Group of the JCOG and mounted on unstained glass slides. This study was separately approved by the JCOG Protocol Review Committee and the institutional review board of each participating institution as the original protocol of these studies (JCOG0001 and 0405) did not include this concept and usage of the material.

IHC and FISH tests

Tumors were centrally tested for HER2 status using IHC (Hercep Test, DAKO, Denmark) and FISH (HER2 FISH pharmDx, DAKO) methods. For IHC analysis, the samples were scored according to modifications of criteria originally published by Hofmann and colleagues [9], as follows: 0, no reactivity or membranous reactivity in $\leq$10 % of the cells; 1+, faint/barely perceptible membranous reactivity in >10 % of the cells, but cells reactive in only parts of their membranes; 2+, weak to moderate complete or basolateral membranous reactivity in >10 % of the tumor cells; 3+, moderate to strong complete or basolateral membranous reactivity in >10 % of the tumor cells. For FISH assessments, an HER2:CEP17 (centromeric probe 17) ratio $\geq$2 was defined as positive for HER2 amplification.

Definition of HER2-positive status

The standard criteria for HER2-positive status, including the HER2 IHC scoring system and FISH assessments, have thus far only been validated for breast cancer. However, the biological differences between breast and gastric tumors, such as tumor heterogeneity and basolateral membrane staining, were recently reported. Therefore, the ToGA trial adopted IHC3+ or FISH positivity (HER2: CEP ratio $\geq$2) as the definition of HER2-positive status. According to subgroup analysis in this trial, a survival benefit from the addition of trastuzumab was recognized for patients with overexpression of HER2 protein, including the IHC2+/FISH+ and IHC3+ subgroups, whereas there was no survival benefit for the IHC0/FISH+ or IHC1+/FISH+ subgroups. The European Medicine Agency has noted that trastuzumab should only be used in patients with metastatic gastric cancer whose tumors have HER2 overexpression as defined by IHC2+ and a confirmatory FISH+ result, or IHC3+ as determined by an accurate and validated assay. Therefore, we chose IHC testing as the primary method for determining HER2 status, while FISH was restricted to cases with equivocal (IHC2+) expression of HER2 protein. In this study, patients classified as IHC3+ or IHC2+/FISH+ were defined as HER2 positive. The HER2 IHC score was independently determined by three different pathologists, each belonging to a different institution: the Hyogo College of Medicine, the Research Center for Innovative Oncology in the National Cancer Center East Hospital, and the National Cancer Center Hospital. Scores were accepted if they were agreed upon by at least two of the pathologists. If a score differed among all three, the final judgment was determined by reference to FISH results in a meeting of the pathologists. Thus, we performed FISH for IHC2+ cases or those with an ambivalent score. These FISH results were also assessed by the three pathologists.

Statistical analysis

All data except for HER2 status were obtained from patient databases managed by the JCOG Data Center. Categorical and continuous data were analyzed using Fisher's exact test and the Wilcoxon rank-sum test, respectively. Multivariate log-linear regression analysis was performed to identify factors independently associated with HER2 positivity. The HER2 positivity rate was estimated in eligible patients whose HER2 status was determined based on either biopsy or resected specimens. Survival analysis was performed in eligible patients for whom resected specimens were obtained because multivariate analysis was conducted to identify the prognostic factors at the postoperative status. The probability of survival for the different subgroups was calculated using the Kaplan-Meier method, and the significance of differences between survival curves was determined using a log-rank test. Multivariate analysis was performed using the stratified Cox's proportional hazards model with the study as strata to identify the primary prognostic indicators independently associated with survival. All P values were two-sided and the significance level was set at $P < 0.05$. All analyses were carried out using SAS version 9.2 (SAS Institute, Inc., Cary, NC).

Results

Among 106 eligible patients in JCOG0001 (n = 55) and JCOG0405 (n = 51), samples of 89 patients from 22 institutions were collected and analyzed (Fig. 1). These materials comprised 86 resected stomach samples and 3 biopsy specimens as the biopsied tumors were unresectable. Sixteen samples were scored as IHC3+, and 8 that were IHC2+ were found to be FISH+. These 24 samples were diagnosed as HER2 positive, for an HER2 positivity rate of 27.0 % [95 % confidence interval (CI) 18.1–37.4 %].

Associations between clinicopathological variables and HER2 status are shown in Table 1. Univariate analysis revealed that the histology of the resected stomach, performance status (PS), and curability had a significant association with HER2 positivity. Differentiated types (papillary and tubular adenocarcinoma) showed

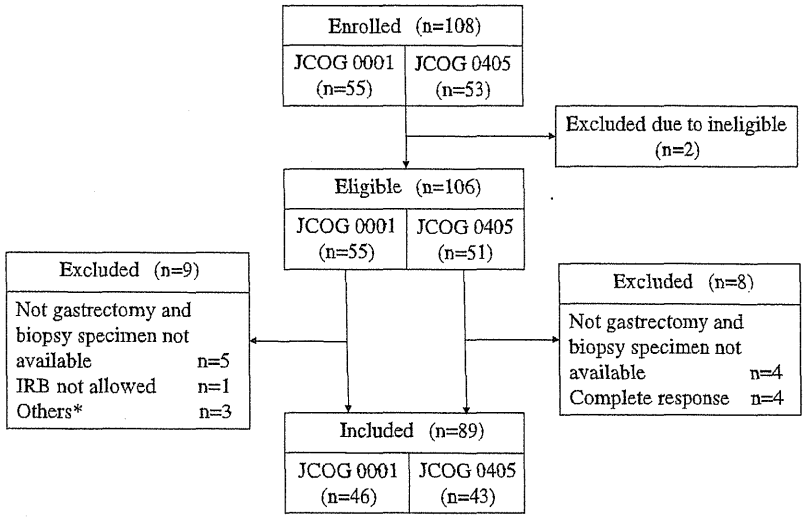

Fig. 1 Study population
* Registration from two institutions which renounced the study group

significantly higher HER2 positivity rates than undifferentiated types (poorly differentiated adenocarcinoma, signet-ring cell carcinoma). HER2 positivity did not affect clinical or histopathological response, although there were significantly more cases of R2 resection in HER2-negative cases. In multivariate analysis, the histological type of the excised specimen was independently related to HER2 overexpression and/or amplification (Table 2). Histological examination of resected stomach samples revealed that 18 of 44 tumors of the differentiated type (40.9 %) were HER2 positive, while only 5 of 42 (11.9 %) tumors of the undifferentiated type were HER2 positive (Table 3).

The estimated 3-year overall survival for HER2-positive cases was 66.7 % and that for HER2-negative cases was 38.7 % ($p = 0.022$), with a hazard ratio (HR) of 0.47 (95 % CI 0.24–0.91) (Fig. 2). The tendency of survival was almost the same in both the JCOG0001 and JCOG0405 trials, OS being always superior in Her2-positive than in -negative cases. However, in a Cox multivariate model that included age (≤64/>64), sex (male/female), clinical nodal factors (bulky N2 without PAN, bulky N2, and PAN), PS (0/1), histology of the resected stomach specimen (differentiated/undifferentiated type), and pathological response (grade 0–1a/grade 1b–3), the hazard ratio of HER2 status (positive/negative) was much higher and came close to 1.0 (HR = 0.88, $P = 0.73$) (Table 4). This result was almost identical to that of a multivariate analysis evaluating survival after enrollment, including pretreatment biopsy instead of resected specimen, age, sex, PS, and clinical nodal factors: the HR for HER2 status was 0.84. We also estimated the survival curve for patients with R0 resection, curability of A or B, by the Kaplan-Meier method as a sensitivity analysis. Three-year survival in Her2+ and Her2- were 65.2 % and 52.2 %, respectively. Log-rank p value was 0.32 and hazard ratio for Her2 + was 0.70 (95 % CI, 0.34-1.43). In multivariate analysis including age, sex, ECOG PS, lymph node status, histological type, and pathological grade using the study as strata, the hazard ratio for Her2+ was 1.04 (95 % CI, 0.48-2.24). Although there is a significant difference in the number of R2 patients, OS curves showed an almost similar tendency with or without exclusion of R2 cases.

As for relapse-free survival for curability A or B, the HR between HER2 positivity and negativity was 1.30 (95 % CI 0.62–2.70) in multivariate analysis, suggesting the difference between survival curves might have been due to other confounding factors.

Discussion

Although HER2 expression has come to be an indispensable factor in determining the therapeutic strategy for recurrent or unresectable advanced gastric carcinoma, the low positive rate in general still discourages clinicians from examining HER2 status before starting chemotherapy. In the present study, the HER2 positivity rate for JGCA-bulky N2 and JGCA-N3 was 27.0 %. This subgroup of gastric cancers showed higher HER2 positivity than ordinary types.

In a review of 42 studies published from 1991 to 2012, the HER2 positivity rate based on IHC scoring ranged widely from 4.4 to 53.4 % [19]. The most significant factor underlying this wide variation is likely the criteria used for determining HER2 expression, as these have not been standardized and thus differ among studies. In 2008, however, Hoffman et al. provided clear criteria based on the results of the ToGA trial, and in the subsequent 2 years the HER2 positivity rate ranged from 9.4 to 15.7 %. Thus, accuracy is now considered to be controlled to a certain degree. Meanwhile, using FISH determination, the

Table 1 Correlation of HER2 status with clinicopathologic variables

	HER2 negative ($n = 65$)	HER2 positive ($n = 24$)	Total ($n = 89$)	P value[a]
Trial, n (%)				
JCOG0001	36 (78.3)	10 (21.7)	46	0.34
JCOG0405	29 (67.4)	14 (32.6)	43	
Age				
Median (range)	63 (42–75)	62 (48–72)	63 (42–75)	0.56
Age, n (%)				
<65	39 (69.6)	17 (30.4)	56	0.46
≥65	26 (78.8)	7 (21.2)	33	
Sex, n (%)				
Male	51 (71.8)	20 (28.2)	71	0.77
Female	14 (77.8)	4 (22.2)	18	
PS, n (%)				
0	63 (75.9)	20 (24.1)	83	0.04
1	2 (33.3)	4 (66.7)	6	
cN, n (%)				
Bulky N2 and PAN	21 (80.8)	5 (19.2)	26	0.61
Bulky N2	31 (70.5)	13 (29.5)	44	
PAN	13 (68.4)	6 (31.6)	19	
Histology (biopsy) n (%)				
pap	2 (100.0)	0 (0.0)	2	0.53
tub1	6 (54.5)	5 (45.5)	11	
tub2	26 (68.4)	12 (31.6)	38	
por1	9 (69.2)	4 (30.8)	13	
por2	19 (86.4)	3 (13.6)	22	
sig	1 (100.0)	0 (0.0)	1	
muc	1 (100.0)	0 (0.0)	1	
Unknown	1 (100.0)	0 (0.0)	1	
Histology (biopsy) n (%)				
pap + tub1 + tub2	34 (66.7)	17 (33.3)	51	0.15
por1 + por2 + sig + muc	30 (81.1)	7 (18.9)	37	
Unknown	1 (100.0)	0 (0.0)	1	
pT, n (%)				
pT1	6 (75.0)	2 (25.0)	8	0.86
pT2	26 (66.7)	13 (33.3)	39	
pT3	22 (73.3)	8 (26.7)	30	
pT4	6 (85.7)	1 (14.3)	7	
pTX	1 (100.0)	0 (0.0)	1	
Unknown	4 (100.0)	0 (0.0)	4	
pN, n (%)				
pN0	3 (60.0)	2 (40.0)	5	0.52
pN1	7 (58.3)	5 (41.7)	12	
pN2	21 (72.4)	8 (27.6)	29	
pN3	30 (76.9)	9 (23.1)	39	
pNX	0 (–)	0 (–)	0	
Unknown	4 (100.0)	0 (0.0)	4	
Histology (resected stomach) n (%)				
pap	3 (100.0)	0 (0.0)	3	0.0114
tub1	8 (53.3)	7 (46.7)	15	
tub2	15 (57.7)	11 (42.3)	26	
por1	24 (82.8)	5 (17.2)	29	
por2	12 (100.0)	0 (0.0)	12	
sig	0 (0.0)	0 (0.0)	0	
muc	1 (100.0)	0 (0.0)	1	
Unknown	2 (66.7)	1 (33.3)	3	

Table 1 continued

	HER2 negative ($n = 65$)	HER2 positive ($n = 24$)	Total ($n = 89$)	P value[a]
Histology (resected stomach) n (%)				
pap + tub1 + tub2	26 (59.1)	18 (40.9)	44	0.0032
por1 + por2 + sig + muc	37 (88.1)	5 (11.9)	42	
Unknown	2 (66.7)	1 (33.3)	3	
Curability, n (%)				
A or B	46 (66.7)	23 (33.3)	69	0.0106
C (include unresection)	19 (95.0)	1 (5.0)	20	
Clinical				
SD/PD	26 (72.2)	10 (27.7)	36	1.000
Response, n (%)				
PR/CR	39 (73.6)	14 (26.4)	53	
Pathological response, n (%)				
Grade 0 or 1a	47 (75.8)	15 (24.2)	62	0.44
Grade ≧1b	18 (66.7)	9 (33.3)	27	

[a] Categorical and continuous data were analyzed using Fisher's exact test and the Wilcoxon signed-rank test, respectively

Table 2 Multivariate analysis of baseline clinicopathologic variables for identification of HER2-positive status

Variables	Risk ratio	95 % CI	P value
Age (years)			
≥65 (vs. <65)	0.57	0.22-1.45	0.24
Sex			
Male (vs. female)	1.19	0.39-3.65	0.76
Histology or resected specimen			
Pap + tub1 + tub2 (vs. por1 + por2 + sig + muc)	3.59	1.33-9.70	0.012
Lymph nodal status			
Bulky N2+ and PAN- (vs. Bulky N2+ and PAN+)	1.41	0.50-3.96	0.52
Bulky N2- and PAN+ (vs. Bulky N2+ and PAN+)	1.44	0.40-5.16	0.58

HR hazard ratio, CI confidence interval, LN16 paraaortic lymph node metastases

Table 3 HER2 positivity rate according to histologic type

	HER2 positive	HER2 negative	Total
Differentiated type			
pap	0 (0.0 %)	3 (100.0 %)	3
tub1	7 (46.7 %)	8 (53.3 %)	15
tub2	11 (42.3 %)	15 (57.7 %)	26
pap + tub1 + tub2	18 (40.9 %)	26 (59.1 %)	44
Poorly differentiated type			
por1 + por2 + sig + muc	5 (11.9 %)	37 (88.1 %)	42

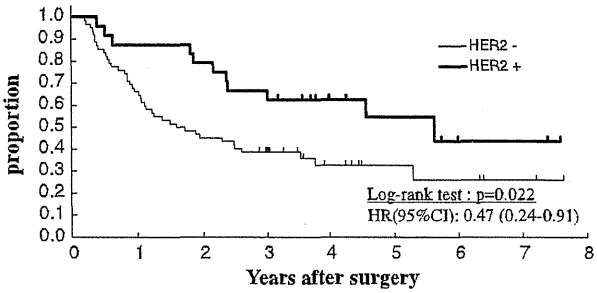

Fig. 2 Kaplan-Meier estimates of overall survival. *HR* hazard ratio, *CI* confidence interval

positivity rate ranged from 8.7–18.1 %, although the dispersion of positive results was not as clear with IHC, possibly because of the lack of clear quantitative criteria in FISH. The HER2 positivity rate in the ToGA trial, if the same definition as in the present study is applied, was just 12.2 %. As the Japanese subjects in this study showed slightly higher positivity (20.0 %), the positivity rate in consecutive series of metastatic and unresectable gastric cancer with or without target lesions in Japan was studied in a prospective manner by the Japanese Foundation for Multidisciplinary Treatment of Cancer (JFMC44-1101) [20, 21]. It was, however, just 15.5 %, equivalent to that of a large Japanese study on adjuvant chemotherapy for stage II/III curatively resected patients in the ACTS-GC study (13.6 %) [11]. Of 829 subjects, 74 were scored as IHC3+ and 38 as IHC2+ and FISH+ (total positive, 113 subjects). In comparison to these results, patients with JGCA-bulky N2 or JGCA-bulky N3 are considered to constitute a

Table 4 Multivariate Analysis

Variables	HR	95 % CI	*P* value
HER2 status positive (vs. negative)	0.88	0.41–1.87	0.73
Clinical nodal factor			
Bulky N2+ and PAN−(vs. Bulky N2+ and PAN+)	0.48	0.24–0.95	0.035
Clinical nodal factor			
Bulky N2− & PAN+(vs. Bulky N2+ and PAN+)	0.75	0.30–1.87	0.53
Histology of resected specimens			
pap + tub1 + tub2 (vs. por1 + por2 + sig + muc)	1.16	0.60–2.23	0.66
PS			
1 (vs. 0)	0.075	0.009–0.61	0.016
Age			
≥65 (vs. <64)	1.87	1.02–3.45	0.045
Sex			
Male (vs. female)	0.44	0.20–0.99	0.048
Pathological response			
Grade ≥1b (vs. Grade 0 or 1a)	0.47	0.22–1.01	0.053

Cox proportional hazards model

subgroup showing high HER2 positivity (27.0 % in total). It has been reported that HER2 overexpression occurs more frequently in differentiated-type carcinoma or gastro-esophageal junctional cancer. Generally, undifferentiated type carcinoma comprises about 60–70 % of advanced gastric carcinoma, making the differentiated type a minority. In the present study, which exclusively enrolled patients with bulky N2 or clinical metastasis to the para-aortic lymph node, the differentiated type accounted for about 50 %, which might have led to the high HER2 positivity rate.

According to a review of 42 studies published from 1991–2012, the relationship between HER2 expression and prognosis has been found to be inconsistent and remains controversial [19, 22, 23]. Accordingly, it is important to carefully interpret the findings of the present study regarding this relationship. We found a tendency toward better relapse-free survival in HER2-positive cases, and overall survival was significantly more favorable (HR = 0.47, $p = 0.022$) in the HER2-positive than in the HER2-negative group. However, in multivariate Cox analysis, HER2 expression was not an independent factor for survival, thus a confounding background factor is suspected. The relatively favorable prognosis in the HER2-positive group was likely affected by the lower proportion of patients who underwent R2 resection, although better OS was observed even excluding R2 patients. This might be related to the fact that while 20 % of HER2-negative patients had diffuse-type histology (por2, sig, or muc according to the Japanese classification), none of the HER2-positive patients did. It is necessary to further examine these results by conducting studies with greater numbers of subjects.

In the present study, approximately 41 % of patients with differentiated type cancer were diagnosed as HER2 positive, while the HER2-positive rate in patients with poorly differentiated type cancer was only about 12 %. The differentiated type constituted about 58 % of biopsy specimens and 51 % of resected specimens, with inconsistency observed in 7 % of cases. There are two possible explanations. First, it is well known that some undifferentiated type tumors (classified by dominance) have moderately differentiated histology in the mucosal layer and therefore are diagnosed as the differentiated type by biopsy. Another possibility is that differentiated portions of tumors were more affected by chemotherapy than undifferentiated ones, resulting in an increase in the number of tumors diagnosed as undifferentiated type defined by quantitative predominance. As HER2 status was determined based primarily on resected specimens, with biopsy specimens used in only a few patients who did not undergo gastrectomy, comparison of HER2 status before and after chemotherapy was impossible in this study. Heterogeneity of HER2 expression in a single tumor is known to be more prominent in gastric cancer than in breast cancer. Several papers, however, have reported relatively high concordance in HER2 status between biopsy specimens and resected material [24–26]. The limited information available in this study hampers further discussion of the effects of chemotherapy in relation to tumor differentiation and HER2 status.

While it is known that overfixation with formalin affects immunostaining, it was previously reported that no difference was observed in HER2 staining intensity between samples with 120 h of fixation and those with 3 h of fixation [27]. It was also shown that when the time from sample collection to fixation exceeded 2 h, signals related to HER2 expression became weak, significantly affecting FISH determination. Furthermore, in IHC determination, intensity is likely to decrease when duration of fixation approaches 1 week. In a previous study of breast carcinoma, scores in the IHC3+ group were not affected even after formalin fixation times over 2 h, while in the FISH group, the peripheral cellular borders became indefinite, FISH signals decreased, and nuclear resolution was reduced [28]. Another report noted that the retention time in a paraffin block might affect IHC or FISH determination of HER2 expression [29]. In the present study, we used specimens collected from subjects who had been registered for two different phase II trials conducted in multiple institutions before the results of the ToGA study were reported. Since fixation method and time were not

standardized in these trials, it is possible that variations in these factors might have affected expression. Moreover, tumor degeneration almost certainly influenced the effects of chemotherapy on immunostaining and FISH results, as the specimens were collected after preoperative chemotherapy. Because of the high heterogeneity of gastric cancer, IHC diagnostic criteria for HER2 overexpression in surgically resected materials differ from those in prior biopsy specimens [9]. When diagnostic criteria were used, the concordance of IHC-based HER2 scoring between surgically resected materials and prior biopsy specimens with an HER2 score of 3+ was reported to be high, and at least three or four fragments seemed sufficient for assessing IHC HER2 status based on biopsy material [30]. In the present study, in fact, the difference in the hazard ratio for overall survival of HER2-positive patients after chemotherapy in two analyses comparing differentiated and undifferentiated types using pretreatment histology based on biopsy or resected specimens was small (0.84 and 0.88). However, further validation of equivalence is needed because of the increasingly frequent use of preoperative chemotherapy, as neoadjuvant treatment is regarded as essential in Japan for patients with JGCA-bulky N2 or JGCA-N3, while they are regarded incurable in the West. Selection of the chemotherapy regimen in neoadjuvant treatment is of paramount importance for these patients.

In conclusion, our results demonstrated that patients with JGCA-bulky N2 or JGCA-N3 constituted a subgroup with gastric cancer marked by a high HER2 positivity rate and may be a target population for trastuzumab administration. Presently, a phase II trial with a preoperative triplet chemotherapy (S-1 + cisplatin + docetaxel) regimen is underway for this subgroup of gastric cancer patients in Japan. Nevertheless, it is necessary to conduct clinical studies to determine whether better prognosis in HER2-positive patients can be attained with multidrug therapy, including trastuzumab. This will aid in establishing treatment development pathways based on the presence of HER2 expression, which is currently the only reliable biomarker in gastric cancer.

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Conflict of interest Dr. Mitsuru Sasako received lecture fees from Taiho Pharmaceutical Co., Ltd., and Chugai Pharmaceutical Co., Ltd. Dr. Atsushi Ochiai received lecture fees from Chugai. The institution of Dr. Tomohiro Matsumoto and Dr. Mitsuru Sasako received research grants from Taiho and Chugai. The institution of Dr. Atsushi Ochiai received research grants from Taiho, Merck Serono Co., Ltd., Bayer Yakuhin, Ltd., and Amgen Inc. The other authors report no conflict of interest.

Appendix

Investigators in participating institutions: Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital, Y. Iwasaki; Sakai Municipal Hospital, H. Furukawa; Gifu Municipal Hospital, H. Oshita; Aichi Cancer Center Research Institute, S. Ito; Iwate Medical University School of Medicine, K. Koeda; Miyagi Cancer Center, T. Fujiya; Osaka National Hospital, T. Tsujinaka; Osaka Medical College, H. Takiuchi; National Hospital Organization Shikoku Cancer Center, A. Kurita; National Defense Medical College, K. Hase; National Cancer Center Hospital East, T. Kinoshita; Tokyo Metropolitan Bokuto Hospital, S. Inoue; Fujita Health University School of Medicine, I. Uyama; National Hospital Organization Sendai Medical Center, T. Saito; Tsubame Rosai Hospital, K. Miyashita; Wakayama Medical University School of Medicine, H. Yamaue; Hiroshima City Hospital, M. Ninomiya

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ORIGINAL ARTICLE

Validity of response assessment criteria in neoadjuvant chemotherapy for gastric cancer (JCOG0507-A)

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Abstract
Background Neoadjuvant chemotherapy may improve outcomes in gastric cancer. Tumor responses can be evaluated with RECIST, Japanese Classification of Gastric Carcinoma (JCGC), and histological criteria. These approaches have not yet been compared.
Methods We analyzed two phase II trials of neoadjuvant chemotherapy using S-1 plus cisplatin. JCOG0210 included patients with linitis plastica and large ulcero-invasive tumors, whereas JCOG0405 comprised those with paraaortic or bulky lymph node metastases. Radiologic evaluations were conducted using RECIST in JCOG0405 and JCGC criteria in JCOG0210, because the latter included many patients without measurable lesions. A histological responder was defined as a patient in whom one-third or more of the tumor was affected. The hazard ratios (HR) for death between responders and non-responders and response rate differences between short- and long-term survivors were estimated.
Results In JCOG0210 ($n = 49$), HR was 0.54 in JCGC responders ($P = 0.059$) and 0.40 in histological responders ($P = 0.005$). The difference in response rates between short- and long-term survivors using histological criteria (34 %, $P = 0.023$) was greater than that using JCGC criteria (24 %, $P = 0.15$). In JCOG0405 ($n = 51$), HR was 0.67 in RECIST responders ($P = 0.35$) and 0.39 in histological responders ($P = 0.030$). In short- and long-term survivors, respectively, RECIST response rates were 62 and 67 % ($P = 0.77$), whereas histological response rates were 33 and 63 % ($P = 0.048$).
Conclusions Histological criteria showed higher response assessment validity than RECIST or JCGC criteria and yielded the best surrogate endpoint for overall survival.

Keywords RECIST · JCGC · JCOG

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Introduction

Gastric cancer is the second-leading cause of cancer deaths worldwide and the most common cancer in Japan and Korea [1]. Although surgery is the standard treatment for resectable gastric cancer [2, 3], the prognosis of patients with advanced tumors is poor [4]. In particular, linitis plastica (Borrmann type 4) and large ulcero-invasive-type (Borrmann type 3) tumors, as well as those with paraaortic nodal metastases or bulky lymph node metastases, have extremely poor outcomes even after curative resection [5, 6]. For these advanced tumors, neoadjuvant chemotherapy

is expected to improve long-term prognoses. The Japan Clinical Oncology Group (JCOG) has conducted two multicenter phase II trials to evaluate the efficacy and safety of S-1 plus cisplatin as a neoadjuvant regimen and has reported promising results [7, 8].

Three criteria for evaluating tumor responses to chemotherapy are currently available. The Response Evaluation Criteria in Solid Tumors (RECIST) is the gold standard in the evaluation of tumor response, but it requires the presence of a measurable lesion [9]. Because resectable gastric cancer seldom has measurable lesions, we cannot use RECIST in the neoadjuvant setting. The Japanese Classification of Gastric Carcinoma (JCGC) includes a response evaluation criterion involving barium X-ray or endoscopic examination, which is useful for tumors without measurable lesions [10]. Furthermore, we can evaluate tumor response histologically in resected specimens. As there have been no studies comparing the validities of these radiologic and histological criteria, we have conducted this correlative study (JCOG0507-A) to find the best surrogate endpoint for overall survival in neoadjuvant studies for gastric and esophageal cancers. In esophageal cancer patients, we had reported that histological response rate was the better surrogate endpoint for survival than RECIST response rate [11]. This article reports the results for gastric cancer, comparing RECIST, JCGC, and histological criteria.

Methods

Patient population

We included all eligible patients from two clinical trials (JCOG0210 and JCOG0405) that were conducted by the JCOG. These phase II trials aimed to evaluate the efficacy and safety of neoadjuvant S-1 plus cisplatin in gastric cancer patients [7, 8]. The eligibility criteria of the JCOG0210 trial included linitis plastica (Borrmann type 4) and ulcero-invasive-type (Borrmann type 3) tumors. In the case of ulcero-invasive tumors, the size of the primary tumor was required to be 8 cm or larger. Between March 2003 and December 2003, 49 eligible patients were enrolled in the JCOG0210 trial. Responses to neoadjuvant chemotherapy were evaluated using JCGC criteria. After preoperative chemotherapy, 41 patients could undergo gastrectomy, which provided tissue samples for use in assessing the histological response to preoperative chemotherapy. Six patients failed in simple laparotomy because of the presence of incurable lesions. Two patients did not undergo surgery for reasons of chemotherapy-related death in one patient and refusal of any protocol treatment in one patient.

The eligibility criteria for the JCOG0405 trial included gastric cancer with paraaortic nodal metastases or bulky lymph nodes. Between February 2005 and June 2007, 51 eligible patients were enrolled in the JCOG0405 trial. Responses to neoadjuvant chemotherapy were evaluated with RECIST. After preoperative chemotherapy, 48 patients could undergo gastrectomy, which provided material to evaluate the histological response to preoperative chemotherapy. Three patients did not undergo surgery because of progressive tumor.

All patients in the JCOG0210 and the JCOG0405 trials gave written informed consent. These trials were approved by the JCOG Clinical Trial Review Committee and the institutional review board of each institution involved. Permission for the secondary use of trial data was included in patients' informed consent for JCOG0210 and JCOG0405. The protocol of this correlative study (JCOG0507-A) was approved by the JCOG Protocol Review Committee. JCOG0405 is registered with UMIN-CTR (http://www.umin.ac.jp/ctr/), identification number C000000094.

Treatments

The same chemotherapy regimen was used in each of the two trials. S-1 was given orally at 80 mg/m^2 for the first 3 weeks of a 4-week cycle. Cisplatin was given as an intravenous infusion of 60 mg/m^2 on day 8 of each cycle. Patients received two 4-week cycles of neoadjuvant S-1 plus cisplatin and then underwent gastrectomy with D2 (in the JCOG0210 trial) or D2 plus paraaortic lymphadenectomy (in the JCOG0405 trial). If curative resection was considered difficult after the second course, addition of a further course of chemotherapy before surgery was permitted only in the JCOG0405 trial. After surgery, no further treatment was given until tumor recurrence.

Response evaluation

After the second course of neoadjuvant chemotherapy, tumor response was evaluated with JCGC criteria based on computed tomography (CT), barium X-ray, and endoscopic examination findings in the JCOG0210 trial, whereas response evaluation using RECIST in the JCOG0405 trial was based only on CT findings. These evaluations were performed by the central reviewers. Response evaluations based on RECIST were not conducted in the JCOG0210 trial because many patients did not have measurable lesions. We could not evaluate the JCGC response in the JCOG0405 trial because barium X-rays and endoscopic examinations were not performed after neoadjuvant chemotherapy.

With the JCGC criteria, overall tumor response depends on the combined responses of primary gastric lesions and metastatic lesions. The details of the JCGC criteria have been described elsewhere [10]. Briefly, morphological changes of gastric lesions are evaluated by X-ray or endoscopic examinations, and the overall responses are classified into four categories: complete response (CR), partial response (PR), no change (NC), or progressive disease (PD). Measurable lesions with at least a 50 % decrease in total tumor size in two dimensions and at least a 30 % decrease in total tumor size in one dimension are classified as PR. Evaluable but nonmeasurable lesions with flattening on X-ray or endoscopic examination, or diffusely infiltrating lesions with at least 50 % enlargement of the gastric lumen in the tumor area by X-ray examination, are also classified as PR. CR or PR cases were treated as responders.

Surgical specimens were assessed histologically, and tumor response was evaluated according to the histological criteria of the JCGC [12]. Briefly, histological evaluations were classified into five categories according to the proportion of the tumor affected by degeneration or necrosis: grade 3, no viable tumor cells remain; grade 2, viable tumor cells remain in less than 1/3 of the tumorous area; grade 1b, viable tumor cells remain in more than 1/3 but less than 2/3 of the tumorous area; grade 1a, viable tumor cells occupy more than 2/3 of the tumorous area; grade 0, no evidence of treatment effect. A histological responder was defined as a patient in whom one third or more of the tumor was affected (grade 1b, 2, or 3). Because the definition of histological responder is controversial, we also evaluated the results when a histological responder was classified as grade 2 or 3. Patients who did not undergo surgery were regarded as non-responders. These evaluations were performed by the pathologists at each institution.

Statistical analysis

The data from all eligible patients were analyzed in this study. Cases in which the tumor was not resected or could not be evaluated were treated as non-responders. With the methods used in this study, a comparison of the overall survival between responders and non-responders was said to have a pitfall because early death cases were classified into the non-responder group. In our study, however, there were no early deaths during the protocol treatment, which implies that minimal bias was induced by the classification system employed in our study.

The relationship of response and overall survival was evaluated using hazard ratios (HRs). The HR for death of responders to non-responders was estimated using the Cox proportional hazard model, and survival distributions were compared using the log-rank test. The difference in response rates between short- and long-term survivors was estimated and tested with Fisher's exact test. Statistical analysis was performed with SAS version 9.2 (SAS Institute, Cary, NC, USA).

Results

Patient characteristics

The clinicopathological characteristics of all eligible patients in the JCOG 0210 and 0405 trials are shown in Table 1. The proportion of male patients in the JCOG0405 trial was higher than that in the JCOG0210 trial. The majority of tumors were of the undifferentiated type in the JCOG0210 trial, whereas the differentiated type was more frequent in the JCOG0405 trial. Pathological node-negative (pN0) patients comprised 16 % of both the JCOG0210 (8 of 49) and JCOG0405 (8 of 51) trial populations.

Response rates

The responses to neoadjuvant S-1 plus cisplatin as evaluated by the JCGC, RECIST, and histological criteria are shown in Table 1. The response rates in the JCOG0210 trial were 57 % [95 % confidence interval (CI), 42–71 %] with the JCGC criteria and 47 % (95 % CI, 33–62 %) with histological criteria. The response rates in the JCOG0405 trial were 65 % (95 % CI, 50–78 %) with the RECIST and 51 % (95 % CI, 37–65 %) with histological criteria.

Survival curves in responders and non-responders

Overall survival curves for the JCOG0210 trial are shown in Fig. 1. The difference of the 3-year overall survival rate between responders and non-responders was 17.8 % (responders, 32.1 %; non-responders, 14.3 %) on JCGC criteria and 27.6 % (responders, 39.1 %; non-responders, 11.5 %) on histological criteria. The HR for death of histological responders to non-responders (0.40; 95 % CI, 0.20–0.77) was lower than that using JCGC criteria (0.54; 95 % CI, 0.28–1.03), and the log-rank P value on histological criteria ($P = 0.005$) was much smaller than that on JCGC criteria ($P = 0.059$).

Overall survival curves for the JCOG0405 trial are shown in Fig. 2. The difference in the 3-year overall survival rate between responders and non-responders was 5.0 % (responders, 60.6 %; non-responders, 55.6 %) on RECIST and 29.1 % (responders, 73.1 %; non-responders, 44.0 %) on histological criteria. The HR for death of histological responders to non-responders (0.39; 95 % CI, 0.17–0.94) was lower than that using the RECIST (0.67;

Table 1 Patient characteristics

	JCOG0210 ($n = 49$)	JCOG0405 ($n = 51$)
Age (years)		
Median	61	63
Range	32–75	42–75
Gender		
Male	28	42
Female	21	9
Borrmann macroscopic type		
0	0	2
1	0	1
2	0	15
3	20	31
4	29	0
5	0	2
Histology		
Differentiated	9	28
Undifferentiated	40	22
Unknown	0	1
Clinical T stage		
cT1	0	1
cT2	2	10
cT3	45	38
cT4	2	2
Clinical N stage		
cN0	16	0
cN1	20	0
cN2	13	25
cN3	0	26
Residual tumor		
R0	31	42
R1 or R2	10	6
Unresected	8	3
Pathological T stage		
pT0	1	2
pT1	4	7
pT2	11	23
pT3	18	15
pT4	7	1
Unresected	8	3
Pathological N stage		
pN0	8	8
pN1	10	5
pN2	16	21
pN3	7	14
Unresected	8	3
Tumor responses evaluated by the JCGC criteria		
CR	0	–
PR	28	–
NC	13	–
PD	3	–
NE	5	–
Tumor responses evaluated by the RECIST		
CR	–	0
PR	–	33
SD	–	14
PD	–	4
Tumor responses evaluated by the histological criteria of the JCGC		
Grade 3	1	1
Grade 2	12	13
Grade 1b	10	12
Grade 1a	9	19
Grade 0	9	3
Unresected	8	3

T stage and N stage were according to the 13th edition of the Japanese Classification of Gastric Carcinoma

JCGC Japanese classification of gastric carcinoma, *CR* complete response, *PR* partial response, *NC* no change, *SD* stable disease, *PD* progressive disease, *NE* not evaluable

95 % CI, 0.29–1.56), and the log-rank P value on histological criteria ($P = 0.030$) was much smaller than that on RECIST ($P = 0.35$).

When a histological responder was classified as grade 2 or 3, the HRs for death of modified histological responders to non-responders were 0.57 (95 % CI, 0.26–1.25) in the JCOG0210 trial and 0.32 (95 % CI, 0.09–1.08) in the JCOG0405 trial. The log-rank P values on modified histological criteria were 0.15 in the JCOG0210 and 0.067 in the JCOG0405.

Response rates in short- and long-term survivors

Because the median overall survival time in all eligible patients in the JCOG0210 was 17.3 months, we divided patients into short- and long-term survivors with a cutoff for overall survival time of 18 months. The respective response rates based on JCGC and histological criteria were 46 % and 31 % in short-term survivors and 70 % and 65 % in long-term survivors (Fig. 3). The difference in response rates between short- and long-term survivors using histological criteria (Fisher's exact test, $P = 0.023$) was greater than that using JCGC criteria (Fisher's exact test, $P = 0.15$).

Although for the JCOG0405 trial the median overall survival time was not reached at the time of this analysis, the 3-year overall survival rate was 59 %. We therefore set

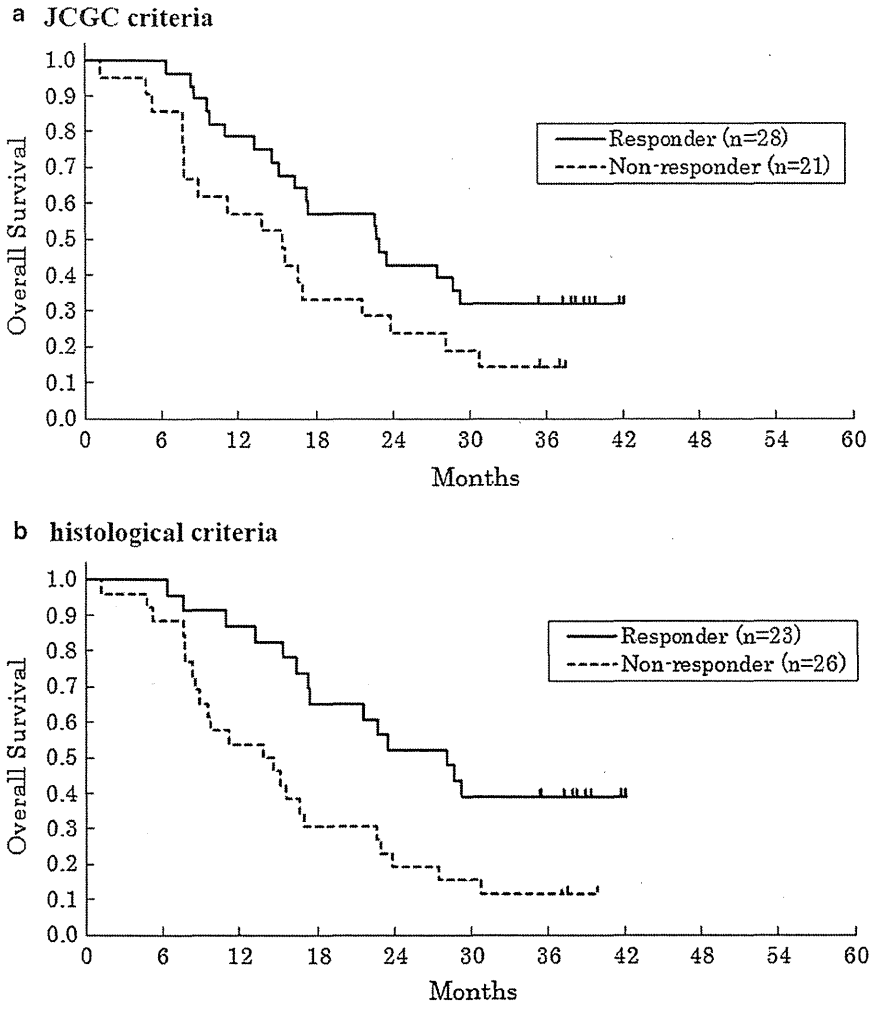

Fig. 1 Overall survival curves between responders and non-responders for the JCOG0210 trial: JCGC criteria (**a**), $P = 0.059$ (log-rank test); histological criteria (**b**), $P = 0.005$ (log-rank test)

the cutoff for overall survival time at 36 months. The respective response rates using RECIST and histological response rates were 62 % and 33 % in short-term survivors and 67 % and 63 % in long-term survivors (Fig. 4). The difference in response rates between short- and long-term survivors using histological criteria (Fisher's exact test, $P = 0.048$) was greater than that using RECIST (Fisher's exact test, $P = 0.77$).

Again, when a histological responder was classified as grade 2 or 3, the differences in response rates between short- and long-term survivors based on modified histological criteria were 16 % (Fisher's exact test, $P = 0.33$) in the JCOG0210 trial and 22 % (Fisher's exact test, $P = 0.11$) in the JCOG0405 trial.

Discussion

In this correlative study of two phase II trials, histological criteria, as compared to RECIST and JCGC criteria, demonstrated a greater difference in both overall survival between responders and non-responders and in response rates between short- and long-term survivors. This result indicates that the histological response was the best surrogate endpoint for overall survival in these neoadjuvant trials for gastric cancer, and the conclusion for gastric cancer was the same as that in esophageal cancer [11], which is very important for the development of cancer treatments. If the histological response can be used as the primary endpoint in neoadjuvant settings, we can evaluate any gastric cancer population regardless of the presence of measurable lesions.

RECIST is the gold standard in the evaluation of tumor responses, but it requires the presence of a measurable lesion. In the present version of RECIST (Ver. 1.1), the criteria for measurable lesions were revised to be stricter: a lymph node must be more than 15 mm in short-axis diameter [13]. There are many unresectable gastric cancer patients without measurable metastatic lesions, because the most frequent pattern of recurrence in advanced or

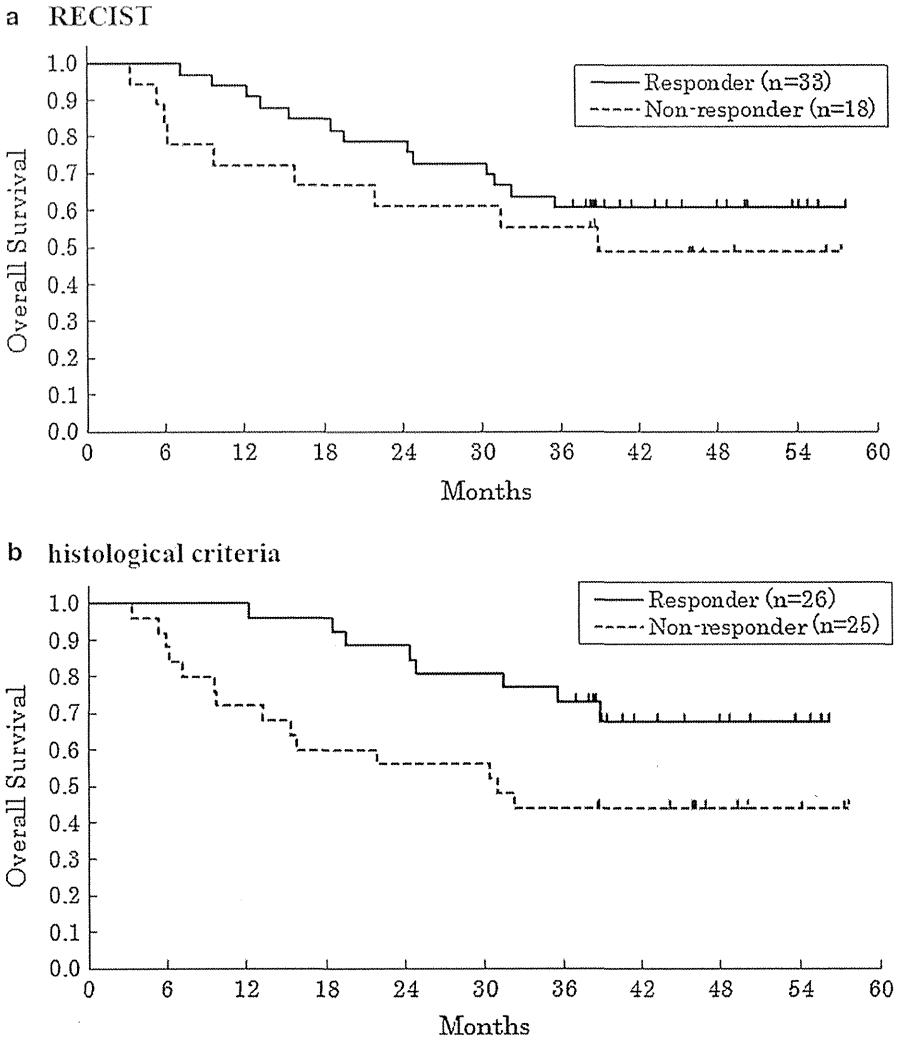

Fig. 2 Overall survival curves between responders and non-responders for the JCOG0405 trial: RECIST (**a**), $P = 0.35$ (log-rank test); histological criteria (**b**), $P = 0.030$ (log-rank test)

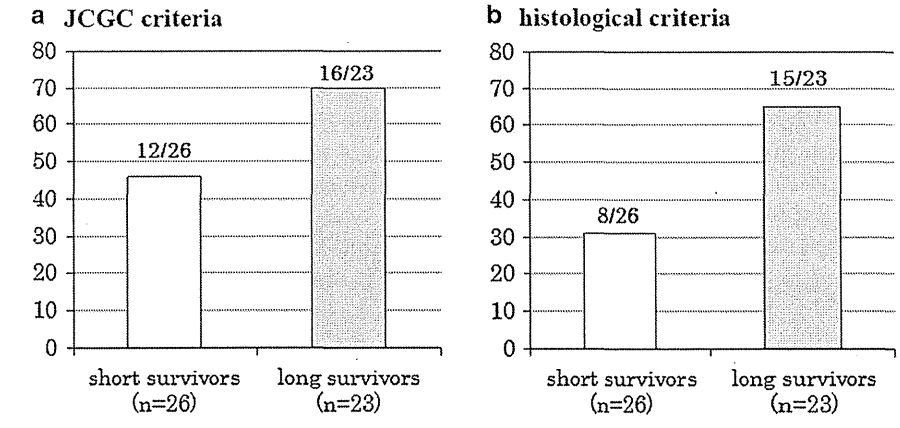

Fig. 3 Comparison of the response rates between short-term (*short survivors*) and long-term (*long survivors*) survivors for the JCOG0210 trial: JCGC criteria (**a**), $P = 0.15$ (Fisher's exact test); histological criteria (**b**), $P = 0.023$ (Fisher's exact test)

recurrent cases is peritoneal seeding. Particularly in neo-adjuvant settings, resectable gastric tumors seldom have measurable lesions. Furthermore, the primary lesion of digestive tract is not suitable for measurable lesion in terms of reproducibility, as the RECIST guideline cautioned.

The JCGC response evaluation criteria were established to evaluate tumor responses even for tumors without measurable lesions. Although it can be used for any type of gastric cancer, evaluation using endoscopic examination is subjective. Furthermore, repetition of barium X-ray or

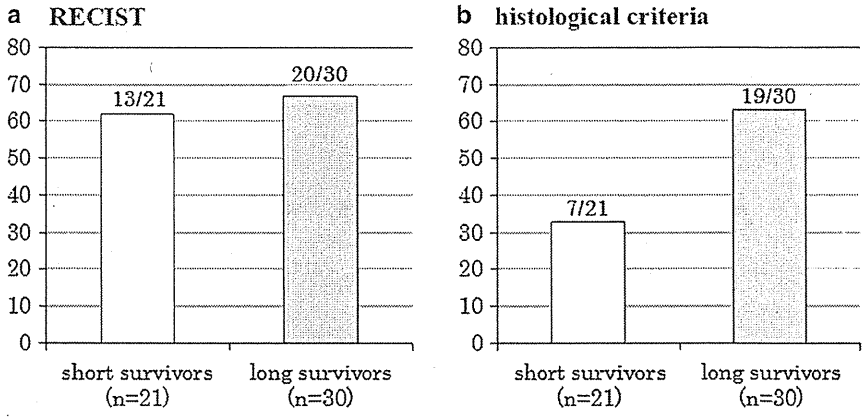

Fig. 4 Comparison of the response rates between short- and long-term survivors for the JCOG0405 trial: RECIST (**a**), $P = 0.77$ (Fisher's exact test); histological criteria (**b**), $P = 0.048$ (Fisher's exact test)

endoscopic examination for evaluation of tumor response is a significant burden for patients. In contrast, histological evaluation does not require any presurgical examination. If the histological response is indeed the most useful indicator in neoadjuvant settings, patients will not need to undergo invasive examinations after chemotherapy.

There are several different histological grading systems for the evaluation of tumor responses in addition to that defined by the JCGC. Becker et al. [14, 15] proposed the following system: tumors with no viable cells are assigned grade Ia; tumors with 1–10 % viable cells, grade Ib; tumors with 10–50 % viable cells, grade II; and tumors with more than 50 % viable cells, grade III. Ajani et al. [16, 17] proposed a grading scheme: cases showing either an absence of tumor cells or necrosis in more than 90 % of the resected tumor were classified as responders. In this study, we used the JCGC grading system, whereby cases showing viable tumor cells remain in less than two thirds are classified as responders, but for our sensitivity analysis we changed the cutoff point from two thirds to one third. Both the JCOG0210 and JCOG0405 trials showed similar results using this grading system.

This study had some limitations. First, histological evaluations were performed only by the pathologists at each institution, although response evaluations using RECIST and JCGC criteria were conducted by the central reviewers. Because histological evaluations are not completely objective, there may have been some issues with inter-rater reliability. However, our JCOG study group institutions are staffed with experts not only in surgery and chemotherapy, but also in pathology. We believe there was little heterogeneity in the histological evaluations performed by this experienced group. Another study is now ongoing to compare the predictive values based on the different scoring systems of histological response after central review by two reference pathologists. A second limitation is that this study enrolled only patients who had received preoperative S-1 plus cisplatin. S-1 plus cisplatin is one of the standard regimens for metastatic gastric cancer [18, 19]. The validity of histological tumor response evaluation may vary with different chemotherapeutic regimens, and further studies are needed to investigate this point.

In conclusion, histological response rate seemed to be a better surrogate endpoint for overall survival than radiologic response rate in studies of neoadjuvant therapy for gastric cancer.

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Gastric Cancer
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ORIGINAL ARTICLE

Evaluation of postgastrectomy symptoms after distal gastrectomy with Billroth-I reconstruction using the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45)

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Abstract

Background Distal gastrectomy with Billroth-I reconstruction (DGBI) is the most commonly used treatment approach for gastric cancer patients in Japan. The aim of this study was to assess and elucidate the effect of different surgical DGBI techniques on postgastrectomy syndrome (PGS) using the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45).

Methods The newly created PGSAS-45 composed of 45 questions was used in this study. The scale was distributed to 2,922 patients who underwent gastrectomy >1 year prior. Completed forms were returned by 2,520 patients (86 %), of which 909 underwent DGBI. The effects of performing the Kocher maneuver, differences in the size of the gastric remnant and differences the anastomosis technique had on the main outcome measures of PGSAS-45 were analyzed.

Results Patients for whom the Kocher maneuver was performed experienced significantly worse meal-related distress and poorer quality of ingestion. Additionally, a less satisfactory physical and mental component summary from the SF-8 was reported. Patients with larger gastric remnants showed significantly better scores on the diarrhea subscale, a slightly better trend for the need for additional meals and dissatisfaction with eating. Regarding the anastomosis technique, there was no difference between the hand-sewn, circular stapler (CS) and linear stapler end-to-end anastomosis, and there was also no difference between the end-to-end and side-to-end anastomosis with the CS.

Conclusions The Kocher maneuver may increase meal-related distress, reduce the quality of ingestion and impart a negative effect on quality of life (QOL). The larger gastric remnants may cause reduction in diarrhea and an improvement in meal-related scores.

For the Japan Postgastrectomy Syndrome Working Party.

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Introduction

Gastric cancer is the most prevalent form of cancer in Japan and in recent years the percentage of patients with early-stage cancer has increased. Gastrectomy is commonly performed and in the cases of early-stage cancer the prognosis is extremely satisfactory, with a 5-year survival rate of ≥90 percent [1]. However, the issue of postgastrectomy syndrome (PGS) experienced by gastrectomy patients who have undergone radical therapy is a serious long-term problem. In addition to decreased oral intake and weight loss due to a reduction in the size of the stomach or total loss of the stomach, PGS symptoms such as dumping syndrome, which includes both systemic and abdominal symptoms, have an effect on long-term postoperative quality of life (QOL). Elucidating the status of PGS and the correlation with gastrectomy is important in the selection of appropriate surgical techniques and methods for the prevention and appropriate treatment of PGS.

A working group was formed in 2006 to standardize the assessment methods of PGS. This working group created the Postgastrectomy Syndrome Assessment Scale-45 (PGSAS-45) for use in comprehensive assessment of postgastrectomy symptoms, living status and QOL [2]. A nationwide, multi-institutional, collaborative, cross-sectional postgastrectomy syndrome assessment study was conducted using this scale. The present study assessed the effect of surgical techniques used in distal gastrectomy with Billroth-I reconstruction (DGBI) on PGS; DGBI is the most commonly used treatment approach for gastric cancer patients in Japan.

Patients and methods

Fifty-two member facilities of the Japanese Postgastrectomy Syndrome Working Party (JPGSWP) participated in this study. Patient inclusion criteria were as follows: (1) gastric cancer patients with pathologically confirmed stage IA or IB disease; (2) patients between 20 and 75 years; (3) patients who underwent gastrectomy for the first time; (4) patients who were not treated with chemotherapy; (5) patients without any recurrence or distant metastasis; (6) patients with an interval of one year or longer after gastrectomy; (7) physical status 0 or 1; (8) fully capable of understanding and responding to the questionnaire; (9) without any other disease or previous surgery which may influence the results of questionnaire more than gastrectomy; (10) without any organ failure or mental disease; and, (11) written informed consent with date and signature of the said person. Patients with active dual malignancy and who underwent concomitant resection of other organs due to another disease were excluded; co-resection equivalent to cholecystectomy was the exception.

We used the newly created PGSAS-45 to assess PGS in this study [2]. This scale is composed of questions pertaining to 45 items. This includes 8 items from the existing SF-8 scale [3], 15 items from the Gastrointestinal Symptom Rating Scale (GSRS) [4] and 22 items judged to be clinically important and newly selected by surgeons in the JPGSWP. Specifically, there are 8 items pertaining to general postgastrectomy symptoms, 2 items pertaining to the type and number of dumping syndromes, 8 items pertaining to the amount of oral intake and quality of ingestion, 1 item pertaining to working (job) conditions and 3 items pertaining to the level of dissatisfaction with daily life. The scale was distributed to the patients participating in this study and they returned the completed forms to the data center by mail. Factor analysis was performed on the data regarding standard gastrectomy (total gastrectomy and distal gastrectomy), and 23 symptom items of the data were clustered into the following 7 subscales (SSs): esophageal reflux, abdominal pain, meal-related distress, indigestion, diarrhea, constipation and dumping. In addition, the total symptom score, quality of ingestion SS, quantity of each meal, necessity for additional meals, dissatisfaction with symptoms, meals and work, as well as dissatisfaction with daily life SS, the physical component summary (PCS), the mental component summary (MCS) from the SF-8 and percentage of change in body weight were analyzed as the main outcome measures. The SS scores represented the average scores for the component items and the total symptom score was calculated from the average of the 7 SS scores. Background data, including patient attributes such as age at the time of administration of the scale, sex, height, and weight, as well as the degree of lymphadenectomy, approach used, detailed surgical method, postoperative period, and other background data were collected from the patients' medical records. This study was registered with the University Hospital Medical Information Network (UMIN) Clinical Trials Registry (No. 000002116). This study was approved by the local ethics committees at each institution.

The scale was distributed to 2,922 patients between July 2009 and December 2010. Completed forms were returned by 2,520 patients (86 %). Of the 2,520 patients from whom data was obtained 152 were excluded from the study because of the following reasons: 90 were aged >75; <1 year had passed since surgery for 29; 8 had combined resections; and 25 were in the "other" category. Thus, 2,368 patients were determined to be qualified, of which 393 underwent total gastrectomy, 909 underwent DGBI,

475 underwent distal gastrectomy with Roux-en-Y reconstruction, 313 underwent pylorus-preserving gastrectomy, 193 underwent proximal gastrectomy and 85 underwent local resection. In this study 909 patients who underwent DGBI were selected for the analysis and effects of performing the Kocher maneuver, differences in the size of the gastric remnant and differences in the anastomosis technique on the main outcome measures were analyzed. The patients whose data of each procedure could not be corrected from the patients' medical records were excluded from each analysis, thus the total number of patients in each analysis resulted in less than 909.

Comparison of the main outcome measures was performed using the t test, with significant differences set at $p < 0.05$. Multi-group comparisons were conducted using analysis of variance (ANOVA) and Bonferroni-Dunn multiple comparisons were used in cases in which $p < 0.1$. When multiple comparisons were performed among 3 groups statistical significance was set at $p < 0.0167$. As a measure of the meaning of the magnitude of the differences, Cohen's d, which is defined as the difference between two means divided by a standard deviation for the data, were calculated as the effect sizes. To interpret effect sizes we followed the suggestion of Cohen [5] and regarded a Cohen's $d \geq 0.2$ and <0.5 as being small, ≥ 0.5 and <0.8 as moderate and ≥ 0.8 as large. Statistical analyses were performed by the biostatisticians mainly using StatView for Windows Ver. 5.0 (SAS Institute Inc.).

Results

Patient and surgical background

The average patient age at the time of completing the questionnaires was 61.6 years and the average postoperative observation period was 40.7 months. Approximately 45 percent of the patients underwent laparoscopic surgery, and in approximately 15 percent patients the celiac branch of the vagus nerve was preserved. Table 1 shows additional patient details.

Kocher maneuver

Comparison of the main outcome measures was conducted between patients in whom the Kocher maneuver was performed and those in whom it was not. In the Kocher maneuver patients significantly worse meal-related distress, poorer quality of ingestion and less satisfactory PCS and MCS were reported. No significant differences were observed for any of the other assessment items (Table 2).

Table 1 DGBI Patient demographic information in DGBI

Number of patients	909
Postoperative period (months)	40.7 ± 30.7
BMI (preoperative)	22.7 ± 3.0
BMI (at the study)	20.9 ± 2.8
Age	61.6 ± 9.1
Gender (male/female)	594/311
Approach (laparoscopic/open)	415/489
Extent of lymph node dissection	
D2	319
D1b	444
D1a	119
D1	8
D1>	4
None	0
Celiac branch of vagus (preserved/divided)	133/754
Combined resection	
Cholecystectomy	80
Splenectomy	0
Others	4
None	743
Size of gastric remnant	
More than half	29
Around one-third	799
Around one-fourth	61
Less than one-fifth	0

DGBI distal gastrectomy with Billroth-I reconstruction

Size of remnant stomach

To assess the effect of the size of the gastric remnant on the main outcome measures gastric remnant sizes were divided into the following 3 groups: $\geq 1/2$, approximately 1/3 and $\leq 1/4$. The size of the gastric remnant had a significant effect on the diarrhea SS and patients with larger gastric remnants showed better scores on the diarrhea SS (Table 3).

Multiple comparisons were conducted on the diarrhea SS, necessity for additional meals and dissatisfaction with meals. Compared with the $\leq 1/4$ stomach remnant group, the $\geq 1/2$ stomach remnant group scored significantly better on the diarrhea SS ($p = 0.0025$). Though the significance levels between the $\geq 1/2$ group and the 1/3 group ($p = 0.033$), and between the 1/3 group and the $\leq 1/4$ group ($p = 0.035$) were marginal in the Bonferroni-Dunn multiple comparisons, the Cohen's d values revealed small but clinically meaningful effect sizes (0.46 and 0.27, respectively). There was no significant difference between the $\geq 1/2$ and 1/3 groups for the necessity for additional meals or between the $\leq 1/4$ and $\geq 1/2$ groups for dissatisfaction with meal; however, in both cases the $\geq 1/2$ group

Table 2 Comparison of the main outcome measures between patients in whom the Kocher maneuver was performed after DGBI and those in whom the Kocher maneuver was not performed

Main outcome measures	With Kocher maneuver (n = 74)		Without Kocher maneuver (n = 771)		p value	Cohen's d
	Mean	SD	Mean	SD		
(Symptoms)						
Esophageal reflux subscale	1.8	1.0	1.7	0.8	≥0.1	
Abdominal pain subscale	1.8	0.7	1.7	0.7	≥0.1	
Meal-related distress subscale	2.3	1.0	2.0	0.9	0.0244	0.26
Indigestion subscale	2.1	0.9	2.0	0.8	≥0.1	
Diarrhea subscale	2.3	1.1	2.1	1.1	≥0.1	
Constipation subscale	2.4	1.1	2.2	1.0	≥0.1	
Dumping subscale	2.1	1.2	2.0	1.0	≥0.1	
Total symptom score	2.1	0.8	2.0	0.7	≥0.1	
(Living status)						
Change in body weight*	−8.8 %	7.9 %	−7.8 %	8.1 %	≥0.1	
Ingested amount of food per meal*	7.1	1.9	7.2	2.0	≥0.1	
Necessity for additional meals	1.9	0.9	1.9	0.8	≥0.1	
*Quality of ingestion subscale**	3.4	1.1	3.8	0.9	0.0006	0.40
Ability for working	1.9	1.0	1.7	0.9	≥0.1	
(QOL)						
Dissatisfaction with symptoms	1.7	0.8	1.8	0.9	≥0.1	
Dissatisfaction at the meal	2.3	1.2	2.2	1.1	≥0.1	
Dissatisfaction at working	1.8	1.0	1.7	0.9	≥0.1	
Dissatisfaction for daily life subscale	1.9	0.8	1.9	0.8	≥0.1	
Physical component summary*	49.3	7.1	50.7	5.3	0.0388	0.22
Mental component summary*	48.5	5.9	50.0	5.6	0.0275	0.27

Integrated subscales are italicized in the table

Outcome measures with *: higher score indicating better condition

Outcome measures without *: higher score indicating worse condition

Interpretation of effect size in Cohen's d: ≥0.20 as small, ≥0.50 as medium, ≥0.80 as large

showed a slightly better trend. No significant differences were observed for any of the other assessment items.

Anastomosis technique

We assessed whether sutured (hand-sewn) anastomosis (n = 336), CS anastomosis (n = 183) and linear stapler (LS) anastomosis (n = 66) had an effect on the main outcome measures for patients in whom end-to-end B–I reconstruction was performed between the remnant stomach and the duodenum. The method of anastomosis had no significant effect on the main outcome measures.

We assessed whether performing end-to-end (n = 183) or side-to-end (n = 295) anastomosis between the gastric remnant and the duodenum had any effect on the main outcome measures for patients who underwent B–I reconstruction using the CS. There was no statistically significant difference on the main outcome measures between two above-mentioned procedures.

Discussion

In Japan more than half of the gastric cancer cases occur in the distal stomach; thus, distal gastrectomy is the most commonly performed procedure. Performing anastomosis in only 1 location is simple and it is the most physiologically appropriate approach because it allows food to pass through the duodenum [6]. Therefore, B–I reconstruction is the preferred post-distal gastrectomy reconstruction technique. The purpose of this study was to assess and elucidate the effect of different surgical techniques on PGS in cases in which DGBI, the most commonly performed gastric cancer surgical procedure in Japan, was performed.

Regardless of whether surgery was performed or anticancer drugs were administered, the effectiveness of treatment and post-treatment symptoms were evaluated using a patient-reported outcome (PRO) health-related quality of life (HRQOL) assessment. HRQOL was measured using a questionnaire. However, to determine if the resulting data are clinically useful, the method's validity, reliability and reproducibility must be verified. Thus, we used EORTC QLQ-C30 [7, 8], QLQ-STO22 [9, 10], SF-36 [11], GSRS [4] and other QOL questionnaires whose reliability and validity have been verified. However, because these questionnaires were not designed to assess PGS, they may not be able to fully assess the symptoms that are particular to postgastrectomy patients or the functional disabilities in daily life that are experienced by postgastrectomy patients. Thus, to perform a comprehensive

Table 3 Comparison of the main outcome measures between patients with different gastric remnant sizes after DGBI

Main outcome measures	Size of gastric remnant						p value	p value	
	≥1/2 (n = 29)		Approximately 1/3 (n = 799)		≤1/4 (n = 61)		(ANOVA)	(B/D)	Cohen's d
	Mean	SD	Mean	SD	Mean	SD			
(Symptoms)									
Esophageal reflux subscale	1.6	0.8	1.7	0.8	1.8	0.8	≥0.1		
Abdominal pain subscale	1.6	0.7	1.7	0.7	1.8	0.7	≥0.1		
Meal-related distress subscale	2.0	0.9	2.0	0.9	2.2	0.8	≥0.1		
Indigestion subscale	2.0	1.1	2.0	0.8	2.1	0.9	≥0.1		
								0.0333 (a)	0.46
Diarrhea subscale	1.7	0.8	2.1	1.1	2.4	1.2	0.0088	0.0345 (b)	0.27
								0.0025* (c)	0.72
Constipation subscale	2.2	1.0	2.2	1.0	2.1	0.9	≥0.1		
Dumping subscale	1.8	1.0	2.0	1.0	2.0	0.9	≥0.1		
Total symptom score	1.8	0.7	2.0	0.7	2.0	0.7	≥0.1		
(Living status)									
Change in body weight*	−5.9 %	10.5 %	−8.0 %	8.1 %	−9.0 %	6.9 %	≥0.1		
Ingested amount of food per meal*	7.9	1.9	7.1	2.0	6.9	1.8	≥0.1		
Necessity for additional meals	1.5	0.6	1.9	0.8	1.8	0.7	0.0791	0.0246 (a)	0.47
*Quality of ingestion subscale**	3.9	0.9	3.8	0.9	3.6	3.6	≥0.1		
Ability for working	1.7	0.9	1.8	0.9	1.7	0.8	≥0.1		
(QOL)									
Symptoms dissatisfaction	1.8	0.9	1.8	0.9	2.0	0.9	≥0.1		
Meal dissatisfaction	1.8	1.0	2.2	1.1	2.3	1.0	0.0821	0.0371 (c)	0.52
Work dissatisfaction	1.6	0.8	1.7	0.9	1.7	0.9	≥0.1		
Dissatisfaction for daily life subscale	1.7	0.8	1.9	0.8	2.0	0.8	≥0.1		
Physical component summary*	51.0	4.8	50.5	5.6	50.8	5.2	≥0.1		
Mental component summary*	51.7	5.4	49.8	5.7	50.3	5.0	≥0.1		

Integrated subscales are italicized in the table

Outcome measures with *: higher score indicating better condition

Outcome measures without *: higher score indicating worse condition

ANOVA: one-way analysis of variance; B/D: Bonferroni/Dunn multiple comparisons; (a) ≥1/2 vs. approximately 1/3; (b) approximately 1/3 vs. ≤1/4; (c) ≥1/2 vs. ≤1/4

In ANOVA a p value less than 0.05 was considered statistically significant

In Bonferroni/Dunn multiple comparisons a p value <0.0167 was considered statistically significant

Interpretation of effect size in Cohen's d: ≥0.20 as small, ≥0.50 as medium, ≥0.80 as large

assessment of PGS, JPGSWP developed the PGSAS-45 and assessed its validity [2]. In addition, this scale was also used to compare PGS between Billroth-I and Roux-en-Y procedures following distal gastrectomy [12]. The present study used PGSAS-45 to assess the effect of the Kocher maneuver, the size of the gastric remnant and the anastomosis technique on postgastrectomy symptoms, living status and QOL in cases in which DGBI was performed.

The Kocher maneuver is a procedure in which an incision is made in the retroperitoneum on the right side of the descending duodenum, and then the duodenum and the head of the pancreas are mobilized to the left. It was originally reported as a maneuver to mobilize the duodenum that was performed by Kocher during a gastroduodenal anastomosis in 1903 [13, 14]. The Kocher maneuver is sometimes performed during gastrectomy for gastric cancer to confirm enlargement of and sample the paraaortic lymph node and to reduce the strain on the anastomotic site when performing B–I reconstruction. However, there have been no studies on the effect of the Kocher maneuver on PGS. The present study showed that performance of the Kocher maneuver results in poor scores for meal-related distress and quality of ingestion SS as well as poor scores for PCS and MCS from the SF-8. Meal-related