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.

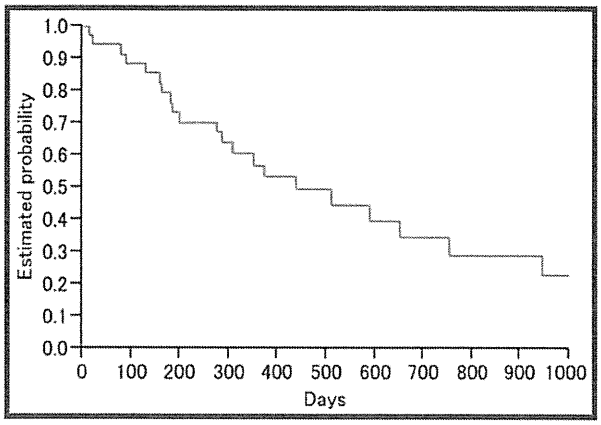
Results

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.

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 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

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.

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SHORT COMMUNICATION

Survival analysis of adjuvant chemotherapy with S-1 plus cisplatin for stage III gastric cancer

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Abstract
Background We previously reported that S-1 plus cisplatin was feasible as adjuvant chemotherapy for stage III gastric cancer after D2 gastrectomy. Herein we evaluate the recurrence-free survival and overall survival rates as secondary endpoints based on updated follow-up data.
Methods Patients with stage III gastric cancer who underwent D2 gastrectomy were enrolled. Treatment consisted of 3 cycles of S-1 (40 mg/m^2 PO) twice daily on days 1–21 and cisplatin (60 mg/m^2 IV) on day 8, and S-1 was given on days 1–28 every 6 weeks until 1 year after surgery.
Results From August 2007 to September 2009, 63 patients were accrued. Overall, 34 and 25 patients had stage IIIA and IIIB disease, respectively. After a median follow-up of 3.9 years, 16 patients experienced recurrence and 11 patients died. The 3-year recurrence-free survival rate was 74.1 % (95 % CI: 60.8–83.5 %, IIIA 81.8 %, IIIB 64.0 %). The 3-year overall survival rate was 84.5 % (95 % CI: 72.3–91.6 %, IIIA 87.9 %, IIIB 80.0 %).

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Recurrence sites included the peritoneum ($n = 8$), hematogenous sites ($n = 6$), and lymph nodes ($n = 4$).
Conclusion The present results indicate that adjuvant therapy with S-1 plus 3 cycles of cisplatin may provide a survival benefit to patients with stage III gastric cancer.

Keywords Adjuvant chemotherapy · Gastric cancer · S-1 · Cisplatin

Introduction

In 2007, the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) demonstrated the efficacy of S-1 for stage II–III Gastric Cancer (GC) patients who underwent curative resection with D2 gastrectomy [1, 2]. The addition of S-1 improved the overall survival (OS) rate, with a low incidence of adverse events and good compliance. According to this result, in Japan, the currently recommended adjuvant treatment after D2 gastrectomy is S-1 for 1 year. However, the 5-year OS rates in stage III patients receiving S-1 have been less satisfactory: 67.1 and 50.2 % for stage IIIA and IIIB, respectively. Therefore, identification of more effective treatments for stage III GC is urgently needed. So firstly we evaluated the feasibility of S-1 plus cisplatin, that is now considered to be one of the standard regimens for metastatic or recurrent GC [3] as adjuvant chemotherapy for Stage III GC after D2 gastrectomy.

As results, treatment completion rates after 3 cycles of S-1 plus cisplatin were 72 % (42/58; 95 % CI: 60–84 %; 57 % [12/21] before and 81 % [30/37] after the protocol amendment). Grade 3/4 toxicities included neutropenia (40 %), anorexia (28 %), and febrile neutropenia (4 %) before the protocol amendment, and neutropenia (37 %), anorexia (8 %), and febrile neutropenia (3 %) after the amendment implementation. Therefore, we concluded that the amended S-1 plus cisplatin regimen is feasible as adjuvant chemotherapy [4].

In this report, we evaluate the recurrence-free survival (RFS) and OS as secondary endpoints based on updated follow-up data.

Methods

Patients eligible for this trial had either stage IIIA (T2,N2; T3,N1; T4,N0) or stage IIIB (T3,N2; T4,N1) [5] gastric adenocarcinoma and had undergone D2 gastrectomy with R0 surgical resection. Additional details were described as previously [4]. The protocol was approved by the institutional review board at each participating center. Treatment according to the original protocol was initiated 4–8 weeks after surgery with 3 cycles of S-1 plus cisplatin (SP) followed by S-1 for up to 1 year. In the SP step, each cycle consisted of 40 mg/m^2 S-1 taken orally twice-daily for 21 days plus a 2-hour infusion of 60 mg/m^2 cisplatin on day 8. Each cycle was administered at 5-week intervals. In the S-1 step, 40 mg/m^2 S-1 was taken for 28 days at 6-week intervals. During enrollment, some toxicity was reported during the first cycle of SP, particularly neutropenia and anorexia. To minimize patient's risk, we elected to amend the protocol. Treatment according to the amended protocol was initiated 4–6 weeks after surgery and consisted of the following: the first cycle of chemotherapy consisted of S-1 monotherapy, and cisplatin was added to cycles 2, 3, and 4. After that, S-1 was administered for up to 1 year. Tumor assessments with ultrasonography, computed tomography, and GI endoscopy and radiography were performed every 6 months for first 2 years after surgery, and annually thereafter (maximum follow-up 5 years). RFS was defined as the time from enrollment to the recurrence or death, whichever occurred first. OS was defined as the time from enrollment to death from any cause.

Results

From August 2007 to July 2009, 63 patients (25 patients in the original protocol, 38 patients in the amended protocol) were accrued from five Japanese institutions. Overall, 34 patients (54 %) had stage IIIA disease and 25 (40 %) had stage IIIB disease. The patient clinical characteristics have been reported previously [4]. After enrollment, 5 patients were deemed ineligible due to confirmed stage II disease ($n = 2$), stage Ib disease ($n = 1$), stage IV disease ($n = 1$), and cancer other than GC ($n = 1$).

OS and RFS were analyzed in 58 eligible patients. At the time of data cut-off on July 31, 2012, 11 patients had died, 5 patients were alive with recurrence, and the remaining 42 patients were alive without recurrence. The median follow-up period was 46 months. All patients could be followed-up for at least 3 years from the date of surgery. Kaplan–Meier estimates are shown that the 3-year OS rate was 84.5 % (95 % CI: 72.3–91.6 %) (Fig. 1a); and the 3-year RFS rate was 74.1 % (95 % CI: 60.8–83.5 %) (Fig. 1b). According to disease stage, the 3-year OS rate of patients with stage IIIA disease was 87.9 % (95 % CI: 70.9–95.3 %) (Fig. 2a), and the 3-year RFS rate was 81.8 % (95 % CI: 63.9–91.4 %) (Fig. 2b). The 3-year OS rate of patients with stage IIIB disease was 80.0 % (95 % CI: 58.4–91.1 %) (Fig. 2a). The 3-year RFS rate was 64.0 % (95 % CI: 42.2–79.4 %) (Fig. 2b).

In addition, there was no significant difference in survival between the original protocol and the amended

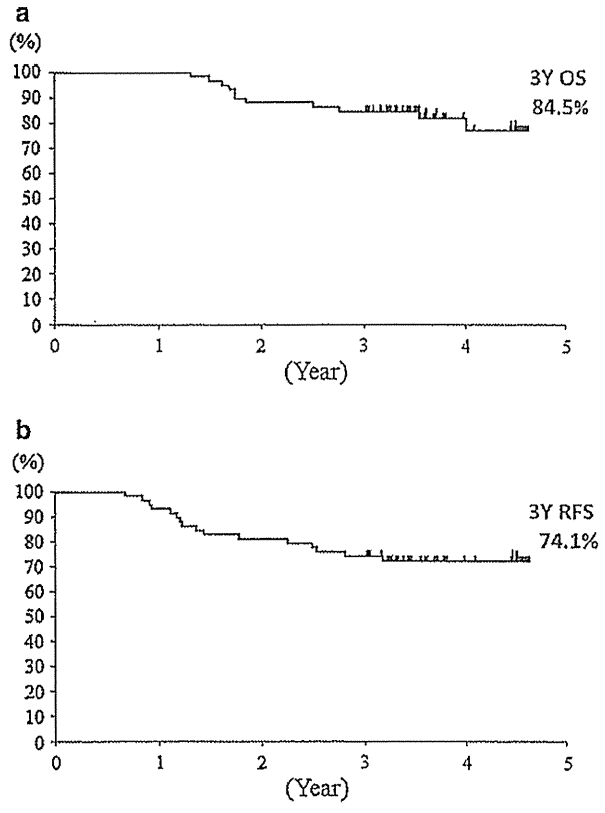

Fig. 1 Kaplan–Meier estimates of a overall survival and b relapse-free survival for all eligible patients

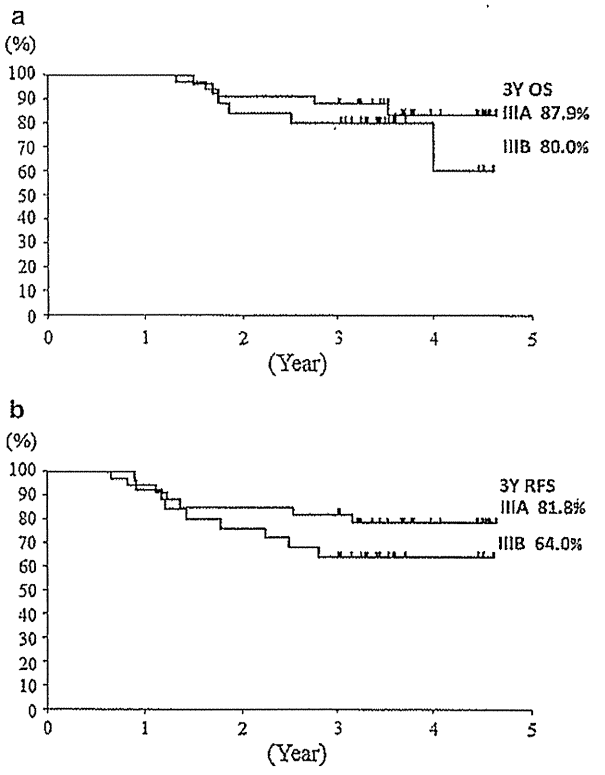

Fig. 2 Kaplan–Meier estimates of a overall survival and b relapse-free survival for patients with stage IIIA and IIIB gastric cancer

protocol. The 3-year OS rate of patients with stage IIIA disease in the original protocol ($n = 16$) and the amended ($n = 17$) was 87.5 and 88.2 %, respectively, and the 3-year RFS rate was 75.0 and 82.4 %, respectively. The 3-year OS rate of patients with stage IIIB disease was 80.0 % in the original protocol ($n = 5$) and the amended protocol ($n = 20$), and the 3-year RFS rate was 60.0 and 65.0 %, respectively.

The most common sites of relapse were the peritoneum ($n = 8$), hematogenous sites ($n = 6$), and lymph nodes ($n = 4$). Two patients experienced relapses simultaneously in the liver and the lymph nodes. No local relapse was observed. After relapse, the median survival time was estimated to be 351 days. Subsequent therapies were taxanes ($n = 7$), SP ($n = 4$), S-1 ($n = 3$), and CPT-11 ($n = 1$), and 1 case underwent surgery (oophorectomy) followed by paclitaxel.

Discussion

In this study, postoperative S-1 plus 3 cycles of cisplatin demonstrated promising efficacy with respect to 3-year RFS and OS for stage III GC.

Recently, the results of the CLASSIC trial indicated that adjuvant capecitabine and oxaliplatin improved 3-year disease-free survival (DFS) compared with surgery alone in GC patients [6]. The subgroup analysis suggested that combined capecitabine and oxaliplatin were beneficial not only for stage II patients but also for stage IIIA and stage IIIB patients (the hazard rates compared to surgery alone were 0.57 and 0.57, respectively). This result suggests that combination therapy with fluoropyrimidine and a platinum agent may be more beneficial than fluoropyrimidine alone in patients with stage III disease after D2 gastrectomy.

Although small-sample comparisons should be made with caution, there was no significant difference in survival between the original protocol and the amended protocol. It is suggested that delay of cisplatin administration in our amended protocol didn't sacrifice the efficacy in terms of survival. Consequently, we believe that completion of 3 cycles of cisplatin is important, even though we changed the first cycle to S-1 monotherapy and delayed additional cisplatin until cycles 2, 3, and 4. Moreover, our amended protocol was beneficial in the reduction of grade 3/4 anorexia and nausea, even though we did not use NK-1 receptor antagonists, because they were not approved in Japan at that time. Now we could manage the

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

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

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

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EDITORIAL

The earlier the better?

Masanori Terashima

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In the past, post-gastrectomy patients had to undergo fasting with a nasogastric tube for as long as 5–7 days. Then, patients would be started on a liquid diet and gradually transitioned to a soft diet, upon confirming that the esophagogastrogram detected no sign of leakage. Early oral feeding was avoided because it was believed to increase the risk of postoperative complications.

In the late 1990s, however, a combination of early oral feeding, early mobilization, and sufficient pain control using epidural analgesia reportedly improved the recovery of patients with colorectal cancer [1]. This protocol was further refined and integrated into a fast-track methodology or enhanced recovery after surgery (ERAS) [2], which rapidly spread throughout the world with the widespread acceptance of laparoscopic minimal invasive surgery. Several randomized controlled trials (RCTs) [3, 4] and meta-analyses [5, 6] revealed that ERAS reduced the length of hospital stay and morbidity after colorectal surgery without compromising patient safety. European guidelines strongly recommend postoperative early feeding and perioperative oral nutritional support, such as carbohydrate administration, along with preoperative education, adequate postoperative analgesia, and early mobilization [7, 8].

In gastric cancer, introduction of early oral feeding has been very limited, possibly because of the fear of increasing postoperative complications related to upper gastrointestinal anastomosis. Hirao et al. [9] evaluated the feasibility of early oral feeding in patients with gastric cancer. In that study, patients in the early oral feeding group were started on a liquid diet on the 2nd postoperative day (POD 2) and transitioned to a solid diet on POD 6, and their outcomes were compared with those of control patients undergoing the conventional regimen, i.e., initiation of a solid diet on the POD 10. A significant decrease in the length of postoperative hospital stay and higher daily oral intake of calories on POD 10 were observed in the early oral feeding group. Although this study was the first to demonstrate the feasibility of early oral feeding in patients with gastric cancer, the regimen was far from being "fast track," as the length of postoperative hospital stay was 18.5 days even in the early oral feeding group.

Implementation of various ERAS programs for gastric cancer has been reported since 2010. Grantcharov and Kehlet [10] evaluated the efficacy of an ERAS program in 32 patients with gastric cancer, gastrointestinal stromal tumor (GIST), and benign diseases, who, after undergoing laparoscopic gastrectomy, were started on oral feeding on POD 2 with planned discharge on POD 3. Two major complications were reported, but morbidity was sufficiently low, with no deaths within 30 days. Median length of hospital stay was only 4 days. Yamada et al. [11] also evaluated the feasibility and efficacy of an ERAS program, in which 91 post-gastrectomy patients were placed on oral nutritional supplementation on POD 2 and then transitioned to a soft diet on POD 3. Compared with 100 control patients, those in the ERAS group had a significantly earlier oral intake start day, oral intake recovery, flatus, and defecation, and also had significantly less postoperative pain.

Two RCTs on ERAS have been reported in Korea. The first trial was conducted at Catholic University [12], where 54 patients scheduled to undergo gastrectomy were randomly allocated into control and early feeding groups; the control group was started on a soft diet on POD 4, whereas

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the early feeding group was started on a liquid diet on POD 2 and transitioned to a soft diet on POD 3. The primary endpoint was the duration of hospital stay. The early oral feeding group had a significantly shorter duration of hospital stay and time of gas passage. The second RCT, reported by Yonsei University [13], included 47 patients who had undergone laparoscopic distal gastrectomy. The patients were randomly assigned to the fast-track or conventional pathway group. The fast-track protocol consisted of intensive preoperative education, short duration of fasting, preoperative carbohydrate load, early postoperative ambulation, early feeding, and sufficient pain control. In the fast-track and conventional groups, a liquid diet was started on POD 2 and POD 4, respectively, and a soft diet was started on POD 4 and POD 5, respectively. The possible and actual durations of postoperative hospital stay (primary endpoint) were significantly shorter in the fast-track group than in the conventional group. Moreover, the need for additional pain control was significantly less, and several QOL factors significantly improved, in the fast-track group.

In addition to these studies, the safety and efficacy of ERAS programs have been demonstrated even in gastric cancer surgery, albeit with delayed initiation of oral feeding. In ERAS programs for colorectal cancer, a normal diet is recommended as soon as patients become lucid after surgery. On the contrary, in most gastric cancer studies, a soft diet is started on POD 3 or POD 4 after safety is confirmed with a liquid diet on POD 2. It is speculated that surgeons might have concerns about anastomotic complications resulting from early oral feeding.

Jeong et al. [14] conducted a single-arm prospective trial to evaluate the feasibility of early oral feeding in patients with gastric cancer. In this trial, patients were started on a soft diet with lunch on POD 1, and their outcomes were compared with those of historical controls. In the early oral feeding group, the average diet start day was 1.8 days, and 39 % of patients were able to eat more than two-thirds of provided food on the 1st POD. There was no increase in postoperative complications. These observations led to the conclusion that postoperative oral nutrition is safe and feasible on POD 1 after gastrectomy. This report is meaningful in that the feasibility of early feeding in patients with gastric cancer was demonstrated. Yet, there were several limitations worth noting. First, the median age of this cohort was 59.9 years, which is about 10 years younger than those previously reported in studies targeting Japanese or Western patients. Furthermore, the authors indicated that compliance with early oral feeding was poor in patients aged 70 years or older. Thus, further confirmatory studies in other countries are required. Another major issue is the usefulness of the entire ERAS pathway. Despite the large difference in oral feeding start day, the difference in duration of hospital stay was only 1.5 days, suggesting that early oral feeding may not be the only factor affecting the duration of postoperative hospital stay.

Is it better to start a soft diet on POD 1 in patients with gastric cancer? The answer is both Yes and No. Caution is required when evaluating early oral feeding and ERAS programs. Previous ERAS studies are mostly single-institution studies with a small sample size. A comprehensive evaluation of ERAS programs, including early oral feeding, would require RCTs in a multi-institutional setting with a large sample size. Moreover, appropriate inclusion and exclusion criteria for each program, especially regarding age and comorbidities, are needed in future studies.

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ORIGINAL ARTICLE

Influence of endoscopic submucosal dissection on additional gastric resections

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Abstract
Background Widespread application of endoscopic submucosal dissection (ESD) for early gastric cancer (EGC) results in noncurative resection in some patients. The influence of preceding ESD on additional gastric resections has not been completely evaluated.
Methods Endoscopic, surgical, and pathological records of 255 patients who underwent additional gastrectomy after noncurative ESD at a single prefectural cancer center from September 2002 to December 2010 were reviewed. The estimated gastric resection based on endoscopic images before ESD was compared with the actual gastric resection performed after ESD.
Results Altered gastric resection was performed in 4 (1.6 %) of the 255 patients. In 3 patients, total gastrectomy was performed instead of distal gastrectomy; in 1 patient, distal gastrectomy was performed instead of pylorus-preserving gastrectomy because of an insufficient distance from the cardia or pylorus caused by contraction of the ESD scar. Standard gastrectomy including total or distal gastrectomy with D2 lymph node dissection was performed in 33 patients because of deep submucosal invasion with positive/indefinite vertical margins. The final pathology revealed pT2 or deeper in 10 patients.
Conclusions In conclusion, 98.4 % patients underwent the scheduled gastric resection before ESD, and the preceding gastric ESD had almost no influence on changing the gastric resection of the additional surgery. Although rare, the preceding ESD may necessitate alterations in gastric resection to widen the surgical area because of contraction of ESD scar for lesions near the cardia or pylorus.
Mini abstract A retrospective study of additional gastrectomy after noncurative ESD showed that the preceding ESD had almost no influence on changing the gastric resection of the additional surgery.

Keywords Endoscopic submucosal dissection · Early gastric cancer · Total gastrectomy · Distal gastrectomy · Proximal gastrectomy

Introduction

Patients with early gastric cancer (EGC) with negligible risk of lymph node metastasis are good candidates for endoscopic resection [1, 2]. Because of the widespread use of endoscopic submucosal dissection (ESD), many patients diagnosed with EGC have been successfully treated by ESD with curative intent [3–6]. EGC lesions indicated for endoscopic resection are defined by size, histology, and estimated depth [7]. However, because an accurate pathological diagnosis is possible only after total resection of the lesion, some lesions may be judged to have undergone noncurative resection on the basis of the risk of lymph node metastasis. Therefore, lesions presenting with pathological risk factors for metastasis, such as lymphovascular

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infiltration, deep submucosal invasion, and positive surgical margins, should undergo gastrectomy with lymph node dissection [8–10].

The standard surgery for gastric cancer involves resection of at least two-thirds of the stomach with D2 lymph node dissection [7]. For cT1cN0 tumors, modified gastric resections such as pylorus-preserving or proximal gastrectomy are becoming more common in Japan because of the lesser extent of lymph node dissection [11].

ESD allows for en bloc resection with sufficient tumor-negative margins, even for large EGC lesions; therefore, the artificial ulcer scars created by ESD may cause fibrotic contraction over a larger area [12, 13]. Although some studies have reported that laparoscopic surgery after noncurative ESD is a safe and feasible procedure [14, 15], no reports about the influence of ESD on additional gastric resections exist. Therefore, this study aimed to clarify the influence of preceding ESD on additional gastric resections among patients who failed to achieve curative ESD.

Patients and methods

Among all patients treated by ESD from September 2002 to December 2010 at Shizuoka Cancer Center Hospital (Shizuoka, Japan), 255 patients with 261 lesions underwent additional gastrectomy because of noncurative resection. Endoscopic images obtained before ESD were retrospectively reviewed, and the appropriate extent of gastric resection was estimated for each lesion. Gastric resection was decided as in Table 1, according to the treatment guidelines for gastric cancer adopted by the Japanese Gastric Cancer Association in 2010 [7]. In our institution, pylorus-preserving gastrectomy was first introduced in 2008. Pathological and surgical patient records were reviewed, and lesion characteristics, reasons for noncurative ESD, and actual gastric resections performed were evaluated.

Table 1 Indication of gastric resections for early gastric cancer

Gastric resection	Indication
Total gastrectomy	Proximal distance from the cardia is <2 cm
Distal gastrectomy	Proximal distance from the cardia is 2 cm or more
Pylorus-preserving gastrectomy	Lesions in the middle portion of the stomach with a distal distance of at least 4 cm
Proximal gastrectomy	Proximal lesions where more than half of the distal stomach can be preserved
Total remnant gastrectomy	Lesions in a remnant stomach

From Japanese Gastric Cancer Association [7]

Absolute indication for endoscopic resection

differentiated-type adenocarcinoma, UL(-), cT1a, ≤2 cm

Expanded indication for endoscopic resection

differentiated-type adenocarcinoma, UL(-), cT1a, >2 cm
differentiated-type adenocarcinoma, UL(+), cT1a, ≤3 cm
Undifferentiated-type adenocarcinoma, UL(-), cT1a, ≤2 cm

Fig. 1 Indication criteria of early gastric cancer for endoscopic resection proposed by the Japanese Gastric Cancer Treatment Guidelines. *UL* ulceration findings

Evaluation of EGC before ESD

Before ESD, all the patients were evaluated by esophagogastroduodenoscopy (GIF-H260; Olympus, Tokyo, Japan) with chromoendoscopy. For lesions suspected of submucosal invasion, additional endosonography was performed. A biopsy of the lesion was performed to diagnose the histological cancer type before ESD. Several biopsies around the estimated border of the lesion were performed to confirm areas with nonneoplastic mucosa. The lesions were categorized as absolute indication, expanded indication, and contraindication for ESD according to the criteria for endoscopic resection proposed by the treatment guidelines (Fig. 1) [7]. The treatment of all EGC patients was discussed at our institutional cancer board, which consists of endoscopists, gastroenterologists, and surgeons.

According to the Japanese Gastric Cancer Treatment Guidelines 2010 (ver. 3) [7], ESD was deemed to be curative when all the following conditions were fulfilled: (a) en bloc resection with margins free of cancer and no lymphovascular infiltration; (b) differentiated-type pT1a cancer without ulcerative findings; (c) a differentiated-type pT1a lesion, no larger than 3 cm in diameter, with ulcerative findings; (d) a differentiated-type pT1b lesion (SM1, invasion less than 500 μm below the muscularis mucosa) no larger than 3 cm in diameter; and (e) an undifferentiated-type pT1a lesion no larger than 2 cm in diameter, without ulcerative findings. A resection that did not satisfy any of these criteria was considered to be noncurative. This retrospective study was approved by the ethics committee of Shizuoka Cancer Center Hospital (Approval No.: 24-J114-24-1-3).

Results

Demographic and lesion characteristics are summarized in Table 2. Nearly half (122; 47 %) of the 261 lesions in the 255 patients (81 % male; median age, 69 years) were

Table 2 Demographic and tumor characteristics of 261 lesions in 255 patients who underwent additional gastric resection after noncurative endoscopic submucosal dissection (ESD)

Age	
Median (range)	69 (37–89)
Gender	
Male/female	206/49
Location	
Upper portion	69 (26 %)
Middle portion	122 (47 %)
Lower portion	70 (27 %)
Indication for endoscopic resection (ER)	
Absolute	97 (37 %)
Expanded	121 (46 %)
Contraindicated	43 (17 %)
Reason for noncurative resection (with overlapping)	
pT1b-(SM2)	153 (59 %)
pT1b-(SM1), >3 cm	31 (12 %)
UL(+), >3 cm	25 (10 %)
Undifferentiated type, >2 cm or UL (+) or pT1b	17 (7 %)
ly (+)	93 (36 %)
v (+)	49 (19 %)
HM+ or indefinite	15 (6 %)
VM+ or indefinite	55 (21 %)
Time from ESD to surgery	
Median, day (range)	70 (23–470)
Surgical procedure	
Open surgery	236 (93 %)
Laparoscopic surgery	19 (7 %)
Operation time, min	
Mean, SD	198 (±55)
Intraoperative blood loss, ml	
Mean, SD	307 (±287)

UL ulcerative findings, *ly* lymph vessel infiltration, *v* vascular infiltration, *HM+* positive horizontal margin, *VM+* positive vertical margin, *SD* standard deviation

located in the middle portion of the stomach. Deep submucosal invasion was the most common reason leading to a judgment of noncurative ESD (153/261, 59 %). Additional gastrectomy was performed at a median of 70 days after ESD. Most patients (236/255, 93 %) underwent open surgery. Laparoscopy-assisted distal gastrectomy (DG) was performed in 14 patients, and laparoscopy-assisted pylorus-preserving gastrectomy (PPG) was performed in 5 patients. The mean operation time was 198 min, and the mean intraoperative blood loss was 307 ml. Only one case of intraabdominal adhesion required partial resection of the mesocolon. This case had a perforation during the preceding ESD and was sealed using endoclips.

The estimated gastric resections before ESD and the resections actually performed are shown in Fig. 2. Among 164 patients in whom DG with D1+ lymph node dissection (D1+) was the estimated gastric resection, the actual resection after ESD was DG with D1+ in 134, DG with D2 lymph node dissection (D2) in 26, total gastrectomy (TG) with D1+ in 3, and local resection in 1. In the 3 patients, the lesions were located in the upper portion of the stomach, and the ulcer scar after ESD was near the cardia, with an insufficient proximal margin. A representative case is shown in Fig. 3. The proximal distance was estimated to be 5 cm from the cardia before ESD, which was performed without complications, but the resection was noncurative because of lymph vessel infiltration. Two months after ESD, the artificial ulcer scar caused fibrotic contraction, and the gastric resection was changed to TG. Local resection was performed in one patient because of an intraoperative finding of peritoneal metastasis. This patient was an 81-year-old woman with two EGCs. A preoperative computed tomography scan showed no lymph node metastasis. ESD was uneventful, and both lesions were resected en bloc with negative margins. Both lesions were undifferentiated type with a depth of pT1b and were positive for lymphatic infiltration with diameters of 8 and 15 mm, respectively.

Among 23 patients in whom PPG with D1+ was the estimated gastric resection, the actual resection after ESD was PPG with D1+ in 17, DG with D1+ in 1, and DG with D2 in 5. Among the 6 patients who underwent DG, 5 were in the noncurative category because of deep submucosal invasion with positive vertical margins. Therefore, DG with D2 was performed. The other patient underwent DG because the distal distance was shortened by fibrotic contraction after ESD (Fig. 4). For this patient, ESD was noncurative because of diffuse-type EGC with vascular infiltration. Although the estimated distance was 5 cm from the pylorus before ESD, the distance was shortened to <3 cm after ESD.

Among 50 patients in whom proximal gastrectomy (PG) with D1+ was the estimated gastric resection, the actual resection after ESD was PG with D1 in 48 and TG with D2 in 2. In the 2 patients who underwent TG, ESD was noncurative because of deep submucosal invasion of lesions with positive vertical margins. Therefore, TG with D2 was performed.

Among 36 patients with deep submucosal invasion and positive/indefinite vertical margins, D2 was performed in 22; the other 14 underwent D1 because of advanced age or poor physical condition. Residual tumor was found in 9 (25 %) patients. The final pathological depth of the main tumor was pT1b in 26 (72 %) patients and pT2 or deeper in 10 (28 %). Lymph node metastasis was positive in 10 (28 %) of the 36 patients.

In total, altered gastric resection was performed in 4 (1.6 %) of the 255 patients because of fibrotic contraction

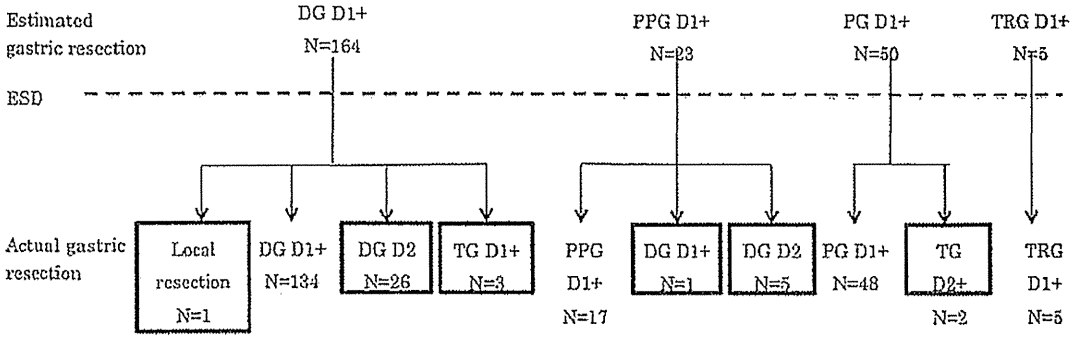

Fig. 2 Estimated gastric resection before endoscopic submucosal dissection (ESD) and actual resection performed after noncurative ESD. Patients undergoing surgery with modifications are indicated by *squares*. *DG* distal gastrectomy, *PPG* pylorus-preserving gastrectomy, *PG* proximal gastrectomy, *TRG* total remnant gastrectomy, *N* number of patients

of the ESD scar. The lesion characteristics of these 4 patients are shown in Table 3. All specimens had cancer-free margins. The size of the resected specimen was large in comparison with the size of the lesion.

The extent of lymph node dissection was altered in 13 % of the patients (33/255). In addition to the 22 patients with pT1b with positive/indefinite vertical margins, 1 patient with pT2 with a negative vertical margin, 7 patients with massive lymphovascular infiltration, and 3 patients with an intraoperative finding of suspected lymph node metastasis underwent D2 dissection.

Discussion

Because of the growing incidence of EGC in Japan, several minimally invasive surgical procedures have been developed, such as ESD, laparoscopic surgery, and PPG [11, 14–16]. PPG has been reported as a safe and effective surgery in terms of nutritional advantage and a lower incidence of gallstone [17–19]. Better quality of life can be expected in patients who undergo these minimally invasive treatments compared with those who undergo TG with extensive lymphadenectomy. ESD is the most recent endoscopic resection technique capable of removing EGC lesions that fulfill particular conditions of negligible risk of lymph node metastasis; furthermore, it preserves the stomach at the same time. Because a precise diagnosis of the risk of lymph node metastasis is impossible before treatment, and to decrease the risk of overtreatment, ESD is sometimes used for diagnostic intent. Goto et al. [20] reported that ESD as a staging measure may not necessarily lead to a worse prognosis after additional gastrectomy in patients with EGC. Therefore, a substantial number of patients will be found to have undergone noncurative ESD on the basis of the histological findings of the resected specimen.

Because the lesions indicated for ESD are larger than those indicated for endoscopic mucosal resection (EMR), the surgical duration is often longer [21, 22] and the artificial ulcers that form after ESD tend to be larger [12]. Therefore, the effect of thermocoagulation is expected to be greater than that of EMR. A pathological study using gastrectomy specimens obtained by noncurative ESD reported that fibrosis was observed in the muscle layer proper or deeper [13]. Intraabdominal adhesions induced by ESD ulceration reportedly result in time-consuming procedures and greater blood loss during additional laparoscopic gastrectomy [23], whereas others have reported little to no influence on early postoperative outcomes [14, 15]. Tsujimoto et al. [15] reported no difference in operation duration and intraoperative blood loss between laparoscopic gastrectomy with or without preceding ESD. In our study, we experienced only one case of intraabdominal adhesion induced by ESD that required partial resection of the mesocolon. However, the influence of preceding ESD on additional gastric resection remains unclear.

The results of this study showed that alterations in gastric resection occurred in 1.6 % of patients following noncurative ESD. Generally, gastrectomy with lymph node dissection should be performed for patients with submucosal invasion with or without margin involvement after noncurative ESD [24]. However, it remains unclear whether a modified resection technique such as PG or PPG with D1 or D1+ lymph node dissection is suitable for these patients. Therefore, in the current study, for patients with deep submucosal invasion with positive/indefinite vertical margins, the lesion depth was managed as cT2 and standard gastrectomy with D2 was performed. In fact, remnant cancer and/or lymph node metastasis was positive in 28 % of the patients. Also, in these patients, preceding ESD altered the extent of lymph node dissection to a more extended dissection (D1+ to D2).

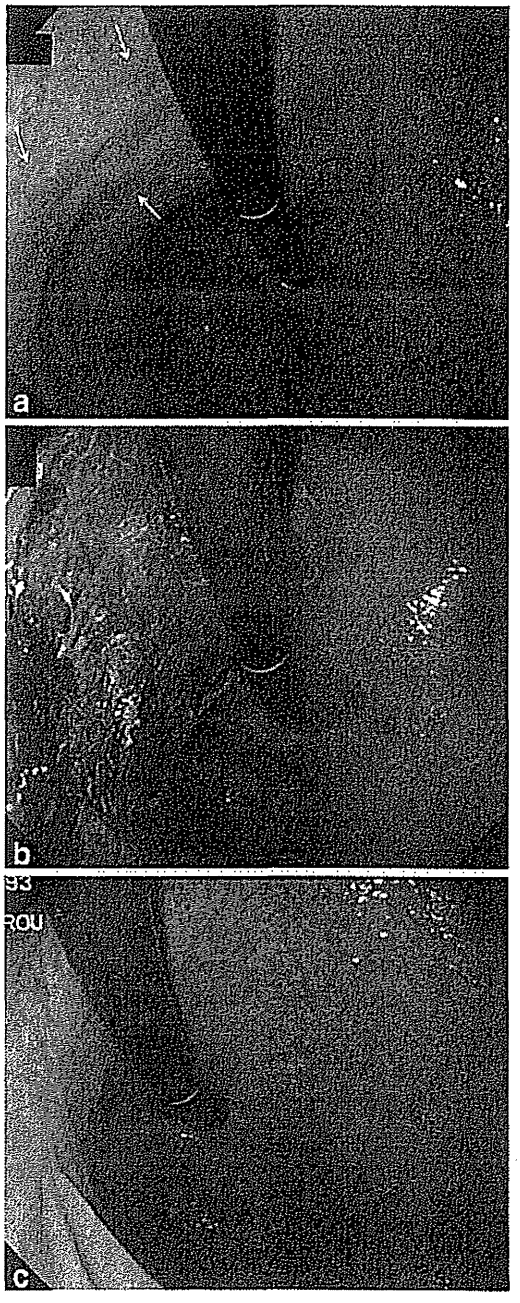

Fig. 3 Representative endoscopic images. a A 0–IIc cT1a(M) lesion (diameter, 20 mm) on the lesser curvature of the upper body at an estimated proximal distance of 5 cm. b An artificial ulcer that formed immediately after ESD. The proximal distance from the edge of the ESD ulcer has shortened to less than 5 cm. c Two months after ESD. The proximal distance of the scar is nearly 2 cm from the cardia. Therefore, the estimated resection before ESD of DG was changed to TG

Our study included 43 patients with lesions preoperatively assessed as contraindication for ESD. The main reason for contraindication was the clinical depth of T1b, and the reason to undergo ESD as an initial treatment included advanced age and desire of the patient. A total of 155 patients were diagnosed as pT1b or deeper from the result of ESD. The diagnostic sensitivity of submucosal invasion in our hospital is 73 % [10], which is not inferior to that of previous reports [25]. It is particularly difficult to estimate the correct depth of lesions with ulceration findings. We aggressively perform diagnostic ESD for lesions of unknown depth to avoid surgery for lesions that could be treated by ESD. Therefore, a few lesions were diagnosed as pT2 by final pathological results. Improved diagnosis can avoid unnecessary ESD.

Although the resection margins were negative, DG or PPG as the estimated gastric resection had to be altered to TG (three patients) or DG (one patient) because of contraction of the ESD ulcer. The possibility of leaving a portion of the stomach was lost in these three patients because the resected ESD specimens were markedly larger than the tumors. Regardless, the resection line was determined by careful endoscopic observation to obtain sufficient tumor-negative margins. Large lesions of submucosal and undifferentiated-type cancers have been reported as risk factors for tumor-positive lateral margins after ESD [26]. Therefore, the resection line may have been set for a wide resection. Contraction is reportedly an important factor for the healing of large ESD ulcers [12, 13]. For lesions in which the surgical resection line comes near the cardia or pylorus ring, the surgeon must keep in mind that ESD will cause fibrotic contraction and shorten the distance from the cardia or pylorus.

Several limitations of this study must be addressed. First, the study was retrospective, and the gastric resection was retrospectively estimated on the basis of endoscopic images. In general practice, gastric resections are decided not only by the location of the lesion but also by patient age and physical condition, as well as the presence of hiatus hernia and the shape of the stomach. However, our study is unique because no previous study, to our knowledge, has investigated the influence of preceding ESD on additional gastric resections. Second, our stance on lesions with deep submucosal invasion with positive/indefinite vertical margins was to manage them as cT2, and standard gastrectomy with D2 was performed. However, the appropriate resection has not been established, and further studies are warranted.

In conclusion, 98.4 % patients underwent scheduled gastric resection before ESD, and the preceding gastric ESD had almost no influence on changing the gastric resection of the additional surgery. Although rare, the preceding ESD may necessitate alterations in gastric resection to widen the surgical area because of the contraction of lesions near the cardia or pylorus.

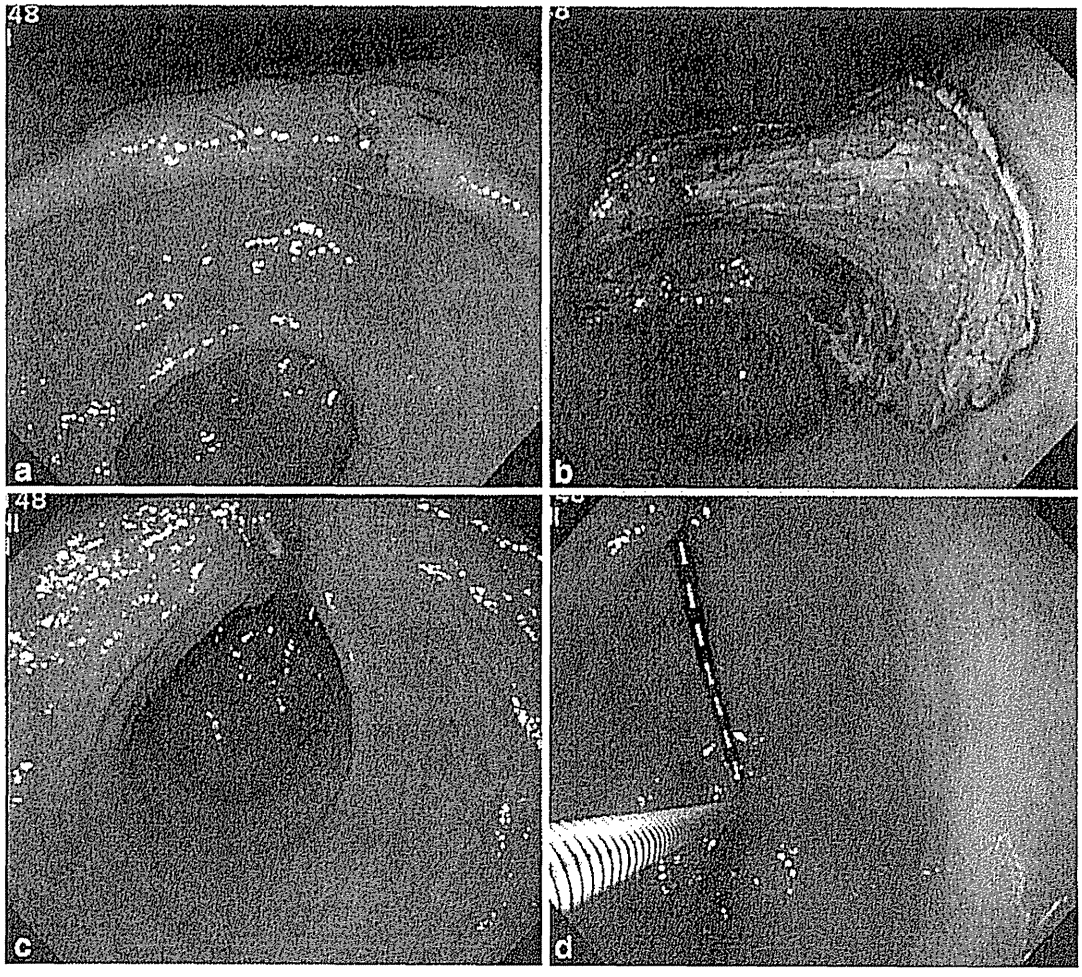

Fig. 4 Representative endoscopic images. **a** A 0–IIc lesion (diameter, 30 mm) on the lesser curvature of the gastric angle. The distal margin from the pylorus is estimated at 4 cm. **b** An artificial ulcer immediately after ESD. The distal distance from the edge of the ESD ulcer to the pylorus is shortened. **c**, **d** Two months after ESD. The distal distance from the scar to the pylorus is less than 3 cm. Therefore, the estimated resection before ESD of PPG was changed to DG

Table 3 Characteristics of four lesions with altered gastric resection resulting from fibrotic contraction after ESD

Loc	Circ	Type	Depth	Histology	Size of lesion (mm)	UL	Margins	ly, v	Size of specimen (mm)	Alteration in surgical resection
U	AW	0–IIa	pSM2	tub1	25	–	negative	–	50 × 40	PG to TG
U	LC	0–IIc	pSM2	tub1	34	–	negative	+	72 × 36	PG to TG
U	PW	0–IIc	pSM1	tub1	24	+	negative	+	51 × 49	PG to TG
M	LC	0–IIc	pSM1	por	30	+	negative	+	62 × 55	PPG to DG

Loc location, *U* upper portion, *Circ* circumference, *AW* anterior wall, *LC* lesser curvature, *PW* posterior wall, *tub1* well-differentiated adenocarcinoma, *por* poorly differentiated adenocarcinoma, *UL* ulcerative findings, *ly* lymph vessel infiltration, *v* vascular infiltration, *PG* proximal gastrectomy, *TG* total gastrectomy, *PPG* pylorus-preserving gastrectomy

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Postgastrectomy Syndrome Assessment Scale (PGSAS)-45 and Changes in Body Weight are Useful Tools for Evaluation of Reconstruction Methods Following Distal Gastrectomy

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ABSTRACT

Background. Billroth-I (BI) and Roux-en-Y (RY) are well-known reconstruction methods that are conducted following distal gastrectomy. However, the relative merits of these 2 methods are not well documented. The newly developed Postgastrectomy Syndrome Assessment Scale (PGSAS)-45 is an integrated questionnaire consisting of 45 items, including 8 items from the 8-Item Short-Form Health Survey (SF-8), 15 items from the Gastrointestinal Symptom Rating Scale, and 22 items selected by gastric surgeons. Postoperative QOL ratings were evaluated for each reconstruction method using PGSAS-45.

Methods. The PGSAS-45 questionnaire was distributed to 2,922 patients who underwent gastrectomies at 52 medical institutions. Among the questionnaires distributed, 2520 (86 %) were retrieved and 2368 (81 %) met eligibility requirements. Statistical analyses were conducted to compare 1,384 of the eligible questionnaires, including responses from patients who underwent BI ($n = 909$) and RY ($n = 475$) procedures.

Results. BI procedures were associated with significantly longer postoperative periods, a significantly greater size of gastric remnants, and a higher frequency of laparoscopic approaches and celiac branch preservation. Postoperative QOL analysis indicated that BI procedures resulted in significantly lower postoperative weight loss and significantly higher esophageal reflux symptoms than RY procedures. There was no significant difference between the two groups on other outcome measures.

Conclusions. Although weight loss was significantly lower following BI procedures, esophageal reflux symptoms were significantly higher. Either BI or RY procedures may be recommended based on the individual patient's condition after distal gastrectomy. The newly developed QOL questionnaire, PGSAS-45 and changes in body weight proved useful for evaluation of QOL following gastrectomy.

Gastric cancer is very common and is the second most common cause of cancer deaths in the world. It is the most prevalent form of cancer in Japan and East Asia.[1] The treatment of gastric cancer often requires gastrectomy with sufficient lymphadenectomy. Surgical treatment demonstrates sufficient disease control, particularly in early stages of gastric cancer. The 5-year overall survival rate in

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Japanese gastrectomy patients with stage I gastric cancer has been shown to exceed 90 %.[2] Among the major surgical procedures available for gastric cancer treatment, distal gastrectomy (DG) is most commonly used, as the majority of tumors in Asian gastric cancer patients are localized within the distal stomach.[2] Following DG, the two major reconstruction methods that are used worldwide are Billroth-I (BI) procedures and Roux-en-Y (RY) procedures. BI procedures are more commonly performed than RY procedures in Japan, while RY procedures are more common in Western countries.[3–5] BI procedures are advantageous in retaining physiological food passage; however, esophageal reflux is more frequently observed following BI procedures than RY procedures. Also, RY procedures entail longer operation times, as well as higher rates of postoperative stasis and stomal ulceration.[6] To determine the optimal reconstruction procedure following DG, several randomized controlled trials (RCT) have been performed.[7–9] Although minimal differences in the frequency of esophageal reflux have been reported from these studies, no significant differences have been observed between the 2 procedures. In addition, postgastrectomy symptoms were not fully evaluated in these RCTs. So, optimal evaluation methods of patient symptoms following BI and RY procedures had not yet been established.[10]

The Japan Postgastrectomy Syndrome Working Party was founded in order to investigate symptoms and lifestyle changes among patients who underwent gastrectomy. This group collaboratively developed a questionnaire to evaluate general features, i.e., symptoms, living status, and QOL among postoperative gastrectomy patients. Using this questionnaire, a nationwide, multi-institution surveillance study was performed. The QOL ratings of patients who underwent BI and RY procedures following DG were compared in order to determine the optimal reconstruction method to ensure long-term QOL for postoperative patients.

PATIENTS AND METHODS

Patients

A total of 52 institutions participated in this study. Patient eligibility criteria were: (1) diagnosis of pathologically confirmed stage IA or IB gastric cancer, (2) first-time gastrectomy status, (3) age $\geq$20 and $\leq$75 years, (4) no history of chemotherapy, (5) no recurrence or distant metastasis indicated, (6) gastrectomy conducted 1 or more years prior to enrollment date, (7) performance status (PS) $\leq$1 on the Eastern Cooperative Oncology Group (ECOG) scale, (8) full capacity to understand and respond to the questionnaire, (9) no history of other diseases or surgeries that might influence responses to the questionnaire, (10) no presence of organ failure or mental illness, and (11) written informed consent. Patients with dual malignancy or concomitant resection of other organs (with coresection equivalent to cholecystectomy being the exception) were excluded. As for the time interval between surgery and questionnaire, we determined more than 1 year, because this study was mainly focused on the evaluation of long-term QOL and previous study had demonstrated that the conditions of the patients with more than 1 year after gastrectomy were generally stable.[11]

QOL Assessment

The Postgastrectomy Syndrome Assessment Scale (PGSAS)-45 is a newly developed, multidimensional quality of life questionnaire (QLQ) based on the 8-Item Short-Form Health Survey (SF-8) and the Gastrointestinal Symptom Rating Scale (GSRS).[12–14] The PGSAS-45 questionnaire consists of a total of 45 questions, with 8 items from the SF-8, 15 items from the GSRS, and 22 clinically important items selected by the Japan Postgastrectomy Syndrome Working Party (Table 1). The PGSAS-45 questionnaire includes 23 items pertaining to postoperative symptoms (items 9–33), including 15 items from the GSRS and 8 newly selected items. In addition, 12 questionnaire items pertaining to dietary intake, work, and level of satisfaction with daily life were selected. Dietary intake items include 5 about the amount of food ingested (items 34–37 and 41) and 3 about the quality of ingestion (items 38–40). One questionnaire item pertains to work (item 42), while 3 items address the level of satisfaction with daily life (items 42–45). For the 23 symptom items, a 7-grade (1–7) Likert scale was used. A 5-grade (1–5) Likert scale was used for all other items except for items 1, 4, 29, 32, and 34–37. For items 1–8 and 38–40, higher scores indicate better conditions. For items 9–28, 30, 31, 33, and 41–45, higher scores indicate worse conditions.

Study Methods

This study used continuous sampling from a central registration system for participant enrollment. The questionnaire was distributed to all eligible patients as they presented to participating clinics. After completing the questionnaire, patients were instructed to return forms to the data center. All QOL data from questionnaires were matched with individual patient data collected via case report forms (CRF). For the evaluation of body weight changes, we did not include it as questionnaire. Instead, we measured the patients' body weight at the time of visit and compared with the preoperative body weight in medical records.

This study was registered with the University Hospital Medical Information Network's Clinical Trials Registry