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TOPIC HIGHLIGHT

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Current status of function-preserving surgery for gastric cancer

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Abstract

Recent advances in diagnostic techniques have allowed the diagnosis of gastric cancer (GC) at an early stage. Due to the low incidence of lymph node metastasis and favorable prognosis in early GC, function-preserving surgery which improves postoperative quality of life may be possible. Pylorus-preserving gastrectomy (PPG) is one such function-preserving procedure, which is expected to offer advantages with regards to dumping syndrome, bile reflux gastritis, and the frequency of flatus, although PPG may induce delayed gastric emptying. Proximal gastrectomy (PG) is another function-preserving procedure, which is thought to be advantageous in terms of decreased duodenogastric reflux and good food reservoir function in the remnant stomach, although the incidence of heartburn or gastric fullness associated with this procedure is high. However, these disadvantages may be overcome by the reconstruction method used. The other important problem after PG is remnant GC, which was reported to occur in approximately 5% of patients. Therefore, the reconstruction technique used with PG should facilitate postoperative endoscopic examinations for early detection and treatment of remnant gastric carcinoma. Oncologic safety seems to be assured in both procedures, if the preoperative diagnosis is accurate. Patient selection should be carefully considered. Although many retrospective studies have demonstrated the utility of function-preserving surgery, no consensus on whether to adopt function-preserving surgery as the standard of care has been reached. Further prospective randomized controlled trials are necessary to evaluate survival and postoperative quality of life associated with function-preserving surgery.

Key words: Gastric cancer; Function preserving surgery; Quality of life; Pylorus preserving surgery; Proximal gastrectomy

Core tip: We reviewed the current status of two function-preserving surgeries for gastric cancer (GC), pylorus-preserving surgery and proximal gastrectomy (PG). Although both procedures appear to be oncologically safe for early GC, issues regarding postoperative quality of life remain, especially with PG. The effect of the reconstruction method after PG on postoperative quality of life was analyzed, including the novel double tract reconstruction method, which is expected to overcome disadvantages associated with esophagogastrostomy and jejunal interposition reconstruction. Although some reports showed a benefit with function-preserving surgery, further randomized trials are needed.

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INTRODUCTION

Recent developments in screening programs and endoscopic techniques have allowed the diagnosis of gastric cancer (GC) at an early stage[1]. Early GC (EGC) makes up 50% of the diagnosed cases and the five-year survival rate of EGC treated with surgery is over 90% in Japan[2]. Due to the low incidence of lymph node metastasis and the favorable prognosis of EGC, areas of gastric resection and lymph node dissection areas could be reduced to preserve postoperative gastric function. Although the Japanese GC treatment guidelines advocate resection of at least two-thirds of the stomach with D2 node dissection as the standard treatment for most stages of advanced GC, the guidelines also describe less invasive procedures such as pylorus-preserving gastrectomy (PPG), proximal gastrectomy (PG), and other minimally invasive procedures as investigational treatments (Figure 1)[3].

Here we review PPG and PG as function-preserving procedures for GC.

PPG

PPG was initially used to treat peptic ulcers[4]. Starting in the late 1980s, some surgeons performed PPG in selected patients with EGC to improve postoperative gastric function and maintain patient quality of life[5]. PPG is generally thought to offer several advantages over conventional distal gastrectomy (DG) with Billroth I reconstruction in terms of the incidence of dumping syndrome, bile reflux gastritis, and the frequency of flatus, although the operative duration of PPG is longer than that of DG.

During the procedure, the distal part of the stomach is resected, but a pyloric cuff 2-3 cm wide is preserved[6,7]. The right gastric artery and the infrapyloric artery are preserved to maintain the blood supply to the pyloric cuff. In addition, the hepatic and pyloric branches of the vagal nerves are preserved to maintain pyloric function. The celiac branch of the posterior vagal trunk is sometimes preserved. All regional nodes except the suprapyloric nodes (No. 5) should be dissected as in the standard D2 procedure. However, there are technical challenges associated with completing all of these procedures. Shibata *et al*[8] conducted a questionnaire survey on the PPG procedure in Japanese institutions. According to their report, the vagus nerve was preserved at 73.5% of the institutions, the infrapyloric artery was preserved in 49.4%, and partial dissection of the suprapyloric lymph nodes was performed in 56.2%. These differences in the procedure may affect postoperative gastric function after PPG, leading to postoperative symptoms.

INDICATIONS AND ONCOLOGIC SAFETY OF PPG

Since function-preserving surgeries such as PPG are usually less extensive, patient selection for these procedures should be carefully considered in terms of oncologic safety. In particular, in order to maintain pyloric cuff function with PPG, lymph nodes at the suprapyloric and infrapyloric stations may be incompletely dissected due to preservation of the right gastric artery, the infrapyloric artery, and the hepatic and pyloric branches of the vagus nerves[9-11].

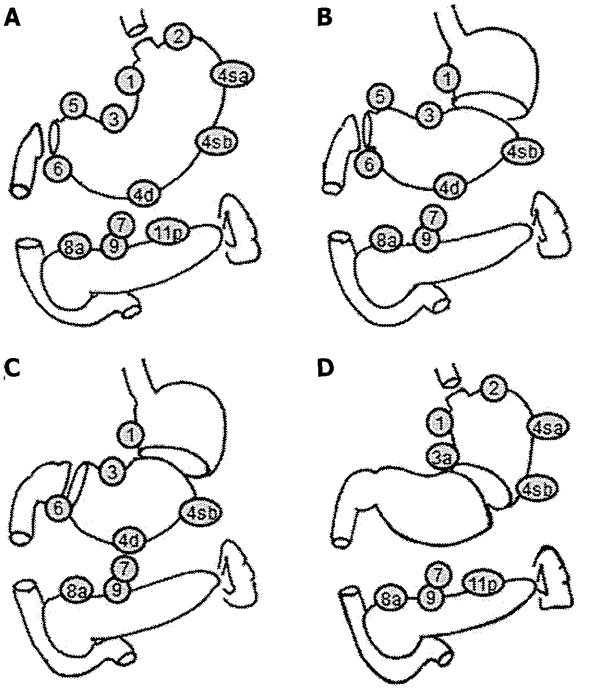

Figure 1 Extent of D1+ lymph node dissection in pylorus-preserving gastrectomy and proximal gastrectomy. A: Total gastrectomy; B: Distal gastrectomy; C: Pylorus-preserving gastrectomy; D: Proximal gastrectomy. The number of lymph node stations is according to the classification of the Japanese Gastric Cancer Association.

In general, PPG is performed in patients who are preoperatively diagnosed with cT1N0M0 primary GC in the middle third of the stomach when the distal border of the tumor is approximately 4-5 cm away from the pylorus[9-12]. This indication is based on the incidence of lymph node metastasis in patients who have undergone conventional gastrectomy[13-16].

Kim *et al*[17] reported that the incidence of lymph node metastasis at the suprapyloric and infrapyloric stations in EGC located in the middle third of the stomach after PPG and conventional DG was 0.45% (1/220) and 0.45% (1/220), respectively. In addition, Kong *et al*[18] showed that the incidence of lymph node metastasis at the suprapyloric and infrapyloric stations in EGC located $\geqslant$ 5 cm from the pylorus was 0.46% (1/219) and 0.90% (2/221), respectively. Both studies also found that the mean number of suprapyloric lymph nodes dissected was significantly lower after PPG than that with conventional DG, but no significant difference was found for infrapyloric lymph nodes. However, incomplete dissection of lymph nodes at the suprapyloric station is considered acceptable because of the low incidence of metastasis. Therefore, patients who are clinically diagnosed with T1N0 disease

Table 1 Postoperative symptomatic outcomes after pylorus-preserving surgery

Ref.	Procedure	No. of patients	Endoscopic findings (%)				Symptom (%)			Change of body weight (%)
			Esophagitis	Food residue	Bile reflux	Gastritis	Reflux	Fullness	Dumping	
Matsuki *et al*[21], 2012	PPG	433	11	19	3	11	6	2		94
Morita *et al*[24], 2013	PPG	408	6	28	12	10	6	9	4	92
Ikeguchi *et al*[25], 2010	PPG	24	35	71			0	4	0	97
	DG-B1	30	26	16			3	10	10	90
Park do *et al*[26], 2008	PPG	22			0	0	32	32		
	DG-B1	17			25	17	46	40		
Nunobe *et al*[27], 2007	PPG	194	6	22	7	12	7	10		93.9
	DG-B1	203	2	13	8	8	6	13		90.2
Tomita *et al*[28], 2003	PPG	10	0	60		10	0	40	0	94.3
	DG-B1	22	23	18		64	68	18	23	91.3
Yamaguchi *et al*[29], 2004	PPG	28		61		28	20	44	12	94.6
	DG-B1	58		33		57	27	36	36	91.3
Nakane *et al*[30], 2000	PPG	25	4	56	4	8	4	35	0	90
	DG-B1	25	8	36	40	68	0	0	4	93

PPG: Pylorus-preserving surgery; DG: Distal gastrectomy; B1: Billroth-I reconstruction.

could be candidates for PPG without suprapyloric lymph node dissection.

The five-year survival rate after PPG with modified D2 lymph node dissection ranges from 95% to 98%[10,11,19-21]. This rate is comparable to the five-year survival rate after gastric resection for EGC, which ranges from 90% to 98%[2,22,23]. In terms of oncologic safety, PPG seems reasonably safe for EGC when the accuracy of preoperative diagnosis can be assured.

POSTOPERATIVE SYMPTOMATIC OUTCOMES AFTER PPG

The advantage of PPG is the prevention of postgastrectomy symptoms such as dumping syndrome and bile reflux gastritis, as well as reduced frequency of flatus. As shown in Table 1, the ratio of dumping syndrome and bile reflux gastritis was quite low in PPG compared to DG. However, delayed gastric emptying (DGE) after PPG resulting in patient-reported gastric fullness could be a disadvantage of PPG[21,24-30], which make PPG inappropriate in elderly patients and those with hiatus hernia or esophagitis[29,30]. The incidence of gastric stasis after PPG based on endoscopic studies ranges from 19% to 70%, compared to 13% to 36% after DG. Michiura *et al*[31] showed that food intake along with DGE was improved with time. Moreover, the reservoir function of the remnant stomach may promote better body weight (BW) recovery after PPG than after DG with Billroth I reconstruction[21,24,25,27,28].

Preserving the vagal nerve and the infrapyloric artery is thought to prevent gastric stasis[10,32,33], although these techniques have not been evaluated in randomized clinical trials. The length of the pyloric cuff is another important factor with regards to preservation of pyloric function. Nakane *et al*[34] reported that retaining a pyloric cuff of 2.5 cm results in a lower incidence of postoperative stasis compared to retaining a pyloric cuff of 1.5 cm as severe postoperative edema of the pyloric cuff might affect gastric wall motility after PPG. Morita *et al*[24] showed that retaining a pyloric cuff over 3 cm did not affect the incidence of postoperative stasis compared to retaining a pyloric cuff of less than 3 cm. At Japanese institutions, the retained pyloric cuff is usually between 2 and 4 cm[8,35]. Moreover, Hiki *et al*[6] argued that the infrapyloric and right gastric veins should be preserved to maintain blood flow in order to prevent postoperative edema of the pyloric cuff. Complete dissection of both veins could induce severe edema of the pyloric cuff, resulting in long-term postoperative retention of food in the residual stomach.

PG

The incidence of proximal GC has increased in recent years[36]. Total gastrectomy (TG) and PG with lymph node dissection are both performed for EGC located in the upper third of the stomach (U-EGC). In a retrospective study of Japanese institutions, Takiguchi *et al*[37] found that a quarter of the 586 patients with U-EGC underwent PG.

PG is generally thought to offer advantages over conventional TG with Roux-en-Y reconstruction in terms of retention of food in the remnant stomach. On the other hand, heartburn or gastric fullness due to esophageal reflux or gastric stasis is a potential disadvantage. However, these advantages and disadvantages depend on the reconstruction method used.

During the procedure, all regional nodes except the splenic hilar nodes (No. 10), the distal splenic nodes (No. 11d), the suprapyloric nodes (No. 5), and the infrapyloric nodes (No. 6) are dissected, although the dissection of the distal lesser curvature nodes (No. 3) and the right gastroepiploic artery (No. 4d) is incomplete. The hepatic and pyloric branches of the vagal nerve are preserved to

Table 2 Postoperative symptomatic outcomes after proximal gastrectomy

Ref.	Procedure	No. of patients	Endoscopic findings (%)			Symptom (%)			Change of body weight (%)
			Esophagitis	Stenosis	Food residue	Reflux	Fullness	Dumping	
Masuzawa *et al*[41], 2014	PG-EG	49				18	16	0	87
	PG-JI	32				16	0	0	86
	TG-RY	122				12	3	8	85
Nozaki *et al*[42], 2013	PG-JI	102	3		32				88
	TG-RY	49	2						86
Katai *et al*[43], 2010	PG-JI	128	2		9	6		3	88.9
Katai *et al*[44], 2003	PG-JI	45	0			4		9	88.5
Tokunaga *et al*[45], 2008	PG-EG	36	30						
	short-PG-JI	18	9						
	long-PG-JI	22	0						
Ahn *et al*[46], 2013	LAPG-EG	50	32	12					
	LATG-RY	81	4	5					
An *et al*[47], 2008	PG-EG	89	29	38					86.4
	TG-RY	334	2	7					87.4
Yoo *et al*[48], 2004	PG-EG	74	16	35					
	TG-RY	185	1	8					
Tokunaga *et al*[50], 2009	PG-EG	38				8	3		86
	PG-JI	45				9	22		86
Ahn *et al*[52], 2013	LAPG-EG	50		8		32			94
	LAPG-DT	43		5	49	5		12	96.3
Nomura *et al*[53], 2014	PG-JI	10	10			0	30		91.2
	PG-DT	10	10			10	20		87.1

LAPG: Laparoscopy-assisted proximal gastrectomy; LATG: Laparoscopy-assisted total gastrectomy; PG: Proximal gastrectomy; TG: Total gastrectomy; EG: Esophagogastrostomy reconstruction; RY: Roux-en-Y reconstruction; JI: Jejunal interposition reconstruction; DT: Double tract reconstruction.

maintain the function of the remnant stomach and pylorus as in PPG[7].

INDICATIONS AND ONCOLOGIC SAFETY OF PG

In general, to maintain both curability and functional capacity of the remnant stomach, PG is performed in patients who are preoperatively diagnosed with cT1N0M0 primary GC in the upper third of the stomach when at least half of the stomach can be preserved[38].

In patients undergoing PG, the lymph nodes in the lesser curvature (No. 3) and near the right gastroepiploic artery (No. 4d) are incompletely dissected. Thus, the surgical curability of GC may be lower with PG than with TG. However, Ooki *et al*[39] reported that proximal GC confined to the muscularis propria (mp) is not associated with lymph node metastasis at the right gastroepiploic artery (No. 4d), suprapyloric (No. 5), or infrapyloric (No. 6) stations. Sasako *et al*[40] reported that after curative gastrectomy, lymph node metastasis occurs at the suprapyloric and infrapyloric stations in patients with GC located in the upper third of the stomach in approximately 3% and 7% of cases, respectively. Although these percentages seem high, approximately half of the patients had T2 or more advanced GC and the incidence of metastasis may be lower in patients with EGC. Therefore, patients who are clinically diagnosed with T1N0 disease could be candidates for PG without dissection of the right gastroepiploic artery, suprapyloric, and infrapyloric lymph nodes.

The five-year survival rate after PG ranges from 90.5% to 98.5%[41-47]. Some studies have demonstrated that PG confers a survival benefit comparable to that of TG, the standard procedure for GC located in the upper third of the stomach[41,46-48]. Therefore, PG seems oncologically safe for EGC.

POSTOPERATIVE SYMPTOMATIC OUTCOMES AFTER PG

PG is generally thought to offer several advantages over conventional TG with Roux-en-Y reconstruction (Table 2). Ichikawa *et al*[49] reported that reduced food intake volume occurred less often in patients who underwent PG compared to TG. Masuzawa *et al*[41] reported that postoperative nutritional status as analyzed by blood tests such as serum albumin and hemoglobin was better after PG than TG. However, no studies have shown a superior outcome with PG as compared to TG in terms of postoperative BW, with the exception of one study which compared PG with jejunal interposition (JI) for reconstruction and TG at one year after surgery[41,42,47]. Moreover, compared to TG, PG was associated with a much higher rate of complications such as heartburn and anastomotic stenosis, which led An *et al*[47] to conclude that PG is not a better option for U-EGC than TG[46]. However, the reconstruction method was limited to esophagogastrostomy (EG) in these reports which did not demonstrate that PG was better. Therefore, the evaluation of other reconstruction methods is necessary.

Currently, three procedures, TG with Roux-en-Y reconstruction (TG-RY), PG-EG, and PG-JI, are widely

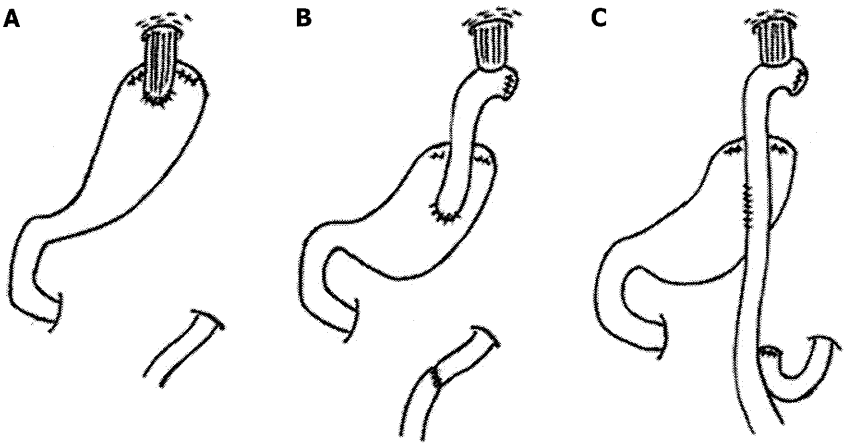

Figure 2 Reconstruction methods after proximal gastrectomy. A: Esophagogastrostomy; B: Jejunum interposition; C: Double tract.

Table 3 Comparison of the reconstruction methods after proximal gastrectomy

	PG-EG	PG-JI	PG-DT
Advantage	Short operation time	Low incidence of reflux esophagitis	Low incidence of reflux esophagitis Low incidence of DGE
Disadvantage	High incidence of reflux esophagitis High incidence of anastomotic stenosis	Long operation time High incidence of DGE	Long operation time Sometimes difficult for endoscopic evaluation of remnant stomach

PG: Proximal gastrectomy; EG: Esophagogastrostomy reconstruction; JI: Jejunal interposition reconstruction; DT: Double tract reconstruction; DGE: Delayed gastric emptying.

used to treat U-EGC in Japan (Figure 2, Table 3)[37]. Double tract (DT) reconstruction and jejunal pouch reconstruction have also been used in a small number of patients. A survey of Japanese institutions regarding reconstruction methods after PG showed that the most frequently used method was EG (48%), followed by JI (28%), DT (13%), and pouch reconstruction (7%)[35].

PG-EG is the simplest procedure since there is a single anastomotic site, but it is associated with a high incidence of reflux esophagitis[46,47]. PG-JI may prevent regurgitation of the gastric contents, resulting in a lower incidence of reflux esophagitis, but the procedure is slightly complicated. Several studies have compared the postoperative outcomes of PG-EG and PG-JI. The incidence of esophageal reflux as evaluated by endoscopic findings and symptoms was reported to be lower after PG-JI compared to PG-EG[41,45]. However, the questionnaire conducted by Tokunaga *et al*[50] showed that abdominal fullness was more frequently observed after PG-JI than after PG-EG, because the interposed jejunum may prevent the smooth passage of food. The length of interposed jejunum is important in preventing esophageal reflux, but a longer length may induce abdominal fullness.

The other important problem after PG is remnant GC (RGC). Ohyama *et al*[51] reported that RGC was observed in 5% of 316 patients after PG. They also showed that advanced RGC was more likely in patients after PG-JI with a longer length of interposed jejunum (> 15 cm) or PG-DT, and cancer-related death was only observed in patients who underwent these reconstruction methods. Tokunaga *et al*[45] reported that endoscopic evaluation of the remnant stomach could not be performed in 50% of patients after PG-JI with interposed jejunum > 10 cm, compared to 22% in patients after PG-JI with interposed jejunum ≤ 10 cm. They concluded that a length of 10 cm or shorter is preferable for endoscopic evaluation of the remnant stomach. The type of reconstruction chosen after PG should facilitate postoperative endoscopic examinations for early detection and treatment of RGC.

PG-DT has been attempted to improve postoperative outcomes after PG. PG-DT has three anastomotic sites; esophagojejunostomy, jejunogastrostomy and jejunojejunostomy. The length of interposed jejunum is from 10 to 20 cm between esophagojejunostomy and jejunogastrostomy, and about 20 cm between jejunogastrostomy and jejunojejunostomy. Food passes through the remnant stomach or the jejunum by two routes in PG-DT. PG-DT is thought to offer the same advantages as PG-JI, including the prevention of esophageal reflux, but it is expected to be better than PG-JI with regards to DGE, because an alternative route for food exists if DGE occurs. Only a few studies have analyzed postoperative outcomes after PG-DT. Ahn *et al*[52] evaluated postoperative complications after PG-DT compared to PG-EG; they concluded that PG-DT is a feasible, simple, and novel method. They showed that the incidence of anastomotic stenosis and reflux symptoms was lower after PG-DT than PG-EG and BW was better maintained. Nomura *et al*[53] evaluated

postoperative outcomes after PG-DT *vs* PG-JI. Although their study had a small sample size, they showed that the BW ratio was significantly higher in the PG-JI group than in the PG-DT group. The incidence of esophageal reflux was 10% in both groups. Further studies are needed to assess the clinical utility of PG-DT.

CONCLUSION

Function-preserving surgery has already been performed in some of the high volume institutions in Japan and South Korea, and it seems to be useful in terms of postoperative quality of life and oncologic safety. However, indications should be carefully considered, because function-preserving surgery usually involves less extensive procedures, resulting in the possibility of inadequate treatment for more deeply invasive tumors. Preoperative evaluation is very important in selecting the appropriate candidates for function-preserving surgery.

Laparoscopy-assisted PPG and PG has several advantages over conventional PPG and PG in terms of reduced intraoperative blood loss, postoperative pain and fast recovery from invasive surgery[54,55]. Since some studies reported that the oncological curability was assured[33,56,57], laparoscopic function-preserving gastrectomy is considered to be feasible by surgeons with sufficient experience in laparoscopic gastrectomy.

Many retrospective studies have shown the usefulness of function-preserving surgery, but there has been no consensus to adopt function-preserving surgery as the standard of surgery. To establish function-preserving surgery as the gold standard for patients with EGC, prospective randomized controlled trials that compare PPG or PG with conventional gastrectomy and evaluate survival and postoperative quality of life are necessary.

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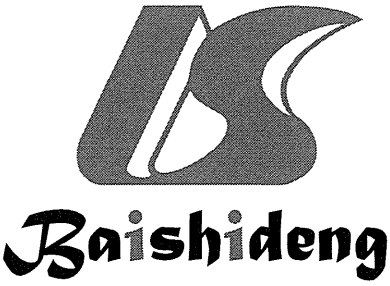

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ORIGINAL ARTICLE

Feasibility of laparoscopy-assisted total gastrectomy in patients with clinical stage I gastric cancer

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Abstract
Background Laparoscopy-assisted total gastrectomy (LATG) for gastric cancer is not yet widespread because of the technical difficulty of reconstruction. We have performed LATG on 100 patients with clinical stage I gastric cancer. This study investigated the short-term outcomes of LATG.
Methods Between September 2001 and September 2012, 100 patients with clinical stage I gastric cancer underwent LATG with D1 plus beta or D2 lymphadenectomy. Roux-en-Y esophagojejunostomy was performed intracorporeally using end-to-side anastomosis with a circular stapler (the purse-string suture method). The primary endpoint was the proportion of postoperative complications during hospitalization.
Results Mean operation time was 249 min; mean blood loss was 182 ml. There were no conversions to open surgery. According to the Clavien–Dindo classification, there were 8 grade II (8 %) and 10 grade IIIa/b (10 %) complications. There were no treatment-related deaths or grade IV complications. The most frequent complication was anastomotic or stump leakage (6 %), followed by pancreatic fistula (5 %). Reoperations were required in two patients with leakage.
Conclusions The short-term outcomes of LATG in our study involving 100 patients were outlined. LATG for gastric cancer patients should be attempted preferably in a clinical trial setting by surgeons with sufficient experience in laparoscopic gastrectomy.

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Keywords LATG · LTG · Laparoscopic · Purse-string suture

Introduction

The feasibility of laparoscopy-assisted distal gastrectomy (LADG) has been assessed in many studies [1–3]. A multicenter phase II study has demonstrated that LADG can be performed safely by surgeons with sufficient experience [4]. Large-scale phase III trials of LADG versus open distal gastrectomy for clinical stage I gastric cancer are now ongoing in Japan and Korea. Although long-term outcomes have not yet been evaluated, LADG has recently become a common surgical procedure in both countries.

Nevertheless, laparoscopy-assisted total gastrectomy (LATG) is not yet widespread. The reconstruction required in LATG is technically much more difficult than that in LADG. Only a few Korean studies have evaluated the feasibility of LATG with more than 100 patients [5, 6], so the safety of LATG is still controversial. We have performed LATG with the purse-string suture anastomosis on 100 patients with clinical stage I gastric cancer. This is the first Japanese study involving 100 patients to evaluate short-term outcomes after LATG.

Methods

Patients

Between September 2001 and September 2012, 110 consecutive patients with clinical stage I (T1N0M0, T1N1M0,

and T2N0M0) gastric cancer underwent LATG at the Osaka University Hospital. Cases of stump carcinoma were excluded from this study. Because 10 of 110 cases underwent the OrVil method or the overlap method (side-to-side anastomosis with a linear stapler) anastomosis, we analyzed only 100 cases with the purse-string suture anastomosis in this study. Clinical evaluation of tumor depth (cT) and lymph node metastasis (cN) were determined by preoperative evaluations with both endoscopy and computed tomography. The details of the methods for preoperative T staging have been reported elsewhere [7]. All tumors were histologically diagnosed as adenocarcinoma of the stomach. Clinical stage was classified according to the Japanese Classification of Gastric Carcinoma, second English edition [8]. Informed consent for LATG was obtained from all patients before surgery.

Surgery

Surgeons performed LATG and lymph node dissection according to the Japanese Gastric Cancer Treatment Guidelines in principle [9]. Patients with cT1 carcinoma underwent D1 plus beta dissection, including station nos. 7, 8a, and 9. Patients with cT2 disease underwent D2 or D2 minus splenic hilum node (station no. 10). D2 minus station no. 10 was treated as D1 plus beta in this study.

For reconstruction, Roux-en-Y esophagojejunostomy was performed with the purse-string suture method as previously reported [10]. In brief, the esophageal stump was sewn over with interrupted sutures laparoscopically or by using a device called the Endostich, and the anvil of a circular stapler was inserted into the esophageal stump. The purse-string suture was tied and reinforced with a monofilament pre-tied loop. A circular stapler inserted into the distal side of the jejunum was introduced into the abdominal cavity through the minilaparotomy site, and esophagojejunostomy was performed. Anastomotic leaks were evaluated using air insufflation.

All operations were performed or supervised by surgeons with sufficient experience with laparoscopic gastrectomies and who were certified by the Japan Society for Endoscopic Surgery.

Statistical analysis

The primary endpoint of this study was the incidence of postoperative complications during hospitalization. The grading of complications was based on the Clavien–Dindo classification system [11]. All statistical analyses were performed using SPSS Statistics software, version 20 (Chicago, IL, USA).

Results

The background characteristics of the 100 patients in this study are shown in Table 1. Ninety percent of patients were diagnosed as cT1. Only 6 patients (6 %) had clinically positive lymph nodes.

Surgical results are shown in Table 2. D1 plus beta dissection was performed in 95 cases (95 %) and D2 in 5 cases (5 %). All patients received Roux-en-Y reconstruction. Mean operation time was 249 min and mean blood loss was 182 ml. No patients required conversion to open surgery. Two of 7 patients who received splenectomy did so because of either preoperative comorbidity of thrombocytopenia or intraoperative bleeding from the splenic vein.

Table 3 lists the postoperative complications that occurred during hospitalization. Clavien–Dindo grade II complications occurred in eight patients (8 %) whereas those of grade IIIa/b occurred in ten patients (10 %). There were no treatment-related deaths or grade IV complications. The most frequent complication was anastomotic or stump leakage (6 %), followed by pancreatic fistula (5 %). Among the six leakage cases, four occurred in the esophagojejunal anastomosis, one in the duodenum stump, and one in the duodenum stump and the distal side of the jejunum stump. No patients suffered from anastomotic stricture. Reoperations were required in two patients with leakage.

Table 1 Clinical characteristics

	$n = 100$
Age (years)	
Median	63
Range	29–85
Gender	
Male	75 (75 %)
Female	25 (25 %)
Body mass index (kg/m^2)	
Median	22.5
Range	16.2–28.0
Clinical T	
T1	90 (90 %)
T2	10 (10 %)
Clinical N	
N0	94 (94 %)
N1	6 (6 %)
Clinical stage	
IA	84 (84 %)
IB	16 (16 %)

Clinical TNM stages were classified according to the Japanese Classification of Gastric Carcinoma, second English edition

Table 2 Surgical results

	$n = 100$
Lymph node dissection	
D1 plus beta[a]	95 (95 %)
D2	5 (5 %)
Combined resection	
Spleen	7 (7 %)
Gallbladder	6 (6 %)
Operation time (min)	
Mean ± SD	249 ± 47
Blood loss (ml)	
Mean ± SD	182 ± 183
Number of dissected lymph nodes	
Mean ± SD	38 ± 16

[a] D2 minus station no. 10 was treated as D1 plus beta in this study

Table 3 Postoperative complications

	$n = 100$
Any complications	
Grade II	8 (8 %)
Grade IIIa/b	10 (10 %)
Leakage	
Grade II	0
Grade IIIa/b	6 (6 %)
Pancreatic fistula	
Grade II	1 (1 %)
Grade IIIa/b	5 (5 %)
Bleeding	
Grade II	4 (4 %)
Grade IIIa/b	0
Pneumonia	
Grade II	4 (4 %)
Grade IIIa/b	0
Bowel obstruction	
Grade II	2 (2 %)
Grade IIIa/b	0
Reoperation	2 (2 %)

Grading of complications was based on the Clavien–Dindo classification

Discussion

Laparoscopy-assisted total gastrectomy is still not widespread because of the technical difficulty of the reconstruction. Several reports have been issued on the feasibility of LATG, but only a few Korean studies have evaluated the feasibility of LATG in populations of more than 100 patients [5, 6]. We have performed LATG with the purse-string suture anastomosis in 100 patients with clinical stage I gastric cancer. Compared with the previous Korean studies and a small-scale Japanese study evaluating the safety of LATG [5, 6, 12, 13], we were able to perform LATG with more favorable surgical results in terms of operation time. Regarding the incidence of postoperative complications, our study showed better or similar results compared to previous studies of LATG. The incidence of anastomotic leakage in our study was 6 % (6/100), including 1 case of duodenum stump leakage and 1 case of leakage of the duodenum stump and the distal side of the jejunum stump. Previous randomized controlled studies have reported that incidence rates of anastomotic leakage after open total gastrectomy ranged from 3.8 % to 6.8 % [14–16]. Nomura et al. [17] reported the result of a retrospective large-scale study of open total gastrectomy. Although they reported the esophagojejunal leakage rate after stapled anastomosis as 1.0 % using only the data of the recent 6 years, the overall incidence of esophagojejunal anastomosis leakage was 2.9 % (27/943). Indeed, our result of the incidence of esophagojejunal anastomosis leakage (4.0 %) was slightly higher than their result, so we think we should continue to make efforts for reducing the complication rate.

In this study we used only the purse-string suture anastomosis method. The purse-string suture method is simple and is similar to the anastomosis method in open total gastrectomy. The safety of this method has been already reported by other institutions [18, 19]. It requires fewer devices and costs less, and has the advantage of only rarely causing stenosis. Besides the purse-string suture method, two anastomosis methods (the OrVil method and the overlap method) have been reported as useful anastomosis procedures in LATG [20–23]. Although we have performed LATG with the OrVil method or the overlap method for ten cases outside this study, the incidence of anastomotic leakage of grade IIIa/b was 30 % (3/10). The reason for this high incidence was considered to be the inexperience of the surgeons with these methods. These methods might be safer if they were performed more frequently, thus increasing our overall level of expertise.

The risk of postoperative complications is affected by the skill of each individual surgeon. In our case series, six surgeons performed LATG. There was no clear difference among them in the incidence of postoperative complications. Furthermore, all operations were performed or supervised by surgeons with sufficient experience with laparoscopic gastrectomy and who were certified by the Japan Society for Endoscopic Surgery. Also, all surgeons had abundant experience with open gastrectomy. With regard to the learning curve, the incidence of postoperative complications did not show a clear decrease despite the surgeons' increasing expertise. However, in the recent 2 years (after January 2011), there was only one pancreatic

fistula and no anastomotic leakage. During this period, a fixed team of two surgeons (S.T. and Y.K.) have performed LATG in most cases. Even if the learning curves of individual surgeons do not affect the incidence of complications, a fixed team consisting of the same surgeons could perform LATG more safely.

At this point there are insufficient data concerning long-term outcomes after LATG. Several ongoing randomized control trials are comparing long-term survival between laparoscopic and open distal gastrectomy. Long-term outcomes after LATG should be also evaluated by randomized control trials to establish the possibility of a new standard for the surgical treatment of clinical stage I gastric cancer.

In conclusion, the short-term outcomes of LATG in our study involving 100 patients have been outlined. LATG for gastric cancer patients should be attempted preferably in the clinical trial setting by surgeons with sufficient experience in laparoscopic gastrectomy.

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Subgroups of Patients With Very Large Gastrointestinal Stromal Tumors With Distinct Prognoses: A Multicenter Study

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Background and Objectives: Any gastrointestinal stromal tumors (GISTs) larger than 10 cm are classified as "high risk" according to the modified National Institutes of Health consensus criteria. We conducted a multicenter study to identify a subgroup with moderate prognosis even within the "high-risk" group.

Methods: We retrospectively collected data on 107 patients with tumors ≥10 cm from a multicenter database of GIST patients. Patients with macroscopic residual lesions or tumor rupture were excluded. The relationship between recurrence-free survival (RFS) and clinicopathological factors was analyzed.

Results: The median tumor size and mitotic count were 12.5 cm and 8/50 HPF. The RFS rate was 58.5% at 3 years, 52.1% at 5 years. Only mitotic count was an independent prognostic factor of RFS in the multivariate analysis ($P = 0.001$). The hazard ratio for recurrence in the subgroup with mitotic count >5/50 HPF was 2.91 (95% confidence interval, 1.53 to 5.56). The subgroup with mitotic count ≤5/50 HPF showed significantly better RFS than the mitotic count >5/50 HPF subgroup ($P < 0.001$).

Conclusions: Mitotic count is closely associated with outcome in patients with large GISTs. This suggests that the subset of large GISTs with low mitotic counts may be considered as "intermediate-risk" lesions.

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KEY WORDS: **large GISTs; high risk; mitosis; mitotic count**

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common mesenchymal tumors in the gastrointestinal tract. GISTs are thought to share a common progenitor cell with the interstitial cells of Cajal, and usually have activating mutations in either c-kit or platelet-derived growth factor receptor alpha (PDGFRA) [1–4]. Tyrosine kinase inhibitors such as imatinib and sunitinib are highly effective against GISTs with c-kit or PDGFRA mutations [5–8]. Since large-scale, randomized controlled trials have recently demonstrated a survival advantage with adjuvant imatinib after GIST resection [9,10], accurate evaluation of the risk of recurrence is needed. Fletcher et al. [11] proposed a simple prognostic classification system using only the size and mitotic count of the resected tumor. Joensuu [12] modified the criteria to include not only size and mitotic count, but also tumor location and the presence of tumor rupture; this modified National Institutes of Health (NIH) consensus criteria is now widely used in clinical practice [13]. With this modified criteria, GISTs with size greater than 10 cm, mitotic count more than 10/50 high power fields (HPF), or rupture are all classified as "high risk." However, the 10-year recurrence-free survival (RFS) of GISTs larger than 10 cm was reported to be over 30%, while that of GISTs with a mitotic count of more than 10/50 HPF was reported as under 20% in a population-based cohort study [14]. Furthermore, almost all GISTs with tumor rupture recur after surgery [14]. Since the "high risk" group may be heterogeneous in terms of prognosis, we evaluated the long-term outcomes of over 100 patients with GISTs that were 10 cm or larger in order to identify a subgroup with moderate prognosis even within the "high-risk" group.

METHODS

Patients

From the registries conducted by the Kinki GIST Study Group and the department of Gastroenterological Surgery of Osaka University Hospital, we retrospectively collected data of 2,002 patients with GISTs who underwent resection. We identified 107 eligible GIST patients who underwent resection between October 25, 1986 and May 28, 2010. All tumors were immunohistologically diagnosed as GISTs, and were 10 cm or larger. Histological evaluations were performed by the pathologists at each institution. Patients with macroscopic residual lesions (R2) or tumor rupture were excluded from this study. None of patients had peritoneal dissemination or distant metastasis at the time of surgery. Tumors with invasion into adjacent organs underwent combined resection. No patients underwent neoadjuvant or adjuvant treatment until recurrence. Data on patients' age at surgery, sex, tumor location, type of surgery, tumor size, mitotic count, and survival outcome were

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collected. Genetic mutations were not analyzed in this study. This study was approved by the Steering Committee of the Kinki GIST Study Group.

Statistics

The primary endpoint of this study was RFS. RFS was defined as the time from surgery to either the first recurrence or death from any cause. Overall survival (OS) was defined as the time from surgery to death from any cause. Data for patients who had not had an event were censored as of the date of the final observation. Survival curves were estimated using the Kaplan–Meier method and compared using the log-rank test. The impact of clinicopathological factors (age, sex, tumor location, tumor size, and mitotic count) on survival was analyzed with univariate and multivariate analyses using the Cox proportional hazards model. P values less than 0.05 were considered statistically significant. All statistical analyses were performed using SPSS Statistics software, version 20 (IBM Corp., Armonk, NY).

RESULTS

The baseline characteristics of the 107 patients are shown in Table I. The median age was 63 years, and the patients were evenly divided by sex. The most common tumor location was the stomach (68.2%), followed by the small intestine (20.6%). More than half of the patients underwent partial resection of the stomach or small intestine, and a quarter of the patients needed combined resection of other organs. The median tumor size was 12.5 cm. The proportion of patients with mitotic count >5/50 HPF was 55.1%, and the median value of mitotic count was 8/50 HPF.

The median follow-up time in this study was 49 months. The RFS rate of all patients was 58.5% at 3 years, 52.1% at 5 years, and 43.9% at 10 years (Fig. 1A), while the OS rate was 88.1% at 3 years, and 79.4% at 5 years, and 63.5% at 10 years (Fig. 1B). The subgroups of which tumor location was stomach or small intestine did not show the significant difference on RFS ($P = 0.40$) (Fig. 2A) and OS ($P = 0.76$) (Fig. 2B), while the subgroup with mitotic count ≤5/50 HPF had significantly better RFS than the group with mitotic count >5/50 HPF ($P < 0.001$) (Fig. 3A). These two subgroups based on mitotic count also had significantly different OS ($P = 0.020$) (Fig. 3B). In the univariate and multivariate analyses, only mitotic count emerged as a significant prognostic factor of RFS, and the hazard ratios of recurrence in the subgroup with mitotic count >5/50 HPF were 2.91 (95% confidence interval, 1.53 to 5.56; $P = 0.001$) (Table II). Neither tumor location nor tumor size affected survival. If the cutoff of mitosis was set on 10/50 HPF, the hazard ratio of recurrence in the multivariate analysis was 2.41 (95% confidence interval, 1.34 to 4.35; $P = 0.003$).

TABLE I. Clinicopathological Characteristics

	n = 107
Age (years)	
Median	63
Range	33–91
Sex	
Male	54 (50.5%)
Female	53 (49.5%)
Tumor location	
Stomach	73 (68.2%)
Small intestine	22 (20.6%)
Duodenum	6 (5.6%)
Large intestine	3 (2.8%)
Omentum	2 (1.9%)
Esophagus	1 (0.9%)
Type of surgery	
Partial resection of stomach	39 (36.4%)
Partial resection of small intestine	23 (21.5%)
Distal or proximal gastrectomy	17 (15.9%)
Total gastrectomy	17 (15.9%)
Other procedure	11 (10.3%)
Combined resection of other organs	
Yes	26 (24.3%)
No	81 (75.7%)
Tumor size (cm)	
Median	12.5
Range	10.0–30.0
Mitotic count	
≤5/50 HPF	48 (44.9%)
6—10/50 HPF	14 (13.1%)
>10/50 HPF	45 (42.1%)

HPF, high power fields.

DISCUSSION

There are several different staging systems to predict the prognosis of GISTs. According to the modified NIH consensus criteria, which is frequently used in clinical practice, any GISTs larger than 10 cm in size is classified into a "high risk" group regardless of the mitotic count or tumor location [12,13]. In other words, the significance of tumor size, mitotic count, and tumor location are given the same weight in terms of the risk of recurrence, but the survival of these three categories are clearly distinct [14]. Our study demonstrated that prognosis of GISTs that are 10 cm or larger without tumor rupture was significantly affected by mitotic count, but not tumor size or tumor location. If the cutoff of mitosis was changed from 5/50 HPF to 10/50 HPF, the result was similar to the original one. The prognosis of patients with very large tumors and low mitotic count was relatively good, even though they are in the "high risk" group in the modified NIH consensus criteria, if there was no tumor rupture at the time of surgery.

Herein, we report the 5-year RFS rate of GIST patients with tumors 10 cm or larger to be 52.1%. Some previous studies have reported the prognosis of very large GISTs based on subgroup analyses. DeMatteo et al. [15] reported that the 5-year RFS rate in 39 patients with tumors 10 cm or larger was approximately 45% in their retrospective study. In another large-scale retrospective study by Joensuu et al. [14], the 5-year RFS rates in 176 patients with tumors between 10.1 and 15.0 cm and 115 patients with tumors >15.0 cm were approximately 50% and 35%, respectively. These studies included also cases involving tumor rupture, whereas our study excluded cases with tumor rupture. Since it is well known that almost all patients with tumor rupture at surgery experience recurrence [14,16,17], we examined the survival impact of only tumor location, tumor size, and mitotic count in our study. Taking into account the differences in the patient between these studies and our study, the survival results of patients with very large GISTs seem to be similar. However, our study is the first to evaluate RFS and OS only in patients with very large GISTs without tumor rupture.

Although tumor location is commonly considered to be a prognostic factor, there was no significant difference of survival between tumor location of stomach and small intestine in this study. Indeed, our results were not different from those in the previous studies. For instance, if we presume a GIST patient with tumor of 12.5 cm and 8 mitosis/50 HPF (these variables are median values in our study), the 5-year RFS is predicted as <10% regardless of tumor location (stomach or small intestine) by Memorial Sloan-Kettering Cancer Center nomogram [18]. Furthermore, Miettinen staging system predicts the recurrence rate of that case as 86% in either location [19]. Thus, it is considered that tumor location did not affect survival for large GIST with high mitotic count.

This study has some limitations. This is a retrospective study and included old cases that were resected in 1980s and 1990s. Although all patients were definitely diagnosed with GISTs by immunohistochemical examination, tyrosine kinase inhibitors such as imatinib or sunitinib were not available after recurrence for most of the older cases. This may

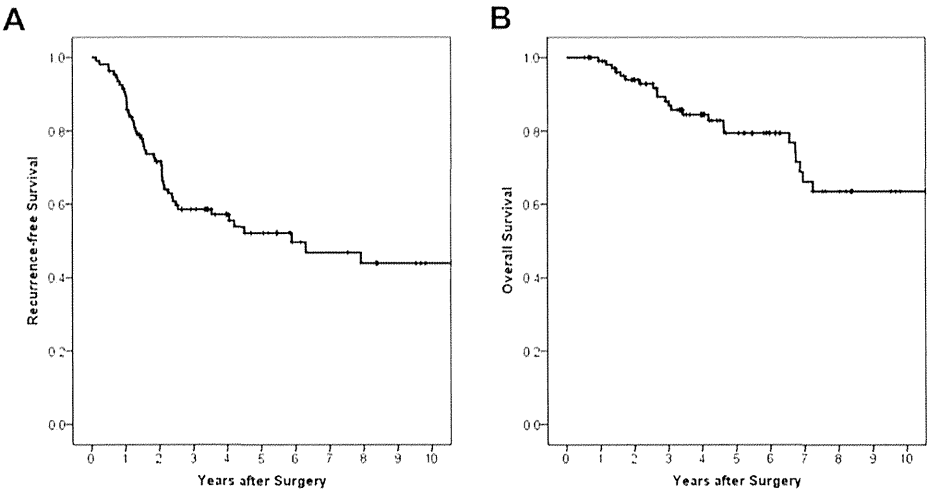

Fig. 1. Recurrence-free survival (**A**) and overall survival (**B**) in all patients with tumors $\geq$10 cm in size.

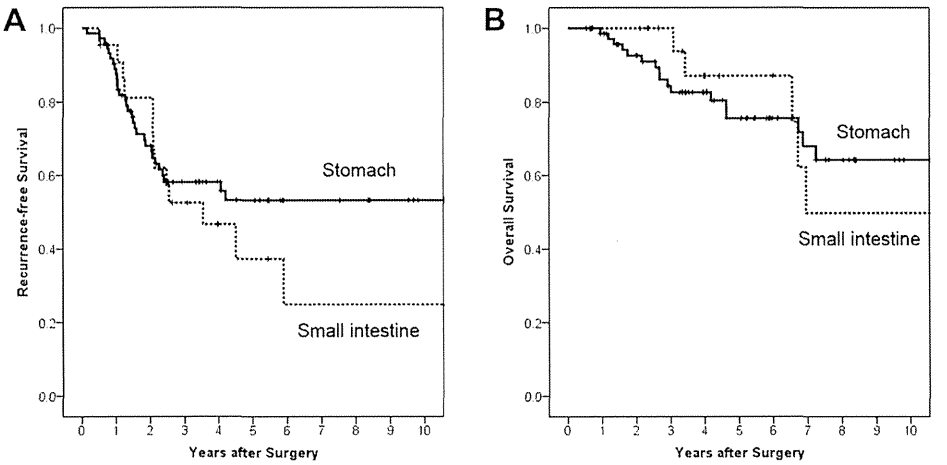

Fig. 2. Recurrence-free survival (**A**) and overall survival (**B**) stratified by location (stomach versus small intestine).

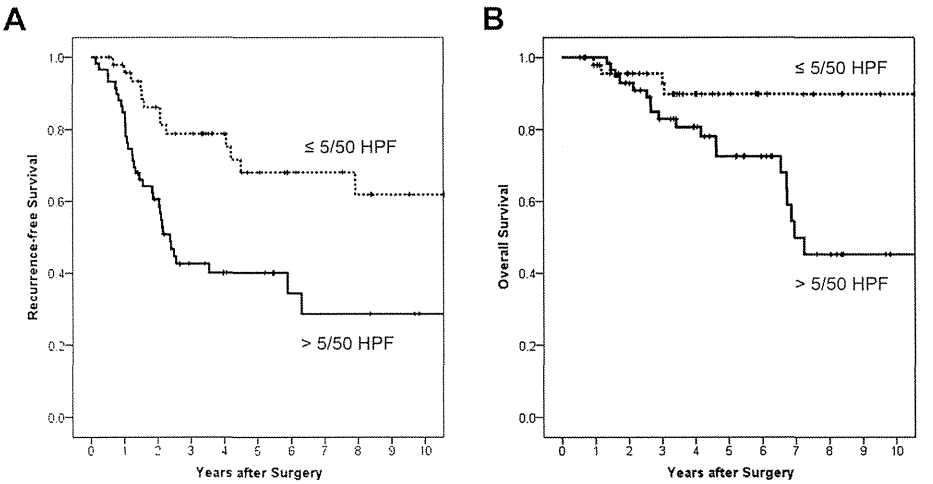

Fig. 3. Recurrence-free survival (**A**) and overall survival (**B**) stratified by mitotic count. HPF, high power fields.

TABLE II. Association of Clinicopathological Factors with Recurrence-Free Survival

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95% CI)	*P* value	Hazard ratio (95% CI)	*P* value
Age (≤63 years)	1.42 (0.80–2.52)	0.24	1.32 (0.73–2.38)	0.36
Sex (male)	1.81 (1.01–3.24)	0.045	1.65 (0.89–3.04)	0.11
Tumor location (not stomach)	1.21 (0.68–2.14)	0.53	1.35 (0.76–2.41)	0.31
Tumor size (>12.5 cm)	1.10 (0.63–1.94)	0.73	1.33 (0.75–2.37)	0.33
Mitotic count (>5/50 HPF)	2.99 (1.57–5.68)	0.001	2.91 (1.53–5.56)	0.001

CI, confidence interval; HPF, high power fields.
Age and tumor size were dichotomized by the median value.

have some effect on OS, so we analyzed RFS as the primary endpoint of this study. Another limitation of our study is the lack of available data on genetic mutations, which have been reported to have prognostic importance [20–22]. Further study of the clinical significance of genetic mutations in very large GISTs is needed. An international phase II trial of neoadjuvant imatinib for gastric GISTs 10 cm or larger is currently underway in eastern Asia (UMIN-CTR, UMIN000003114). Since this trial prospectively collects data on genetic mutations, the impact of genetic mutations on the survival of patients with very large GISTs may be clarified in the future.

CONCLUSION

Although GISTs larger than 10 cm are classified into a "high risk" group in the modified NIH consensus criteria, it may be reasonable to consider tumors with low mitotic count as "intermediate-risk" lesions. In this retrospective series of large GISTs, mitotic count ≤5/50 HPF was associated with improved outcomes as compared to those with mitotic count >5/50 HPF.

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Efficacy of Endoscopic Gastroduodenal Stenting for Gastric Outlet Obstruction due to Unresectable Advanced Gastric Cancer: A Prospective Multicenter Study

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Background and Objectives: Gastroduodenal stents for gastric outlet obstruction due to unresectable advanced gastric cancer are increasingly used; however, their effects have not been fully evaluated.
Methods: A multicenter prospective observational study was performed. Patients were eligible if they had stage IV gastric cancer with a gastric outlet obstruction scoring system (GOOSS) score of 0 (no oral intake) or 1 (liquids only). Self-expandable metallic stents were delivered endoscopically. The effects of stents were evaluated.
Results: Twenty patients were enrolled and 18 were eligible (15 men, three women; median age, 70 years). Stent placement was successfully performed in all patients, with no complications. After stenting, a GOOSS score of 2 (soft solids only) or 3 (low-residue or full diet) was achieved in 13 (72%) patients. An improvement in the GOOSS score by one or more points was obtained in 16 (94%) patients. The median duration of fasting and hospital stay was 3 (range, 0–9) days and 18 (6–168) days, respectively. Chemotherapy was performed after stenting in 13 (72%) patients.
Conclusions: Gastroduodenal stents are thought to be feasible, safe, and effective for gastric outlet obstruction due to unresectable advanced gastric cancer, with rapid clinical relief and a short hospital stay.
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KEY WORDS: **gastric outlet obstruction; stomach neoplasms; stent**

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide and leads to a poor prognosis. In Japan, early detection has increased the number of curative resections and diminished the number of cancer deaths. However, many cases are still detected in the unresectable advanced stage. Advanced gastric cancer often results in gastric outlet obstruction (GOO). GOO causes vomiting, nausea, weight loss, and intolerance to oral feeding, and diminishes the quality of life in these patients who have limited life expectancies. Chemotherapy is indicated for patients with unresectable advanced gastric cancer. However, it is difficult for patients with GOO to orally take S-1, which is included in the first-line regimen for unresectable gastric cancer recommended in Japanese gastric cancer treatment guidelines 2010 [1].

The treatment for GOO has traditionally been surgical gastrojejunostomy. Previously, we have reported the clinical outcome for palliative gastrojejunostomy in unresectable advanced gastric cancer, resulting in good improvement of oral food intake with acceptable morbidity and mortality [2]. However, invasiveness of surgery with general anesthesia is problematic because most of those with GOO have a poor general condition.

Currently, endoscopic placement of self-expandable metallic stents (SEMSs) is increasingly used as a less invasive method for palliative treatment of GOO caused by biliary-pancreatic malignancies. The efficacy and safety of SEMSs have been reported with an early food intake, short hospital stay, and low total hospital costs [3,4]. However, the effects of SEMSs for GOO with gastric cancer have not been fully evaluated.

In Japan, SEMSs were not common because this procedure was not included in the Japanese health insurance system. In April 2010, the Japanese payment system for medical services was revised, and endoscopic gastroduodenal stent placement for GOO due to malignancies was approved by the Japanese health insurance system.

Abbreviations: GOO, gastric outlet obstruction; SEMS, self-expandable metallic stent; OS, overall survival; UICC, the International Union Against Cancer; PS, Eastern Cooperative Oncology Group Performance Status; GOOSS, gastric outlet obstruction scoring system; BW, body weight; T, depth of tumor invasion; N, lymph node metastasis; M, distant metastasis; MST, median survival time.

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In this study, we aimed to prospectively evaluate the effect of SEMSs on the rate of improvement of clinical symptoms in patients with GOO due to unresectable advanced gastric cancer. Additional aims were to study the feasibility, complications, duration of fasting after stenting, duration of the hospital stay, feasibility of chemotherapy after stenting, need for re-intervention, and overall survival (OS). This is the first prospective multicenter study to evaluate the effects of SEMSs for GOO due to advanced gastric cancer.

MATERIALS AND METHODS

Patients and Data Retrieval

This prospective multicenter clinical trial was carried out at 11 institutions belonging to the Clinical Study Group of Osaka University, Upper GI Group between February 2011 and January 2013. Eligibility criteria for participation included the following: non-surgically treated patients with histologically diagnosed primary gastric adenocarcinoma, which was not estimated to be curatively resectable by clinical examinations, with clinical cancer stage IV according to the International Union Against Cancer (UICC) TNM classification (7th edition) [5]; aged equal to or older than 20 years; aged equal to or younger than 90 years; with an Eastern Cooperative Oncology Group Performance Status (PS) score of 0–2 [6]; with a GOO scoring system (GOOSS) score of 0 or 1 [7]; and considered to be alive for more than 3 months. Patients with GOO due to recurrent cancer, with active bleeding from the tumor, who could not receive an endoscopic examination, with additional obstruction of the oral side of the stomach, with additional obstruction of the small or large intestine, who had already undergone SEMS placement, who could not answer the questionnaire about quality of life, or who were considered inappropriate for participants, were excluded. The presence of duodenal invasion was not excluded.

The institutional review board of each hospital approved the protocol. All participants provided written informed consent. This study was performed by the Clinical Study Group of Osaka University, Upper GI Group, which conducted investigator-initiated trials and was composed of hospitals affiliated from the Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine. The data center, located at the Multicenter Clinical Study Group at the Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, was responsible for central monitoring and statistical analyses under supervision of the statistician in charge.

Procedures

Endoscopic stent placement was performed using the Wallflex™ duodenal stent (Boston Scientific, Natick, MA) under conscious sedation. It is an uncovered-SEMS with a diameter of 22 mm at the mid-body, and 60, 90, or 120 mm long depending on the case. After a guidewire was correctly positioned distal to the stricture, a stent catheter was advanced over the wire through the working channel of a therapeutic endoscope and the stent was released under fluoroscopic control.

Outcomes and Definitions

The primary outcome was an improvement in the ability to tolerate an oral solid diet after stenting as assessed by the GOOSS score. Secondary outcomes included the technical success rate, complications, the duration of post-interventional fasting, the duration of the post-interventional hospital stay, the feasibility of chemotherapy after stenting, the need for re-intervention, and OS.

Food intake was assessed by the standardized GOOSS score as follows: 0 = no oral intake, 1 = liquids only, 2 = soft solids, and 3 = almost complete or full diet [7]. The ability to take a solid diet was indicated by a GOOSS score of 2 or 3. Technical success was defined as deployment of the SEMS across the stricture, with patency visualized both fluoroscopically and endoscopically. Complications were defined as any adverse event related to SEMS placement, such as bleeding, perforation, and jaundice.

Sample Size and Data Analysis

A sample size of 20 patients had been planned when the trial was designed, considering that the number of GOO cases due to gastric cancer in the institutions of the Clinical Study Group of Osaka University, Upper GI Group was approximately 60 per year. The projected accrual period was 2 years.

The following parameters were collected and analyzed: sex, age, GOOSS score, body weight (BW), height, PS, albumin levels, total lymphocyte count, hemoglobin levels, previous chemotherapy, tumor location, macroscopic tumor type, depth of tumor invasion (T), lymph node metastasis (N), and distant metastasis (M) according to the Japanese classification of gastric carcinoma (3rd English edition) [8]. Interventional outcomes and complications were collected. GOOSS scores, BW, PS, albumin levels, lymphocyte count, and hemoglobin levels, at 1, 2, and 4 weeks, and every other 4 weeks after stenting, were recorded until the 24th week. The date of the start of oral intake, the date of hospital discharge, post-interventional therapy, including re-stenting, surgery, and chemotherapy, and the date and causes of death were also recorded. The survival time was defined as the duration from the date of stenting to death.

Statistical Analysis

Differences in parameters after stenting were compared with baseline (pre-interventional) values by the Wilcoxon signed-ranks test. P values were derived from two-tailed tests, and differences were considered significant at $P < 0.05$. Analyses were performed using StatView® software (version 5.0 for Macintosh; SAS Institute Inc., Cary, NC).

RESULTS

Patients' Characteristics

Twenty patients from six institutions were enrolled between March 2011 and July 2012. One patient with a GOOSS score of 2 and one patient with cancer stage IIIB were excluded. Therefore, the clinical data of 18 patients were retrieved and analyzed in this study. The clinical characteristics of the 18 patients are summarized in Table I.

Outcome of Stent Placement

SEMS placement was technically successful in all cases, and no complications were encountered. The ability to take solid food orally was achieved by 13 (72%) patients, in whom six had a GOO score of 2 and seven had a GOOSS score of 3. The remaining five patients who could not take solid food included three patients whose GOOSS score improved from 0 to 1, one patient whose GOOSS score remained as 0, and one patient who died within 1 week after stenting. A total of 16 (94%) out of 17 patients showed an improvement of the GOOSS score. The mean GOOSS scores were 1.7, 1.9, 1.8, 1.8, 1.8, 2.1, 2.3, and 2.2, at 1, 2, 4, 8, 12, 16, 20, and 24 weeks after stenting, respectively. The change in GOOSS scores by the post-stenting week is shown in Figure 1. The median duration of post-stenting fasting was 3 (range, 0–9 days) days. The median duration of hospitalization was 18 (6–168 days) days

TABLE I. Clinical Features of Patients Who Underwent Endoscopic Gastroduodenal Stent Placement for Gastric Outlet Obstruction Due to Unresectable Advanced Gastric Cancer

Variables		
Sex	Male/female	15/3
Age	(Year)	70 (48–90)*
GOOSS score	0/1	10/8
Body weight	(kg)	48 (29–71)*
Body mass index	(kg/m^2)	18.8 (13.1–22.9)*
PS	0/1/2	5/6/7
Albumin	(g/dl)	2.7 (1.7–3.8)*
Lymphocyte	($/mm^3$)	1068 (602–1,657)*
Hemoglobin	(g/dl)	9.1 (6.6–13.5)*
Pre-interventional chemotherapy	+/−	8/10
Tumor location	L/ML/UML	14/3/1
Tumor type	2/3/4	4/8/6
Depth of tumor invasion (T)	3/4a/4b	3/10/5
Lymph node metastasis (N)	1/2/3a/3b/X	3/4/9/1/1

PS, Eastern Cooperative Oncology Group Performance Status score; GOOSS, gastric outlet obstruction scoring system; Tumor location, Tumor type, T, and N are written according to the Japanese Classification of Gastric Carcinoma the 3rd English edition; *, median (range).

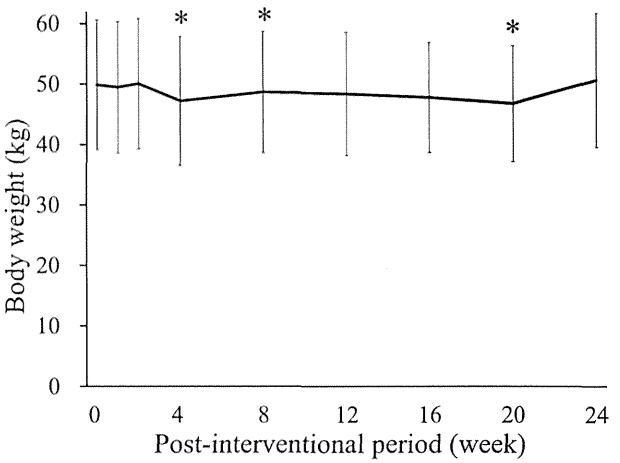

Fig. 2. Changes in the mean body weight at baseline (0) and during follow-up after stenting. Body weight after re-intervention was not included. Bars represent the standard deviation. Asterisks represent significant differences ($P < 0.05$) compared with baseline values using the Wilcoxon signed-ranks tests.

after stenting. Post-stenting chemotherapy was provided to 13 (72%) patients, including 10 patients with an S-1-containing regimen.

Additional therapy included re-stenting in two patients, surgical gastrojejunostomy in three patients, and gastrectomy in one patient. Two patients who could eat solid food after stenting, but then returned to no oral intake because of re-obstruction, received additional SEMS placement on the 105th and 126th post-stenting day, which resulted in good oral intake of solid food. One patient with development of re-obstruction after stenting could take solid food after gastrojejunostomy on the 69th post-stenting day. One patient with inadequate improvement of GOO after stenting could not eat solid food after gastrojejunostomy on the 45th post-stenting day. The other patient who could take solid food after stenting and developed tumor perforation after chemotherapy underwent surgery for peritonitis and gastrojejunostomy on the 165th postoperative day. A patient who had GOO and peritoneal metastasis due to gastric cancer underwent SEMS placement and received chemotherapy with S-1, cisplatin, and trastuzumab. Curative gastrectomy could be performed on the 76th post-stenting day because the peritoneal metastasis disappeared after two cycles of the regimen. The cancer stage was ypT4aN3bM0 stage IIIB.

Changes in Nutritional Values and Performance Status

BW, PS, albumin levels, total lymphocyte count, and hemoglobin levels, at 1, 2, and 4 weeks, and every other 4 weeks after stenting, were recorded until the 24th week and compared with baseline values. BW was significantly decreased at 4, 8, and 20 weeks after stenting compared with baseline, however, no significant increase in BW compared with the baseline value was observed during follow-up (Fig. 2). There were no significant changes in PS (Fig. 3), albumin levels (Fig. 4), lymphocyte count, and hemoglobin levels during the follow-up.

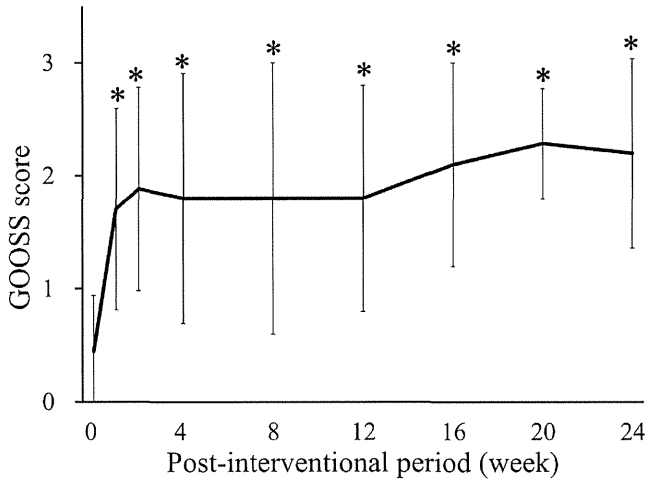

Fig. 1. Changes in the mean gastric outlet obstruction scoring system (GOOSS) score at baseline (0) and during follow-up after stenting. GOOSS scores after re-intervention were not included. Bars represent the standard deviation. Asterisks represent significant differences ($P < 0.05$) compared with baseline values using the Wilcoxon signed-ranks tests.

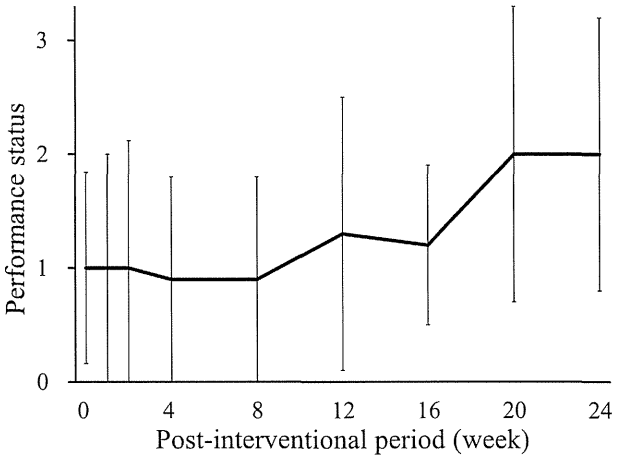

Fig. 3. Changes in the mean Eastern Cooperative Oncology Group Performance Status (PS) score at baseline (0) and during follow-up after stenting. PS scores after re-intervention were not included. Bars represent the standard deviation. There were no significant differences between baseline and post-interventional values by the Wilcoxon signed-ranks tests.