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

Table 6 Inter-factor correlations among symptom subscales of the PGSAS-45

Subscale	I	II	III	IV	V	VI	VII
I. Esophageal reflux	1.000						
II. Abdominal pain	**0.590**	1.000					
III. Meal-related distress	**0.598**	**0.608**	1.000				
IV. Indigestion	**0.545**	**0.549**	**0.584**	1.000			
V. Diarrhea	0.276	*0.374*	*0.364*	*0.450*	1.000		
VI. Constipation	*0.391*	*0.445*	*0.447*	*0.454*	0.274	1.000	
VII. Dumping	**0.514**	**0.607**	**0.640**	**0.575**	*0.467*	*0.391*	1.000
Interpretation of effect size	*r*						
Small	≥0.100						
Medium	*≥0.300*						
Large	**≥0.500**						

The fonts of values of *r* were varied according to their effect size; 'Small' as normal fonts, 'Medium' as italic fonts and 'Large' as bold fonts

PGS [1–6]. Although the primary objective of gastrectomy is to cure cancer, the second most important goal is to minimize PGS-related adverse events and to preserve the patients' QOL. This goal is particularly important in the Far East where gastric cancer is often found at early clinical stages so that more patients manage to survive their cancer and consequently need to face the PGS in the long term [9]. It is known that the type of gastrectomy affects the incidence and severity of PGS [10–21], and various procedures to preserve or reconstruct gastric function have been proposed to confront these problems [7, 8]. To gain deeper understanding of the PGS, a group of iatrogenic disorders, and treat them appropriately, it is important to grasp the impact of various symptoms, along with feeding problems and body weight loss, to the living status and QOL of the patients. In addition, identifying the problems and their correlations with various types of surgical procedures may lead to evolution of a novel surgical technique as well as more adequate selection of conventional technique to circumvent the problems. However, instruments designed to focus on the evaluation of PGS have not been established to date.

Patient-reported outcome directly reflects the symptoms and complaints of patients. This type of report is particularly valuable as an endpoint when evaluating QOL after surgery because PGS often is detected only through complaints from the patients [22]. Several studies made comparisons between different surgical procedures to find which procedure is beneficial for the patients from the point of view of PGS, but these comparisons often looked only at specific outcomes that particularly aroused the interest of the investigators [17, 19] and were not necessarily comprehensive and convincing. Moreover, using arbitrary endpoints renders comparisons between different studies impossible. More recently, investigators turned to the established and authorized questionnaires for comparisons between gastric surgery procedures [10–15, 18, 20], because there are several combinations of core questionnaires and disease-specific modules that are considered appropriate and have been approved for evaluation of QOL [23, 24]. A combination of SF-36, a core questionnaire, and GSRS, a symptom-specific QOL, has been one of the examples [11, 14], but the GSRS may have a tendency to overlook some of the symptoms that are peculiar to the patients who have undergone gastrectomy and are unusual for other disorders of the gastrointestinal tract. EORTC QLQ-C30 [25], a cancer-specific core questionnaire, and STO-22 [26] is another combination that has been used to evaluate postgastrectomy patients [12, 13]. However, these questionnaires have been developed to evaluate QOL of the patients who are burdened with cancer and are receiving treatments rather than those who became cancer free through surgery but are suffering from PGS.

The investigators who wish to evaluate PGS had thus been obliged to turn to modules designed for other purposes because of the lack of an optimally constructed questionnaire. Therefore, there are possibilities that a large proportion of these studies have overlooked several important postgastrectomy symptoms that actually affect the living status of the patients but cannot be evaluated by conventional scales. More recently, Nakamura et al. reported on DAUGS, a questionnaire designed to measure symptoms after upper gastrointestinal surgery, and the actual attempt to use this in the clinical setting [16, 21]. However, items concerning living status or QOL of the patients rather than the symptoms were lacking in the DAUGS.

PGSAS-45 was constructed through contribution of several expert surgeons with abundant experience coping with postgastrectomy patients as the only comprehensive questionnaire that is suitable for evaluating patients who have undergone various types of gastrectomy and reconstruction. PGSAS-45 is a package with complex structures

and includes items from multiple dimensions. Its core stems from internationally acclaimed questionnaires in that it contains items from SF-8 [27] and GSRS under the permission of each copyright owner for this study. GSRS has five subscales that are in common with the PGSAS-45 and has been extensively used to evaluate patients with various disorders of the gastrointestinal tract [28, 29]. However, it does not cover some symptoms that are peculiar to postgastrectomy patients such as postprandial satiation and symptoms related to the dumping syndrome. PGSAS-45 was constructed through contributions of several expert surgeons during the comprehensive item generation phase. Inclusion of the 8 additional symptom-related items that were proposed and selected by the surgeons to evaluate postgastrectomy patients is expected to increase sensitivity to more meticulously detect and evaluate the PGS. Multivariate regression analysis has shown through larger β coefficients that the 8 items actually correlated more significantly with most of the subscales looking at the living status and QOL of the patients when compared with the 15 items derived from GSRS. Moreover, the R^2 values of the JPGSWP items as calculated by the bivariate regression analysis were almost equivalent to R^2 values of all symptom items calculated by the multivariate analysis, indicating that the 8 items had a decisive role in evaluating the effect of surgery on the living status and QOL of the patients. The relatively large effect size of the total symptoms in the R^2 value, which was calculated by multivariate analysis, indicates that the symptom has a certain impact on living status and QOL in the postgastrectomy patients (Table 4).

Factor analysis resulted in construction of five subscales that are in common with the GSRS. Two of these subscales actually contained items that are different from the GSRS. In addition, two novel subscales, meal-related distress and dumping, were generated that would apparently result in extra sensitivity to detect symptoms. Two further subscales showing dissatisfaction for daily life and quality of ingestion were added to augment QOL and living status domains. Cronbach's α is a coefficient of internal consistency and is commonly used as an estimate of the reliability. The interpretation of Cronbach's α is shown in Table 5. Acceptable internal consistency was observed in all nine subscales, including the four new subscales.

Conclusions

In conclusion, we have developed a useful multidimensional integrated quality of life measure, PGSAS-45. This questionnaire benefited from addition of the eight symptom-related items derived from comprehensive item generation process contributed by expert surgeons, and led to generation of two additional subscales: meal-related distress subscale and dumping subscale. It is expected to serve as a gold standard in the evaluation of PGS and provide a meticulous profile of symptoms in postgastrectomy patients. Furthermore, the PGSAS study generated a prospective multi-institutional database of HRQOL assessed by PGSAS-45 among patients who were treated by the six most frequent types of gastrectomy. Several comparative analyses using these data and main outcome measures as defined in the current study are ongoing, and results are awaited.

Acknowledgments This study was supported by a grant from Jikei University and the Japanese Society for Gastro-surgical Pathophysiology. This study was conducted by JPGSWP and registered to UMIN-CTR #000002116 entitled as "A study to observe correlation between resection and reconstruction procedures employed for gastric neoplasms and development of postgastrectomy syndrome." The results of this study were presented at Digestive Disease Week 2013, Orland, FL, USA [30]. The authors thank all the physicians who participated in this study and the patients whose cooperation made this study possible.

References

1. Bolton JS, Conway WC 2nd. Postgastrectomy syndromes. Surg Clin N Am. 2011;91(5):1105–22.
2. Carvajal SH, Mulvihill SJ. Postgastrectomy syndromes: dumping and diarrhea. Gastroenterol Clin N Am. 1994;23(2):261–79.
3. Cooperman AM. Postgastrectomy syndromes. Surg Annu. 1981;13:139–61.
4. Eagon JC, Miedema BW, Kelly KA. Postgastrectomy syndromes. Surg Clin N Am. 1992;72(2):445–65.
5. Harju E. Metabolic problems after gastric surgery. Int Surg. 1990;75(1):27–35.
6. Jay BS, Burrell M. Iatrogenic problems following gastric surgery. Gastrointest Radiol. 1977;2(3):239–57.
7. Katai H. Function-preserving surgery for gastric cancer. Int J Clin Oncol. 2006;11(5):357–66.
8. Lehnert T, Buhl K. Techniques of reconstruction after total gastrectomy for cancer. Br J Surg. 2004;91(5):528–39.
9. Maruyama K, Kaminishi M, Hayashi K, Isobe Y, Honda I, Katai H, et al. Gastric cancer treated in 1991 in Japan: data analysis of nationwide registry. Gastric Cancer. 2006;9(2):51–66.
10. Endo S, Nishida T, Nishikawa K, Yumiba T, Nakajima K, Yasumasa K, et al. Motility of the pouch correlates with quality of life after total gastrectomy. Surgery (St. Louis). 2006;139(4):493–500.
11. Hayami M, Seshimo A, Miyake K, Shimizu S, Kameoka S. Effects of emptying function of remaining stomach on QOL in postgastrectomy patients. World J Surg. 2012;36(2):373–8.
12. Huang CC, Lien HH, Wang PC, Yang JC, Cheng CY, Huang CS. Quality of life in disease-free gastric adenocarcinoma survivors: impacts of clinical stages and reconstructive surgical procedures. Dig Surg. 2007;24(1):59–65.
13. Kobayashi D, Kodera Y, Fujiwara M, Koike M, Nakayama G, Nakao A. Assessment of quality of life after gastrectomy using EORTC QLQ-C30 and STO22. World J Surg. 2011;35(2):357–64.
14. Kono K, Iizuka H, Sekikawa T, Sugai H, Takahashi A, Fujii H, et al. Improved quality of life with jejunal pouch reconstruction after total gastrectomy. Am J Surg. 2003;185(2):150–4.

15. Lee MS, Ahn SH, Lee JH, Park do J, Lee HJ, Kim HH, et al. What is the best reconstruction method after distal gastrectomy for gastric cancer? Surg Endosc. 2012;26(6):1539–47.
16. Nakamura M, Kido Y, Yano M, Hosoya Y. Reliability and validity of a new scale to assess postoperative dysfunction after resection of upper gastrointestinal carcinoma. Surg Today. 2005;35(7):535–42.
17. Nakane Y, Michiura T, Inoue K, Iiyama H, Okumura S, Yamamichi K, et al. A randomized clinical trial of pouch reconstruction after total gastrectomy for cancer: which is the better technique, Roux-en-Y or interposition? Hepatogastroenterology. 2001;48(39):903–7.
18. Namikawa T, Kitagawa H, Okabayashi T, Sugimoto T, Kobayashi M, Hanazaki K. Roux-en-Y reconstruction is superior to Billroth I reconstruction in reducing reflux esophagitis after distal gastrectomy: special relationship with the angle of His. World J Surg. 2010;34(5):1022–7.
19. Nunobe S, Okaro A, Sasako M, Saka M, Fukagawa T, Katai H, et al. Billroth I versus Roux-en-Y reconstructions: a quality-of-life survey at 5 years. Int J Clin Oncol. 2007;12(6):433–9.
20. Svedlund J, Sullivan M, Liedman B, Lundell L, Sjodin I. Quality of life after gastrectomy for gastric carcinoma: controlled study of reconstructive procedures. World J Surg. 1997;21(4):422–33.
21. Takiguchi S, Yamamoto K, Hirao M, Imamura H, Fujita J, Yano M, et al. A comparison of postoperative quality of life and dysfunction after Billroth I and Roux-en-Y reconstruction following distal gastrectomy for gastric cancer: results from a multi-institutional RCT. Gastric Cancer. 2012;15(2):198–205.
22. Karanicolas PJ, Bickenbach K, Jayaraman S, Pusic AL, Coit DG, Guyatt GH, et al. Measurement and interpretation of patient-reported outcomes in surgery: an opportunity for improvement. J Gastrointest Surg. 2011;15(4):682–9.
23. Borgaonkar MR, Irvine EJ. Quality of life measurement in gastrointestinal and liver disorders. Gut. 2000;47(3):444–54.
24. Moyer CA, Fendrick AM. Measuring health-related quality of life in patients with upper gastrointestinal disease. Dig Dis. 1998;16(5):315–24.
25. Aaronson NK, Ahmedzai S, Bergman B, Bullinger M, Cull A, Duez NJ, et al. The European Organization for Research and Treatment of Cancer QLQ-C30: a quality-of-life instrument for use in international clinical trials in oncology. J Natl Cancer Inst. 1993;85(5):365–76.
26. Vickery CW, Blazeby JM, Conroy T, Arraras J, Sezer O, Koller M, et al. Development of an EORTC disease-specific quality of life module for use in patients with gastric cancer. Eur J Cancer. 2001;37(8):966–71.
27. Turner-Bowker DM, Bayliss MS, Ware JE Jr, Kosinski M. Usefulness of the SF-8 Health Survey for comparing the impact of migraine and other conditions. Qual Life Res. 2003;12(8):1003–12.
28. Svedlund J, Sjodin I, Dotevall G. GSRS—a clinical rating scale for gastrointestinal symptoms in patients with irritable bowel syndrome and peptic ulcer disease. Dig Dis Sci. 1988;33(2):129–34.
29. Revicki DA, Wood M, Wiklund I, Crawley J. Reliability and validity of the Gastrointestinal Symptom Rating Scale in patients with gastroesophageal reflux disease. Qual Life Res. 1998;7(1):75–83.
30. Nakada K, Ikeda M, Takahashi M, Kinami S, Yoshida M, Uenosono Y, et al. Development and validation of PGSAS-45, an integrated questionnaire to assess postgastrectomy syndrome. Gastroenterology. 2013;144(5 suppl 1):S-1111.

Journal of Surgical Oncology 2014;109:208–212

Efficacy of Endoscopic Gastroduodenal Stenting for Gastric Outlet Obstruction due to Unresectable Advanced Gastric Cancer: A Prospective Multicenter Study

SHUNJI ENDO, MD,[1] SHUJI TAKIGUCHI, MD,[2]* YASUHIRO MIYAZAKI, MD,[2] KAZUHIRO NISHIKAWA, MD,[3] HIROSHI IMAMURA, MD,[4] KO TAKACHI, MD,[5] YUTAKA KIMURA, MD,[6] ATSUSHI TAKENO, MD,[7] SHIGEYUKI TAMURA, MD,[7] MASAKI MORI, MD,[2] AND YUICHIRO DOKI, MD,[2] on behalf of the CLINICAL STUDY GROUP OF OSAKA UNIVERSITY (CSGO), UPPER GI GROUP

[1]*Department of Gastroenterological Surgery, Higashiosaka City General Hospital, Osaka, Japan*
[2]*Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Osaka, Japan*
[3]*Department of Surgery, Osaka General Medical Center, Osaka, Japan*
[4]*Department of Surgery, Sakai City Hospital, Osaka, Japan*
[5]*Department of Surgery, Kinki Central Hospital, Hyogo, Japan*
[6]*Department of Surgery, NTT West Osaka Hospital, Osaka, Japan*
[7]*Department of Surgery, Kansai Rosai Hospital, Hyogo, Japan*

Background and Objectives: Gastroduodenal stents for gastric outlet obstruction due to unresectable advanced gastric cancer are increasingly used; however, their effects have not been fully evaluated.
Methods: A multicenter prospective observational study was performed. Patients were eligible if they had stage IV gastric cancer with a gastric outlet obstruction scoring system (GOOSS) score of 0 (no oral intake) or 1 (liquids only). Self-expandable metallic stents were delivered endoscopically. The effects of stents were evaluated.
Results: Twenty patients were enrolled and 18 were eligible (15 men, three women; median age, 70 years). Stent placement was successfully performed in all patients, with no complications. After stenting, a GOOSS score of 2 (soft solids only) or 3 (low-residue or full diet) was achieved in 13 (72%) patients. An improvement in the GOOSS score by one or more points was obtained in 16 (94%) patients. The median duration of fasting and hospital stay was 3 (range, 0–9) days and 18 (6–168) days, respectively. Chemotherapy was performed after stenting in 13 (72%) patients.
Conclusions: Gastroduodenal stents are thought to be feasible, safe, and effective for gastric outlet obstruction due to unresectable advanced gastric cancer, with rapid clinical relief and a short hospital stay.
J. Surg. Oncol. 2014;109:208–212. © 2013 Wiley Periodicals, Inc.

KEY WORDS: **gastric outlet obstruction; stomach neoplasms; stent**

INTRODUCTION

Gastric cancer is one of the most common cancers worldwide and leads to a poor prognosis. In Japan, early detection has increased the number of curative resections and diminished the number of cancer deaths. However, many cases are still detected in the unresectable advanced stage. Advanced gastric cancer often results in gastric outlet obstruction (GOO). GOO causes vomiting, nausea, weight loss, and intolerance to oral feeding, and diminishes the quality of life in these patients who have limited life expectancies. Chemotherapy is indicated for patients with unresectable advanced gastric cancer. However, it is difficult for patients with GOO to orally take S-1, which is included in the first-line regimen for unresectable gastric cancer recommended in Japanese gastric cancer treatment guidelines 2010 [1].

The treatment for GOO has traditionally been surgical gastrojejunostomy. Previously, we have reported the clinical outcome for palliative gastrojejunostomy in unresectable advanced gastric cancer, resulting in good improvement of oral food intake with acceptable morbidity and mortality [2]. However, invasiveness of surgery with general anesthesia is problematic because most of those with GOO have a poor general condition.

Currently, endoscopic placement of self-expandable metallic stents (SEMSs) is increasingly used as a less invasive method for palliative treatment of GOO caused by biliary-pancreatic malignancies. The efficacy and safety of SEMSs have been reported with an early food intake, short hospital stay, and low total hospital costs [3,4]. However, the effects of SEMSs for GOO with gastric cancer have not been fully evaluated.

In Japan, SEMSs were not common because this procedure was not included in the Japanese health insurance system. In April 2010, the Japanese payment system for medical services was revised, and endoscopic gastroduodenal stent placement for GOO due to malignancies was approved by the Japanese health insurance system.

Abbreviations: GOO, gastric outlet obstruction; SEMS, self-expandable metallic stent; OS, overall survival; UICC, the International Union Against Cancer; PS, Eastern Cooperative Oncology Group Performance Status; GOOSS, gastric outlet obstruction scoring system; BW, body weight; T, depth of tumor invasion; N, lymph node metastasis; M, distant metastasis; MST, median survival time.

*Correspondence to: Shuji Takiguchi, Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita, 565-0871 Osaka, Japan. Fax: 81-6-6789-3259.
E-mail: stakiguchi@gesurg.med.osaka-u.ac.jp

Received 30 August 2013; Accepted 14 October 2013

DOI 10.1002/jso.23486

Published online 6 November 2013 in Wiley Online Library (wileyonlinelibrary.com).

In this study, we aimed to prospectively evaluate the effect of SEMSs on the rate of improvement of clinical symptoms in patients with GOO due to unresectable advanced gastric cancer. Additional aims were to study the feasibility, complications, duration of fasting after stenting, duration of the hospital stay, feasibility of chemotherapy after stenting, need for re-intervention, and overall survival (OS). This is the first prospective multicenter study to evaluate the effects of SEMSs for GOO due to advanced gastric cancer.

MATERIALS AND METHODS

Patients and Data Retrieval

This prospective multicenter clinical trial was carried out at 11 institutions belonging to the Clinical Study Group of Osaka University, Upper GI Group between February 2011 and January 2013. Eligibility criteria for participation included the following: non-surgically treated patients with histologically diagnosed primary gastric adenocarcinoma, which was not estimated to be curatively resectable by clinical examinations, with clinical cancer stage IV according to the International Union Against Cancer (UICC) TNM classification (7th edition) [5]; aged equal to or older than 20 years; aged equal to or younger than 90 years; with an Eastern Cooperative Oncology Group Performance Status (PS) score of 0–2 [6]; with a GOO scoring system (GOOSS) score of 0 or 1 [7]; and considered to be alive for more than 3 months. Patients with GOO due to recurrent cancer, with active bleeding from the tumor, who could not receive an endoscopic examination, with additional obstruction of the oral side of the stomach, with additional obstruction of the small or large intestine, who had already undergone SEMS placement, who could not answer the questionnaire about quality of life, or who were considered inappropriate for participants, were excluded. The presence of duodenal invasion was not excluded.

The institutional review board of each hospital approved the protocol. All participants provided written informed consent. This study was performed by the Clinical Study Group of Osaka University, Upper GI Group, which conducted investigator-initiated trials and was composed of hospitals affiliated from the Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine. The data center, located at the Multicenter Clinical Study Group at the Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, was responsible for central monitoring and statistical analyses under supervision of the statistician in charge.

Procedures

Endoscopic stent placement was performed using the Wallflex™ duodenal stent (Boston Scientific, Natick, MA) under conscious sedation. It is an uncovered-SEMS with a diameter of 22 mm at the mid-body, and 60, 90, or 120 mm long depending on the case. After a guidewire was correctly positioned distal to the stricture, a stent catheter was advanced over the wire through the working channel of a therapeutic endoscope and the stent was released under fluoroscopic control.

Outcomes and Definitions

The primary outcome was an improvement in the ability to tolerate an oral solid diet after stenting as assessed by the GOOSS score. Secondary outcomes included the technical success rate, complications, the duration of post-interventional fasting, the duration of the post-interventional hospital stay, the feasibility of chemotherapy after stenting, the need for re-intervention, and OS.

Food intake was assessed by the standardized GOOSS score as follows: 0 = no oral intake, 1 = liquids only, 2 = soft solids, and 3 = almost complete or full diet [7]. The ability to take a solid diet was indicated by a GOOSS score of 2 or 3. Technical success was defined as deployment of the SEMS across the stricture, with patency visualized both fluoroscopically and endoscopically. Complications were defined as any adverse event related to SEMS placement, such as bleeding, perforation, and jaundice.

Sample Size and Data Analysis

A sample size of 20 patients had been planned when the trial was designed, considering that the number of GOO cases due to gastric cancer in the institutions of the Clinical Study Group of Osaka University, Upper GI Group was approximately 60 per year. The projected accrual period was 2 years.

The following parameters were collected and analyzed: sex, age, GOOSS score, body weight (BW), height, PS, albumin levels, total lymphocyte count, hemoglobin levels, previous chemotherapy, tumor location, macroscopic tumor type, depth of tumor invasion (T), lymph node metastasis (N), and distant metastasis (M) according to the Japanese classification of gastric carcinoma (3rd English edition) [8]. Interventional outcomes and complications were collected. GOOSS scores, BW, PS, albumin levels, lymphocyte count, and hemoglobin levels, at 1, 2, and 4 weeks, and every other 4 weeks after stenting, were recorded until the 24th week. The date of the start of oral intake, the date of hospital discharge, post-interventional therapy, including re-stenting, surgery, and chemotherapy, and the date and causes of death were also recorded. The survival time was defined as the duration from the date of stenting to death.

Statistical Analysis

Differences in parameters after stenting were compared with baseline (pre-interventional) values by the Wilcoxon signed-ranks test. P values were derived from two-tailed tests, and differences were considered significant at $P < 0.05$. Analyses were performed using StatView® software (version 5.0 for Macintosh; SAS Institute Inc., Cary, NC).

RESULTS

Patients' Characteristics

Twenty patients from six institutions were enrolled between March 2011 and July 2012. One patient with a GOOSS score of 2 and one patient with cancer stage IIIB were excluded. Therefore, the clinical data of 18 patients were retrieved and analyzed in this study. The clinical characteristics of the 18 patients are summarized in Table I.

Outcome of Stent Placement

SEMS placement was technically successful in all cases, and no complications were encountered. The ability to take solid food orally was achieved by 13 (72%) patients, in whom six had a GOO score of 2 and seven had a GOOSS score of 3. The remaining five patients who could not take solid food included three patients whose GOOSS score improved from 0 to 1, one patient whose GOOSS score remained as 0, and one patient who died within 1 week after stenting. A total of 16 (94%) out of 17 patients showed an improvement of the GOOSS score. The mean GOOSS scores were 1.7, 1.9, 1.8, 1.8, 1.8, 2.1, 2.3, and 2.2, at 1, 2, 4, 8, 12, 16, 20, and 24 weeks after stenting, respectively. The change in GOOSS scores by the post-stenting week is shown in Figure 1. The median duration of post-stenting fasting was 3 (range, 0–9 days) days. The median duration of hospitalization was 18 (6–168 days) days

TABLE I. Clinical Features of Patients Who Underwent Endoscopic Gastroduodenal Stent Placement for Gastric Outlet Obstruction Due to Unresectable Advanced Gastric Cancer

Variables		
Sex	Male/female	15/3
Age	(Year)	70 (48–90)*
GOOSS score	0/1	10/8
Body weight	(kg)	48 (29–71)*
Body mass index	(kg/m^2)	18.8 (13.1–22.9)*
PS	0/1/2	5/6/7
Albumin	(g/dl)	2.7 (1.7–3.8)*
Lymphocyte	($/mm^3$)	1068 (602–1,657)*
Hemoglobin	(g/dl)	9.1 (6.6–13.5)*
Pre-interventional chemotherapy	+/−	8/10
Tumor location	L/ML/UML	14/3/1
Tumor type	2/3/4	4/8/6
Depth of tumor invasion (T)	3/4a/4b	3/10/5
Lymph node metastasis (N)	1/2/3a/3b/X	3/4/9/1/1

PS, Eastern Cooperative Oncology Group Performance Status score; GOOSS, gastric outlet obstruction scoring system; Tumor location, Tumor type, T, and N are written according to the Japanese Classification of Gastric Carcinoma the 3rd English edition; *, median (range).

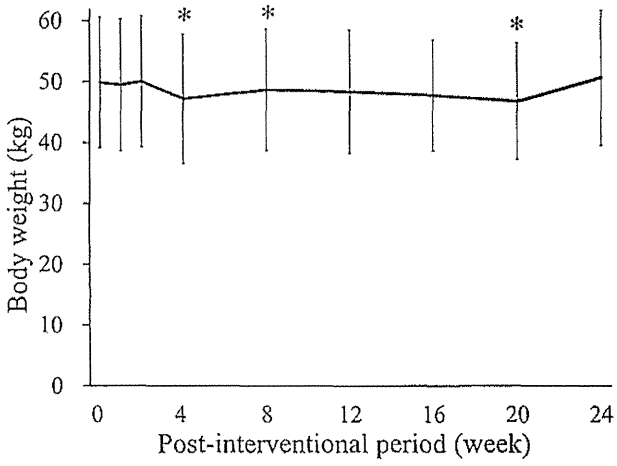


Fig. 2. Changes in the mean body weight at baseline (0) and during follow-up after stenting. Body weight after re-intervention was not included. Bars represent the standard deviation. Asterisks represent significant differences ($P < 0.05$) compared with baseline values using the Wilcoxon signed-ranks tests.

after stenting. Post-stenting chemotherapy was provided to 13 (72%) patients, including 10 patients with an S-1-containing regimen.

Additional therapy included re-stenting in two patients, surgical gastrojejunostomy in three patients, and gastrectomy in one patient. Two patients who could eat solid food after stenting, but then returned to no oral intake because of re-obstruction, received additional SEMS placement on the 105th and 126th post-stenting day, which resulted in good oral intake of solid food. One patient with development of re-obstruction after stenting could take solid food after gastrojejunostomy on the 69th post-stenting day. One patient with inadequate improvement of GOO after stenting could not eat solid food after gastrojejunostomy on the 45th post-stenting day. The other patient who could take solid food after stenting and developed tumor perforation after chemotherapy underwent surgery for peritonitis and gastrojejunostomy on the 165th postoperative day. A patient who had GOO and peritoneal metastasis due to gastric cancer underwent SEMS placement and received chemotherapy with S-1, cisplatin, and trastuzumab. Curative gastrectomy could be performed on the 76th post-stenting day because the peritoneal metastasis disappeared after two cycles of the regimen. The cancer stage was ypT4aN3bM0 stage IIIB.

Changes in Nutritional Values and Performance Status

BW, PS, albumin levels, total lymphocyte count, and hemoglobin levels, at 1, 2, and 4 weeks, and every other 4 weeks after stenting, were recorded until the 24th week and compared with baseline values. BW was significantly decreased at 4, 8, and 20 weeks after stenting compared with baseline, however, no significant increase in BW compared with the baseline value was observed during follow-up (Fig. 2). There were no significant changes in PS (Fig. 3), albumin levels (Fig. 4), lymphocyte count, and hemoglobin levels during the follow-up.

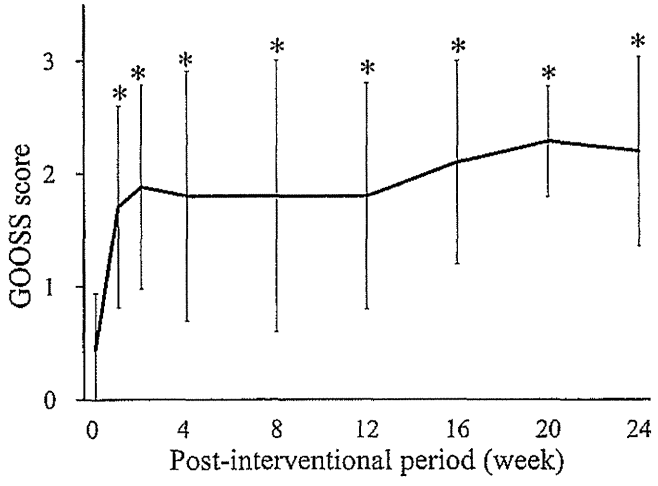


Fig. 1. Changes in the mean gastric outlet obstruction scoring system (GOOSS) score at baseline (0) and during follow-up after stenting. GOOSS scores after re-intervention were not included. Bars represent the standard deviation. Asterisks represent significant differences ($P < 0.05$) compared with baseline values using the Wilcoxon signed-ranks tests.

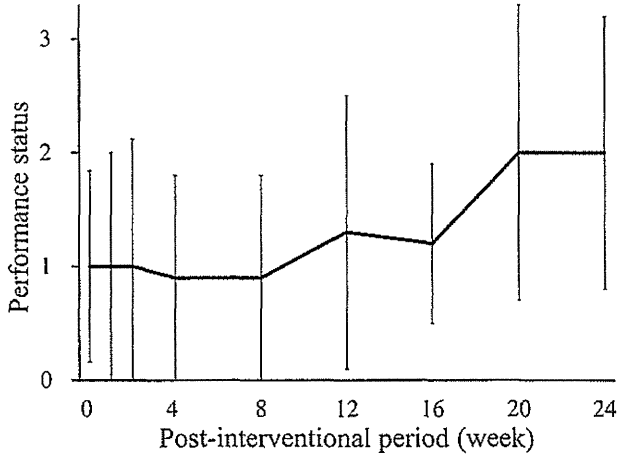


Fig. 3. Changes in the mean Eastern Cooperative Oncology Group Performance Status (PS) score at baseline (0) and during follow-up after stenting. PS scores after re-intervention were not included. Bars represent the standard deviation. There were no significant differences between baseline and post-interventional values by the Wilcoxon signed-ranks tests.

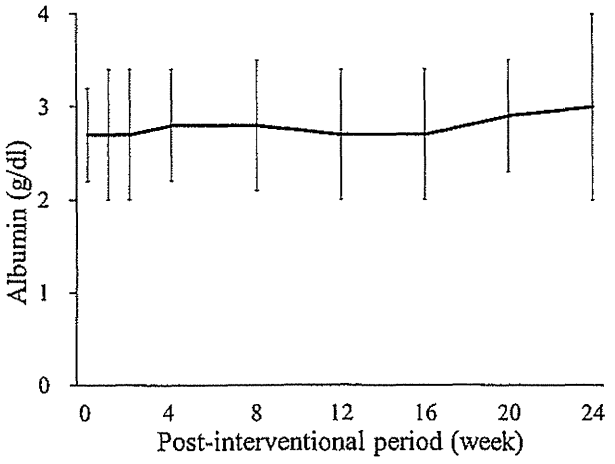


Fig. 4. Changes in the mean albumin levels at baseline (0) and during follow-up after stenting. Albumin levels after re-intervention were not included. Bars represent the standard deviation. There were no significant differences between baseline and post-interventional values by the Wilcoxon signed-ranks tests.

Overall Survival

At the time of analysis, 17 patients had died. The cause of death was gastric cancer in every case. The median survival time (MST) was 186 days and the 1-year survival rate was 11%.

DISCUSSION

The SEMS has been increasingly used for the palliation of malignant GOO, mainly due to biliary-pancreatic cancer. Some studies have reported the effects of SEMSs for GOO [3,4,9–11]. However, for the first time, we evaluated the effects of SEMSs for GOO due to advanced gastric cancer by a prospective multicenter study. We found that SEMSs in gastric cancer resulted in an acceptable improvement in oral intake with excellent technical success, without any complications.

Previous retrospective analyses concerning the effects of SEMSs for malignant GOO have reported similar clinical outcomes. Chandrasegaram et al. [4] reported that 69% and 77% patients could eat solids or puree on the 5th and 10th post-stenting days, respectively. Canena et al. [9] also reported that solid food intake (GOOSS score of 2–3) was achieved by 72% of patients within 5 days after stenting, which is similar to our study. They reported that the mean GOOSS score was 1.76 at 5 days after stenting, and 1.64 during the follow-up. Compared with these data, our patients maintained a good GOOSS score, ranging from 1.7 to 2.3 during follow-up. Although some other reports have mentioned a remarkably higher rate of clinical success with GOO, the definition of improvement of GOO differs [10–12]. An improvement of the GOOSS score by one or more points was obtained in 94% of patients in our series. However, this improvement in GOO failed to lead to improvement in nutritional parameters and general condition, including BW, PS, albumin levels, lymphocytes, and hemoglobin levels.

In the current study, five patients could not eat solid food after SEMS placement. All of them had a GOOSS score of 0 and a PS of 2. One patient died on the 6th day after stenting, and one died on the 17th day after stenting. One patient needed gastrojejunostomy, one needed central venous port placement, and the other patient did not receive any additional intervention because of a poor general condition. However, among 13 patients who could eat solid food after stenting, only two patients had a PS of 2 and the other 11 patients had a PS of 0 or 1. Considering these data, the ability to take solid food after stenting might partially depend on PS. Sasaki et al. [10] also showed that a poor PS was a poor predictive factor of solid intake. Patients with a PS of 2 would be more likely to be lying in bed, which makes oral intake difficult because advanced cancer in the stomach results in lost migration activity and patients require the assistance of gravity to let food pass through the stent. In fact, the patient with a PS of 2 who could not eat solid food after stenting could also not eat solid food after gastrojejunostomy.

The change in the GOOSS showed that GOOSS scores were maintained at approximately 2 from the 1st week to the 24th week after stenting. In Figure 1, GOOSS scores after re-intervention were not included. Four patients maintained GOOSS scores of 2–3 for 24 weeks after stenting without re-intervention, while three patients required re-intervention due to re-obstruction on the 69th, 105th, and 126th days. No et al. [12] reported that the median duration between SEMS placement for gastric cancer and the recurrence of obstructive symptoms was 125 days. Some studies, including those on gastric cancer and biliary-pancreatic malignancies, found that stent patency lasted for 4–17 months [4,9,11], although the duration of stent patency is thought to be difficult to evaluate objectively. Recurrent obstruction is caused by tumor ingrowth or overgrowth, and remains an important problem of SEMSs. Additional SEMS placement was performed for two cases in our series with good results. Recent reports have also described the effectiveness of additional SEMS insertion using a stent-in-stent procedure [4,11,12]. Additional SEMS placement may be a feasible choice for recurrent obstruction after stenting.

Chemotherapy is also expected to improve maintenance of stent patency, mainly as a result of reducing tumor ingrowth or overgrowth. In our series, chemotherapy was administered in most patients soon after stenting. Ability of oral intake of S-1 is important for treating patients with unresectable advanced gastric cancer because S-1 is a key drug for unresectable advanced gastric cancer [13]. Notably, one patient in our series with peritoneal metastasis underwent curative resection after SEMS placement and chemotherapy. Less invasiveness of endoscopic SEMS placement enabled the patient to start chemotherapy as soon as the 8th day after stenting. Furthermore, if this patient had undergone surgical gastrojejunostomy instead of SEMS placement, the next surgery of gastrectomy would have been difficult and complicated. In this patient, gastrectomy was performed without difficulty by fully mobilizing the duodenal bulbus and resecting the duodenum just distal to the SEMS. This patient showed the advantages of SEMS placement in terms of early administration of chemotherapy and the technical ease of gastrectomy when chemotherapy was effective. This patient is doing well with good oral intake for 16 months after stenting and 13 months after gastrectomy.

The MST after stenting was 186 days, which is compatible with that in a recent Korean report after stenting for gastric cancer (189 days) [12]. For patients who underwent chemotherapy including the S-1 regimen, the MST was 9.1 months, which is similar to the reported MST of patients with advanced gastric cancer who underwent S-1 chemotherapy (11.0 months) [13]. Therefore, the ability of chemotherapy with S-1 after stenting leads to a survival benefit.

CONCLUSIONS

We prospectively analyzed the effectiveness of endoscopic gastroduodenal SEMS placement for GOO due to unresectable advanced gastric cancer. This procedure was technically successful in every patient, and 72% of patients could eat solid food. The duration of post-interventional fasting and hospitalization was short. Gastroduodenal SEMSs are thought to be feasible, safe, and effective for GOO due to unresectable advanced gastric cancer. This palliative treatment might become the choice of treatment for GOO. A further study is being planned to compare SEMSs and gastrojejunostomy by a randomized controlled trial in our multicenter group.

REFERENCES

1. Japanese Gastric Cancer Association. Japanese gastric cancer treatment guidelines 2010 (ver. 3). Gastric Cancer 2011;14:113–123.
2. Takeno A, Takiguchi S, Fujita J, et al.: Clinical outcome and indications for palliative gastrojejunostomy in unresectable advanced gastric cancer: Multi-institutional retrospective analysis. Ann Surg Oncol 2013;20:3527–3533.
3. Jeurnink SM, Steyerberg EW, van Hooft JE, et al.: Dutch SUSTENT Study Group. Surgical gastrojejunostomy or endoscopic stent placement for the palliation of malignant gastric outlet obstruction (SUSTENT study): A multicenter randomized trial. Gastrointest Endosc 2010;71:490–499.
4. Chandrasegaram MD, Eslick GD, Mansfield CO, et al.: Endoscopic stenting versus operative gastrojejunostomy for malignant gastric outlet obstruction. Surg Endosc 2012;26:323–329.
5. Sobin LH, Gospodarowicz MK, Wittekind C: TNM classification of malignant tumors, 7th edition. Oxford: Wiley -Blackwell; 2009;pp 73–77.
6. Oken MM, Creech RH, Tormey DC, et al.: Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5:649–655.
7. Adler DG, Baron TH: Endoscopic palliation of malignant gastric outlet obstruction using self-expanding metal stents: Experience in 36 patients. Am J Gastroenterol 2002;97:72–78.
8. Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma: 3rd English edition. Gastric Cancer 2011;14:101–112.
9. Canena JM, Lagos AC, Marques IN, et al.: Oral intake throughout the patients' lives after palliative metallic stent placement for malignant gastroduodenal obstruction: A retrospective multicentre study. Eur J Gastroenterol Hepatol 2012;24:747–755.
10. Sasaki T, Isayama H, Nakai Y, et al.: Predictive factors of solid food intake in patients with malignant gastric outlet obstruction receiving self-expandable metallic stents for palliation. Dig Endosc 2012;24: 226–230.
11. Sasaki T, Isayama H, Maetani I, et al.: Japanese multicenter estimation of WallFlex duodenal stent for unresectable malignant gastric outlet obstruction. Dig Endosc 2013;25:1–6.
12. No JH, Kim SW, Lim CH, et al.: Long-term outcome of palliative therapy for gastric outlet obstruction caused by unresectable gastric cancer in patients with good performance status: Endoscopic stenting versus surgery. Gastrointest Endosc 2013;78:55–62.
13. Koizumi W, Narahara H, Hara T, et al.: S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): A phase III trial. Lancet Oncol 2008;9:215–221.

Anticancer Original Research Paper

Phase II study of S-1 monotherapy in patients over 75 years of age with advanced gastric cancer (OGSG0404)

Hiroshi Imamura[1], Tomono Kishimoto[2], Hiroya Takiuchi[3], Yutaka Kimura[4], Takashi Morimoto[5], Motohiro Imano[6], Shohei Iijima[7], Keishi Yamashita[8], Kentaro Maruyama[9], Toshio Otsuji[10], Yukinori Kurokawa[11], Hiroshi Furukawa[6]

[1]Department of Surgery, Toyonaka Municipal Hospital,Toyonaka, Osaka, Japan, [2]Department of Surgery, Sakai Municipal Hospital, Sakai, Osaka, Japan, [3]Cancer Chemotherapy Center, Osaka Medical College Hospital, Takatsuki, Osaka, Japan, [4]Department of Surgery, Sakai Municipal Hospital, Sakai, Osaka, Japan, [5]Department of Surgery, Yao Municipal Hospital,Toyonaka, Osaka, Japan, [6]Department of Surgery, Kinki University Hospital, Faculty of Medicine, Osaka-Sayama, Osaka, Japan, [7]Department of Surgery, Kinki Central Hospital, Itami, Hyogo, Japan, [8]Kawagoe Gastroenterical Hospital, Kawagoe, Saitama, Japan, [9]Department of Surgery, Moriguchi Keijinkai Hospital, Moriguchi Osaka, Japan, [10]Department of Gastrointestinal Medicine, Dongo Hospital, Yamatotakada, Nara, Japan, [11]Department of Gastroenterological Surgery, Osaka University Graduate School of Medicine, Suita, Osaka, Japan

Background: S-1 + cisplatin (CDDP) is the standard treatment for advanced gastric cancer (AGC) in Japan and Korea. However, the usefulness of S-1 based chemotherapy for elderly patients is unclear. Therefore, we conducted a multicenter phase II study of S-1 monotherapy for AGC in elderly patients.
Materials and Methods: Chemotherapy-naïve patients aged over 75 years with AGC were enrolled. The starting dose of S-1 was determined on the basis of body surface area and modified according to the creatinine clearance value. S-1 was administered twice a day during a 4-week period followed by a 2-week rest period.
Results: Thirty-five patients were enrolled. The response rate (RR) was 14.3% and the median overall survival was 14.6 months. Grade 3 or more severe adverse events consisted of anaemia (3%), neutropaenia (3%), anorexia (3%), and fatigue (6%). There were no treatment-related deaths.
Conclusion: Our study indicates that S-1 monotherapy is safe and well tolerated in chemotherapy-naïve elderly patients with AGC, but exerts limited activity when given using a tailor-made dosing strategy based on renal function.

Keywords: S-1 monotherapy, Gastric cancer, Elderly, Phase II study

Introduction

In 2008, the estimated numbers of new gastric cancer cases and deaths from this disease worldwide were 0.99 million and 0.74 million, respectively. While these numbers are decreasing in developed countries, gastric cancer is still the fourth most common malignancy and the second leading cause of death following lung cancer. Sixty percent of gastric cancer cases worldwide occur in East Asia, including Japan, South Korea, and China.[1]

The proportion of elderly people in the Japanese population is increasing. According to a report by the Center for Cancer Control and Information Services of the National Cancer Center, the annual proportion of patients aged 75 years or older among the total number of patients who died of or were newly diagnosed with gastric cancer has been increasing.[2] Generally, as the functions of vital organs, particularly the kidneys and liver, decrease and complications develop in elderly patients, the toxicity of treatments can increase. Therefore, the risk–benefit analysis in relation to treatments for the elderly might be different from those for younger patients.

In many clinical phase III studies involving patients with advanced gastric cancer (AGC) in Japan the upper age limit for eligibility is 75 years. A similar age limit has been set in studies such as the SPIRITS study,[3] which evaluated S-1-based combination therapy with CDDP (SP, the standard therapy

Correspondence to: Hiroshi Imamura, Toyonaka Municipal Hospital, Japan.
Email: imamurahiroshisakai@yahoo.co.jp

DOI 10.1179/1973947813Y.0000000116

for AGC in Japan), as well as the JCOG9205,[4] JCOG9912,[5] and GC0301/TOP-002 studies.[6] Thus, no standard therapy has yet been established for patients over age 75 years with AGC.

A subgroup analysis by age group was also conducted on the SPIRITS data to evaluate the overall survival (OS) time using the Cox proportional-hazards model.[3] The hazard ratio for patients younger than 60 years was 0.75 (95% CI, 0.61–0.92); this showed the usefulness of SP. However, the hazard ratio for patients aged 60–69 years was 0.98 (95% CI, 0.82–1.17), whereas it was 0.95 (95% CI, 0.71–1.27) for patients aged 70–74 years. These observations suggest that SP is not significantly more effective than S-1 monotherapy for elderly patients.

On the basis of the above information, we planned a Phase II study to evaluate the safety and efficacy of S-1 monotherapy in chemotherapy-naive patients aged 75 years or older with AGC.

However, decreases in organ function with age are a concern in elderly patients. One report stated that creatinine clearance (Ccr), an index of kidney function, correlates negatively with age.[7] A study examining S-1 use showed that reduced renal function is a risk factor for adverse drug reactions resulting from S-1 use, particularly haematological toxicity.[8] The starting dose of S-1 was determined on the basis of the body surface area (BSA) and modified according to the Ccr value to devise a tailor-made regimen.

Materials and methods

Patients

Between November 2004 and June 2008, chemotherapy-naïve patients over 75 years of age with AGC were enrolled at nine institutions. All had proven unresectable advanced or recurrent gastric cancer with measurable lesions, and no prior chemotherapy except adjuvant chemotherapy completed 6 months or more prior to enrolment. Their Eastern Cooperative Oncology Group performance status (PS) was 2 or less. All patients had the ability to ingest orally, and adequate organ functions, as confirmed by the following laboratory data: leukocyte count ≧ 4000/mm^3 but < 12 000/mm^3, neutrophil count ≧ 2000/mm^3, platelet count ≧ 100 000/mm^3, haemoglobin ≧ 8.0 g/dL, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≦ 2.5 × the upper limit of normal (ULN), total bilirubin ≦ 1.0 × ULN, serum creatinine ≦ 1.2 mg/dL, and calculated creatinine clearance (Ccr) ≧ 30 mL/min. Survival expectancy was at least 3 months for all of these patients, each of whom provided written informed consent. The study was approved by the institutional review boards of each participating facility.

Treatment dose and schedule

Individual dose of S-1 (20–60 mg) was given orally twice daily in the morning and the evening. The starting dose of S-1 was determined on the basis of BSA and modified according to the Ccr value to obtain a tailor-made regimen (Table 1), and 4-week courses were administered, each followed a by a 2-week rest period. Courses were repeated as tolerated. Ccr values were the observed or calculated values obtained from the Cockcroft–Gault formula.[9] S-1 was interrupted for leukopaenia or neutropaenia ≧ grade 3; thrombocytopaenia ≧ grade 2; haemoglobin ≦ 8.0 g/dL; AST and/or ALT ≧ 150 IU/L; total bilirubin ≧ 1.5 × ULN or non-haematological toxicities of grade 2 or more. Treatment was resumed on recovery, with consideration given to dose reduction by one dose level. When there was no recovery from adverse events even after a 4-week drug-free interval, resumption of S-1 was disallowed and the protocol treatment was discontinued.

Toxicity criteria

Adverse events were evaluated at least once every week for courses 1 and 2, and then once every 2 weeks from course 3 onwards, during the study period according to the NCI-Common Toxicity Criteria (NCI-CTC version 2.0).

Response criteria

The tumour response was evaluated every 4 weeks for courses 1–3, every 4–6 weeks from course 4 onwards, after the beginning of protocol treatment according to the Japanese Classification of Gastric Carcinoma, 13th edition.[10–12] As a reference, the tumour response was evaluated every 4–6 weeks after the beginning of therapy according to Response Evaluation Criteria in Solid Tumors (RECIST version 1.0).[13]

Statistical analysis

On the assumption that the threshold RR would be 11%, and the expected RR as 30%, the necessary number of subjects was calculated to be 29 with alpha = 0.05 (one-tailed) and beta = 0.2. With consideration of ineligible patients, the target number of patients was 35. The primary endpoint was the RR (the Japanese Classification of Gastric Carcinoma), and the secondary endpoints were safety, time to

Table 1 Starting dose of S-1 and number of patients

	Ccr (mL/min)			
BSA (m^2)	≧ 80	80–50	50–30	≦ 30
≧ 1.5	120 mg/day (n = 1)	100 mg/day (n = 11)	80 mg/day (n = 2)	Do not administer
1.25–1.5	100 mg/day (n = 1)	80 mg/day (n = 9)	50 mg/day (n = 6)	
≦ 1.25	80 mg/day (n = 0)	50 mg/day (n = 3)	40 mg/day (n = 2)	

treatment failure (TTF; including progression, death, or early discontinuation of protocol treatment), progression free survival (PFS), and OS. Time to treatment failure, PFS, and OS were estimated by the Kaplan–Meier method using the enrolment date as the initial date of the study.

This trial is registered in the UMIN clinical trial registered system, under number UMIN000000661.

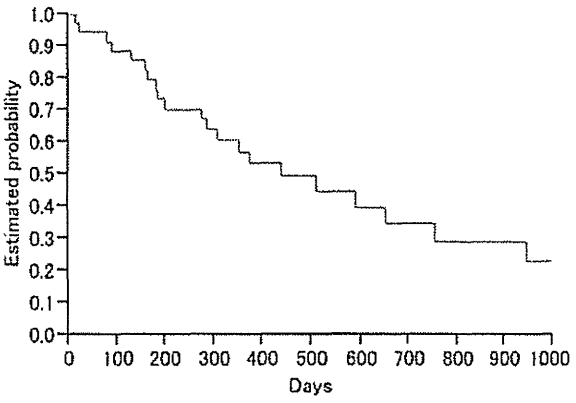
Results

Patient characteristics

In total, 35 patients were enrolled between November 2004 and June 2008. The patient characteristics are shown in Table 2. There were 21 males and 14 females. The median age was 78 years (range 75–86 years), and 19/12 and 4 patients had a PS of 0, 1, and 2, respectively. Ten patients (29%) had diffuse-type gastric cancer. Twenty-two patients had AGC at diagnosis, the rest had recurrent disease after previous surgical intervention. None of the patients had received prior chemotherapy including adjuvant chemotherapy. The starting dose determined by BSA and Ccr was 120 mg in one patient, 100 mg in 12, 80 mg in 11, 50 mg in 9, and 40 mg in 2. In 15 patients the primary tumour was still *in situ*.

Efficacy

Table 3 shows the RR and the disease control rate (DCR) determined by extramural review. Among the 35 patients, none achieved a complete response (CR) while a partial response (PR) was seen in five, resulting in a RR of 14.3% (95% CI, 4.8–30.3%). Because the lower boundary of the 95% CI of the RR (4.8%) did not exceed the threshold RR (11%), the null hypothesis was not rejected and the primary endpoint was not met. The DCR, including 15 patients showing no change (NC), was 57.1% (95% CI, 40.7–73.5%).



Median survival time was 14.6 months (95% CI, 9.2–25.1 months).

Figure 1 Median survival time (MST).

Median survival time (MST), as shown in Fig 1 was 14.6 months (95% CI, 9.2–25.1 months), median PFS was 2.9 months (95% CI, 2.2–4.7 months), and median TTF was 2.6 months (95% CI, 1.8–4.1 months).

Toxicity

Table 4 shows adverse events. There were no treatment-related deaths. Frequent haematologic adverse events include leukopaenia (all grades, 11.8%), neutropaenia (11.8%), anaemia (64.7%), and thrombocytopaenia (20.6%). Frequent non-haematologic adverse events included nausea/vomiting (14.7%), anorexia (47.1%), fatigue (14.7%), stomatitis (5.9%), and diarrhoea (11.8%). As for serious adverse events, neutropaenia (2.9%), anaemia (2.9%), anorexia (2.9%), and fatigue (5.9%) of grade 3 were relatively frequent, but there were no grade 4 episodes.

Table 2 Patient characteristics

		No. of patients (n = 35)
Gender	Male	21
	Female	14
Age	Median	78
	Range	75–86
PS	0	19
	1	12
	2	4
Advanced/recurrent	Advanced	22
	Recurrent	13
Primary lesions	+	15
	−	20
Histology	Intestinal	24
	Diffuse	10
	Others	1
Initial dose of S-1 (mg)	120	1
	100	12
	80	11
	50	9
	40	2

Discussion

We set out to assess the viability of S-1 monotherapy in patients at least 75 years of age with AGC.

In the efficacy analysis, the RR was 14.3% (95% CI, 4.8–30.3%). A Phase II study conducted prior to this investigation in Japan showed a RR of 21.2% (80% CI, 13.6–31.6%), which is a positive result with the lower limit of the CI exceeding the threshold value of 10%.[14] In contrast, the lower limit of the CI was below the threshold value of 10% in the present study.

Table 3 Response rate (RR) and disease control rate (DCR)

No. of patients	Response					RR (95%CI)	p-value (two-side)	DCR (95%CI)
35	CR	PR	NC	PD	NE	14.30% (4.8–30.3)	$P = 0.584$	57.10% (40.7–73.5)
	0	5	15	10	5			

In this study, Ccr values were calculated by the Cockcroft–Gault formula even though this formula has not been validated for patients over 70 years of age. It is thought that the standard dose determined using BSA and Ccr values calculated by the Cockcroft–Gault formula as indices might be lower than the optimal dose of S-1. In contrast, the results of a Phase II study assessing S-1 monotherapy in patients with non-small cell lung cancer age 75 years or older were reported.[15] In that study, Ccr values were also calculated by the Cockcroft–Gault formula. Among the eight patients in their study who underwent PK monitoring, the area under the curve for 5FU was equivalent to that seen in patients with normal renal function treated with standard S-1 dosing, suggesting that 5FU exposure was adequate. This observations were consistent with the fact that neither treatment-related deaths nor grade 4 adverse events were observed in our study. Compared with the incidence of severe adverse events in patients less than 75 years of age in the JCOG9912 and SPIRITS studies, the incidence of severe adverse events in this study was not high. S-1 monotherapy given according to this dosing strategy was both safe and well tolerated in our patients group (Table IV).

The median PFS of 2.9 months (95% CI, 2.2–4.7 months) in this study was approximately the same as the median TTF of 2.6 months (95% CI, 1.8–4.1 months), suggesting that S-1 monotherapy in elderly patients results in few discontinuations of treatment due to adverse events. Among the reasons for treatment discontinuation in this study, those due to adverse events accounted for 8.6% (3 out of 35 cases) and tumour progression accounted for 71.4% (25 out of 35 cases).

As described above, the median PFS in this study was 2.9 months. The subjects of this study had measurable lesions. Generally, tumour progression events can more easily be confirmed by conducting imaging studies in patients with measurable lesions than in patients without measurable lesions, and this may have resulted in a shorter PFS. Our median PFS of 2.9 months was shorter than those reported in other Phase III studies examining S-1 monotherapy. This finding may be attributable to the subjects of this study having had measurable lesions.

In this study, MST was 14.6 months (95% IC, 9.2–25.1 months), which was similar to the results of other studies examining S-1 monotherapy.[14]

Currently, SP is the recommended standard chemotherapy for chemotherapy-naive patients with AGC in Japan. However, as discussed previously, in elderly patients, the decreased effectiveness of SP as compared with S-1 monotherapy with advancing age is a concern.[3] The subgroup analysis of the SPIRITS data showed an interaction between the presence and absence of measurable lesions ($P = 0.01$). This finding demonstrated the usefulness of SP, with a hazard ratio of 0.54 (95% CI, 0.35–0.83) for patients without measurable lesions and a hazard ratio of 1.10 (95% CI, 0.82–1.47) for patients with measurable lesions, and suggested that the effectiveness of this therapy decreased when it was combined with CDDP. Because decreased effectiveness when combined with CDDP is a concern in elderly patients with measurable lesions, S-1 monotherapy is considered to be more suitable than SP.

Additionally, an age-based subgroup analysis was conducted for OS in the START study. Hazard ratios in the S-1 based combination chemotherapy with docetaxel group were 0.874 (95% CI, 0.678–1.128) for patients younger than 65 years and 0.881 (95% CI, 0.691–1.124) for those 65 years or older; this finding demonstrated S-1 based combination therapy with docetaxel to be more useful than S-1 monotherapy in both age groups. These results suggest that S-1 based combination chemotherapy with docetaxel may be more useful than S-1 monotherapy and SP therapy

Table 4 Adverse events

	Phase II study						JCOG9912	SPIRITS
	No. of patients				All grades	≧ Grade3	≧ Grade3	≧ Grade3
Grade	1	2	3	4	(%)	(%)	(%)	(%)
Leukopaenia	3	1	0	0	11.8	0	1	2
Neutropaenia	2	1	1	0	11.8	2.9	6	11
Anaemia	10	11	1	0	64.7	2.9	13	4
Thrombocytopaenia	6	1	0	0	20.6	0	–	0
ALT/AST	0	0	1	0	2.9	2.9	5	–
T-Bil	2	1	0	0	8.8	0	4	–
Nausea/	4	1	0	0	14.7	0	6	1
Vomiting							–	2
Anorexia	10	5	1	0	47.1	2.9	12	6
Fatigue	3	0	2	0	14.7	5.9	5	1
Stomatitis	1	1	0	0	5.9	0	2	0
Diarrhoea	3	1	0	0	11.8	0	8	3

There were no treatment-related deaths.

for elderly patient with gastric cancer. Presently, a Phase II study to confirm the effectiveness of S-1 plus docetaxel for elderly patients with AGC is underway at OGSG and has been designated OGSG0902 (UMIN Trial ID: UMIN000002785). The results of this study are pending.

Acknowledgements

We are indebted to the physicians and all other co-medical staff who contributed to this study. We thank J. Patrick Barron of the International Medical Communications Centre of Tokyo Medical University (Tokyo, Japan) for his review of this report. We also thank Ms Akiko Hotta and Ms Hiroko Maruyama at the OGSG data center for their excellent secretarial assistance. We particularly thank Dr T. Shimokawa for support with the statistics. The author thanks Mr Eisuke Matsunaga and Mr Tetsuya Fujita for their helpful advice.

The authors have no conflicts of interest to report.

References

1 Jemal A, Bray F, Melissa M, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61:69–90.
2 Vital Statistics Japan (Ministry of Health, Labour and Welfare). http://www.mhlw.go.jp/english/database/db-hw/index.html
3 Koizumi W, Narahara H, Hara T, Takagane A, Akiya T, Takagi M, *et al.* S-1 plus cisplatin versus S-1 alone for first-line treatment of advanced gastric cancer (SPIRITS trial): a phase III trial. Lancet Oncol. 2008;9(3):215–21.
4 Ohtsu A, Shimada Y, Shirao K, Boku N, Hyodo I, Saito H, *et al.* Randomized phase III trial of fluorouracil alone versus fluorouracil plus cisplatin versus uracil and tegafur plus mitomycin in patients with unresectable, advanced gastric cancer. The Japan clinical oncology group study (JCOG9205). J Clin Oncol. 2003;21:54–9.
5 Boku N, Yamamoto S, Fukuda H, Shirao K, Doi T, Sawaki A, *et al.* Fluorouracil versus combination of irinotecan plus cisplatin versus S-1 in metastatic gastric cancer: a randomised phase 3 study. Lancet Oncol. 2009;10(11):1063–9.
6 Narahara H, Iishi H, Imamura H, Tsuburaya A, Chin K, Imamoto H, *et al.* Randomized phase III study comparing the efficacy and safety of irinotecan plus S-1 with S-1 alone as first-line treatment for advanced gastric cancer (study GC0301/TOP-002). Gastric Cancer. 2011;14(1):72–80.
7 Hamaguchi A *et al.*: Jin To Toseki [Kidney and Dialysis] 2002;52(3):273–7.
8 Yamanaka T, Matsumoto S, Teramukai S, Ishiwata R, Nagai Y, Fukushima M. Safety evaluation of oral Fluoropyrimidine S-1 for short- and long-term delivery in advanced gastric cancer:analysis of 3,758 patients. Cancer Chemother Pharmacol. 2008;61:335–343.
9 Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31–41.
10 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma (In Japanese), 13th edn. Tokyo:Kanchara;1999.
11 Japanese Gastric Cancer Association. Japanese classification of gastric carcinoma 2nd English edition response assessment of chemotherapy and radiotherapy for gastric carcinoma: clinical criteria. Gastric Cancer. 2001;4:1–8.
12 Kurihara M, Aiko T. The new Japanese classification of gastric carcinoma: revised explanation of 'response assessment of chemotherapy and radiotherapy for gastric carcinoma'. Gastric Cancer. 2001;4:9–13.
13 Therasse P, Arbuck SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, *et al.* New guidelines to evaluate the response to treatment in solid tumors J Natl Cancer Inst. 1999;92(3):205–16.
14 Koizumi W, Akiya T, Sato A, Sakuyama T, Sasaki E, Tomidokoro T, *et al.* Phase II study of S-1 as first-line treatment for elderly patients over 75 years of age with advanced gastric cancer: the Tokyo Cooperative Oncology Group study. Cancer Chemother Pharmacol. 2010;65:1093–99.
15 Shiroyama T, Kijima T, Komuta K, Yamamoto S, Minami S, Ogata Y, *et al.* Phase II tailored S-1 regimen study of first-line chemotherapy in elderly patients with advanced and recurrent non-small cell lung cancer. Cancer Chemother Pharmacol. 2012;70:783–9.

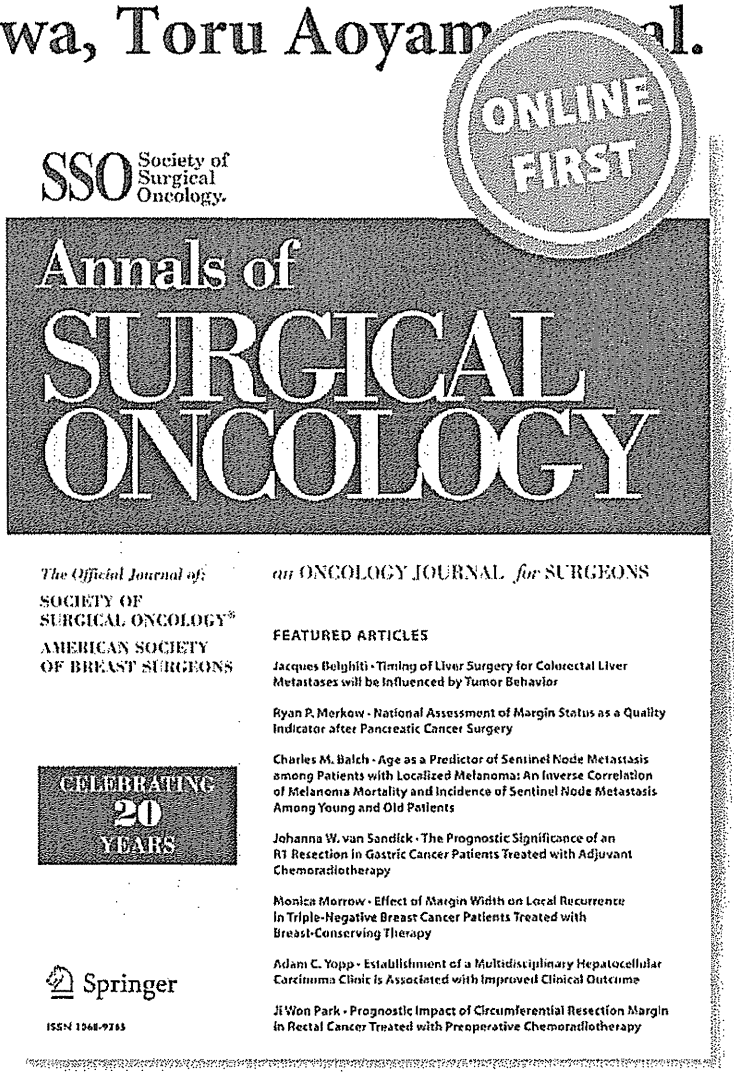
Accuracy of CT Staging of Locally Advanced Gastric Cancer after Neoadjuvant Chemotherapy: Cohort Evaluation within a Randomized Phase II Study

Takaki Yoshikawa, Kazuaki Tanabe, Kazuhiro Nishikawa, Yuichi Ito, Takanori Matsui, Yutaka Kimura, Shinichi Hasegawa, Toru Aoyam[illegible]al.

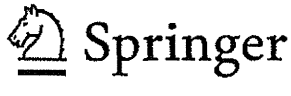
Annals of Surgical Oncology

ISSN 1068-9265

Ann Surg Oncol
DOI 10.1245/s10434-014-3615-8



Springer



Ann Surg Oncol
DOI 10.1245/s10434-014-3615-8

Annals of
SURGICAL ONCOLOGY
OFFICIAL JOURNAL OF THE SOCIETY OF SURGICAL ONCOLOGY

ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Accuracy of CT Staging of Locally Advanced Gastric Cancer after Neoadjuvant Chemotherapy: Cohort Evaluation within a Randomized Phase II Study

Takaki Yoshikawa, MD, PhD[1], Kazuaki Tanabe, MD[2], Kazuhiro Nishikawa, MD[3], Yuichi Ito, MD[4], Takanori Matsui, MD[5], Yutaka Kimura, MD, PhD[6], Shinichi Hasegawa, MD[1], Toru Aoyama, MD[1], Tsutomu Hayashi, MD[1], Satoshi Morita, PhD[7], Yumi Miyashita[8], Akira Tsuburaya, MD[9], and Junichi Sakamoto, MD[10]

[1]Department of Gastrointestinal Surgery, Kanagawa Cancer Center, Yokohama, Japan; [2]Department of Gastrointestinal Surgery, Hiroshima University, Hiroshima, Japan; [3]Department of Surgery, Osaka General Medical Center, Osaka, Japan; [4]Department of Gastroenterological Surgery, Aichi Cancer Center, Nagoya, Japan; [5]Department of Surgery, Aichi Cancer Center, Aichi Hospital, Okazaki, Japan; [6]Department of Surgery, NTT West Osaka Hospital, Osaka, Japan; [7]Department of Biostatistics and Epidemiology, Yokohama City University Medical Center, Yokohama, Japan; [8]Data Center, Nonprofit Organization ECRIN, Okazaki, Japan; [9]Clinical Research Center, Shonan Kamakura General Hospital, Kamakura, Japan; [10]Tokai Central Hospital, Kakamigahara, Japan

ABSTRACT

Background. Accuracy of the radiologic diagnosis of gastric cancer staging after neoadjuvant chemotherapy remains unclear.

Methods. Patients enrolled in the COMPASS trial, a randomized phase II study comparing two and four courses of S-1 plus cisplatin and paclitaxel and cisplatin followed by gastrectomy, were examined. The radiologic stage was determined by using thin-slice computed tomography (CT) or multidetector low CT by following Habermann's method.

Results. A total of 75 patients registered in the COMPASS study who underwent surgical resection were examined in this study. The radiologic T and pathologic T stages were not significantly correlated ($p = 0.221$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 42.7, 10.7, and 46.7%, respectively. When patients were stratified according to the pathologic response of the primary tumor, the correlation was not significant in either the responders ($n = 32$, $p = 0.410$) or the nonresponders ($n = 43$, $p = 0.742$). The radiologic accuracy was 37.5% in the responders and 42.7% in the nonresponders. The radiologic N and pathologic N stages were significantly correlated ($p = 0.000$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 44, 29.3, and 26.7%, respectively. When stratifying the patients with measurable lymph nodes according only to the radiologic response, the correlation was significant in the nonresponders ($n = 23$, $p = 0.035$) but not in the responders ($n = 28$, $p = 0.634$). The radiologic accuracy was 39.3% in the responders and 52.1% in the nonresponders.

Conclusions. Restaging using CT after neoadjuvant chemotherapy for gastric cancer is considered to be inaccurate and unreliable. In particular, the radiologic T-staging determined after neoadjuvant chemotherapy should not be considered in clinical decision-making.

Gastric cancer is the second leading cause of cancer death worldwide, accounting for 736,000 deaths in 2008.[1] Complete surgical resection is essential for curing gastric cancer. Recent large phase III studies have demonstrated that multimodality treatment including surgery significantly improves the survival of locally advanced disease compared with surgery alone, postoperative adjuvant chemotherapy with S-1 in Japan, postoperative adjuvant chemotherapy with capecitabine plus oxaliplatin in Korea and the United States, and preoperative and postoperative chemotherapy with epirubicin, cisplatin, and fluorouracil in the United Kingdom.[2–8]

Neoadjuvant chemotherapy is a promising treatment for gastric cancer when considering intensive chemotherapy with a relatively toxic regimen.[2] Even with treatment

First Received: 19 October 2013

T. Yoshikawa, MD, PhD
e-mail: yoshikawat@kcch.jp

Published online: 05 March 2014

including D2 gastrectomy and adjuvant chemotherapy, the prognosis of stage III tumors is not satisfactory.[5] Neoadjuvant chemotherapy has been tested in several phase III trials in eastern Asia where D2 gastrectomy and adjuvant chemotherapy is a standard treatment.[2] After administering neoadjuvant chemotherapy, physicians must evaluate tumor progression and the response to treatment in order to continue or stop the chemotherapy and to assess resectability with respect to surgery and determine the most appropriate surgical procedure to fit the tumor stage considering the benefits and risks of surgery.

Endoscopic ultrasonography (EUS) and computed tomography (CT) are standard approaches for staging primary gastric cancer. The diagnostic accuracy of T-staging is 77.1 to 88.9% on CT and 65 to 92.1% on EUS, whereas that of N-staging is 51 to 71% on CT and 63 to 78% on EUS.[9,10] However, there are no reliable data with respect to restaging after neoadjuvant chemotherapy. Previously, several small studies demonstrated that preoperative EUS is inaccurate in patients who receive neoadjuvant chemotherapy.[11,12] Regarding CT, Park et al.[13] reported that the accuracy of T- and N-staging after neoadjuvant chemotherapy using CT is 57 and 37%, respectively. However, the sample size was only 38 in their study, and the evaluation criteria for assessing tumor depth were not defined. Moreover, the criteria for determining nodal metastasis were not optimized.

To evaluate the radiologic accuracy of restaging after neoadjuvant chemotherapy using CT, the present study was conducted as an exploratory analysis of a randomized phase II study that strictly defined primary staging, neoadjuvant chemotherapy, restaging after neoadjuvant chemotherapy, and the surgical procedures.

PATIENTS AND METHODS

Patients registered into the randomized phase II COMPASS trial who received gastrectomy with nodal dissection were examined in this study. The details of the COMPASS trial have been described in a previous article.[14] Briefly, the key eligibility criteria included T2–3/N+ or T4aN0 in cases of scirrhous or junctional tumors, T2–3 with nodal metastasis to the major branched artery, T4aN+ , T4b, paraaortic nodal metastases, or resectable minimal peritoneal metastases confirmed on laparoscopy. The use of staging laparoscopy was mandatory to diagnose peritoneal metastasis. The eligible patients were randomized to receive two courses of S-1 plus cisplatin, four courses of S-1 plus cisplatin, two courses of paclitaxel plus cisplatin, or four courses of paclitaxel plus cisplatin. The primary end point of the COMPASS trial is the 3-year overall survival rate and will recruit 60 to 80 subjects. This study was conducted in a cohort of consecutive patients recruited into the COMPASS trial.

Regarding the S-1 plus cisplatin regimen, S-1 (80 mg/m^2) was given orally twice daily for the first 3 weeks of a 4-week cycle, and cisplatin was given as an intravenous infusion of 60 mg/m^2 on day 8 of each cycle, as previously described.[15] With respect to the paclitaxel plus cisplatin regimen, paclitaxel (60 mg/m^2) and cisplatin (25 mg/m^2) were administered on days 1, 8, and 15 as one course repeated every 4 weeks.[16] The neoadjuvant chemotherapy was discontinued in cases of documented disease progression, unacceptable toxicity, or withdrawal of consent.

Two to six weeks after the completion of neoadjuvant chemotherapy or when the tumors progressed during treatment, the patients proceeded to surgery. R0 resection was achieved with gastrectomy and standard D2 lymphadenectomy.[17] Paraaortic nodal dissection or combined resection of a small portion of the peritoneum or adjacent organs was permitted for curative intent; however, more invasive procedures, such as pancreaticoduodenectomy or Appleby's surgery, were not. When macroscopically curative surgery was achieved, the protocol treatment was terminated.

The radiologic diagnosis of T and N was determined by using thin-slice CT with a 5- to 7-mm thickness or multidetector low CT by following Habermann's method.[18,19] T1 tumors were defined as tumors that could not be found on images or that had focal thickening of the inner layer with a visible outer layer of the gastric wall and a clear fat plane around the lesion. T2 tumors were defined as tumors with focal or diffuse thickening of the gastric wall with transmural involvement and a smooth outer border of the wall or only a few small linear strands of soft tissue extending into the fat plane involving less than one-third of the tumor extent. T3 tumors were defined as transmural tumors with obvious blurring of at least one-third of the tumor extent or wide reticular strands surrounding the outer border of the tumor. T4 tumors were defined as tumors with obliteration of the fat plane between the gastric tumor and the adjacent organ or invasion of an adjacent organ. The regional lymph nodes were considered to be involved by metastases if they measured larger than 8 mm in the short-axis diameter. Tumor progression was evaluated according to the 7th edition of the International Union against Cancer TNM classification.[20,21] The radiologic response of the lymph nodes was evaluated according to version 1.0 of the Response Evaluation Criteria for Solid Tumors.[22] The surgical specimens were pathologically evaluated as grade 0 when degeneration and/or necrosis were absent within the tumor, grade 1a when these areas accounted for less than one-third of the tumor, grade 1b when these areas accounted for more than one-third and less than two-thirds of the tumor, grade 2a when these areas accounted for more

than two-thirds of the tumor, although tumor tissue apparently remained, grade 2b when only minimal tumor cells remained, and grade 3 when no residual tumor was detected.[17] Patients with grade 1b, 2a, 2b, or 3 tumors were classified as responders, whereas those with grade 0 or 1 tumors were classified as nonresponders.

All statistical analyses were performed by using the SPSS version 18.0 software program. Correlations between the two groups were analyzed with the chi-square test.

RESULTS

Between October 2009 and July 2011, a total of 83 patients were enrolled in the COMPASS study. All patients were eligible and received neoadjuvant chemotherapy. Among these 83 patients, 6 did not proceed to surgery because of tumor progression, 2 received bypass surgery because of peritoneal metastasis, and 75 underwent surgical resection and were entered into this study. The background characteristics of these 75 patients are shown in Table 1.

The relationship between the radiologic T and pathologic T stage is demonstrated in Table 2. No significant correlation was found in the 75 patients ($p = 0.221$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 42.7% (32 of 75), 10.7% (8 of 75), and 46.7% (35 of 75), respectively.

A pathologic response of the primary tumor was observed in 32 patients. When stratifying the patients according to the pathologic response (Table 3), the correlation was not significant in either the responders ($n = 32$, $p = 0.410$) or the nonresponders ($n = 43$, $p = 0.742$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 37.5% (12 of 32), 3.1% (1 of 32), and 59.4% (19 of 32), respectively, in the responders and

TABLE 1 Background of the patients ($n = 75$)

Variable	Data	
Age (years)	Median	66
	Range	32–80
Sex	Male/Female	53/22
Performance status	0/1	74/1
Macroscopic type	0	1
	1	5
	2	20
	3	34
	4	8
	5	7
Histologic type	Differentiated	14
	Undifferentiated	56
Clinical T	T2	1
	T3	6
	T4a	64
	T4b	4
Clinical N	N0	12
	N1	37
	N2	17
	N3	9
Regimen	Two courses of S-1 plus cisplatin	20
	Four courses of S-1 plus cisplatin	18
	Two courses of paclitaxel plus cisplatin	18
	Four courses of paclitaxel plus cisplatin	19

TABLE 2 Relationship between clinical T after neoadjuvant chemotherapy and pathologic T

Clinical T	Pathologic T						Total
	T0	T1	T2	T3	T4a	T4b	
T1	0[a]	0[b]	0[c]	0[c]	0[c]	0[c]	0
T2	2[a]	0[a]	2[b]	2[c]	0[c]	0[c]	6
T3	0[a]	3[a]	0[a]	6[b]	4[c]	1[c]	14
T4a	2[a]	3[a]	6[a]	18[a]	24[b]	1[c]	54
T4b	0[a]	0[a]	0[a]	1[a]	0[a]	0[b]	1
Total	4	6	8	27	28	2	75

[a] Overdiagnosis
[b] Accurate diagnosis
[c] Underdiagnosis

TABLE 3 Relationship between clinical T after neoadjuvant chemotherapy and pathologic T by stratifying the pathologic response of the primary tumor

Clinical T	Pathologic T						Total
	T0	T1	T2	T3	T4a	T4b	
Responder							
T1	0[a]	0[b]	0[c]	0[c]	0[c]	0[c]	0
T2	2[a]	0[a]	2[b]	1[c]	0[c]	0[c]	5
T3	0[a]	2[a]	0[a]	4[b]	0[c]	0[c]	6
T4a	2[a]	2[a]	4[a]	5[a]	6[b]	0[c]	19
T4b	0[a]	0[a]	0[a]	0[a]	2[a]	0[b]	2
Total	4	4	6	10	8	0	32
Nonresponder							
T1	0[a]	0[b]	0[c]	0[c]	0[c]	0[c]	0
T2	0[a]	0[a]	0[b]	1[c]	0[c]	0[c]	1
T3	0[a]	1[a]	0[a]	2[b]	4[c]	1[c]	8
T4a	0[a]	1[a]	2[a]	12[a]	18[b]	1[c]	34
T4b	0[a]	0[a]	0[a]	0[a]	0[a]	0[b]	0
Total	0	2	2	15	22	2	43

[a] Overdiagnosis
[b] Accurate diagnosis
[c] Underdiagnosis

46.5% (20 of 43), 16.3% (7 of 43), and 37.2% (16 of 43), respectively, in the nonresponders.

The relationship between the radiologic N and pathologic N stage is shown in Table 4. A significant correlation was found in all 75 patients ($p = 0.000$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 44% (33 of 75), 29.3% (22 of 75), and 26.7% (20 of 75), respectively. For the diagnosis of nodal positivity, the radiologic accuracy, sensitivity, and specificity were 70.7% (53 of 75), 84.9% (45 of 53), and 36.4% (8 of 22), respectively.

Fifty-one patients had measurable lymph nodes according to RECIST version 1.0. Among these patients, a radiologic response was observed in 28 cases. When the 51 patients with measurable lymph nodes were stratified according to the radiologic response (Table 5), the correlation was significant in the nonresponders ($n = 23$, $p = 0.035$) but not in the responders ($n = 28$, $p = 0.634$). The radiologic accuracy and rates of underdiagnosis and overdiagnosis were 39.3% (11 of 28), 21.4% (6 of 28), and 39.3% (11 of 28), respectively, in the responders and 52.1% (12 of 23), 21.7% (5 of 23), and 26.1% (6 of 23), respectively, in the nonresponders.

TABLE 4 Relationship between clinical N after neoadjuvant chemotherapy and pathologic N

Clinical N	Pathologic N				Total
	N0	N1	N2	N3	
N0	8[a]	5[c]	3[c]	0[c]	16
N1	12[b]	9[a]	11[c]	0[c]	32
N2	2[b]	6[b]	15[a]	3[c]	26
N3	0[b]	0[b]	0[b]	1[a]	1
Total	22	20	29	4	75

[a] Accurate diagnosis
[b] Overdiagnosis
[c] Underdiagnosis

TABLE 5 Relationship between clinical N after neoadjuvant chemotherapy and pathologic N by stratifying the radiologic response of the lymph node

Clinical N	Pathologic N				Total
	N0	N1	N2	N3	
Responder					
N0	1[a]	0[c]	1[c]	0[c]	2
N1	6[b]	4[a]	4[c]	0[c]	14
N2	2[b]	3[b]	6[a]	1[c]	12
N3	0[b]	0[b]	0[b]	0[a]	0
Total	9	7	11	1	28
Nonresponder					
N0	0[a]	0[c]	0[c]	0[c]	0
N1	3[b]	3[a]	3[c]	0[c]	9
N2	0[b]	3[b]	8[a]	2[c]	13
N3	0[b]	0[b]	0[b]	1[a]	1
Total	3	6	11	3	23

[a] Accurate diagnosis
[b] Overdiagnosis
[c] Underdiagnosis

Discussion

This study evaluated the accuracy of radiologic diagnosis after neoadjuvant chemotherapy in 75 patients enrolled in the prospective randomized phase II COMPASS study, which predefined radiologic criteria for T- and N-staging. The radiologic overall accuracy was 42.7% for T-staging and 44% for N-staging. Previously, we examined the radiologic accuracy of primary staging determined according to the same criteria using CT in 315 patients with primary resectable gastric cancer and demonstrated that the radiologic accuracy was 71.4% for T-staging and 75.9% for N-staging.[19] Compared with the primary staging, restaging after neoadjuvant chemotherapy was found to be inaccurate and unreliable.

With respect to T-staging after neoadjuvant chemotherapy, the radiologic T and pathologic T stages were not significantly correlated. The overall accuracy was only 42.7%. These results suggest that T-staging using CT provides no clinical information and should not be considered in clinical decision-making. Previously, Park et al.[13] reported that the accuracy of T restaging was 47% on EUS and 57% on CT. The accuracy reported in their study was slightly better than that observed in the present results. In this study, the radiologic accuracy was 37.5% in the responders and 46.5% in the nonresponders, which suggests that the radiologic accuracy is affected by the response of the primary tumor. In Park and colleagues' study, the response rate and accuracy stratified according to the response were not demonstrated.[13]

Most cases of misdiagnosis of the T stage are due to overdiagnosis. Park et al.[13] also reported similar results. Chemotherapy acts on tumor tissue and induces a variety of changes of in both the tumor and stroma, including necrosis, inflammation, and fibrosis.[23] The depth of tumor invasion may become shallow if these changes occur in the tumor tissue. Chemotherapy-induced stromal changes can cause difficulties in distinguishing the wall layer of the stomach on CT, by which overdiagnosis and/or misdiagnosis can occur. When the T stage was examined by separating the patients according to the pathologic response of the primary tumor, the radiologic accuracy was lower and the rate of overdiagnosis was higher in the responders than in the nonresponders. However, the radiologic accuracy was not significantly high, even in the nonresponders. It should be clarified whether chemotherapy-