

表1 胃癌に対するロボット手術に関する報告

番号	報告者	報告年	国	施設	研究デザイン	症例数		
						ロボット	腹腔鏡	開腹
1	Hashizume	2003	日本	九州大学	総説			
2	Takeji	2006	日本	九州大学	CS	5		
3	Anderson	2007	米国	City of Hope, Duarte	CS	7		
4	Patriti	2008	イタリア	San Matteo degli Infermi 病院	CS	13		
5	Pugliese	2009	イタリア	di Niguarda Ca' Granda 病院	CS	9	46	
6	Song	2009	韓国	Yonsei 大学	CC	20	20	
7	Song	2009	韓国	Yonsei 大学	CS	100		
8	Tomulescu	2009	ルーマニア	Fundeni Clinical Institute	CS	14		
9	Hur	2010	韓国	Ajou 大学	CS	7		
10	Kim	2010	韓国	Dong-A 大学	CC	16	12	11
11	Pugliese	2010	イタリア	di Niguarda Ca' Granda 病院	CC	18	52	
12	Caruso	2011	イタリア	Siena 大学	CC	29		120
13	D'Annibale	2011	イタリア	San Giovanni-Addolorata 病院	CS	24		
14	Isogaki	2011	日本	藤田保健衛生大学	CS	61		
15	Lee	2011	韓国	Catholic 大学	CS	12		
16	Patriti	2011	イタリア	San Matteo degli Infermi 病院	CS	17		
17	Woo	2011	韓国	Yonsei 大学	CC	236	591	
18	Eom	2012	韓国	National Cancer Center	CC	30	62	
19	Huang	2012	台湾	Taipei Veterans 総合病院	CC	39	64	586
20	Kang	2012	韓国	Ajou 大学	CC	100	282	
21	Kim	2012	韓国	Yonsei 大学	CC	436	861	4542
22	Park	2012	韓国	National Cancer Center	CH	30	120	
23	Park	2012	韓国	Korea 大学	CS	20×3 施設	225	
24	Uyama	2012	日本	藤田保健衛生大学	CC	25		
25	Vasilescu	2012	ルーマニア	Fundeni Clinical Institute	CS	2		
26	Vasilescu	2012	ルーマニア	Fundeni Clinical Institute	CS	41		
27	Yoon	2012	韓国	National Cancer Center	CC	36	65	
28	Hyun	2013	韓国	Korea 大学	CC	38	83	
29	Kim	2013	韓国	Yonsei 大学	CC	172	481	
30	Liu	2013	中国	Subei 人民病院	CS	110		
31	Park	2013	韓国	National Cancer Center	CS	207		
32	Tokunaga	2013	日本	静岡がんセンター	前向き臨床 第Ⅱ相試験	18		
33	Junfeng	2014	中国	Third Military Medical 大学	CC	120	394	
34	Noshiro	2014	日本	佐賀大学	CC	21	160	
35	Park	2014	韓国	National Cancer Center	CH	30		
36	Son	2014	韓国	Yonsei 大学	CC	51	58	

CS：ケースシリーズ，CC：ケースコントロール，CH：コホート研究

内容	文献
da Vinci と Zeus の使用経験	Surg Clin North Am
消化器疾患 73 例 (うち胃癌 7 例) に対するロボット手術の臨床経験	Int J Med Robot
D2 郭清を伴うロボット支援下幽切 (8 例), 全摘 (4 例), 噴切 (1 例) の臨床経験	Surg Endosc
ロボット手術 9 例の臨床経験. 腹腔鏡下手術と短期成績の比較	Surg Endosc
ロボット手術導入初期 20 例の短期成績を同一術者の腹腔鏡下手術 20 例と比較	Eur J Surg Oncol
ロボット手術導入初期 100 例の短期成績	Surg Endosc
ロボット手術 147 例 (うち胃切除 14 例) の臨床経験	Ann Surgery
ロボット支援下での縫合による再建術式の評価	Chirurgia (Bucur)
ロボット手術と腹腔鏡下手術, 開腹手術との比較	J Laparoendosc Adv Surg Tech A
ロボット手術と腹腔鏡下手術の 5 年生存率の比較	Surg Endosc
ロボット手術と開腹手術における D2 郭清症例の短期成績と長期成績の比較	Surg Endosc
D2 郭清を伴うロボット手術の臨床経験	Int J Med Robot
ロボット手術 61 例の臨床試験	J Surg Res
cStage I 症例に対するロボット手術 12 例の臨床経験	Pathobiology
食道胃接合部癌 17 例に対するロボット手術の臨床経験	Am J Surg
ロボット手術と腹腔鏡下手術の短期成績の比較	Int J Med Robot
ロボット手術と腹腔鏡下手術の短期成績の比較	Arch Surg
ロボット手術, 腹腔鏡下手術, 開腹手術の短期成績の比較	Eur J Surg Oncol
ロボット手術と腹腔鏡下手術の短期成績の比較. ロボット手術のラーニングカーブ	J Gastrointest Surg
ロボット手術, 腹腔鏡下手術, 開腹手術の術後合併症の比較	J Gastric Cancer
ロボット手術と腹腔鏡下手術における手術侵襲, コストの比較	Br J Surg
ロボット手術におけるラーニングカーブの検討	Br J Surg
ロボット手術と腹腔鏡下手術の D2 郭清における短期成績の比較	Surgical Endosc
ロボット手術 2 例の臨床経験	World J Surg
ロボット手術 41 例の臨床経験	Acta Chir Belg
早期胃癌に対する胃全摘術におけるロボット手術と腹腔鏡下手術の短期成績の比較	Chirurgia (Bucur)
ロボット手術経験 20 例以上の術者によるロボット手術と腹腔鏡下手術の短期成績の比較	Surg Endosc
単一術者におけるロボット手術と腹腔鏡下手術のラーニングカーブの比較	Ann Surg Oncol
D2 郭清を伴うロボット手術の臨床経験	Eur J Surg Oncol
ロボット手術の臨床経験. 初期 100 例と後期 100 例の比較	World J Gastroenterol
cStage I A 症例を対象としたロボット支援下幽門側胃切除の安全性を評価した臨床第 II 相試験	J Gastric Cancer
ロボット手術と腹腔鏡下手術の短期成績の比較	Gastric Cancer
電気メスを使用したロボット手術の安全性評価	Surg Endosc
ロボット手術の術後 QOL の評価	Surg Endosc
脾温存胃全摘, D2 郭清におけるロボット手術と腹腔鏡下手術の比較	World J Surg
	Surg Endosc

表2 ロボット胃切除術のメタ解析

報告者	報告年	国	施設	比較	解析対象論文*	結果			
						手術時間	出血量	在院日数	肛門側マージン
Liao	2013	中国	Southern 医科大学	RG vs OG	10, 12, 19, 21	OG<RG	OG>RG	OG>RG	
Hyun	2013	韓国	Korea 大学	RG vs LG vs OG	10, 11, 12, 18, 19, 21, 27, 28, 不明1件	LG<RG, OG<RG	OG>RG	OG>RG	
Marano	2013	韓国	Yonsei 大学	RG vs LG vs OG	10, 11, 12, 17, 18, 19, 27	LG<RG, OG<RG	LG>RG	OG>RG	
Xiong	2013	中国	Sichuan 大学	RG vs LG	10, 11, 19, 20, 21, 23, 24, 27, 28	LG<RG	LG>RG	LG>RG	LG<RG
Liao	2013	中国	Southern 医科大学	RG vs LG	11, 19, 20, 21, 27, 28, 中国語論文1件	LG<RG	LG>RG		
Xiong	2012	中国	Chongqing 医科大学	RG vs LG	11, 10, 17	LG<RG	LG>RG		
Shen	2014	中国	中国人民解放军 総合病院	RG vs LG	11, 17, 19, 20, 21, 24, 27, 28	LG<RG	LG>RG		LG<RG

LG：腹腔鏡下手術，OG：開腹手術，RG：ロボット手術

\*：表1の番号を示す。

短いことが指摘されている。また Kim ら<sup>13)</sup> は同一術者におけるロボット手術と腹腔鏡下手術のラーニングカーブを比較し、腹腔鏡手術では 261 例で手術時間が安定したのに対し、ロボット手術では 121 例で安定した手術時間に到達したとしている。さらに手術成功率の指標として CUSUM score を用いて解析したところ、腹腔鏡下手術では 80 例で cut-off が存在したのに対し、ロボット手術では cut-off が存在しなかったとしている。すなわち、腹腔鏡下手術に習熟している外科医が行えば、ロボット手術は 1 例目から安全に行えることが示唆されている。現在のロボット胃切除の手技は基本的に腹腔鏡下胃切除の手技を踏襲していることを考えれば、これは当然の結果であると思われる。さらに現在、日本内視鏡外科学会からの提言でも、術者は技術認定取得医であることも合理的と思われる。

当科においても、ロボット手術の導入に際しては内視鏡外科学会の提言を遵守し、初期の 2 例は指導医を招請して実施し、3 例目から 10 例目までは技術認定医 A が術者、技術認定医 B が第一助手を、11 例目以降は技術認定医 A と B が交互に術者と第一助手となり手術を施行した。図 2 に手術時間の推移を示したが、施設としては 30 例目くらいで手術時間が安定しているが、術者 B は極めて少ない症例数で到達している。これは個人の能力に加えて、導入初期からの第

一助手としての経験が反映されているものと思われる。現在、多くの施設で導入している da Vinci Si ではデュアルコンソールが可能となっているため、今後はさらに効率のよい技術の習得が可能となるものと思われる。

## 胃全摘

ロボット手術では腹腔鏡下手術よりも自由度の高い鉗子を使用できるため、より高度な技術が要求される手技で、その優位性が証明される可能性がある。胃癌の手術においては胃全摘でより高度の技術が要求され、腹腔鏡下手術では特に脾動脈周囲や脾門部のリンパ節郭清、再建手技の難易度が高いと考えられている。胃全摘に限ってロボット手術と腹腔鏡下手術を比較した論文が韓国から 2 編報告されている (表 3)<sup>14,15)</sup>。いずれの報告においてもロボット手術は腹腔鏡下手術に比較し手術時間が長いこと以外に、両術式間で有意な差が認められなかった。ただし、Yonsei 大学の D2 郭清に限った検討では、脾動脈周囲と脾門部の郭清リンパ節個数はロボット手術で有意に多かった<sup>15)</sup>。前述したように、ロボット手術は導入早期の成績であることを考慮すれば、より高度な技術を要する部位において腹腔鏡下手術よりも有用な術式となる可能性が示

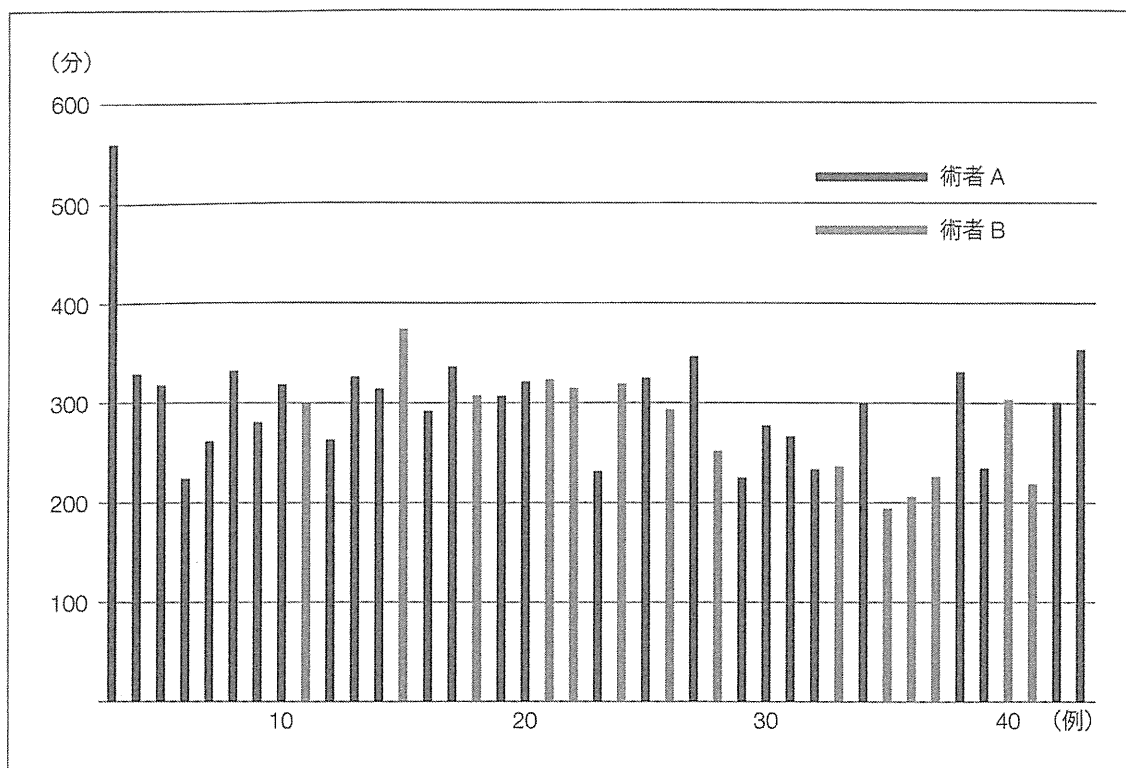


図2 当科におけるロボット胃切除術の手術時間の推移

表3 胃全摘におけるロボット手術と腹腔鏡手術の比較

報告者	報告年	国	施設	手術手技	症例数	手術時間	出血量	郭清リンパ節個数	術後合併症	在院日数
Yoon	2012	韓国	National Cancer Center	RTG	36	305.8+115.8	—	42.8+12.7	16.70%	8.8+3.3
				LTG	65	201.2+57.7	—	39.4+13.4	15.40%	10.3+10.8
						$p < 0.001$		$p = 0.209$	$p = 0.866$	$p = 0.416$
Son	2014	韓国	Yonsei 大学	RTG	51	264.1+46.7	163.4+255.1	47.2*	7.8%**	8.6+12.0
				LTG	58	210.3+61.1	210.7+254.9	42.8	8.60%	7.9+4.8
						$p < 0.001$	$p = 0.360$	$p = 0.210$	$p = 0.883$	$p = 0.666$

\* : 10+#11 : RTG 3.8 vs LTG 1.9 ( $p = 0.014$ ), \*\* : Clavien-Dindo 分類 Grade 2 以上

RTG : robot-assisted total gastrectomy, LTG : laparoscopy-assisted total gastrectomy

唆されている。

## 今後の展望

現時点でロボット支援胃切除の腹腔鏡下胃切除に対する明確な優越性は証明されていない。しかしながら、鉗子の可動制限を受けないことは腹腔鏡下手術に対する大きなメリットであることは否定のできない事実であり、今後のデバイスの開発や手技の工夫などにより、より有用性の高い手技となる可能性が高い。最大の欠点とされている触覚の欠如に関しても、視覚からの補

正が極めて有用で、ある程度慣れることによりマスターコントローラーと鉗子の動作具合から組織に対する緊張の度合いを計り知ることが可能で、virtual tactileが存在するものと思われる。いずれにせよある程度手技が習熟した時点で、腹腔鏡下手術に対する優越性を検証する臨床試験の実施が必要となるものと思われる。

コストの問題に関しても、現時点では1社寡占の状態であるが、今後、順次主要な特許が切れることにより他社から同様な機器が開発、販売されることが期待される。特に、わが国の工業ロボット技術は世界でも

群を抜いているので、次元の異なる優れた機器が開発可能と思われる。ぜひとも政府主導で産学官連携のプロジェクトとして進めていただきたいものである。

保険適用に関しては今後、臨床試験により腹腔鏡下手術に対する何らかの優越性を証明することが必須と思われる。海外からの報告では示されていないものの、われわれおよびその他の施設から、ロボット支援下胃切除では合併症が少ないことが報告されており<sup>2,16)</sup>、一つの臨床指標となりうるものと思われる。

現時点では機器があまりにも高価なため、胃切除に関しては研究的側面が強いと感じられるが、1980年代の腹腔鏡下胆嚢摘出術導入の歴史を振り返ってみれば、ある程度普及した時点で大きなスケールメリットが生ずるため、コストの問題は速やかに解消されるものと思われる。そのためにも国内開発機器の登場は不可欠であり、今後の国内企業の動向に注目したい。

## 文献

- 1) Hashizume M, Sugimachi K : Robot-assisted gastric surgery. Surg Clin North Am 83 : 1429-1444, 2003
- 2) Tokunaga M, Sugisawa N, Kondo J, et al : Early phase II study of robot-assisted distal gastrectomy with nodal dissection for clinical stage IA gastric cancer. Gastric Cancer 17 : 542-547, 2014
- 3) Liao G, Chen J, Ren C, et al : Robotic versus open gastrectomy for gastric cancer : a meta-analysis. PLoS One 8 : e81946, 2013
- 4) Hyun MH, Lee CH, Kim HJ, et al : Systematic review and meta-analysis of robotic surgery compared with conventional laparoscopic and open resections for gastric carcinoma. Br J Surg 100 : 1566-1578, 2013
- 5) Marano A, Choi YY, Hyung WJ, et al : Robotic versus Laparoscopic versus Open Gastrectomy : A Meta-Analysis. J Gastric Cancer 13 : 136-148, 2013
- 6) Xiong J, Nunes QM, Tan C, et al : Comparison of short-term clinical outcomes between robotic and laparoscopic gastrectomy for gastric cancer : a meta-analysis of 2495 patients. J Laparoendosc Adv Surg Tech A 23 : 965-976, 2013
- 7) Liao GX, Xie GZ, Li R, et al : Meta-analysis of outcomes compared between robotic and laparoscopic gastrectomy for gastric cancer. Asian Pac J Cancer Prev 14 : 4871-4875, 2013
- 8) Xiong B, Ma L, Zhang C : Robotic versus laparoscopic gastrectomy for gastric cancer : a meta-analysis of short outcomes. Surg Oncol 21 : 274-281, 2012
- 9) Shen WS, Xi HQ, Chen L, Wei B : A meta-analysis of robotic versus laparoscopic gastrectomy for gastric cancer. Surgical endoscopy, 2014
- 10) Kang BH, Xuan Y, Hur H, et al : Comparison of Surgical Outcomes between Robotic and Laparoscopic Gastrectomy for Gastric Cancer : The Learning Curve of Robotic Surgery. J Gastric Cancer 12 : 156-163, 2012
- 11) Park SS, Kim MC, Park MS, et al : Rapid adaptation of robotic gastrectomy for gastric cancer by experienced laparoscopic surgeons. Surg Endosc 26 : 60-67, 2012
- 12) Zhang X, Tanigawa N : Learning curve of laparoscopic surgery for gastric cancer, a laparoscopic distal gastrectomy-based analysis. Surgical endoscopy 23 : 1259-1264, 2009
- 13) Kim HI, Park MS, Song KJ, et al : Rapid and safe learning of robotic gastrectomy for gastric cancer : Multidimensional analysis in a comparison with laparoscopic gastrectomy. Eur J Surg Oncol 2013
- 14) Yoon HM, Kim YW, Lee JH, et al : Robot-assisted total gastrectomy is comparable with laparoscopically assisted total gastrectomy for early gastric cancer. Surg Endosc 26 : 1377-1381, 2012
- 15) Son T, Lee JH, Kim YM, et al : Robotic spleen-preserving total gastrectomy for gastric cancer : comparison with conventional laparoscopic procedure. Surg Endosc, 2014
- 16) Uyama I, Kanaya S, Ishida Y, et al : Novel integrated robotic approach for suprapancreatic D2 nodal dissection for treating gastric cancer : technique and initial experience. World J Surg 36 : 331-337, 2012

TERASHIMA Masanori, et al  
 静岡県立静岡がんセンター胃外科  
 〒411-8777 静岡県駿東郡長泉町下長窪 1007

## MEDICAL BOOK INFORMATION

医学書院

# 消化器外科レジデントマニュアル 第3版

監修 小西文雄  
 編集 力山敏樹

●B6変型 頁336 2014年  
 定価:本体4,200円+税  
 ISBN978-4-260-01964-4

消化器外科対象疾患の診断・治療に関する解説はもとより、術前検査の進め方、抗菌薬の投与方法、術期の栄養管理、化学療法の注意点、緩和ケアの実際等々、外科診療の現場で必要とされる知識・情報をコンパクトにまとめたポケットマニュアル。知りたいことを素早く確認できるポイントに絞った記載は、カンファレンスや患者への説明などにおいても有用。外来で、病棟で、常に携帯したい実践的な1冊。

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

Masao Yoshida · Naomi Kakushima · Masanori Tokunaga · Masaki Tanaka · Kohei Takizawa · Kenichiro Imai · Kinichi Hotta · Hiroyuki Matsubayashi · Yutaka Tanizawa · Etsuro Bando · Taiichi Kawamura · Masanori Terashima · Hiroyuki Ono

Received: 6 June 2014 / Accepted: 17 October 2014  
© Springer Science+Business Media New York 2014

### 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

---

M. Yoshida · N. Kakushima (✉) · M. Tanaka · K. Takizawa · K. Imai · K. Hotta · H. Matsubayashi · H. Ono  
Division of Endoscopy, Shizuoka Cancer Center, 1007  
Shimonagakubo, Nagaizumi, Sunto-gun, Shizuoka 411-8777,  
Japan  
e-mail: kakushin-ky@umin.ac.jp

M. Yoshida  
e-mail: ma.yoshida@scchr.jp

M. Tokunaga · Y. Tanizawa · E. Bando · T. Kawamura · M. Terashima  
Division of Gastric Surgery, Shizuoka Cancer Center, Shizuoka,  
Japan

**Table 1** Absolute and expanded indications for endoscopic resection

Absolute indication
Differentiated-type intramucosal cancer $\leq 20$ mm in size without ulceration
Expanded indications
Differentiated-type intramucosal cancer $\geq 20$ mm in size without ulceration
Differentiated-type intramucosal cancer $\leq 30$ mm in size with ulceration
Undifferentiated-type intramucosal cancer $\leq 20$ 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) <sup>†</sup> $\leq 30$ mm in size

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

<sup>†</sup> ASA American society of anesthesiologists

<sup>‡</sup> 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

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

Procedure time, median (range), min	52 (10–155)
Adverse events, <i>n</i> (%)	
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, <i>n</i> (%)	
Differentiated type	38 (100)
Undifferentiated type	0 (0)
Depth of tumor, <i>n</i> (%)	
pT1a	31 (81.6)
pT1b	
SM1 (Invasion depth < 500 μm)	6 (15.8)
SM2 (Invasion depth ≥ 500 μm)	1 (2.6)
Ulceration, <i>n</i> (%)	6 (15.8)
Lymphovascular infiltration, <i>n</i> (%)	1 (2.6)
En bloc resection plus R0 resection, <i>n</i> (%)	37 (97.4)
Curability, <i>n</i> (%)	
Curative resection	35 (92.1)
Noncurative resection	3 (7.9)

#### ER endoscopic resection

II, 4 patients (12.9 %); stage III, 1 patient (3.2 %); and stage IV, 1 patient (3.2 %).

#### 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

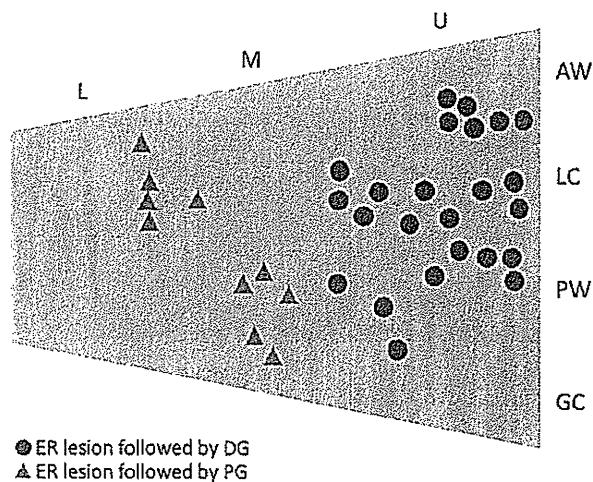
**Table 5** Results of gastrectomy after curative endoscopic resection ( $n = 31$ )

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 $\mu$ m)	5 (16.1)
SM2 (Invasion depth $\geq$ 500 $\mu$ m)	12 (38.7)
pT2 (MP, muscularis propria) or beyond	8 (25.8)
Lymph node metastasis, $n$ (%)	11 (35.5)
Distant metastasis <sup>†</sup> , $n$ (%)	1 (3.2)
Final stage <sup>‡</sup> , $n$ (%)	
I	25 (80.6)
II	4 (12.9)
III	1 (3.2)
IV	1 (3.2)

ER endoscopic resection

<sup>†</sup> The case of distant metastasis was peritoneal lavage cytology positive<sup>‡</sup> 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

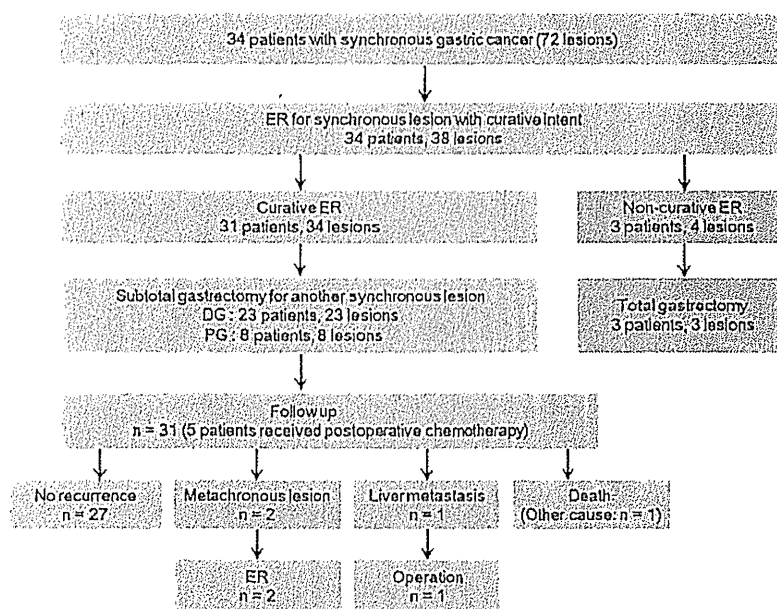
ER, particularly ESD, has been accepted as the most effective and less invasive treatment for superficial gastric neoplasms. ER was comparable to surgery in terms of risk of death when endoscopic curative resection was achieved [11, 12]. Although risks of remnant gastric cancer remain because of preservation 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

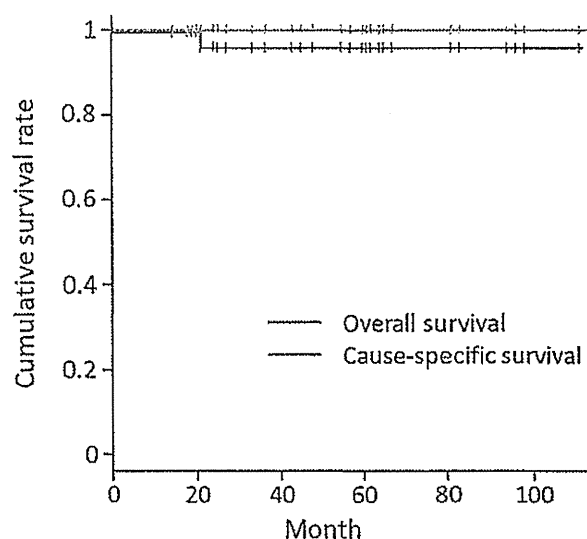


**Table 6** Clinical outcomes in 31 patients who underwent subtotal gastrectomy after pre-emptive endoscopic resection

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

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



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

opportunity for minimally invasive surgery in patients with synchronous gastric cancers with promising oncological outcomes and maintains QOL.

**Acknowledgments** The authors thank the SCC clinical trial management center (Mr. Keita Mori) for data management and helpful comments about statistics.

**Disclosures** Masao Yoshida, Naomi Kakushima, Masanori Tokunaga, Masaki Tanaka, Kohei Takizawa, Kenichiro Imai, Kinichi Hotta, Hiroyuki Matsubayashi, Yutaka Tanizawa, Etsuro Bando,

Taiichi Kawamura, Masanori Terashima, and Hiroyuki Ono have no conflict of interest or financial ties to disclose.

## References

- Martin RCG, Jaques D, Brennan M, Karpeh M (2002) Achieving RO resection for locally advanced gastric cancer: is it worth the risk of multiorgan resection? *J Am Coll Surg* 194:568–577
- Japanese Gastric Cancer Association (2011) Japanese gastric cancer treatment guidelines 2010 (ver. 3). *Gastric Cancer* 14:113–123
- Kim AR, Cho J, Hsu YJ, Choi MG, Noh JH, Sohn TS, Bae JM, Yun YH, Kim S (2012) Changes of quality of life in gastric cancer patients after curative resection: a longitudinal cohort study in Korea. *Ann Surg* 256:1008–1013
- Jentschura D, Winkler M, Strohmeier N, Rumstadt B, Hagmüller E (1997) Quality-of-life after curative surgery for gastric cancer: a comparison between total gastrectomy and subtotal gastric resection. *Hepatogastroenterology* 44:1137–1142
- Kiyama T, Mizutani T, Okuda T, Fujita I, Tokunaga A, Tajiri T, Barbul A (2005) Postoperative changes in body composition after gastrectomy. *J Gastrointest Surg* 9:313–319
- Gotoda T, Yanagisawa A, Sasako M, Ono H, Nakanishi Y, Shimoda T, Kato Y (2000) Incidence of lymph node metastasis from early gastric cancer: estimation with a large number of cases at two large centers. *Gastric Cancer* 3:219–225
- Soetikno R, Kaltenbach T, Yeh R, Gotoda T (2005) Endoscopic mucosal resection for early cancers of the upper gastrointestinal tract. *J Clin Oncol* 23:4490–4498
- Hirasawa T, Gotoda T, Miyata S, Kato Y, Shimoda T, Taniguchi H, Fujisaki J, Sano T, Yamaguchi T (2009) Incidence of lymph node metastasis and the feasibility of endoscopic resection for undifferentiated-type early gastric cancer. *Gastric Cancer* 12:148–152
- Rembacken BJ, Gotoda T, Fujii T, Axon AT (2001) Endoscopic mucosal resection. *Endoscopy* 33:709–718
- Gotoda T (2007) Endoscopic resection of early gastric cancer. *Gastric Cancer* 10:1–11
- Choi KS, Jung HY, Choi KD, Lee GH, Song HJ, Kim do H, Lee JH, Kim MY, Kim BS, Oh ST, Yook JH, Jang SJ, Yun SC, Kim SO, Kim JH (2011) EMR versus gastrectomy for intramucosal gastric cancer: comparison of long-term outcomes. *Gastrointest Endosc* 73:942–948
- Chiu FW, Teoh AY, To KF, Wong SK, Liu SY, Lam CC, Yung MY, Chan FK, Lau JY, Ng EK (2012) Endoscopic submucosal dissection (ESD) compared with gastrectomy for treatment of early gastric neoplasia: a retrospective cohort study. *Surg Endosc* 26:3584–3591
- Everett SM, Axon AT (1997) Early gastric cancer in Europe. *Gut* 41:142–150
- Jang MY, Cho JW, Oh WG, Ko SJ, Han SH, Baek HK, Lee YJ, Kim JW, Jung GM, Cho YK (2013) Clinicopathological characteristics of synchronous and metachronous gastric neoplasms after endoscopic submucosal dissection. *Korean J Intern Med* 28:687–693
- Ono H, Kondo H, Gotoda T, Shirao K, Yamaguchi H, Saito D, Hosokawa K, Shimoda T, Yoshida S (2001) Endoscopic mucosal resection for treatment of early gastric cancer. *Gut* 48:225–229
- Kakushima N (2011) Endoscopic submucosal dissection using the insulated-tip knife. *Tech Gastrointest Endosc* 13:63–69
- Tanaka M, Ono H, Hasuike N, Takizawa K (2008) Endoscopic submucosal dissection of early gastric cancer. *Digestion* 77(Suppl 1):23–28
- Nashimoto A, Akazawa K, Isobe Y, Miyashiro I, Katai H, Kodera Y, Tsujitani S, Seto Y, Furukawa H, Oda I, Ono H, Tanabe S, Kaminishi M (2013) Gastric cancer treated in 2002 in Japan: 2009 annual report of the JGCA nationwide registry. *Gastric Cancer* 16:1–27
- Hosokawa O, Kaizaki Y, Watanabe K, Hattori M, Douden K, Hayashi H, Maeda S (2002) Endoscopic surveillance for gastric remnant cancer after early cancer surgery. *Endoscopy* 34:469–473
- Nozaki I, Hato S, Kobatake T, Ohta K, Kubo Y, Nishimura R, Kurita A (2014) Incidence of metachronous gastric cancer in the remnant stomach after synchronous multiple cancer surgery. *Gastric Cancer* 17:61–66
- Nonaka S, Oda I, Makazu M, Haruyama S, Abe S, Suzuki H, Yoshinaga S, Nakajima T, Kushima R, Saito Y (2013) Endoscopic submucosal dissection for early gastric cancer in the remnant stomach after gastrectomy. *Gastrointest Endosc* 78:63–72
- Nishide N, Ono H, Kakushima N, Takizawa K, Tanaka M, Matsubayashi H, Yamaguchi Y (2012) Clinical outcomes of endoscopic submucosal dissection for early gastric cancer in remnant stomach or gastric tube. *Endoscopy* 44:577–583
- Oda I, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S (2006) A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 9:262–270
- Fujishiro M, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Kobayashi K, Hashimoto T, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M (2006) Successful nonsurgical management of perforation complicating endoscopic submucosal dissection of gastrointestinal epithelial neoplasms. *Endoscopy* 38:1001–1006
- Minami S, Gotoda T, Ono H, Oda I, Hamanaka H (2006) Complete endoscopic closure of gastric perforation induced by endoscopic resection of early gastric cancer using endoclips can prevent surgery (with video). *Gastrointest Endosc* 63:596–601
- Ichikawa D, Komatsu S, Kubota T, Okamoto K, Shiozaki A, Fujiwara H, Otsuji E (2014) Long-term outcomes of patients who underwent limited proximal gastrectomy. *Gastric Cancer* 17:141–145
- Karanicolas P, Graham D, Gönen M, Strong V, Brennan M, Coit D (2013) Quality of life after gastrectomy for adenocarcinoma: a prospective cohort study. *Ann Surg* 257:1039–1046
- Iwasaki Y, Sasako M, Yamamoto S, Nakamura K, Sano T, Katai H, Tsujinaka T, Nashimoto A, Fukushima N, Tsuburaya A (2013) Phase II study of preoperative chemotherapy with S-1 and cisplatin followed by gastrectomy for clinically resectable type 4 and large type 3 gastric cancers (JCOG0210). *J Surg Oncol* 107:741–745

## 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

Koji Nakada · Masami Ikeda · Masazumi Takahashi · Shinichi Kinami · Masashi Yoshida · Yoshikazu Uenosono · Yoshiyuki Kawashima · Atsushi Oshio · Yoshimi Suzukamo · Masanori Terashima · Yasuhiro Kodera

Received: 3 September 2013 / Accepted: 13 January 2014 / Published online: 11 February 2014  
© The International Gastric Cancer Association and The Japanese Gastric Cancer Association 2014

### 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  $\alpha$  (0.65–0.88).

For the Japan Postgastrectomy Syndrome Working Party.

K. Nakada (✉)  
Department of Surgery, The Jikei University School of Medicine, 3-25-8, Nishishimbashi, Minato-ku, Tokyo 105-8461, Japan  
e-mail: nakada@jikei.ac.jp

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

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

S. Kinami  
Department of Surgical Oncology, Kanazawa Medical School, Kanazawa, Japan

M. Yoshida  
Surgery and Digestive Diseases Center, International University of Health and Welfare, Mita Hospital, Tokyo, Japan

Y. Uenosono  
Department of Digestive Surgery, Kagoshima University Graduate School of Medicine, Kagoshima, Japan

Y. Kawashima  
Division of Gastroenterological Surgery, Saitama Cancer Center, Saitama, Japan

A. Oshio  
Faculty of Letters, Arts and Sciences, Waseda University, Tokyo, Japan

Y. Suzukamo  
Department of Physical Medicine and Rehabilitation, Tohoku University Graduate School of Medicine, Sendai, Japan

M. Terashima  
Division of Gastric Surgery, Shizuoka Cancer Center, Shizuoka, Japan

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

**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		Total symptom scale (above seven subscales)		
		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				
		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*	Five-point Likert scale	Quality of ingestion subscale* (items 38–40)
				35	Ingested amount of food per day*		
		36		Frequency of main meals			
		Meals (quality)	37	Frequency of additional meals			
38			Appetite*				
39			Hunger feeling*				
40			Satiety feeling*				
Meals (amount) 2	41	Necessity for additional meals					
	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
QOL	42	Ability for working	1.84	0.88
	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

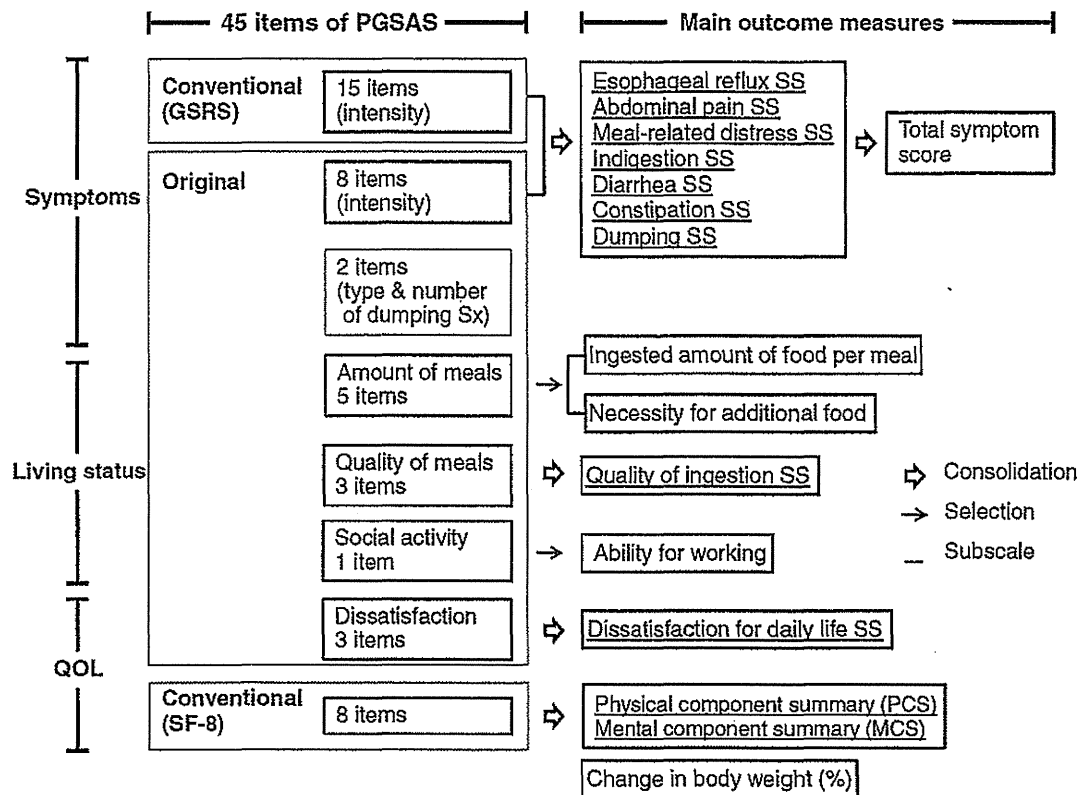


Fig. 1 The process of consolidation and selection to constitute main outcome measures

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 center. 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

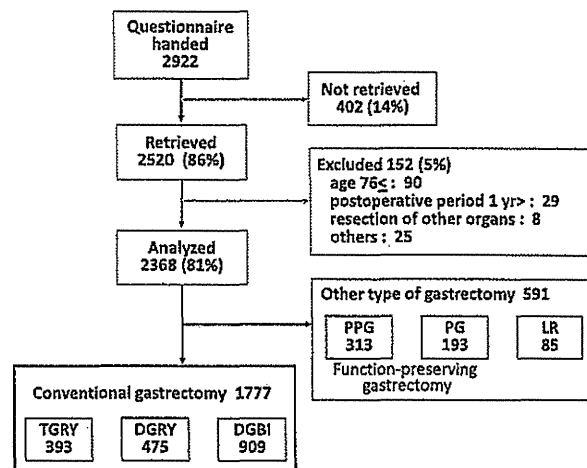


Fig. 2 Outline of the study

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  $\alpha$  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  $62.1 \pm 9.2$  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  $37 \pm 27$  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  $9.5 \pm 8.0$  %. 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 ( $\beta$ ) 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
<b>I. Esophageal reflux subscale</b>									
Acid regurgitation	1.81	1.12	<b>0.968</b>	-0.031	-0.059	-0.005	0.013	-0.020	-0.065
Bile regurgitation	1.77	1.07	<b>0.932</b>	-0.094	-0.127	0.048	-0.001	0.018	0.020
Heartburn	1.75	1.01	<b>0.638</b>	0.236	0.091	0.004	-0.048	-0.025	-0.067
Nausea and vomiting	1.49	0.93	<b>0.617</b>	-0.039	0.222	-0.144	0.049	0.029	0.091
<b>II. Abdominal pain subscale</b>									
Sucking sensations in the epigastrium	1.49	0.82	0.231	<b>0.782</b>	-0.309	-0.006	0.000	0.047	0.042
Abdominal pains	1.74	0.96	0.049	<b>0.781</b>	0.176	-0.052	0.001	-0.042	-0.024
Lower abdominal pains	1.87	1.11	-0.258	<b>0.547</b>	0.322	0.025	0.117	0.108	0.070
<b>III. Meal-related distress subscale</b>									
Postprandial fullness	2.39	1.21	0.051	0.004	<b>0.786</b>	0.019	-0.030	0.021	0.081
Early satiation	2.41	1.21	0.019	-0.002	<b>0.738</b>	0.006	-0.009	0.073	0.089
Sense of foods sticking	1.79	1.07	0.388	-0.259	<b>0.550</b>	-0.026	0.000	-0.019	0.160
<b>IV. Indigestion subscale</b>									
Increased flatulence	2.72	1.43	-0.098	-0.245	-0.118	<b>0.880</b>	0.110	0.108	0.080
Borborygmus	1.87	1.06	0.056	0.107	-0.065	<b>0.723</b>	0.050	-0.135	0.084
Abdominal distension	1.99	1.12	0.008	0.138	0.174	<b>0.675</b>	-0.049	0.034	-0.067
Eructation	1.70	0.97	0.211	0.141	0.197	<b>0.546</b>	-0.121	-0.001	-0.210
<b>V. Diarrhea subscale</b>									
Increased passage of stools	2.13	1.29	-0.004	0.035	-0.072	0.003	<b>0.957</b>	-0.045	-0.030
Loose stools	2.10	1.18	0.009	0.032	-0.034	-0.018	<b>0.940</b>	-0.027	-0.054
Urgent need for defecation	2.19	1.30	0.039	-0.064	-0.030	-0.040	<b>0.895</b>	0.008	0.019
<b>VI. Constipation subscale</b>									
Decreased passage of stools	2.12	1.25	-0.001	0.029	-0.043	-0.029	-0.068	<b>0.956</b>	-0.016
Hard stools	1.96	1.12	0.017	0.027	-0.012	-0.058	-0.113	<b>0.942</b>	-0.021
Feeling of incomplete evacuation	2.42	1.16	-0.037	-0.125	0.099	0.099	0.301	<b>0.667</b>	-0.039
<b>VII. Dumping subscale</b>									
Late dumping symptoms	1.81	1.17	0.005	0.020	0.001	0.048	-0.053	0.006	<b>0.837</b>
Early dumping general symptoms	1.99	1.21	-0.001	-0.031	0.289	-0.057	0.047	-0.053	<b>0.778</b>
Early dumping abdominal symptoms	2.32	1.31	-0.124	0.112	0.369	0.067	0.248	0.004	<b>0.391</b>

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 GRS 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  $\alpha$ , 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 ( $r > 0.3$ ).