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World Journal of Surgery

Long-term Outcome after Proximal Gastrectomy with Jejunal Interposition for Gastric Cancer Compared with Total Gastrectomy

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Abstract
Background Proximal gastrectomy (PG) has been widely accepted as treatment for early gastric cancer located in the upper third of the stomach. Reconstruction by jejunal interposition has been known to reduce reflux esophagitis for PG patients. The aim of this study was to compare the long-term outcomes of patients who underwent PG with jejunal interposition with those treated by total gastrectomy (TG).
Methods Data on 102 cases of PG with jejunal interposition and 49 cases of TG with Roux-Y reconstruction for gastric cancer were analyzed retrospectively in terms of overall survival, weight maintenance, anemia and nutritional status, and endoscopic findings.
Results Median follow-up time was 59 months in the both groups. There was no significant difference in the overall 5-year survival rate between the PG group (94 %) and the TG group (84 %). The PG group showed significantly better body weight maintenance at the first year. The laboratory blood tests showed that the PG group had a significantly better red blood cell count and hemoglobin and hematocrit levels at the second and third year. However, postoperative endoscopic surveillance detected reflux esophagitis (3 %), peptic ulcer (9 %), and metachronous gastric cancer (5 %) in the PG group.
Conclusions Proximal gastrectomy maintains comparable oncological radicality to TG and is preferred over TG in terms of preventing postoperative anemia. However, periodic endoscopic follow-up is necessary to monitor the upper gastrointestinal tract.

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Introduction

Gastric cancer is one of the most common types of solid tumor, and it is estimated to be the fourth most common in terms of morbidity and the second most frequent cause of cancer death in the world [1]. In recent years, the frequency of cancers in the upper third of the stomach has been increasing in both Western and Asian countries [2–4]. As a function-preserving operation for such lesions, proximal gastrectomy (PG) has been widely accepted because it maintains comparable oncological radicality to total gastrectomy (TG), the standard operation for the lesions [5–8]. Although reflux symptoms and esophagitis had been major postoperative problems for patients who underwent PG [9, 10], a sphincter-substituting reconstruction called "jejunal interposition" has minimized these symptoms and improved the long-term outcome [11–13]. There has been one meta-analysis [14] and several reports comparing the long-term outcomes of TG and those of PG with jejunal interposition [15, 16], PG with jejunal pouch interposition [17] and PG with esophagogastrostomy [5, 8, 16, 18]. Because these reports differ in their conclusions, it remains controversial whether PG provides a better long-term outcome than TG. We conducted a large-scale comparison study with the aim of clarifying the long-term outcome of PG with jejunal interposition by comparing it to that of TG with Roux-Y reconstruction in terms of overall survival, weight maintenance, anemia and nutritional status, and endoscopic findings.

Patients and methods

All clinical diagnoses and pathological examinations of the resected specimens in this study were classified according

to AJCC/UICC cancer staging guidelines (7th ed.) [19]. The indication for PG in our institute is gastric cancer located in the upper third [20] of the stomach with it clinically staged as T1-2N0M0. The techniques for PG with jejunal interposition have already been described [11]. From January 1999 to December 2008, we performed PG with jejunal interposition on 107 patients with gastric cancer at the Shikoku Cancer Center and experienced no postoperative deaths (Fig. 1). None of these patients had prophylactic cholecystectomy or other combined resections. From this PG group, we selected 102 patients for this study who underwent postoperative surveillance at the Shikoku Cancer Center for more than 1 year.

We compared the long-term outcomes after PG to outcomes seen after TG. In the same period (1999–2008), there were 321 cases of TG performed for gastric cancer at the Shikoku Cancer Center. From this group we selected the 51 patients who were clinically diagnosed as having T1-2N0M0 gastric cancer [19] and underwent TG with Roux-Y reconstruction. Although most of these TG patients underwent prophylactic cholecystectomy, no other combined resection such as splenectomy was carried out in these patients. The final selection criteria involved those who underwent postoperative surveillance at the Shikoku Cancer Center for more than 1 year, resulting in 49 TG patients (Fig. 1).

R0 resection was achieved for all patients in this study. Following surgery, prophylactic antireflux medications such as camostat mesilate, H2-blocker, or proton pump inhibitor were not given to any patient. Prophylactic antianemia medication such as a vitamin B12 injection or oral iron supplements was also not administered to any patient. The patients underwent laboratory examinations, chest X-rays, and CT scans every 6 months. Surveillance by upper endoscopy was done annually for PG patients and every 2–3 years for TG patients. In surveillance endoscopy, the reflux esophagitis was graded using the Los Angeles classification system [21]. The patients with residual food grade ≥ 3 by the RGB classification [22] were diagnosed as having residual food. The definition for metachronous gastric cancer in the remnant stomach was described previously [23]. The red blood cell count, hemoglobin level, and hematocrit level were used as indicators of postoperative anemia. Total protein, serum albumin, and total cholesterol were used as indicators of postoperative nutritional status.

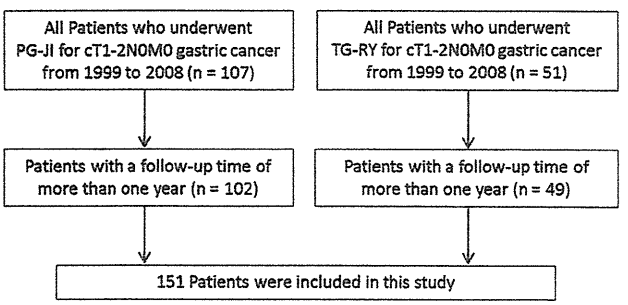

Fig. 1 Study design. *PG-JI* proximal gastrectomy with jejunal interposition, *TG-RY* total gastrectomy with Roux-Y reconstruction. Staging was classified according to the 7th edition of AJCC/UICC cancer staging system [19]

JMP 9 statistical software (SAS Institute, Inc., Cary, NC, USA) was used for all statistical analyses. The overall survival was calculated by the Kaplan–Meier method and analyzed by the log-rank test. Pearson's χ^2 test or Wilcoxon test was used to compare the two groups. The level of significance was set at $p < 0.05$.

Results

The characteristics of the groups are given in Table 1. The age and sex distribution were similar in the two groups. Although a less extensive lymphadenectomy was carried out during the operation in the PG group, there was no significant difference between the two groups. Vagal nerve preservation was carried out in 75 PG patients (74 %), while no patients underwent vagal preservation in TG group. Tumor size was significantly larger in the resected specimen in the TG group, and the TG group had significantly more cases with undifferentiated type cancer upon histological examination. In the pathological examination, a significantly more advanced T factor and stage were seen in the TG group.

After median follow-up periods of 59 months (range = 12–147) in the PG group and 59 months (range = 14–116) in the TG group, there have been nine deaths in the PG group and eight deaths in the TG group. Figure 2 shows the overall survival curves for both groups. The 5-year survival rate was 94 % for the PG group and 84 % for the TG group, and the log-rank test showed no significant difference between the two groups. In the PG group, two patients died from cancer recurrence, two patients died from cancers other than gastric cancer, three patients died from benign disease, and two patients died from unknown causes. In the TG group, six patients died from cancer recurrence, one patient died from cancers other than gastric cancer, and one patient died from benign disease.

The PG group showed better body weight maintenance until the third year, with the difference during the first year being statistically significant (Fig. 3). The percent preoperative body weight at the third year was 88 % in the PG group and 86 % in the TG group and was not significantly different between the two groups.

In the postoperative laboratory examination of blood, we used the red blood cell count, hemoglobin level, and

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

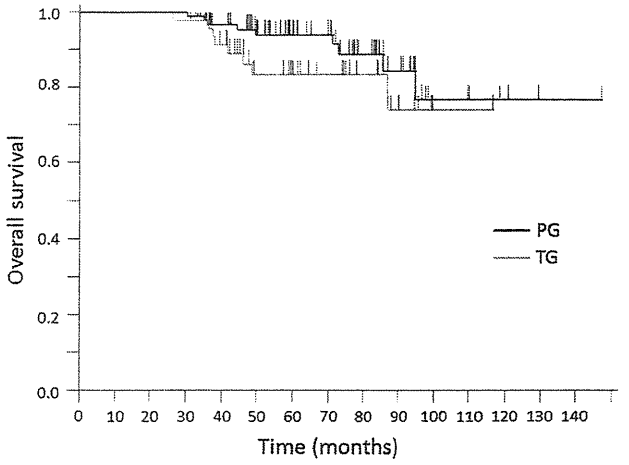

Fig. 2 The overall survival curves after proximal and total gastrectomy. There is no significant difference between the two groups by the log-rank test ($p = 0.189$). *PG* proximal gastrectomy (*black line*), *TG* total gastrectomy (*gray line*)

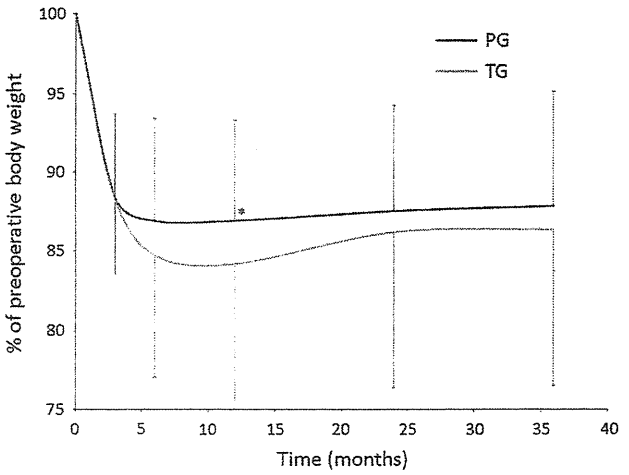

Fig. 3 The percentage of postoperative body weight to the preoperative. Data are expressed as mean ± standard deviation. *PG* proximal gastrectomy (*black line*), *TG* total gastrectomy (*gray line*). *$p = 0.034$

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

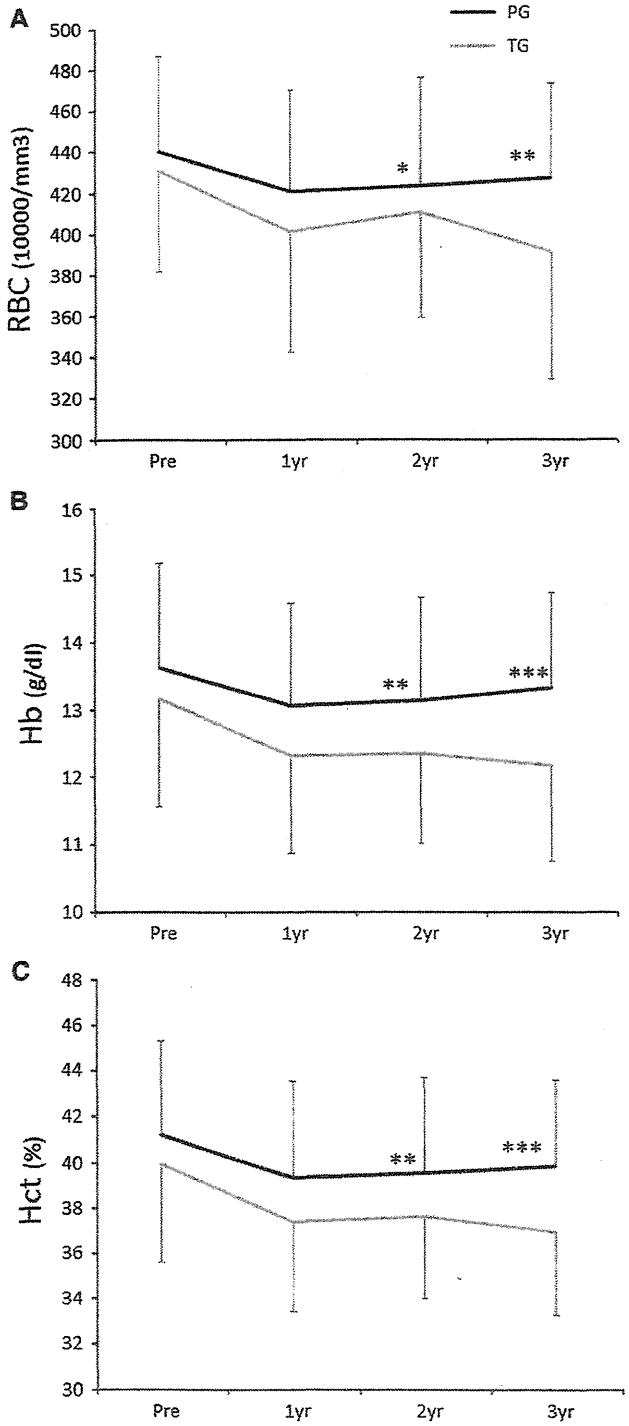

Fig. 4 The laboratory examination related to postoperative anemia. **a** *RBC* red blood cell count, **b** *Hb* hemoglobin level, **c** *Hct* hematocrit level, *PG* proximal gastrectomy (*black line*), *TG* total gastrectomy (*gray line*), *Pre* preoperative, *1yr* the first year, *2yr* the second year,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

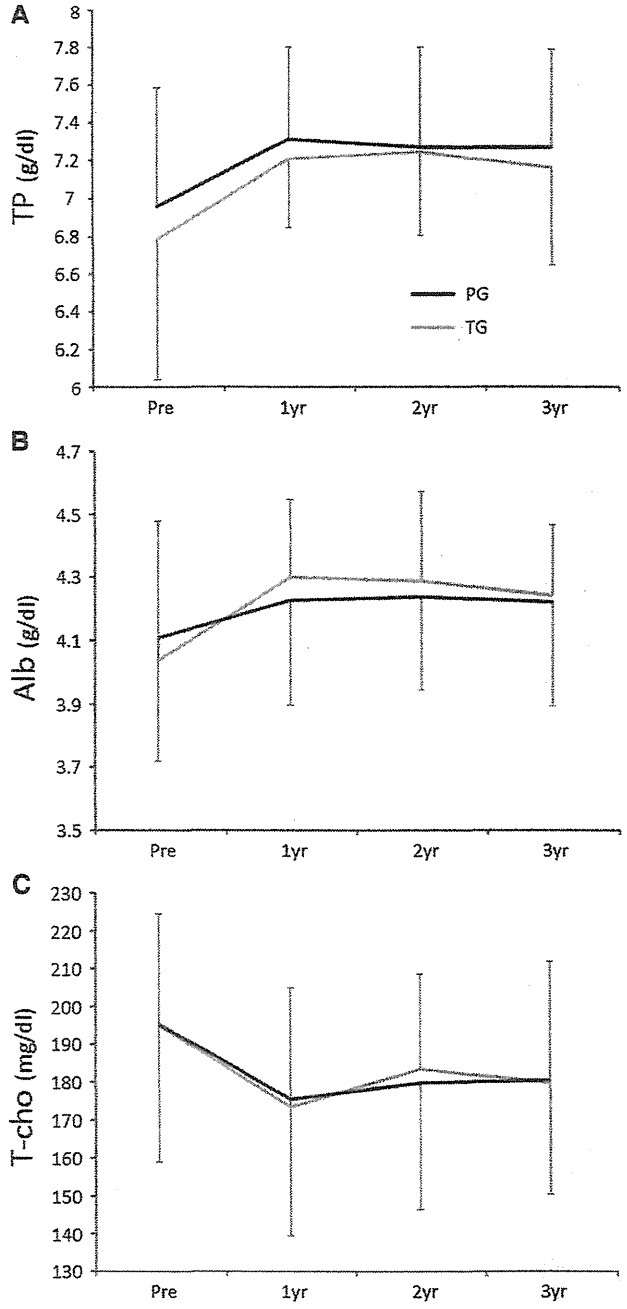

Fig. 5 The blood chemistry test related to postoperative nutritional status. **a** *TP* total protein, **b** *Alb* serum albumin, **c** *T-cho* total cholesterol. *PG* Proximal gastrectomy (*black line*), *TG* total gastrectomy (*gray line*). *Pre* preoperative, *1yr* the first year, *2yr* the second 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.

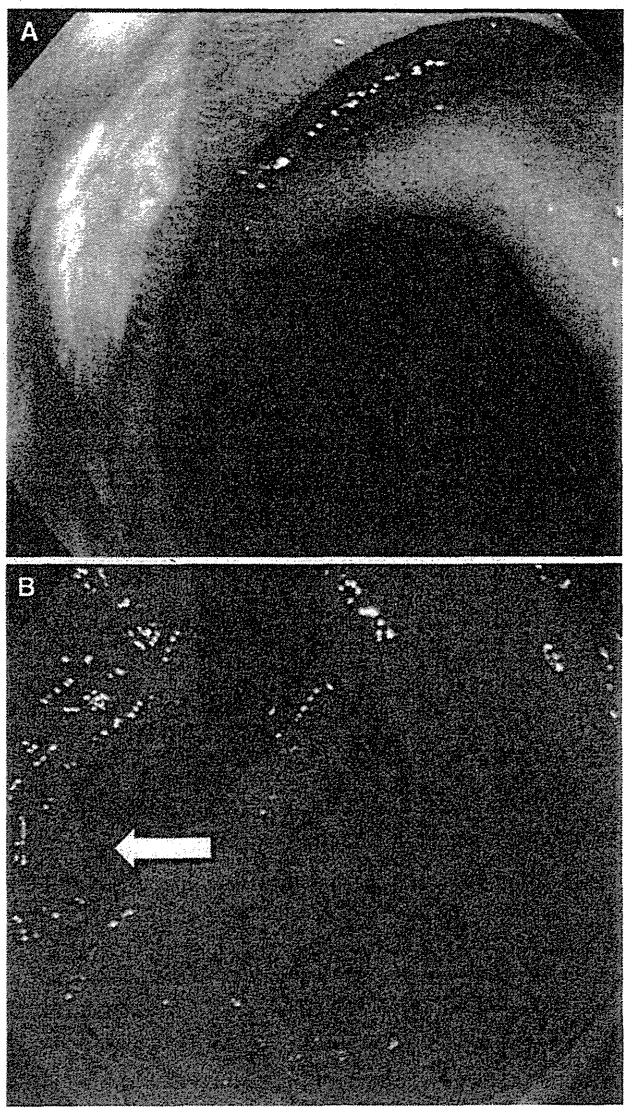

Fig. 6 The typical photographs of the peptic ulcer after proximal gastrectomy at the interposed jejunum near the jejunogastrostomy. **a** A photograph looking down from the interposed jejunum. **b** A photograph looking up from the gastric remnant. The *arrow* is pointing to the location of the peptic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

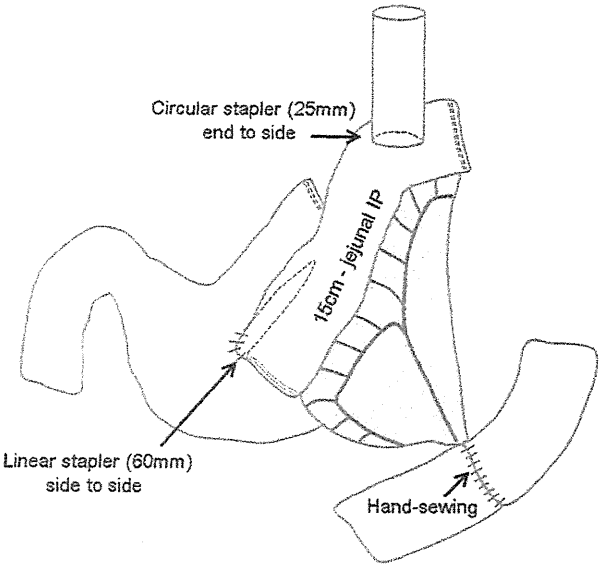

Fig. 1 Schematic of the completed reconstruction

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

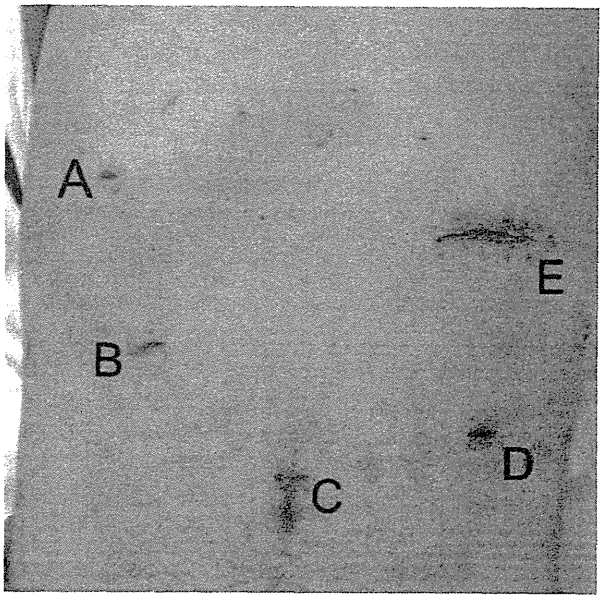

Fig. 2 Photo of the postoperative scars, indicating the placements of surgical ports. 5 mm ports were used at *A* and *D*, and 12 mm ports were used at *B*, *C*, and *E*. Port *E* was extended for the 50 mm minilaparotomy

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.

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

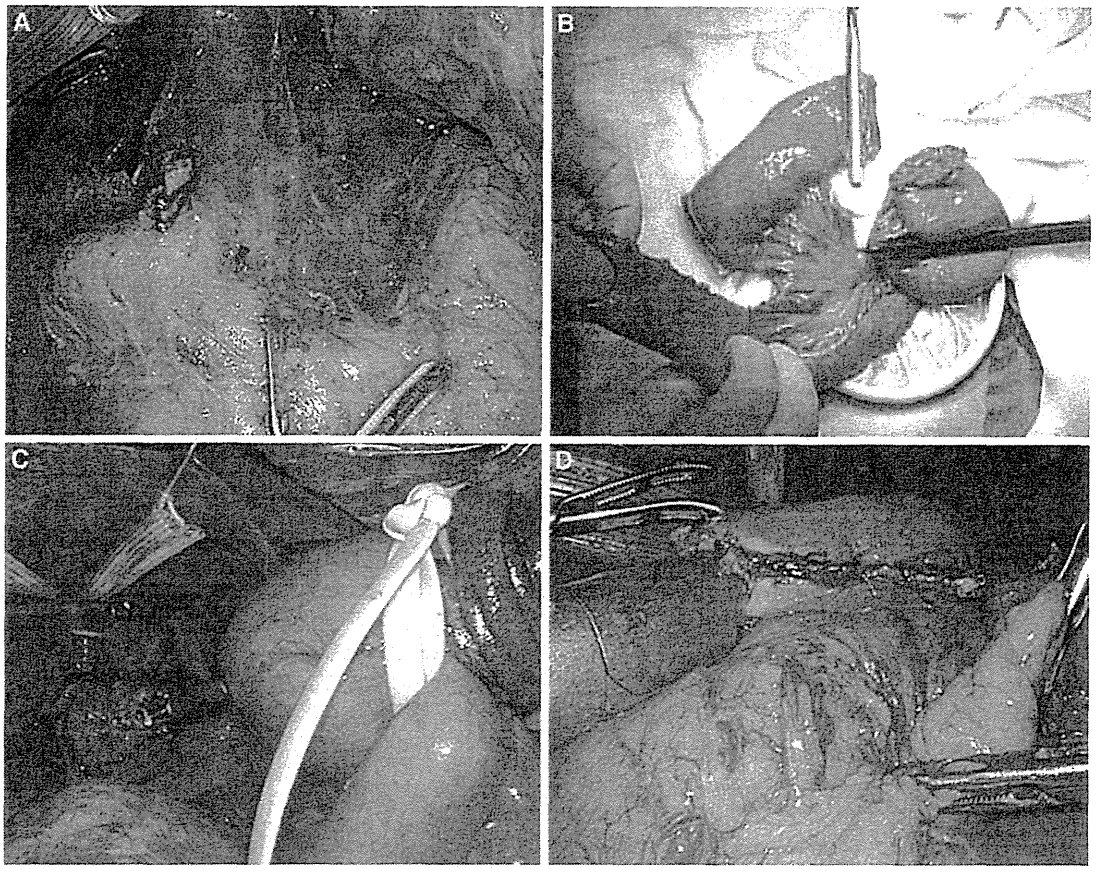

Fig. 3 **A** After lymph node dissection around the celiac artery. **B** Creation of the jejunal interposition via minilaparotomy. **C** Intracorporeal esophagojejunostomy using a *circular stapler*. **D** Intracorporeal jejunogastrostomy using a *linear stapler*

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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Sentinel Node Mapping for Gastric Cancer: A Prospective Multicenter Trial in Japan

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ABSTRACT

Purpose
Complicated gastric lymphatic drainage potentially undermines the utility of sentinel node (SN) biopsy in patients with gastric cancer. Encouraged by several favorable single-institution reports, we conducted a multicenter, single-arm, phase II study of SN mapping that used a standardized dual tracer endoscopic injection technique.

Patients and Methods
Patients with previously untreated cT1 or cT2 gastric adenocarcinomas < 4 cm in gross diameter were eligible for inclusion in this study. SN mapping was performed by using a standardized dual tracer endoscopic injection technique. Following biopsy of the identified SNs, mandatory comprehensive D2 or modified D2 gastrectomy was performed according to current Japanese Gastric Cancer Association guidelines.

Results
Among 433 patients who gave preoperative consent, 397 were deemed eligible on the basis of surgical findings. SN biopsy was performed in all patients, and the SN detection rate was 97.5% (387 of 397). Of 57 patients with lymph node metastasis by conventional hematoxylin and eosin staining, 93% (53 of 57) had positive SNs, and the accuracy of nodal evaluation for metastasis was 99% (383 of 387). Only four false-negative SN biopsies were observed, and pathologic analysis revealed that three of those biopsies were pT2 or tumors > 4 cm. We observed no serious adverse effects related to endoscopic tracer injection or the SN mapping procedure.

Conclusion
The endoscopic dual tracer method for SN biopsy was confirmed as safe and effective when applied to the superficial, relatively small gastric adenocarcinomas included in this study.

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INTRODUCTION

Gastric cancer remains a major cause of cancer death throughout Asia. Although advances in multimodal approaches have significantly improved management of localized and resectable gastric cancer, gastrectomy with regional lymphadenectomy remains the mainstay of multimodal therapeutic strategies. Gastrectomy with D2 lymph node dissection (D2 gastrectomy) has become a standard surgical approach for resectable gastric cancer worldwide.[1-3] Although improved long-term results were reported after D2 gastrectomy in comparison with D1 gastrectomy, surgical morbidity after D2 gastrectomy remains significant, particularly in Western countries.[4] Furthermore, the incidence of regional lymph node metastasis is limited in patients with cT1 or T2N0 gastric cancer, whereas D2 gastrectomy seems to be an overly invasive surgery for patients with pN0 gastric cancer. Nevertheless, because of the limitations of the sensitivity of preoperative diagnostic imaging methods to detect pathologic metastasis in regional lymph nodes, D2 gastrectomy has become a standard procedure to ensure cure, even for clinically node-negative patients. Therefore, we hypothesized that sentinel node (SN) mapping offers a promising tool to resolve this issue.[5,6] SN mapping was applied to the upstaging of colorectal cancer as an initial clinical application in GI malignancies.[7]

Although there are controversial aspects regarding the application of SN mapping in gastric cancer, which has a relatively complicated lymphatic flow, several successful single-institution studies have been reported.[8-11] However, the indications and the procedures applied for SN mapping in these previous reports varied. Therefore, a prospective

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multicenter trial with a fixed standard protocol was considered essential for establishing solid evidence that confirms the clinical significance of SN mapping in gastric cancer. A study group of the Japan Society of Sentinel Node Navigation Surgery analyzed the results of the previous studies and formulated an optimal procedure for SN mapping using the dual tracer method with technetium 99m–labeled tin colloid and 1% isosulfan blue dye (Lymphazurin, TycoHealth Care, Tokyo, Japan) in which the detection rate and sensitivity to detect metastasis by SN biopsy was relatively high.[5,10] Twelve institutions with established SN mapping protocols in place and experienced surgical staffs participated in this prospective study in which the validity of the SN concept and current optimal indications and procedures for gastric cancer treatment were evaluated.

PATIENTS AND METHODS

Patients

Patients with histologically confirmed clinical T1N0M0 or T2N0M0 adenocarcinoma of the stomach (International Union Against Cancer [UICC] TNM Classification, 6th edition) with single primary lesions (≤ 4 cm) without previous treatment, including endoscopic mucosal resection or endoscopic submucosal dissection, were preoperatively considered for inclusion in this study. Clinical staging was made by preoperative endoscopy and computed tomography. Endoscopic ultrasound was not routinely performed in the patients included in this study. Patients with apparent T3/T4 tumors, nodal or distant metastasis diagnosed intraoperatively, extensive abdominal adhesion, or poor general condition during surgery were excluded from the study. Patients with a history of drug-related allergy or active asthma were also excluded because of the potential risk of anaphylactic reaction after blue dye injection. All patients enrolled onto this study were preoperatively registered in a central data center.

All patients provided written informed consent. This study was approved by all local institutional review boards and conducted in accordance with the Good Clinical Practice guidelines and the Declaration of Helsinki. The 12 hospitals that participated in this multicenter prospective study had previous experience (> 30 patients each) with SN mapping for gastric cancer using the dual tracer method.

SN Mapping Procedure

The dual tracer method with radiolabeled tin colloid and blue dye was performed as previously described.[5] Briefly, the day before surgery, 20 mL of technetium 99m tin colloid solution (0.5 mL × 4 points; total 150 MBq; 0.3 mCi at the time of surgery) was injected in four quadrants of the submucosal layer of the primary lesion by using an endoscopic puncture needle. Intraoperatively, the gastrocolic ligament was divided to visualize all possible directions of lymphatic flow from the stomach. The 1% isosulfan blue dye was injected via intraoperative endoscopy in exactly the same manner as the preoperative injection of the radioactive tracer. Within 15 minutes, the lymphatic vessels and lymph nodes were dyed blue and imaged. Simultaneously, a handheld gamma probe was used to locate the radioactive SN. Lymph nodes with radioactivity > 10× background activity were defined as hot nodes. Hot and/or blue nodes were identified as the SNs in this study. In principle, the dual tracer technique was performed as an ideal SN mapping procedure in this study. However, the radioguided method alone was also permitted per our protocol in cases in which it was difficult to intraoperatively inject the blue dye.

Intraoperative Histologic Examination of SNs

Harvested SNs were subjected to intraoperative histologic examination by hematoxylin and eosin (HE) staining by using one representative cut surface of a frozen section of each SN. Intraoperative histologic examinations were optional and were performed on a case-by-case basis.

Surgical Procedure

After SN mapping, D2 or modified D2 gastrectomy was performed for all patients by using the therapeutic guidelines recommended by The Japan Gastric Cancer Association for standard care of this patient population.

Evaluation of SN Mapping for Gastric Cancer

The primary end point of the study was sensitivity to detect metastasis on the basis of SN status. Secondary end points included SN detection rate, number and distribution of identified SNs, and rate of adverse effects as a result of SN mapping. The pathologic status of SNs and all harvested non-SNs after D2 or modified D2 gastrectomy were examined by HE staining of one representative cut surface of a paraffin-embedded specimen.

Statistical Consideration

We reasoned that a sensitivity of 95% in patients with lymph node metastasis would indicate clinical usefulness, whereas a rate of 85% would be the lower limit of interest. On the basis of this assumption, we calculated that 89 patients were needed to provide a 90% power for a two-sided 0.05 level of a type I error. Taking ineligible patients into account, we planned to include 100 patients with lymph node metastasis. Assuming that approximately 20% of the patients in the study population had lymph node metastasis, the sample size was set at 500. Statistical analysis of the data was performed by using χ^2 and Fisher's exact tests.

RESULTS

Patients and Treatment

From July 2004 to March 2008, 433 patients were preoperatively enrolled onto this study. As shown in Figure 1, seven patients were

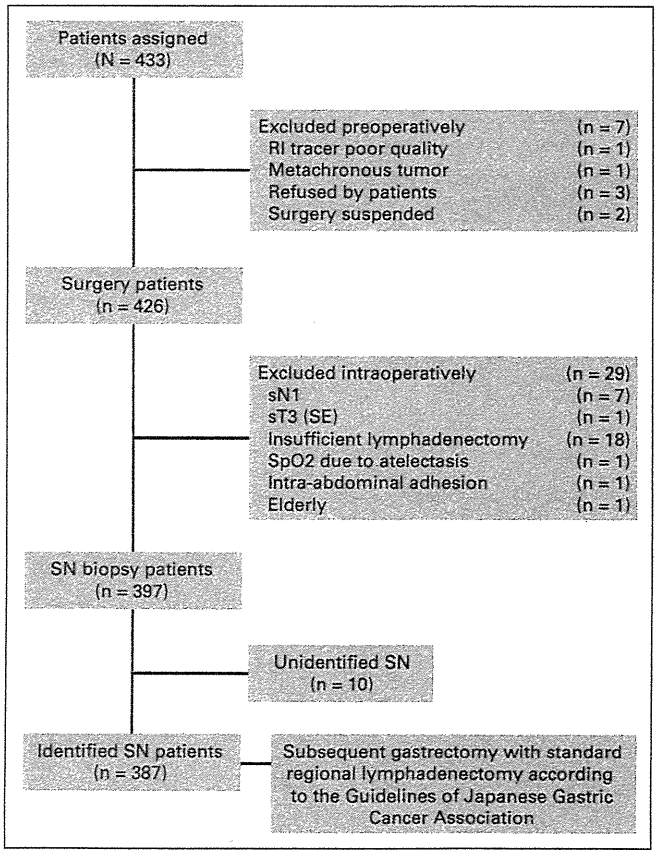

Fig 1. Flow of accrued patients. RI, radioisotope; SE, tumor penetration of serosa; SN, sentinel node; SpO_2, pulse oximeter oxygen saturation.

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Table 1. Patient Characteristics (N = 397)

Characteristic	No.	%	G	A	L	P
Age, years						
Median	63					
Range	29-87					
Sex						
Male	264	66				
Female	133	34				
Location of tumor (in stomach)						
Upper third	76		5	6	41	24
Middle third	176		30	30	67	49
Lower third	145		31	22	63	29
cT factor						
T1	341	86				
T2	56	14				
Tumor size, cm (measured after gastrectomy)						
Median	3.0					
Range	0.6-10.0					

Abbreviations: A, anterior wall; G, greater curvature; L, lesser curvature; P, posterior wall.

Table 2. Adverse Effects (N = 397)

Adverse Effect	No.	%
Administration of the tracers		
Allergic reaction to the radioactive tracer	0	0
Allergic reaction to the dye tracer	0	0
Intraoperative remarkable findings		
Pigmentation (transient)	1	0.3
SpO_2 ↓ (transient)	3	0.8
Postoperative complications		
Pneumonia	2	0.5
Anastomotic leakage	1	0.3
Pancreatic leakage	2	0.5
Intra-abdominal abscess	5	1.3
Anastomotic stenosis	1	0.3
Small bowel obstruction	4	1.0
Bleeding	2	0.5
Thrombus/embolism	1	0.3

Abbreviation: SpO_2, pulse oximeter oxygen saturation.

preoperatively excluded and 29 others were excluded on the basis of intraoperative findings according to the protocol eligibility criteria. In 18 patients, the extent of lymphadenectomy was not sufficient for several reasons, including severe intra-abdominal adhesion, obesity, or the patients' and/or surgeon's desire for minimized gastrectomy, such as partial resection. Finally, 397 patients underwent SN biopsies (Table 1). We diagnosed 341 lesions (86%) as primary T1 lesions. In addition to the radioguided method, 363 patients (91%) underwent dye-guided SN mapping. Laparoscopy-assisted gastrectomy was performed in 161 patients (41%). Intraoperative histologic examinations were performed on frozen sections from 301 patients (76%).

Adverse Effects of SN Biopsy

No serious allergic reactions were observed after tracer injection, except for instances of transient pigmentation (0.3%) and decreased pulse oximeter oxygen saturation (0.8%), which might have been related to the intraoperative dye injection (Table 2). These reactions were observed intraoperatively and sufficiently controlled while the patient was under general anesthesia. As indicated in Table 2, there was no significant increase in the number of postoperative complications caused by the SN biopsy procedures or standard surgery.

Results of SN Biopsy

The SN detection rate determined by using the dual tracer method was 97.5% (387 of 397; Table 3). Three (30%) of the 10 patients with undetected SNs underwent radioguided mapping alone. Lymph node metastasis was diagnosed in 57 (14.7%) of 387 patients, and the incidence of lymph node metastasis was significantly higher in cT2 tumors than in cT1 tumors ($P < .001$). Of the 57 patients with lymph node metastasis, 53 (93.0%) showed positive SNs. The accuracy of metastatic status based on SN evaluation was 99.0% (383 of 387). In 32 (60.4%) of 53 patients with positive SNs, lymph node metastases were limited to only SNs. Of 21 SN-positive/non–SN-positive patients, 15 (71.4%) had metastatic non-SNs within SN basins and six (28.6%) had metastatic non-SNs located outside the SN basins but within the extent of the D2 lymph node dissection. Four patients had false-negative SN biopsy results of whom three had either pT2 or primary tumors > 4 cm or both (Fig 2A).

Diagnostic Accuracy of the Primary Tumor

We evaluated differences in clinical and pathologic tumor depth (UICC TNM Classification, 6th edition) and primary tumor diameter (Table 3). Notably, 314 (94.3%) of 333 cT1 (mucosa + submucosa) patients were diagnosed as pT1 (mucosa + submucosa), but only 26 (48.1%) of 54 cT2 (muscularis propria + subserosa) patients were diagnosed as pT2 (muscularis propria + subserosa). Regarding pT3 (tumor penetration of serosa), one (0.3%) cT1 and three (5.6%) cT2 patients (a total of four [1.0%] of 387 patients with cT1 or cT2) were diagnosed as pT3. Regarding tumor diameter, 78 (20.2%) of 387 tumors were > 4 cm.

Sensitivity of Intraoperative Pathologic Detection of Metastases in SNs Using Frozen Tissue Sections

Intraoperative examinations showed that nine patients were SN negative, but permanent tissue sections were SN positive. The sensitivity of metastatic SN detection that uses intraoperative frozen sections was 79% when based on patients and 70% when based on lymph nodes. In seven (78%) of these nine patients, metastatic spread was limited to the SNs. In the remaining two patients, metastases were limited to the area within the SN basins.

Distribution of SNs

The distribution of SNs is shown in Figures 2B to 2D. SNs were located outside the area of D2 lymph node dissection in 1% of patients with primary tumors in the upper third, 3% in the middle third, and 6% in the lower third of the stomach, respectively.

DISCUSSION

The results of this multicenter prospective trial demonstrated that SN mapping for gastric cancer with the dual tracer method is a feasible and safe procedure. The detection rate of SNs and the

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Table 3. Results of SN Biopsy and Diagnostic Accuracy of Tumor Depth

Variable	All Patients (N = 397)		cT1 Patients (n = 341)		cT2 Patients (n = 56)		*P*
	No.	%	No.	%	No.	%	
SN identification							.64
Detected	387	97.5	333	97.7	54	96.4	
Undetected	10	2.5	8	2.3	2	3.6	
No. of identified SNs							.13
Mean	5.6		5.5		6.1		
± SD (per patient)	3.1		3.2		2.8		
pN factor	387		333		54		<.001
pN positive	57	14.7	32	9.6	25	46.3	
pN negative	330	85.3	301	90.4	29	53.7	
SN metastasis	57		32		25		.62
pSN positive	53	93.0	29	90.6	24	96.0	
pSN negative (false negative)	4	7.0	3	9.4	1	4.0	
SN/non-SN metastatic status	387		333		54		< .001
SN positive/non-SN negative	32	8.3	21	6.3	11	20.4	
SN positive/non-SN positive	21	5.4	8	2.4	13	24.1	
SN negative /non-SN negative	330	85.3	301	90.4	29	53.7	
SN negative/non-SN positive	4	1.0	3	0.9	1	1.9	
Pathologic T factor	387		333		54		< .001
T1 (M + SM)	339	87.6	314	94.3	25	46.3	
T2 (MP + SS)	44	11.4	18	5.4	26	48.1	
T3 (SE)	4	1.0	1	0.3	3	5.6	
T4 (SI)	0		0		0		

Abbreviations: M, mucosa; MP, muscularis propria; SD, standard deviation; SE, tumor penetration of serosa; SI, tumor invasion to adjacent structures; SM, submucosa; SN, sentinel node; SS, subserosa.

sensitivity of detection of regional lymph node metastasis by SN biopsy were comparable to previously reported data regarding breast cancer and melanoma.[13,14]

Regarding indications for SN mapping, patients with clinically evident lymph node metastasis were excluded because the purpose of this technique was to identify clinically undetectable lymph node involvement. T3 or T4 tumors in which the anatomically natural lymphatic drainage routes might be obstructed or altered were also considered as not within the evaluation range of this study. Previous single-institution studies suggested that cT1 tumors would be the most suitable indication for this procedure. To confirm the proper indications of SN biopsy in terms of the depth of the primary lesions, patients with clinically T1 or T2 tumors with a primary lesion diameter of ≤ 4 cm were enrolled onto this prospective study. We concluded that SN mapping is indicated in cT1 lesions because the false-negative rate was significantly higher in cT2 tumors than in cT1 tumors in this study.

Our results also suggested that meticulous attention to an accurate preoperative diagnosis of the T factor is necessary to optimize SN mapping. Notably, the diagnostic accuracy of cT2 is not currently sufficient; therefore, the clinical application of SN mapping should be limited to cT1 tumors. Furthermore, if the primary tumor is diagnosed as cT1, but pT2 or deeper in patients who undergo function-preserving gastrectomy based on SN mapping, additional treatment, including surgery or chemoradiotherapy, should be considered.

The SN hypothesis is applied to patients at risk of lymph node metastasis, which is diagnosed by the characteristics of the primary tumor, but having clinically undetectable regional metastatic nodes, as confirmed by preoperative diagnostic imaging. Therefore, patients indicated for endoscopic treatment such as endoscopic mucosal resection and endoscopic submucosal dissection were excluded from the selection criteria for SN biopsy (additional detail is provided in the Appendix, online only).[15,16] Although an SN biopsy is technically feasible for lesions > 4 cm, the volume and injection points for the tracers must be considered in each case. Furthermore, tumors > 4 cm are not practical targets for minimally invasive and modified surgery based on SN status. We could not identify additional exclusion criteria such as the histologic type in this trial because of the limited number of patients with false-negative SN biopsy results. Furthermore, we found no clinical issues to account for the failure to identify SNs in the 10 patients with undetected SNs. Nonetheless, our results suggested that the dual tracer method might have been responsible for the higher SN detection rate compared with the radio-guided method alone.

At this time, radio-guided SN mapping combined with dye-guided real-time visualization of lymphatic vessels and SNs is recommended as a reliable SN detection method in gastric cancer. Although there remain several controversial points regarding performance of the actual procedure, such as the type of dye, the injection route (submucosal or subserosal), the volume of tracer, and the observation timing,[17] the multicenter study group of the Japan Society of Sentinel Node Navigation Surgery has adopted an optimal procedure for SN mapping of gastric cancer from a previous single-institution experience. We chose to use technetium 99m tin colloid, which has a relatively large particle size. In our experience, tin colloid migrates into the SNs within 2 hours and remains there for > 20 hours until it is phagocytized by macrophages. Endoscopic injection enables us to accurately inject the tracer, even laparoscopically, compared with

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