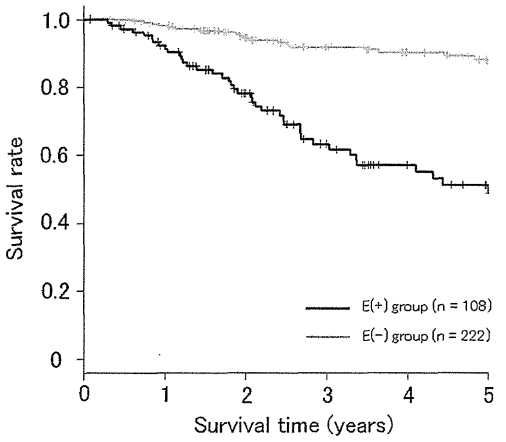

Fig. 1. Overall survival curves of patients. The 5-year overall survival rate is significantly better in the group of patients without esophageal invasion [E (−) group, 86.8%] than in the group with esophageal invasion [E (+) group, 48.7%, $P < 0.001$].

depth, nodal status, and splenectomy were included as covariates. $P < 0.05$ was considered significant. All statistical analyses were conducted using R Statistics version 2.13.1.

RESULTS

There were no differences in sex, age, and histology between the groups of patients in this study (Table I). The tumor diameter was larger and epicenter of the tumor was closer to the EGJ in the E (+) group than in the E (−) group. Disease was more advanced in the E (+) group than in the E (−) group, and peritoneal lavage cytology was positive more frequently in the E (+) group (16%) than in the E (−) group (4%, $P < 0.001$).

The details of treatments provided and early surgical outcomes are shown in Table II. A total of 6% of patients in the E (+) group required the thoracoabdominal approach and total gastrectomy and splenectomy were more frequently performed in the E (+) group than in the E (−) group. R0 resection rate was 96% in the E (−) group, whereas it was 80% in the E (+) group ($P < 0.001$). Prolonged operation time, increased blood loss, and longer duration of postoperative hospital stay were observed in the E (+) group. The incidence of postoperative morbidity was higher in the E (+) group (59%) than in the E (−) group (30%) although postoperative mortality was not observed in either group.

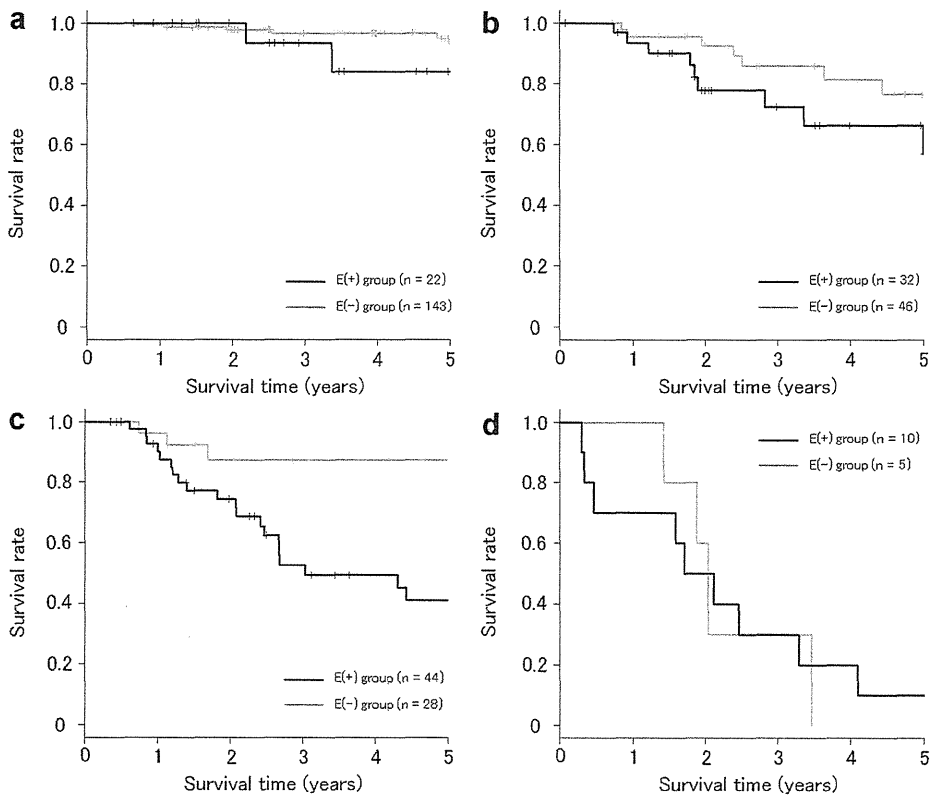

Fig. 2. Overall survival curves of patients stratified by pathological stage according to the classification system for gastric cancer. **a**: Overall survival curves of stage I patients. The 5-year overall survival rate is 84.0% in patients with esophageal invasion and 93.1% in those without esophageal infiltration ($P = 0.213$). **b**: Overall survival curves of stage II patients. The 5-year overall survival rate is 56.9% in patients with esophageal infiltration and 63.9% in those without esophageal infiltration ($P = 0.196$). **c**: Overall survival curves of stage III patients. The 5-year overall survival rate is 41.1% in patients with esophageal infiltration and 87.2% in those without esophageal infiltration ($P = 0.0139$). **d**: Overall survival curves of stage IV patients. The 5-year overall survival rate is 9.5% in patients with esophageal infiltration and 0% in those without esophageal infiltration ($P = 0.968$).

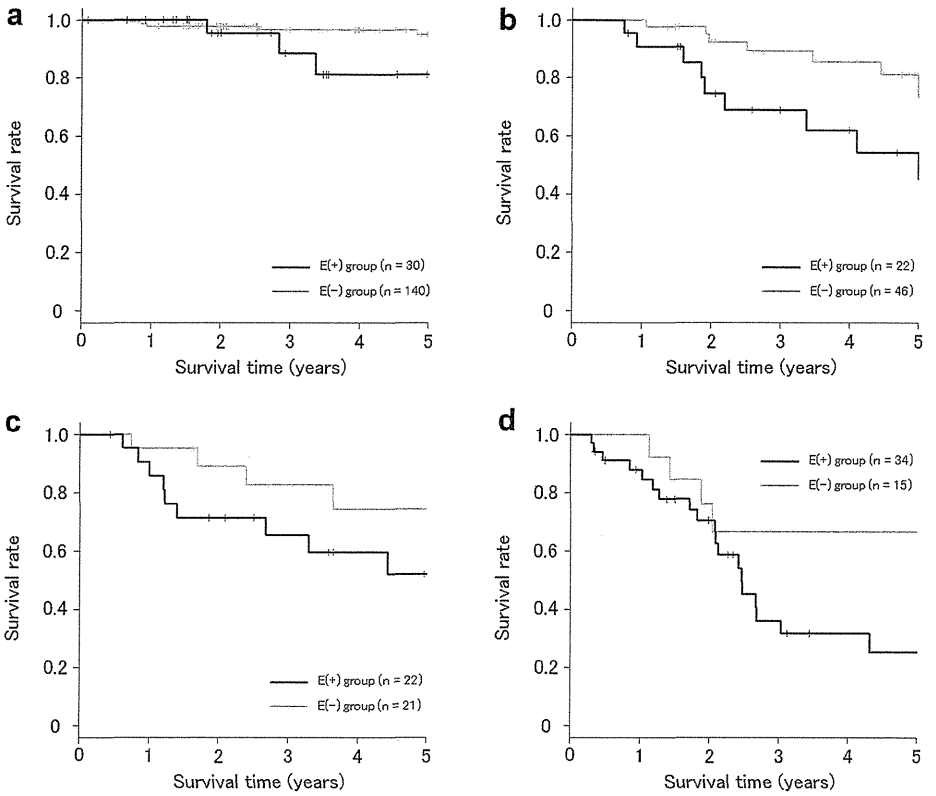

Fig. 3. Overall survival curves of patients stratified by nodal status. **a**: Overall survival curves of N0 patients. The 5-year overall survival rate is 81.0% in patients with esophageal invasion and 94.9% in those without esophageal infiltration ($P = 0.111$). **b**: Overall survival curve of N1 patients. The 5-year overall survival rate is 45.2% in patients with esophageal infiltration and 73.3% in those without esophageal infiltration ($P = 0.050$). **c**: Overall survival curves of N2 patients. The 5-year overall survival rate is 52.1% in patients with esophageal infiltration and 74.4% in those without esophageal infiltration ($P = 0.144$). **d**: Overall survival curves of N3 patients. The 5-year overall survival rate is 25.3% in patients with esophageal infiltration and 66.6% in those without esophageal infiltration ($P = 0.124$).

The survival curves of patients who underwent R0 or R1 gastrectomy are shown in Figure 1. The 5-year survival rate was significantly better in the E (−) group (86.8%) than in the E (+) group (48.7%, $P < 0.001$). Survival curves were also stratified by the pathological stage and nodal status. In the survival analysis, we tentatively adopted classifications systems for gastric cancer to both groups.

The survival curves stratified by pathological stage using the classification for gastric cancer are shown in Figure 2a–d. In addition, the survival curves stratified by nodal status are shown in Figure 3a–d. The 5-year survival curves for patients tend to be better in the E (−) group than in the E (+) group except for patients with stage IV disease.

The results of the multivariate analysis are shown in Table III. Esophageal invasion (hazard ratio; 3.323, 95% Confidential Interval; 1.815–6.082) was selected as an independent prognostic factor. In addition, histology, curability, tumor depth, nodal status, and splenectomy were also selected as independent prognostic factors.

TABLE III. Result of Multivariate Analysis

	Hazard ratio	95% Confidential interval	*P*-value
Age (≥65 vs. <65 years)	1.443	0.976–2.132	0.066
Sex (male vs. female)	0.855	0.489–1.493	0.581
Location of the epicenter (within 20 mm vs. 20–50 mm from the EGJ)	0.816	0.486–1.369	0.44
Histology (diffentiated vs. undiffentiated)	0.58	0.365–0.923	0.022
Tumor depth (T2, T3, T4 vs. T1)	3.719	1.506–9.182	0.004
Lymph node status (N+ vs. N−)	3.221	1.427–7.273	0.005
Curability (R1, R2/R0)	4.272	2.479–7.360	<0.001
Esophageal invasion (+/−)	3.323	1.815–6.082	<0.001
Tumor diameter (≥50 mm vs. <50 mm)	0.829	0.561–1.223	0.343
Type of surgery (TG vs. PG)	0.668	0.293–1.525	0.338
Splenectomy (yes vs. no)	1.853	1.125–3.049	0.015

EGJ, esophagogastric junction.

DISCUSSION

This study demonstrates that patients without esophageal invasion [E (−) group] have better overall survival than those with esophageal invasion [E (+) group]. Tumor diameter was larger and pathological T and N stage were more advanced in the E (+) group than in the E (−) group. Accordingly, curative resection was achieved less frequently in the E (+) group than in the E (−) group, which may be responsible for the poor survival outcome in the E (+) group. The same trend was observed even after stratification by pathological stage and nodal status in patients undergoing R0 or R1 surgery. Multivariate analysis also identified esophageal invasion as an independent prognostic factor.

One possible reason for the poor long-term outcome in the E (+) group compared to the E (−) group is the complicated anatomical structures around the EGJ. Surgery is generally difficult in patients with esophageal invasion because thoracostomy is sometimes required to secure the surgical margin. In the present study, proximal resection margin was shorter in the E (+) group (10 mm) than in the E (−) group (20 mm) presumably due to difficulty in securing resection margin in the E (+) group. In addition, difficulty in surgical procedure might be associated with higher local recurrence rate in the E (+) group (4.5%) than in the E (−) group even after R0 or R1 gastrectomy (data not shown).

A recent study revealed the existence of lymphatic flow from the lower esophagus into the lower mediastinal node [3]. This lymphatic flow could adversely affect the disease outcome for patients through metastatic spread to the lower mediastinal lymph node although the therapeutic value of mediastinal lymph node dissection remains controversial [9–11]. In the present study, few patients in the E (−) group received lower mediastinal lymph node dissection, therefore the actual incidence and therapeutic value of lower mediastinal lymph node dissection could not be determined.

Different tumor diameter between the groups is another contributing factor for the poor long-term outcome in the E (+) group. Bando et al. [12] reported magnitude of serosal change was associated with peritoneal metastasis and affected long-term outcome of patients. In the present study, median tumor diameter was longer and positive peritoneal lavage cytology was more frequently observed in E the (+) group than in the E (−) group; thus we included tumor diameter as a covariate in the subsequent multivariate analysis (cut-off value of 50 mm was selected as a median tumor diameter of all patients). However, it was not selected as an independent prognostic factor.

Our investigations revealed that patients who had an epicenter within 2 cm of the EGJ were more frequently observed in the E (+) group than in the E (−) group. The distribution and prognostic value of Siewert type classification have been investigated in both Western and Eastern countries [5,13–16]. Siewert type I AEG is extremely rare in Eastern countries, and most AEGs have been classified as type II or III [5,9,16–18]. The survival rate among each Siewert type is still contentious with the worst long-term outcome reported in Siewert type III AEG followed by type II, and type I [13]. Other investigations have reported there is either no significant difference [5,9,16,17] or a better survival rate in type III AEG [15,18]. In this study, the location of tumor epicenter was not selected as an independent prognostic factor.

Thoracostomy was required in 6% of patients in the E (+) group, whereas it was required only in one patient in the E (−) group. In addition, splenectomy was frequently performed in the E (+) group. These procedures are associated with increased intraoperative blood loss, prolonged operation time, and increased incidence of postoperative morbidity [9,13,15,17,19–21]. The aggressive surgery that was frequently performed in the E (+) group is one of the contributing factors that led to poor early surgical outcomes in the present study.

The present retrospective study has some limitations. Firstly, patient's background data and selected treatment, including surgical procedure and postoperative adjuvant chemotherapy, may be different between the groups. Secondly, we assessed the epicenter of the tumor and the location of the EGJ retrospectively with formalin-fixed specimen, and it is sometimes difficult particularly in patients with far advanced disease. To overcome these limitations, prospective data collection with determined treatment strategy by the protocol will be necessary.

In conclusion, patients in the E (+) group represented a more advanced stage and a poorer long-term outcome. Furthermore, esophageal invasion was identified as an independent prognostic factor. The establishment of multimodal treatment is necessary to improve the survival outcome of these patients. Further study is necessary to clarify whether patients with esophageal invasion should be classified using the system for esophageal cancer or by another method.

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Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

Clinical Cancer Research

Imaging, Diagnosis, Prognosis

Impact of Expression of Human Epidermal Growth Factor Receptors EGFR and ERBB2 on Survival in Stage II/III Gastric Cancer

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Abstract

Purpose: EGF receptor (EGFR) and HER2 positivity are considered to be negative prognostic factors in gastric cancer. Biomarker analysis was conducted to evaluate the impact of EGFR and HER2 expression on the outcome of patients enrolled in the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC), a randomized controlled trial comparing postoperative adjuvant S-1 therapy with surgery alone in 1,059 patients with stage II/III gastric cancer.

Experimental Design: Formalin-fixed, paraffin-embedded surgical specimens were retrospectively examined in 829 patients (78.3%). The effects of EGFR and HER2 positivity on survival were analyzed on the basis of the 5-year survival data from the study. EGFR positivity was defined as an immunohistochemistry (IHC) score of 3+, and HER2 positivity as an IHC score of 3+ or an IHC score of 2+ with a positive dual-color *in situ* hybridization status.

Results: EGFR and HER2 were positive in 75 (9.0%) and 113 (13.6%) patients, respectively. The overall and relapse-free survival rates were significantly lower in EGFR-positive patients than in EGFR-negative patients, whereas they were similar in HER2-positive and HER2-negative patients. Multivariate analysis showed that EGFR positivity correlated with poor outcomes [HR = 1.504; 95% confidence interval (CI) = 1.020–2.149; $P = 0.040$]. Treatment with S-1 improved survival compared with surgery alone, irrespective of EGFR and HER2 status.

Conclusions: EGFR positivity, but not HER2 positivity, was associated with poor patient outcomes after curative resection of stage II/III gastric cancer. There was no interaction between S-1 and EGFR or HER2 status with respect to survival outcome. *Clin Cancer Res; 18(21); 5992–6000. ©2012 AACR.*

Introduction

Gastric cancer is the second leading cause of cancer-related deaths worldwide, and the highest mortality rates have been reported in East Asia, including Japan, Korea, and China (28.1 per 100,000 males, 13.0 per 100,000 females; ref. 1). The mainstay of treatment of gastric cancer is surgery; however, in stage II (excluding T1 disease) and stage III (moderately advanced) disease, many patients suffer recurrence, even after curative resection. Various regimens for adjuvant chemotherapy have been implemented to prevent this.

S-1 (TS-1; Taiho Pharmaceutical Co. Ltd.) is an oral fluoropyrimidine preparation, combining tegafur, gimeracil, and oteracil potassium (2). The Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC), which was a prospective randomized phase III trial, showed that S-1 was more effective than surgery alone in East Asian patients with stage II/III gastric cancer (3, 4). However, the 5-year overall survival (OS) rate in patients with stage IIIB disease was 50.2% in the S-1 group in a subset analysis, suggesting room for improvement (4). There is a need to evaluate the effectiveness of intensive preoperative and/or postoperative chemotherapy with multiple agents, including some new biologic agents, in patients at high risk of relapse.

The type I HER family has 4 homologous members: HER1/erbB1 [EGF receptor (EGFR)], HER2/erbB2 (HER2), HER3/erbB3, and HER4/erbB4. All members share a

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Note: Supplementary data for this article are available at Clinical Cancer Research Online (http://clincancerres.aacrjournals.org/).

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doi: 10.1158/1078-0432.CCR-12-1318

Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

Translational Relevance

The clinical significance of EGF receptor (EGFR) and HER2 overexpression remains to be fully defined because not all previous studies have shown an association between overexpression of these receptors and poor outcomes of patients with gastric cancer. We studied archived specimens obtained from 829 patients enrolled in the Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer (ACTS-GC) trial at 65 centers. All specimens were evaluated by standard methods and unified criteria in a central laboratory. The results provide compelling evidence that an EGFR 3+ status on immunohistochemical analysis, but not HER2 positivity, is significantly associated with poor outcomes after curative resection of stage II/III gastric cancer. There was no apparent interaction between S-1 and EGFR or HER2 status with respect to survival.

common structure, with an extracellular ligand-binding domain, a transmembrane domain, and an intracytoplasmic tyrosine kinase domain. Ligand binding to these receptors induces the formation of receptor homodimers and heterodimers, and the activation of downstream signaling pathways. The HER family might therefore contribute to malignant progression. In gastric cancers, overexpressions of EGFR and HER2 are considered prognostic factors, and have been targeted by novel biologic agents (5–10). Recently, the first phase III Trastuzumab for Gastric Cancer (ToGA) trial showed that trastuzumab enhanced the efficacy of chemotherapy in HER2-positive advanced gastric cancer, indicating that HER2 expression might predict the response to anti-HER2 agents even in gastric cancer (11). However, the clinical significance of EGFR and HER2 overexpression remains to be fully defined because not all studies have shown an association with poor outcomes (12, 13).

The present study therefore explored the protein expression of EGFR and HER2 using immunohistochemical analysis and gene amplification of *HER2* by dual-color *in situ* hybridization (dual-ISH) in gastric cancer tissues obtained from patients enrolled in the ACTS-GC. We retrospectively evaluated the impact of the expression of these receptors on treatment outcomes.

Materials and Methods

Patients and sample collection

Tumor tissue was collected from patients enrolled in the ACTS-GC. The inclusion criteria and the treatment protocol were as described previously (3, 4).

The present biomarker study was designed retrospectively after the completion of the first interim analysis of the ACTS-GC. Archived formalin-fixed, paraffin-embedded (FFPE) specimens obtained by surgical resection were available for 829 (78.3%) of the 1,059 patients who were enrolled in the ACTS-GC at 65 centers. The specimens were shipped to the National Cancer Center Hospital East (Kashiwa, Japan), where immunohistochemical and dual-ISH analyses were conducted, and the results were evaluated. The protocol of this biomarker study was approved by the ethics committee of the Japanese Gastric Cancer Association and the Institutional Review Board of each participating hospital.

IHC

All of the reagents and instruments for IHC were manufactured by Ventana Medical Systems, Inc. FFPE sections (thickness = 3–5 μm) were automatically stained with Ventana BenchMark ULTRA using primary antibodies against EGFR (CONFIRM EGFR 3C6) and HER2 (I-VIEW PATHWAY anti-HER2/neu 4B5), and a Ventana iView DAB Universal Kit, according to the manufacturer's protocol. Staining was evaluated using light microscopy and was interpreted by 2 independent pathologists (K. Kitada and A. Ochiai) who were blinded to all clinical information. Tumor cell-membrane immunostaining was scored using a 4-grade scale (0, 1+, 2+, or 3+). EGFR reactivity was scored as 0 if there was no membranous reactivity within the tumor, or as 1+, 2+, or 3+ depending on the intensity above the background level (7). We followed the consensus panel recommendations for HER2 scoring in gastric cancer (14).

Dual-ISH

All reagents and instruments for dual-ISH were manufactured by Ventana Medical Systems, Inc. Dual-ISH analyses for *HER2* were carried out for specimens with IHC scores of 2+ or 3+ with Ventana Benchmark ULTRA, using DNA cocktail probes [*HER2* and *CEP17* (centromeric probe 17)] according to the manufacturer's protocol. For each specimen, the numbers of *HER2* signals (silver ISH, black) and *CEP17* signals (red ISH, red) were counted for 20 nuclei, and the *HER2/CEP17* ratio was calculated by dividing the total number of *HER2* signals by the total number of *CEP17* signals. Negativity for *HER2* gene amplification was defined as an *HER2/CEP17* ratio of less than 1.8, whereas positivity was defined as an *HER2/CEP17* ratio of more than 2.2. If the *HER2/CEP17* ratio was in the equivocal range (1.8–2.2), the number of *HER2* and *CEP17* signals was counted for 20 additional nuclei, and the *HER2/CEP17* ratio was calculated from the results of 40 nuclei. Eventually, amplification of *HER2* was defined as an *HER2/CEP17* ratio of 2.0 or more, based on a partially modified version of the *HER2* scoring system for breast cancer (15).

Definition of positivity

For EGFR, an IHC score of 3+ was defined as positive, and IHC scores of 0, 1+, and 2+ were defined as negative. For HER2, an IHC score of 3+ or an IHC score of 2+ with a dual-ISH *HER2/CEP17* ratio of 2.0 or more was defined as positive, and IHC scores of 0 and 1+ or a score of IHC 2+ with a dual-ISH *HER2/CEP17* ratio of less than 2.0 were defined as negative (14).

Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

Reverse-transcription PCR

Representative hematoxylin and eosin–stained slides of FFPE specimens were reviewed by a pathologist to estimate tumor load per sample. Slide sections 10 μm in thickness were then stained with nuclear fast red (Sigma-Aldrich) for manual microdissection. Tumor tissue was selected at a magnification of 5 to 10 times and dissected from the slide using a scalpel, as described previously (16).

RNA isolation from tumor tissue and the cDNA preparation steps were conducted as described previously (17), with a slight modification in the extraction step, using RNeasy Mini Elute spin-columns (Qiagen).

Gene expression levels of *EGFR* and *HER2* were determined by means of TaqMan real-time PCR (Life Technologies) as described previously (17). β-Actin was used as an endogenous reference gene. The detection of amplified cDNA results in a cycle threshold (C_t) value, which is inversely proportional to the amount of cDNA. Gene expression values (relative mRNA levels) are expressed as ratios (differences between the C_t values) between the gene of interest (*EGFR* or *HER2*) and a reference gene (β-actin). This reference gene provides a baseline measurement for the amount of RNA isolated from a specimen.

Statistical analysis

Survival curves were estimated using the Kaplan–Meier product-limit method, and the statistical significance of differences between survival curves was assessed using the log-rank test. Univariate and multivariate survival analyses were conducted using a Cox proportional hazards model. Categorical data analysis was conducted using the χ^2 test. Either the Wilcoxon test or the Kruskal–Wallis test was used to assess correlations between groups. Results were considered statistically significant at $P < 0.05$. All statistical analyses were carried out with the SAS software package version 9.1 and JMP software version 8.01 (SAS Institute Inc.).

We estimated what minimum difference in survival would be required with EGFR- or HER2-positive cancers to show a survival difference as compared with EGFR- or HER2-negative cancers, respectively. We assumed that patients with EGFR- or HER2-positive tumors would have poorer outcomes. Given a positivity rate of 10%, 15%, or 20%, demonstration of a statistically significant difference in survival between patients with positive tumors and those with negative tumors would require HRs of at least 1.624, 1.520, and 1.465, respectively, assuming a 2-sided $\alpha = 0.05$ and a power = 80% in a proportional hazards model.

Results

Patients and sample collection

When the biomarker population of this study was compared with the total population of ACTS-GC as previously reported (3), there was no significant difference between these groups (Table 1). The IHC results were obtained for both EGFR and HER2 expression in all 829 specimens as follows: EGFR grade 0, 204 (24.6%); EGFR grade 1+, 372 (44.9%); EGFR grade 2+, 178 (21.5%); EGFR grade 3+, 75 (9.0%); HER2 grade 0, 443 (53.4%); HER2 grade 1+, 210 (25.3%); HER2 grade 2+, 101 (12.2%); and HER2 grade 3+, 75 (9.0%). Representative examples of immunostaining for EGFR and HER2 are shown in Supplementary Fig. S1 and S2.

Dual-ISH analyses were conducted on 176 specimens with a HER2 IHC score of 2+ or 3+. The IHC score and dual-ISH status for HER2 were as follows: IHC 2+/dual-ISH negative, 63 (7.6%); IHC 2+/dual-ISH positive, 38 (4.6%); IHC 3+/dual-ISH negative, 2 (0.2%); and IHC 3+/dual-ISH positive, 72 (8.7%). Dual-ISH could not be determined in one specimen, but this was classified as HER2-positive because the IHC score was 3+. IHC 3+ scores were generally consistent with dual-ISH positive status (72/74 cases; 97.3%), whereas IHC 2+ scores were not (38/101 cases; 37.6%).

We also measured the relative gene-expression levels of *EGFR* and *HER2* by reverse-transcription PCR (RT-PCR) analysis in tumor tissue dissected from FFPE specimens. The IHC scores for EGFR and HER2 significantly correlated with their gene-expression levels ($P < 0.001$, Kruskal–Wallis test; Supplementary Fig. S3).

Eventually, we classified 75 cases (9.0%) as positive for EGFR and 113 (13.6%) as positive for HER2. The groups were well balanced with respect to EGFR and HER2 status and other factors (Table 1). Both EGFR and HER2 positivities were more common among differentiated type than undifferentiated type tumors (EGFR, 58.7%, $P < 0.001$; HER2, 75.2%, $P < 0.001$ [χ^2-test]). HER2 positivity was associated with male gender ($P < 0.001$), older age ($P = 0.0052$), and lower tumor stage ($P < 0.001$), whereas EGFR positivity was not (Supplementary Table S1). Eighteen cases (2.2%) were positive for both EGFR and HER2, 57 (6.9%) were positive for EGFR alone, and 95 (11.5%) were positive for HER2 alone.

Effects of EGFR and HER2 expressions on survival

Five-year OS and relapse-free survival (RFS) were 73.6% [95% confidence interval (CI) = 69.3%–77.9%] and 66.7% (95% CI = 62.1%–71.3%), respectively, in the S-1 group, compared with 61.9% (95% CI = 57.1%–66.7%) and 53.7% (95% CI = 48.8%–58.7%) in the surgery-only group, respectively. These figures were similar to the ACTS-GC 5-year follow-up data (4).

EGFR-positive status was significantly associated with worse outcomes in the study group as a whole (Table 2, Fig. 1A; Kaplan–Meier curves for the OS of patients according to the EGFR IHC score are shown in Supplementary Fig. S4). The results for 5-year RFS were similar to those for 5-year OS (Table 2). EGFR-positive status was also associated with worse outcomes in both the S-1 group and the surgery-only group (Table 2). Irrespective of EGFR status, the 5-year OS in the S-1 group was longer than that in the surgery-only group (Fig. 1B and C).

In contrast, there was no correlation between HER2 status and patient outcomes in the study group as a whole (Table 2, Fig. 2A). The 5-year RFS was similar to the 5-year OS (Table 2). HER2-positive status was not associated with outcomes in either the S-1 group or the surgery-only group

Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

Table 1. Characteristics of the patients

	Entire population of ACTS-GC			Biomarker study population of ACTS-GC		
	S-1 (n = 529)	Surgery only (n = 530)	P value[a]	S-1 (n = 415)	Surgery only (n = 414)	P value[a]
Sex, n (%)			0.98			0.90
Male	367 (69.4)	369 (69.6)		282 (68.0)	283 (68.4)	
Female	162 (30.6)	161 (30.4)		133 (32.0)	131 (31.6)	
Age, n (%)			0.86			0.72
<60	199 (37.6)	195 (36.8)		160 (38.6)	158 (38.2)	
60–69	193 (36.5)	215 (40.6)		149 (35.9)	161 (38.9)	
70–80	137 (25.9)	120 (22.6)		106 (25.5)	95 (22.9)	
Median, y	63	63		63	62	
Range, y	27–80	33–80		27–80	33–80	
Tumor stage, n (%)			0.81			0.93
T1	1 (0.2)	0 (0)		1 (0)	0 (0)	
T2	289 (54.6)	286 (54.0)		222 (53.5)	223 (53.9)	
T3	225 (42.5)	232 (43.8)		180 (43.4)	182 (44.0)	
T4	14 (2.6)	12 (2.3)		12 (2.9)	9 (2.2)	
Nodal stage, n (%)[b]			0.72			0.52
N0	51 (9.6)	64 (12.1)		40 (9.6)	52 (12.6)	
N1	296 (56.0)	281 (53.0)		233 (56.1)	222 (53.6)	
N2	182 (34.4)	185 (34.9)		142 (34.2)	140 (33.8)	
N3	0 (0)	0 (0)		0 (0)	0 (0)	
Lymph-node metastases, n (%)		0.37			0.18	
0	51 (9.6)	64 (12.1)		40 (9.6)	52 (12.6)	
1–6	331 (62.6)	325 (61.3)		254 (61.2)	254 (61.4)	
7–15	117 (22.1)	113 (21.3)		97 (23.4)	85 (20.5)	
≥16	30 (5.7)	28 (5.3)		24 (5.8)	23 (5.6)	
Cancer stage, n (%)[c]			0.78			0.48
II	236 (44.6)	238 (44.9)		183 (44.1)	189 (45.7)	
IIIA	202 (38.2)	207 (39.1)		159 (38.3)	162 (39.1)	
IIIB	90 (17.0)	85 (16.0)		73 (17.6)	63 (15.2)	
IV	1 (0.2)	0 (0)		0 (0)	0 (0)	
Histologic type, n (%)[d]			0.73			0.91
Differentiated	214 (41.6)	209 (40.3)		166 (40.0)	166 (40.1)	
Undifferentiated	301 (58.4)	307 (59.7)		249 (60.0)	245 (59.2)	
EGFR status, n (%)			—			0.54
Negative	—	—		380 (91.6)	374 (90.3)	
Positive	—	—		35 (8.4)	40 (9.7)	
HER2 status, n (%)			—			0.77
Negative	—	—		357 (86.0)	359 (86.7)	
Positive	—	—		58 (14.0)	55 (13.3)	

NOTE: Characteristics of the patients in entire population of ACTS-GC was referred by ref. 3.

[a]P values for sex, EGFR status, and HER2 status were calculated with the use of the χ^2 test. P values for age, tumor stage, nodal stage, number of lymph-node metastases, cancer stage (Japanese classification), and histologic type were calculated with the use of the Wilcoxon test.

[b]Nodal stages according to the Japanese classification were defined as follows: N0, no evidence of lymph node metastasis; N1, metastasis to group 1 lymph nodes; N2, metastasis to group 2 lymph nodes; N3, metastasis to group 3 lymph nodes. Groups 1, 2, and 3 are regional lymph node classifications defined according to the location of the primary tumor and are based on the results of studies of lymphatic flow at various tumor sites and the observed survival associated with metastasis at each nodal station (i.e., position in relation to primary node).

[c]Cancer stages according to the Japanese classification were defined as follows: stage IA, T1N0; stage IB, T1N1 or T2N0; stage II, T1N2, T2N1, or T3N0; stage IIIA, T2N2, T3N1, or T4N0; stage IIIB, T3N2 or T4N1; stage IV, T4N2, any T stage with N3, or distant metastasis.

[d]In entire population of ACTS-GC, histologic type was classified among eligible patients (n = 1,034). In the surgery-only group of biomarker study population, cancers could not be classified as differentiated or undifferentiated in 3 patients.

Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

Table 2. Univariate analysis of OS and RFS according to the status of EGFR and HER2

				OS			RFS		
Marker	Group	Status	Number of patients	5-year survival (%)	HR (95% CI)	*P* value (log-rank)	5-year survival (%)	HR (95% CI)	*P* value (log-rank)
EGFR									
	All	Negative	754	69.0	1		61.3	1	
		Positive	75	55.4	1.642 (1.139–2.366)	0.007	49.9	1.451 (1.030–2.045)	0.033
	S-1	Negative	380	74.9	1		68.2	1	
		Positive	35	60.0	1.787 (1.018–3.134)	0.043	51.4	1.773 (1.066–2.950)	0.027
	Surgery only	Negative	374	63.1	1		54.3	1	
		Positive	40	51.2	1.514 (0.936–2.449)	0.091	48.7	1.219 (0.767–1.939)	0.402
HER2									
	All	Negative	716	68.3	1		60.0	1	
		Positive	113	64.5	1.155 (0.822–1.624)	0.406	62.3	0.991 (0.716–1.371)	0.955
	S-1	Negative	357	74.2	1		66.5	1	
		Positive	58	69.9	1.170 (0.697–1.965)	0.552	68.2	1.000 (0.609–1.643)	1.000
	Surgery only	Negative	359	62.4	1		53.5	1	
		Positive	55	58.8	1.167 (0.742–1.833)	0.504	56.0	0.997 (0.649–1.530)	0.988

(Table 2). Similarly, there was no correlation between the 75 patients with IHC 3+ and patient outcomes (5-year OS in the IHC 3+ and in the IHC 0/1+/2+ were respectively 64.7% and 68.1%, HR = 1.178, 95% CI = 0.807–1.720, log-rank $P = 0.396$; and 5-year RFS in the IHC 3+ and in the IHC 0/1+/2+ were respectively 62.2% and 60.1%, HR = 0.942, 95% CI = 0.625–1.418, log-rank $P = 0.773$). Irrespective of HER2 status, the 5-year OS in the S-1 group was longer than that in the surgery-only group (Fig. 2B and C).

Multivariate analysis in overall study population

The prognostic relevance of EGFR and HER2 was assessed using a multivariate proportional hazards model adjusted for the following established clinical prognostic factors: treatment arm, gender, age, cancer stage (Japanese classification of gastric carcinoma, 2nd English edition; ref. 18), and histologic type (Table 3). Although treatment arm and cancer stage were the strongest prognostic factors, EGFR status was also an independent prognostic factor.

Subgroup analysis

The OS in the study group as a whole was analyzed according to gender, age, cancer stage, histologic type, and EGFR/HER2 status; no interaction was found between S-1 treatment and any of these factors (Fig. 3). Kaplan–Meier estimates of OS plotted according to EGFR (Fig. 1B and C) and HER2 status (Fig. 2B and C) revealed that S-1 treatment improved survival irrespective of EGFR or HER2 status.

Discussion

The present study retrospectively evaluated the influence of EGFR and HER2 expression on the outcomes of patients enrolled in the ACTS-GC. EGFR positivity was found to be associated with worse outcomes, in agreement with earlier findings (5–7, 9). Although most previous studies defined EGFR positivity as an IHC score of 2+ and 3+, no consensus definition has been reached. To the best of our knowledge, this is the first study to show that EGFR IHC 3+ status correlates significantly with poor outcome in patients with gastric carcinoma.

Kim and colleagues reported a similar distribution of EGFR protein-expression IHC scores to those of the present study in 511 specimens of gastric carcinoma tissue (7). They also reported that 13 (61.9%) of 21 cases with IHC scores of 3+ showed *EGFR* gene amplification or high polysomy on FISH, whereas this was observed in only 14 (11.8%) of 119 cases with scores of 2+. Our present study confirmed that the EGFR IHC scores significantly correlated with *EGFR* gene-expression levels. Moreover, the median *EGFR* gene expression for cases with IHC scores of 3+ was higher than that for cases with scores of 0, 1+, and 2+ (Supplementary Fig. S3A), suggesting that a score of 3+ could be a new criterion for defining EGFR positivity in gastric cancer. This was strongly linked to EGFR overexpression and poor outcomes for patients with gastric carcinoma in this study (Supplementary Fig. S4).

Multivariate analysis revealed that an IHC score of EGFR 3+ was an independent predictor of unfavorable outcomes. As well as being a prognostic marker, EGFR positivity might be a predictor of response to EGFR-targeted therapy in gastric cancer. A phase II study showed a significant association between increased *EGFR* gene copy number (≥4.0) and OS in a subset of patients with gastric and esophagogastric junction cancer who received cetuximab combined with oxaliplatin/leucovorin/5-fluorouracil (19, 20). In addition, among 58 patients with metastatic colorectal carcinoma (mCRC) who received panitumumab in a previous study, 6 of 20 patients with an *EGFR* gene copy number more than 2.47 had an objective response, whereas no tumor response was observed in patients with copy numbers below this ($P = 0.0009$; ref. 21). Similarly, an increased *EGFR* copy number was significantly associated with response to cetuximab therapy in patients with mCRC (22), although the relationship between EGFR

Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

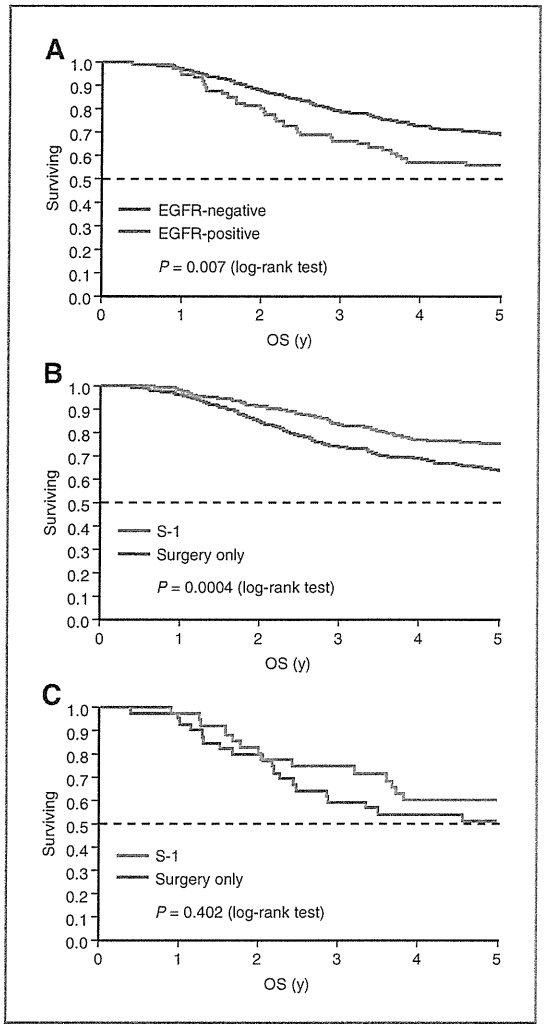

Figure 1. Kaplan–Meier curves for OS according to EGFR status. For EGFR, an IHC score of 3+ was defined as positive, and IHC scores of 0, 1+, and 2+ were defined as negative. A, OS for all patients ($n = 829$): EGFR-negative ($n = 754$) versus EGFR-positive ($n = 75$). B, OS for patients with EGFR-negative tumors: S-1 group ($n = 380$) versus surgery-only group ($n = 374$). C, OS for patients with EGFR-positive tumors: S-1 group ($n = 35$) versus surgery-only group ($n = 40$).

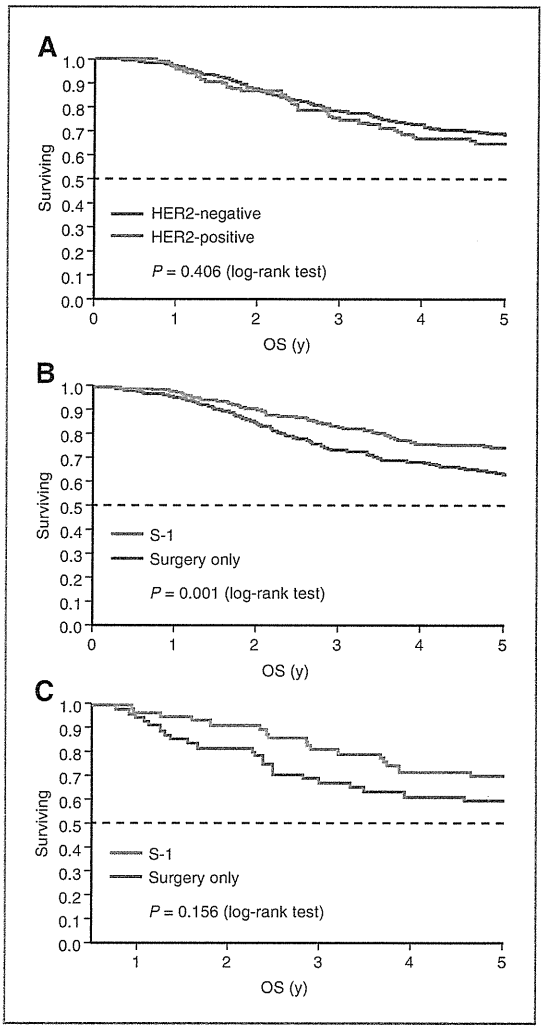

Figure 2. Kaplan–Meier curves for OS according to HER2 status. A, OS for all patients ($n = 829$): HER2-negative ($n = 716$) versus HER2-positive ($n = 113$). B, OS for patients with HER2-negative tumors: S-1 group ($n = 357$) versus surgery-only group ($n = 359$). C, OS for patients with HER2-positive tumors: S-1 group ($n = 58$) versus surgery-only group ($n = 55$).

overexpression on IHC and the response to cetuximab remains controversial (23).

Although *KRAS* mutation status is used as a negative predictive marker for EGFR-targeted agents in colorectal cancer, the frequency of *KRAS* mutations in gastric cancer seems to be relatively low (3%–21%; ref. 24). Several phase III trials of combined chemotherapy with EGFR-targeted agents, such as cetuximab, panitumumab, and lapatinib are ongoing in patients with unresectable advanced gastric cancer (10); detailed information on alterations of the EGFR protein or gene in these trials is needed to predict the response to anti-EGFR therapy in gastric cancer more accurately (19).

The frequency of EGFR overexpression on IHC in gastric carcinoma ranges from 2% to 30% (7, 8, 25). Possible reasons for this wide variation include differences in fixation techniques, antibodies, scoring systems, subjectivity of pathologist interpretation, and intratumoral staining heterogeneity. To improve the accuracy of assessing EGFR positivity, additional gene-amplification analysis might be useful, as conducted for HER2, and standardized EGFR testing procedures should be established.

The prevalence of HER2 overexpression on IHC in the present study fell within the previously reported range (median positive rate = 18%; range = 4%–53%; ref. 12).

Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

Table 3. Cox regression multivariate analysis of prognostic factors for OS in all patients

Factor	Group	Number of patients	5-year survival (%)	HR (95% CI)	*P* value
Arm	Surgery only	414	61.9	1	
	S-1	415	73.6	0.617 (0.481–0.790)	<0.001
Sex	Male	565	67.2	1	
	Female	264	69.0	0.988 (0.757–1.301)	0.932
Age, y	<60	318	69.5	1	
	60–69	310	72.2	1.242 (1.057–1.460)	
	70–80	201	58.4	1.544 (1.118–2.132)	0.009
Cancer stage (Japanese classification)	II	372	77.0	1	
	IIIa	321	63.7	1.683 (1.431–1.979)	
	IIIb	136	52.2	2.833 (2.048–3.918)	<0.001
Histologic type	Differentiated	332	65.1	1	
	Undifferentiated[a]	497	69.6	0.894 (0.684–1.171)	0.412
EGFR status	Negative	754	69.0	1	
	Positive	75	55.4	1.504 (1.020–2.149)	0.040
HER2 status	Negative	716	68.3	1	
	Positive	113	64.5	1.068 (0.736–1.514)	0.722

[a]Including 3 patients with gastric cancer categorized into neither differentiated nor undifferentiated type.

Consistent with the results of Begnami and colleagues (8), the concordance between IHC (scores 2+ and 3+) and dual-ISH (positive) was 62.9% in the present study; most IHC 3+ results corresponded with dual-ISH positive status (98.6%), whereas IHC 2+ tumors showed relatively low concordance between IHC score and dual-ISH status (37.6%). The present results are also in agreement with the finding that HER2 positivity is more prevalent among differentiated-type tumors than undifferentiated-type tumors (6, 8, 11). Consequently, we consider our present evaluation of HER2 status to be realistic.

The role of HER2 as a prognostic factor in gastric cancer remains controversial. A recent systematic review assessing the impact of HER2 overexpression on survival found that 20 studies (57%) reported no difference in OS, 2 (6%) showed significantly longer OS in patients with HER2 overexpression, and 13 (37%) found significantly worse OS in patients with HER2 overexpression (12). To the best of our knowledge, the present investigation is the first large biomarker study to evaluate the influence of HER2 positivity on the postoperative outcomes of patients with gastric cancer enrolled in a randomized phase III trial. Trastuzumab was not administered to these patients until the completion of the 5-year follow-up, because it had not been approved at that time. The present results therefore provide strong evidence that HER2 status does not influence outcomes after D2 dissection for locally advanced gastric cancer in East Asian patients, in contrast to breast cancer.

Although it is unclear why EGFR overexpression was a prognostic marker in this study and HER2 overexpression was not, it might be partially explained by the fact that gastric cancer is a heterogeneous disease. A recent study reported that patients with HER2-positive gastric tumors have longer OS than those with HER2-negative tumors. This finding was based on an analysis of 381 patients with metastatic gastric/gastroesophageal junction cancer. On subgroup analysis, similar differences in OS according to HER2 status were seen in the subgroup of patients with intestinal-type cancer but not in those with diffuse-type cancer (26). Because the subgroup of patients with intestinal-type cancer includes a higher proportion of HER2-positive cases than EGFR-positive cases, as shown in Table 2, the association between intestinal-type and good outcomes may mask potential prognostic effects of HER2 positivity. Further understanding of the molecular biologic and pathologic characteristics of gastric cancer is considered necessary to improve EGFR and HER2 targeting in this disease.

Neither EGFR nor HER2 was associated with the efficacy of S-1; this was not surprising because neither one is thought to have an appreciable impact on the metabolism or mechanism of action of S-1. In several preclinical studies on mice, the antitumor activity of S-1 combined with trastuzumab, lapatinib, or cetuximab was greater than that of either drug alone on xenografts of gastric cancer cells overexpressing HER2 or EGFR. This enhancement of activity was considered to be mediated by thymidylate synthase (27, 28). These experimental results suggest that S-1 combined with an EGFR- or HER2-targeted agent (or both) is a promising regimen for patients with EGFR/HER2-positive gastric cancer.

In conclusion, the current study provides compelling evidence that EGFR 3+ status, but not HER2 status, on IHC is significantly associated with worse patient outcomes after curative resection of stage II/III gastric cancer. Furthermore, there is no apparent interaction between S-1 and EGFR or HER2 status with respect to survival. We therefore propose

Published OnlineFirst September 12, 2012; DOI:10.1158/1078-0432.CCR-12-1318

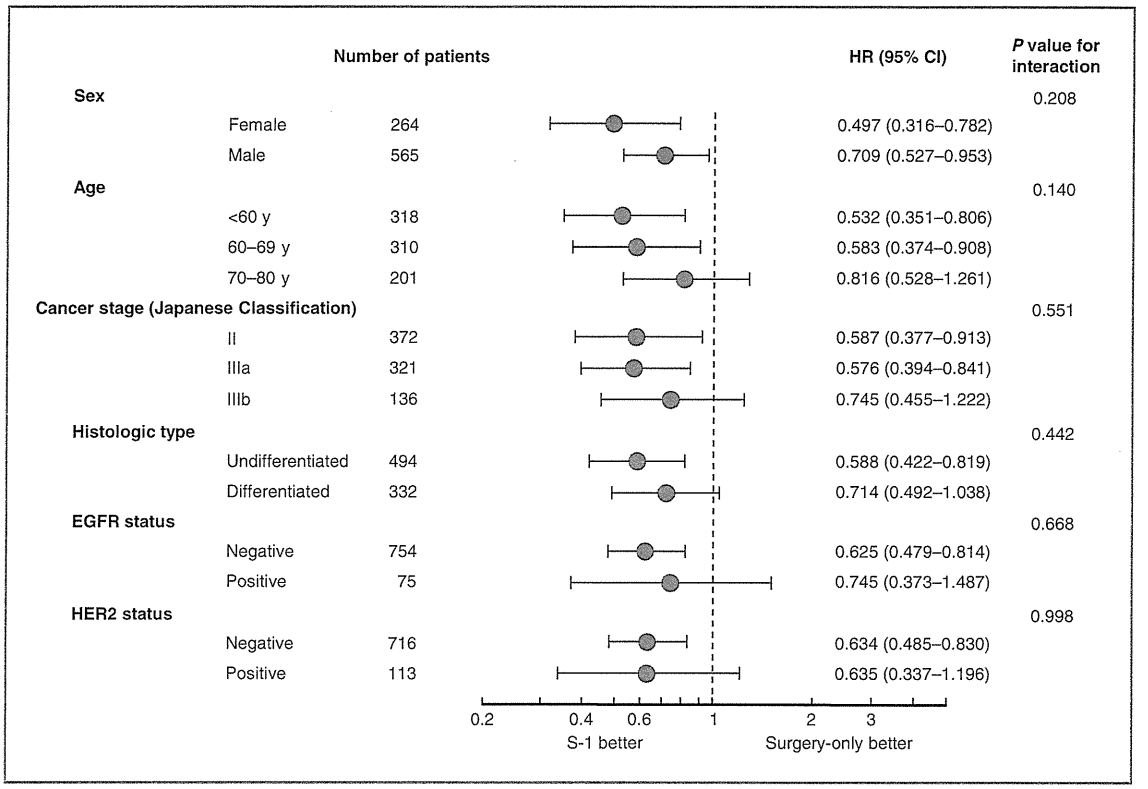

Figure 3. Subgroup analysis for OS. In the surgery-only group, cancers could not be classified as differentiated or undifferentiated in 3 patients.

that EGFR status should be evaluated in future clinical trials of EGFR-targeted agents. S-1 combined with EGFR/HER2-targeted agents merits further investigation in patients with gastric cancer.

Disclose of Potential Conflicts of Interest

A. Ochiai: commercial research grant, Taiho Pharmaceutical Co.; Ltd., other commercial research support, Chugai; and consultant/advisory board, Roche Diagnostic. W. Ichikawa: honoraria from speakers bureau, Taiho Pharmceutical Co., Ltd. H. Katai: commercial research grant and honoraria from speakers bureau, Taiho Pharmaceutical Co. Ltd. T. Sano: honoraria from speakers bureau, Taiho Pharmaceutical Co. Ltd. and Chugai Pharmaceutical. The funding source of this study had no role in the study design, data collection, data analysis, or interpretation.

Authors' Contributions

Conception and design: M. Terashima, K. Kitada, A. Ochiai, W. Ichikawa, M. Sasako
Development of methodology: A. Ochiai, M. Sasako
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K. Kitada, A. Ochiai, S. Sakuramoto, H. Katai, T. Sano, H. Imamura, M. Sasako
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M. Terashima, K. Kitada, A. Ochiai, W. Ichikawa, I. Kurahashi
Writing, review, and/or revision of the manuscript: M. Terashima, K. Kitada, W. Ichikawa, H. Katai, T. Sano, M. Sasako
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): K. Kitada, H. Katai, T. Sano, M. Sasako
Study supervision: M. Terashima, A. Ochiai

Acknowledgments

The authors dedicate this article to the memory of Prof. Tetsuro Kubota, who contributed to the conception and design of the study. The authors thank the patients and their families, and the investigators from the 65 institutions for their cooperation. The authors also thank Prof. J. Patrick Barron, Chairman of the Department of International Medical Communications, Tokyo Medical University (Tokyo, Japan), a remunerated consultant of Taiho Pharmaceutical Co., Ltd., for his review of this report.

Grant Support

This study was funded by Taiho Pharmaceutical Co., Ltd. (Tokyo, Japan).
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Received April 22, 2012; revised September 4, 2012; accepted September 4, 2012; published OnlineFirst September 12, 2012.

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World J Surg (2012) 36:2637–2643
DOI 10.1007/s00268-012-1721-y

World Journal of Surgery

Survival Benefit of Palliative Gastrectomy in Gastric Cancer Patients with Peritoneal Metastasis

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Published online: 21 July 2012

Abstract
Background The survival benefit of palliative gastrectomy in patients with peritoneal metastasis as a single incurable factor remains unclear.
Methods A total of 148 gastric cancer patients with peritoneal metastasis underwent gastrectomy or chemotherapy at the Shizuoka Cancer Center between September 2002 and December 2008 and were included in this study. The effects of gastrectomy and chemotherapy on their long-term outcome were investigated. Multivariate analysis was also performed to identify independent prognostic factors.
Results Gastrectomy was performed in 82 patients and subsequent chemotherapy was administered to 55. Chemotherapy was selected as an initial treatment for 66 patients. Median survival time (MST) was identical between patients with and without gastrectomy (13.1 vs. 12.0 months; $P = 0.410$). Conversely, MST was significantly longer in patients who received chemotherapy (13.7 months) than those who did not (7.1 months; $P = 0.048$). According to the results of multivariate analysis, chemotherapy (hazards ratio [HR] = 0.476; 95 % CI = 0.288–0.787) was selected as an independent prognostic factor, while gastrectomy was not.
Conclusions The results of the present study did not show a survival benefit of palliative gastrectomy in selected patients with peritoneal metastasis. Instead, chemotherapy has to be considered as an initial treatment for these patients.

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Introduction

Gastric cancer is diagnosed frequently and is the second leading cause of cancer-related deaths in Japan [1]. Although the long-term outcome of early gastric cancer is good, that of advanced gastric cancer is dismal, particularly when combined with other incurable factors [2–4]. Recent advances in chemotherapy have improved the survival rate of gastric cancer patients with incurable factors. However, survival rates remain limited and there is still room for improvement in the survival rate [5, 6].

The incurable factors observed frequently in patients with advanced gastric cancer are peritoneal, liver, and distant lymph node metastases [7, 8]. Better survival rates were reported in Japan following gastrectomy plus metastasectomy if the incurable factors were liver or para-aortic lymph node metastases and if the surgery was curative [9–12]. In contrast, curative resections are difficult in patients with widespread peritoneal metastasis, which is the most frequently observed incurable factor [13–16]. Although a few surgeons have reported the efficacy of performing a peritonectomy, this concept has not been accepted widely, even in Japan [17].

Previously, a number of authors investigated the feasibility of palliative gastrectomy in patients with incurable factors [14, 18–24]. However, each study included patients with a range of incurable factors; therefore, the effect of gastrectomy in selected patients with peritoneal metastasis remains unclear. The aim of the present study was to clarify the effects of gastrectomy on gastric cancer patients

with peritoneal metastasis. The appropriate treatment strategy in patients with localized peritoneal metastasis was also investigated.

Materials and methods

Patients

Between September 2002 and December 2008, 279 gastric cancer patients with peritoneal metastasis underwent gastrectomy or chemotherapy at the Shizuoka Cancer Center, Japan. Of these, 131 patients had incurable factors other than peritoneal metastasis so the remaining 148 patients with no other obvious incurable factors were included in this study. Pathological examination of biopsy specimens from the stomach revealed adenocarcinoma in all patients. Patients who had received any previous treatment for gastric cancer were not included in the present study. Peritoneal metastasis was diagnosed histopathologically in patients who underwent laparotomy (106 patients) or was diagnosed clinically using computed tomography in patients who did not undergo laparotomy (42 patients).

The patients' characteristics and surgical and pathological findings were collected retrospectively from our prospectively recorded database and individual patient records. The patients' clinicopathological characteristics were analyzed, and survival curves were compared according to the treatment modalities administered (gastrectomy and chemotherapy). Multivariate analysis was also conducted to identify independent prognostic factors.

This study followed ethical guidelines for human subjects and was approved by the institutional review board of the Shizuoka Cancer Center.

Pretreatment examinations

Computed tomography (CT) with contrast medium was performed as a routine pretreatment examination in all patients except those with poor renal function or with an allergy to the contrast medium. Patients were regarded as having clinically evident peritoneal metastasis (cP+) if the CT findings showed obvious peritoneal metastasis which included massive ascites, cirrhosal implants of the intra-abdominal area or on the small or large bowel, remarkably increased visceral fat density, and omental metastasis. If CT did not show any obvious peritoneal metastasis, patients were regarded as not having clinically evident peritoneal metastasis (cP−).

Macroscopic type was classified according to the Japanese Gastric Cancer Association (JGCA) classification system [25]. Histological type was also classified according to the JGCA classification system, in which tubular and papillary adenocarcinoma are defined as differentiated adenocarcinoma, while poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous adenocarcinoma are defined as undifferentiated adenocarcinoma.

The degree of peritoneal metastasis was classified in patients who underwent laparotomy as follows: P0, no implants to the peritoneum; P1, cancerous implants to the region directly adjacent to the stomach peritoneum (above the transverse colon), including the greater omentum; P2, several scattered metastases to the distant peritoneum and ovarian metastasis alone; and P3, numerous metastases to the distant peritoneum [26].

Indications for gastrectomy

In patients with P1, gastrectomy was performed if macroscopic curative resection was expected. Gastrectomy was also selected as an initial treatment in patients with tumor-associated symptoms such as bleeding or gastric outlet obstruction even if curative resection could not be expected. If patients had P2 or P3 peritoneal metastasis and they did not have tumor-associated symptoms, gastrectomy would not be performed in principle.

Statistics

All continuous data are presented as the median (range). Survival rates were calculated using the Kaplan–Meier method, and the log-rank test was used to compare the groups. In this study, overall survival time was defined as time from initial treatment (surgery or chemotherapy) to any death, including noncancer-related death.

Independent prognostic factors were identified using the Cox proportional hazards model. In the analysis, each patient's age (<60 or ≥ 60 years old), sex, clinically evident peritoneal metastasis (cP− or cP+), gastrectomy (performed or not performed), chemotherapy (received or not received), Eastern Cooperative Oncology Group (ECOG) performance status (0, 1 or 2, 3), macroscopic type (type 4 or other), and histology (differentiated or undifferentiated) were included as covariates. The Bonferroni test was used during multiple comparisons. A P value <0.05 was considered significant. All statistical analyses were conducted using *R* version 2.13.1.

Results

The patient characteristics are indicated in Table 1. Macroscopic type 3 tumors were observed in 43 % of the patients and type 4 tumors were observed in 39 %. Tumors were undifferentiated in three-fourths of the patients. The pretreatment ECOG performance status was generally good

(≤1) and was 2 or higher in 10 % of patients. Gastrectomy was performed in 82 patients and subsequent chemotherapy was administered to 55 of these patients. Chemotherapy was selected as an initial treatment in 66 patients. We also compared the background data between patients according to the treatment provided. There were no differences between any two groups with respect to sex, ECOG performance status, histology, and macroscopic type. The median age was significantly different between the groups, with patients who received gastrectomy only the oldest followed by patients who received both gastrectomy and chemotherapy. The incidence of clinically evident peritoneal metastasis was significantly higher in patients who underwent chemotherapy only than in those who underwent gastrectomy only or both gastrectomy and chemotherapy.

Table 2 lists the treatments provided. Of the 82 patients who underwent gastrectomy, total gastrectomy was performed more frequently (67 %) than distal gastrectomy (33 %). S1-based chemotherapy was the most frequently selected treatment regimen in this study. Of 121 patients who received chemotherapy, second-line chemotherapy was given in 64 % of patients and third-line chemotherapy was administered in 35 % of patients.

Figure 1 shows the overall survival curve of all patients. Of the 148 patients, 137 were followed until their death. Median follow-up period of survivors was 29.7 months. One-year and three-year overall survival rates were 53.9 and 18.1 %, respectively. Figure 2a shows the overall survival curves of patients with and without gastrectomy. The median survival time (MST) of patients with gastrectomy was 13.1 months ($n = 82$) and that without gastrectomy was 12.0 months ($n = 66$; $P = 0.410$). Overall survival curves of patients who did or did not receive chemotherapy are shown in Fig. 2b. MST was significantly longer in patients who received chemotherapy (13.7 months; $n = 121$) than in those who did not (7.1 months; $n = 27$; $P = 0.048$).

Table 3 shows the results of the Cox proportional hazards model. Chemotherapy [hazards ratio (HR) = 0.476; 95 % CI = 0.288–0.787], ECOG performance status 0 or 1(HR = 0.278; 95 % CI = 0.156–0.495), and macroscopic tumor types other than type 4 (HR = 0.566; 95 % CI = 0.377–0.848) were selected as independent prognostic factors, while gastrectomy was not selected.

Table 1 Patient characteristics

		Gastrectomy	Chemotherapy	Gastrectomy + chemotherapy
Number (*n*)	148	27	66	55
Age (years)[a]	65 (20–85)	77 (53–85)	60 (20–77)	67 (34–76)
Sex (*n*)				
Male	90	18	36	36
Female	58	9	30	19
Performance status (*n*)				
0 or 1	133	23	58	52
2 or 3	15	4	8	3
Histology (*n*)				
Differentiated	36	7	20	9
Undifferentiated	112	20	46	46
Macroscopic type (*n*)				
≠type 4	90	19	35	36
type 4	58	8	31	19
Clinically evident peritoneal metastasis[b]				
Yes (cP+)	62	2	51	9
No (cP)	86	25	15	46
Gastrectomy (*n*)				
Yes	82	27	0	55
No	66	0	66	0
Chemotherapy (*n*)				
Yes	121	0	66	55
No	27	27	0	0

[a] The differences between each group are statistically significant ($P < 0.0167$ between any two groups)

[b] The difference is statistically significant between patients who underwent chemotherapy and those who underwent gastrectomy. It is also statistically significant between patients who underwent chemotherapy and those who underwent gastrectomy + chemotherapy

Table 2 Treatments provided

Gastrectomy	82
Total gastrectomy	55
Distal gastrectomy	27
Chemotherapy	121
5-FU	8
S1	43
S1/CDDP	27
MTX/5-FU	28
CPT11/CDDP	5
Others	10
Number of regimens administered	
1st line	44
2nd line	35
3rd line	24
4th line	16
5th line	1
6th line	1

FU fluorouracil, *CDDP* cisplatin, *MTX* methotrexate, CPT11 irinotecan

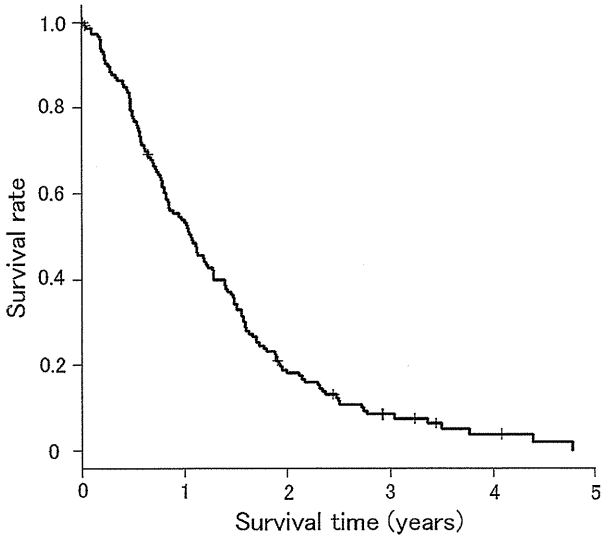

Fig. 1 Survival curves of patients included in this study. MST is 390 days. One- and three-year survival rates are 53.9 and 18.1 %, respectively

Investigation of 40 patients with localized peritoneal metastasis (P1)

The degree of peritoneal metastasis was confirmed by laparotomy in 106 of the 148 patients: it was P1 in 40 patients, P2 in 12 patients, and P3 in 54 patients. Survival analysis was conducted in 40 patients with P1 peritoneal metastasis. R0 resection according to 6th edition of the TNM classification was performed in 18 patients and the MST for these patients (26.4 months) was longer than that of the 16 patients who underwent R1 or R2 gastrectomy (Fig. 3, 12.3 months; $P < 0.001$) [27].

Discussion

Recent advances in chemotherapy regimens have improved the survival rates of gastric cancer patients with incurable factors. Koizumi et al. [5] reported an MST of 13 months in patients with advanced gastric cancer who were treated with S1 and cisplatin, and Bang et al. [6] reported a 13.8 month median overall survival time in patients with HER2-positive advanced gastric cancer who were treated with trastuzumab plus chemotherapy. However, to date, the effects of chemotherapy are limited and the 5 year survival rate of patients with unresectable gastric cancer remains grim [5, 6].

The feasibility of palliative gastrectomy in patients with unresectable gastric cancer is under debate [14, 18–24]. Many studies have examined a variety of patients with gastric cancer; however, the type and the number of incurable factors differed among patients. To the best of our knowledge, the present study is the first report that investigates a similar group of patients who all had peritoneal metastasis but did not have other obvious incurable factors. Therefore, we were able to identify the appropriate treatment strategy for patients with peritoneal metastasis with less bias than the previous studies.

The present study showed that there was no survival benefit associated with palliative gastrectomy. Instead, we recommend chemotherapy, as long as patients do not have tumor-associated symptoms. Sarela et al. [13, 14], and Kahlke et al. [20] also did not recommend palliative gastrectomy if patients did not have tumor-associated symptoms because it did not affect the patient's survival time. In contrast, Kim et al. [19] and Li et al. [23] recommended palliative gastrectomy, and Lin et al. [28] recommended palliative gastrectomy with subsequent chemotherapy to improve the survival rate of patients.

Multivariate analysis identified pretreatment ECOG performance status, macroscopic tumor type, and chemotherapy as independent prognostic factors. Macroscopic tumor type 4 is a widely accepted prognostic factor, and the incidence of peritoneal metastasis associated with type 4 tumors is higher than with other macroscopic tumor types [3, 4, 22]. Poor ECOG performance status is also a well-known independent prognostic factor in advanced malignancies [13, 16, 20]. Sarela et al. [13] reported that poor ECOG performance status is an independent prognostic factor in patients with peritoneal metastasis, as found in our study.

We also investigated the efficacy of R0 surgery in patients with localized peritoneal metastasis and found that

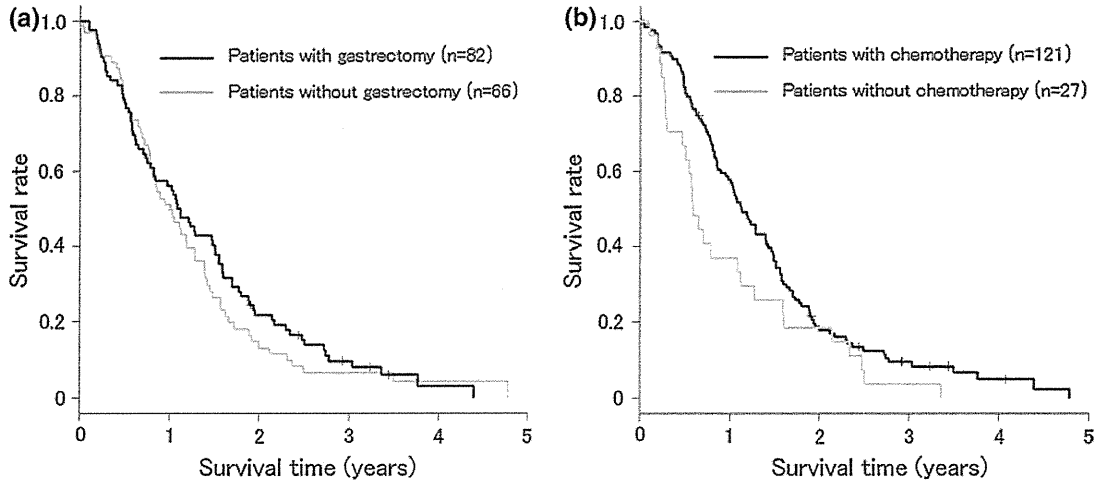

Fig. 2 **a** Survival curves of patients with or without gastrectomy. There is no difference in MST between patients with gastrectomy (13.1 months; $n = 82$) and those without gastrectomy (12.0 months; $n = 66$; $P = 0.410$). **b** Survival curves of patients who received or did not receive chemotherapy. MST was significantly longer for patients who received chemotherapy (13.7 months; $n = 121$) than for those who did not (7.1 months; $n = 27$; $P = 0.048$)

Table 3 Results of multivariate analysis

Covariates	*P* value	Hazard ratio (HR)	95 % CI
Age (<60 years vs. ≥60 years)	0.830	1.045	0.700–1.559
Sex (male vs. female)	0.516	0.879	0.596–1.297
cP (cP− vs. cP+)	0.122	0.681	0.419–1.108
Gastrectomy (yes vs. no)	0.897	1.031	0.646–1.647
Chemotherapy (yes vs. no)	0.004	0.476	0.288–0.787
ECOG performance status (0,1 vs. 2,3)	<0.001	0.278	0.156–0.495
Macroscopic type (≠type 4 vs. type 4)	0.006	0.566	0.377–0.848
Histology (differentiated vs. undifferentiated)	0.290	0.466	0.454–1.256

ECOG Eastern Cooperative Oncology Group

the survival rate was better in patients who were able to undergo curative resection than those who were not. Ouchi et al. [18] segregated patients according to the degree of peritoneal metastasis (P1 vs. P2 or P3) because they believed that the tumor load must also be taken into account. Moreover, Hioki et al. [29] reported a better outcome in patients with localized peritoneal metastasis following gastrectomy than in those with widespread peritoneal metastasis, and emphasized that patients with a good performance status and localized peritoneal metastasis should be considered appropriate surgical candidates. Based on the results from these reports it may be plausible to distinguish whether patients have localized or widespread peritoneal metastases in order to establish the appropriate treatment strategy for these patients.

However, it has been reported that the accuracy of computed tomography for diagnosing peritoneal metastasis is limited, and the degree of peritoneal metastasis would not be diagnosed without laparotomy [30]. Recently, the feasibility of diagnostic laparoscopy, which is less invasive than laparotomy and more sensitive for finding peritoneal metastasis than computed tomography, was reported [31, 32]. In our institute, we also perform this procedure in patients in whom a high incidence of peritoneal metastasis was estimated. However, we began diagnostic laparoscopy in the middle of 2008 so most of the patients in the present series did not receive diagnostic laparoscopy before treatment.

There are limitations associated with this retrospective study. These include a possible bias in the selection of treatment strategies, including chemotherapeutic regimens and indication for gastrectomy, and the possibility that patient backgrounds differ between groups. In fact, patient age and the incidence of clinically evident peritoneal metastasis were different between groups. Therefore, we conducted multivariate analysis including these factors as covariates. To overcome these problems and to obtain conclusive results, a well-designed prospective trial is necessary. Groups in Japan and Korea are currently collaborating on an international randomized controlled trial

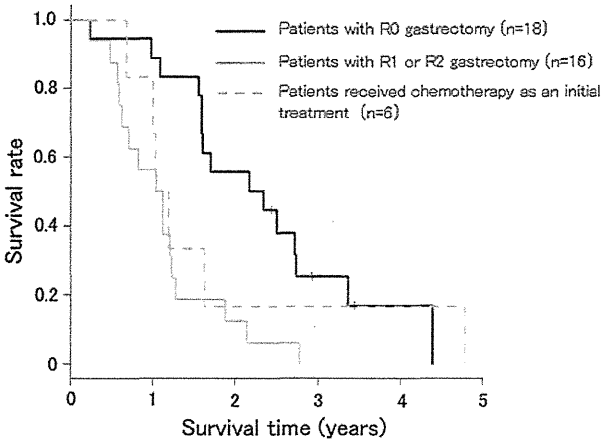

Fig. 3 Survival curves of 40 patients with localized peritoneal metastasis confirmed by laparotomy. MST was significantly longer in 18 patients who underwent R0 gastrectomy (26.4 months) than in 16 patients who underwent R1 or R2 gastrectomy (12.3 months; $P < 0.001$). MST for 18 patients with R0 gastrectomy was also longer than that for six patients who received chemotherapy as an initial treatment (12.5 months), although this was not statistically significant ($P = 0.414$)

investigating the efficacy of gastrectomy in gastric cancer patients with a single incurable factor. Therefore, we must await the results of this study, although the patients being investigated in the prospective study are not identical to those included in the present study [33].

In the present study, we used overall survival to evaluate the efficacy of each treatment. We could not evaluate patient quality of life after treatment, the burden of care, and cost because it was difficult to collect these data retrospectively. However, these factors should also be taken into account, particularly in patients with incurable disease [34]. If poor quality of life and increased burden of care were observed in patients who had undergone gastrectomy, they would further reinforce the arguments against gastrectomy in patients having peritoneal metastasis.

In conclusion, the results of the present study did not show a survival benefit with palliative gastrectomy in patients with peritoneal metastasis. Instead, chemotherapy has to be considered an initial treatment for these patients. We still have to await the result of randomized controlled trial being performed in the East to address this specific issue.

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