cisplatin-induced emesis easier by using NK-1 receptor antagonists with this regimen.

In conclusion, adjuvant therapy with S-1 plus 3 cycles of cisplatin may reduce recurrence and improve survival in patients with stage III GC who underwent D2 gastrectomy. This treatment should be considered for use as an experimental arm for comparison to S-1 in future postoperative adjuvant phase III trials.

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Conflict of interest The authors have declared no conflicts of interest.

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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

Toru Masuzawa · Shuji Takiguchi · Motohiro Hirao · Hiroshi Imamura · Yutaka Kimura · Junya Fujita · Isao Miyashiro · Shigeyuki Tamura · Masahiro Hiratsuka · Kenji Kobayashi · Yoshiyuki Fujiwara · Masaki Mori · Yuichiro Doki

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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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T. Masuzawa · S. Takiguchi (✉) · Y. Fujiwara · M. Mori · Y. Doki
Department of Gastroenterological Surgery, Graduate School of Medicine, Osaka University, 2-2 Yamadaoka, Suita, Osaka 565-0871, Japan
e-mail: stakiguchi@gesurg.med.osaka-u.ac.jp

M. Hirao
Department of Surgery, Osaka National Hospital, Osaka, Japan

H. Imamura
Department of Surgery, Sakai Municipal Hospital, Sakai, Japan

Y. Kimura
Department of Surgery, NTT West Japan Hospital, Osaka, Japan

J. Fujita
Department of Surgery, Toyonaka Municipal Hospital, Toyonaka, Japan

I. Miyashiro
Department of Surgery, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan

S. Tamura
Department of Surgery, Kansai Rosai Hospital, Amagasaki, Japan

M. Hiratsuka
Department of Surgery, Itami City Hospital, Itami, Japan

K. Kobayashi
Department of Surgery, Kinki Central Hospital of Mutual Aid Association of Public School Teachers, Itami, Japan

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

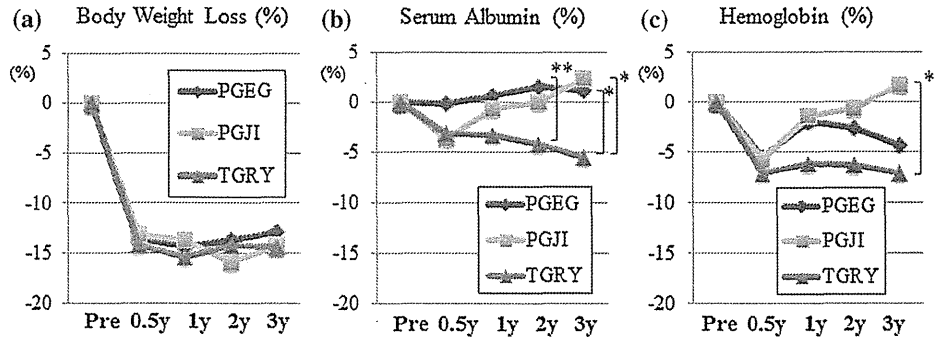

Fig. 1 Postoperative changes in body weight and in albumin and hemoglobin levels, $*p < 0.05$ and $**p < 0.01$. **a** Average changes in body weight after surgery for the three procedure groups. There were no significant differences in the three groups. **b** Average changes in serum albumin levels after 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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ORIGINAL ARTICLE

Long-term quality-of-life comparison of total gastrectomy and proximal gastrectomy by Postgastrectomy Syndrome Assessment Scale (PGSAS-45): a nationwide multi-institutional study

Nobuhiro Takiguchi · Masazumi Takahashi · Masami Ikeda · Satoshi Inagawa · Shugo Ueda · Takayuki Nobuoka · Manabu Ota · Yoshiaki Iwasaki · Nobuyuki Uchida · Yasuhiro Kodera · Koji Nakada

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Abstract
Background Although proximal gastrectomy (PG) is widely accepted as a function-preserving operation for early upper-third gastric cancer, postoperative disorders, such as reflux or gastric stasis, have often been pointed out. From the perspective of postoperative disorder, the choice of total gastrectomy (TG) or PG for such cancers is still controversial. By using the newly developed Postgastrectomy Syndrome Assessment Scale (PGSAS)-45, the quality of life after TG and PG was compared.
Methods The PGSAS-45 consists of 45 items composed of the SF-8 and GSRS scales and 22 new items. The main outcomes are measured by seven subscales (SS) covering symptoms, physical and mental component summary (SF-8), meals (amount and quality), ability to work, dissatisfaction for daily life, and change in body weight. A total of 2,368 eligible questionnaires were acquired from 52 institutions. From these, 393 patients with TG and 193 patients with PG were selected and compared.
Results The PG was better than TG in terms of body weight loss (TG 13.8 % vs. PG 10.9 %; $p = 0.003$), necessity for additional meals (2.4 vs. 2.0; $p < 0.001$), diarrhea SS (2.3 vs. 2.0; $p = 0.048$), and dumping SS (2.3 vs. 2.0; $p = 0.043$). There were no differences in the other main outcome measures.
Conclusions Proximal gastrectomy appears to be valuable as a function-preserving procedure for early upper-third gastric cancer.

Keywords Proximal gastrectomy · Total gastrectomy · Postgastrectomy syndrome · Quality of life · Stomach cancer

N. Takiguchi (✉)
Division of Gastroenterological Surgery, Chiba Cancer Center, 666-2 Nitona-cho, Chuo-ku, Chiba 260-0801, Japan
e-mail: ntaki@chiba-cc.jp

M. Takahashi
Division of Gastroenterological Surgery, Yokohama Municipal Citizen's Hospital, Yokohama, Japan

M. Ikeda
Department of Surgery, Asama General Hospital, Saku, Japan

S. Inagawa
Department of Surgery, University of Tsukuba, Tsukuba, Japan

S. Ueda
Department of Gastroenterological Surgery, Kitano Hospital, The Tazuke-Kofukai Medical Research Institute, Osaka, Japan

T. Nobuoka
Department of Surgery I, Sapporo Medical University School of Medicine, Sapporo, Japan

M. Ota
Department of Surgery II, School of Medicine, Hamamatsu University, Hamamatsu, Japan

Y. Iwasaki
Division of Surgery, Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Tokyo, Japan

N. Uchida
Department of Surgery, Haramachi Red-Cross Hospital, Agatsuma, Gunma, Japan

Y. Kodera
Department of Gastroenterological Surgery, Graduate School of Medicine, Nagoya University, Nagoya, Japan

K. Nakada
Department of Surgery, The Jikei University School of Medicine, Tokyo, Japan

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Introduction

Gastric cancer remains the second leading cause of cancer death in the world and is the most frequent malignancy in Japan, South America, and Eastern Europe [1, 2]. Long-term survivors after radical gastrectomy have been increasing as the result of better early detection and improved surgical techniques [3–5]. The better surgical outcome has led to greater interest in the quality of life (QOL) of gastrectomized patients. For prevalence of postgastrectomy disorder, the procedures used in gastrectomy for early gastric cancer are designed as function-preserving operations or various reconstructions to restore postoperative QOL [6]. Although the postgastrectomy disorders greatly influence the living condition (QOL) of gastrectomized patients, there are limits to evaluation of outpatients because of the difficulty in measuring subjective and physical symptoms. In recent years, questionnaires have been developed to create objective rating systems for QOL [7–11]. The Japan Postgastrectomy Syndrome Working Party was founded in order to investigate symptoms and lifestyle changes among patients who have undergone gastrectomy. This Working Party collaboratively developed a questionnaire to evaluate the symptoms, i.e., living status and QOL, among gastrectomized patients. Using this questionnaire, a nationwide, multi-institution surveillance study was performed.

The frequency of cancers in the upper third of the stomach and gastroesophageal junction has been increasing in both Western and Asian countries [12–15]. Total gastrectomy (TG) and proximal gastrectomy (PG) are operative options for proximal gastric cancer. In PG, the gastric fundic gland region is kept, and gastric-acid secretion and Castle intrinsic factor are maintained, but patients often suffer from reflux or gastric stasis. The choice of TG or PG has been discussed from the viewpoint of postoperative disorders, especially reflux esophagitis and nutrition. By using the newly developed Postgastrectomy Syndrome Assessment Scale (PGSAS-45), QOL after TG and PG for gastric cancer was compared.

Methods

Patients

Fifty-two institutions participated in this study. The PGSAS-45 questionnaire was distributed to 2,922 patients between July 2009 and December 2010. Of these forms, 2,520 (86.2 %) were retrieved, of which 152 were deemed ineligible because of patient age >75 years ($n = 90$), postoperative period <1 year ($n = 29$), co-resection of other organs ($n = 8$), and other factors ($n = 25$). As a result, 2,368 questionnaires (81 %) were decided as eligible for inclusion in various analyses related to the PGSAS-45. Of these, 393 patients who had undergone TG and 193 who had undergone PG were identified and retrieved for the current study (Fig. 1).

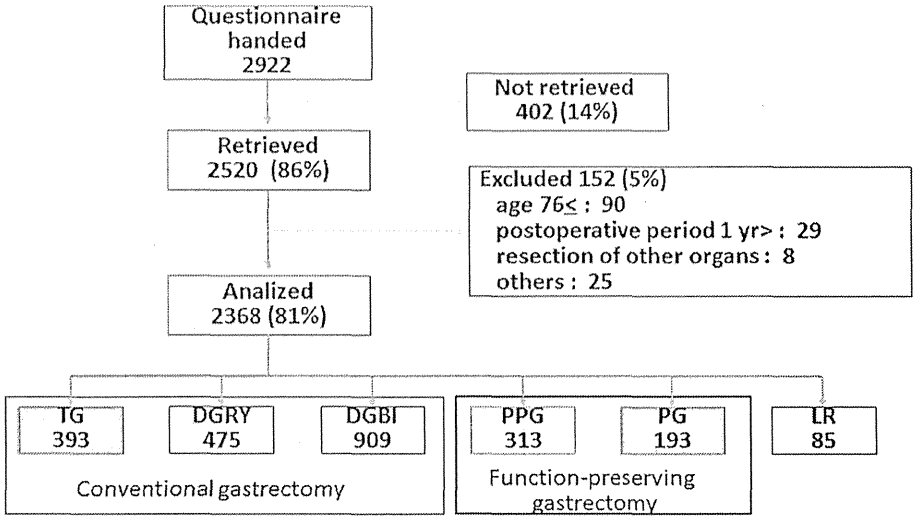
Patient eligibility criteria

Patient eligibility criteria were: (1) pathologically confirmed stage IA or IB gastric cancer; (2) first-time gastrectomy; (3) age ≥ 20 and ≤ 75 years; (4) no history of chemotherapy; (5) no known recurrence or distant metastasis; (6) gastrectomy conducted one or more years prior to the enrollment date; (7) performance status (PS) ≤ 1 on the Eastern Cooperative Oncology Group (ECOG) scale; (8) full capacity to understand and respond to the questionnaire; (9) no history of other diseases or operations that might influence the responses to the questionnaire; (10) no organ failure or mental illness; and (11) provision of written informed consent. Patients with dual malignancy or concomitant resection of other organs (with co-resection equivalent to cholecystectomy being the exception) were excluded.

QOL assessment

The PGSAS-45 is a newly developed, multidimensional QOL questionnaire (QLQ) based on the Short-Form Health Survey (SF-8) [16] and the Gastrointestinal Symptom Rating Scale (GSRS) [17–20]. The PGSAS-45 questionnaire consists of 45 questions, with eight items from the SF-8, 15 from the GSRS, and 22 clinically important items selected by the Japan Postgastrectomy Syndrome Working Party (Table 1). The PGSAS-45 questionnaire includes 23 items pertaining to postoperative symptoms (items 9–33), including 15 items from the GSRS and eight newly selected items. In addition, 12 questionnaire items pertaining to dietary intake, work, and level of satisfaction for daily life are included. Dietary intake items include five about the amount of food ingested (items 34–37 and 41) and three about the quality of ingestion (items 38–40). One questionnaire item pertains to work (item 42), while three address the level of satisfaction for daily life (items 42–45). For the 23 symptom items, a seven-grade (1–7) Likert scale is used. A five-grade (1–5) Likert scale is used for all other items except 1, 4, 29, 32, and 34–37. For items 1–8, 34, 35 and 38–40, higher scores indicate better conditions. For items 9–28, 30, 31, 33, and 41–45, higher scores indicate worse conditions. The main outcome measures were refined through consolidation and selection. Twenty-three symptom items were consolidated into seven symptom subscales by factor analysis, as listed in Tables 1 and 2. Assessment data include total symptom score, quality of ingestion subscale, level of satisfaction for daily life, physical component summary (PCS), and mental component

Fig. 1 Outline of the study



TG: Total gastrectomy with Roux-en-Y reconstruction
DGRY: Distal gastrectomy with Roux-en-Y reconstruction
DGBI: Distal gastrectomy with Billroth I reconstruction
PPG: Pylorus preserving gastrectomy
PG: Proximal gastrectomy
LR: Local resection

summary (MCS) of the SF-8 as main outcome measures. In addition, the following results were selected as main outcome measures: changes in body weight, amount of food ingested per meal, necessity for additional meals, ability to work, dissatisfaction with symptoms, dissatisfaction at the meal, and dissatisfaction at working. Each subscale score is calculated as the mean of composed items, and the total symptom score is calculated as the mean of seven symptom subscales (Table 2).

Study methods

This study utilized continuous sampling from a central registration system for participant enrollment. The questionnaire was distributed to all eligible patients as they presented to participating clinics. Patients were instructed to return completed forms to the data center. All QOL data from questionnaires were matched with individual patient data collected via case report forms.

This study was registered with the University Hospital Medical Information Network's Clinical Trials Registry (UMIN-CTR; registration number 000002116). It was approved by the ethics committees at all institutions. Written informed consent was obtained from all enrolled patients.

Statistics

In comparing patient QOLs after TG and PG, statistical methods included the t test and Chi square test. All outcome measures that exhibited significant difference in univariate analysis were further analyzed using multiple regression analysis. $p < 0.05$ was considered statistically significant. In the case of $p < 0.1$ by univariate analysis, Cohen's d was calculated. In the case of $p < 0.1$ in multiple regression analysis, standardization coefficient of regression (β), a decision coefficient (R^2), and the p value were calculated and shown in a table. Cohen's d, β, and R^2 measure effect sizes. Interpretation of effect sizes were 0.2 $\leq$ small, 0.5 $\leq$ medium, and 0.8 $\leq$ large in Cohen's d; 0.1 $\leq$ small, 0.3 $\leq$ medium, and 0.5 $\leq$ large in β; and 0.02 $\leq$ small, 0.13 $\leq$ medium, and 0.26 $\leq$ large in R^2.

StatView software for Windows Ver. 5.0 (SAS Institute Inc.) was used for all statistical analyses.

Results

Patient characteristics

Background data of both groups of patients are shown in Table 3. Reconstruction procedures were not regulated by the protocol, and depended on the principle of the institution or discretion of each surgeon. Consequently, whereas all patients treated by TG (393 patients) underwent Roux en Y reconstruction, the reconstruction after PG (193 patients) was varied and consisted of gastro-esophagostomy (115 patients), jejunal interposition (34 patients), and jejunal pouch interposition (44 patients).

Table 1 Structure of PGSAS-45

Domains	Subdomains	Items		Subscales
QOL	SF-8 (QOL)	1 Physical functioning*	Five-point or six-point Likert scale	Physical component summary*
		2 Role physical*		Mental component summary*
		3 Bodily pain*		
		4 General health*		
		5 Vitality*		
		6 Social functioning*		
		7 Role emotional*		
		8 Mental health*		
Symptoms	GSRS (symptoms)	9 Abdominal pains	Seven-point Likert scale except items 29 and 32	Esophageal reflux subscale (items 10, 11, 13, 24)
		10 Heartburn		Abdominal pain subscale (items 9, 12, 28)
		11 Acid regurgitation		Meal-related distress subscale (items 25–27)
		12 Sucking sensations in the epigastrium		Indigestion subscale (items 14–17)
		13 Nausea and vomiting		Diarrhea subscale (items 19, 20, 22)
		14 Borborygmus		Constipation subscale (items 18, 21, 23)
		15 Abdominal distension		Dumping subscale (items 30, 31, 33)
		16 Eructation		
		17 Increased flatus		Total symptom scale (above seven subscales)
		18 Decreased passage of stools		
		19 Increased passage of stools		
		20 Loose stools		
		21 Hard stools		
		22 Urgent need for defecation		
		23 Feeling of incomplete evacuation		
	Symptoms	24 Bile regurgitation		
		25 Sense of foods sticking		
		26 Postprandial fullness		
		27 Early satiation		
		28 Lower abdominal pains		
		29 Number and type of early dumping symptoms		
		30 Early dumping general symptoms		
		31 Early dumping abdominal symptoms		
		32 Number and type of late dumping symptoms		
		33 Late dumping symptoms		

Table 1 continued

Domains	Subdomains	Items	Subscales
Living status	Meals (amount) 1	34 Ingested amount of food per meal*	–
		35 Ingested amount of food per day*	
		36 Frequency of main meals	
		37 Frequency of additional meals	
	Meals (quality)	38 Appetite*	Quality of ingestion subscale* (items 38–40)
		39 Hunger feeling*	
		40 Satiety feeling*	
	Meals (amount) 2	41 Necessity for additional meals	–
	Social activity	42 Ability for working	–
QOL	Dissatisfaction (QOL)	43 Dissatisfaction with symptoms	Dissatisfaction for daily life subscale (items 43–45)
		44 Dissatisfaction at the meal	
		45 Dissatisfaction at working	

In items or subscales with * higher score indicates better condition. In items or subscales without * higher score indicates worse condition. Each subscale is calculated as the mean of composed items or subscales (except PCS and MCS of SF-8). Items 29 and 32 do not have score. Therefore, they were analyzed separately

Table 2 Domains and main outcome measures

Domains/subdomains		Main outcome measures
Symptoms	Subscales	Seven symptom subscales
		Esophageal reflux (10, 11, 13, 24), *abdominal pain* (9, 12, 28), *meal-related distress* (25–27), *indigestion* (14–17), *diarrhea* (19, 20, 22), *constipation* (18, 21, 23), *dumping* (30, 31, 33)
	Total	*Total symptom score*
Living status	Body weight	Change in body weight (%)*
	Meals (amount)	Ingested amount of food per meal* (34)
		Necessity for additional meals (41)
	Meals (quality)	*Quality of ingestion subscale** (38–40)
	Work	Ability for working (42)
QOL	Dissatisfaction	Dissatisfaction with symptoms (43), at the meal (44), at working (45)
		Dissatisfaction for daily life subscale (43–45)
	SF-8	*Physical component summary** (1–5)
		*Mental component summary** (4–8)

Main outcome measures that are italicized are composed of more than two items. In items or subscales with *, higher score indicates better condition; in items or subscales without *, higher score indicates worse condition. Each subscale is calculated as the mean of composed items or subscales

In the PG group, the mean postoperative period was significantly longer (TG 35.0 ± 24.6 months vs. PG 40.5 ± 28.1 months; $p = 0.0163$), and the rates of celiac and pyloric branch preservation were significantly higher, while the rates of laparoscopic approaches, D2 lymph node dissection, and combined resections were significantly lower than in the TG group.

QOL assessments

The results of the main outcome measures by univariate analysis are shown in Table 4. The body weight loss (TG 13.8 % vs. PG 10.9 %; $p = 0.0001$; Cohen's $d = 0.35$), diarrhea subscale (TG 2.3 vs. PG 2.0; $p = 0.0016$; Cohen's $d = 0.29$), and dumping subscale (TG 2.3 vs. PG 2.0; $p = 0.0118$; Cohen's $d = 0.24$) in the PG group were significantly lower than those in the TG group.

The necessity for additional meals was significantly lower in the PG group than in the TG group (TG 2.4 vs. PG 2.0; $p < 0.001$; Cohen's $d = 0.40$), which indicates a better status in the PG group. However, the constipation subscale value of the PG group was significantly higher than that of the TG group (TG 2.1 vs. PG 2.3; $p = 0.0145$; Cohen's $d = 0.21$), and the quality of ingestion subscale value of the PG group was significantly lower than that of

Table 3 Patient background and operative features

Type of gastrectomy	TG Mean (SD)	PG Mean (SD)	*p* value
Number of patients	393	193	
Postoperative period (months)	35.0 (24.6)	40.5 (28.1)	0.0163
Age	63.4 (9.2)	63.7 (7.7)	>0.1
Sex (male/female)	276/113	139/53	>0.1
BMI (preoperative)	23.0 (3.3)	23.1 (3.0)	>0.1
Operation background			
Approach (laparoscopic/open)	97/293	33/159	0.0364
Celiac branch of vagus (preserved/divided)	12/371	83/105	<0.0001
Pyloric branch of vagus (preserved/divided)	4/379	120/62	<0.0001
Extent of lymph node dissection			<0.0001
D2	164	7	
D1b	192	93	
D1a	28	72	
D1	4	7	
D1>	0	6	
None	0	0	
Combined resection			<0.0001
Cholecystectomy	83	14	
Splenectomy	52	2	
Others	2	1	
None	246	162	

TG Roux en Y reconstruction (n = 393); *PG* Gastro-esophagostomy (n = 115), Jejunal interposition (n = 34), Jejunal pouch interposition (n = 44)

Table 4 Main outcome measures by univariate analysis

Measure	TG		PG		Cohen's *d*	*p* value
	Mean	SD	Mean	SD		
Change in body weight*	−13.80 %	7.90 %	−10.90 %	8.20 %	0.35	0.0001
Esophageal reflux subscale	2.0	1.0	2.0	1.0		>0.1
Abdominal pain subscale	1.8	0.8	1.7	0.7		>0.1
Meal-related distress subscale	2.6	1.1	2.6	1.1		>0.1
Indigestion subscale	2.3	0.9	2.2	0.8		>0.1
Diarrhea subscale	2.3	1.2	2.0	1.0	0.29	0.0016
Constipation subscale	2.1	0.9	2.3	1.1	0.21	0.0145
Dumping subscale	2.3	1.1	2.0	1.0	0.24	0.0118
Total symptom score	2.2	0.7	2.1	0.7		>0.1
Ingested amount of food per meal*	6.4	1.9	6.5	1.9		>0.1
Necessity for additional meals	2.4	0.8	2.0	0.8	0.40	<0.0001
*Quality of ingestion subscale**	3.8	0.9	3.6	1.0	0.20	0.0281
Ability for working	2.0	0.9	2.0	0.9		>0.1
Dissatisfaction with symptoms	2.1	1.0	2.0	0.9		>0.1
Dissatisfaction at the meal	2.8	1.1	2.7	1.1		>0.1
Dissatisfaction at working	2.1	1.1	2.0	1.1		>0.1
Dissatisfaction for daily life subscale	2.3	0.9	2.2	0.9		>0.1
*Physical component summary**	49.6	5.6	49.5	6.1		>0.1
*Mental component summary**	49.2	6.0	49.0	6.0		>0.1

Integrated subscales are italicized in the table

For outcome measures with * higher score indicates better condition; for outcome measures without * higher score indicates worse condition

the TG group (TG 3.8 vs. PG 3.6; $p = 0.0281$; Cohen's $d = 0.20$), both of which indicate worse status of the PG group.

The physical and mental component summaries were not different in the two groups.

To eliminate confounding factors, multiple regression analysis was performed by adding postoperative period, age, sex, surgical approach, and celiac branch of vagal nerve preservation as explanatory variables (Table 5). Although the effect size of the advantages in PG over TG is relatively small, comparing the type of gastrectomy, the PG group was better than the TG group in body weight loss ($\beta = 0.148$; $p = 0.003$), diarrhea ($\beta = 0.097$; $p = 0.048$), dumping ($\beta = 0.106$; $p = 0.043$), and necessity for additional meals ($\beta = 0.192$; $p < 0.001$). Constipation and quality of ingestion, which were worse in the PG group by univariate analysis, showed no difference by multivariate analysis.

Multiple regression analysis revealed that the postoperative period influenced the extent of body weight loss ($\beta = 0.097$; $p = 0.030$), diarrhea ($\beta = -0.076$; $p = 0.078$), and quality of ingestion ($\beta = 0.092$; $p = 0.0365$). This means that as the postoperative period lengthens, body weight loss and diarrhea improve.

The age influenced the constipation subscale ($\beta = 0.147$; $p = 0.001$), dumping ($\beta = -0.114$; $p = 0.010$), and the quality of ingestion ($\beta = -0.126$; $p = 0.034$). At older ages, although dumping decreased, constipation increased.

Diarrhea was often found in men ($\beta = 0.137$; $p = 0.001$), and surgical approach and celiac branch preservation had little influence on any of the main outcome measures by multiple regression analysis.

Discussion

Optimal evaluation methods for postgastrectomy disorders are important for selecting and improving the operative procedures and maintaining the high QOL for gastric cancer patients [21–23]. The Japan Postgastrectomy Syndrome Working Party developed a questionnaire to evaluate general features; i.e., symptoms, living status, and QOL, among gastrectomized patients. Using this questionnaire, a nationwide, multi-institution surveillance study was performed. This was the first nationwide survey of its type and involved 52 medical institutions throughout Japan. The necessary QOL data were collected from 2,520 patients, and the final sample size, following exclusion and participant selection, was sufficient for statistical validity of this type of study.

In recent years, a tendency to increasing numbers of proximal gastric cancers has been reported, and early detection and potentially curative operations by PG for upper-third gastric cancers have been increasing [24, 25].

Table 5 Main outcome measures by multivariate analysis

Measure	Type of gastrectomy (TG)		Postoperative period		Age		Gender (male)		Approach (laparoscopic)		Celiac branch of vagus (preserved)		R^2	p value
	β	p value	β	p value	β	p value	β	p value	β	p value	β	p value		
Change in body weight	−0.148	0.003	0.097	0.030		>0.1		>0.1		>0.1		>0.1	0.037	0.0024
Diarrhea subscale	0.097	0.048	−0.076	0.078		>0.1	0.137	0.001		>0.1		>0.1	0.045	0.0002
Constipation subscale	−0.086	0.081		> 0.1	0.147	0.001		>0.1		>0.1		>0.1	0.030	0.0108
Dumping subscale	0.106	0.043		> 0.1	−0.114	0.010		>0.1		>0.1		>0.1	0.039	0.0027
Necessity for additional meals	0.192	0.0001		> 0.1	0.085	0.045		>0.1	0.083	0.058		>0.1	0.052	< 0.0001
*Quality of ingestion subscale**		>0.1	0.092	0.037	−0.126	0.003		>0.1		>0.1		>0.1	0.033	0.0056

Integrated subscales are italicized in the table

For outcome measures with * higher score indicates better condition; for outcome measures without * higher score indicates worse condition

If β is positive, the score of the outcome measure of the patients belonging to the category in brackets is higher in cases when the factor is a nominal scale, and the score of outcome measure of the patients with larger values is higher in cases when the factor is a numeral scale

In this study, the effect of tumor progression was removed by constraining patient selection to those with pathologic Stage IA/IB disease, and it is thought that accurate QOL comparison between operative procedures is possible under these circumstances. Although QOL scores usually depend on the time after surgery, Kobayashi et al. [11] reported that the QOL after gastrectomy was impaired during a few months after surgery, but more or less stabilized at around 6 months after surgery. This is the reason that, in this nationwide survey, we chose to evaluate patients who had lived for 12 months or more after surgery. In addition, we used multiple regression analysis with time relapse after surgery as one of variables so as to adjust this problem.

Whereas the reconstruction for TG was only by the Roux-en-Y method, the reconstructions of PG could be by esophagogastrostomy, jejunal interposition, and jejunal pouch interposition [6]. Because the best reconstruction for PG has not yet been established, various procedures are performed. However, as the gastric fundic gland region is preserved in PG, gastric-acid secretion and production of Castle intrinsic factor and ghrelin, a gut hormone known increase to appetite, are maintained [26, 27].

In the PG group, the rates of celiac and pyloric branch vagal nerve preservation were significantly higher, and the rates of laparoscopic approaches, D2 lymph node dissection, and combined resection were significantly lower than in the TG group. Standard TG is composed of more D1b dissection and sacrifice of the vagal nerve, often with combined resection, such as of the spleen and gallbladder [6, 28]. On the other hand, PG, which is a function-preserving operation, usually consists of less than D1b dissection and preservation of the vagal nerve [6]. The differences in the surgical background are caused by the procedure itself. Therefore, there seems to be no problem in comparing the QOL scores of these two groups.

From the results of the main outcome measures by univariate and multivariate analysis, body weight loss, diarrhea, dumping, and necessity for additional meals were significantly lower in the PG than in the TG group. Although esophageal reflux is common after PG [29, 30], various reconstruction methods have recently been described that reduce this problem [31, 32]. In this study, there was no difference in the esophageal reflux subscale values between the groups. This result suggests that PG is not necessarily disadvantageous with regard to reflux.

As three types of reconstruction with various modifications were performed with PG reconstruction, it is necessary to compare the three procedures in future studies. Dumping symptoms, such as early dumping with systemic symptoms, early dumping with abdominal symptoms, and late dumping, were examined in detail. Late dumping was significantly less common in the PG than in the TG group. Also, a tendency toward less early dumping with abdominal symptoms was seen in the PG group (data not shown). As a result, PG performed well on the dumping subscale. Although PG reflected the storage capacity and pylorus-preserving function, in TG, solid food is passed rapidly to the jejunum because of no storage ability [33].

Although the constipation subscale results and quality of ingestion subscale values were worse with PG than with TG by univariate analysis, multivariable regression analysis revealed that there were no statistical differences in these subscales as the result of the type of gastrectomy. Body weight loss and quality of ingestion subscale improved if the postoperative period was long. This means that gastrectomized patients adapt in some ways to the anatomic changes over time, even after more than 1 year following gastrectomy.

Multivariable regression analysis showed that dumping decreased and constipation increased with advancing age. This result may reflect the known intestinal peristaltic decrease in older patients [34–37].

By multivariable regression analysis, men were more likely to have diarrhea than women. This may be a consequence of the fact that the intestinal transit time is longer in women than in men at equivalent ages [37–39]. As for the effect of the surgical approaches and celiac branch preservation, no differences were found by multivariable regression analysis.

There were no statistical differences between the groups with regard to ability to work, dissatisfaction with symptoms, dissatisfaction at working, dissatisfaction for daily life subscale, PCS, or MCS. It is suggested that daily life is largely unchanged and that statistically different post-gastrectomy disorders do not have a major effect on adaptation.

In conclusion, although the effect size of the advantages of PG over TG is relatively small, our results indicate that PG is useful as a function-preserving procedure for early upper-gastric cancer. Although this study is limited in that it is retrospective and examines a single time point, it suggests the value of PG, use of which should be encouraged. To confirm this conclusion, a randomized study to determine the most desirable reconstruction for PG to achieve a good long-term QOL will have to be conducted using the PGSAS-45 questionnaire and successive endoscopic examinations.

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Conflict of interest The authors declare no conflicts of interest with regard to this manuscript.

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Original article

Neoadjuvant chemotherapy with S-1 and cisplatin followed by D2 gastrectomy with para-aortic lymph node dissection for gastric cancer with extensive lymph node metastasis

A. Tsuburaya[1], J. Mizusawa[2], Y. Tanaka[3], N. Fukushima[4], A. Nashimoto[5] and M. Sasako[6] on behalf of the Stomach Cancer Study Group of the Japan Clinical Oncology Group

[1]Shonan Kamakura General Hospital, Kamakura, [2]Japan Clinical Oncology Group Data Centre/National Cancer Centre, Tokyo, [3]Saitama Cancer Centre, Saitama, [4]Yamagata Prefectural Central Hospital, Yamagata, [5]Niigata Cancer Centre Hospital, Niigata, and [6]Hyogo College of Medicine, Nishinomiya, Japan

Correspondence to: Dr A. Tsuburaya, Shonan Kamakura General Hospital, 1370-1, Okamoto, Kamakura 2478533, Japan (e-mail: tuburayaa@gmail.com)

Background: Locally advanced gastric cancer with extensive regional and/or para-aortic lymph node (PAN) metastases is typically unresectable and associated with poor outcomes. This study investigated the safety and efficacy of S-1 plus cisplatin followed by extended surgery with PAN dissection for gastric cancer with extensive lymph node metastasis.

Methods: Patients with gastric cancer with bulky lymph node metastasis along the coeliac artery and its branches and/or PAN metastasis received two or three 28-day cycles of S-1 plus cisplatin, followed by gastrectomy with D2 plus PAN dissection. The primary endpoint was the percentage of complete resections with clear margins in the primary tumour (R0 resection). A target sample size of 50 with one-sided α of 0·105 and β of approximately 0·2 corresponded to an expected R0 rate of 65 per cent and a threshold of 50 per cent.

Results: Between February 2005 and June 2007, 53 patients were enrolled, of whom 51 were eligible. The R0 resection rate was 82 per cent. Clinical and pathological response rates were 65 and 51 per cent respectively. The 3- and 5-year overall survival rates were 59 and 53 per cent respectively. During chemotherapy, grade 3/4 neutropenia occurred in 19 per cent and grade 3/4 non-haematological adverse events in 15·4 per cent. The incidence of grade 3/4 adverse events related to surgery was 12 per cent. There were no reoperations or treatment-related deaths.

Conclusion: For locally advanced gastric cancer with extensive lymph node metastasis, 4-weekly S-1 plus cisplatin followed by surgery including PAN dissection was safe and effective for some patients. Further investigation of this treatment strategy is warranted.

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Introduction

Gastric cancer is the second most common malignancy in the world, and surgical resection remains a vital part of curative treatment for most patients despite recent advances in chemotherapy[1,2]. Cure is attained by complete resection of the primary tumour and regional lymph nodes (R0 resection)[3]. The tumour node metastasis (TNM) staging system of the International Union Against Cancer (UICC) defines para-aortic lymph nodes (PANs) as distant metastasis[4]. Although the Japanese Gastric Cancer Association (JGCA)[5] previously defined PANs as regional nodes, the latest JGCA classification[6] excluded PANs from regional lymph nodes on the basis that prophylactic PAN dissection for curable gastric cancer did not improve survival compared with D2 alone in the Japan Clinical Oncology Group (JCOG) 9501 trial[7,8]. In addition, to unify the gastric cancer staging system, the JGCA classification[6] adopted a large portion of the UICC TNM staging system.

A standard treatment strategy including a role for PAN dissection for more advanced nodal disease has not yet been established. Although bulky nodal involvement surrounding the coeliac artery and its branches is defined as regional metastasis (N2), R0 resection is rarely achieved. Once there is PAN metastasis the outlook is extremely poor,

even after R0 resection. According to collected data in the JCOG Stomach Cancer Study Group, 3-year survival of 86 patients with both clinical and pathological PAN metastasis who underwent surgery was only 5 per cent. In Western countries, tumours with PAN or bulky N2 disease are nearly always considered surgically incurable. Chemotherapy is often used with palliative intent, but patients rarely survive for more than 3 years in response to chemotherapy alone or non-curative surgery followed by chemotherapy[9].

A phase II study of neoadjuvant chemotherapy with irinotecan plus cisplatin followed by D2 surgery with PAN dissection (JCOG0001)[10] was terminated in 2003, owing to a treatment-related death rate greater than 5 per cent. The observed 3-year survival rate of 27 per cent was nevertheless promising, supporting the need for a safer and more effective regimen for these patients.

As a result of two randomized phase III trials (JCOG9912[11] and SPIRITS[12]), 5-weekly S-1 (tegafur, 5-chloro-2,4-dihydropyrimidine and potassium oxonate) plus cisplatin became the standard first-line chemotherapy in Japan. On the basis of achieving better responses with greater dose intensity in the neoadjuvant setting[13,14] and a subsequent study (JCOG0210)[15] confirming feasibility of a 4-weekly regimen, the present study investigated the efficacy and safety of neoadjuvant chemotherapy with 4-weekly S-1 plus cisplatin followed by D2 gastrectomy with PAN dissection for locally advanced gastric cancer with extensive lymph node metastasis.

Methods

Data handling was performed by the JCOG Data Centre. The study protocol was approved by the Clinical Trial Review Committee of the JCOG and the institutional review board at each participating centre. The study was undertaken in accordance with the Declaration of Helsinki and the Japanese Ethical Guidelines for Clinical Studies. This trial was registered at the University Hospital Medical Information Network Clinical Trials Registry as UMIN C000000094 (http://www.umin.ac.jp/ctr/).

Patients were recruited to the study between February 2005 and June 2007. Eligibility criteria are summarized in *Table 1*. Patients with advanced gastric cancer with bulky N2 and/or PAN metastasis who were suitable candidates for chemotherapy and surgery were enrolled. Informed consent was obtained from all patients. Patients with type 4 tumours (linitis plastica) were excluded.

Neoadjuvant chemotherapy

S-1 was given orally twice daily for the first 3 weeks of a 4-week cycle. The dose of S-1 administered was calculated according to the patient's body surface area as follows: less than 1·25 m^2, 40 mg; 1·25–1·5 m^2, 50 mg; and greater than 1·5 m^2, 60 mg. Cisplatin was given as an intravenous infusion of 60 mg/m^2 on day 8 of each cycle.

Between day 22 and 28 (or day 29 and 35 if the administration of cisplatin was delayed for more than 7 days) of the second cycle of chemotherapy, resectability was evaluated based on contrast-enhanced computed tomography (CT). If curative resection was considered difficult (unlikely to achieve R0), but there was objective evidence of shrinkage of nodal disease without progressive

Table 1 Eligibility criteria

Inclusion criteria
Histologically proven gastric adenocarcinoma
Type 0, 1, 2, 3 or 5
Bulky N2 (≥ 3 cm, or at least two adjacent tumours ≥ 1·5 cm) and/or PAN (≥ 1 cm) metastases
PAN and/or bulky N2 metastases confirmed by contrast-enhanced CT
No distant metastasis (M0) except for PAN confirmed by contrast-enhanced CT
No more than 3 cm invasion to oesophagus
Peritoneal lavage cytology-negative for cancer cells by staging laparoscopy
Aged 20–75 years
ECOG performance status 0 or 1
No history of chemotherapy and radiotherapy for any cancer, and surgery for stomach
No previous surgery for gastric cancer except bypass surgery and endoscopic resection
Fair oral intake with or without bypass surgery
Sufficient organ function
WBC count ≥ 4000/mm^3 and ≤ 12 000/mm^3
Platelet count ≥ 100 000/mm^3
AST and ALT ≤ 100 units/l
Total bilirubin ≤ 1·5 mg/dl
Creatinine ≤ 1·5 mg/dl and creatinine clearance ≥ 60 ml/min
Haemoglobin ≥ 8·0 g/dl
Written informed consent
Exclusion criteria
Synchronous or metachronous (within 5 years) malignancy other than carcinoma *in situ*
Pregnancy or lactation
Mental illness that may hinder participation in study
Need for continuous treatment with corticosteroid, flucytosine, phenytoin or warfarin
Allergic reactions to iodine
Severe co-morbidities such as ileus, pneumonitis, ischaemic heart disease, liver cirrhosis or active hepatitis
Myocardial infarction within 6 months
Unable to complete protocol treatment as judged by attending physicians

N2, second-tier lymph nodes along the coeliac artery and its branches; PAN, para-aortic lymph node; CT, computed tomography; ECOG, Eastern Cooperative Oncology Group; WBC, white blood cell; AST, aspartate aminotransferase; ALT, alanine aminotransferase.