

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

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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

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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

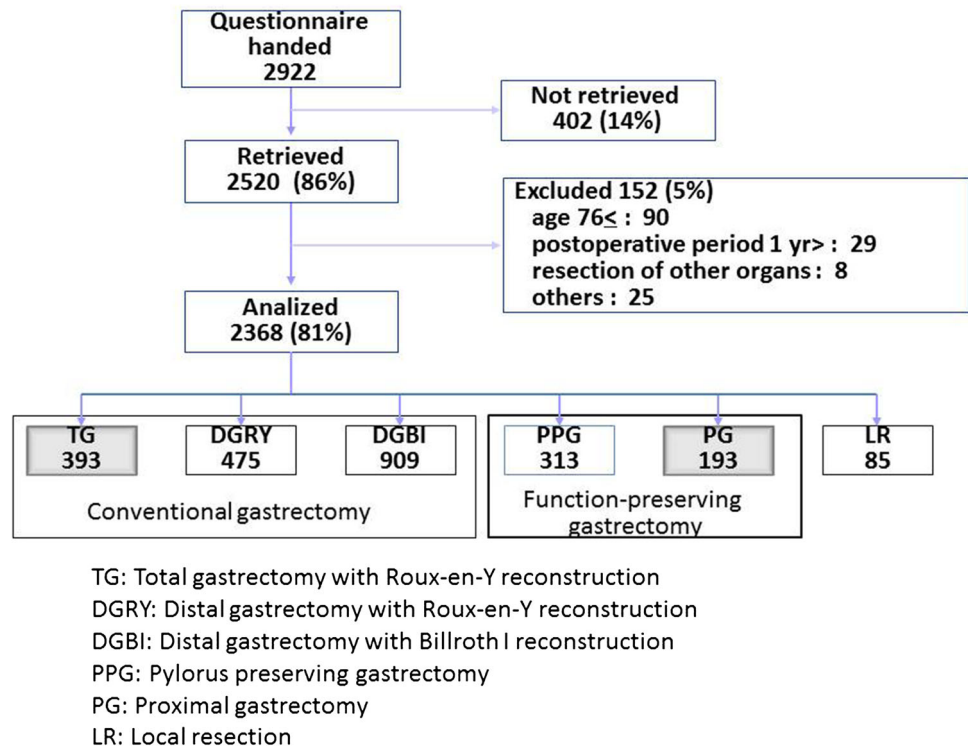
result, 2,368 questionnaires (81 %) were decided as eligible for inclusion in various analyses related to the PGSAS-45. Of these, 393 patients who had undergone TG and 193 who had undergone PG were identified and retrieved for the current study (Fig. 1).

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

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-esophagotomy (115 patients), jejunal interposition (34 patients), and jejunal pouch interposition (44 patients).

Table 1 Structure of PGSAS-45

Domains	Subdomains	Items	Five-point or six-point Likert scale	Subscales
QOL	SF-8 (QOL)	1 Physical functioning* 2 Role physical* 3 Bodily pain* 4 General health* 5 Vitality* 6 Social functioning* 7 Role emotional* 8 Mental health*		Physical component summary* Mental component summary*
Symptoms	GSRS (symptoms)	9 Abdominal pains 10 Heartburn 11 Acid regurgitation 12 Sticking sensations in the epigastrium 13 Nausea and vomiting 14 Borborygmus 15 Abdominal distension 16 Eructation 17 Increased flatus 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 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	Seven-point Likert scale except items 29 and 32	Esophageal reflux subscale (items 10, 11, 13, 24) Abdominal pain subscale (items 9, 12, 28) Meal-related distress subscale (items 25–27) Indigestion subscale (items 14–17) Diarrhea subscale (items 19, 20, 22) Constipation subscale (items 18, 21, 23) Dumping subscale (items 30, 31, 33) Total symptom scale (above seven subscales)
	Symptoms			

Table 1 continued

Domains	Subdomains	Items	Subscales
Living status	Meals (amount) 1	34 Ingested amount of food per meal*	Quality of ingestion subscale* (items 38–40)
		35 Ingested amount of food per day*	
	36 Frequency of main meals		
	37 Frequency of additional meals		
	38 Appetite*		
Meals (quality)	39 Hunger feeling*	Five-point Likert scale	
	40 Satiety feeling*		
QOL	Meals (amount) 2	41 Necessity for additional meals	Dissatisfaction for daily life subscale (items 43–45)
		42 Ability for working	
	Social activity	43 Dissatisfaction with symptoms	
		Dissatisfaction (QOL)	
	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	Seven symptom subscales <i>Esophageal reflux</i> (10, 11, 13, 24), <i>abdominal pain</i> (9, 12, 28), <i>meal-related distress</i> (25–27), <i>indigestion</i> (14–17), <i>diarrhea</i> (19, 20, 22), <i>constipation</i> (18, 21, 23), <i>dumping</i> (30, 31, 33)
Living status	Total <i>Total symptom score</i>
	Body weight Change in body weight (%)*
	Meals (amount) Ingested amount of food per meal* (34) Necessity for additional meals (41)
	Meals (quality) <i>Quality of ingestion subscale*</i> (38–40)
QOL	Work Ability for working (42)
	Dissatisfaction Dissatisfaction with symptoms (43), at the meal (44), at working (45) <i>Dissatisfaction for daily life subscale</i> (43–45)
	SF-8 <i>Physical component summary*</i> (1–5) <i>Mental component summary*</i> (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)	<i>p</i> 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), Jejunum interposition (*n* = 34), Jejunum pouch interposition (*n* = 44)

Table 4 Main outcome measures by univariate analysis

Measure	TG		PG		Cohen's <i>d</i>	<i>p</i> value
	Mean	SD	Mean	SD		
Change in body weight*	-13.80 %	7.90 %	-10.90 %	8.20 %	0.35	0.0001
<i>Esophageal reflux subscale</i>	2.0	1.0	2.0	1.0		>0.1
<i>Abdominal pain subscale</i>	1.8	0.8	1.7	0.7		>0.1
<i>Meal-related distress subscale</i>	2.6	1.1	2.6	1.1		>0.1
<i>Indigestion subscale</i>	2.3	0.9	2.2	0.8		>0.1
<i>Diarrhea subscale</i>	2.3	1.2	2.0	1.0	0.29	0.0016
<i>Constipation subscale</i>	2.1	0.9	2.3	1.1	0.21	0.0145
<i>Dumping subscale</i>	2.3	1.1	2.0	1.0	0.24	0.0118
<i>Total symptom score</i>	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
<i>Quality of ingestion subscale*</i>	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
<i>Dissatisfaction for daily life subscale</i>	2.3	0.9	2.2	0.9		>0.1
<i>Physical component summary*</i>	49.6	5.6	49.5	6.1		>0.1
<i>Mental component summary*</i>	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 ($\beta = 0.092$; $p = 0.037$). 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 ($\beta = -0.126$; $p = 0.003$). 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	>0.1	>0.1	>0.1	>0.1	0.037	0.0024
<i>Diarrhea subscale</i>	0.097	0.048	-0.076	0.078	>0.1	0.137	0.001	0.137	0.001	>0.1	>0.1	>0.1	0.045	0.0002
<i>Constipation subscale</i>	-0.086	0.081	>0.1	>0.1	0.147	0.001	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1	0.030	0.0108
<i>Dumping subscale</i>	0.106	0.043	>0.1	>0.1	-0.114	0.010	>0.1	>0.1	>0.1	>0.1	>0.1	>0.1	0.039	0.0027
Necessity for additional meals	0.192	0.0001	>0.1	>0.1	0.085	0.045	>0.1	0.083	0.058	>0.1	>0.1	>0.1	0.052	<0.0001
<i>Quality of ingestion subscale*</i>	>0.1	>0.1	0.092	0.037	-0.126	0.003	>0.1	>0.1	>0.1	>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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