal infection	5 (4·5)	16 (2·7)	0·353‡
Wound infection	2 (1·8)	7 (1·2)	0·637‡
Reoperation	1 (0·9)	5 (0·8)	1·000‡
Time until start of flatus (days)*	2·3(0·9)	2·4(0·8)	0·976§
Time until start of oral intake (days)*	2·3(2·0)	2·2(1·7)	0·570§
Postoperative hospital stay (days)*	13·6(7·3)	13·3(7·3)	0·698§

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †χ^2 test, except ‡Fisher's exact test and §Student's t test.

Table 4 Effect of interval between endoscopic resection and subsequent surgery on clinical outcome

	≤ 2 months ($n = 61$)	> 2 months ($n = 50$)	P†
Duration of operation (min)*	229·3(61·2)	231·1(60·5)	0·877‡
Blood loss (ml)*	67·3(104·0)	39·5(52·4)	0·072‡
No. of harvested lymph nodes*	27·5(9·4)	29·4(13·0)	0·384‡
Coeliac branch of vagus nerve preserved	20 (33)	26 (52)	0·041
No. with postoperative complications	10 (16)	6 (12)	0·275
Postoperative hospital stay (days)*	14·7(9·0)	12·3(4·3)	0·061‡

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). †χ^2 test, except ‡Student's t test.

LAG within 2 months and 50 patients who underwent LAG more than 2 months after endoscopic resection. There were no significant differences in operative and postoperative outcomes between the two groups, apart from a significantly lower rate of preservation of the coeliac branch of the vagus nerve in patients who received LAG within 2 months after endoscopic resection (33 *versus* 52 per cent; $P = 0·041$) (*Table 4*).

Table 5 Univariable analysis of factors associated postoperative complications

	Without complications ($n = 630$)	With complications ($n = 81$)	P†
Age (years)*	61·3(11·8)	62·9(10·8)	0·261‡
Sex (M : F)	385 : 245	60 : 21	0·165
Body mass index (kg/m^2)*	22·5(3·2)	23·8(3·5)	0·001‡
Co-morbidity	194 (30·8)	36 (44)	0·013
Previous upper abdominal surgery	28 (4·4)	4 (5)	0·777§
Location of lesion (third of stomach)			0·728
Upper	24 (86)	4 (14)	
Middle	377 (89·3)	45 (10·7)	
Lower	229 (87·7)	32 (12·3)	
Location of lesion			0·209
Lesser curvature	236 (89·1)	29 (10·9)	
Greater curvature	132 (84·1)	25 (15·9)	
Anterior wall	115 (89·8)	13 (10·2)	
Posterior wall	147 (91·3)	14 (8·7)	
Previous endoscopic resection	95 (15·1)	16 (20)	0·275
Surgeon's experience of LAG			0·693
< 50	227 (88·0)	31 (12·0)	
≥ 50	403 (89·0)	50 (11·0)	
Duration of operation (min)*	228·6(53·5)	235·1(55·5)	0·305‡
Blood loss (ml)*	54·3(106·6)	69·7(101·4)	0·218‡
Lymph node dissection			0·554
D1 + α	2 (100)	0 (0)	
D1 + β	7 (78)	2 (22)	
D1 + β + 11p	546 (88·3)	72 (11·7)	
D2	75 (91)	7 (9)	
Coeliac branch of vagus nerve preserved			0·207
No	280 (87·0)	42 (13·0)	
Yes	350 (90·0)	39 (10·0)	
Type of surgery			0·788
LADG (Billroth I)	304 (88·6)	39 (11·4)	
LADG (Roux-en-Y)	92 (86·8)	14 (13·2)	
LAPPG	234 (89·3)	28 (10·7)	
No. of harvested lymph nodes*	31·1(10·5)	30·5(8·8)	0·615‡

Values in parentheses are percentages unless indicated otherwise; *values are mean(s.d.). LAG, laparoscopy-assisted gastrectomy; LADG, laparoscopy-assisted distal gastrectomy; LAPPG, laparoscopy-assisted pylorus-preserving gastrectomy. †χ^2 test, except ‡Student's t test and §Fisher's exact test.

Risk factors associated with postoperative complications

Univariable analyses showed that body mass index and preoperative co-morbidity affected postoperative complications (*Table 5*). Multivariable analysis identified

body mass index (at least 24 kg/m^2) as an independent risk factor for postoperative complications (odds ratio 1·90, 95 per cent confidence interval 1·17 to 3·07; $P = 0·009$).

Discussion

EGC is considered a good indication for a minimally invasive approach such as endoscopic resection or LAG. When there is no risk of lymph node metastasis, endoscopic resection is similar to surgery in terms of curability but less invasive and more cost effective[17]. EMR, the so-called strip biopsy method, is widely accepted as a standard treatment for EGC in Japan[17,18]. ESD increases *en bloc* and histologically complete resection rates[19]. In the present study, 111 patients needed further surgery after endoscopic resection to achieve cure, of whom 98 had undergone ESD.

LAG has advantages over conventional open gastrectomy, including less intraoperative blood loss, less postoperative pain, faster recovery and shorter hospital stay[10,20]. When LAG is carried out after endoscopic resection, the influence of the endoscopic procedure on the stomach and surrounding tissue has to be taken into account. Endoscopic resection-induced inflammation causes oedema, fibrosis, and adhesions of both the stomach and surrounding tissue. In the present study, these changes were observed in almost all patients who had undergone endoscopic resection, being most apparent in the five patients who experienced gastric perforation. Although the mean duration of operation and estimated blood loss were comparable between groups of patients who had or had not undergone endoscopic resection, several surgical aspects differed. D1 + β + 11p was the most common type of lymph node dissection in both groups, whereas D2 dissection, which probably retrieves more lymph nodes[21], was performed less frequently in the endoscopic resection group. Among patients who had a non-D2 lymph node dissection, the mean number of dissected lymph nodes was smaller in the endoscopic resection group (data not shown). Inflammation caused by endoscopic resection probably influenced the subsequent lymph node dissection. However, the extent of lymph node dissection and number of harvested lymph nodes were sufficient to achieve cure and for determining pathological lymph node metastasis in both groups[12]. The rate of preservation of the coeliac branch of the vagus nerve was lower in the endoscopic resection group, especially in patients who had LAG within 2 months after the endoscopic procedure. To preserve the coeliac branch of the vagus nerve, it is very important to have clear surgical anatomy in the vicinity of the nerve. When endoscopic resection is carried out for EGC in the lesser curvature or posterior wall of the stomach, inflammation surrounding the vagus nerve might increase the difficulty of nerve preservation.

In spite of differences in surgical procedures, the postoperative complication rate, recovery and hospital stay were similar in the two groups, indicating that endoscopic resection had little influence on early postoperative outcomes. A previous study documented that abdominal adhesions caused by previous laparotomy did not affect the surgical outcome of LAG[22].

There were several clinical differences between the two groups in this study. The endoscopic group had a higher proportion of men and elderly patients, and preoperative co-morbidities including diabetes and hypertension were more common, which might indicate a higher risk of postoperative complications. Nevertheless, a previous study showed that postoperative complications of LAG did not increase significantly in elderly patients with more preoperative co-morbidities[21], consistent with the present results. Multivariable analysis revealed body mass index as the only independent risk factor for postoperative complications. Thus, endoscopic resection had little influence on early postoperative outcome of LAG.

The present study had some limitations. It included all patients who had undergone endoscopic resection previously, but the influence of type of endoscopic procedure was not analysed. Detailed information on the endoscopic procedure used in each patient could not be obtained because some patients underwent endoscopic resection in other hospitals. Complications caused by endoscopic resection, such as perforation, might lead to more adhesions and will probably increase the difficulty of LAG. This study included only five patients who experienced perforation during endoscopic resection, which was not sufficient for analysis. Further studies are warranted to clarify the effect of the endoscopic procedure on subsequent LAG.

The long-term outcome of the group who had endoscopic resection is unknown because of the short follow-up. However, other studies have reported satisfactory long-term survival after LAG for EGC[23,24]. In the present study, most patients in the endoscopic resection group underwent modified D2 lymphadenectomy (D1 + β with or without 11p), with an adequate number of dissected lymph nodes, and the rate of lymph node metastasis was very low at 6·3 per cent, all of which predict good long-term outcome.

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Efficacy of celiac branch preservation in Roux-en-y reconstruction after laparoscopy-assisted distal gastrectomy

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Background. *The present study investigated the efficacy of preserving the celiac branch of the vagus nerve after laparoscopy-assisted distal gastrectomy (LADG) with Roux-en-Y (R-Y) reconstruction.*
Methods. *Between January 2004 and September 2008, a total of 159 consecutive patients who underwent LADG for gastric carcinoma were classified into groups according to preservation of the celiac branch of the vagus nerve—preservation group (P-LADG;* n = *70) and the resection group (R-LADG;* n = *89). The parameters analyzed included patient and tumor characteristics, operative details, postoperative outcomes, and nutritional state. The endoscopic findings of the gastric remnant and lower esophagus were evaluated at 12 months postoperatively.*
Results. *In regard to postoperative complications, no significant differences were found between groups. With R-LADG, 14 patients suffered from dumping syndrome (15.7%), compared with only 2 patients with P-LADG (2.9%;* P = *.007). The amount of meal consumption compared with the preoperative value and the rate of weight reduction at 12 months postoperatively did not differ significantly between groups. Endoscopic findings showed significantly more residue with P-LADG (34.3%) than with R-LADG (16.9%;* P = *.011).*
Conclusion. *The celiac branch is useful in regulating gastrointestinal motility by maintaining postoperative physiologic function. Celiac branch preservation seems to represent a feasible and beneficial method for LADG. (Surgery 2011;149:22-8.)*

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DISORDERS SUCH AS MALABSORPTION, POSTPRANDIAL DUMPING SYNDROME, REFLUX ESOPHAGITIS, ALKALINE GASTRITIS, AND DELAYED GASTRIC EMPTYING are all unfavorable sequelae in patients after distal gastrectomy.[1-3] These functional disturbances induce a variety of postgastrectomy symptoms that adversely affect the patient's quality of life. Various limited surgical procedures for early gastric cancer (EGC) that allow functional preservation of the gastric remnant, therefore, are being performed to reduce these disorders and maintain quality of life.

Injury to the hepatic branches from the anterior vagal trunk and autonomic nerves around the common hepatic artery (CHA) is known to result in gallstone formation,[4,5] and injury to the celiac branch from the posterior vagal trunk reportedly impairs pancreatic insulin release.[6,7] To prevent such disorders, methods to preserve the vagus nerve system have been introduced in distal gastrectomy for EGC. Conversely, in Japan, laparoscopy-assisted distal gastrectomy (LADG) increasingly has been employed for the treatment of gastric cancer to improve quality of life in the early and late postoperative phases.[8,9] Recently, vagus nerve preservation has been combined with laparoscopic gastrectomy, as laparoscopic surgery offers the advantage of a magnified view that allows clear identification of the nerve branches.[5,10]

Hagiwara et al[11] reported that preservation of the celiac branch in distal gastrectomy reduces postgastrectomy disturbances, and it demonstrated good visceral function in 5 patients using barium radiography; however, the underlying mechanisms were not clearly explained in their report. To evaluate the roles and mechanisms of action for the celiac branch, some studies have addressed the pathophysiology of the upper gastrointestinal tract. Yunoki[12] reported that the celiac branch of the vagus nerve is not essential to the initiation

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of interdigestive motor activities but plays a role in increasing the frequency of recurring motor activity during the interdigestive state. Ando et al[6] reported that the motility index of gastrointestinal motility was higher with the preservation of the celiac branch than with the resection of the celiac branch in fasted and fed states, but no significant differences were found in gastric emptying.

The effects of celiac branch preservation after distal gastrectomy on the gastrointestinal tract have yet to be clarified. This study evaluated the influences of the celiac branch from a clinical perspective in LADG with Roux-en-Y (R-Y) reconstruction.

METHODS

Between January 2004 and September 2008, 159 consecutive patients with preoperatively diagnosed early gastric carcinoma without lymph node metastasis underwent LADG in the Department of Esophagogastric Surgery at Tokyo Medical and Dental University. The extent of lymph node dissection was D1 plus alpha or beta, as defined by the Japanese Gastric Cancer Association guidelines.[13] All operations were performed by 3 expert surgeons. Patients were enrolled retrospectively in the present study, after excluding 2 patients with simultaneous operations for other cancers and 1 patient who had undergone laparoscopic surgery for transverse colon cancer. A preoperative assessment was made by endoscopy, endoscopic ultrasonography, abdominal ultrasonography, and computer tomography for characterization of the tumors. Preservation of the celiac branch of the vagus nerve was performed for lesions preoperatively diagnosed as mucosal cancer without lymph node metastasis, and the operator made the final judgment of whether to perform nerve preservation in consideration of the physical situation of the patient. Patients were classified according to preservation of the celiac branch into a preservation group (P-LADG; n = 70) and a resection group (R-LADG; n = 89). The following parameters were recorded: patient age and sex; American Society of Anesthesiologists-physical status (ASA-PS) classification, body mass index (BMI), tumor characteristics, operative time, estimated blood loss, postoperative hospital stay, postoperative complications, and clinical symptoms. Postoperative complications were defined as any event requiring specific medical or surgical treatment. All patients were interviewed 12 months postoperatively about clinical symptoms such as heartburn, diarrhea, constipation, and early dumping syndrome (EDS). EDS was identified if any of the following symptoms (based on the criteria for dumping syndrome established by the Japan Society of Gastroenterological Surgery[14]) were present immediately after eating: palpitations, pallor, suffusion, abdominal pain, weakness, sweating, or dizziness. Diarrhea was defined as a postoperative new-onset change in bowel habits resulting in 2 or more loose or watery stools in 1 week, with or without postprandial abdominal cramps or urgency. Nutritional parameters were assessed postoperatively by body weight, food intake, and laboratory findings (serum albumin and total cholesterol). Abdominal ultrasonography and computed tomography were performed 12 months postoperatively to detect postoperative recurrence. Endoscopic examination was performed on all patients at 12 months postoperatively to evaluate the condition of the lower esophageal mucosa and gastric remnant stump as well as to detect the presence of bile and the amount of residue in the gastric stump. Endoscopic findings of the gastric remnant were evaluated according to the "residue, gastritis, bile" classification.[15] The incidence of gastritis and residue of grade 2 or greater were calculated.

Surgical procedures for LADG. The anatomical distribution and numbering of regional lymph nodes were based on the Japanese classification of the gastric carcinoma, 2nd English ed.[16]

LADG was conducted in a standard manner, as described.[5] Briefly, the patient was placed in the reverse Trendelenburg position. A 5-trocar technique was used for the laparoscopic procedures. The first 12-mm trocar and flexible electrolaparoscope (Fujinon, Tokyo, Japan) were introduced through an umbilical incision after creating low-pressure pneumoperitoneum (10 mmHg) using an open technique. Lymph nodes along the left gastric artery (LGA), CHA, and celiac axis were dissected in addition to D1 lymph node dissection. The procedure began with a division of the omentum along the gastroepiploic vessels to harvest lymph nodes (No. 4d) using ultrasonically activated coagulating shears (laparoscopic coagulating curved shears [LCS]; Ethicon Endo-Surgery, Cincinnati, OH). The main root of the left gastroepiploic vessels was divided using a LigaSure device (Valleylab; TycoHealthcare, Norwalk, CT), then lymph nodes along these vessels were harvested (No. 4sb). Roots of the right gastroepiploic vein were identified and secured with clips. The right gastroepiploic artery then was isolated and divided at the origin. Through this procedure, the infrapyloric lymph nodes (No. 6) were dissected. The duodenum was transected using an endoscopic liner stapler (Endo-GIA; United States Surgical,

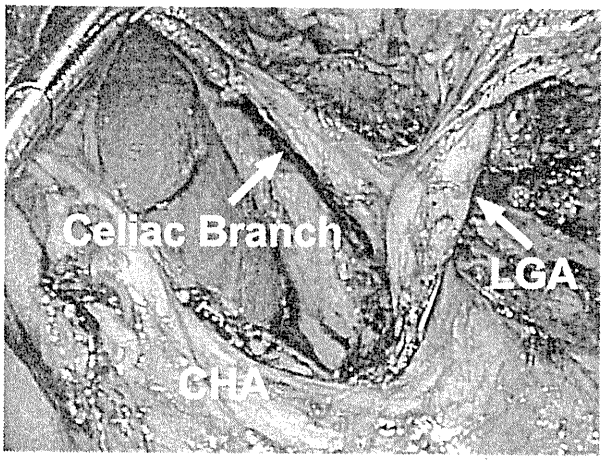

Fig 1. Exposure of the junction of the celiac branch and LGA. The celiac branch runs to the celiac ganglion along the LGA.

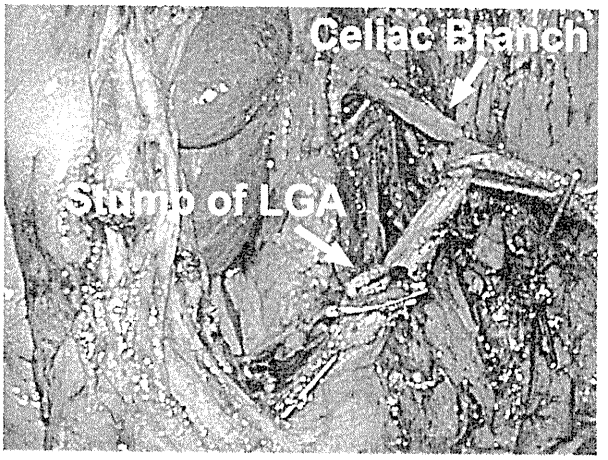

Fig 2. The LGA was divided at the position where the celiac branch joins the LGA.

Norwalk, CT). A seromuscular suture with a laparoscopic hand-sewn technique was used for the duodenal stump. The right gastric vessels were divided and suprapyloric lymph nodes (No. 5) were dissected. The lesser omentum was divided toward the abdominal esophagus to remove the right paracardial lymph nodes (No. 1) and the lymph nodes along the lesser curvature (No. 3) as well as to preserve the hepatic branch from the anterior vagal trunk. When the celiac branch was preserved, the posterior vagal trunk running along the posterior wall of the abdominal esophagus was isolated with vessel tape. Celiac branches of the posterior vagal trunk run down along the lesser curvature to the celiac ganglion. Lymph nodes along the anterior CHA (No. 8) were dissected toward the celiac artery by LCS. In this step, the hepatic nerve plexus running along the CHA was preserved. Lymph nodes along the LGA (No. 7) and celiac artery (No. 9) were stripped toward the position where the celiac branch of the posterior vagal trunk joins the LGA (Fig 1). The LGA was divided with double clips after isolation of the celiac branch. The vessel tape then was retracted to the right, and the gastric branches were divided using the LCS. Vagus nerve-preserving lymph node dissection was completed (Fig 2).

In the reconstruction phase, a small midline upper abdominal incision 5 cm in length was made. The stomach was externalized through the incision and dissected with the linear stapling device at least 1 cm proximal to the tumor site. After the remnant stomach was returned to the abdominal cavity, the jejunum was externalized through the incision, and the mesentery and jejunum were divided at a portion 25 cm distal to the ligament of Treitz. Extracorporeal anastomosis of the proximal end of the jejunum to the distal jejunum was created 30 cm distal from the jejunal division using Endo-GIA (45 mm, white cartridge). The common entry hole was closed using a 1-layer running suture. After returning the jejunum to the abdominal cavity, the jejunal loop was brought up the antecolic route and isoperistaltic gastrojejunostomy was performed by side-to-side anastomosis using the Endo-GIA (60 mm, blue cartridge). The common entry hole was closed using a 1-layer running suture.

Statistical analysis. All values except postoperative hospital stay are expressed as mean ± standard deviation with comparisons between groups made using the χ^2 test and Student t test. Postoperative hospital stay is expressed as median ± median absolute deviation (MAD) and comparisons between groups were made using the Mann–Whitney U test. Values of $P < .05$ were considered statistically significant. Statistical analysis was performed using StatView software (Abacus Concepts, Berkeley, CA).

RESULTS

Characteristics and operative records of patients are summarized in Table I. No significant differences were observed between groups for age, ASA-PS, BMI, stage of gastric cancer, operative time, estimated blood loss, retrieved lymph nodes, or postoperative hospital stay. A significant difference was found in sex ratio between groups. The time to first flatus was shorter in P-LADG than in R-LADG, although the difference was not statistically significant.

Table I. Patients characteristics and operation records

	P-LADG (70)	*R-LADG (89)*	P *value*
Age (year)	63.1 ± 11.7	63.2 ± 13.4	.950
Sex (male/female)	42/28	66/23	.058
ASA-PS			
1	40	42	.159
2	25	41	
3	2	6	
BMI (kg/m^2)*	22.1 ± 2.0	23.3 ± 2.4	.078
Stage (*n*)			
IA	62	71	.438
IB	7	14	
II	1	3	
IIIA	0	1	
Operation time (min)*	265.7 ± 52.0	271.9 ± 45.0	.233
Blood loss (mL)	76.1 ± 87.4	99.3 ± 77.6	.079
Retrieved LN (number)	34.5 ± 14.0	33.9 ± 13.7	.813
Time to first flatus (day)*	2.5 ± 0.5	3.0 ± 1.0	.063
Time to fever resolution (day)*	4.0 ± 1.0	4.0 ± 1.0	.233
Postoperative hospital stay (day) (range)*	6.5 ± 1.5 (4–27)	7.0 ± 1.0 (5–47)	.205

Values are mean ± SD.
*Values represent median ± MAD.
LN, Lymph node.

Table II. Postoperative complications

	P-LADG (70)	*R-LADG (89)*	P *value*
Anastomotic leakage (%)	0.0	0.0	—
Anastomotic stricture (%)	2.9	2.2	.807
Delirium (%)	1.4	6.7	.105
Wound infection (%)	1.4	2.2	.707

In regard to postoperative complications, no significant differences were identified between groups (Table II). Anastomotic leakage was not observed. Four patients suffered from anastomotic stricture. With R-LADG, 1 patient required endoscopic balloon dilation, and the remainder was treated conservatively. No cases of so-called functional stasis after R-Y reconstruction were found in the present study.

Clinical symptoms were examined 12 months postoperatively. Incidence of heartburn, diarrhea, and constipation did not differ between groups. Dumping syndrome was seen in 14 patients with R-LADG (15.7%), compared with only 2 patients with P-LADG (2.9%; $P = .007$; Table III).

The state of nutrition is shown in Table IV. No significant difference was observed in the rate of weight reduction at 12 months postoperatively between groups. The amount of meal consumed compared with preoperative value at 12 months postoperatively did not differ significantly between groups. Serum albumin and total cholesterol levels at 12 months postoperatively were similar between groups.

Endoscopic findings were evaluated by 2 expert scopists at 12 months postoperatively (Table V). The amount of residue over grade 2 was significantly greater with P-LADG (34.3%) than with R-LADG (16.9%; $P = .011$). No significant differences were found in remnant gastritis, bile reflux, and reflux esophagitis between groups.

Mean follow-up periods for P-LADG and R-LADG were 45.5 ± 14.6 months and 30.6 ± 12.6 months, respectively. Two R-LADG patients died from peritoneal recurrence and heart failure at 27 and 46 months after the operation, respectively. All remaining patients are currently alive without recurrence.

DISCUSSION

The vagus nerve comprises afferents and efferents known as sensory neurons and motor neurons respectively, and 90% of the subdiaphragmatic vagus nerve consists of afferents. Afferents in the celiac branch innervate the celiac plexus and then distribute across the alimentary canal from the duodenum to the transverse colon, as well as to the body and tail of the pancreas, and transmit information from visceral organs to the hypothalamus.[17] Conversely, the celiac branch plays a role as an efferent pathway for neuroregulation related to glucose-sensitive units in the hepato-portal system.[18]

Table III. Results of questionnaire about postoperative condition

	P-LADG (70)	*R-LADG (89)*	P *value*
Clinical symptom (%)			
Heartburn	8.6	9.0	.927
Diarrhea	14.3	9.0	.295
Constipation	15.7	6.7	.696
Dumping syndrome	2.9	15.7	.007

Table IV. Nutritional status at 12 month after operation

	P-LADG (70)	*R-LADG (89)*	P *value*
Body weight (%)	90.2 ± 6.2	90.1 ± 7.4	.940
Food intake (%)	81.2 ± 15.3	82.9 ± 13.5	.471
Serum albumin (mg/dl)	4.3 ± 0.9	4.3 ± 0.3	.565
Total cholesterol (mg/dl)	183.8 ± 30.6	188.8 ± 110.7	.725

Values are mean ± SD.

EDS is a serious complication that may occur after gastric surgery in about 5–10% of patients.[19] EDS, typically starting 10–30 min postprandially, usually involves both vasomotor and gastrointestinal complaints. EDS results from a release of intestinal hormones such as bradykinin, serotonin, and histamine, which lead to a large fluid shift from the intravascular space into the intestinal lumen and to subsequent decreases in the quantity of circulating plasma. The vasodilator plasma bradykinin is generated by the action of proteolytic kininogenase enzymes on plasma globulin substrates. In a previous report, greatly increased levels of free plasma bradykinin were found during a dumping attack, whereas blood serotonin concentration remained within the normal range.[20]

Several studies have suggested that the intestinal sensory innervation plays an important role in physiologic regulation.[21,22] Miao et al[17,23] reported that the sensitivity of nociceptive-neuroendocrine negative feedback control is modulated by activity in abdominal vagal afferents. Specifically, the inhibition of bradykinin-induced plasma extravasation generated by this negative feedback loop was potentiated by about 2 orders of magnitude after selectively cutting the celiac branches of the subdiaphragmatic vagus nerve but not after cutting the gastric or hepatic branches. In the study of esophagectomy, patients with vagal sparing were significantly less likely to experience EDS than patients who had undergone either transhiatal or en bloc esophagectomy.[24,25] In the present study, the incidence of EDS was significantly lower with P-LADG than with R-LADG ($P = .007$). Celiac afferents that innervate the small intestine reportedly respond to distension or contraction of the organ and to intraluminal chemical stimulation,[26-28] and afferent activity in the celiac branch is considered to be involved in the regulation of nociceptive system-initiated depression of bradykinin-induced plasma extravasation.

After distal gastrectomy, the remnant stomach usually does not contract.[29] In a study using canine models, no obvious phase III contractions were observed in the remnant stomach after distal gastrectomy, regardless of celiac branch preservation.[6] Contractile patterns of the duodenum reportedly influence gastric emptying after B-I gastrectomy,[30] and motility of the efferent limb reportedly is closely related to gastric emptying after distal gastrectomy with R-Y gastrojejunostomy.[31] Van der Mijle et al[32] reported that motility disturbances in the Roux limb were not observed more frequently in patients with either moderately or severely impaired vagal function compared with patients with normal vagal function after R -Y gastrojejunostomy. Conversely, Woodward et al[33] reported that animals with gastric vagotomy showed significantly faster gastric emptying than animals with truncal vagotomy ($P = .02$) after anterectomy and R-Y gastrojejunostomy; however, the relationship between gastric emptying and motility of the jejunum has yet to be clarified. The effects of the vagus nerve system on gastrointestinal motility after distal gastrectomy with R-Y reconstruction have not been elucidated. In this study, the amount of residue was significantly greater with P-LADG than with R-LADG ($P = .011$); however, incidences of heartburn and levels of food intake were similar between groups, and no cases of poor gastric emptying affecting food intake were found. The symptoms of early dumping are thought to result from the rapid emptying of hyperosmolar chyme into the small bowel. The low incidence of EDS in P-LADG may be related to frequent stasis in the Roux limb as a result of celiac branch preservation.

Diarrhea is significantly more common after truncal vagotomy than after selective vagotomy.[34] Postvagotomy diarrhea is caused by the rapid entry of fluid, electrolytes, and malabsorbed nutrients into the colon after meals.[35,36] In this study, a decreased incidence of diarrhea was not observed in patients with celiac branch preservation.

Table V. Endoscopic findings of the gastric remnant and the lower esophagus

	P-LADG (70)	*R-LADG (89)*	P *value*
Residual food (%)	34.3	16.9	.011
Remnant gastritis (%)	8.6	7.9	.872
Bile reflux (%)	2.9	4.5	.591
Reflux esophagitis (%)	7.1	16.9	.067

Rosa-e-Silva et al reported that patients with type I diabetes mellitus and sympathetic denervation show an abnormally rapid transit of a liquid meal through the distal small bowel, which may play a part in diarrhea production.[37] Ichikura et al reported that patients with lymph node dissection around the celiac artery were significantly more likely to complain of diarrhea than those without (P = .001).[38] Denervation of the sympathetic nervous system (celiac and mesenteric plexus and splanchnic nerves) after lymph node dissection, thus, is considered to influence the occurrence of postoperative diarrhea. Serotonin reportedly mediates fast and slow excitatory neurotransmissions and is implicated in gastrointestinal disorders such as irritable bowel syndrome, diarrhea, and functional dyspepsia.[39,40] Serotonin stimulates vagal and enteric afferent nerve fibers, which initiate the peristaltic reflux and also plays a role in descending pathways from the brainstem that modulate afferent information processed by the dorsal horn. These serotonergic descending fibers are considered important as inhibitors of sympathetic outflow.[41] Postgastrectomy diarrhea, thus, may be attributed to disorders of the adrenergic and serotonergic neurons controlling gastrointestinal function, as well as to sympathetic nervous denervation.

Laparoscopic surgery has the advantage of providing a magnified view that allows precise manipulation of blood vessels and nerves. Observation from various angles enables the identification of the celiac branch located in the back of the stomach. We believe that the laparoscopic approach is more suited to delicate procedures such as nerve preservation as compared with conventional open operations.

In conclusion, we consider celiac branch preservation as beneficial in reducing EDS by maintaining postoperative physiologic function, and operative outcomes did not differ significantly regardless of celiac branch preservation in our study; however, because the roles of the celiac nerve in reducing dumping syndrome have not been elucidated, the present results should be verified in a long-term follow-up of these patients, and additional randomized control studies are warranted to determine the clinical efficacy of preserving the celiac branch in LADG.

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Original article

Safety and feasibility of laparoscopy-assisted distal gastrectomy with suprapancreatic nodal dissection for clinical stage I gastric cancer: a multicenter phase II trial (JCOG 0703)

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Abstract

Background. **Although the number of patients undergoing laparoscopy-assisted distal gastrectomy (LADG) has been increasing, a prospective study with a sample size sufficient to investigate the benefit of LADG has never been reported. We conducted a multi-institutional phase II trial to evaluate the safety of LADG with nodal dissection for clinical stage I gastric cancer patients.**

Methods. **The subjects comprised patients with clinical stage I gastric cancer who were able to undergo a distal gastrectomy. LADG with D1 plus suprapancreatic node dissection was performed. The primary endpoint was the proportion of patients who developed either anastomotic leakage or a pancreatic fistula. The secondary endpoints included surgical morbidity and short-term clinical outcome.**

Results. **Between November 2007 and September 2008, 176 eligible patients were enrolled. The proportion of patients who developed anastomotic leakage or a pancreatic fistula was 1.7%. The overall proportion of in-hospital grade 3 or 4 adverse events was 5.1%. The short-term clinical outcomes were as follows: 43.2% of the patients requested an analgesic on postoperative days 5–10; the median time from surgery until the first episode of flatus was 2 days; and 88 patients (50.0%) had a body temperature of 38°C or higher during their hospital stay.**

Conclusions. **This trial confirmed the safety of LADG performed by credentialed surgeons in terms of the incidence of anastomotic leakage or pancreatic fistula formation. A phase III trial (JCOG 0912) to confirm the noninferiority of LADG to an open gastrectomy in terms of overall survival is ongoing.**

Key words Gastric cancer · Laparoscopy-assisted distal gastrectomy · Morbidity

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Introduction

The proportion of patients with early gastric cancer among all gastric cancer patients has increased to more than 50% at major institutions in Japan [1]. The Japanese guidelines allow laparoscopy-assisted gastrectomy as an investigational treatment for early gastric cancer, with consideration of the patient's performance status [2]. Since Kitano et al. [3] reported the first laparoscopy-assisted gastrectomy in 1994, this technique has attracted the attention of surgeons. A nationwide survey of laparoscopic surgery for gastric cancer has shown that the total number of patients who were treated using a laparoscopic technique has increased and that this increase was most remarkable among patients with cT1N0 (stage IA), cT1N1 (stage IB), and cT2N0 (stage IB) tumors [4].

D1 + suprapancreatic node dissection for stage I tumors could indeed be considered as excessive surgery in western countries because of their low incidence of suprapancreatic node metastasis. However, a Japanese database showed that N2 node metastasis was found in 5.8% of patients with T1 tumors (submucosal [SM]) and in 17% with T2 tumors (muscularis propriae [MP]) [5]. Surgeons should aim at a cure rate of 100% as a general concept. Therefore, Japanese guidelines demand D1 + suprapancreatic node dissection for this population (i.e., those with clinical stage I gastric cancer).

Recent advances in operative techniques and endoscopic instrumentation have led to the standardization of laparoscopy-assisted distal gastrectomy (LADG) with suprapancreatic node dissection among experienced laparoscopic surgeons. Although whether this modality is appropriate for cancer treatment remains a concern, the technical difficulties of LADG have been

gradually solved. Several studies have reported that LADG allows a better quality-of-life outcome than an open distal gastrectomy (ODG) [6–11]. Although several studies have reported that LADG is a safe procedure with regard to morbidity and mortality [12, 13], other studies have reported that LADG has a higher risk of surgical morbidities such as anastomotic leakage, stenosis, and pancreatic fistula formation than ODG [14, 15]. Therefore, the safety of LADG should first be confirmed as an initial step.

On the other hand, several retrospective and small prospective studies have reported that the long-term results of LADG are similar to those of ODG [15, 16]. However, a prospective study with a sample size sufficient to investigate the long-term survival of LADG has not yet been reported. Thus, once the safety of LADG has been confirmed, the long-term survival after LADG should be evaluated as a next step.

The present report describes a multi-institutional phase II trial conducted by the Gastric Cancer Surgical Study Group of the Japan Clinical Oncology Group (JCOG 0703) to evaluate the safety of LADG with nodal dissection for clinical stage I gastric cancer patients. If the safety of LADG was verified, a subsequent phase III trial was to be designed to evaluate the noninferiority of LADG to ODG in terms of long-term survival.

Patients and Methods

Our study was designed as a multicenter, prospective phase II trial. The study protocol was approved by the JCOG Protocol Review Committee and the institutional review boards (IRBs) of each of the 17 participating Japanese hospitals before the activation of the study. The inclusion criteria were as follows: histologically confirmed adenocarcinoma of the stomach, a c-stage IA (T1N0) or IB (T1N1/T2N0) tumor according to the *Japanese classification of gastric carcinoma, 2nd English edition* [17], no indications for endoscopic mucosal resection (EMR) according to the Japanese endoscopic treatment guidelines [2] ("no indications for EMR" corresponds to a clinical node-positive or clinical node-negative status with any of the following criteria: a tumor size 2 cm or larger, invasion to the submucosa or deeper, a histologically undifferentiated type, the presence of an ulcer or ulcerative scar [in the case of depressed type], or the impossibility of an en-bloc resection), a distal gastrectomy-treatable tumor located in the middle or lower third of the stomach, no involvement of the duodenum, a patient age of 20–80 years, an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0 or 1, a body mass index (BMI) of less than 30 kg/m^2, the absence of a recurrent tumor after EMR, no prior upper abdominal surgery or intestinal resection other than an appendectomy, no prior chemotherapy or radiotherapy for any malignancy, adequate organ function, and written informed consent. The exclusion criteria were as follows: a synchronous or metachronous (within 5 years) malignancy other than carcinoma in situ or mucosal cancer, pregnancy or lactation, severe mental disease, the systemic administration of corticosteroids, unstable angina or myocardial infarction within 6 months before registration, uncontrolled hypertension, diabetes mellitus (both uncontrolled and controlled with insulin), and severe respiratory disease requiring continuous oxygen therapy.

After the inclusion/exclusion criteria were confirmed by telephoning or faxing the JCOG Data Center, the patients were registered in this JCOG 0703 trial.

Surgery

An LADG with D1 plus suprapancreatic node dissection was performed. The extent of the suprapancreatic node dissection was decided according to the surgical T and N stage of the tumor, based on the second version of the *Gastric cancer treatment guidelines in Japan* [2]. If the intraoperative findings revealed a tumor stage of II or greater, the LADG was converted to an ODG. Patients requiring a pylorus-preserving distal gastrectomy, but not a total gastrectomy, were included in this series. The size of the minilaparotomy incision was 6 cm or less, in principle. The reconstruction approach and the surgical method following resection were not specified. Postoperative analgesia, such as the use of epidural anesthesia, also was not specified. Requests for analgesia on postoperative days 5–10 were recorded. Adjuvant chemotherapy with S-1 for 1 year was recommended for patients with a curative resection and a pathological stage II, IIIA, or IIIB tumor.

Follow-up

All the enrolled patients were followed up at least every 6 months for the first 2 years and then every year for another 3 years until 5 years after the close of registration. Blood tests, an upper gastrointestinal endoscopy, and an abdominal computed tomography examination were performed every year.

Quality control of surgery

Before the start of this trial, all participating surgeons agreed to the technical details for LADG. Significant experience in gastric cancer surgery, especially in LADG

and ODG, was a prerequisite for a surgeon's participation in the trial. Only surgeons who had performed 30 or more LADG procedures and 30 or more ODG procedures were selected. Furthermore, we performed a central review of the surgical procedure by photographing all the surgeries and by videotaping arbitrarily selected surgeries. To assess compliance with the lymphadenectomy, the number of dissected nodes at all stations was recorded on the case report forms and the results were monitored.

Endpoints

The primary study endpoint was the proportion of patients who developed either anastomotic leakage or a pancreatic fistula, defined as the proportion of patients with either a grade 1 or greater anastomotic leakage or a grade 2 or greater pancreatic fistula among all the operated patients. The secondary endpoints were overall survival (OS), relapse-free survival (RFS), the proportion of LADG completions, the proportion of conversions from LADG to ODG, surgical morbidity, and the short-term clinical outcomes. The OS and RFS are not reported in this article because the current follow-up time was not long enough.

In this trial, adverse events were classified based on the Common Terminology Criteria for Adverse Events version 3.0 (CTCAE v 3.0). Anastomotic leakage and pancreatic fistula formation were also categorized based on the CTCAE v 3.0, with the following supplementary explanation of the *JCOG surgical morbidity criteria* [18]: a grade 1 or more anastomotic leakage was diagnosed radiologically and was recorded regardless of its clinical significance; a grade 2 or greater pancreatic fistula was diagnosed when fluid with a high amylase concentration drained from the peripancreatic area and led to an infection. The completion of LADG was defined as the proportion of patients without conversion from LADG to ODG among all the operated patients. The proportion of conversions from LADG to ODG was defined as the proportion of patients with a conversion among the patients who were diagnosed before gastrectomy as having clinical stage IA or IB. As for both the completion of LADG and the proportion of conversions, all LADG cases that required a skin incision of more than 6 cm were regarded as conversions to an ODG. The expected values for LADG completions and the proportion of conversions were stated as 70% and 5% in the protocol.

The short-term clinical outcomes were: (i) the proportion of patients requesting an analgesic on postoperative days 5–10, (ii) the time from the end of surgery until the first episode of flatus, (iii) the highest body temperatures during the first 3 days after surgery, and (iv) the highest body temperatures during hospitalization. The expected values for these four endpoints were 20% or less, within 3 days, 38 °C or less, and 38 °C or less, respectively. The data regarding analgesic use were collected on postoperative days 5–10 because epidural anesthesia was administered on the first 3 or 4 postoperative days in most patients.

Study design and statistical methods

This trial evaluated the safety of LADG in terms of the incidence of either anastomotic leakage or pancreatic fistula formation. If the incidence of these two postoperative complications was as low as expected, a subsequent phase III trial was designed to evaluate the noninferiority of LADG to ODG in terms of overall survival. In this phase II trial, the sample size was 170 cases, providing a 90% power under the hypothesis of a primary endpoint with an expected value of 3% and a threshold value of 8%, using one-sided testing at a 10% significance level. The expected value was decided according to the postoperative outcome of 1493 patients who had undergone an ODG at institutions belonging to the Gastric Cancer Surgical Study Group in 2004; among these patients, the proportion of those who developed anastomotic leakage was 1.3% and the proportion of those who developed pancreatic fistula formation was 0.5%. All the statistical analyses were performed using SAS software version 9.1 (SAS Institute, Cary, NC, USA).

This study was registered with UMIN-CTR [www.umin.ac.jp/ctr/], identification number UMIN000000874.

Results

Patient characteristics

Between November 2007 and September 2008, 177 patients from 14 out of the 17 hospitals with IRB approval were registered in the trial. One patient was deemed ineligible after enrollment because of a lack of written informed consent, which originated from a miscommunication among the patient's physicians.

The patients' characteristics are summarized in Table 1. The clinical and histological stages in the text are described based on the *Japanese classification of gastric carcinoma, 2nd English edition* [17], while the results shown in Table 2 are based on both the *Japanese classification of gastric carcinoma* (hereafter "Japanese classification") and the International Union Against Cancer (UICC) TNM classification, 6th edition. The median age of the patients was 59 years. The male-to-female ratio was nearly 1:1. More than 90% of the patients had clinical

Table 1. Baseline characteristics

Age (years)	
Median	59
Range	24–80
Sex, no. (%)	
Male	91 (51.7%)
Female	85 (48.3%)
Body-mass index (BMI), no. (%)	
<20	42 (23.9%)
20–24.9	107 (60.8%)
≥25.0	27 (15.3%)
Tumor location, no. (%)	
Upper third of stomach	0
Middle third of stomach	114 (64.8%)
Lower third of stomach	62 (35.2%)
Clinical T stage, no. (%)[a]	
T1	163 (92.6%)
T2	13 (7.4%)
Clinical node status, no. (%)[a]	
N0	175 (99.4%)
N1	1 (0.6%)
Clinical stage, no. (%)[a]	
IA	162 (92.0%)
IB	14 (8.0%)

[a] The distributions of c-stage were the same in the *Japanese classification of gastric carcinoma, 2nd English edition* [17] and in the International Union Against Cancer (UICC) TNM classification, 6th edition

Table 2. Histological findings

Histological type, no. (%)	
Differentiated	69 (39.2%)
Undifferentiated	107 (60.8%)
Tumor size (cm)	
Median	2.5
Range	0.5–10.0
Histological T stage, no. (%) (same in the Japanese and UICC classifications)	
T1	156 (88.6%)
T2	19 (10.8%)
T3	1 (0.6%)
Histological node status (Japanese), no. (%)	
N0	149 (84.7%)
N1	22 (12.5%)
N2	5 (2.8%)
Histological stage (Japanese), no. (%)	
IA	140 (79.5%)
IB	23 (13.1%)
II	9 (5.1%)
IIIA	4 (2.3%)
Histological node status (UICC), no. (%)	
N0	149 (84.7%)
N1	25 (14.2%)
N2	2 (1.1%)
Histological stage (UICC), no. (%)	
IA	140 (79.5%)
IB	22 (12.5%)
II	14 (8.0%)

Japanese, *Japanese classification of gastric carcinoma, 2nd English edition* [17]; UICC, UICC TNM classification, 6th edition

stage IA (cT1N0) disease. The median body mass index was 21.8. About two-thirds of the tumors were located in the middle third of the stomach.

The histological findings are shown in Table 2. Early gastric cancer (T1) was confirmed pathologically in about 90% of the patients. The proportion of patients with nodal involvement was 15.3% overall (27 out of 176 patients). About 20% of the node-positive patients had suprapancreatic node metastasis. The accuracy of the preoperative diagnosis of stage I (Japanese classification) disease was 92.6%. Adjuvant chemotherapy with S-1 was performed in 14 patients (8.0%).

Operative procedures (Table 3)

All the operations were performed with curative intent. The median duration of the operations was 250 min. A distal gastrectomy or a pylorus-preserving distal gastrectomy was performed in 174 patients. A total gastrectomy was performed in 2 patients after the identification of a positive left gastroepiploic node and a positive proximal margin, respectively. The proportion of Billroth I operations was about 50%, and this procedure was the most commonly used method.

All the patients underwent a D1 plus some extent of suprapancreatic dissection. Thirty of the 176 patients underwent a D2 lymphadenectomy.

The median length of the skin incision was 5 cm. The length of the skin incision was more than 6 cm in 5 patients. The LADG was successfully completed in 170 (96.6%; 95% confidence interval [CI], 92.7–98.7) of the 176 patients, which was far better than the expected value (70%). One patient was diagnosed as having stage II disease prior to gastrectomy, and the procedure was converted to an ODG.

The surgical procedure was converted from an LADG to an ODG in 5 patients with a preoperative diagnosis of clinical stage IA or IB; consequently, the proportion of conversions was 2.9% (95% CI, 0.9%-6.5%), which was lower than expected. The reasons for conversion were a positive proximal resected margin ($n = 1$), difficulty with the anastomosis ($n = 1$), a skin incision longer than 6 cm ($n = 1$), and bleeding ($n = 2$).

The median blood loss was 43.5 ml, and blood transfusions were required in 3 patients. The median postoperative hospital stay was 12 days (range, 7–58 days).

Operative complications and deaths

Minor injuries (grade 1, CTCAE v 3.0) were observed in two patients during the operations (transverse colon, right gastroepiploic vein).

Grade 1 or greater anastomotic leakage was observed in two patients. Grade 2 or greater pancreatic fistula formation was observed in two patients. One patient