disease, a further course of chemotherapy was given before surgery. If curative resection was considered difficult without any shrinkage of the metastasis, the protocol treatment was terminated.

Surgery

Criteria for surgery included: R0 resection deemed possible according to CT at the end of the final course of chemotherapy, and a white blood cell (WBC) count greater than 3000/mm^3 and a platelet count above 100 000/mm^3 at 14–20 days after the final administration of S-1. If the patient did not fulfil the criteria but was considered to be in a state of bone marrow recovery, then thresholds of 2000/mm^3 for WBC count and 50 000/mm^3 for platelet count were used. Patients underwent surgery within 14 days of fulfilling these criteria. Laparoscopic surgery was not allowed.

After laparotomy, resectability was evaluated again and, if intraperitoneal wash cytology was negative, R0 resection was attempted by D2 gastrectomy with PAN dissection, as described previously[8]. If necessary, to achieve R0 resection, splenectomy and/or distal pancreatectomy was carried out in combination with D2 plus PAN dissection, and resection margins were checked by intraoperative pathological examination if a positive margin was suspected. Protocol treatment was considered completed when a patient had received two or three cycles of neoadjuvant chemotherapy and had undergone R0 resection by D2 gastrectomy with PAN dissection. No further treatment was given until tumour recurrence.

Surgical quality control

Operative methods and pathology results were recorded according to the second edition of the Japanese Classification of Gastric Carcinoma[5]. During the study, participating surgeons and data centre representatives met three times per year to monitor the study. At each meeting, videos of surgical procedures including nodal dissection in selected procedures were presented by participating institutions to confirm standardization of surgical technique. To assess compliance with lymphadenectomy, the number of dissected nodes was recorded. Information concerning the major operative morbidities (anastomotic leak, pancreatic fistula and abdominal abscess) was included on the case report form. Duration of operation, blood loss, blood transfusion requirement and reoperation details were also recorded. Hospital mortality was defined as postoperative death from any cause within 30 days, or death within the same hospital admission.

Endpoints and evaluation

The primary endpoint was the percentage of R0 resections. Secondary endpoints were 3-year survival, percentage protocol completion, clinical and pathological response, and toxicities. Periodic monitoring was done twice a year for safety, and interim analysis for the primary endpoint was planned for the first 25 patients. The final analysis was planned for 3 years after the last enrolment but 5-year survival as a secondary endpoint and extended final analysis were added in 2009 because the observed 3-year survival was unexpectedly favourable.

Clinical response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.0 among all eligible patients, based on CT with central independent review. Surgical specimens were evaluated pathologically and graded according to the proportion of tumour affected by degeneration or necrosis: grade 0, no part of tumour affected; grade 1a, less than one-third affected; grade 1b, between one-third and two-thirds affected; grade 2, between two-thirds and entire tumour affected; and grade 3, no residual tumour[16]. A pathological response was defined as one-third or more of the primary tumour affected (grade 1b, 2 or 3)[10]. Responses in lymph nodes were also evaluated by identification of viable tumour cells, degeneration or necrosis in the plane of largest dimension including the hilum. Adverse events from chemotherapy and surgery were evaluated by the National Cancer

Table 2 Patient and tumour characteristics

	No. of patients (n = 53)
Age (years)*	63 (42–75)
Sex ratio (M : F)	43 : 10
ECOG performance status	
0	53 (100)
1	0 (0)
Macroscopic type	
0	2 (4)
1	1 (2)
2	15 (28)
3	33 (62)
5	2 (4)
Histology	
Differentiated	29 (55)
Undifferentiated	23 (43)
Other	1 (2)
Node status	
Bulky N2 only	26 (49)
PAN only	15 (28)
PAN and bulky N2	12 (23)

Values in parentheses are percentages unless indicated otherwise; *values are median (range). ECOG, Eastern Cooperative Oncology Group; PAN, para-aortic lymph node.

Institute Common Toxicity Criteria version 2.0[17]. It was expected that the incidence of anastomotic leakage would be less than 10 per cent, that the incidence of pancreas-related complications (including abdominal abscess) would be less than 60 per cent, and that the incidence of grade 3/4 non-haematological adverse events during chemotherapy would be less than 33 per cent.

Statistical analysis

The R0 resection rate was 65 per cent in JCOG0001[10] and the efficacy of S-1 plus cisplatin was expected to be superior and toxicity milder than that of irinotecan plus cisplatin in JCOG0001. A sample size of 50 was required for Southwest Oncology Group two-stage design with an interim one-sided α of 0·03, final one-sided α of 0·105, β of approximately 0·2, expected R0 rate of 65 per cent, and threshold of 50 per cent.

Overall survival was calculated from the date of enrolment to the date of death from any cause and was censored at the last follow-up. Among those with R0/R1 resection, relapse-free survival (RFS) was calculated from the date of enrolment to the date of relapse or death from any cause and was censored at the last verifiable relapse-free date. Survival curves were estimated using the Kaplan–Meier method, and compared by means of the log rank test. Treatment was considered safe if point estimates of treatment-related death did not exceed 5 per cent. Statistical analysis was performed with SAS® version 9.1 or 9.2 (SAS Institute, Cary, North Carolina, USA).

Results

Between February 2005 and June 2007, 53 patients entered the study from 19 institutions. Follow-up was performed for 5 years after the last patient was enrolled. *Table 2* shows patient demographics and tumour characteristics; 72 per cent of patients had bulky N2 and 51 per cent had PAN metastasis. Two patients were not eligible for full analysis, including one whose haematology results did not meet the inclusion criteria and another who had neither bulky N2 nor PAN metastasis at the outset. This latter patient was included in the analysis of chemotherapy adverse events (*Fig. 1*).

Response to chemotherapy

Of 52 patients who received chemotherapy, four discontinued treatment owing to adverse events and two because of progressive disease. The clinical response rate for all eligible patients was 65 (95 per cent confidence interval (c.i.) 50 to 78) per cent. There were no complete responses, a

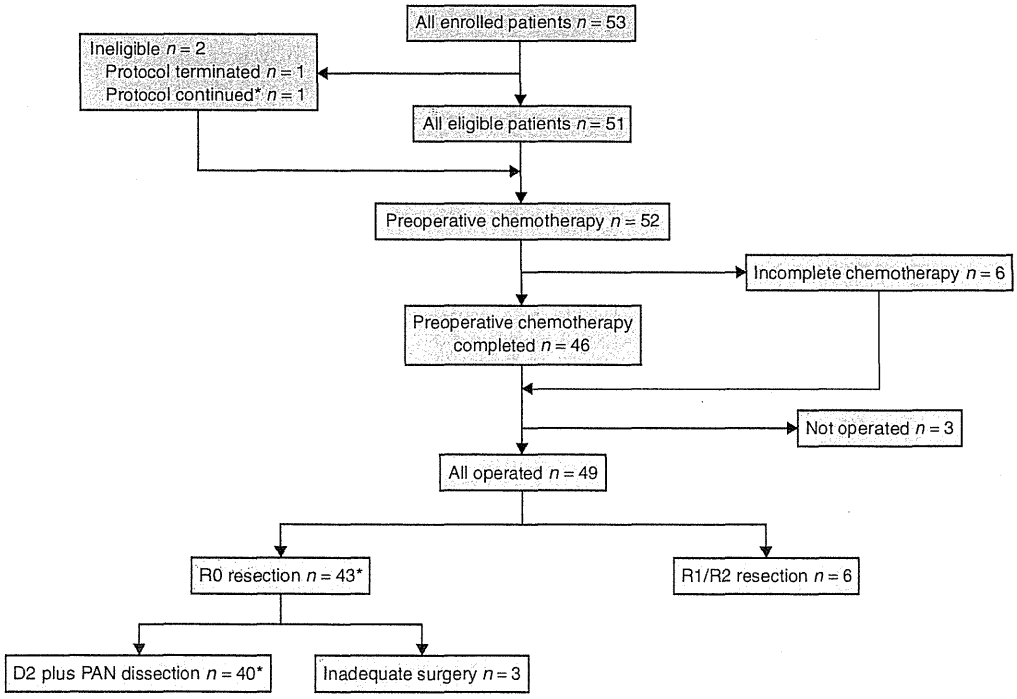

Fig. 1 Flow of patients from registration to surgery. *Including one ineligible patient. PAN, para-aortic lymph node

Table 3 Surgical findings in 49 operated patients

	No. of patients ($n = 49$)
Duration of surgery (min)*	350 (185–645)
Blood loss (ml)*	847 (80–4486)
Blood transfusion	
Autotransfusion	1 (2)
Allotransfusion	14 (29)
Plasma	2 (4)
Combined resection	
Pancreas	5 (10)
Spleen	27 (55)
Adrenal gland	2 (4)
Gallbladder	29 (59)
Tumour size (cm)*	5·5 (0–15)

Values in parentheses are percentages unless indicated otherwise; *values are median (range).

Table 4 Pathological findings in 49 patients

	No. of patients ($n = 49$)
Tumour depth	
No tumour (CR)	2 (4)
pT1 (m/sm)	7 (14)
pT2 (mp/ss)	23 (47)
pT3 (se)	16 (33)*
pT4 (si)	1 (2)
Lymph node metastases	
pN0	8 (16)
pN1	5 (10)
pN2	21 (43)
pN3†	15 (31)*
Pathological response (primary tumour)	
Grade 0	3 (6)
Grade 1a	19 (39)
Grade 1b	13 (27)*
Grade 2	13 (27)
Grade 3	1 (2)

Values in parentheses are percentages. Pathological findings were recorded according to the Japanese Classification of Gastric Carcinoma (2nd English edition). *Including one ineligible patient. †Metastasis to group 3 lymph nodes including para-aortic lymph node. CR, complete response; pT, pathological tumour category; m/sm, mucosa/submucosa; mp/ss, muscularis propria/subserosa; se, serosa; si, invasion of adjacent structures; pN, pathological node category.

partial response in 33 patients, stable disease in 14, progressive disease in four and one patient was considered not evaluable on central review.

Surgical and pathological findings

Among 49 patients who had chemotherapy and proceeded to surgery, R0 resection was achieved in 43 and R1/2 resection in six (*Fig. 1*). The R0 resection rate among 51 eligible study patients (the primary endpoint) was 82 (95 per cent c.i. 69 to 92) per cent. This was much higher than the prespecified threshold of 50 per cent ($P < 0{\cdot}001$, exact binomial test). The surgical data are summarized in *Table 3*. Approximately 30 per cent of patients received blood transfusions, and more than one-half underwent combined resection of the spleen or gallbladder.

Only 17 (35 per cent) of 49 tumours were exposed to the serosa, and 15 (31 per cent) were staged pathologically as pN3, including PAN, metastasis (*Table 4*). According to the initial node status in 48 eligible patients who underwent surgery, pN3 disease was found in five of 24 patients with bulky N2 disease only, four of 14 with bulky PAN involvement alone, and five of ten with both bulky N2 and PAN-positive tumours. The pathological response for primary tumours in eligible patients was 51 (95 per cent c.i. 37 to 65) per cent, including one grade 3. Eight patients with pN0 tumours were considered to have had a complete pathological response in the lymph nodes.

Table 5 Morbidity after surgery in 49 patients

	Grade*			
	1	2	3	4
Deep vein thrombosis	–	0	2	0
Wound infection	0	0	0	0
Pneumonia	–	2	0	0
Atelectasis	3	0	0	0
Mechanical obstruction	0	0	0	0
Pancreatic fistula	4	7	0	0
Abdominal abscess	1	7	0	0
Anastomotic leakage	0	3	0	0
Anastomotic stenosis	0	0	0	–
Other	5	2	4	0
Total	13	21	6	0

*National Cancer Institute Common Toxicity Criteria version 2.0.

Adverse events from chemotherapy, and surgical complications

Grade 3 or 4 toxicity during chemotherapy among all 52 treated patients included leucopenia (4 per cent), neutropenia (19 per cent), anaemia (13 per cent), thrombocytopenia (4 per cent), febrile neutropenia (2 per cent), nausea (4 per cent), anorexia (10 per cent) and diarrhoea (2 per cent). The incidence of grade 3/4 non-haematological adverse events was 15 per cent. There were no chemotherapy-related deaths.

Morbidity after surgery is summarized in *Table 5*. In total, six grade 3/4 adverse events occurred in six patients (12 per cent). Any grade of anastomotic leakage, pancreatic fistula and intra-abdominal abscess occurred in 6, 22 and 16

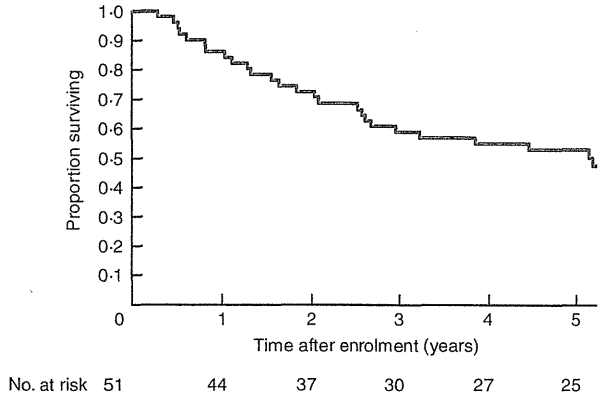

Fig. 2 Kaplan–Meier overall survival curve for the 51 eligible patients

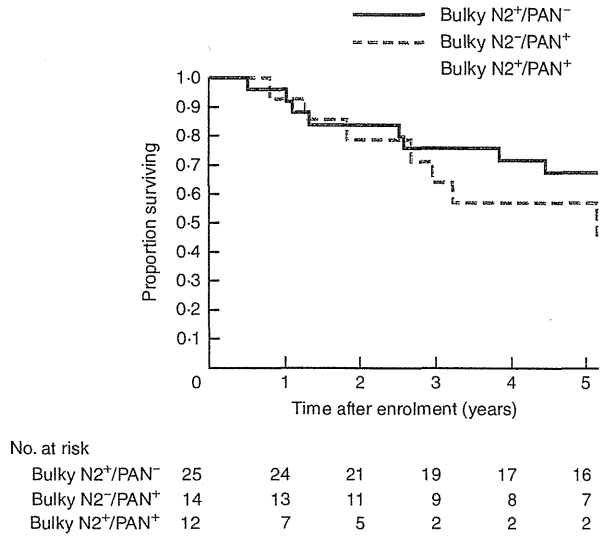

Fig. 3 Kaplan–Meier overall survival curve by lymph node status. PAN, para-aortic lymph node

per cent of patients respectively. There was no reoperation, treatment-related or in-hospital death.

Overall and relapse-free survival

Among all eligible patients, 3- and 5-year overall survival rates were 59 (95 per cent c.i. 44 to 71) and 53 (38 to 65) per cent in all eligible patients (*Fig. 2*). Overall survival varied according to lymph node involvement. The 5-year survival rate was 68 per cent in patients with bulky N2 disease alone, 57 per cent in those with PAN involvement only, and 17 per cent in those patients with both bulky N2 and PAN metastasis. Five-year survival was better in patients with only one of these risk factors than in patients with both risk factors ($P < 0{\cdot}001$) (*Fig. 3*). Among 42 eligible patients who underwent R0 resection, 3- and 5-year RFS rates were both 50 (34 to 64) per cent (*Fig. 4*).

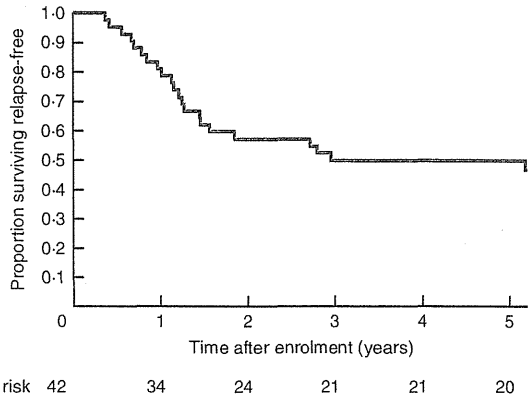

Fig. 4 Kaplan–Meier relapse-free survival curve for the 42 eligible patients who underwent R0 resection

Discussion

This multi-institutional phase II trial of neoadjuvant chemotherapy followed by surgery with PAN dissection (JCOG0405) achieved much higher 3- and 5-year survival rates (59 and 53 per cent respectively) than reported in the earlier trial, JCOG0001, in which the 3-year survival rate was 27 per cent[10]. As eligibility criteria, patient backgrounds and standard of surgery were similar in both trials, this result implies that preoperative S-1 plus cisplatin was much more effective than the irinotecan plus cisplatin regimen. The primary endpoint was the R0 resection rate and, at 82 per cent, this was higher than the prespecified threshold and that seen in JCOG0001 (65 per cent).

In much of Europe, epirubicin, cisplatin and infused fluorouracil (ECF) is the standard chemotherapy regimen, derived from the MAGIC trial[18]. In this trial, 86·0 per cent of patients completed three cycles of ECF before surgery, and 41·6 per cent completed all six cycles before and after surgery. As preoperative staging was not described[18] and because patients with clinically undetectable peritoneal seeding were not excluded, it is difficult to compare the results of MAGIC with those of the present study. In the MAGIC trial, the R0 resection rate in the ECF group was 69·3 per cent with evidence of downstaging in both tumour (25 per cent) and lymph nodes (13 per cent). As the majority of the patients in the present study would have been deemed unresectable in Western countries, the R0 resection rate of 82 per cent is high and suggests that neoadjuvant chemotherapy had a marked effect. On this basis, S-1

plus cisplatin seems a promising neoadjuvant regimen for gastric cancer with extensive lymph node metastasis.

In many Asian countries, including Japan, perioperative chemotherapy with ECF has not been regarded as the standard treatment for gastric cancer, mainly because 5-year survival in the surgery-alone arm in the MAGIC trial was unacceptably low (23·0 per cent). Data from two randomized phase III trials in patients with metastatic gastric cancer (JCOG9912[11], SPIRITS[12]) have been used to establish a standard treatment regimen in Japan based on S-1. Acceptable rates of grade 3/4 neutropenia (40 and 19 per cent respectively in patients who received 5- and 4-weekly S-1 plus cisplatin), and the adoption of S-1 in the postoperative setting as a result of the Adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC)[19], make use of the S-1–cisplatin combination attractive in further studies.

The role of PAN dissection for tumours treated by neoadjuvant chemotherapy is unknown. In the present trial, downstaging after chemotherapy was unclear, but 16 per cent of patients had no residual tumour in lymph nodes (pN0), and 10, 43 and 31 per cent of patients had metastases in N1, N2 and N3 lymph node tiers including PAN respectively. This is in contrast to JCOG9501[7] where only 8·5 per cent of patients had metastases in PANs and excision of these nodes did not improve survival compared with D2 alone. A *post hoc* analysis of JCOG9501 suggested that the effect of PAN dissection was significantly greater in node-negative than in node-positive patients, potentially reflecting the importance of removing occult disease in apparently negative nodes. In the present trial, 5-year overall survival rates were 68, 57 and 17 per cent for patients with clinically bulky N2-positive disease, those with PAN-positive disease and patients with both types of nodal involvement respectively. Although there was a difference in outcome between patients with involvement of a single lymph node tier and those with tumours involving both tiers, recognizing these groups after chemotherapy but before surgery remains problematic.

This study is limited by not being a randomized trial that compared either chemotherapy regimens or extent of lymph node dissection. The Stomach Cancer Study Group of JCOG carried out only a single-arm trial to study neoadjuvant chemotherapy followed by D2 plus PAN dissection, mainly owing to the limited numbers of patients. As a result of the favourable outcomes in this study, neoadjuvant S-1 plus cisplatin seems the tentative standard treatment for locally advanced gastric cancer with extended lymph node metastasis. A further phase II study has been initiated for patients with advanced gastric cancer with bulky N2 and/or PAN metastasis, using docetaxel plus S-1–cisplatin as a candidate regimen in comparison with S-1 plus cisplatin, with a view to a future randomized clinical trial[20].

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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

TABLE 1 Structure of the PGSAS-45 Questionnaire (domains/items/subscales)

Domains		Items		Subscales
SF-8	1	Physical functioning*	5- or 6-point Likert scale	Physical component summary (PCS)*
	2	Role physical*		Mental component summary (MCS)*
	3	Bodily pain*		
	4	General health*		
	5	Vitality*		
	6	Social functioning*		
	7	Role emotional*		
	8	Mental health*		
GSRS	9	Abdominal pain	7-point Likert scale, except items 29 and 32	Esophageal reflux subscale (items 10, 11, 13, 24)
	10	Heartburn		Abdominal pain subscale (items 9, 12, 28)
	11	Acid regurgitation		Meal-related distress subscale (items 25–27)
	12	Sucking sensations in the epigastrium		Indigestion subscale (items 14–17)
	13	Nausea and vomiting		Diarrhea subscale (items 19, 20, 22)
	14	Borborygmus		Constipation subscale (items 18, 21, 23)
	15	Abdominal distension		Dumping subscale (items 30, 31, 33)
	16	Eructation		
	17	Increased flatus		Total symptom scale (above 7 subscales)
	18	Decreased passage of stool		
	19	Increased passage of stool		
	20	Loose stool		
	21	Hard stool		
	22	Urgent need for defecation		
	23	Feeling of incomplete evacuation		
Symptoms	24	Bile regurgitation		
	25	Sense of food sticking		
	26	Postprandial fullness		
	27	Early satiation		
	28	Lower abdominal pain		
	29	Number and type of early dumping symptoms		
	30	Early dumping general symptoms		
	31	Early dumping abdominal symptoms		
	32	Number and type of late dumping symptoms		
	33	Late dumping symptoms		
Meals (amount) 1	34	Ingested amount of food per meal*		–
	35	Ingested amount of food per day*		
	36	Frequency of main meals		
	37	Frequency of additional meals		
Meals (quality)	38	Appetite*	5-point Likert scale	Quality of ingestion subscale* (items 38–40)
	39	Hunger feeling*		
	40	Satiety feeling*		
Meals (amount) 2	41	Necessity for additional meals		–
Social activity	42	Ability for working		–

TABLE 1 continued

Domains	Items	Subscales
Dissatisfaction	43 Dissatisfaction with symptoms	Dissatisfaction for daily life subscale (items 43–45)
	44 Dissatisfaction at the meals	
	45 Dissatisfaction at working	

In items or subscales with *, higher scores indicate better conditions
In items or subscales without *, higher scores indicate worse conditions
Each subscale is calculated as the mean of composed items or subscales, except PCS or MCS of SF-8
Items 29 and 32 do not have scores; these items were analyzed separately

(UMIN-CTR; registration No. 000002116). This study was approved by local ethics committees at each institution. Written informed consent was obtained from all enrolled patients.

Statistics

The comparison of patient QOL following BI and RY procedures included the *t* test and Chi squared test statistical methods. All items that exhibited significant variations in univariate analysis were further analyzed using multiple regression analysis; $p < .05$ was considered statistically significant. StatView software for Windows Ver. 5.0 (SAS Institute Inc.) was used for all statistical analyses.

RESULTS

Retrieving the Questionnaire

The PGSAS-45 questionnaire was distributed to 2,922 patients between July 2009 and December 2010. Of those distributed, 2520 (86 %) were retrieved. Among the 2520 retrieved documents, 152 were determined to be ineligible because of: age >75 years ($n = 90$), postoperative period <1 year ($n = 29$), resection of other organs ($n = 8$), and other factors ($n = 25$). As a result, 2,368 patients were determined to be eligible for inclusion in the analysis. Of the eligible 2,368 patients, 393 had undergone total gastrectomy, 909 had undergone DGBI, 475 had undergone DGRY, 313 had undergone pylorus-preserving gastrectomy, 193 had undergone proximal gastrectomy, and 85 had undergone local resection. In this study, 909 patients underwent DGBI and 475 patients underwent DGRY were selected for inclusion.

Patient Characteristics

Demographic information for all study participants is listed in Table 2. In patients who underwent BI procedures,

TABLE 2 Patient characteristics

	BI	RY	*P* value
Number of patients	909	475	
Postoperative period (months)	40.7 ± 30.7[a]	31.7 ± 18.0[a]	<.0001
Age	61.6 ± 9.1[a]	62.0 ± 9.1[a]	.529
Gender			
Male	594	318	.518
Female	311	154	
Preoperative BMI[b]	22.7 ± 3.0[a]	22.9 ± 3.0[a]	.190
Postoperative BMI[b]	20.9 ± 2.8[a]	20.8 ± 2.7[a]	.680
Approach			
Open	489	320	<.0001
Laparoscopic	415	152	
Extent of lymph node dissection[c]			
D0	4	0	.568
D1	8	3	
D1a	119	60	
D1b	444	246	
D2	319	163	
Preservation of celiac branch			
Preserved	133	28	<.0001
Divided	754	442	
Combined resection			
None	743	402	.698
Gallbladder	80	51	
Miscellaneous	4	2	
Size of gastric remnant			
More than half	29	10	<.0001
One-third	799	299	
One-fourth	61	139	
Less than one-fifth	0	22	

[a] Mean ± SD
[b] Body mass index
[c] According to Japanese gastric cancer treatment guidelines

TABLE 3 Outcome measures included in the PGSAS-45 Questionnaire

Item No.	
Main outcome measures	
–	Change in body weight (%)
10, 11, 13, 24	Esophageal reflux subscale[a]
9, 12, 28	Abdominal pain subscale[a]
25–27	Meal-related distress subscale[a]
14–17	Indigestion subscale[a]
19, 20, 22	Diarrhea subscale[a]
18, 21, 23	Constipation subscale[a]
30, 31, 33	Dumping subscale[a]
9–28, 30, 31, 33	Total symptom score[a]
34	Ingested amount of food per meal*
41	Necessity of additional meals
38–40	Quality of ingestion subscale*[a]
42	Ability for working
43	Dissatisfaction with symptoms
44	Dissatisfaction at the meals
45	Dissatisfaction at working
43–45	Dissatisfaction for daily life subscale[a]
1–5	Physical component summary*[a]
4–8	Mental component summary*[a]
Other outcome measures (symptoms)	
9	Abdominal pain
10	Heartburn
11	Acid regurgitation
12	Sucking sensations in the epigastrium
13	Nausea and vomiting
14	Borborygmus
15	Abdominal distension
16	Eructation
17	Increased flatus
18	Decreased passage of stool
19	Increased passage of stool
20	Loose stool
21	Hard stool
22	Urgent need for defecation
23	Feeling of incomplete evacuation
24	Bile regurgitation
25	Sense of food sticking
26	Postprandial fullness
27	Early satiation
28	Lower abdominal pain
30	Early dumping general symptoms
31	Early dumping abdominal symptoms
33	Late dumping symptoms
Other outcome measures (dumping)	
29	Existence of early dumping general symptoms (yes/no)
29	Existence of early dumping abdominal symptoms (yes/no)
29	Existence of any early dumping symptoms (yes/no)
32	Existence of late dumping symptoms (yes/no)
29	Number of early dumping general symptoms
29	Number of early dumping abdominal symptoms
29	Number of any early dumping symptoms
32	Number of late dumping symptoms
Other outcome measures (meals)	
35	Ingested amount of food per day*
36, 37	Frequency of daily meals
38	Appetite*
39	Hunger feeling*
40	Satiety feeling*

In items or subscales with *, higher scores indicates better conditions

In items or subscales without *, higher scores indicates worse conditions

[a] Integrated subscales

the mean postoperative period was significantly longer, frequencies of laparoscopic approaches and celiac branch preservation were significantly higher, and the size of gastric remnants was significantly greater than in patients who underwent RY procedures. All patients underwent R0 resection in both groups.

Refinement of QOL Measure

Based on data from the retrieved PGSAS-45 questionnaires, outcome measures were refined through consolidation and selection. A total of 23 symptom items were consolidated into 7 symptom subscales as listed in Tables 1 and 3. Assessment data included: total symptom score, quality of ingestion, level of satisfaction with daily life, physical component summary (PCS) of SF-8, and mental component summary (MCS) of SF-8 as main outcome measures (Table 3). In addition, the following results were selected as main outcome measures: changes in body weight, amount of food ingested per meal, necessity for additional meals, ability for working, dissatisfaction with symptoms, dissatisfaction at the meals, and dissatisfaction at working. Each subscale score was calculated as the mean of composed items, and total symptom score was calculated as the mean of 7 symptom subscales (Table 3). Although change in body weight was not included in the questionnaire, we included loss of body weight as 1 of the main outcome measures in this study because body weight loss significantly influences patient's QOL after gastrectomy.

TABLE 4 Univariate analysis of main outcome measures following Billroth-I (BI) and Roux-en-Y (RY) procedures

Main outcome measures	BI		RY		Cohen's *d*	*P* value
	Mean	SD	Mean	SD		
Change in body weight	−7.9 %	0.08	−8.9 %	0.07	0.14	.022
Esophageal reflux subscale[a]	1.70	0.82	1.49	0.65	0.29	<.0001
Abdominal pain subscale[a]	1.69	0.75	1.66	0.80		.519
Meal-related distress subscale[a]	2.05	0.88	2.09	0.88		.502
Indigestion subscale[a]	1.99	0.84	2.04	0.84		.230
Diarrhea subscale[a]	2.12	1.10	2.06	1.14		.335
Constipation subscale[a]	2.23	1.03	2.12	1.02	0.11	.063
Dumping subscale[a]	1.96	1.00	1.97	1.01		.957
Total symptom score[a]	1.96	0.68	1.92	0.67		.324
Ingested amount of food per meal	7.12	1.96	7.23	1.99		.323
Necessity of additional meals	1.86	0.78	1.90	0.81		.394
Quality of ingestion subscale*[a]	3.80	0.91	3.76	0.91		.497
Ability for working	1.75	0.87	1.83	0.88		.119
Dissatisfaction with symptoms	1.81	0.92	1.81	0.92		.903
Dissatisfaction at the meals	2.19	1.08	2.18	1.11		.886
Dissatisfaction at working	1.67	0.89	1.72	0.98		.389
Dissatisfaction for daily life subscale[a]	1.89	0.83	1.90	0.86		.842
Physical component summary*[a]	50.52	5.52	50.77	5.62		.446
Mental component summary*[a]	49.86	5.74	49.84	5.68		.955

Outcome measures with * indicate higher scores and therefore better conditions

Outcome measures without * indicate higher scores and therefore worse conditions

[a] Integrated subscales

TABLE 5 Multivariate analysis of main outcome measures

Items	Change in body weight		Esophageal reflux subscale	
	β[a]	*P* value	β[a]	*P* value
Type of gastrectomy [DGBI]	0.052	.069	0.142	<.001
Postoperative period (months)	–	.290	–	.739
Age (years)	−0.064	.022	0.054	.047
Gender [male]	–	.154	−0.060	.028
Approach [laparoscopic]	–	.219	–	.421
Celiac branch of vagus [preserved]	0.079	.006	−0.053	.057
R^2	0.02	<.001	0.028	<.001

DGBI distal gastrectomy Billroth-I

Multiple regression analysis was performed if the *P* value of the item/subscale in the univariate analysis was <.05

[a] If β is positive, the score of the outcome measure of the patient belonging to the category in brackets is higher in cases when the factor is a nominal scale, and the score of the outcome measure of the patient with larger values is higher in cases when the factor is a numeral scale

QOL Assessments

Calculated QOL measurements of patients following BI and RY procedures were compared according to the aforementioned criteria (Table 4). Among the main outcome measures, patients who underwent BI procedures showed significantly lower weight loss and significantly higher esophageal reflux than patients who underwent RY procedures. There were no other significant differences in QOL.

To eliminate confounding factors, multiple regression analysis was performed by adding postoperative period, age, gender, surgical approach, and celiac branch preservation as explanatory variables (Table 5). Weight loss was shown to be influenced by age and celiac branch preservation, and esophageal reflux subscale was shown to be influenced by age and gender. Reconstruction method was a borderline significant independent predictive factor for weight loss and the most significant independent predictive factor for esophageal reflux subscale.

Each symptom item within the esophageal reflux subscale, such as heartburn ($p = .002$), acid reflux ($p < .0001$), nausea and vomiting ($p = .023$), and bile regurgitation ($p < .0001$), was significantly worse with BI procedures than with RY procedures. Symptoms of flatus were significantly worse with RY procedures ($p = .001$). Defecation symptom, such as passage of stool ($p = .004$), was significantly worse with BI procedures. There was no significant difference in QOL scores between the two groups of patients for other symptoms, meals, work, or dissatisfaction for daily life.

DISCUSSION

This study assessed QOL among postoperative DG patients, comparing two methods of surgical reconstruction.

This comparison was conducted through the use of the PGSAS-45 questionnaire, which was developed for the measurement of QOL in gastrectomized patients. This was the first nationwide survey of its type and involved 52 medical institutions throughout Japan. QOL data were successfully collected from 2,520 patients, and the final sample size, following exclusion and participant selection, was sufficient for this type of study.

Patient demographic analysis indicated that patients who underwent BI procedures had longer postoperative periods and higher frequencies of both laparoscopic gastrectomy and celiac branch preservation. In Japan, laparoscopic operations are mainly used to treat early gastric cancer.[15,16] The celiac branch is frequently preserved in limited surgical interventions for early gastric cancer. There is a possibility that these differences may affect patient QOL following gastrectomy. However, the extent of lymph node dissection, which was anticipated to have a significant effect on postoperative symptoms, did not differ between the two study groups. Therefore, there seems to be no problems with comparing the QOL scores between these two groups. The size of gastric remnants was larger in patients who underwent BI procedures, possibly due to the preference of Japanese surgeons. Many Japanese surgeons prefer BI for larger gastric remnant to avoid roux stasis by RY reconstruction, while they prefer RY for smaller gastric remnants to prevent esophageal reflux. Thus, this discrepancy may reflect the preferences of Japanese surgeons.[3,4,6]

Among the main outcome measures, significant differences were only observed for loss of body weight and esophageal reflux symptoms. It is speculated that weight loss may be affected by dietary intake, but there were no significant differences in amount of food per meal or necessity of additional meals. Although weight loss was influenced by age and celiac branch preservation, multiple regression analysis showed reconstruction methods to be a predictive factor with borderline significance. As the size of gastric remnant was significantly different between BI and RY, we also performed ANOVA followed by multiple comparisons according to the size of the remnant stomach. There was no significant influence of size of gastric remnant on the degree of weight loss (data not shown). These results suggest the possibility that physiological reconstruction methods have an effect on digestion and absorption of ingested food. However, significant differences in weight loss between BI and RY procedures have not been reported in any previously performed RCTs.[7–9] In the present study, the actual difference in weight loss and the effect size Cohen's *d* value was relatively small. It is postulated that even a slight difference was significantly detected because of large sample size. We did not include body weight in the questionnaire, because the body weight declared by patients is sometimes unreliable. All of the patients included in this study were informed about the study at the time of visit. So, in order to obtain a reliable body weight data, we measured the patients' body weight at the clinic and compared it with the preoperative body weight in medical records. We thought accurate data collection was more important than obtaining uncertain data from patient's memory with respect to the body weight changes. Therefore, we did not include body weight in the questionnaire.

In contrast to weight changes, BI procedures have shown to be disadvantageous for esophageal reflux. All symptom items related to esophageal reflux showed unfavorable results. Although these symptoms were affected by age and gender (as shown through multiple regression analysis), reconstruction methods were shown to be significant independent predictive factors. It was previously shown, via endoscopic observation or hepatobiliary scans, that bile reflux and gastritis were more frequently observed following BI procedures than RY procedures.[7–9] However, the incidence of reflux esophagitis is still controversial. Hirao et al.[8] reported a higher incidence of reflux esophagitis with BI procedures than with RY procedures. However, other investigators found no significant difference in the incidence of reflux esophagitis following each of these reconstruction methods.[7,9] This discrepancy remains the same in retrospective analysis. Most investigators have reported that bile reflux and gastritis are more frequently observed following BI procedures than RY procedures. However, the incidence of reflux esophagitis is still controversial. One study reported a significantly higher incidence of reflux esophagitis with BI procedures, while others reported no difference between BI and RY procedures.[3,17,18] Based on these reports, it is speculated that bile reflux may have occurred frequently following BI reconstruction, and that this reflux may have caused gastritis (observable via endoscopy). The incidence of reflux esophagitis may be lower based on several mechanisms that prevent bile from traveling from the stomach to the esophagus. These mechanisms contribute to a longer onset period and low incidence for development of esophagitis from transient bile reflux. Shinoto et al.[18] performed a questionnaire assessment of reflux symptoms, indicating that 63 % of patients who underwent BI procedures reported symptoms, while none of the patients who underwent RY procedures reported symptoms of esophageal reflux. In this series, the incidences of reflux esophagitis by endoscopic observation were 57 % for BI procedures and 21 % for RY procedures, respectively. Similarly, Nunobe et al.[3] reported that reflux esophagitis by endoscopic observation was found in 5 of 203 patients who underwent BI procedures and none of the 182 patients who underwent RY procedures. However, questionnaire data documented reflux symptoms in 13 of 203 patients who

underwent BI procedures and in none of the 182 patients who underwent RY procedures. That study reported that "Although there was a large difference between the groups in the proportions of patients who complained of heartburn, the difference in the incidence of endoscopically recognizable esophagitis was much smaller, with borderline significance." These results suggest that questionnaires may be more sensitive than endoscopic observation in detecting esophageal reflux. The newly developed PGSAS-45 also shows sensitivity to differentiation of reflux symptoms between BI and RY procedures.

In other outcomes measured, symptoms of flatus were significantly better following BI procedures. However, multiple regression analysis indicated that flatus was influenced by postoperative period and celiac branch preservation (data not shown), indicating that results may be affected by these factors. Constipation was shown to be more frequent in patients who underwent BI procedures. Nunobe et al.[3] reported that altered bowel habits were significantly worse in patients who underwent BI procedures than in those who underwent RY procedures. The PGSAS-45 questionnaire used in this study addressed bowel habits: "Tell us about your present bowel habits (diarrhea and constipation)." Hence, the precise incidences of diarrhea and constipation in study participants are unknown. In the present study, the incidence of diarrhea was not significantly different between BI and RY procedures, but there is a possibility that the incidence of constipation may increase after BI reconstruction.

This study has a limitation worth noting. Specifically, the study was not a prospective study and the investigation was conducted at a single time point. In particular, chronological changes are thought to be the most important issue in evaluating a patient's QOL after gastrectomy. However, we mainly focused on the long-term QOL, and we collected data more than 1 year after gastrectomy, because Kobayashi et al.[11] had reported that the conditions of the patients with more than 1 year after gastrectomy were generally stable. In addition, we performed multiple regression analysis with postoperative period as an item in order to eliminate the influence of postoperative period on patient's QOL. Further validation by prospective clinical trials with assessment of early to long-term QOL is required.

Several investigators have assessed QOL following total gastrectomy, but no large-scale QOL assessment following DG has been published to date.[10] This is the first study to use the PGSAS-45 questionnaire for investigating patient QOL following gastrectomy. The results of this study are well aligned with previously reported findings, including those of past RCTs. Based on the minimal difference in QOL between the two reconstructive methods, either BI or RY procedures may be recommended based on the individual patient's condition. At least, BI reconstruction should be avoided in order to prevent reflux esophagitis in patients having risk for gastroesophageal reflux such as small gastric remnant, hiatal hernia, or loss of His angle. In addition, results show the newly developed PGSAS-45 questionnaire to be a useful tool, as well as changes in the body weight, for evaluating patient QOL following gastrectomy.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

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

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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

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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-

induced stromal changes occur regardless of the tumor response.

The radiologic N and pathologic N stages were significantly correlated even though the radiologic overall accuracy of N-staging was only 44%. Moreover, the radiologic accuracy and sensitivity of the diagnosis of nodal positivity were both high: 70.7 and 84.9%, respectively. These results suggest that N-staging using CT is not accurate for diagnosing each N category, although it is useful for diagnosing nodal positivity. Previously, Park et al. [13] reported that the accuracy of N restaging was 39% on EUS and 37% on CT, whereas that of nodal positivity was 68% on both EUS and CT in 38 patients. Their results support our data. The sensitivity for diagnosing nodal positivity in this study was high, at 84.9%; however, the specificity was low, at 36.4%, thus suggesting that radiologically determined positive findings are reliable, whereas negative findings are not.

We next examined the accuracy of N-staging by stratifying the radiologic nodal response. The radiologic accuracy was low, at 39.3%, in the responders and higher, at 52.1%, in the nonresponders, which suggests that the radiologic accuracy of N-staging decreases when metastatic nodes respond to chemotherapy. The rates of underdiagnosis and overdiagnosis were almost half in the overall cohort and the nonresponders; however, overdiagnosis was a major cause of misdiagnosis in the responders. Among the responders, eight (89%) of nine patients with pathologic N0 disease were radiologically misdiagnosed as being node-positive. This result suggests that the enlarged nodes did not disappear even though the nodal metastasis pathologically disappeared.

In conclusion, restaging of gastric cancer after neoadjuvant chemotherapy by using CT is inaccurate and unreliable. In particular, the radiologic T stage determined after neoadjuvant chemotherapy should not be considered in clinical decision-making.

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