Table 3 Univariate and multivariate analyses of clinical risk factors for a significant loss of skeletal muscle after TG

Characteristics	Univariate analysis			Multivariate analysis		
	No. of patients	No. of patients having loss of skeletal muscle >10 %	*P* value	HR	95 % CI	*P* value
Age (years)						
<65	44	12	0.7191	1	0.194–2.462	0.5694
≥65	58	14		0.692		
Sex						
Male	71	18	0.9614	1	0.207–5.991	0.9014
Female	31	8		1.112		
Diabetes mellitus						
Present	9	4	0.1839	1	0.019–1.086	0.0601
Absent	93	22		0.143		
Postoperative complications according to the Clavien–Dindo classification						
Grade ≤II	94	24	0.9736	1	0.052–6.291	0.6469
Grade ≥III	8	2		0.571		
Pathological stage						
I	50	3	0.0001	1	0.178–11.14	0.7457
II/III	52	23		1.408		
Adjuvant chemotherapy						
None or <6 months	64	4	<0.0001	1	3.487–203.1	0.0016
≥6 months	38	22		26.61		
Preoperative SMI (cm^2/m^2)						
<45	46	10	0.4319	1	0.382–11.39	0.3965
≥45	56	16		2.084		
Preoperative ATI (cm^2/m^2)						
<75	54	10	0.0901	1	0.761–11.21	0.1182
≥75	48	16		2.921		

TG total gastrectomy, *SMI* skeletal muscle index, *ATI* adipose tissue index, *HR* hazard ratio, *CI* confidence interval

Table 4 Percent decrease in body mass components after TG: effect of adjuvant chemotherapy of ≥6 months

Body mass components (% decrease after TG)	Adjuvant chemotherapy of ≥6 months		*P* value
	Present ($n = 38$)	Absent ($n = 64$)	
Body weight	15.3 ± 8.66	14.4 ± 8.25	0.5838
SMI	10.2 ± 6.46	3.83 ± 5.84	<0.001
ATI	65.3 ± 38.1	66.1 ± 35.1	0.9324

following gastrectomy. In this study, the postoperative changes in body composition after TG consisted mainly of the depletion of fat, as seen in previous studies [13–15, 24]. In fat tissue, a reduction of 56.1 ± 36.4 % in subcutaneous plus intramuscular adipose tissue and a reduction of 77.4 ± 39.0 % in visceral adipose tissue were observed in this study (data not shown). Previous CT image analyses reported decreases in subcutaneous adipose tissue and visceral adipose tissue of approximately 20–40 % and 50–60 %, respectively [25, 26]. These findings suggest that the mass of visceral adipose tissue decreases more than that of subcutaneous plus intramuscular adipose tissue after TG. It has been speculated that the decrease in visceral adipose tissue is caused predominantly by the withdrawal of hypothetical gastric hormonal factors, which could increase fat mobilization or inhibit fat deposition within the visceral cavity [25].

Twenty-six patients (25.5 %) showed a significant loss of skeletal muscle of more than 10 % at 1 year after TG. Although no other studies have evaluated changes in skeletal muscle mass following gastrectomy using CT image analysis, one study using multifrequency bioelectrical impedance analysis reported an 8 % loss of body protein at 6 months after TG [15]. In addition, among critically ill patients admitted to the intensive care unit, >10 % loss in rectus femoris cross-sectional area was considered as clinically relevant muscle wasting [27]. Therefore, we defined a significant loss of skeletal muscle mass as a decrease in L3 skeletal muscle area of at least 10 % of the preoperative value.

Adjuvant chemotherapy with S-1, an oral 5-fluorouracil (5-FU) agent, for ≥6 months was identified as the single independent risk factor for a significant loss of skeletal muscle in the multivariate analysis, whereas sex, age, presence of DM, postoperative complications, pathological stage, and preoperative SMI and ATI were not associated with a significant loss of skeletal muscle (Table 3). When comparing body composition at 1 year after TG between patients who had received adjuvant S-1 chemotherapy for ≥6 months with those who did not (Table 4), there were no significant differences in body weight and ATI decreases, whereas SMI decreased significantly in patients receiving adjuvant S-1 chemotherapy ($P < 0.001$). This finding could suggest that the amount of oral intake had less influence on the loss of skeletal muscle than adjuvant chemotherapy. In addition, Awad et al. [23] demonstrated a significant association of preoperative 5-FU-based chemotherapy with reductions in fat-free mass of as much as 6 % in patients with esophagogastric cancer, using the method employed in this study of analyzing transverse CT images at the third lumbar vertebral level. These combined results suggest that 5-FU might affect the loss of skeletal muscle, although the precise mechanism is unknown. Another anticancer agent, doxorubicin, has recently been shown to cause a catabolic response in skeletal muscle through oxidative stress by elevating the serum levels of inflammatory cytokines, especially tumor necrosis factor (TNF), resulting in a loss of skeletal muscle mass leading to weakness and fatigue [28]. One study reported delayed skeletal muscle dysfunction in survivors of childhood acute lymphoblastic leukemia, in which repeated administration of combination chemotherapy drugs (e.g., vincristine, glucocorticoids, doxorubicin, methotrexate, asparaginase) was strongly implicated [29]. These findings suggest that chemotherapy could affect skeletal muscle loss.

On the other hand, gastrointestinal toxicities such as nausea and vomiting are frequently observed in patients receiving chemotherapy after gastrectomy [30–32]. They could cause appetite loss and decreased physical activity, and a lifestyle with lesser physical activity could potentially contribute to the loss of skeletal muscle mass. In this context, Abdiev et al. [33] raised the possibility, in patients with early gastric cancer, that laparoscopic distal gastrectomy may be beneficial in maintaining muscle mass because of an early recovery to preoperative physical activity. However, it remains uncertain whether the laparoscopic approach could prevent skeletal muscle loss even in patients receiving postoperative chemotherapy after TG.

In this study, 38 of 52 (73.1 %) patients with pathological stage II/III disease tolerated adjuvant S-1 therapy for ≥6 months after surgery. The Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) [34] reported a similar compliance (77.9 %) with S-1 therapy for ≥6 months, suggesting that our patients were not exceptional in this regard.

With respect to the appropriate duration of adjuvant chemotherapy with S-1, the Japan Clinical Oncology Group (JCOG) has launched a phase III trial comparing 6 versus 12 months S-1 administration in stage II gastric cancer patients [35]. A shortened period of S-1 might help early recovery of physical activity through diminishing skeletal muscle loss.

This study showed that TG caused significant postoperative changes in body composition and particularly pronounced reductions in skeletal muscle mass in patients receiving extended adjuvant chemotherapy. Marked decreases in skeletal muscle mass have been associated with poor functional status and high mortality in cancer patients, including those with gastric cancer [36, 37]. Preventing the loss of skeletal muscle mass after TG may lead to improved outcomes and better quality of life. In our patients, skeletal muscle loss had no impact on survival (data not shown). Skeletal muscle depletion in relapsed patients such as those with cancer cachexia [37] might have a completely different meaning as a prognostic factor from that caused by chemotherapy in non-relapsed patients.

Although no nutritional interventions have yet been proven effective for preventing the loss of skeletal muscle after TG, perioperative enteral nutrition enriched with eicosapentaenoic acid (EPA) was shown to preserve lean body mass in patients undergoing esophageal cancer surgery [38]. A phase III trial is currently ongoing to evaluate the effects of perioperative nutrition enriched with EPA on body weight and lean body mass after TG for T2–T4a gastric cancer [39]. Another promising approach demonstrated that short-term administration of ghrelin maintained lean body mass at 14 days after TG [40]. An oral ghrelin mimetic over 12 months significantly increased fat-free mass in healthy older adults [41]. These results suggest that ghrelin might become a potential candidate for preventing skeletal muscle loss after TG.

Although to the best of our knowledge this is the first study examining skeletal muscle loss after TG and its exacerbation by extended adjuvant chemotherapy, the retrospective nature of this study performed in a single institution and the relatively small size of the studied population warrant further studies.

In conclusion, skeletal muscle loss was exacerbated by extended adjuvant chemotherapy after TG. Appropriate nutritional intervention should be identified to maintain skeletal muscle mass and achieve improved outcomes.

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

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Efficacy and long-term outcome of pre-emptive endoscopic resection and surgery for multiple synchronous gastric cancers

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Abstract
Background In cases of synchronous gastric cancers (SGC) that include one for surgical indication and another for endoscopic resection (ER) in two different regions of the stomach, patients can avoid total gastrectomy and undergo subtotal gastrectomy following successful pre-emptive ER. The aim of this study was to evaluate the feasibility and efficacy of pre-emptive endoscopic resection and surgery (PRES) with curative intent for such SGCs.
Methods Between September 2002 and December 2012, 34 patients with SGCs (72 lesions) underwent PRES. Our institutional principals of PRES ensure the following: (1) treatment with curative intent, (2) multiple lesions indicated for ER and surgery, (3) evasion of TG following successful pre-emptive ER, (4) exclusion of type 4 and large type 3 (>80 mm) tumors, and (5) nonemergent cases such as hemorrhage, perforation, and obstruction. Clinicopathological characteristics and technical data were evaluated for all patients, and long-term outcomes were analyzed in patients who obtained curative ER and underwent subtotal gastrectomy.
Results Curative ER was obtained in 31 patients (91.1 %), and subtotal gastrectomy was performed a median of 44 days after ER. Final stages were as follows: stage I, 25 patients (80.6 %); stage II, four patients (12.9 %); stage III, one patient (3.2 %); and stage IV, one patient (3.2 %). The 5-year overall and cause-specific survival rates were 96.3 % (95 % confidence interval 89.4–100 %) and 100 %, respectively.
Conclusions PRES was feasible and effective as the first treatment of choice for multiple SGCs. PRES enables minimally invasive surgery with promising oncological outcomes.

Keywords Gastric cancer · Endoscopic resection · Gastrectomy · Minimally invasive surgery · Quality of life

Prognoses of patients with gastric cancer have improved with earlier diagnosis and advances in multimodal treatments. However, surgical resection remains the only curative option for patients with invasive gastric cancers [1]. The standard gastrectomy for gastric cancer is defined by resection of at least two-thirds of the stomach and dissection of D2 lymph nodes [2], and it includes total gastrectomy (TG) and distal gastrectomy (DG). Proximal gastrectomy (PG) is often chosen for early gastric cancers in the upper third of the stomach without lymph node metastases. Previous reports suggest that subtotal gastrectomy, including DG and PG, improves alimentary symptoms and avoids functional limitations in comparison with TG [3–5]. Thus, subtotal gastrectomy is usually performed when a satisfactory resection margin can be obtained.

Endoscopic resection (ER) is considered to be a radical treatment for early gastric cancers, which have a very low risk of lymph node metastasis [6–8]. ER, particularly

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Table 1 Absolute and expanded indications for endoscopic resection

Absolute indication
Differentiated-type intramucosal cancer ≤20 mm in size without ulceration
Expanded indications
Differentiated-type intramucosal cancer ≥20 mm in size without ulceration
Differentiated-type intramusocal cancer ≤30 mm in size with ulceration
Undifferentiated-type intramucosal cancer ≤20 mm in size without ulceration

(from reference 2)

Table 2 Histopathological criteria for curative endoscopic resection

En bloc resection, negative horizontal and vertical margin, no lymphovascular infiltration, and
Within absolute indication, or
Within expanded indications, or
Differentiated-type submucosal superficial cancer (SM1)† ≤30 mm in size

† Less than 500 microns from the muscularis mucosae. (from reference 2)

endoscopic submucosal dissection (ESD), is a standard therapy in Japan and Korea and is increasingly used globally [9, 10]. The Japanese Gastric Cancer Association has established an indication for ER (Table 1), and histopathological curative criteria (Table 2) have been developed in consideration of the incidence of lymph node metastasis [2]. ER has lower risks of alimentary problems, functional limitations, and medical costs than surgery. Nonetheless, both ER and surgery are associated with similar long-term survival outcomes and tumor recurrence if lesions meet curative criteria [11, 12].

The prevalence of multiple synchronous gastric cancers is reportedly 2–14 % [13, 14]. In cases of synchronous gastric cancers that include surgically resectable lesions, lesions are often removed as a whole even if other lesions are within the indication for ER. Nonetheless, TG is required when synchronous lesions are located at two different regions, such as in the upper third and lower third of the stomach. However, pre-emptive ER for ER-indicated lesions may provide chances for patients to avoid TG and to preserve the digestive function of the stomach. Subtotal gastrectomy may be warranted following successful pre-emptive ER. We have practiced the strategy of pre-emptive endoscopic resection and surgery (PRES) with curative intent for such synchronous gastric cancers. However, the clinical impact of this strategy remains unclear. Therefore, the present study aimed to evaluate the feasibility and efficacy of PRES.

Materials and methods

Patients

We enrolled 34 patients with multiple synchronous gastric cancers (72 lesions, 2.1 lesions/patient) who underwent PRES at the Shizuoka Cancer Center (SCC) between September 2002 and December 2012. In this single-center cohort study, data were prospectively collected from the institutional database and were retrospectively analyzed. All the patients provided written informed consent, and the study protocol was approved by the institutional review board of SCC (institutional code number, 25-J127-25-1-3). Before treatment, all the patients underwent upper endoscopy, upper gastrointestinal tract radiography, and computerized tomography (CT). Our institutional principals of PRES ensure the following: (1) treatment with curative intent, (2) multiple lesions indicated for ER and surgery, (3) evasion of TG following successful pre-emptive ER, (4) exclusion of type 4 and large type 3 (>80 mm) tumors, and (5) nonemergent cases such as hemorrhage, perforation, and obstruction. Treatment plans were discussed and agreed upon by gastroenterologists and surgeons at our institutional cancer board. Patients who previously underwent chemotherapy and/or radiation therapy for gastric cancers and those who did not undergo TG even after noncurative ER were excluded from the present study.

Pre-emptive ER

Tumors for ER indication included 38 lesions and were all resected using ESD. All operators were experienced endoscopists. A solution of mixed saline and hyaluronate was used to create submucosal cushions. The mucosa around the lesion was circumferentially cut, and the submucosa was dissected using an insulation-tipped knife (IT-knife or IT-Knife 2; Olympus Medical, Tokyo, Japan). These techniques have been previously described in detail [15–17]. Perforations were diagnosed by endoscopy or by the presence of free air on chest and abdominal X-rays after ESD. Delayed bleeding was defined as clinical evidence of bleeding after ESD that required endoscopic hemostasis. Procedure times, adverse events, en bloc resection rates, and curative resection rates were evaluated in all the patients.

Histopathological evaluations

ER specimens were fixed in 10 % formalin solution and were sectioned at 2-mm intervals. Specimens were embedded in paraffin and were cut into 3-μm-thick sections for hematoxylin and eosin staining. Detailed observations of vascular involvement were performed using Elastica–

Masson staining and immunostaining with D2-40 antibodies (Dako, Tokyo, Japan). Pathological diagnoses were made by experts of gastrointestinal pathology according to Japanese classifications [2]. The criteria for declaring R0 resection were defined as en bloc resection with lateral and vertical margins that are free from tumor cells. Curative resection was evaluated on the basis of histopathological curative criteria (Table 2).

Surgery

Tumors for surgical indication included 34 lesions. After curative resection by ER, subtotal gastrectomy and lymph node dissection were performed. Suitable types of surgery and lymphadenectomy were selected according to the Japanese gastric cancer treatment guidelines [2]. PG was indicated for clinical T1N0 tumors in the upper third of the stomach when more than lower two-thirds of the stomach could be preserved. DG was chosen for tumors in the lower two-thirds of the stomach when a satisfactory proximal resection margin could be obtained. Since 2008, pylorus-preserving gastrectomy has been performed for clinical T1N0 tumors in the middle third of the stomach. However, TG and lymph node dissections were performed after failure of curative resection in lesions for ER.

Follow-up

After surgery, the patients were intensively followed up at SCC and in cooperation with their family doctors. All the patients underwent physical examinations and blood tests at the 1st, 3rd, 6th, and 12th month and every 12 months thereafter. All the patients who underwent R0 surgical resections were subjected to annual esophagogastroduodenoscopy (EGD) and CT. Some patients with stage II or III disease underwent CT once in 6 months. Since December 2006, postoperative adjuvant chemotherapy was administered to patients with stage II or III disease (except for T3N0 cases). Metachronous lesions were diagnosed using endoscopic biopsy specimens. Recurrence of lymph node metastases and distant metastases was confirmed on the basis of imaging.

Statistical analysis

All variables are presented as the median and range. Overall and cause-specific survival curves were calculated using the Kaplan–Meier method with the date of pre-emptive ER as the starting point. Statistical analyses were performed using SPSS statistical analysis software (IBM SPSS Statistics, version 21) and R (free software programming language, version 3.0.2).

Results

Characteristics of the study population

A total of 34 patients with 72 synchronous gastric cancers were recruited, including 31 males and 3 females. The median patient age was 68 years (range, 48–83 years). The clinicopathological characteristics of the patients and lesions are summarized in Table 3. Two patients had additional hypopharyngeal cancers and 1 had gingival cancer. Among 38 endoscopically resected lesions, 24 lesions (63.2 %) were located in the upper third, 10 (26.3 %) were located in middle third, and 4 (10.5 %) were located in lower third of the stomach. Clinical indications for ER were divided into absolute indications for 29 lesions (76.3 %) and expanded indications for 9 lesions (23.7 %). Among 34 surgically resected lesions, 8 (23.5 %) were located in the upper third, 15 (44.1 %) were located in the middle third, and 11 (32.4 %) were located in the lower third of the stomach. Clinical stages at pretreatment evaluation were as follows: stage I, 28 patients (82.4 %); stage II, 5 patients (14.7 %); and stage III, 1 patient (2.9 %).

Results of pre-emptive ER

The results of pre-emptive ER are summarized in Table 4. The median procedure time was 52 min (range, 1–155 min). The median size of endoscopically resected tumors was 20 mm (range, 3–78 mm), and 31 lesions (81.6 %) were mucosal cancers and 7 lesions (18.4 %) were submucosal cancers (1 lesion had invaded to a depth $\geq$ 500 μm). En bloc plus R0 resection was achieved in 37 lesions (97.4 %). The remaining case was positive for cancer cells at the vertical margin. Curative ER was obtained for 35 lesions (92.1 %). Perforations and delayed bleeding occurred in 5 (13.2 %) and 3 (7.9 %) lesions, respectively. All adverse events were managed endoscopically, and no patient required blood transfusions. The median hospital stay after ER was 5 days (range, 4–20 days).

Results of gastrectomy

Thirty-one patients underwent subtotal gastrectomy after curative ER. DG was performed in 23 patients (74.2 %), and PG was performed in 8 patients (25.8 %; Table 5). Corresponding locations of ER lesions are shown in Fig. 1. The median period from ER to gastrectomy was 44 days (range, 7–101 days). The median operation time and estimated blood loss were 199 min (range, 140–316 min) and 285 ml (range, 10–929 ml), respectively. The median size of surgically resected tumors was 38 mm (range, 14–70 mm), and 6 lesions (19.4 %) were mucosal cancers,

Table 3 Clinicopathological characteristics of patients with synchronous gastric cancer

Patients/lesions, *n*	34/72
Age, median (range), years	68 (48–83)
Gender, *n* (%)	
Male	31 (91.2)
Female	3 (8.8)
ASA physical status classification†, *n* (%)	
Class 1	10 (29.4)
Class 2	18 (52.9)
Class 3	6 (17.6)
Concomitant disease, *n* (%)	
Cardiovascular disease	5 (14.7)
Diabetes	6 (17.6)
Respiratory disease	2 (5.9)
Liver disease	2 (5.9)
Other cancer	3 (8.8)
Endoscopically resected lesions ($n = 38$)	
Lesion location, *n* (%)	
Upper third	24 (63.2)
Middle third	10 (26.3)
Lower third	4 (10.5)
Macroscopic type, *n* (%)	
Elevated (0–I, 0–IIa)	16 (42.1)
Flat and depressed (0–IIb, 0–IIc)	22 (57.9)
Clinical indications for endoscopic resection, n (%)	
Absolute indication	29 (76.3)
Expanded indication	9 (23.7)
Surgically resected lesions ($n = 34$)	
Lesion location, *n* (%)	
Upper third	8 (23.5)
Middle third	15 (44.1)
Lower third	11 (32.4)
Macroscopic type, *n* (%)	
Elevated (0–I, 0–IIa)	5 (14.7)
Flat and depressed (0–IIb, 0–IIc)	23 (67.6)
Type 1	0 (0)
Type 2	4 (11.8)
Type 3	2 (5.9)
Clinical stage‡, *n* (%)	
I	28 (82.4)
II	5 (14.7)
III	1 (2.9)

† *ASA* American society of anesthesiologists

‡ Clinical staging was classified according to the 7th UICC; I, IA, or IB; II, IIA, or IIB; III, IIIA, IIIB, or IIIC

17 (54.8 %) were submucosal cancers, and 8 (25.8 %) were advanced cancers. Lymph node metastasis was observed in 11 patients (35.5 %). In 1 patient, cancer cells were detected using peritoneal lavage cytology. Final stages were as follows: stage I, 25 patients (80.6 %); stage II, 4 patients (12.9 %); stage III, 1 patient (3.2 %); and stage IV, 1 patient (3.2 %).

Table 4 Results of endoscopic resection (34 patients/38 lesions)

Procedure time, median (range), min	52 (10–155)
Adverse events, *n* (%)	
Perforation	5 (13.2)
Delayed bleeding	3 (7.9)
Hospital stay after ER, median (range), day	5 (4–20)
Tumor size, median (range), mm	20 (3–78)
Histological type, *n* (%)	
Differentiated type	38 (100)
Undifferentiated type	0 (0)
Depth of tumor, *n* (%)	
pT1a	31 (81.6)
pT1b	
SM1 (Invasion depth < 500 μm)	6 (15.8)
SM2 (Invasion depth ≥ 500 μm)	1 (2.6)
Ulceration, *n* (%)	6 (15.8)
Lymphovascular infiltration, *n* (%)	1 (2.6)
En bloc resection plus R0 resection, *n* (%)	37 (97.4)
Curability, *n* (%)	
Curative resection	35 (92.1)
Noncurative resection	3 (7.9)

ER endoscopic resection

Long-term outcomes after PRES

A flow chart of the clinical course is shown in Fig. 2. The group of 31 patients who underwent subtotal gastrectomy was followed up for a median period of 48 months (range, 14–111 months), during which metachronous lesions were detected in 2 patients (6.5 %) and liver metastasis was detected in 1 patient (3.2 %; Table 6). The metachronous lesions were mucosal and were treated endoscopically. The liver metastasis was found in a patient with mucosal cancer for pre-emptive ER and submucosal cancer with lymph node metastasis for surgery, and the final stage was IB. The recurrence site was surgically resected. No death occurred because of gastric cancer, and 1 patient died of other cause (gingival cancer). The 5-year overall and cause-specific survival rates were 96.3 % (95 % confidence interval 89.4–100 %) and 100 %, respectively (Fig. 3).

Discussion

In the present study, we present the results of PRES, which is a new strategy that uses pre-emptive ER to minimize

Table 5 Results of gastrectomy after curative endoscopic resection ($n = 31$)

Period from ER to gastrectomy, median (range), day	44 (7–101)
Operation, *n* (%)	
Distal gastrectomy	23 (74.2)
Proximal gastrectomy	8 (25.8)
Operation time, median (range), min	199 (140–316)
Blood loss, median (range), ml	285 (10–929)
Tumor size, median (range), mm	38 (14–70)
Histological type, *n* (%)	
Differentiated type	25 (80.6)
Undifferentiated type	6 (19.4)
Depth of tumor, *n* (%)	
pT1a	6 (19.4)
pT1b	
SM1 (Invasion depth < 500 μm)	5 (16.1)
SM2 (Invasion depth ≥ 500 μm)	12 (38.7)
pT2 (MP, muscularis propria) or beyond	8 (25.8)
Lymph node metastasis, *n* (%)	11 (35.5)
Distant metastasis[†], *n* (%)	1 (3.2)
Final stage[‡], *n* (%)	
I	25 (80.6)
II	4 (12.9)
III	1 (3.2)
IV	1 (3.2)

ER endoscopic resection

[†] The case of distant metastasis was peritoneal lavage cytology positive

[‡] Final staging was classified according to the 7th UICC; I, IA, or IB; II, IIA, or IIB; III, IIIA, IIIB, or IIIC

surgery and preserve the digestive function of the stomach. Subtotal gastrectomy tends to result in fewer alimentary symptoms and functional limitations than TG [3–5], and it is the first choice of treatment. In the present study, TG was avoided by PRES in 31 patients (91.2 %, 31/34). The median transition period from ER to gastrectomy was 44 days, ER was not an obstacle to surgery, and long-term outcomes of this strategy were favorable. With recent advances in the treatment of gastric cancer, long-term survival is expected after curative resection [18]. Therefore, it has become more important to maintain the quality of life (QOL) after gastrectomy. In particular, patients in the early stages of gastric cancer benefited from preservation of the stomach and had longer-term survival. Thus, PRES facilitated preservation of QOL in early-stage subjects.

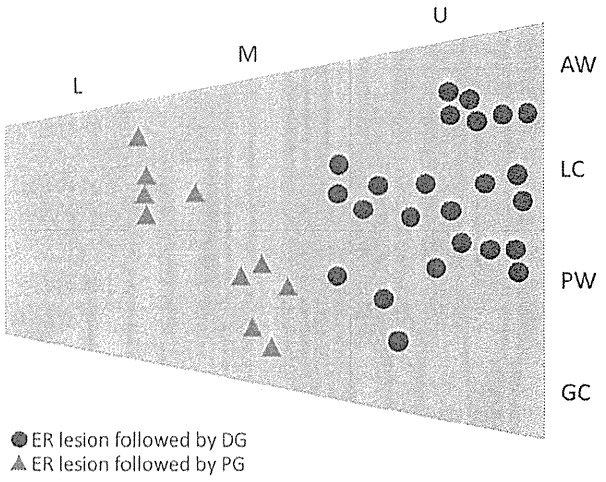

Fig. 1 Locations of 34 ER lesions followed by subtotal gastrectomy. *U* upper third, *M* middle third, *L* lower third, *AW* anterior wall, *LC* lesser curvature, *PW* posterior wall, *GC* greater curvature, *ER* endoscopic resection, *DG* distal gastrectomy, *PG* proximal gastrectomy

ER, particularly ESD, has been accepted as the most effective and less invasive treatment for superficial gastric neoplasms. ER was comparable to surgery in terms of risk of death when endoscopic curative resection was achieved [11, 12]. Although risks of remnant gastric cancer remain because of preservation of the stomach [19, 20], superficial gastric cancers in the remaining stomach are reportedly controlled by ER [21, 22]. Accordingly, 2 of the present cases (6.5 %) had metachronous lesions, which were treated by ER and did not recur.

ER-related perforations and delayed bleeding occurred in 5 (13.2 %) and 3 cases (7.9 %), respectively. These rates were a little higher than those reported previously [23], potentially reflecting the small sample size of the present study. However, these adverse events were managed endoscopically, and no transfusions were required. Previous studies indicate the feasibility of nonsurgical management of perforations following successful immediate endoscopic closure of the perforation [24, 25].

The 5-year overall survival of patients who underwent PRES was 96.3 %, and no death occurred because of gastric cancer. Liver metastasis occurred in 1 patient who underwent PG for a T1b tumor after curative ER for a synchronous T1a tumor. However, lymphovascular infiltrations and lymph node metastases were observed in surgically resected specimens from this patient, and the period of recurrence from surgery was 8.6 months. Thus, liver metastasis could not be avoided even after TG.

Among indications for PRES in the present study, PG was accepted as an additional gastric resection. Regarding

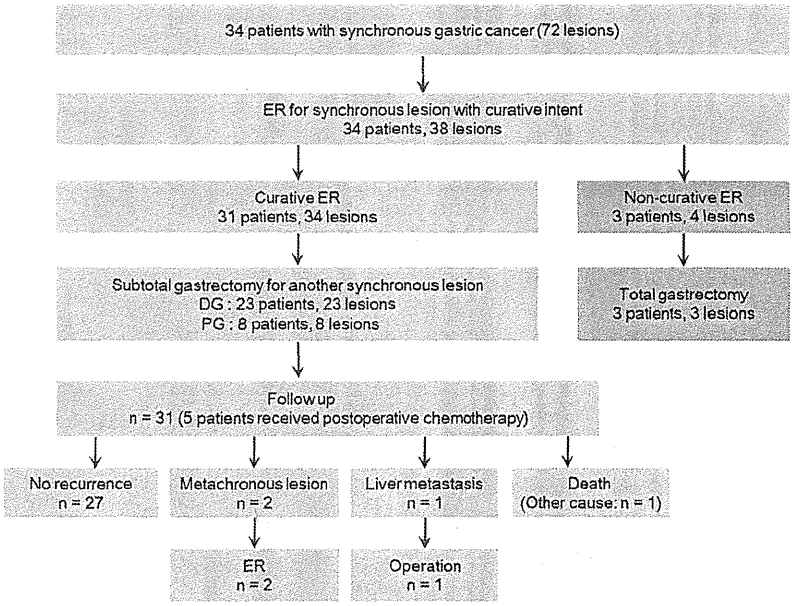

Fig. 2 Flow chart of patients included in the study. Clinical outcomes are shown. Patients underwent subtotal gastrectomy if ER specimens were evaluated as curative resections. *ER* endoscopic resection, *DG* distal gastrectomy, *PG* proximal gastrectomy

Table 6 Clinical outcomes in 31 patients who underwent subtotal gastrectomy after pre-emptive endoscopic resection

Follow-up period, median (range), month	48 (14–111)
Postoperative chemotherapy, *n* (%)	5 (16.1)
Pattern of recurrence, *n* (%)	
Metachronous lesion	2 (6.5)
Lymph node metastasis	0
Distant metastasis	1 (3.2)
5-year overall survival (%)	96.3
5-year cause-specific survival (%)	100

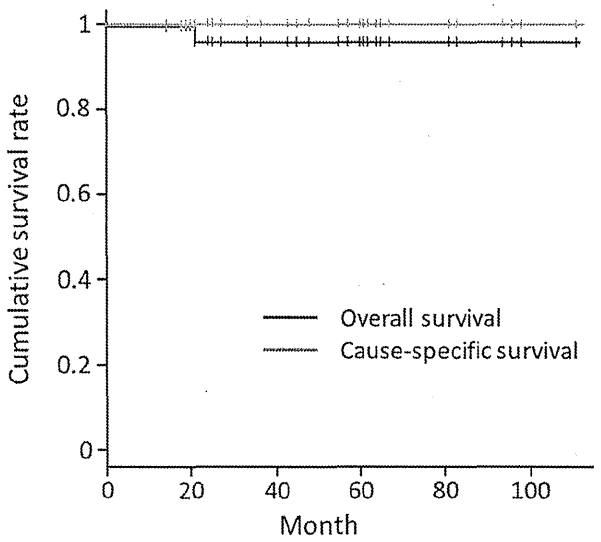

Fig. 3 Overall and cause-specific survival curves for patients who underwent pre-emptive endoscopic resection and surgery for synchronous gastric cancers

postoperative nutrition and anemia, PG has theoretically more advantages than TG. A recent study reported that PG facilitates the maintenance of body weight and prevention of postoperative anemia and provides similar oncological outcomes to TG in patients with early gastric cancers [26]. However, others have reported that postoperative QOL after TG is superior to that after PG, presumably because they included more patients suffering from postoperative symptoms [27]. Although controversial, gastric resection using PG instead of TG was possible in 8 cases. Furthermore, the present study excluded patients with type 4 and large type 3 tumors (>80 mm) because (1) it was difficult to estimate the invaded area precisely owing to massive submucosal invasions, and (2) long-term outcomes are estimated to be poor [28] so that these patients could not benefit from PRES.

Although further studies are required, partial preservation of the stomach did not cause death in any in the present study. These data suggest that PRES provides the opportunity for minimally invasive surgery in patients with synchronous gastric cancers with promising oncological outcomes and maintains QOL.

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ORIGINAL ARTICLE

Characteristics and clinical relevance of postgastrectomy syndrome assessment scale (PGSAS)-45: newly developed integrated questionnaires for assessment of living status and quality of life in postgastrectomy patients

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Abstract
Background Lack of a suitable instrument to comprehensively assess symptoms, living status, and quality of life in postgastrectomy patients prompted the authors to develop postgastrectomy syndrome assessment scale (PGSAS)-45.
Methods PGSAS-45 consists of 45 items in total: 8 items from SF-8, 15 items from GSRS, and an additional 22 items selected by 47 gastric surgeons. Using the PGSAS-45, a multi-institutional survey was conducted to determine the prevalence of postgastrectomy syndrome and its impact on everyday life among patients who underwent various types of gastrectomy. Eligible data were obtained from 2,368 patients operated and followed at 52 institutions in Japan. Of these, data from 1,777 patients were used in the current study in which symptom subscales of the PGSAS-45 were determined. We also considered the characteristics of the postgastrectomy syndrome and to what extent these symptoms influence patients' living status and quality of life (QOL).
Results By factor analysis, 23 symptom-related items of PGSAS-45 were successfully clustered into seven symptom subscales that represent esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation, and dumping. These seven symptom subscales and two other subscales measuring quality of ingestion and dissatisfaction for daily life, respectively, had good internal consistency in terms of Cronbach's α (0.65–0.88).

For the Japan Postgastrectomy Syndrome Working Party.

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Conclusion PGSAS-45 provides a valid and reliable integrated index for evaluation of symptoms, living status, and QOL in gastrectomized patients.

Keywords Postgastrectomy syndrome · Questionnaires · Quality of life · Gastrectomy

Introduction

Postgastrectomy syndrome (PGS) remains a serious drawback for gastric cancer survivors after gastrectomy [1–6]. PGS includes numerous symptoms related to the loss of the stomach, leading to impairments in living status and quality of life (QOL). Several surgical procedures have been sought to maintain or even to reconstruct the gastric functions through preservation of nerves and other anatomical structures and through sophistication in the method of reconstruction [7, 8]. Hard data showing benefits of various considerations in surgical procedure have been scarce, however, partly because of the lack of adequate endpoints when these procedures are evaluated in clinical trials. It is important, therefore, to be able to weigh the intensity of the various symptoms that emerge after gastrectomy and elucidate to what extent they affect the patients. If an appropriate instrument is available, we shall be able to identify which surgical procedure can be helpful in preventing or ameliorating PGS. Evidence-based knowledge in this area of interest is mandatory for adequate selection of surgical procedure, especially at reconstruction.

To establish an adequate instrument to measure the incidence and relevance of the PGS in terms of patient-reported outcome, the Japanese Postgastrectomy Syndrome Working Party led by the authors designed and constructed a new integrated questionnaire, the Postgastrectomy Syndrome Assessment Scale (PGSAS)-45, to specifically assess symptoms, living status, and QOL of the patients who underwent gastrectomy. A nationwide multi-institutional study was then undertaken to validate the PGSAS-45 and to survey the incidence and intensity of the PGS observed after various surgical procedures.

Standard procedures for scale development in medical research and practice were used to construct a valid, reliable, and clinically useful scale for the assessment of PGS. In the current article, this challenging process is described with particular emphasis on the selection and aggregation of the list of symptoms. The structure and characteristics of the final version of PGSAS-45 were then disclosed. Through findings from a clinical study to validate the PGSAS-45, characteristics of PGS among postgastrectomy patients were summarized, and the influence of the symptoms on the QOL and living status of the patients was identified.

Patients and methods

The Japanese Postgastrectomy Syndrome Working Party

The Japanese Postgastrectomy Syndrome Working Party (JPGSWP), established in 2006, is a voluntary organization of surgeons whose aims were (1) to construct a standardized instrument to evaluate PGS and (2) to use the instrument to identify the optimal surgical procedure that minimizes impairment of QOL among patients who undergo gastrectomy. The JPGSWP has grown during the process and currently consists of 212 surgeons and 52 other medical staff persons (pharmacologists, nurses, and nutritionists) from various Japanese institutions. The first task undertaken by the JPGSWP, thus, was to construct the PGSAS-45.

Development of a new questionnaire, PGSAS-45

PGSAS-45 was designed to comprehensively characterize and evaluate symptoms, living status, and QOL of patients who underwent gastrectomy (Table 1). It was expected to provide a realistic image of the status of the patients and to be regarded as a gold standard in surveillance of the PGS and evaluation of various types of gastrectomy and reconstruction.

First, a comprehensive item pool or list of items representing symptoms and functions was generated. For this purpose, data on PGS were collected from a variety of sources such as published articles and abstracts of domestic surgical meetings. In addition, symptoms that were actually claimed to have been the cause of annoyance for the patients or considered to have affected their everyday lives were retrieved through scrutiny of an earlier questionnaire survey from 252 patients who underwent gastrectomy and by direct interview with 117 patients. This comprehensive and potentially over-inclusive list of items and symptoms was then reviewed to determine which items should be retained. To do so, the list was dispatched by mail to 51 members of the JPGSWP who were asked to arrange the items in the order of clinical importance. Although the items related to issues of significant clinical importance were not to be deleted (all items that were considered by more than 50 % of the surgeons as clinically relevant were to be retained), the total number of items was expected to be within 50. Forty-seven of the 51 surgeons (92 %) eventually responded and met at a consensus meeting in March 2007 to discuss which items should eventually be retained to construct the PGSAS-45.

Further discussion among the JPGSWP members and interviews with the experts in QOL evaluation (Y.S.) were carried out and, through empirical verification, items that

Table 1 Structure of postgastrectomy syndrome assessment scale (PGSAS)-45 (domains/subdomains/items/subscales)

Domains	Subdomains	Items			Subscales
QOL	SF-8	1	Physical functioning*	Five- 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	Gastrointestinal Symptom Rating Scale (GSRS) items	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	Nausea and vomiting		
		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		
	PGSAS-specific items	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		
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*	Five-point Likert scale	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		–
Quality of life (QOL)	Dissatisfaction	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 physical component summary and mental component summary of SF-8

Items 29 and 32 do not have a score. Thus, they were analyzed separately

Table 2 Outcome measures in PGSAS (patients after conventional gastrectomy: $N = 1,777$)

Domain	Item number (#)	Main outcome measures	Mean	SD
Symptoms	10, 11, 13, 24	Esophageal reflux subscale	1.71	0.85
	9, 12, 28	Abdominal pain subscale	1.70	0.77
	25–27	Meal-related distress subscale	2.19	0.96
	14–17	Indigestion subscale	2.07	0.87
	19, 20, 22	Diarrhea subscale	2.14	1.11
	18, 21, 23	Constipation subscale	2.17	1.01
	30, 31, 33	Dumping subscale	2.04	1.04
	9–28, 30, 31, 33	Total symptom score	2.00	0.70
Living status	–	Change in body weight (%)*	−9.5	8.0
	34	Ingested amount of food per meal*	7.00	1.97
	41	Necessity for additional meals	1.98	0.81
	38–40	Quality of ingestion subscale*	3.78	0.92
	42	Ability for working	1.84	0.88
QOL	43	Dissatisfaction with symptoms	1.87	0.95
	44	Dissatisfaction at the meal	2.32	1.13
	45	Dissatisfaction at working	1.79	0.97
	43–45	Dissatisfaction for daily life subscale	2.00	0.87
	1–8	Physical component summary*	50.4	5.6
	1–8	Mental component summary*	49.7	5.8
Domain	Item number (#)	Other outcome measures (symptom)	Mean	SD
Symptoms	9	Abdominal pains	1.74	0.96
	10	Heartburn	1.76	1.02
	11	Acid regurgitation	1.81	1.12
	12	Sucking sensations in the epigastrium	1.50	0.82
	13	Nausea and vomiting	1.50	0.94
	14	Borborygmus	1.87	1.06
	15	Abdominal distension	2.00	1.12
	16	Eructation	1.70	0.97
	17	Increased flatus	2.72	1.43
	18	Decreased passage of stools	2.13	1.25
	19	Increased passage of stools	2.13	1.29
	20	Loose stools	2.10	1.18
	21	Hard stools	1.96	1.12
	22	Urgent need for defecation	2.19	1.30
	23	Feeling of incomplete evacuation	2.43	1.16
	24	Bile regurgitation	1.77	1.07
	25	Sense of foods sticking	1.79	1.08
	26	Postprandial fullness	2.39	1.21
	27	Early satiation	2.41	1.21
	28	Lower abdominal pains	1.87	1.11
	30	Early dumping general symptoms	1.96	1.20
	31	Early dumping abdominal symptoms	2.34	1.31
	33	Late dumping symptoms	1.81	1.17

Table 2 continued

Domain	Item number (#)	Other outcome measures (dumping)	Mean	SD
Symptoms	29	Existence of early dumping general symptoms [Y/N]	915	802
	29	Existence of early dumping abdominal symptoms [Y/N]	1,175	542
	29	Existence of either early dumping symptoms [Y/N]	1,293	424
	32	Existence of late dumping symptoms [Y/N]	715	891
	29	Number of early dumping general symptoms	1.95	1.30
	29	Number of early dumping abdominal symptoms	1.94	1.11
	29	Number of any early dumping symptoms	2.87	2.04
	32	Number of late dumping symptoms	1.85	1.24
Domain	Item number (#)	Other outcome measures (meals)	Mean	SD
Living status	35	Ingested amount of food per day*	7.30	2.02
	36, 37	Frequency of daily meals	4.99	1.45
	38	Appetite*	4.27	1.11
	39	Hunger feeling*	3.21	1.30
	40	Satiety feeling*	3.85	1.19

In items or subscales with *, higher score indicates better condition

In items or subscales without *, higher score indicates worse condition

have characteristics in common were aggregated. The item pool was further reduced by excluding items that were considered to represent symptoms with a low incidence or are not definitely related to the PGS. To speed up the process of compiling a valid scale, a decision was made to include items from relevant and internationally acclaimed questionnaires. All items from Short Form-8 Health (SF-8) and Gastrointestinal Symptom Rating Scale (GSRS) surveys were subsequently selected for inclusion with permissions from relevant organizations for this study. Thus, PGSAS-45 was established in April 2009.

Structure of the PGSAS-45 (Tables 1, 2; Fig. 1)

PGSAS-45, the end product of the current project with 45 items, became a HRQOL instrument with multidimensional structure consisting of three domains: symptom domain, living status domain, and QOL domain, each consisting of several subdomains (Tables 1, 2; Fig. 1). Twenty-two of the items that had originally been proposed by the JPGSWP members were selected to be retained and added to all 8 items from SF-8 (items 1–8) and all 15 items from GSRS (items 9–23) to constitute the PGSAS-45.

As a symptom domain, 10 original items proposed by the JPGSWP members (items 24–33) were added to the 15 items from GSRS. Of these 10 items, 8 items inquire intensity of symptoms that are actually observed as PGS but had not been evaluated by the conventional questionnaires. The other 2 items (items 29 and 32) inquire whether the patients suffer from early or late dumping syndrome, and the number and types of symptoms if they do. The living status domain consists entirely of the original items proposed by the JPGSWP members and can be stratified into three subdomains (Table 1; Fig. 1). Items 34–37 and 41 constitute the subdomain for the amount of food ingested, and items 38–40 constitute the subdomain for quality of food intake. A subdomain for social activity consists of a single item (item 42). The QOL domain consists of all 8 items from the SF-8 and 3 original items proposed by the JPGSWP members. These 3 items focused on the issue of dissatisfaction in everyday life caused by symptoms (item 43), feeding problems (item 44), and impaired social activity (item 45), and constitute the dissatisfaction subdomain (Table 1; Fig. 1). Twenty-three of the 25 items in the symptom domain (items 29 and 32 excepted) inquire about intensity of symptoms and are rated on a 7-point Likert scale. One of the 5 items of the amount of food ingested subdomain, all 3 items of the quality of food intake subdomain, the single item for social activity subdomain, and all 3 items of the dissatisfaction subdomain were rated on a 5-point Likert scale (Table 1). High scores denote favorable outcome in items 1–8 and items 34, 35, and 38-40, whereas low scores indicate superior outcome in items 9–28, 30, 31, 33, and 41–45.

PGSAS (PGS assessment) study, a multi-institutional cross-sectional study

A multi-institutional cross-sectional study involving 52 institutions (25 university hospitals, 8 cancer centers, and 19 community hospitals) was conducted by the JPGSWP to assess the patient-reported outcome using the PGSAS-45

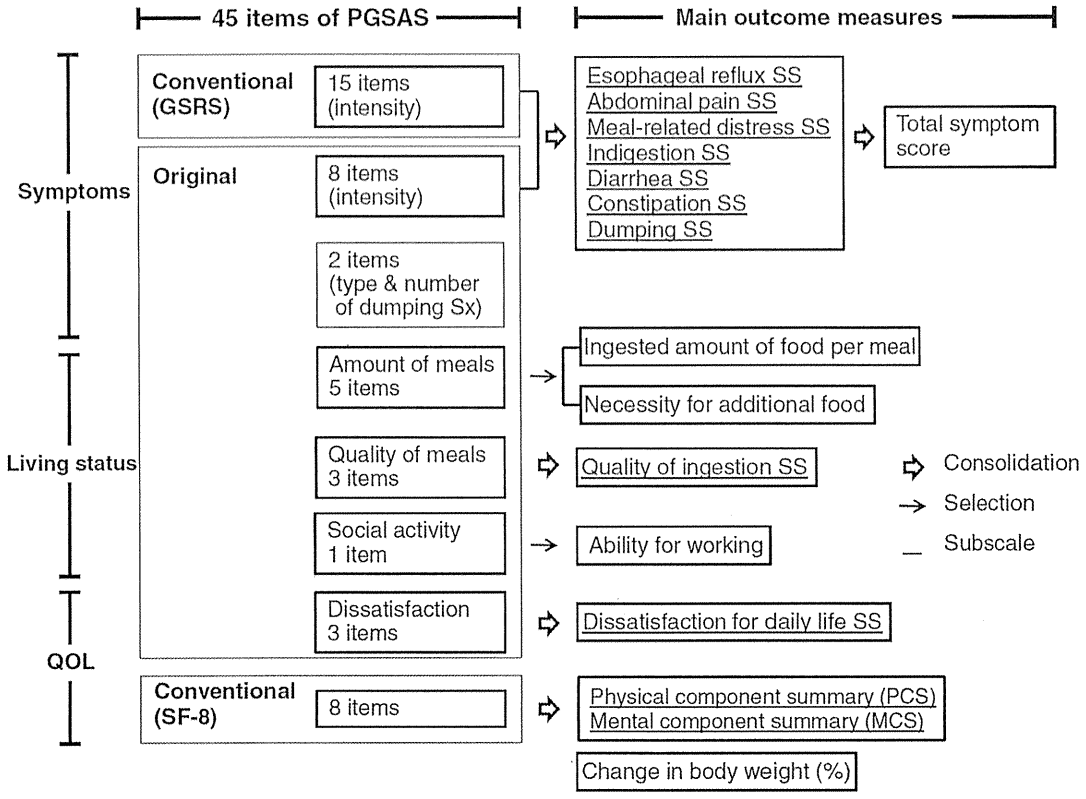

Fig. 1 The process of consolidation and selection to constitute main outcome measures

and to validate this instrument. This study was approved by the institutional review committee (IRB) of Jikei University and subsequently by the IRBs of all participating institutions.

Patients who underwent surgery for gastric cancer and were confirmed pathologically to have stage I disease were eligible. In addition, the patient had to be between 20 and 75 years of age, have undergone no chemotherapy, have lived for more than 1 year after surgery, have no signs of recurrence at the point of assessment, and be without active cancer in other sites. Consecutive sampling of the eligible patients in the outpatient clinic was conducted after obtaining written informed consent. The patients were given the questionnaire sheets together with a stamped and addressed envelope and were asked to fill in the answers and post the sheets to the data cancer. In addition, data regarding background of the patients such as age, gender, height, body weight before surgery and at the time of assessment, time interval since the surgery, the extent of lymphadenectomy (D-number), surgical approach, and details of the surgery performed were retrieved from the medical records and sent to the data center by the medical staff.

Of the 2,922 patients who were handed the questionnaire sheets between July 2009 and December 2010, 2,520 (86 %) responded and 2,368 were confirmed to be eligible for the

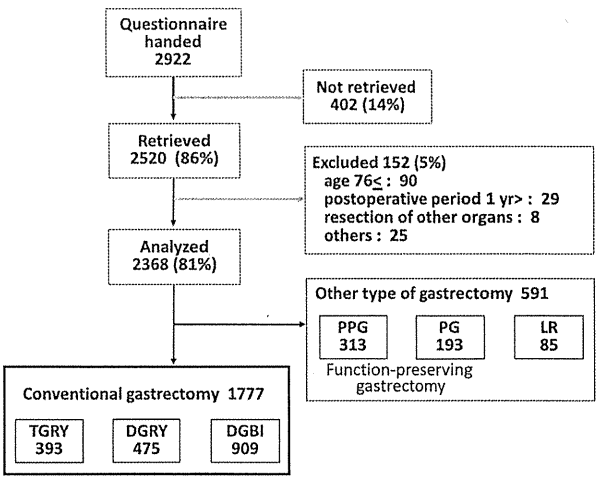

Fig. 2 Outline of the study

study. Of these, data from 1,777 patients who underwent either total or distal gastrectomy were used in the current study to assess construct validity for the PGSAS-45 (Fig. 2). Using these data, we explored relevance of the eight original items proposed by the JPGSWP members that were selected and added to the items derived from the GSRS to constitute the symptom domain of the PGSAS-45.

In addition to validation of the PGSAS-45, we intended to evaluate the PGS of patients who underwent radical gastrectomy for gastric cancer, and to what extent the symptoms influence the patients' living status or QOL.

Statistical analyses

Statistical analyses were performed by the biostatisticians mainly using StatView for Windows Ver. 5.0 (SAS Institute, Cary, NC, USA).

Bivariate and multivariate regression analyses were performed to evaluate correlations between the sum of scores for the 15 symptom-related items derived from GSRS or the 8 symptom-related items proposed by the JPGSWP members and scores related to living status and QOL. Factor analysis was used to decide which of the 23 symptom-related items should be clustered to form each symptom subscale. Cronbach's α was calculated from the pairwise correlations between items to verify the internal consistency of the items in each subscale. Correlations between the scores for each of the 7 symptom subscales were calculated in terms of Pearson's r, where effect size is considered to be large when $r > 0.5$.

Results

Characteristics and living status of the patients after conventional gastrectomy

Of the 1,777 patients, 1,188 (66.9 %) were male; the patients had a mean age of 62.1 ± 9.2 years. Of the patients, 393 underwent total gastrectomy, 909 underwent distal gastrectomy with Billroth type I reconstruction, and 475 underwent distal gastrectomy with Roux-en-Y reconstruction. The mean time interval between surgery and retrieval of the questionnaires was 37 ± 27 months. Table 2 summarizes the mean values and standard deviation of the main outcome measures and other items evaluated in the PGSAS study. The mean values of the symptom subscales indicate that the symptoms that adversely affect patient well-being are, in the order of importance, meal-related distress, constipation, diarrhea, indigestion, dumping, esophageal reflux, and abdominal pain. The mean loss of body weight at the time the patients were evaluated was 9.5 ± 8.0 %. The amount of food consumed per meal was approximately 70 % of the amount ingested before surgery, and the mean number of meals per day was five. Patient dissatisfaction with life was more closely related to meals rather than their symptoms or their jobs. In contrast, physical and mental components as evaluated by SF-8 were not seriously affected because both scores were around 50 by norm-based scoring.

Factor structure after weighting 23 symptom-related items of the PGSAS-45

Related items were clustered into a subscale to allow more simplified evaluation with a smaller number of scores when necessary. Items 1–8 derived from the SF-8 constitute the physical component summary (PCS) and the mental component summary (MCS). Items 38–40 constitute the quality of ingestion subscale and items 43–45 constitute the dissatisfaction for daily life subscale.

Similarly, the 23 symptom-related items of the PGSAS-45, which are rated on a 7-point Likert scale, were clustered into subscales, each consisting of 3–4 related items (GSRS actually has five symptom subscales). For this purpose, factor analysis using the principal factor method with Promax rotation was performed for the observed responses to the 23 symptom-related items of the PGSAS-45 (Table 3). Consequently, the 23 items were stratified into seven subgroups in which factor loading took maximal values for all the items and sufficiently large values of 0.7 or higher for most of the items. Thus, factor analysis identified seven clinically relevant subscales, which were named from their content as follows: 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), and dumping subscale (items 30, 31, 33). Five of these seven subscales were named the same way as the subgroups of the GSRS, which are termed syndromes, of which three subscales (indigestion, diarrhea, and constipation) had similar content with the corresponding syndromes whereas two other subscales (esophageal reflux and abdominal pain) were dissimilar.

All these seven subscales could further be aggregated as a total symptom score, which is calculated as a mean value of the seven symptom subscales.

Clinical relevance of the eight additional items proposed by the JPGSWP members

The 8 symptom-related JPGSWP items, rated on a 7-point Likert scale, were compared with the 15 items derived from GSRS in terms of the correlation between the sum of these scores and the scores of the items reflecting either the living status, QOL, or change in body weight. The standardized partial regression coefficients (β) took larger values for the JPGSWP items in almost the items reflecting either the living status or QOL, with the exception of the MCS. The R^2 values of the JPGSWP items as evaluated by bivariate regression analysis were larger than that of the GSRS items across all outcome measures assessing living status and QOL and were

Table 3 Factor structures in the 23 symptom items of PGSAS-45

Factor and item	Mean	SD	Factor loading						
			I	II	III	IV	V	VI	VII
I. Esophageal reflux subscale									
Acid regurgitation	1.81	1.12	**0.968**	−0.031	−0.059	−0.005	0.013	−0.020	−0.065
Bile regurgitation	1.77	1.07	**0.932**	−0.094	−0.127	0.048	−0.001	0.018	0.020
Heartburn	1.75	1.01	**0.638**	0.236	0.091	0.004	−0.048	−0.025	−0.067
Nausea and vomiting	1.49	0.93	**0.617**	−0.039	0.222	−0.144	0.049	0.029	0.091
II. Abdominal pain subscale									
Sucking sensations in the epigastrium	1.49	0.82	0.231	**0.782**	−0.309	−0.006	0.000	0.047	0.042
Abdominal pains	1.74	0.96	0.049	**0.781**	0.176	−0.052	0.001	−0.042	−0.024
Lower abdominal pains	1.87	1.11	−0.258	**0.547**	0.322	0.025	0.117	0.108	0.070
III. Meal-related distress subscale									
Postprandial fullness	2.39	1.21	0.051	0.004	**0.786**	0.019	−0.030	0.021	0.081
Early satiation	2.41	1.21	0.019	−0.002	**0.738**	0.006	−0.009	0.073	0.089
Sense of foods sticking	1.79	1.07	0.388	−0.259	**0.550**	−0.026	0.000	−0.019	0.160
IV. Indigestion subscale									
Increased flatus	2.72	1.43	−0.098	−0.245	−0.118	**0.880**	0.110	0.108	0.080
Borborygmus	1.87	1.06	0.056	0.107	−0.065	**0.723**	0.050	−0.135	0.084
Abdominal distension	1.99	1.12	0.008	0.138	0.174	**0.675**	−0.049	0.034	−0.067
Eructation	1.70	0.97	0.211	0.141	0.197	**0.546**	−0.121	−0.001	−0.210
V. Diarrhea subscale									
Increased passage of stools	2.13	1.29	−0.004	0.035	−0.072	0.003	**0.957**	−0.045	−0.030
Loose stools	2.10	1.18	0.009	0.032	−0.034	−0.018	**0.940**	−0.027	−0.054
Urgent need for defecation	2.19	1.30	0.039	−0.064	−0.030	−0.040	**0.895**	0.008	0.019
VI. Constipation subscale									
Decreased passage of stools	2.12	1.25	−0.001	0.029	−0.043	−0.029	−0.068	**0.956**	−0.016
Hard stools	1.96	1.12	0.017	0.027	−0.012	−0.058	−0.113	**0.942**	−0.021
Feeling of incomplete evacuation	2.42	1.16	−0.037	−0.125	0.099	0.099	0.301	**0.667**	−0.039
VII. Dumping subscale									
Late dumping symptoms	1.81	1.17	0.005	0.020	0.001	0.048	−0.053	0.006	**0.837**
Early dumping general symptoms	1.99	1.21	−0.001	−0.031	0.289	−0.057	0.047	−0.053	**0.778**
Early dumping abdominal symptoms	2.32	1.31	−0.124	0.112	0.369	0.067	0.248	0.004	**0.391**

Extraction method: principal factor method with Promax rotation

Maximum value of factor loading for each item was expressed as bold fonts

almost equivalent to R^2 values evaluated by multivariate analysis (Table 4). These facts indicate that the symptoms asked in the JPGSWP items were significantly more associated with the well-being of the patients than the GSRS items.

Internal consistency of items in each subscale of the PGSAS-45

In addition to the seven symptom-related subscales, two additional subscales have been proposed: a subscale showing quality of food intake and a subscale showing dissatisfaction in daily life. Internal consistency of the items in each of the nine subscales was acceptable, as shown by the Cronbach's α, ranging from 0.65 to 0.88 (Table 5).

Interrelationship between symptom subscales

Correlations between the scores for each symptom subscale are summarized in Table 6. Significant interrelationship ($r > 0.5$) was observed between five subscales—esophageal reflux, abdominal pain, meal-related distress, indigestion, and dumping—whereas the interrelationship between these and two remaining subscales, diarrhea and constipation, were relatively weak ($r > 0.3$).

Table 4 Significance of added 8 symptoms to 15 symptoms of GSRS for evaluating living status and QOL in the gastrectomized patients

	Simple linear regression analysis						Multiple linear regression analysis					
	Sum of GSRS Sx (15)			Sum of added Sx (8)			Sum of GSRS Sx (15)		Sum of added Sx (8)			
	b	*p* value	R^2	*b*	*p* value	R^2	β	*p* value	β	*p* value	R^2	*p* value
Change in body weight (%)*	−0.117	<0.0001	(0.014)	−0.181	<0.0001	0.033	(0.074)	0.0851	−0.240	<0.0001	0.035	<0.0001
Ingested amount of food per meal*	−0.277	<0.0001	0.077	*−0.340*	<0.0001	0.116	(−0.020)	≥0.1	*−0.324*	<0.0001	0.116	<0.0001
Necessity for additional meals	0.288	<0.0001	0.083	*0.365*	<0.0001	*0.133*	(−0.004)	≥0.1	*0.368*	<0.0001	*0.133*	<0.0001
Ability for working	*0.369*	<0.0001	*0.137*	*0.424*	<0.0001	*0.180*	(0.091)	0.0196	*0.353*	<0.0001	*0.183*	<0.0001
Dissatisfaction with symptoms	**0.533**	<0.0001	**0.284**	**0.613**	<0.0001	**0.375**	0.127	0.0002	**0.512**	<0.0001	**0.381**	<0.0001
Dissatisfaction at the meal	*0.480*	<0.0001	*0.230*	**0.580**	<0.0001	**0.336**	(0.054)	≥0.1	**0.537**	<0.0001	**0.338**	<0.0001
Dissatisfaction at working	*0.475*	<0.0001	*0.226*	**0.553**	<0.0001	**0.306**	(0.098)	0.0058	*0.476*	<0.0001	**0.310**	<0.0001
Dissatisfaction for daily life subscale	**0.579**	<0.0001	**0.335**	**0.682**	<0.0001	**0.464**	0.105	0.0007	**0.598**	<0.0001	**0.469**	<0.0001
Physical component summary*	*−0.443*	<0.0001	*0.196*	*−0.481*	<0.0001	*0.231*	−0.166	<0.0001	*−0.349*	<0.0001	*0.241*	<0.0001
Mental component summary*	*−0.458*	<0.0001	*0.210*	*−0.461*	<0.0001	*0.212*	−0.249	<0.0001	−0.269	<0.0001	*0.235*	<0.0001
Interpretation of effect size	*b*, β	R^2										
None–very small	<(0.100)	<(0.020)										
Small	≥0.100	≥0.020										
Medium	*≥0.300*	*≥0.130*										
Large	**≥0.500**	**≥0.260**										

In items or subscales with *, higher score indicating better condition. In items or subscales without *, higher score indicating worse condition

The fonts of values of *b*, β or R^2 were varied according to their effect size; 'None-very small' as parenthetic, 'Small' as normal fonts, 'Medium' as italic fonts and 'Large' as bold fonts

Table 5 Internal consistency of each subscale of the PGSAS-45

Subscales	Cronbach's α
Esophageal reflux	0.83
Abdominal pain	0.71
Meal-related distress	0.76
Indigestion	0.74
Diarrhea	0.88
Constipation	0.81
Dumping	0.80
Quality of ingestion	0.65
Dissatisfaction for daily life	0.81
Interpretation of Cronbach's α	
Excellent	$0.9 \leq \alpha$
Good	$0.7 \leq \alpha < 0.9$
Acceptable	$0.6 \leq \alpha < 0.7$
Poor	$0.5 \leq \alpha < 0.6$
Unacceptable	$\alpha < 0.5$

Main outcome measures and other outcome measures in the PGSAS study (Table 2)

After the validation process, data obtained by the PGSAS study will undergo subsequent analyses, mainly comparisons between different surgical procedures, and the results will be published in due time. For use in these analyses, main outcome measures were determined.

Seven symptoms subscales, total symptom score, a subscale showing quality of feeding, a subscale showing dissatisfaction in life, PCS, and MCS were selected as main outcome measures in the future analyses. In addition, the amount of food per meal occasion (item 34) and necessity of an additional meal (item 41) were added as single items because they correlated well with the ability to work (item 42) and various QOL measures such as PCS, MCS, and dissatisfaction for daily life subscale (data not shown). Dissatisfaction with the symptoms, dissatisfaction at the meal, and dissatisfaction during work (items 43–45) were also added as single items to see how these affected QOL of the postgastrectomy patients. Apart from the scores derived from PGSAS-45, body weight loss (percentage of body weight loss in relationship to preoperative weight) as obtained from the medical record was added as the main outcome measures.

Discussion

After gastrectomy, patients suffer from various illnesses and functional problems comprehensively referred to as