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Comparison of Perioperative and Long-term Outcomes of Total and Proximal Gastrectomy for Early Gastric Cancer: A Multi-institutional Retrospective Study

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Abstract

Background Various surgical procedures are used to treat early gastric cancers in the upper third of the stomach (U-EGCs). However, there is no general agreement regarding the optimal surgical procedure.

Methods The medical records of 203 patients with U-EGC were collected from 13 institutions. Surgical procedures were classified as Roux-en-Y esophagojejunostomy after total gastrectomy (TG-RY), esophagogastrostomy after proximal gastrectomy (PG-EG), or jejunal interposition after PG (PG-JI). Patient clinical characteristics and perioperative and long-term outcomes were compared among these three groups.

Results TG-RY, PG-EG, and PG-JI were performed in 122, 49, and 32 patients, respectively. Tumors were larger in TG-RY patients than in PG-EG and PG-JI patients, and undifferentiated-type gastric adenocarcinoma tended to be more frequent in TG-RY than in PG-EG. The operative time was shorter for PG-EG than for PG-JI and TG-RY. Hospital stay and early postoperative complications were not different for the three procedures. With respect to gastrectomy-associated symptoms, a "stuck feeling" and heartburn tended to be more frequent in PG-EG patients, while dumping syndrome and diarrhea were more frequent in TG-RY patients. Post-surgical weight loss was not different among the three groups, however, serum albumin and hemoglobin levels tended to be lower in TG-RY patients.

Conclusion Three surgical procedures for U-EGC did not result in differences in weight loss, but PG-EG and PG-JI were better than TG-RY according to some nutritional markers. In U-EGC, where patients are expected to have long survival times, PG-EG and PG-JI should be used rather than TG-RY.

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Introduction

Gastric cancer (GC) is one of the most common cancers worldwide [1, 2] and has one of the highest morbidity rates of all cancers in Japan [3, 4]. In recent years, a high participation rate for endoscopic screening has shown that early GC (EGC) accounts for almost 50 % of all GCs [5, 6]. The high curative rate of EGC and the low frequency of distal perigastric node metastases has allowed the development of more limited modified procedures that improve patient quality of life without compromising cure rates [7–15].

Currently, total gastrectomy (TG) and proximal gastrectomy (PG) with lymph node dissection are both considered standard procedures for treating EGC located in the upper portion of the stomach (U-EGC) [16, 17]. Historically, esophagogastrostomy after PG (PG-EG) was widely used for treating U-EGC [18], however, this procedure often leads to severe reflux esophagitis [16, 19–21] and many surgeons were reluctant to perform it. Some surgeons instead performed TGs, while others chose to perform other reconstructions that did not cause severe reflux esophagitis, such as jejunal interposition after PG (PG-JI; [10, 22–25]).

Both Roux-en-Y reconstruction after TG (TG-RY) and PG-JI also have drawbacks. Specifically, TG-RY limits patients to eating small meals and can result in vitamin deficiencies due to nutrient malabsorption [9]. While PG-JI prevents reflux esophagitis, it is such a complicated procedure that it should be performed only at high-volume centers. In addition, the supposed advantages of PG-JI, such as the ability of PG-JI patients to eat larger meals and prevention of postsurgical weight loss, were less dramatic than expected [26, 27].

Currently, all three procedures, i.e., TG-RY, PG-EG, and PG-JI, are widely used for treating U-EGC in Japan regardless of lesion location or characteristics [28]. Because no large-scale trial has been performed to compare these procedures, it seems that individual surgeons decide on the best surgical approach based on their previous experience. Notably, our institution, in which about 50–100 GC operations are performed per year, treats only a few cases of U-EGC per year (about 13 % of EGC cases [29] and about 5–6 % of all GC cases [18, 28]); thus, it was impossible to compare these procedures using only cases at a single institution. Therefore, we had to perform a multi-institutional study to investigate the perioperative and long-term outcomes of TG-RY, PG-EG, and PG-JI. We previously reported the current status of procedure choice for U-EGC at 19 hospitals in Japan [28]. By adding the investigation of short- and long-term outcomes, including nutrition index such as body weight, serum albumin, and hemoglobin, we attempted to verify the differences among three procedures.

Materials and methods

Patients

A retrospective survey was performed using data from 19 hospitals, including Osaka University and associated hospitals. Each hospital conducted at least 10 gastrectomies per year and was approved as a training institute by the Japanese Society of Gastroenterological Surgery. From 1998 to 2005 there were 9,643 surgical treatments of GC at the 19 hospitals, and 586 patients had U-EGC. Based on pathological and/or clinical findings, U-EGC was defined as a GC if it had invaded (at most) the submucosal (sm) layer and if both the proximal and distal margins were located in the upper third of the stomach. Of the 586 patients with U-EGC, 203 who met the following requirements in 13 hospitals were enrolled in this study (Supplementary Table 1): (1) complete peri- and postoperative medical information was available from the medical records. (2) Pathology reports showed a negative margin. (3) There was no metastasis in other organs at the time of the operation. (4) The patient received no pre- or postoperative adjuvant chemotherapy. (5) The patient underwent PG-EG, PG-JI, or TG-RY, which were the procedures that were used most at the institutions.

Clinical characteristics

Pre- and postoperative information was collected from the patients' medical records. Early postoperative complications were defined as events that led to hospitalization. Late postoperative complaints were determined from medical records after patient discharge. Both early and late dumping syndromes were classified as dumping syndrome.

Surgical treatment

TG involved removal of the entire stomach, while PG involved removal of the upper part of the stomach from the esophagogastric junction to the cutting line with adequate surgical margins for the anal edge of the tumor. Standard D1 + β lymph node dissection, including lymph node stations 1–3, 4sa, 4sb, 7, and 8, was performed for all patients; lymph node stations 11 and 9 was optionally removed in some patients. No patients underwent abdominal aortic lymph node dissection. Surgical treatment using RY reconstruction was described previously [28].

After resection of the upper part of the stomach, EG (PG-EG) was performed by anastomosing the abdominal esophagus with the anterior wall of the remnant stomach. Although reconstruction of JI (PG-JI) was slightly different in different institutions or in different periods, PG-JI was generally performed as follows. The proximal jejunum

(about 10–15 cm) was brought retrocolically for anastomosis with the esophagus and the remnant stomach. Esophagojejunum anastomosis was performed with an end-to-end or end-to-side anastomosis technique, and jejunogastric anastomosis was performed with the anterior wall of the remnant stomach.

The selection of procedure to use and any additional procedures was the decision of each institution. Some institutions favor one operative procedure over the others (Supplementary Table 1).

The initial pathological diagnosis was followed by the official report from each hospital, which was prepared by certified pathologists. The clinicopathological classification was based on the guidelines set out in the Japanese Classification of Gastric Carcinoma.

Statistical analysis

The statistical significance of the difference between two parameters was determined using Student's t test or Fisher's exact test. Statistical significance was set at $p < 0.05$ (two-sided). Statistical analyses were performed using JMP® version 8.0.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Clinical characteristics of U-EGC patients

TG-RY, PG-EG, and PG-JI were performed in 122 (60.1 %, included 10 laparoscopic cases), 49 (24.1 %), and 32 (15.8 %) patients, respectively (Table 1). The median age of the patients in the PG-EG, PG-JI, and TG-RY groups was 64.0, 65.0, and 63.0 years, respectively. There were no significant differences in age or sex among the groups. The median tumor size in the PG-EG, PG-JI, and TG-RY groups was 2.2, 2.0, and 3.0 cm, respectively, with a significant difference between the TG-RY and PG-EG groups ($p = 0.0002$) and between the TG-RY and PG-JI groups ($p < 0.0001$). As for histological type, the TG-RY group had more undifferentiated-type gastric adenocarcinomas [37 (30.3 %)] than the PG-EG group [6 (12.8 %)] ($p = 0.0188$). In terms of the pathological T factor, 30 (61.2 %) of the PG-EG, 20 (62.5 %) of the PG-JI, and 63 (51.6 %) of the TG-RY patients had sm-invasive cancer. In terms of the pathological N factor, 1 (2.0 %) of the PG-EG, 2 (6.2 %) of the PG-JI, and 5 (4.1 %) of the TG-RY patients had localized lymph node metastasis. There were no significant differences among the groups. As for pathological stage, the PG-JI group had a higher percentage of stage IB patients [6 (18.7 %)] than did the TG-RY group [6 (4.9 %)] ($p = 0.0186$). Pyloroplasty, fundoplasty, and vagus nerve preservation were performed in 14, 16, and 30 patients, respectively.

Table 1 Patient characteristics

	PG-EG ($n = 49$)	PG-JI ($n = 32$)	TG-RY ($n = 122$)
Age (median ± SD)	64.0 ± 7.7	65.0 ± 12.1	63.0 ± 10.0
Sex [*n* (%)]			
M	36 (73.5)	25 (78.1)	89 (73.0)
F	13 (26.5)	7 (21.9)	33 (27.0)
Tumor size (cm) (median ± SD)	2.2 ± 1.3*	2.0 ± 0.7*	3.0 ± 2.5*
Histology [*n* (%)]			
Differentiated	41 (87.2)**	23 (74.2)	85 (69.7)**
Undifferentiated	6 (12.8)	8 (25.8)	37 (30.3)
Unknown[a]	2	1	0
pT [*n* (%)]			
m	19 (38.8)	12 (37.5)	59 (48.4)
sm	30 (61.2)	20 (62.5)	63 (51.6)
pN [*n* (%)]			
N0	48 (98.0)	30 (93.8)	117 (95.9)
N1	1 (2.0)	2 (6.2)	5 (4.1)
pStage [*n* (%)]			
IA	45 (91.8)	26 (81.3)**	116 (95.1)**
IB	4 (8.2)	6 (18.7)	6 (4.9)

PG-EG esophagogastrostomy after proximal gastrectomy, *PG-JI* jejunal interposition after proximal gastrectomy, *TG-RY* Roux-en-Y reconstruction after total gastrectomy

* Significant difference between TG-RY and PG-EG ($p = 0.0002$) and between TG-RY and PG-JI ($p < 0.0001$); **significant difference between two groups ($p < 0.05$)

[a] The histological information of these three patients was lost during the study

Operative results

The median operating time for the PG-EG, PG-JI, and TG-RY groups was 185, 230, and 225 min, respectively, with a significant difference between the PG-EG and PG-JI groups ($p = 0.0001$) and the PG-EG and TG-RY groups ($p < 0.0001$; Table 2). The median operative blood loss was 280, 331, and 368 ml, respectively. Blood loss was greater in the TG-RY group than in the PG-EG group ($p = 0.0337$). The median postoperative hospitalization time was 20, 23, and 22 days, respectively. Although the PG-EG group had a shorter median hospitalization time than the other groups, there was no significant difference.

Early postoperative complications

The early postoperative complication rate was 8.2 % (4/49) in the PG-EG group, 9.4 % (3/32) in the PG-JI group, and 13.1 % (16/122) in the TG-RY group. There were no

Table 2 Operative data and early postoperative complications

	PG-EG ($n = 49$)	PG-JI ($n = 32$)	TG-RY ($n = 122$)
Operative data (median ± SD)			
Operating time (min)	185 ± 48*	230 ± 43*	225 ± 41*
Blood loss (ml)	280 ± 247**	331 ± 182	368 ± 316**
Postoperative hospitalization (days)	20 ± 17	23 ± 31	22 ± 28
Early postoperative complications [*n* (%)]			
Total	4 (8.2)	3 (9.4)	16 (13.1)
Anastomotic leakage	0 (0.0)	0 (0.0)	6 (4.9)
Anastomotic stenosis	2 (4.1)	1 (3.1)	2 (1.6)
Abdominal abscess	0 (0.0)	0 (0.0)	8 (6.6)
Other complications	2 (4.1)	2 (6.3)	3 (2.5)
Reoperation	0 (0.0)	0 (0.0)	2 (1.6)

* Significant difference between PG-EG and PG-JI ($p = 0.0001$) and between PG-EG and TG-RY ($p < 0.0001$); **significant difference between the two groups ($p = 0.0337$)

Table 3 Late postoperative complaints

	PG-EG ($n = 49$)	PG-JI ($n = 32$)	TG-RY ($n = 122$)
Total complaints	20 (40.8)	9 (28.1)	49 (40.2)
Stuck feeling	8 (16.3)[a]	0 (0.0)[a]	3 (2.5)[a]
Dumping syndrome	0 (0.0)	0 (0.0)	10 (8.2)
Heartburn	9 (18.4)	5 (15.6)	14 (11.5)
Diarrhea	0 (0.0)	2 (6.3)	9 (7.4)
Ileus symptoms	0 (0.0)	0 (0.0)	6 (4.9)
Other complaints	3 (6.1)	2 (6.3)	9 (7.4)

[a] PG-EG had a higher rate of stenosis than did PG-JI ($p = 0.0195$) and TG-RY ($p = 0.0023$)

significant differences in early postoperative complications among the groups.

Late postoperative complaints (Table 3)

Having a "stuck feeling" and heartburn tended to be more frequent in the PG-EG group than in the PG-JI and TG-RY groups (stuck feeling: 16.3, 0.0, and 2.5 %; heartburn: 18.4, 15.6, and 11.5 %). There was a significant difference in the stuck feeling complaint between groups (PG-EG vs. PG-JI, $p = 0.0195$; PG-EG vs. TG-RY, $p = 0.0023$). Notably, dumping syndrome and diarrhea tended to be more frequent in the TG-RY group than in the PG-EG and PG-JI groups (dumping syndrome: 8.2, 0.0, and 0.0 %; diarrhea: 7.4, 0.0, and 6.3 %), but the differences were not statistically significant. The overall late postoperative complaint rate was 40.8 % in the PG-EG group, 28.1 % in the PG-JI group, and 40.2 % in the TG-RY group. The PG-JI group had a lower rate of late postoperative complaints than the other groups but the differences were not statistically significant.

Postoperative nutritional evaluation

Nutritional indicators such as body weight and serum albumin and hemoglobin levels were investigated in the patients (Fig. 1). To determine the percentage changes in nutritional indicators, changes in the values were divided by preoperative values and then multiplied by 100. For body weight, the percentage from the preoperative weight to 3 years after surgery was similar among the groups and there were no significant differences. For the serum albumin level, the TG-RY group had significantly lower levels than the other groups 2 and 3 years after the operation (PG-EG vs. TG-RY, $p = 0.007$ at 2 years and $p = 0.012$ at 3 years; PG-JI vs. TG-RY, $p = 0.036$ at 3 years). The hemoglobin level was significantly worse in the TG-RY group than in the PG-JI group 3 years after the operation ($p = 0.046$ at 3 years).

Survival data

The average follow-up duration in the study population was 53.1 months, and 13 cases (6.4 %) were lost to follow-up during the first year because of transfer, relocation, or changing hospital. The overall 5-year survival rates were 94.0 % (PG-EG), 94.4 % (PG-JI), and 99.1 % (TG-RY). Four patients died during follow-up: one patient died from aortic aneurysm rupture (707 days) and one died from hepatic cirrhosis (1,172 days), and the cause of death of one patient was unknown (1,584 days). One patient treated by TG-RY died from liver metastasis of the GC (349 days). There was no operation-related death. Remnant stomach carcinomas were found in two patients treated by PG-EG and in one patient treated with PG-JI. The time from the surgical treatment to finding the remnant carcinomas was 2 and 6 years in the PG-EG patients and 6 years in the PG-JI patient.

Discussion

This retrospective multicenter study found some differences among patients treated by PG-EG, PG-JI, and TG-RY for U-EGC. Most previous studies were retrospective single-center studies and needed too long a period of time for collecting sufficient numbers of the cases. In contrast, our study was a multicenter study over a relatively short time period, which meant that the cases of U-EGC in this study underwent operations under the same conditions (e.g., using similar anastomosis techniques and suturing

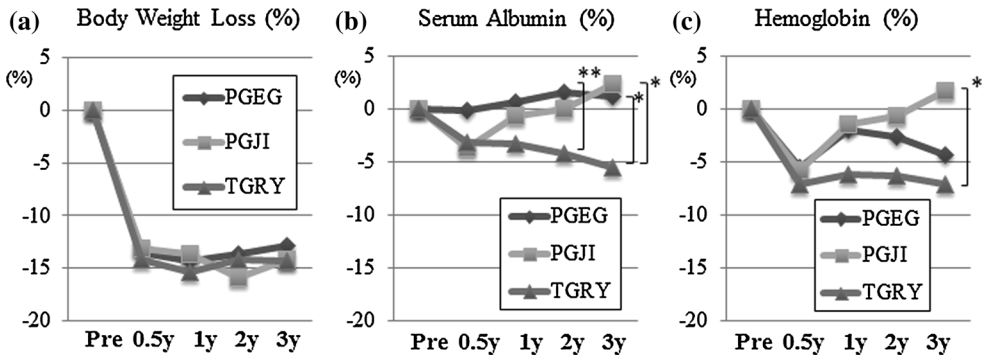

Fig. 1 Postoperative changes in body weight and in albumin and hemoglobin levels, $*p < 0.05$ and $**p < 0.01$. **a** Average changes in body weight after surgery for the three procedure groups. There were no significant differences in the three groups. **b** Average changes in serum albumin levels after surgery for the three procedure groups. The average serum albumin levels did not change significantly in the PG-EG and PG-JI groups but decreased in the TG-RY group (PG-EG vs. TG-RY, $p = 0.007$ at 2 years, $p = 0.012$ at 3 years; PG-JI vs. TG-RY, $p = 0.036$ at 3 years). **c** Average changes in the hemoglobin levels after surgery for the three procedure groups. Only the PG-JI group maintained the preoperative hemoglobin level, while the levels in the TG-RY group decreased ($p = 0.046$ at 3 years)

instruments) and that all patients received drugs such as proton pump inhibitors.

In the present study, the median size of the tumors treated by TG-RY was larger than the median tumor size in the PG groups. There were more undifferentiated-type gastric adenocarcinomas in the TG-RY group than in the PG-EG group. However, there were no differences among the groups in terms of tumor depth or lymph node metastasis. It seems that lymph node metastasis and tumor depth, which influences lymph node metastasis, were not important in terms of choosing to perform TG versus PG. Many surgeons probably thought D2 lymph node resection (especially peripyloric lymph nodes) was not necessary for U-EGC because nodal metastasis in the distal perigastric nodes is very rare [9, 17]. On the other hand, the size of the remnant stomach, which is influenced by tumor size and histology, did seem to be an important factor in choosing the procedure. It fact, in answering our questionnaire, many surgeons pointed out that an indication for using PG was that more than half of the stomach could be preserved. Many surgeons believed that a smaller remnant stomach after PG negated the benefit of performing PG.

The operating time was shorter and there was less blood loss for PG-EG compared to PG-JI and TG-RY. This is mainly because operating time and blood loss are influenced by the number of anastomoses involved and distal perigastric node dissection, and PG-EG involves just one anastomosis and localized node dissection. In a 35-patient study of three EGC surgical procedures, Ichikawa et al. [18] reported that PG-EG had a shorter operating time and resulted in less blood loss than the other procedures. Moreover, Shiraishi and colleagues [8, 26, 27] studied 51 patients and also reported that PG-EG was a better procedure than TG-RY in terms of operating time and blood loss. Thus, our findings were similar to those of others in terms of operative factors.

There was no significant difference in early postoperative complications among the three procedures. Interestingly, the number of anastomoses and the extent of resection did not affect the occurrence of anastomotic leakage, stenosis, and abdominal abscess.

Of the late postoperative complaints, experiencing a stuck feeling and heartburn were more common in PG-EG patients, while dumping syndrome and diarrhea were more common in TG-RY patients. PG-EG patients tended to have the flow of food disrupted and to experience heartburn and the sensation that food is stuck. In contrast, in TG-RY patients the flow of food tended to be so rapid as to increase the incidence of dumping syndrome and diarrhea. However, there was no significant difference in the total complaint rate among the three procedures. An et al. [16] reported that PG-EG led to a higher frequency of symptoms of stenosis and reflux than did TG-RY and that PG-EG resulted in a higher complication rate than TG-RY. Matsushiro et al. [19] and Zhang et al. [20] reported that fundoplasty improved the frequency of reflux. In addition, administration of proton pump inhibitors can mitigate reflux symptoms so that they occur less frequently and are less severe. In the present study, although the tendency to experience a stuck feeling in the PG-EG group was similar to that found in a previous study [16], the frequency of this complaint was not so high as to influence the total complaint rate. Although there was no significant difference in the total complaint rate among the three treatment groups, the PG-JI group had a lower rate than the other two groups.

In the postoperative nutritional evaluation, there was little difference among the three treatment groups in terms of changes in body weight. A previous study by An et al. [16] reported that there was no difference in body weight loss in patients treated with PG-EG versus TG-RY (13.9 vs. 11.7 % 1 year after surgery). Shiraishi et al. [26] also

reported that there was no difference in weight loss between patients treated by PG-EG and by TG-RY (−12.7 and −10.5 kg 1 year after surgery). Katai et al. [23] reported in a retrospective study that body weight loss of patients treated by PG-JI was 11.1 % while that of patients treated by TG-RY was 15.8 % 1 year after surgery. The changes in body weight found in the present study were similar to those reported in these studies, with median weight losses in the PG-EG, PG-JI, and TG-RY groups of 14.3, 13.6, and 15.4 %, respectively, 1 year after surgery. These findings suggest that preserving the distal stomach might not be an important factor in body weight maintenance after surgery. On the other hand, TG-RY patients tended to have greater declines in their serum albumin and hemoglobin levels. Decreased absorption of albumin in TG-RY patients might be related to the loss of gastric acid and pepsin, and the anemia in TG-RY patients might be related to a loss of intrinsic factor and gastric acid. Only a few studies looked at hemoglobin and serum albumin changes, and Yoo et al. [14] reported that hemoglobin levels in TG-RY patients tended to be low. An et al. [16] reported that hemoglobin levels in PG-EG patients were significantly higher than those in TG-RY patients and no authors found a significant difference in serum albumin changes among U-EGC patients treated with different surgical procedures. In the present study, our findings suggested that the preserved distal stomach was adequate for maintaining hemoglobin and serum albumin levels after surgery.

In the present study, the choice of procedures for U-EGC tended to be influenced not by the presence and risk of lymph node metastasis but by the size of the remnant stomach. TG-RY tended to be used to reduce the stomach volume by a greater amount. In the perioperative period, PG-EG was the most minimally invasive procedure of the three and thus might be suitable for high-risk patients such as the elderly or patients with organ damage. In terms of early postoperative complications, there were no differences among the three procedure groups. On the other hand, in terms of late postoperative complaints, PG-JI patients tended to have fewer complaints and PG-EG patients tended to more often have a stuck feeling; however, the differences were too small to result in a significant difference in the total complaint rate. In evaluating postoperative nutrition, there was no difference in body weight loss among the three groups; however, the PG-JI and PG-EG groups, but especially the PG-JI group, had smaller decreases in hemoglobin and serum albumin levels. In this respect, every procedure showed different profiles. Surgeons need to choose the best suitable procedure for patients with U-EGC.

The present study was a multi-institutional retrospective study. Because U-EGC is a relatively uncommon disease, it was difficult to conduct a randomized or prospective study at a single institution. This was designed as a multi-institutional study in order to analyze more patients. To confirm these observations, a prospective randomized trial that involves a longer trial period and more institutions should be performed.

Conclusion

This study found that patients who underwent one of three surgical procedures for U-EGC showed different characteristics in terms of tumor background, operation complexity, postoperative symptoms, and nutritional status. Although there was no difference in postoperative body weight loss, PG-EG and PG-JI were as safe as TG-RY and were superior in terms of patient postoperative nutritional status. Because of this, PG-EG or PG-JI should be used for surgical treatment of U-EGC.

Notably, the present study is a retrospective study, and a prospective randomized trial in a larger cohort is needed to confirm these observations and to help determine the criteria for selecting the most suitable procedure for each patient.

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