Table 1 Characteristics of the patients

Characteristics	Proximal (102)	Total (49)	*p* value
Age [median (range)] (years)	67 (44–85)	71 (34–86)	0.391[c]
Sex [No. (%)]			0.591[d]
Male	79 (77)	36 (73)	
Female	23 (23)	13 (27)	
Lymphadenectomy[a] [No. (%)]			0.053[d]
D1	15 (15)	2 (4)	
D1+/D2	87 (85)	47 (96)	
Tumor size [median (range)] (mm)	25 (5–100)	50 (7–210)	< 0.001[c]
Histological Grade[b] [No. (%)]			0.025[d]
G1/G2 (differentiated)	73 (72)	26 (53)	
G3/G4 (undifferentiated)	29 (28)	23 (47)	
Pathological T factor[b] [No. (%)]			0.007[d]
pT1	83 (81)	30 (61)	
pT2	8 (8)	9 (19)	
pT3	10 (10)	5 (10)	
pT4a	1 (1)	5 (10)	
Pathological N factor[b] [No. (%)]			0.086[d]
pN0	90 (88)	35 (72)	
pN1	6 (6)	7 (14)	
pN2	4 (4)	5 (10)	
pN3	2 (2)	2 (4)	
Pathological stage[b] [No. (%)]			0.040[d]
IA	77 (75)	24 (50)	
IB	12 (12)	10 (20)	
IIA/IIB	8 (8)	10 (20)	
IIIA/IIIB/IIIC	5 (5)	5 (10)	

[a] According to Japanese gastric cancer treatment guidelines 2010 (ver. 3) [31]

[b] According to AJCC/UICC 7th edition [19]

[c] Wilcoxon test

[d] Pearson's χ^2 test

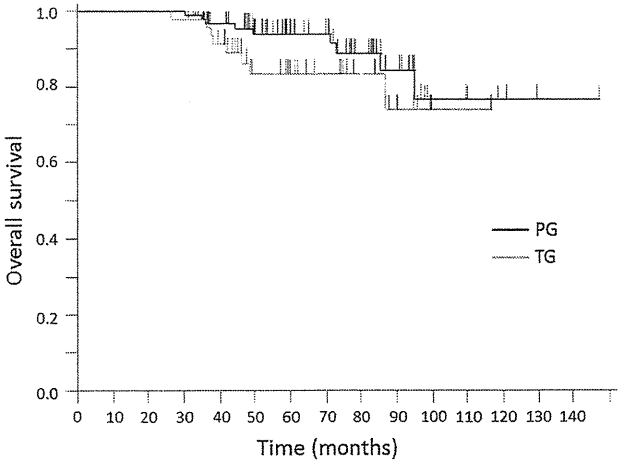

Fig. 2 The overall survival curves after proximal and total gastrectomy. There is no significant difference between the two groups by the log-rank test ($p = 0.189$). *PG* proximal gastrectomy (*black line*), *TG* total gastrectomy (*gray line*)

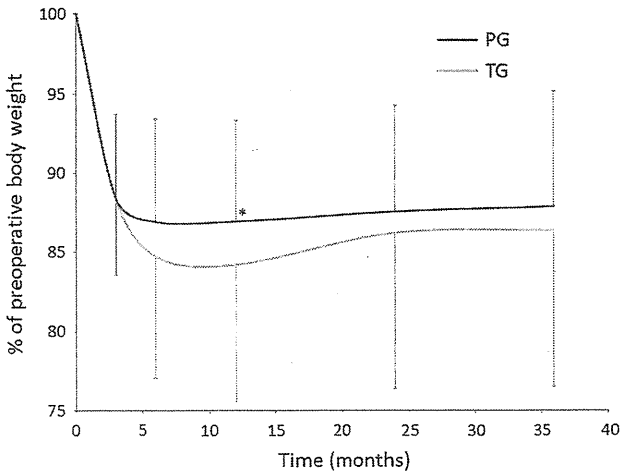

Fig. 3 The percentage of postoperative body weight to the preoperative. Data are expressed as mean ± standard deviation. *PG* proximal gastrectomy (*black line*), *TG* total gastrectomy (*gray line*). *$p = 0.034$

hematocrit level as an indicator of anemia. The three indicators gradually dropped in the TG group after the operation. In contrast, they were well maintained in the PG group until the third year. All three indicators were significantly higher in the PG group at the second and third year (Fig. 4). In blood chemistry tests, we used the level of total protein, serum albumin, and total cholesterol as an indicator of postoperative nutritional status (Fig. 5). We did not see any significant difference between the two groups at any time point.

Ninety-five patients in the PG group and 44 patients in the TG group underwent upper endoscopic postoperative surveillance at least one time (Table 2). The frequency of the examination was significantly greater in the PG group. Reflux esophagitis was observed in three PG patients and in one TG patient. There was no significant difference between the two groups. Nine patients (9 %) in the PG group were diagnosed as having a peptic ulcer in the reconstructed jejunum and/or gastric remnant. In contrast, the examination detected no peptic ulcers in the reconstructed jejunum in the TG group. The difference between the two groups was statistically significant. The typical image of the peptic ulcer is shown in Fig. 6. Peptic ulcers formed at the interposed jejunum near the jejunogastrostomy. All patients with peptic ulcers were medicated with H2-blocker or proton pump inhibitor and all were cured following treatment. Endoscopic

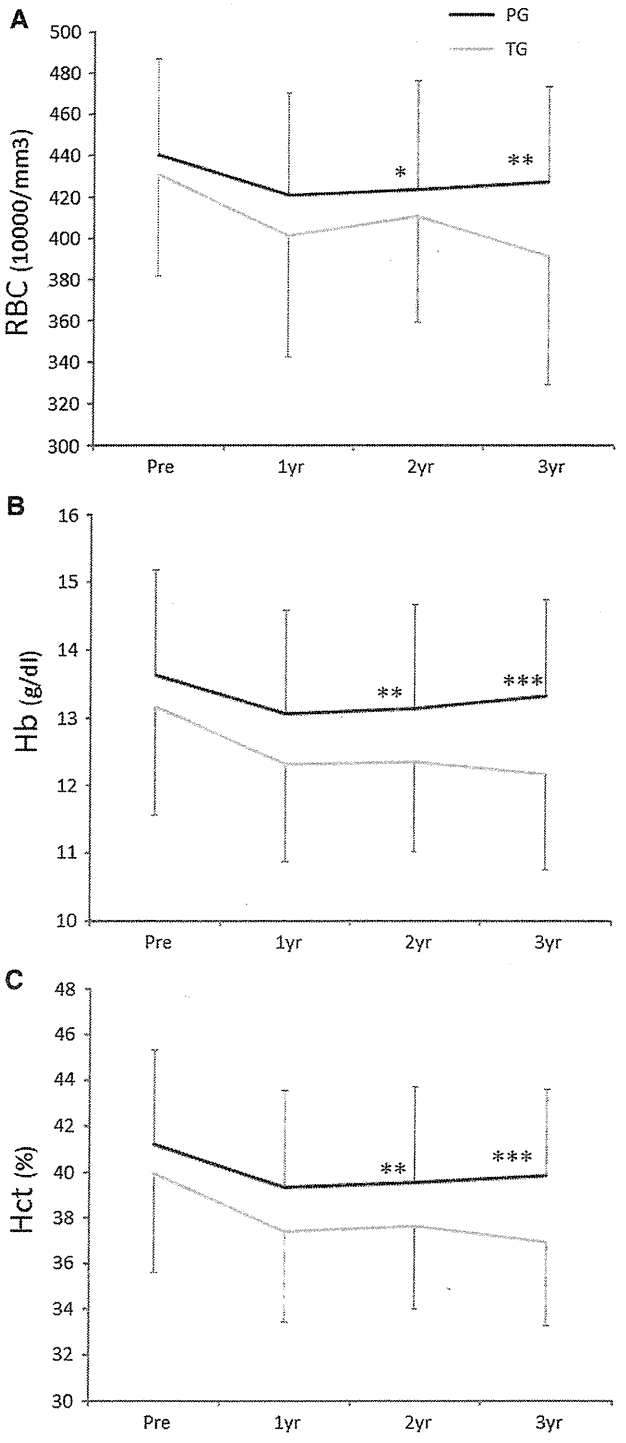

Fig. 4 The laboratory examination related to postoperative anemia. **a** *RBC* red blood cell count, **b** *Hb* hemoglobin level, **c** *Hct* hematocrit level, *PG* proximal gastrectomy (*black line*), *TG* total gastrectomy (*gray line*), *Pre* preoperative, *1yr* the first year, *2yr* the second year, *3yr* the third year after surgery. Data are expressed as mean ± standard deviation. $*p < 0.05$, $**p < 0.01$; $***p < 0.001$

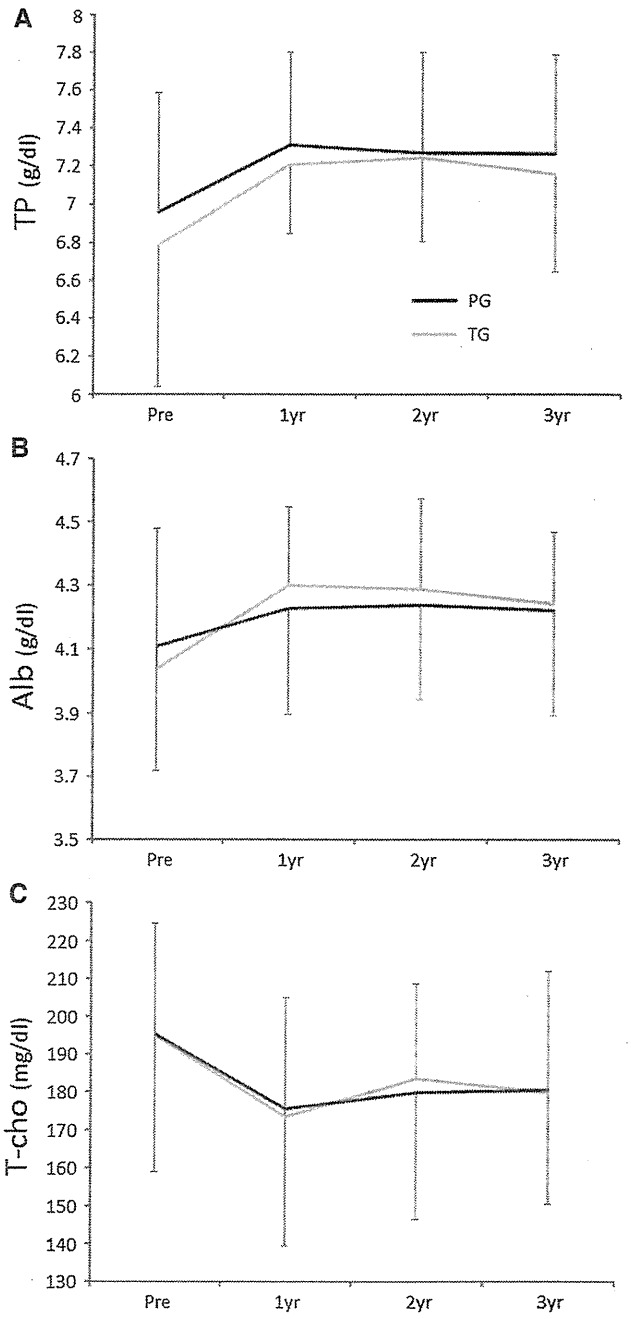

Fig. 5 The blood chemistry test related to postoperative nutritional status. **a** *TP* total protein, **b** *Alb* serum albumin, **c** *T-cho* total cholesterol. *PG* Proximal gastrectomy (*black line*), *TG* total gastrectomy (*gray line*). *Pre* preoperative, *1yr* the first year, *2yr* the second year, *3yr* the third year after surgery. Data are expressed as mean ± standard deviation. No statistically significant difference was seen between the two groups at any time point

examination also showed that 30 patients (32 %) in the PG group had grade 3 [22] or worse residual food in the remnant stomach and needed reexamination later. Metachronous gastric cancer was detected during examination in five patients (5 %) in the PG group. After the diagnosis, four patients underwent total resection of the remnant stomach and one patient underwent endoscopic submucosal resection. Curative resection was done for all five patients and no patients recurred to date.

Table 2 Findings from upper endoscopic postoperative surveillance

Times of endoscopy [median (range)]	Proximal (95) 4 (1–14)	Total (44) 1 (1–7)	*p* value < 0.001[a]
Endoscopic findings [No. (%)]			
Reflux esophagitis[c]	3 (3)	1 (2)	0.747[b]
Grade A	1	0	
Grade B	1	1	
Grade D	1	0	
Peptic ulcer	9 (9)	0 (0)	0.032[b]
Residual food[c]	30 (32)	NA	NA
Metachronous gastric cancer[c]	5 (5)	NA	NA

NA not applicable according to the definitions

[a] Wilcoxon test

[b] Pearson's χ^2 test

[c] See "Patients and methods" section for each definition

There were some late postoperative complications. Six PG patients experienced anastomotic stenosis (3 patients at esophagojejunostomy and 3 patients at jejunogastrostomy) and underwent successful balloon dilatation, while no TG patients suffered from anastomotic stenosis. Five patients in the PG group and one patient in the TG group who did not undergo prophylactic cholecystectomy experienced cholelithiasis and/or cholangitis and needed surgical intervention or medications. Intestinal obstruction occurred in two patients in the PG group and they were successfully treated with an ileus tube, while there were no patients in the TG group diagnosed with intestinal obstruction.

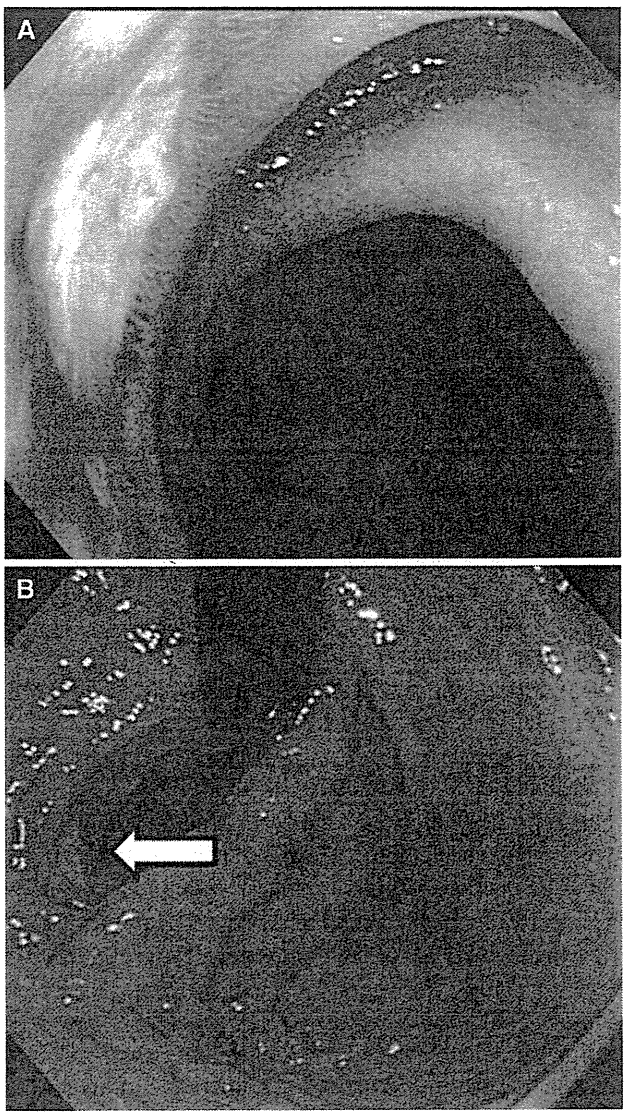

Fig. 6 The typical photographs of the peptic ulcer after proximal gastrectomy at the interposed jejunum near the jejunogastrostomy. **a** A photograph looking down from the interposed jejunum. **b** A photograph looking up from the gastric remnant. The *arrow* is pointing to the location of the peptic ulcer

Discussion

We limited the indication of PG to cT1-2N0M0 gastric cancer patients because we had previously confirmed in a TG study (data not shown) that pT1-2 gastric cancer located in the upper third of the stomach did not show any pathological lymph node metastasis at stations #4d, #5, and #6 [20], which are not dissected and remain in PG patients [11]. We chose patients with cT1-2N0M0 gastric cancers who underwent TG with Roux-Y reconstruction during the same period to compare the long-term outcomes. None of these TG patients underwent splenectomy, which could affect the long-term outcome. We chose the Roux-Y reconstruction method for TG because of its simplicity and wide use.

Overall survival

The extent of resection did not appear to affect the oncological radicality because there was no significant difference in the overall survival between the two groups. This result is consistent with those of previous reports [5–8]. In the PG group, we did not experience any lymph node recurrence. However, two patients first had recurrence in their peritoneum and gastric stump and both died from peritoneal dissemination. One of the patients had been diagnosed as cT2N0M0 and was staged as pT3N3M0 after the operation. The tumor was 85 × 55 mm. The other patient had been diagnosed as cT2N0M0 and the resected specimen was classified as pT4aN0M0. The tumor was 53 × 34 mm. Although the pathological surgical margin was negative and R0 resection was carried out in both patients, the pathological T/N factor and tumor size were

beyond our preoperative diagnosis. Since PG is accepted as a function-preserving operation for gastric cancer at a relatively early pathological stage, the preoperative diagnostic accuracy should be improved in the future.

Weight maintenance

In this study, the PG group had a significant advantage in body weight maintenance at the first year. However, this advantage was lost by the second and third year when the body weight of the TG group recovered. We speculate that the difference in body weight maintenance is because of the limited reservoir function in PG with jejunal interposition. It has been reported that PG with jejunal pouch interposition showed significantly better weight maintenance than TG from the first to the third year [17]. PG with jejunal pouch interposition may have some advantage with respect to weight maintenance because reports indicate that this technique supports reservoir function and yields nutritional advantages [24–26].

Postoperative anemia and nutritional status

In this study, PG was preferred over TG in terms of preventing postoperative anemia because red blood cell count, hemoglobin, and hematocrit measurements in the TG group gradually dropped by the third year, while the levels in the PG group were well maintained (Fig. 4). These results are consistent with those of previous reports [8, 17]. One of the causes for the postoperative anemia after TG has been vitamin B12 malabsorption [27, 28]. Since one study [17] reported that serum vitamin B12 levels were significantly better in the PG group than in the TG group at the second and third year, the remnant distal stomach after PG may play an important role in preventing vitamin B12 malabsorption.

Endoscopic findings

In this study, a wide range of remnant gastric comorbidity was seen during surveillance endoscopy in PG patients (Table 2). We observed peptic ulcer formation in nine PG patients. Likewise, several previous studies reported peptic ulcers in the interposed jejunum and remnant stomach after PG [12, 15, 29]. Gastric acid secretion remains in the gastric remnant after PG, so patients should be monitored closely in the follow-up period. Once an ulcer is detected, antisecretion medication such as an H2-blocker or proton pump inhibitor are recommended. Treatment with these drugs cured all patients with peptic ulcers in this study.

In our last two studies [23, 30], we reported that the gastric remnant after PG showed a higher incidence of metachronous cancer. In this study, five PG patients were diagnosed as having metachronous cancer in the gastric remnant. Since the median period between the primary surgery and detection of the metachronous cancer was 50 months (range = 34–101), we recommend long-term surveillance endoscopy to detect such lesions at an early stage.

It has been reported that jejunal interposition improved reflux esophagitis for PG patients when compared to esophagogastrostomy [12, 13]. The reported incidence of reflux esophagitis of 1.7–5.0 % [12, 13] is comparable to our result (3.2 %). This surgical technique lowers reflux because the interposed jejunum served as a sphincter-substituting reconstruction. In this study, the median length of the interposed jejunum was 12 cm (measured intraoperatively, range = 8–20). That was short enough for the endoscope to reach the remnant stomach in all surveyed patients. However, a moderate amount of residual food was observed in 30 % of PG patients in this study, which hindered observation of the entire surface, even with body rolling (grade 3 or worse by RGB classification [22]). All of the patients needed reexamination later. In order to observe the entire surface of the remnant stomach and detect any suspicious lesions or changes at the examination effectively, a full liquid diet may be recommended for the day before the examination.

In conclusion, PG showed comparable oncological radicality to TG. PG is preferred over TG in terms of prevention of postoperative anemia. However, periodic upper endoscopic follow-up is necessary to monitor the upper gastrointestinal tract. PG is not recommended at a hospital that cannot perform the surveillance endoscopy, otherwise the remnant stomach may cause critical comorbidity in PG patients.

Conflict of interest I. Nozaki, S. Hato, T. Kobatake, K. Ohta, Y. Kubo, and A. Kurita have no conflicts of interest to disclose. This work was supported in part by the National Cancer Center Research and Development Fund (23-A-19).

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Laparoscopic proximal gastrectomy with jejunal interposition for gastric cancer in the proximal third of the stomach: a retrospective comparison with open surgery

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Abstract
Background The incidence of cancer in the proximal third of the stomach is increasing. Laparoscopic proximal gastrectomy (LPG) seems an attractive option for the treatment of early-stage proximal gastric cancer but has not gained wide acceptance because of technical difficulties, including the prevention of severe reflux. In this study, we describe our technique for LPG with jejunal interposition (LPG-IP) and evaluate its safety and feasibility.
Methods In this retrospective analysis, we reviewed the data of patients with proximal gastric cancer who underwent LPG-IP ($n = 22$) or the same procedure with open surgery (OPG-IP; $n = 68$) between January 2008 and September 2011. Short-term surgical variables and outcomes were compared between the groups. The reconstruction method was the same in both groups, with creation of a 15 cm, single-loop, jejunal interposition for anastomosis.
Results There were no differences in patient or tumor characteristics between the groups. Operation time was longer in the LGP-IP group (233 vs. 201 min, $p = 0.0002$) and estimated blood loss was significantly less (20 vs. 242 g, $p < 0.0001$). The average number of harvested lymph nodes did not differ between the two groups (17 vs. 20). There also were no differences in the incidence of leakage at the esophagojejunostomy anastomosis (9.1 vs. 7.4 %) or other postoperative complications (27 vs. 32 %). The number of times additional postoperative analgesia was required was significantly less in the LPG-IP group compared with the OPG-IP group (2 vs. 4, $p < 0.0001$).
Conclusions LPG-IP has equivalent safety and curability compared with OPG-IP. Our results imply that LPG-IP may lead to faster recovery, better cosmesis, and improved quality of life in the short-term compared with OPG-IP. Because of the limitations of retrospective analysis, a further study should be conducted to obtain definitive conclusions.

Keywords Proximal gastrectomy · Laparoscopic surgery · Jejunal interposition · Gastric cancer

The safety and efficacy of laparoscopic gastrectomy for the treatment of early gastric cancer have been demonstrated in many clinical studies [1–3]. An increasing number of laparoscopic gastrectomies are currently being performed, especially in eastern countries, which have high incidences of gastric cancer. Because gastric cancer has predominantly been located in the distal stomach in eastern countries, laparoscopic distal gastrectomy for cancer in the middle and distal stomach has been the more commonly performed surgical procedure. However, Japanese surgeons are confronted with an increasing number of gastric cancers involving the proximal third of the stomach, probably because of the aging population. For advanced cancer in the proximal third of the stomach, total gastrectomy with D2 lymph node dissection is standard in Japan [4]. For early-stage cancer in the proximal third, open proximal gastrectomy has been performed to preserve physiological function of the remaining stomach [5–7]. Early cancer is estimated to account for nearly 50 % of gastric cancer currently diagnosed in Japan [8]. In this context,

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laparoscopic proximal gastrectomy (LPG) is likely to be performed with increasing frequency in the near future, if the operative technique becomes well established.

The most difficult technical aspect of LPG may be the anastomosis and reconstruction method, which should prevent reflux esophagitis. Several authors have already reported novel techniques using various reconstruction methods, but an optimal method has not been established. Jejunal interposition acts as a substitute sphincter, which seems to be ideal for the prevention of postoperative reflux from the remnant stomach, but it is not widely used because of the difficulty of performing the complicated anastomotic procedures laparoscopically.

At our institution, open proximal gastrectomy with jejunal interposition (OPG-IP) has been performed since 1992, and LPG with jejunal interposition (LPG-IP) was introduced in 2010. In the present study, we describe our techniques and initial experiences with LPG-IP in the treatment of proximal gastric cancer and evaluate the safety of this approach through a retrospective data review comparing our results with the open procedure.

Methods

This retrospective study reviewed the records of gastric cancer surgery patients at the National Cancer Center Hospital East, Chiba, Japan. From August 1992 to September 2011, 298 proximal gastrectomies for gastric cancer were performed at our institution. OPG-IP was performed until August 2010, and from September 2010 LPG-IP was performed. We retrospectively compared surgical data of the patients who underwent LPG-IP until September 2011 ($n = 22$) with those who underwent OPG-IP with the same reconstruction procedures between January 2008 and August 2010 ($n = 68$; Fig. 1). The decision whether to perform OPG-IP or LPG-IP was based purely on the time period during which the operation was undertaken.

Patients were selected for proximal gastrectomy if they were diagnosed with T1N0M0 gastric cancer located in the proximal third of the stomach, and it was estimated that the distal half of the stomach could be preserved. Preoperative assessment was by gastroendoscopy, abdominal ultrasonography, barium swallow radiography, and computed tomography. After surgery, baseline analgesia was administered to all patients by continuous epidural infusion of ropivacaine plus fentanyl for 2 days, with additional analgesia administered if requested by the patient. Perioperative and postoperative management protocols (clinical pathways) were amended over time, and the length of hospital stay recommended by the protocol was progressively shortened. The latest clinical pathway was adopted in April 2009 and allows patients to start drinking on

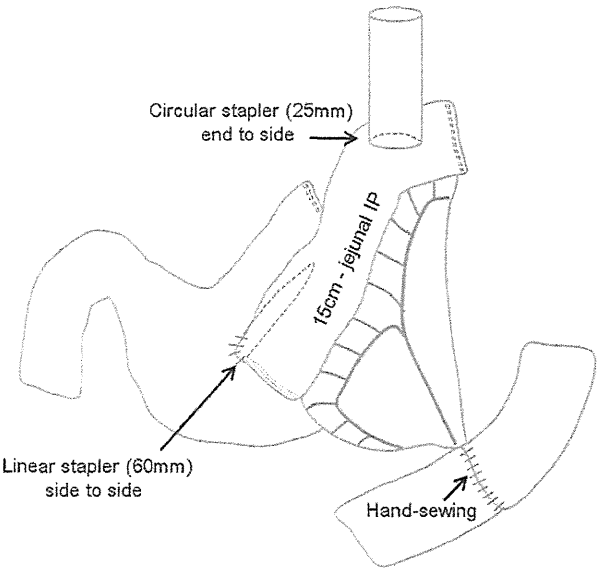

Fig. 1 Schematic of the completed reconstruction

postoperative day (POD) 1 and eating on POD 3 if there are no signs of major complications. Patients may be discharged from POD 8 if they are able to tolerate at least 50 % of a normal diet without fever, pain, or vomiting.

The following variables were recorded by retrospective review of the medical records: age, sex, body mass index (BMI), presence of comorbidity, tumor characteristics, operation time, estimated blood loss, number of times additional analgesia was administered, postoperative complications, number of harvested lymph nodes, and histological findings. To exclude differences due to changes in clinical pathways, parameters reflecting postoperative recovery, such as the time to first drinking or eating and time to hospital discharge, were compared only among patients who underwent surgery from April 2009 to September 2011: 22 patients in the LPG-IP group and 32 patients in the OPG-IP group. Postoperative complications were classified using the Dindo-Clavien classification [9], and complications were classified as grade II or higher were recorded. The extent of lymph node dissection followed the guidelines of the Japanese Gastric Cancer Association [10]. Staging was according to the 7th edition UICC TNM classification. Endoscopy was performed 6 months after surgery to evaluate reflux esophagitis and bile juice reflux into the interposed jejunum.

Surgical procedures for LPG-IP

The patient was placed in the supine position with legs apart. After placement of five trocars (Fig. 2), laparoscopic procedures were performed under a 10 mmHg CO_2 pneumoperitoneum. Mobilization of the stomach and *en bloc* systematic lymph node dissection were performed

laparoscopically. Esophagojejunostomy and jejunogastrostomy were performed laparoscopically, and creation of the jejunal interposition and jejunojejunostomy were performed via minilaparotomy. The distal half of the stomach, the greater omentum, and the spleen were preserved. The suprapancreatic lymph nodes (nos. 7, 8a, 9, and 11p) (Fig. 3A) and the lymph nodes around the cardia (nos. 1 and 2), the lesser curvature (no. 3), and the greater curvature (nos. 4sa and 4sb) were excised. The hepatic and pyloric branches of the vagal nerve were preserved on a case-by-case basis, and pyloroplasty was not performed. After mobilization of the proximal stomach, a detachable intestinal clip was placed on the abdominal esophagus as proximally as possible, and the esophagus was transected using an endoscopic linear stapler. A 5 cm transverse minilaparotomy incision was made in the upper left abdominal wall, and a wound retractor (Alexis Wound Retractor S; Applied Medical, Rancho Santa Margarita, CA) was inserted. The proximal-middle stomach was delivered via the minilaparotomy incision to determine the resection line by palpation of the marking clips placed during preoperative gastroendoscopy, and the stomach was then transected along the planned resection line using a linear stapler. The pneumoperitoneum was reestablished to find the ligament of Treitz, and the proximal jejunum was delivered via the minilaparotomy incision. A single-loop jejunal interposition (15 cm in length) was created approximately 20 cm from the proximal end of the jejunum (Fig. 3B). At the oral side of the jejunal interposition, the mesentery was divided vertically for approximately 7 cm, ligating the marginal artery. At the anal side of the jejunal interposition, the mesentery was divided along the intestine, sacrificing a 10 cm length of jejunum, similar to the procedure reported by Katai et al. [7]. Jejunojejunostomy was performed by hand via the minilaparotomy in an end-to-end fashion using the Gambee method. The mesenteric gap was sutured closed. The pneumoperitoneum was reestablished, and the anvil head of a 25 mm circular stapler (ECS; Ethicon Endosurgery, Cincinnati, OH) was fixed to the distal esophageal stump transabdominally after performing an intracorporeal handsewn pursestring suture via laparoscopy, as previously described by us for laparoscopic total gastrectomy [11]. The main body of the circular stapler was introduced into the jejunal interposition via its oral end and inserted into the abdomen through a surgical glove attached to the wound retractor to prevent the air leakage. The jejunal interposition was brought up in either antecolic or retrocolic fashion depending on the volume of adipose tissue in each case. Esophagojejunostomy was performed laparoscopically in an end-to-side fashion (Fig. 3C), and the oral stump of the interposed jejunum was closed by using an endoscopic linear stapler. A small opening was created on the anterior wall of the remnant stomach, and another small opening was created at the anal-side stump of the jejunal interposition. These openings were anastomosed in a side-to-side fashion using a 60 mm endoscopic linear stapler to form the jejunogastrostomy (Fig. 3D), and the entry hole for the stapler was closed by hand suturing. The esophagojejunostomy anastomosis was immersed in normal saline and tested for leaks by infusing air into the pouch lumen via a nasogastric tube and looking for escaping bubbles.

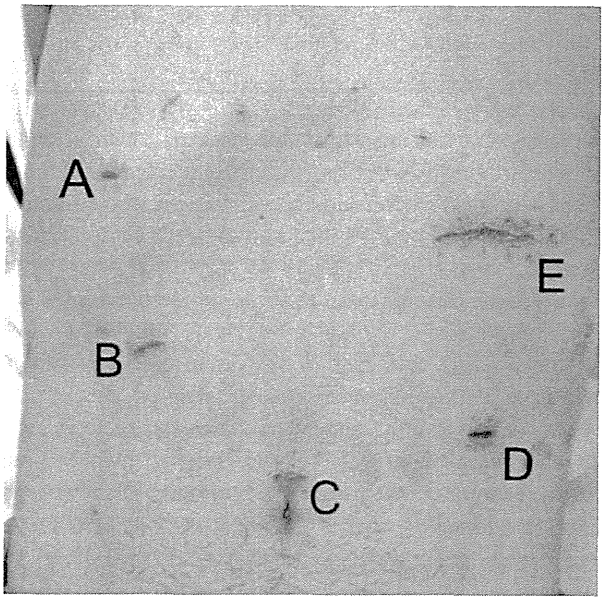

Fig. 2 Photo of the postoperative scars, indicating the placements of surgical ports. 5 mm ports were used at *A* and *D*, and 12 mm ports were used at *B*, *C*, and *E*. Port *E* was extended for the 50 mm minilaparotomy

Surgical procedures for OPG-IP

The same procedures as described above, including the same range of lymph node dissection and the same reconstruction method, were performed via an upper midline abdominal incision.

Statistical analysis

Statistical analyses were performed by using Student's *t* test, χ^2 test, or Fisher's exact probability test. A value of $p < 0.05$ was regarded as significant. All statistical analyses were performed by using Statistical Package for Social Science (SPSS) version 17.0 for Windows software (SPSS, Inc., Chicago, IL).

Results

A total of 90 proximal gastrectomies, including 22 LPG-IP procedures and 68 OPG-IP procedures, were included in

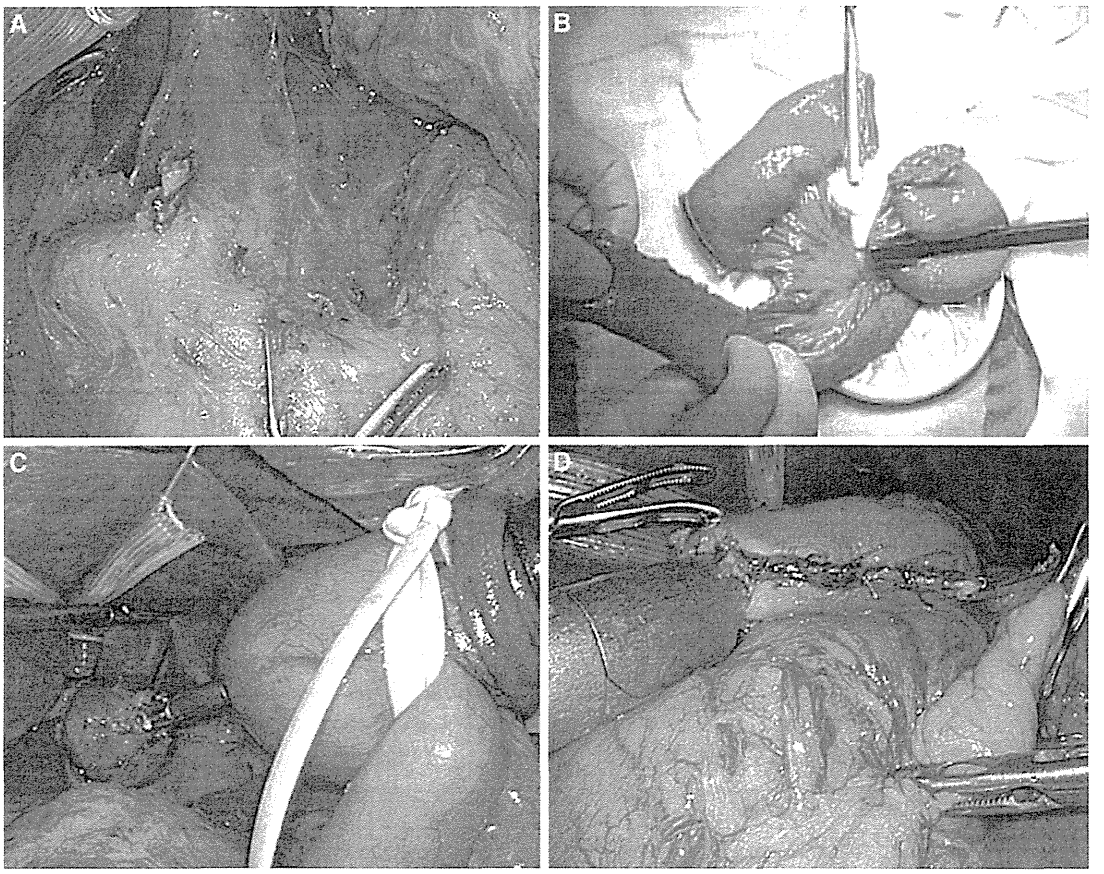

Fig. 3 **A** After lymph node dissection around the celiac artery. **B** Creation of the jejunal interposition via minilaparotomy. **C** Intracorporeal esophagojejunostomy using a *circular stapler*. **D** Intracorporeal jejunogastrostomy using a *linear stapler*

this study. No conversion to open surgery was recorded in the LPG-IP series. Patient characteristics are summarized in Table 1. There were no significant differences in age, sex, BMI, or presence of comorbidity between the two groups. Six patients (27 %) in the LPG-IP group and 15 patients (22 %) in the OPG-IP group underwent endoscopic submucosal resection before surgery and proceeded because pathological examination of specimens showed submucosal invasion or vessel infiltration, indicating the need for radical surgery with lymph node dissection. In the LPG-IP group, the jejunal interposition was brought up in antecolic fashion in 10 patients and in retrocolic fashion in 12 patients, and in the OPG-IP group the jejunal interposition was brought up in antecolic fashion in 21 patients and in retrocolic fashion in 47 patients, according to the surgeons' preferences and decisions. These proportions were not significantly different between groups.

Operation details are shown in Table 2. The operation time was significantly longer in the LPG-IP group (233 (range, 190–321) min) compared with the OPG-IP group (201 (range, 125–272) min; $p = 0.0002$), and the estimated blood loss was significantly less in the LPG-IP group (20 (range, 0–174) g) compared with the OPG-IP group (242 (range, 75–776) g; $p < 0.0001$). There was no difference in the number of harvested lymph nodes between the two groups. Pathological findings are shown in Table 2. There were no differences in the T factor, N factor, or TNM staging between the two groups. A negative surgical margin was achieved in all cases. The rate of accurate preoperative diagnosis in this study was 78.9 %.

Parameters for postoperative recovery are shown in Table 3. First drinking was on POD 1 and first eating was on POD 3 in both groups. Hospital discharge was on POD 11 in the LPG-IP group and on POD 10 in the OPG-IP group, which was not a significant difference. This indicates that most patients followed the planned clinical pathway. However, the number of times that additional analgesia was administered was significantly less in the LPG-IP group (2, range 0–5) compared with the OPG-IP group (4, range 0–9; $p < 0.0001$).

Postoperative complications in the two groups are listed in Table 4. The incidence rate of postoperative complications was not significantly different between the two groups (27 % in the LPG-IP group vs. 32 % in the OPG-IP group).

Table 1 Summary of patients with gastric cancer treated by laparoscopic and open proximal gastrectomy

	LPG-IP ($n = 22$)	OPG-IP ($n = 68$)	p value
Age (years)	64.3 ± 11.6	65.5 ± 9.0	NS
Sex (male/female)	18/4	52/16	NS
BMI	22.8 ± 3.3	22.4 ± 3.2	NS
ESD before surgery (yes/no)	6/16	15/53	NS
Comorbidity			
Absent/present	13/9	34/34	NS
Hypertension	5	20	
Diabetes mellitus	4	13	
COPD	1	1	
Arrhythmia	0	3	
Cardiac angina	2	1	
Other	0	2	

LPG-IP laparoscopic proximal gastrectomy with jejunal interposition, *OPG-IP* open proximal gastrectomy with jejunal interposition, *ESD* endoscopic submucosal dissection, *NS* not significant

Values are mean ± standard deviation

Table 2 Surgical and pathological findings in laparoscopic and open proximal gastrectomy

	LPG-IP ($n = 22$)	OPG-IP ($n = 68$)	p value
Operation time (min)	233 (190–321)	201 (125–272)	0.0002
Blood loss (g)	20 (0–174)	242 (75–776)	<0.0001
No. of dissected lymph nodes	17 (10–32)	20 (10–44)	NS
pT stage			NS
pT1a (M)	5	22	
pT1b (SM)	11	32	
pT2	4	5	
pT3	1	7	
pT4	1	2	
pN stage			NS
pN0	18	58	
pN1	2	8	
pN2	2	2	
TNM stage			NS
IA	16	50	
IB	1	9	
IIA	1	3	
IIB	2	2	
IIIA	2	4	

NS not significant

Values are median (range)

Table 3 Postoperative recovery after laparoscopic and open proximal gastrectomy using the current clinical pathway

	LPG-IP ($n = 22$)	OPG-IP ($n = 32$)	p value
Time to first drinking (POD)	1 (1–7)	1 (1–20)	NS
Time to first eating (POD)	3 (3–10)	3 (3–27)	NS
Time to hospital discharge (POD)	11 (7–32)	10 (7–34)	NS
Additional analgesia (number of times)	2 (0–5)	4 (0–9)	<0.0001

POD postoperative day, *NS* not significant

Values are median (range)

Anastomotic leakage occurred in two patients (9.1 %) in the LPG-IP group and five patients (7.4 %) in the OPG-IP group, all of which occurred at the esophagojejunostomy anastomosis. Among them, one patient in the LPG-IP group developed a grade II pancreatic fistula followed by secondary anastomotic leakage. One patient in the OPG-IP group with a major leakage required emergency reoperation via a thoracoabdominal approach for drainage (grade IIIb), but other patients were treated conservatively. Intra-abdominal hemorrhage requiring reoperation occurred in two patients in the OPG-IP group, and one patient required reoperation (grade IIIb). Anastomotic stricture at the esophagojejunostomy anastomosis occurred in two patients (9.1 %) in the LPG-IP group and four patients (5.9 %) in the OPG-IP group. All of these patients were successfully treated by outpatient endoscopic balloon dilatation. No

Table 4 Postoperative complications after laparoscopic and open proximal gastrectomy

	LPG-IP ($n = 22$)	OPG-IP ($n = 68$)	p value
Absent/present	16/6 (27 %)	46/22 (32 %)	NS
Wound infection, n	2 (9.1 %) grade II	6 (8.8 %) grade II	
Anastomotic leakage, n (%)	2 (9.1 %) grade II	5 (7.4 %) 4 grade II, 1 grade IIIb	
Intra-abdominal hemorrhage, n (%)	0	2 (2.9 %) 1 grade II, 1 grade IIIb	
Pancreatic fistula, n (%)	1 (4.5 %) grade II	1 (1.5 %) grade II	
Intra-abdominal abscess, n (%)	1 (4.5 %) grade II	2 (2.9 %) grade II	
Anastomotic stenosis, n (%)	2 (9.1 %) grade II	4 (5.9 %) grade II	
Cholecystitis, n (%)	0	2 (2.9 %) grade II	

NS not significant

Grade: according to Dindo-Clavien classification

patient complained of reflux symptoms after surgery, and there was no operation-related death. Follow-up endoscopy could be performed 20 of 22 patients (90.9 %) in the LPG-IP group and 61 of 68 patients (89.7 %) in the OPG-IP group. A small amount of bile juice reflux to the remnant stomach or interposed jejunum was observed in 25 % of patients, but esophagitis was recorded in only in one patient (1.1 %) in the OPG-IP group. Endoscopic survey of the remnant stomach was possible in all of the patients.

Discussion

The choice of reconstruction method following LPG remains controversial. Because the optimal method has not been established, a number of techniques are currently used. Most past reports describe direct esophagogastric anastomosis, probably because it is very simple and requires only one anastomosis [12–16]. In these reports, direct esophagogastrostomy was performed by using a linear or circular stapler, with the addition of antireflux measures, similar to Toupet fundoplication. However, it may be impossible to completely prevent reflux in direct esophagogastrostomy. Jejunal interposition has been recognized as a favorable method for preventing severe postoperative reflux and is widely performed in open surgery, but LPG-IP has not gained wide acceptance because of its technical complexities. These complexities include the creation of a pedicled jejunal limb and the requirement for three anastomoses. Until recently, very few reports have described the outcomes of LPG-IP. The first report was by Uyama et al. [17] and described their entirely laparoscopic LPG-IP technique, which they had performed in four cases. Their technique was excellent, but the mean operative time (614 min) was long. In 2002, Ikeda et al. [18] reported three cases of hand-assisted LPG-IP, which shortened operation time. However, no study has evaluated the feasibility and safety of these techniques in a larger series. As far as we know, this is the largest study to report the outcomes of LPG-IP to date and the first to compare the results with open surgery.

At our institution, OPG-IP has long been a standard procedure for the treatment of early-stage gastric cancer in the proximal third of the stomach, and it was therefore natural for us to adopt jejunal interposition to laparoscopic surgery. Our results show that LPG-IP can be performed safely with an equivalent complication rate compared to open surgery. We did not experience any case with symptomatic postoperative reflux. Operation time was longer in laparoscopic surgery than in open surgery, but this difference was approximately 30 min and seems acceptable for a routine surgical procedure. In our procedure, transection of the stomach, creation of the jejunal interposition, and subsequent jejunojejunostomy were performed via minilaparotomy under direct vision, which might have contributed to time-saving. The proximal jejunum was easily delivered via the upper left abdominal incision, and the subsequent creation of the jejunal limb and jejunojejunostomy anastomosis also were easy. The other anastomoses (esophagojejunostomy and jejunogastrostomy) and systematic lymphadenectomy were performed laparoscopically, because laparoscopy provides better vision for these procedures than open surgery regardless of the size of the patient or the thickness of the abdominal wall. The shortened operation time also might be partly due to advancements in instrumentation and skills, because laparoscopic distal gastrectomy is frequently performed in our institution.

Postoperatively, leakage of the esophagojejunostomy anastomosis occurred in two patients (9.1 %) in the LPG-IP group and five patients (7.4 %) in the OPG-IP group. These incidences seem relatively high compared with other reports, which cannot be ignored. In one patient in the LPG-IP group, the pancreatic fistula caused the secondary anastomotic leakage. However, we were not able to determine the reasons for anastomotic leakage in the other patients. The high incidence may reflect the complexity of the jejunal interposition rather than the technical complexity of laparoscopic surgery, because the incidence was relatively high in both groups. This procedure has several different points from a Roux-en-Y anastomosis in total gastrectomy, which may be causes of tension to the interposed jejunum. We speculate that these tensions may influence the esophagojejunostomy. One possible cause of tension is a large feeding artery in a pedicle of the interposed jejunum, because we always make a large artery remain in the pedicle expecting sufficient blood supply. It seems that the retrocolic route may cause less tension when using a pedicled jejunum, but we experienced anastomotic leakage in four patients using the antecolic route and three using the retrocolic route, so the route did not appear to make a difference in this series. Another possible cause of tension to the interposed jejunum may be the remnant stomach, which is also a different point from Roux-en-Y. This tension is likely to be caused if the length of the interposed jejunum is short. We have believed that the 15 cm length interposed jejunum is ideal for the prevention of reflux esophagitis and for postoperative endoscopic survey, but there is not sufficient evidence to determine this definitively. Evaluation of a larger number of cases is required before the reasons for anastomotic leakage can be concluded. Our LPG-IP sample size was small, and it is possible that the incidence rate may be improved following an increase in patient numbers and surgical experience.

The incidence of stenosis at the esophagojejunostomy anastomosis was 9.1 % in the LPG-IP group and 5.9 % in

the OPG-IP group. The tendency for stenosis in open proximal gastrectomy has been reported; Katai et al. [19] reported an incidence of 6.3 %. The incidences recorded in this study seem higher than for total gastrectomy, in which esophagojejunal anastomosis is performed in the same manner [20]. The reason for this is unclear, but it is speculated that the small amount of reflux after partial gastrectomy causes stenosis [14]. We observed a small amount of bile reflux to the interposed jejunum in 25 % of patients on postoperative endoscopy. Stenosis also may be caused by tension to the interposed jejunum as mentioned above. The patients with stenosis were successfully treated by outpatient endoscopic balloon dilatation.

Pancreas-related complications are sometimes experienced in gastric cancer surgery, even when the pancreas is not obviously injured during lymph node dissection. This is probably due to thermal injury by surgical devices or retraction of the pancreas to obtain a better view around the celiac artery. One patient in the LPG-IP group developed a grade II pancreatic fistula, even though no pancreatic injury was recognized intraoperatively. As a result, this patient developed secondary anastomotic leakage. It is important to be conscious of handling the pancreas gently during lymph node dissection.

The relative invasiveness of the procedures is difficult to determine based only on our retrospective study with limited case numbers. Blood loss was significantly less in the LPG-IP group, with the difference being in excess of 200 g. This might be associated with more meticulous laparoscopic techniques due to the magnified view. Time to first drinking, time to first eating, and time to hospital discharge did not differ between the two groups, because the management protocol was same in both groups. However, the requirement for additional analgesia was significantly less in the LPG-IP group. Finally, the cosmetic result is unquestionably better in the LPG-IP group. These results suggest that LPG-IP may have a number of benefits, including a better postoperative quality of life.

Several oncological parameters were evaluated, although they were limited to short-term outcomes. The number of harvested lymph nodes was similar between the two groups, and the median number for both groups was more than 15, which is the number suggested for adequate resection in the American Joint Committee on Cancer guidelines. A negative surgical margin was achieved in all cases. These data suggest that LPG-IP is at least equivalent to OPG-IP in short-term oncological outcomes. The preoperative diagnosis of invasion depth is sometimes underestimated, and in our series some patients were finally diagnosed as T2 or T3, even though their preoperative diagnosis was T1. The rate of accurate preoperative diagnosis in this study was 78.9 %. This suggests that lymph node dissection in proximal gastrectomy should be performed to the level of the celiac trunk (nos. 7, 8a, 9, 11p), which we were able to achieve laparoscopically. Ideally, a more accurate preoperative diagnostic method for depth of invasion should be established.

In conclusion, our initial case series demonstrated that our technique for LPG-IP is technically feasible and safe, and provides similar curability and outcomes to open surgery in the short-term. Our study is limited by its retrospective nature, small number of patients, and short-term follow-up. In this kind of function-preserving surgery, long-term outcomes should be evaluated, including the patients' quality of life. Another large-scale study evaluating long-term outcomes is necessary to confirm these findings.

Disclosures Drs. Takahiro Kinoshita, Naoto Gotohda, Yuichiro Kato, Shinichiro Takahashi, Masaru Konishi, and Taira Kinoshita have no conflict of interest or financial ties to disclose.

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ORIGINAL ARTICLE – THORACIC ONCOLOGY

Clinicopathological Features and Prognostic Factors of Adenocarcinoma of the Esophagogastric Junction According to Siewert Classification: Experiences at a Single Institution in Japan

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ABSTRACT

Background. Treatment strategy for adenocarcinoma of the esophagogastric junction (AEG) remains controversial. The aims of this study are to evaluate results of surgery for AEG, to clarify clinicopathological differences according to the Siewert classification, and to define prognostic factors.

Methods. We retrospectively analyzed 179 consecutive patients with Siewert type I, II, and III AEG who underwent curative (R0) resection at the National Cancer Center Hospital East between January 1993 and December 2008.

Results. Patients with AEG were divided according to tumor: 10 type I (5.6%), 107 type II (59.8%), and 62 type III (34.6%). Larger, deeper tumors and nodal metastasis were more common in type III than type II tumors. No significant differences were seen in 5-year survival rates among the three types: type I (51.4%), type II (51.8%), and type III (62.6%). Multivariate analysis showed that depth of tumor and mediastinal lymph node metastasis were independent prognostic indicators. The recurrence rate for patients with mediastinal lymph node metastasis was 87.5%. The risk factors for mediastinal lymph node metastasis were length of esophageal invasion and histopathological grade.

Conclusions. Mediastinal lymph node metastasis and tumor depth were significant and independent factors for poor prognosis after R0 resection for AEG. Esophageal invasion and histopathological grade were significant and independent factors for mediastinal lymph node metastasis.

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In Western countries, incidence of adenocarcinoma of the esophagogastric junction (AEG) is rapidly increasing. This trend has not occurred in Eastern countries.[1–4] Siewert's classification into three types of tumors, proposed in 1996, defines AEG tumors according to the location of the tumor center in relation to the anatomical esophagogastric junction (EGJ) line. Characteristics differ for each type, making the classification useful for determining optimal treatment strategies.[5]

Surgical resection with lymphadenectomy is the mainstay of treatment for AEG. Though AEG consists of tumor arising from the proximal stomach and distal esophagus, there are various surgical options. Factors that surgeons need to consider are whether the esophagectomy should be subtotal or distal and if it should be combined with total or proximal gastrectomy via transhiatal or transthoracic approach. Currently, Siewert's classification is used to determine treatment strategy, but the approach is still controversial. An optimal surgical strategy has yet to be established.

The distribution of the three types of AEG differs markedly between Eastern and Western countries. In Eastern countries, type II and III cancers are more common than type I. In Western countries, however, the distribution is nearly equal between the three types of adenocarcinoma.[3,6,7] Only a few studies have addressed clinicopathological features of AEG in Japan, and most involved only type II and III cancers.[8,9] One reason for this might be that type I patients at most Japanese institutions are likely to be treated by the

esophageal surgical group, while those with type II or III are treated by the gastric surgical group. In such facilities, there can be two separate databases.

In the present study, we examined databases for both esophageal and gastric cancer to clarify the distribution and clinical outcomes of AEG at a single cancer center hospital in Japan. The aims of this study are to evaluate clinicopathological features and oncological outcomes of AEGs according to Siewert's subtype, and to define predictive factors for prognosis.

PATIENTS AND METHODS

Patients

We retrospectively reviewed a database of 179 consecutive patients with AEG (Siewert's type I, II, and III) who underwent curative surgical resection at the National Cancer Center Hospital East between January 1993 and December 2008. Type III tumors were defined as subcardial cancers infiltrating the EGJ, whose epicenter is within the proximal 5 cm of the stomach; therefore, subcardial cancers not extending into the EGJ were excluded from this study. Follow-up periods ranged from 1.5 to 173 months (median 33 months). Overall survival analysis contained all deaths, including those due to an unrelated cause. Exclusion criteria included prior history of surgery for gastric cancer or gastric stump cancer.

Before surgery, all patients underwent chest radiographs, an abdominal ultrasonography, or a computed tomography (CT) scan for tumor staging. Upper gastrointestinal endoscopy was performed and barium swallows taken. From these findings, we determined preoperative Siewert's subtype and surgical approach. The choice of operation was based on preoperative diagnosis and estimated length of esophageal invasion. The intent was complete surgical resection.

All surgical specimens were delivered to the pathology department after the operations. We took photographs and sketched the appearance of each one and made a detailed record. Pathologists recorded the margin of the tumor, the esophagogastric junction (EGJ), and the tumor center. Based on the pathological and preoperative findings, we measured the distance from the EGJ to the tumor center, then to the oral top of the tumor. This was defined as the length of esophageal invasion. We then recorded the Siewert's type for all specimens.

Data were evaluated based on gender, age, tumor appearance, tumor size, length of esophageal invasion, operative methods, perioperative chemotherapy, tumor pathology and lymph node staging, histological grading, lymphovascular and venous invasion, and recurrence patterns. We also compared these data among the AEG subtypes.

The UICC 7th tumor-node-metastasis (TNM) classification of esophageal cancer was used to describe tumor progression and histopathological grading.[10] The macroscopic appearances of the tumors were divided according to Borrmann's classification.[11] Number of regional lymph node stations was categorized according to the Japanese classification of gastric carcinoma.[12]

Statistical Analyses

Statistical analyses were performed by chi-square test and *t*-test. Cumulative survival rates were generated by the Kaplan–Meier method. Survival curves were compared with the log-rank test. Significant factors were identified by univariate analysis, and further examined by multivariate analysis. Multivariate regression analysis was carried out using the Cox hazards model. All statistical analyses were performed using SPSS (SPSS Inc., Tokyo, Japan) for Windows. p-Value < 0.05 was considered statistically significant.

RESULTS

Patient Population and Tumor Characteristics

Ten of 179 patients had type I (5.6%) tumors, 107 had type II (59.8%), and 62 had type III (34.6%). The characteristics of the patients and surgical approaches are presented in Table 1. There were no significant differences in age and gender between the three subtypes. The superficial tumor type was observed in 40% of patients with type I cancer, whereas it was less common in types II (19.6%) and III (9.7%). In types II and III, Borrmann 3 was the most common macroscopic appearance (42.1% and 56.5%). Borrmann 4 was generally rare, but observed mainly in type III (11.3%).

Tumor size was significantly larger in type III (81.6 mm) than types I (55.1 mm) and II (45.2 mm).There was no significant difference between types II and III in the length of esophageal invasion. The longest esophageal invasion was 70 mm in type I. In types II and III, the longest invasions were 55 mm and 50 mm, respectively. Surgical approaches varied by tumor type. The transthoracic technique was used most often on type I (80%) tumors, which included 50% of right thoracic and 50% of left thoracoabdominal approaches. In contrast, the transhiatal approach was common in type III. In type II, 34.6% of operations were performed transthoracically and 65.4% transhiatally. In type I, subtotal esophagectomy (50%) and proximal gastrectomy with distal esophagectomy (40%) were common, whereas total gastrectomy with distal esophagectomy was common in types II (71.0%) and III (90.3%). We saw no significant difference in the rate of patients who received perioperative chemotherapy.

TABLE 1 Baseline characteristics of patients and surgical approaches ($n = 179$)

Classification	Type I ($n = 10$)	Type II ($n = 107$)	Type III ($n = 62$)	p-value
Age (years)	63.5 (48–83)	65 (30–86)	65.5 (31–62)	NS
Male:female	7:3	85:22	41:21	NS
Macroscopic type				
Superficial	4 (40%)	21 (19.6%)	6 (9.7%)	
Borrmann 1	2 (20%)	7 (6.5%)	3 (4.8%)	
Borrmann 2	2 (20%)	29 (27.1%)	11 (17.7%)	
Borrmann 3	1 (10%)	45 (42.1%)	35 (56.5%)	
Borrmann 4	0	1 (0.9%)	7 (11.3%)	
Unclassifiable	1 (10%)	4 (3.7%)	0	
Tumor size (mm)	45.2 ± 5.1	55.1 ± 2.6	81.6 ± 4.5	<0.001(II/III)
				0.317 (I/II)
Esophageal invasion (mm)	46.3 ± 4.3	15.3 ± 1.1	13.6 ± 1.4	<0.001(II/III)
				0.359 (II/II)
Approaches				
Transthoracic	8 (80%)	37 (34.6%)	10 (16.1%)	0.005 (I/II)
(Right:left)	(4:4)	(7:30)	(0:10)	0.010 (I/III)
Transhiatal	2 (20%)	70 (65.4%)	52 (83.9%)	
Subtotal esophagectomy	5 (50%)	8 (7.5%)	0	
Total gastrectomy with distal esophagectomy	1 (10%)	76 (71.0%)	56 (90.3%)	
Proximal gastrectomy with distal esophagectomy	4 (40%)	23 (21.5%)	6 (9.7%)	
Neoadjuvant chemotherapy	0	0	3 (4.8%)	NS
Adjuvant chemotherapy	1 (10%)	13 (12.1%)	17 (27.4%)	NS

NS not significant

The pathological characteristics of the patients are presented in Table 2. Patients with type III classification had significantly deeper tumors than those with types I and II. Additionally, the frequency of lymph node metastasis was significantly higher in those with type III rather than type II tumors. Similarly, higher tumor stage was observed in those in the type III class than types I and II. The incidence of mediastinal lymph node metastasis was significantly higher in type I patients than in types II and III. Histopathological grading was significantly poorer in type III than type II tumors.

Patterns of Lymph Node Metastasis

Table 3 presents the frequency of lymph node metastasis as well as 5-year survival for each lymph node station. Using these results, we computed the index of estimated benefit from lymph node dissection (IEBLD) using the formula: IEBLD = frequency of metastasis to each lymph node station (%) × 5-year survival rate of metastatic cases (%)/100.[13]

These values are shown in Table 3. The rate of metastasis was high in lymph node stations 1, 2, 3, and 7, and their IEBLDs were also high (7.0–21.0). The metastatic rate of mediastinal lymph nodes was 22.2% in total (40.0% in type I, 21.3% in type II, and 12.5% in type III), and the 5-year survival rate was 17.6%. The IEBLD of the mediastinal lymph node was 3.9, the same as that for the 16th station.

Survival Outcomes

The survival curves for each Siewert type are shown in Fig. 1. We observed no significant difference in overall survival by subtypes. Five-year survival rates were 51.4% in type I, 51.8% in type II, and 62.6% in type III. The median follow-up period of survivors was 33 months. We used Kaplan–Meier survival analysis to assess 11 prognostic factors: age (<65 versus >65 years), gender, tumor size (<60 mm versus >60 mm), Siewert type (type I or II versus III), depth of tumor (T1–2 versus T3–4), existence of lymph node metastasis, existence of mediastinal lymph node metastasis, length of esophageal invasion (<20 mm versus >20 mm), degree of venous and lymphovascular invasion, and histopathological grade (G1, 2 versus G3, 4) (Table 4).

Univariate analysis showed that the following seven factors were associated with survival: depth of tumor

TABLE 2 Pathological characteristics of patients ($n = 179$)

Classification	Type I ($n = 10$)	Type II ($n = 107$)	Type III ($n = 62$)	p-value
UICC 7th T category				
T1a	0	1 (0.9%)	1 (1.6%)	
T1b	4 (40%)	23 (21.5%)	2 (3.2%)	(T1/T2～)
T2	2 (20%)	14 (13.1%)	7 (11.2%)	0.213 (I/II)
T3	3 (30%)	32 (29.9%)	18 (29.0%)	<0.001 (I/III)
T4a	1 (10%)	34 (31.8%)	29 (46.8%)	0.003 (II/III)
T4b	0	3 (2.8%)	5 (8.1%)	
UICC 7th N category				
N0	2 (20%)	43 (40.2%)	12 (193%)	(N0/N1～)
N1	5 (50%)	23 (21.5%)	12 (193%)	0.210 (I/II)
N2	3 (30%)	9 (8.4%)	16 (253%)	0.960 (I/III)
N3	0	32 (29.9%)	22 (355%)	0.005 (II/III)
UICC 7th TNM stage				
IA	1 (10%)	20 (18.7%)	2 (32%)	
IB	1 (10%)	7 (65%)	0	
IIA	0	4 (3.7%)	2 (32%)	(Stage I, II/III, IV)
IIB	3 (30%)	13 (12.1%)	7 (113%)	0.586 (I/II)
IIIA	3 (30%)	14 (131%)	10 (161%)	0.023 (I/III)
IIIB	1 (10%)	4 (3.7%)	7 (113%)	0.002 (II/III)
IIIC	1 (10%)	32 (29.9%)	24 (38.7%)	
IV	0	13 (12.1%)	10 (161%)	
Histopathological grade				
G1/2	6 (60%)	71 (66.4%)	31 (50.0%)	0.685 (I/II)
G3/4	4 (40%)	36 (33.6%)	31 (50.0%)	0.557 (I/III)
				0.036 (II/III)

($p = 0.003$), lymph node metastasis ($p = 0.002$), mediastinal lymph node metastasis ($p = 0.001$), esophageal invasion >20 mm ($p = 0.023$), venous invasion ($p = 0.005$), lymphovascular invasion ($p = 0.022$), and histopathological grade 3/4 ($p = 0.042$). Subsequent multivariate analysis confirmed that only depth of tumor ($p = 0.001$) [95% confidential interval (CI), 1.62–6.16] and mediastinal lymph node metastasis ($p = 0.001$) (95% CI, 1.74–5.92) were significant and independent prognostic indicators after curative resection for AEG (Table 4).

We performed multivariate analysis of seven factors to determine the risk for mediastinal lymph node metastasis. These included age (<65 versus >65 years), gender, tumor size (<60 mm versus >60 mm), Siewert type (types I and II versus III), depth of tumor (T1–2 versus T3–4), length of esophageal invasion (<20 mm versus >20 mm), and histopathological grade (G1, 2 versus G3, 4). We found that esophageal invasion (>20 mm) ($p < 0.001$) (95% CI, 4.28–108.2) and histopathological grade 3/4 ($p = 0.035$) (95% CI, 1.10–15.40) were significant and independent risk factors for mediastinal node metastasis (Table 5).

TABLE 3 Frequency of lymph node metastasis as well as 5-year survival for each station

Lymph node station	Rate of lymph node metastasis (%)				5-Year survival rate (%)	IEBLD
	Type I	Type II	Type III	Total		
1	30.0	42.1	58.1	46.9	44.8	21.0
2	20.0	20.6	24.2	27.9	33.7	9.4
3	30.0	23.4	43.5	36.9	43.4	16.0
4sa	0.0	5.6	14.5	8.4	25.7	2.2
4sb	0.0	2.8	8.1	4.5	0.0	0.0
4d	0.0	1.2	10.2	4.9	0.0	0.0
5	0.0	3.5	3.5	3.5	0.0	0.0
6	0.0	2.6	3.6	3.0	0.0	0.0
7	40.0	22.4	14.5	21.8	32.3	7.0
8	0.0	6.7	13.6	9.3	30.4	2.8
9	0.0	13.3	8.6	10.8	13.8	1.5
10	0.0	3.9	12.3	7.4	30.0	2.2
11p	0.0	14.0	15.5	14.4	38.7	5.6
11d	0.0	6.3	7.1	6.5	0.0	0.0
12	0.0	0.0	3.3	1.5	0.0	0.0
16	0.0	12.2	20.7	15.1	22.7	3.4
Mediastinal	40.0	21.3	12.5	22.2	17.6	3.9

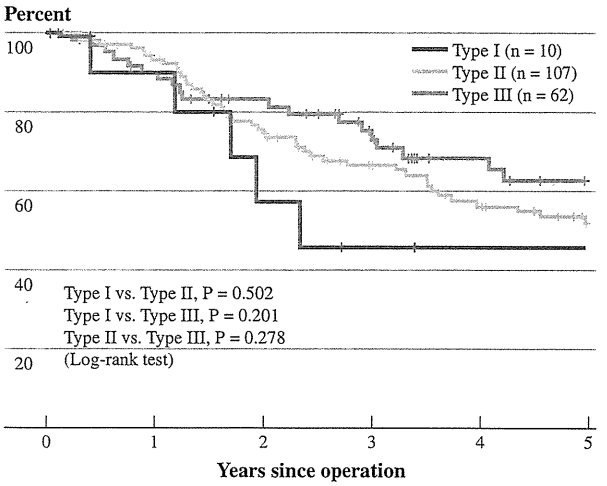

FIG. 1 Survival curves in each type of cancer (type I, II, or III). We saw no significant difference in overall survival by subtype

DISCUSSION

In this single-institution series of 179 AEGs in Japan, the proportions of types I, II, and III cancers were 5.6%, 59.8%, and 34.6%, respectively. After R0 resection, 5-year survival rates were 51.4% for type I, 51.8% for type II, and 62.6% for type III tumors. Mediastinal lymph node metastasis and a deeper tumor were significant and

TABLE 4 Univariate and multivariate predictors of overall survival

	No.	Univariate analysis *p*-value	Multivariate analysis	
			p-value	Hazard ratio (95% CI)
Age (years)				
<65	93	0.826		
≥65	86			
Sex				
Male	133	0.685		
Female	46			
Tumor maximal size (mm)				
<60	89	0.113		
≥60	90			
Siewert type				
Type I, II	117	0.255		
Type III	62			
UICC 7th N category				
T1–2	54	0.003	0.001	3.16 (1.62–6.16)
T3–4	125			
UICC 7th N category				
N0	57	0.002	0.242	
N1–3	122			
Mediastinal nodes				
Negative	163	0.001	0.0001	3.21 (1.74–5.92)
Positive	16			
Para-aortic nodes				
Negative	168	0.018	0.066	
Positive	11			
Esophageal invasion (mm)				
<20	124	0.023	0.351	
≥20	55			
Venous invasion				
Negative	33	0.005	0.395	
Positive	146			
Lymphovascular invasion				
Negative	67	0.022	0.182	
Positive	112			
Histopathological grade				
G1/2	71	0.042	0.363	
G3/4	108			

TABLE 5 Multivariate analysis of mediastinal lymph node metastasis

	Hazard ratio (95% CI)	*p*-value
Esophageal invasion ≥20 mm	21.5 (4.28–108.2)	<0.001
Histopathological grade G3/4	4.12 (1.10–15.10)	0.035

independent factors for poor prognosis. In patients with mediastinal lymph node metastasis, recurrence rate was quite high (87.5%). Although curative surgery is the primary treatment modality for AEG, survival rates in patients with poor prognostic factors are unsatisfactory.

This study shows a significantly higher prevalence of types II and III AEGs in Japan compared with Western nations. Nonetheless, data indicate that the prevalence of AEG is rising in Western countries, but not in the East.[1–4] The distribution of the three types of AEGs also differs between West and East, with type I tumors less frequent in the latter.[3,6,7] Most papers from Japanese institutions have reported on types II and III; data on all three types are scant.[7–9]

To establish the prevalence and trend of types I, II, and III in Japan, we reviewed the database of gastric and esophageal cancers in our hospital. Of the three types, 5.6% were type I, 59.8% type II, and 34.6% type III. These findings are similar to reports from Hasegawa et al. in Japan, Bai et al. in China, and Fang et al. in Taiwan.[6,7,14] The lower frequency of type I AEGs in Eastern countries may be explained by a lower prevalence of gastroesophageal reflux, obesity, and *Helicobacter pylori* infection.

In the present study, we saw no significant differences in age and gender among the three types of cancers, but clinicopathological features differed. Type III cancers were more aggressive than types I and II. Tumors were larger and deeper, with a higher rate of lymph node metastasis. This trend has been reported by other groups. Conversely, we observed no significant difference in rates of tumor progression between types I and II cancers. This may indicate that type III tumors include cardia cancer centered 2–5 cm below the EGJ that enlarges, and then subsequently infiltrates the EGJ. It may also be more difficult to detect early cancer around the cardia than in the distal esophagus by screening endoscopy.

The UICC 6th TNM classification did not include integrated staging criteria for AEGs. They were staged according to criteria for esophageal or gastric cancer.[15] The UICC 7th TNM classification, however, defined AEG as a new disease category to be classified according to staging for esophageal cancer.[10] Here we classified and staged 179 AEGs according to the latest criteria. However, surgeons should note that most type II and III tumors have features of subcardial gastric cancer, which originates in the gastric mucosa. Type I cancer is closely associated with intestinal epithelial metaplasia (Barrett's epithelium). Type II cancer may arise from either Barrett's epithelium or junction epithelium. The etiology of type III relates to the gastric mucosa, in particular an association with *Helicobacter pylori* or atrophic gastritis.

In this study, Barrett's epithelium accounted for 90% (9/10) of type I adenocarcinomas, 10.3% (11/107) of type II, and 0% of type III cancers. These results are similar to those of Siewert and Stein (76.9%, 9.8%, and 2%).[5] Our data suggest that the origins of AEG tumors are somewhat alike in Western and Eastern countries. However, several studies out of Japan disagree. Yuasa et al. found that prevalence of Barrett's epithelium in type II cancer is lower in Japan than in Western countries.[9] Okabayashi et al. suggested that the occurrence of superficial carcinoma of the cardia had no relationship to Barrett's epithelium in Japan.[3]

In the present study, 5-year survival rates were similar among the three types of cancers: 51.4% for type I, and 51.8% and 62.6%, respectively, for types II and III. Although our series only included R0 resection, these outcomes seem better than those from prior reports. Data from Western countries indicate that type I has the best prognosis, followed by types II and III.[5] Conversely, reports from Asian countries show no obvious differences between subtypes. Fang et al. reported similar survival rates between types II and III (59.6% versus 63.5%).[6] The reasons for this discrepancy are unclear. One explanation may be that surgeons in Asian countries are more accustomed to surgery for gastric cancer or D2 dissection, leading to better outcomes in type III tumors.

We also evaluated the frequency of lymph node metastasis as well as 5-year survival for each positive station. To estimate the therapeutic value of lymph node dissection, we calculated IEBLD.[13] Our data show that lymph node stations 1, 2, 3, and 7 (around the cardia, the lesser curvature of the proximal stomach, and root of the left gastric artery) had high rates of metastasis. Nonetheless, patients had relatively good prognoses, suggesting that dissections of the abdominal lymph nodes are vital to AEG patients.

Our data also show that IEBLD were relatively low in dissection of numbers 8 and 9 lymph nodes (around the common hepatic and the celiac artery). However, they suggest benefit from D2 lymphadenectomy in patients with type II and III tumors. At the least, data suggest the need to remove the lymph nodes around the root of the left gastric surgery (no. 7). The rate of mediastinal lymph node metastasis was 22.2% in the present study, but its IEBLD was low, as was the 5-year survival rate of patients (17.6%). This figure is consistent with previous reports. The JCOG 9502 trial (phase III) clearly showed that a thoracoabdominal approach with radical mediastinal node resection did not improve survival in patients with type II or III adenocarcinomas. It did, however, increase surgical risk.[16] Our data may support the results of that trial.

Multivariate analysis showed that depth of tumor and mediastinal lymph node metastasis were independent prognostic indicators after R0 resection for AEG. In our series, 16 patients had mediastinal lymph node metastasis, and the recurrence rate for these patients was 87.5% (14/16), whereas it was 38% (62/163) in those without mediastinal lymph node metastasis. Recurrence patterns in these patients were seven nodal (five para-aortic, two cervical), three hematogenous (liver, bone, brain), three peritoneal, and one anastomotic. Mediastinal lymph node metastasis at operation indicates more systemic spread of cancer cells, and that dissection may not improve the survival rate.

Further multivariate analysis showed that esophageal invasion and histopathological grade were independent risk factors for mediastinal lymph node metastasis. Patients with swollen mediastinal lymph nodes detected by preoperative CT scan are likely to have poor prognosis. Even in patients without swollen mediastinal lymph nodes, those with relatively long esophageal invasion (>20 mm) or poorly differentiated histological type may also have poor prognosis.

Radical surgery is the primary modality in the treatment of AEG cancer. However, long-term outcome in patients with mediastinal lymph node metastasis is still unsatisfactory. For such patients, effective perioperative chemotherapy may improve their prognosis. Phase III trials of perioperative chemotherapy for gastric cancer have been conducted in Japan (ACTS-GC) and the UK (MAGIC trial); both demonstrated significant improvement in survival with perioperative chemotherapy.[17,18] However, only 26% of patients in the MAGIC trial had AEG, and numbers are not available in the ACTS-GC study. A phase III trial to evaluate perioperative chemotherapy in AEG patients is needed. Their poor prognosis creates an urgent need for this research. Therefore, future studies to evaluate the efficacy of perioperative chemotherapy should focus on treatment of AEGs.

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