Significance of Surgical Treatment of Liver Metastases from Gastric Cancer

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Abstract. *Background/Aim: The optimal treatment of liver metastases from gastric cancer (LMGC) remains uncertain. We retrospectively compared surgical treatment with chemotherapy alone and identified prognostic determinants. Patients and Methods: We reviewed the records of 50 consecutive patients with LMGC: 25 patients with gastrectomy plus hepatic resection (group A), 13 patients with palliative gastrectomy (group B), and 12 patients with chemotherapy alone (group C). We compared the overall survival among these three groups, and assessed prognostic factors. Results: Median survival time in groups A, B, and C was 33.4, 10.5, and 8.7 months, respectively. Univariate analysis found T stage, number of liver metastases, and treatment group to be significant prognostic factors. In the multivariate analysis, T stage was shown to be an independent prognostic determinant, while gastrectomy plus hepatic resection was of marginal significance compared with chemotherapy alone. Conclusion: T Stage was a significant prognostic determinant, and gastrectomy plus hepatic resection could be a promising treatment for patients with LMGC.*

Liver metastases from gastric cancer (LMGC) occur in approximately 3.5 to 14% of patients with primary gastric cancer (1-16). Chemotherapy is the most common treatment option for LMGC, since surgical treatment is rarely indicated due to the presence of numerous liver metastases and/or extrahepatic disease, such as peritoneal dissemination and extensive lymph node metastasis. Although chemotherapy for metastatic gastric cancer has recently evolved, the prognosis of patients with LMGC is still disappointing, with a median survival time (MST) of approximately 12 months and a 3-year survival rate of around 5% (17) when treated with chemotherapy alone.

Although palliative gastrectomy was reported to be prognostically beneficial for selected patients with a single non-curative factor including LMGC (18), the efficacy of palliative gastrectomy in patients with liver-only metastases remains uncertain. However, this might be clarified by the results of an ongoing prospective randomized controlled trial investigating the role of palliative gastrectomy for patients with advanced gastric cancer (AGC) with a single non-curative factor (19).

On the other hand, complete resection of the primary gastric tumor and LMGC has resulted in MST of approximately 23 months and a 5-year survival rate of 11-42% (1-16). Hepatic resection provides a potential opportunity for cure, although the complete resection rate for LMGC has been reported to be approximately 20% due to frequently associated peritoneal dissemination or advanced lymph node metastasis.

No standard treatment has yet been established for patients with LMGC, partly because there has only been one report (1) concurrently comparing the three treatment options, and partly because of the variability in patients' background non-curative factors in the literature (1–16). Therefore, in this study, we retrospectively compared these three treatment options and identified prognostic determinants through univariate and multivariate analyses for patients with LMGC as the sole non-curative factor that is considered crucial for better survival (18, 19).

Patients and Methods

Patient inclusion criteria. We retrospectively reviewed the records of 50 consecutive patients with LMGC treated at Osaka National Hospital between January 1, 1995 and December 31, 2009. In this study, patients diagnosed with synchronous or metachronous liver metastasis as a single non-curative factor were included. Those who met any of the following criteria were excluded: (i) any other non-curative factor except for liver metastasis, such as T4 tumor (tumor infiltrating to adjacent organs), para-aortic lymph node metastasis,

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Key Words: Gastric cancer, liver metastasis, hepatic resection, gastrectomy, chemotherapy, prognostic factor.

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Table I. *Patient characteristics.*

	Group A (n=25)	Group B (n=13)	Group C (n=12)	*P*-value
Male/female	23/2	11/2	11/1	0.77
Age (years), median (range)	72 (47-80)	70 (49-78)	67 (54-80)	0.71
Primary tumor				
Intestinal/diffuse	17/8	9/4	7/5	0.81
T Stage: 1/2/3	1/7/17	0/0/13	0/2/10	0.08
N Stage: 0/1/2	7/7/11	2/6/5	4/5/3	0.62
Liver metastasis				
Synchrounous/metachronous	16/9	13/0	12/0	<0.01
Unilobar/bilobar	20/5	4/9	1/11	<0.01
Solitary/multiple	18/7	1/12	1/11	<0.01
Diameter (mm), median (range)	20 (5-98)	20 (10-57)	40 (20-100)	0.02

peritoneal dissemination, positive abdominal lavage cytology, or distant metastasis; (ii) *linitis plastica*; (iii) other concurrently active malignancy; (iv) Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 2 or more at initial diagnosis; and (v) any prior chemotherapy or radiation therapy.

Data collection. Data collected retrospectively include patient characteristics, such as age and gender, pathological characteristic of the primary gastric cancer, clinicopathological characteristics of metastasis, and treatment modality used. The histology of the primary gastric cancer was based on the Lauren classification. T and N stage were classified according to the Japanese Classification of Gastric Carcinoma (20). Clinicopathological characteristics of liver metastasis included timing of emergence, intrahepatic distribution, number of nodules, and maximum diameter of each nodule.

Survival analysis. The therapeutic course of each patient was censored at death or on February 11, 2010. Twelve patients in the gastrectomy plus hepatic resection (group A, n=25), two patients in the palliative gastrectomy (group B, n=13), and three patients in chemotherapy alone (group C, n=12) were alive on February 11, 2010, and treated as censored cases for survival analyses. Overall survival (OS) was defined as the time from the date of diagnosis of liver metastasis to the date of death from any cause or the last follow-up, and was compared among the three treatment options. Univariate analysis was used to assess the association between each clinicopathological factor and OS. A multivariate analysis was performed to identify variables independently associated with OS.

Statistical analysis. With regard to the associations between treatment options and clinicopathological characteristics, the chi-square test was used for categorical variables, and Student's *t*-test or the Wilcoxon test was used for continuous variables as appropriate. OS curves were estimated by the Kaplan–Meier method and compared using the log-rank test. Multivariate Cox's regression analyses were performed to identify prognostic factors for survival by adjusting potential confounding factors. Variables achieving a *p*-value less than 0.05 in the univariate analysis were subsequently introduced into the multivariate analysis. All statistical analyses were performed with JMP software, version 8.0 (SAS Institute, Cary, NC, USA). *P*-values less than 0.05 were considered statistically significant, and all tests were two-sided.

Results

Patient characteristics. The clinicopathological characteristics of the 50 patients are presented in Table I. There were 45 males and 5 females with a median age of 70 (range 47-80) years. These 50 patients were categorized into three groups according to the treatment modality performed. Twenty-five patients in group A underwent complete resection of both the primary gastric cancer and liver metastasis with D2 lymphadenectomy, and 13 patients in group B received D1 gastrectomy with liver metastasis untouched, while 12 patients in group C underwent chemotherapy alone without any surgical intervention. Histologically, approximately two-thirds of the patients had intestinal-type adenocarcinoma and one-third had diffuse-type adenocarcinoma. Most patients had an advanced primary cancer of T3 or deeper, with positive lymph node metastases. There were clear imbalances among the groups with respect to clinicopathological features of liver metastasis. Metachronous metastasis was observed only in group A. The median disease-free interval from primary surgery to the detection of metachronous liver metastasis was 645 (range 240-1682) days. Both unilobar metastasis and solitary metastasis were also more frequent in group A than in groups B and C ($p<0.01$). The maximum tumor diameter was significantly higher in group C than in groups A and B ($p=0.02$). In group A, 10 out of 25 patients received adjuvant chemotherapy, however, this treatment had no impact on OS (data not shown). After hepatectomy, relapse of disease was found in 18 patients, with a median recurrence-free interval of 154 days, involving the remnant liver in 15 patients, lymph nodes in 2 patients, and pleura in 1 patient.

Prognostic factors. The MST ranged from 33.4 months in group A to 8.7 months in group C. The 1-, 3-, and 5-year survival rates were 73.9%, 42.8%, and 36.7% in group A; 46.2%, 23.1%, and 15.4% in group B; and 36.7%, 12.2%, and 0% in group C, respectively. OS in group A was

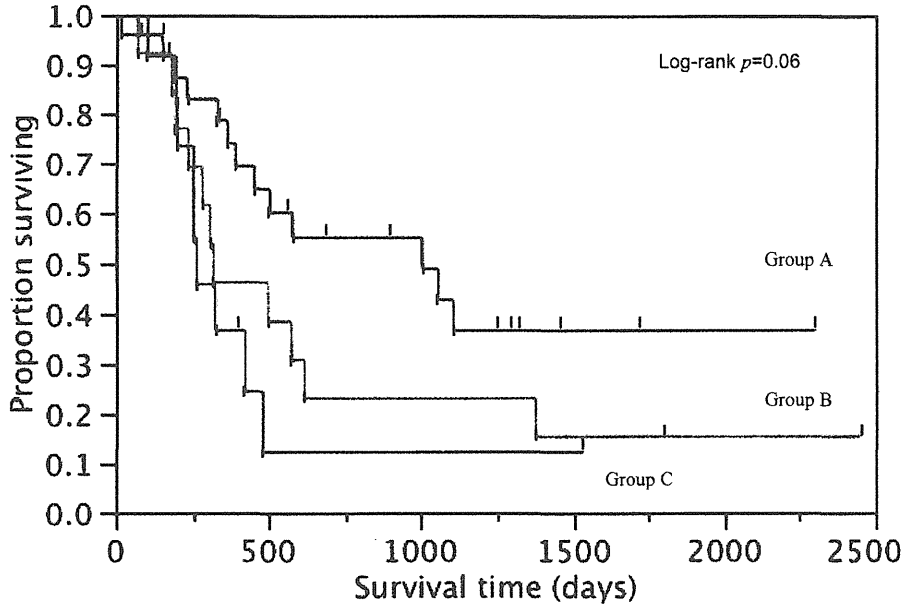

Figure 1. *Overall survival by treatment modality.*

significantly longer than in group C (p=0.04), whereas there was no significant difference in OS between groups A and B (p=0.12), nor B and C (p=0.50), as shown in Figure 1. Hazard ratios (HRs) for death, compared with group A, were 1.93 (95% confidence interval (CI): 0.84-4.33) in group B, and 2.65 (95% CI: 1.07-6.29) in group C. Univariate analysis revealed that T stage, number of liver metastases, and treatment group (group A *versus* group C) were significant prognostic factors, as shown in Table II. T Stage of the primary gastric cancer was the only independent prognostic determinant after adjustment for other factors in the multivariate analysis (HR=13.9; 95% CI=2.8-251.7), as shown in Table III. Treatment modality was not a significant prognostic factor, although gastrectomy plus hepatic resection was of a marginal significance (HR=2.8; 95% CI=0.93-9.26) when compared with chemotherapy alone (group A *versus* group C).

Discussion

The incidence of LMGC has been reported to be approximately 3.5-14% (1-16). Systemic chemotherapy is the most common treatment for LMGC, but it fails to achieve satisfactory outcomes (17, 21). Although the efficacy of surgical treatment for LMGC remains uncertain, palliative gastrectomy might be prognostically beneficial for patients with liver-only metastasis (18, 22). Furthermore, complete resection of both the primary gastric tumor and the LMGC results in MST of approximately 23 months, and a 5-year survival rate of approximately 25% (1-16), although surgical resection of hepatic nodules is rarely indicated due to the presence of extrahepatic non-curative factors, such as peritoneal dissemination and extensive lymph node metastasis. However, these three treatment options have rarely been compared in patients with LMGC as a single non-curative factor.

As summarized in Table IV, there are only retrospective studies in the literature on the efficacy of hepatic resection for LMGC (1-16). In those reports, the number of patients receiving hepatic resection was limited, ranging from 10 to 40, consistent with the rare situation when complete resection of LMGC is indicated. In this study, 25 patients underwent hepatic resection, and our study ranks sixth in terms of sample size as shown in Table IV. Most of the previous studies evaluated the efficacy of hepatic resection alone, while different treatment options were simultaneously compared with hepatic resection in only three studies (1, 15, 16). Okuyama *et al.* (1) compared three different treatment options, hepatic resection plus curative gastrectomy *versus* palliative gastrectomy *versus* chemotherapy alone, as we have done here. However, in contrast to our study, they included patients with non-curative factors other than liver metastasis, which could affect the outcomes of hepatic resection. The remaining two studies (15, 16) compared hepatic resection with palliative gastrectomy. To the best of our knowledge, ours is the first study in which three different treatment options were compared in a head-to-head manner for patients with liver-only metastasis from gastric cancer.

Table II. *Univariate analysis of prognostic factors for overall survival.*

	No. of patients	MST (months)	Survival rate			HR (95% CI)	*P*-value
			1-Year	3-Year	5-Year		
Gender							0.74
Male	45	15.0	56.8	30.7	23.7	1	
Female	5	19.1	66.7	33.3	NA	0.79 (0.13-2.62)	
Age, years							0.83
<70	25	16.0	58.4	30.3	19.0	1	
>70	25	14.0	57.1	31.7	31.7	1.04 (0.50-2.39)	
Histological type							0.92
Intestinal	33	16.5	62.5	28.1	NA	1	
Diffuse	17	12.0	47.8	39.8	39.8	1.04 (0.50-2.39)	
T Stage							<0.01
1, 2	10	NA	100.0	83.3	83.3	1	
3, 4	40	12.0	47.6	20.6	13.2	12.7 (2.73-226.42)	
N Stage							0.34
0, 1	31	16.0	56.8	36.4	30.3	1	
2, 3	19	14.0	59.4	20.8	NA	1.41 (0.69-2.81)	
Timing							0.15
Synchrounous	9	35.1	100	42.9	28.6	1	
Metachronous	41	12.0	48.9	29.5	23.6	1.92 (0.80-5.68)	
Distribution							0.05
Unilobar	25	35.1	72.6	39.3	26.2	1	
Bilobar	25	10.2	44.0	22.0	17.6	2.00 (1.00-4.14)	
Number							0.03
Solitary	20	36.8	70.8	50.1	41.7	1	
Multiple	30	10.8	50.0	19.2	15.4	2.27 (1.09-5.19)	
Size							0.35
<50	38	16.7	59.5	35.6	25.6	1	
>50	12	12.9	50.5	13.4	NA	1.49 (0.62-3.19)	
Treatment group							
A	25	33.4	73.9	42.8	36.7	1	
B	13	10.5	46.2	23.1	15.4	1.93 (0.84-4.33)	0.12
C	12	8.7	36.7	12.2	NA	2.65 (1.07-6.29)	0.04

MST: Median survival time; HR: hazard ratio; CI: confidence interval.

Previous studies demonstrated an MST of 8.8–34 months and a 5-year survival rate of 0-42% after hepatic resection, as shown in Table IV. In the present study, a relatively favorable MST of 33.4 months and a 5-year survival rate of 36.7% were obtained after hepatic resection. The wide difference in OS among studies is partly due to patient selection bias with small sample sizes, although most of the studies adopted liver-only metastasis as a common indication for hepatic resection.

To date, various prognostic factors have been proposed. As shown in Table IV, the number of liver metastases was found to be a significant prognostic factor in five reports, timing of liver metastasis (synchronous or metachronous), lymphatic and venous invasion and T stage of primary gastric cancer in two reports; and intrahepatic distribution of liver metastases, size of hepatic nodules, tumor differentiation, and negative surgical margins in the liver specimen, each in one report with univariate or multivariate analyses. In accordance with these findings, the number of liver metastases and T stage of the primary gastric tumor were significant prognostic factors found in the univariate analysis of this study. In addition, when incorporating treatment modality into the multivariate analysis, hepatic resection was shown to be independently associated with

Table III. *Multivariate analysis of prognostic factors for overall survival.*

Variable	HR	95% CI	*P*-value
T Stage (3, 4 vs. 1, 2)	13.90	2.82-251.70	<0.01
Multiple vs. solitary	1.09	0.37-3.09	0.88
Treatment, B vs. A	1.18	0.43-3.44	0.75
Treatment, C *vs.* A	2.83	0.93-9.26	0.07

HR: Hazard ratio, CI: confidence interval.

Table IV. *Summary of survival outcomes and prognostic indicators for patients undergoing hepatic resection for liver metastasis from gastric cancer.*

First author (ref)	Year	No. of pts. with liver metastasis	No. of pts who underwent hepatic resection	Median survival time (months)	Survival after resection			Prognostic factors	
					1-Year	3-Year	5-Year	Univariate	Multivariate
Okuyama *et al.* (1)	1985	9	9	24	NA	NA	NA		NA
Ochiai *et al.* (2)	1994	21	21	19	NA	NA	NA	T stage, ly, v	NA
Miyazaki *et al.* (3)	1997	21	21	NA	NA	NA	NA	Number, surgical margin	NA
Elias *et al.* (4)	1998	11	11	NA	90	35	NA	NA	NA
Ambiru *et al.* (5)	2001	40	40	12	NA	NA	18	Timing, surgical margin	Timing
Imamura *et al.* (6)	2001	17	17	NA	47	22	0	NA	NA
Saiura *et al.* (7)	2002	10	10	25	50	30	20	NA	NA
Okano *et al.* (8)	2002	90	19	21	77	34	34	Number, differentiation, timing, fibrous pseudocapsule	NA
Zackerl *et al.* (9)	2002	NA	15	8.8	35.7	14.3	0	None	NA
Sakamoto *et al.* (10)	2002	228	22	21	73	38	38	Number, distribution	Number
Shirabe *et al.* (11)	2003	NA	36	NA	64	26	26	ly, v, N stage, number	Ly, v, number
Roh *et al.* (12)	2005	NA	11	19	72.7	NA	27.3	NA	
Sakamoto *et al.* (13)	2007	182	37	31	NA	NA	11	Distribution, v, tumor size	Distribution, tumor size
Koga *et al.* (14)	2007	247	42	34	76	48	42	Number	Number, serosal invasion
Cheon *et al.* (15)	2008	1013	41	17.9	75.3	31.7	20.8	NA	None
Makino *et al.* (16)	2010	63	16	16.0	82.3	46.4	37.1	Stage, distribution, number, hepatic resection, chemotherapy,	Hepatic resection

ly, Lymphatic invasion; v, venous invasion; number, number of liver metastasis; distribution, hepatic distribution; timing, timing of metastasis (synchronous or metachronous); NA, not applicable; pts, patients.

longer survival by Makino *et al.* (16), which is consistent with our findings that gastrectomy plus hepatic resection was of marginal significance as a prognostic factor. T3/4 primary gastric cancer was chosen as an independent prognostic factor in the current study. Although T3/4 disease portends a potential risk for peritoneal seeding, the most frequent cause of death of our patients with T3/4 stage disease was liver metastasis, even after complete resection of the hepatic nodules. It is uncertain to what degree peritoneal seeding affected OS of our patients since accurate diagnosis of peritoneal dissemination was not possible in every case.

As for treatment options, the current study demonstrates the possibility that complete resection of both the primary gastric tumor and liver metastasis might contribute to a better prognosis than chemotherapy alone; however, this finding was of marginal statistical significance in the multivariate analysis. In contrast, there was no prognostic difference between gastrectomy plus hepatic resection and palliative gastrectomy. At present, a prospective randomized controlled trial is underway in Korea and Japan (19) comparing palliative gastrectomy with chemotherapy alone for patients with AGC including those with liver-only metastasis. The treatment option with better outcomes from this trial should be prospectively compared with gastrectomy plus hepatic resection for patients with liver-only metastasis in order to clarify which treatment strategy is optimal.

In conclusion, we believe that this is the first report comparing three different treatment options (gastrectomy plus hepatic resection *versus* palliative gastrectomy *versus* chemotherapy alone) for patients with LMGC as a single non-curative factor. T Stage of the primary gastric tumor was shown to be an independent prognostic factor for patients with LMGC. Limitations of this study, such as its retrospective nature correlating with selection bias between the treatment groups and small sample size, should be taken into account. Although gastrectomy plus hepatic resection might be a promising treatment option, with longer survival for patients with LMGC, further study is needed in a prospective, multi-institutional fashion to establish its role and clarify what constitutes optimal indications for hepatic resection in patients with LMGC.

Conflicts of Interest

The Authors declare that they have no conflicts of interest.

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Optimal indications for second-line chemotherapy in advanced gastric cancer

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As it remains uncertain whether patients with advanced gastric cancer who progress after first-line chemotherapy should receive second-line chemotherapy, we attempted to identify the optimal indications for second-line chemotherapy. In this retrospective study, 101 patients were included in univariate and multivariate analyses to identify clinicopathological variables independently associated with longer survival postprogression (SPP), defined as the time from recognition of disease progression on first-line chemotherapy to death from any cause or last follow-up. The median SPP was 340 days. On multivariate analysis, performance status 2 [hazard ratio (HR), 14.234; 95% confidence interval (CI), 2.766–73.258], serum albumin level less than 3.5 g/dl (HR, 2.088; 95% CI, 1.047–4.060) at initiation of second-line chemotherapy, and time to progression less than 170 days on first-line chemotherapy (HR, 2.497; 95% CI, 1.227–5.083) were identified as independent prognostic factors associated with shorter SPP. The median SPP was 496, 375, and 232 days in patients with 0, 1, and 2 of these 3 negative prognostic factors, respectively ($P=0.0002$). The present study suggests that second-line chemotherapy would not be beneficial in patients with two or more of the following three negative prognostic factors: performance status 2, serum albumin less than 3.5 g/dl at initiation of second-line chemotherapy and time to progression less than 170 days on first-line chemotherapy. *Anti-Cancer Drugs* 23:465–470 © 2012 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Gastric cancer is the second leading cause of cancer-related death worldwide, despite a recent decline in its global incidence [1–3]. Surgical resection is the mainstay of curative treatment for gastric cancer; however, the disease is often too advanced at initial diagnosis to allow for curative surgery. For such patients, the goals of chemotherapy are symptom palliation and prolongation of survival [4]. Despite considerable efforts to develop effective chemotherapy regimens, advanced gastric cancer (AGC) remains a challenging malignancy, with a median survival of 9–13 months [5–8]. Although there are no globally accepted standard regimens for AGC, doublet combinations containing 5-fluorouracil or oral fluoropyrimidines such as S-1 and capecitabine with platinum agents are the most commonly used first-line treatments worldwide [5,7,9]. In Japan, other regimens such as S-1 plus irinotecan [10], S-1 plus a taxane (paclitaxel or docetaxel) [11,12], and irinotecan plus cisplatin [8] have also been vigorously evaluated as first-line treatment in phase II/III trials. In addition, triplet regimens consisting of S-1, cisplatin, and a taxane have recently shown promising results, with a median survival over 15 months [13–15].

Although first-line chemotherapy effectively reduces tumor size in approximately half of patients with AGC, it ultimately fails and leads to disease progression after 4–6 months [5–8]. Whether every patient who progresses after first-line chemotherapy should go on to receive second-line chemotherapy remains under debate. In Japan, Korea, and Italy, on the basis of the results of several studies on second-line chemotherapy [16–20], more than half of patients with AGC receive second-line treatment in clinical practice [21]. Taxanes and irinotecan are the most commonly used agents as second-line chemotherapy [16–20,22]. Recently, in a small randomized phase III study with 40 patients with AGC, best supportive care (BSC) plus second-line irinotecan improved overall survival (OS) over BSC alone [23]. However, patient selection for second-line chemotherapy remains uncertain. Several factors such as performance status (PS), extent of disease, cumulative toxicity of the first-line treatment, history of the agents used, and efficacy of first-line chemotherapy should be taken into consideration when selecting patients who are likely to benefit from second-line chemotherapy [21]. We therefore attempted to identify the optimal indications for second-line chemotherapy in patients with AGC.

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Patients and methods

Patients

Of the 157 patients with primary unresectable or recurrent gastric cancer treated at our institution between April 2000 and January 2010, 101 fulfilled the following inclusion criteria for this retrospective study: (a) histologically proven unresectable or recurrent gastric adenocarcinoma; (b) treatment with second-line chemotherapy after first-line chemotherapy failed; (c) maximum Eastern Cooperative Oncology Group PS of 2 at initiation of second-line chemotherapy; (d) adequate bone marrow function (white blood cell count 3000–12 000 mm^{-3}, platelet count $\geq$ 100 000 mm^{-3}, and hemoglobin $\geq$ 8.0 g/dl), hepatic function (total bilirubin $\leq$ 1.5 mg/dl, serum transaminases $\leq$ 100 U/l), and renal function (serum creatinine $\leq$ upper institutional limit) at initiation of second-line chemotherapy; and (e) no other concurrently active malignancies.

Overall survival and efficacy of first-line chemotherapy

Survival postprogression (SPP) was defined as the time from disease progression on first-line chemotherapy to death from any cause or last follow-up. Time to progression (TTP) on first-line chemotherapy was defined as the interval between initiation of first-line chemotherapy and recognition of disease progression.

During first-line chemotherapy, each patient with a measurable lesion was assessed for response according to the Response Evaluation Criteria in Solid Tumors [24], with computed tomography (CT) scans performed every 2 or 3 months until disease progression. Patients with only nonmeasurable lesions were considered to have stable disease (SD) if neither complete disappearance (CR) nor obvious progression (PD) of the recurrent disease was observed on CT scans.

Statistical analysis

SPP and TTP were calculated using the Kaplan–Meier method and compared with the log-rank test. Univariate and multivariate analyses were performed using the Cox proportional hazards regression model to identify clinicopathological variables independently associated with SPP. Hazard ratios (HR) and 95% confidence intervals (CI) were also calculated. *P*-values less than 0.05 were considered statistically significant and all *P*-values correspond to two-sided significance tests. All statistical analyses were carried out using SAS statistical software 5.0 (SAS Institute Inc., Cary, North Carolina, USA).

Results

Patient characteristics

The clinicopathological characteristics of the 101 patients at the initiation of second-line chemotherapy are shown in Table 1. There were 68 men and 33 women, with a median age of 69 (range, 25–85) years. The majority of patients had a good PS (0 or 1); there were five patients with PS 2. Histologically, 43 patients had intestinal-type adenocarcinoma and 58 had diffuse-type adenocarcinoma Fifty-two patients had primary unresectable gastri cancer and 49 had recurrent disease. There were 6 patients with measurable metastatic lesions, and multipl metastatic sites were present in 13 patients. Sixty-tw patients had serum albumin (Alb) levels of 3.5 g/dl o greater, and 84 patients had C-reactive protein (CRP values below 1.0 mg/dl, whereas 33 patients were anemic with hemoglobin (Hb) less than 10 g/dl.

Table 1 Patient characteristics at initiation of second-line chemotherapy

Number of patients	101
Sex (males/females)	68/33
Age (years), median (range)	69 (25–85)
ECOG performance status	
0–1/2	96/5
Histology (Lauren classification)	
Intestinal/diffuse	43/58
Primary tumor	
Present/absent	52/49
Site of primary tumor	
Cardia/body/antrum/total	14/40/44/3
Measurable lesion	
Present/absent	61/40
Number of metastatic sites	
1/ $\geq$ 2	88/13
Metastatic site	
Lymph node/liver/peritoneum/lung/bone/brain	31/30/42/7/3/
Serum albumin (Alb)	
<3.5 g/dl/ $\geq$ 3.5 g/dl	39/62
C-reactive protein (CRP)	
<1.0 mg/dl/ $\geq$ 1.0 mg	84/17
Hemoglobin (Hb)	
<10 g/dl/ $\geq$ 10 g/dl	33/68

ECOG, Eastern Cooperative Oncology Group.

Chemotherapy regimens

Table 2 summarizes the first-line and second-lin chemotherapy regimens that the patients received. Mos patients (96/101) received S-1-based regimens, with fiv patients treated with irinotecan plus cisplatin. Th majority of patients were participants in clinical trial who were treated according to trial protocols. Chemother apy regimens for nontrial participants were based on th treating physician's discretion.

Second-line regimens included S-1-based regimens (41) taxane monotherapy (30), irinotecan-based regimen (29), and cisplatin plus paclitaxel (1).

Survival time postprogression

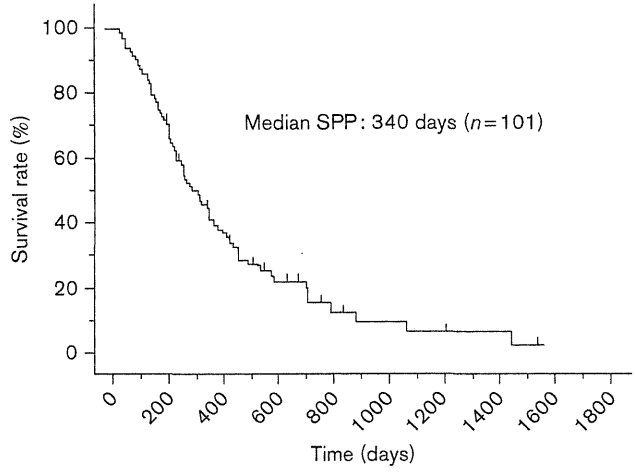
The median follow-up for all 101 patients was 490 days Seventy-one deaths occurred during the study period The median SPP was 340 days, as shown in Fig. 1. Th median TTP on first-line chemotherapy was 178 days The median SPP was significantly longer in the 5 patients with TTP $\geq$ 170 days (median, 434 days) tha in the 47 patients with TTP < 170 days (median, 29 days) ($P = 0.0087$), as shown in Fig. 2.

On first-line chemotherapy, six patients achieved CR an 38 patients achieved a partial response (PR). SD wa

Table 2 Chemotherapy regimens

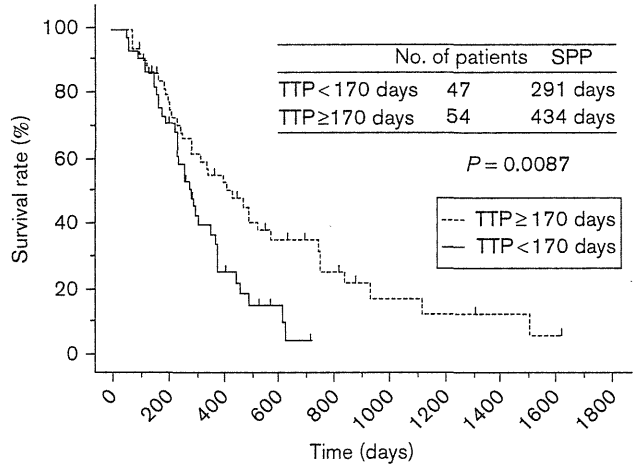
	Number of patients
First-line chemotherapy	
S-1 alone	37
S-1 + cisplatin or oxaliplatin	27
S-1 + irinotecan	9
S-1 + paclitaxel or docetaxel	15
S-1 + cisplatin + taxane	8
Irinotecan + cisplatin	5
Second-line chemotherapy	
S-1 alone	6
S-1 + cisplatin	9
S-1 + irinotecan	17
S-1 + paclitaxel or docetaxel	9
Taxane	30
Irinotecan	17
Irinotecan + cisplatin	12
Cisplatin + paclitaxel	1

Fig. 1



Survival postprogression (SPP).

Fig. 2



Survival postprogression (SPP) according to time to progression (TTP) on first-line chemotherapy.

Table 3 Prognostic factors for survival postprogression

Prognostic factors	Median SPP (days)	*P*	HR	95% CI	*P*
Sex					
Males	382	0.6839	1.491	0.738–3.013	0.2658
Females	314		1		
Age (median)					
<69 years	315	0.8443	1.076	0.596–1.943	0.8077
≥ 69 years	321		1		
Performance status					
2	262	0.4812	14.234	2.766–73.258	0.0015
0–1	351		1		
Histology					
Intestinal	314	0.4326	1.363	0.693–2.681	0.3697
Diffuse	351		1		
Primary tumor					
Present	321	0.0433	0.877	0.415–1.855	0.7315
Absent	358		1		
Measureable lesion					
Absent	340	0.8342	1.040	0.544–1.990	0.9056
Present	375		1		
Number of metastatic site					
≥ 2	178	0.0110	2.140	0.858–5.338	0.1027
0 or 1	376		1		
Albumin (g/dl)					
<3.5	246	0.0295	2.088	1.047–4.060	0.0300
≥ 3.5	401		1		
CRP (mg/dl)					
<1.0	375	0.2119	0.910	0.452–1.830	0.7905
≥ 1.0	278		1		
Hemoglobin (g/dl)					
<10	285	0.2133	0.960	0.522–1.765	0.8947
≥ 10	382		1		
TTP on the first-line chemotherapy median					
<170 days	291	0.0087	2.497	1.227–5.083	0.0116
≥ 170 days	434		1		
Response to the first-line CTX					
SD or PD	314	0.8922	1.270	0.693–2.327	0.4385
PR or CR	351		1		

CI, confidence interval; CR, complete response; CRP, C-reactive protein; CTX, chemotherapy; HR, hazard ratio; PD, progressive disease; PR, partial response; SD, stable disease; SPP, survival postprogression; TTP, time to progression.

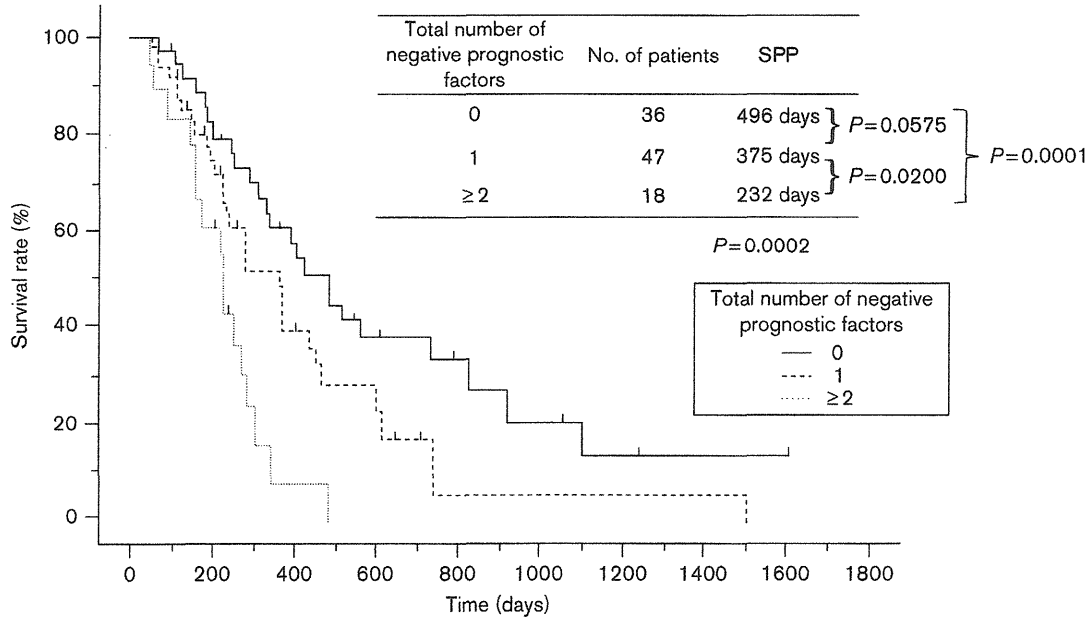
observed in 39 patients, and 18 patients had PD. When categorized by response, the median SPP was 915, 382, 302, and 261 days in patients with CR, PR, SD, and PD, respectively ($P = 0.1671$) (data not shown).

Prognostic factors

The results of univariate and multivariate analyses on the association between various factors, such as sex, age, PS, histology, presence of primary tumor, presence of measurable lesions, number of metastatic sites, TTP on first-line chemotherapy, response to first-line chemotherapy, and Alb, CRP, and Hb values at initiation of second-line chemotherapy and SPP, are summarized in Table 3. PS 2 (HR, 14.234; 95% CI, 2.766–73.258), Alb < 3.5 g/dl (HR, 2.088; 95% CI, 1.047–4.060) at initiation of second-line chemotherapy, and TTP < 170 days on first-line chemotherapy (HR, 2.497; 95% CI, 1.227–5.083) were identified as significant independent prognostic factors for shorter SPP.

In addition, patients were classified according to the number of these three negative prognostic factors they possessed (PS 2, Alb < 3.5 g/dl, and TTP < 170 days on

Fig. 3



Survival postprogression (SPP) according to the number of negative prognostic factors.

first-line chemotherapy) as follows: 36 patients without any negative prognostic factors were scored as 0, 47 patients with one out of three negative prognostic factors were scored as 1, and 18 cases with two or more factors were scored as 2. The median SPP was 496, 375, and 232 days in patients scored as 0, 1, and 2, respectively, with a statistically significant difference between scores of 0–1 and 2 ($P = 0.0002$), as shown in Fig. 3.

Discussion

For patients with AGC, chemotherapy plays an important role in improving survival and symptom alleviation. Even if patients with AGC initially respond to first-line chemotherapy, they ultimately have disease progression. Recently, the combined analysis of two Japanese phase III trials involving 327 patients has demonstrated that second-line chemotherapy contributes to prolonging OS in patients with AGC [25]. In addition, the efficacy of second-line chemotherapy has clearly been demonstrated for the first time in a prospective randomized phase III study, in which second-line irinotecan significantly prolonged OS over BSC in 40 patients with AGC [23]. However, it remains uncertain whether we can distinguish patients who are likely to benefit from second-line chemotherapy from those who would not.

In this study, PS 0–1 and Alb ≥ 3.5 g/dl at initiation of second-line chemotherapy as well as TTP ≥ 170 days on first-line chemotherapy were identified as positive prognostic factors for SPP. In accordance with our findings, other studies have shown that PS 0–1 and TTP greater than 5–6 months on first-line chemotherapy were significantly associated with prolonged OS in patients receiving second-line chemotherapy for AGC [26–28]. Second-line chemotherapy would not be appropriate for patients with considerable PS deterioration and rapid disease progression on first-line chemotherapy. However, data from the Surveillance, Epidemiology, and End Results registry, which enrolls large numbers of patients with metastatic gastric cancer, demonstrate that age, sex, and tumor location were significant independent prognostic factors for OS [29]. When tumor location was included in the multivariate analysis, PS 2, Alb < 3.5 g/dl, and TTP < 170 days on first-line chemotherapy were still identified as independent prognostic factors, whereas age, sex, and tumor location were not (data not shown).

As observed in other studies [26–28,30–32], PS 2 had a significantly negative impact on survival in the multivariate analysis even though only 5% of the study cohort had PS 2. Irrespective of the sample size of patients with PS 2, PS classifications of 0–1 and 2 are generally used to stratify patients in the phase III trials on AGC [5–8,10] due to its well known impact on survival.

In this study, Alb of 3.5 g/dl and CRP of 1.0 mg/dl were adopted as cut-off values because both elevated CRP (> 1.0 mg/dl) and decreased Alb (< 3.5 g/dl) were reported to be significant negative prognostic factors in various types of cancer [33,34]. Although there has been some controversy over whether serum Alb is a useful prognosticator for SPP [28,30] as opposed to PS and TTP,

Alb was independently associated with OS in our cohort. Patients who maintain their nutritional status can better tolerate second-line chemotherapy, which may lead to durable SPP.

Anemia with Hb ≤ 10 g/dl is often found in patients with AGC due to bleeding from the primary lesion, chemotherapy-induced myelosuppression, or nutritional deficiency, and its negative prognostic value has been discussed in several studies [26,27,35]. In the present study, Hb level was not identified as a prognostic factor for SPP, partly due to the comparatively well maintained Hb level at the initiation of second-line chemotherapy (median, 10.6 g/dl) compared with other studies [26,27,35] that found low Hb to be a negative prognostic factor.

Regarding the association between response to the first-line chemotherapy and SPP, positive response (CR plus PR) as assessed by CT scan was not prognostically significant (Table 3). This finding is consistent with a previous report [36] that showed no significant association between positive response to the first-line chemotherapy and longer OS in AGC, despite a moderate correlation between positive response and durable TTP. In contrast, the tumor's metabolic response to chemotherapy, which is observable by PET as a decrease in fluorine-18 fluorodeoxyglucose uptake, has recently been reported to be an independent prognostic factor for OS in patients with AGC receiving preoperative chemotherapy [37,38]. Longer TTP on first-line chemotherapy, which was identified as a positive prognostic factor for SPP in this study, might be predicted by PET scans during first-line chemotherapy.

The total number of negative prognostic factors, such as PS 2, Alb < 3.5 g/dl, and TTP < 170 days, was prognostically significant in this study (Fig. 3). Approximately four-fifths of the patients with 0 or 1 negative factor achieved SPP over 1 year, whereas patients with two or more negative factors had a median SPP of 232 days. Similar prognostic scoring models have been reported in previous studies [26,27]. Catalano *et al.* [26] incorporated five prognostic factors (PS, Hb level, carcinoembryonic antigen value, number of metastatic sites, and TTP under first-line chemotherapy) into a prognostic score. Kanagavel *et al.* [27] proposed a model composed of PS, Hb level, and TTP under first-line chemotherapy. In accordance with our findings, their models were able to differentiate patient prognosis following second-line chemotherapy in good, intermediate, and poor risk categories with a median survival of 12.7–13.5, 6.0–7.1, and 2.0–3.3 months, respectively.

The optimal indications for second-line chemotherapy in patients with AGC are less clearly defined than those for first-line chemotherapy. The present study demonstrated that second-line chemotherapy would not be beneficial in patients with two or more of the following factors: PS 2, Alb < 3.5 g/dl at initiation of the second-line chemotherapy, and TTP < 170 days on first-line chemotherapy. The limitations of this study, which include its retrospective, single-institution nature and the relatively small sample size, need to be taken into account before generalizing the results to daily clinical practice until prospective, multicenter validation is available. However, we believe that our findings will help practitioners prognosticate on the disease course and facilitate decision-making regarding second-line chemotherapy by physicians, patients, and their caregivers.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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ORIGINAL ARTICLE – GASTROINTESTINAL ONCOLOGY

Posttherapy Nodal Status, Not Graded Histologic Response, Predicts Survival after Neoadjuvant Chemotherapy for Advanced Gastric Cancer

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ABSTRACT

Background. Neoadjuvant chemotherapy (NAC) has been attempted as a means of improving survival of potentially resectable advanced gastric cancer (AGC). In the course of exploring the most promising NAC regimen, a superior surrogate marker reflecting overall survival (OS) is necessary. We investigated prognostic factors in AGC patients who underwent NAC followed by gastric resection and evaluated whether histologic response to NAC was predictive of survival.

Methods. Seventy consecutive patients with gastric cancer treated with NAC followed by surgical resection between Jan 1, 2000, and Dec 31, 2009, at Osaka National Hospital were identified from a prospective database. Prognostic factors for OS were investigated by univariate and multivariate analyses.

Results. Median survival time for all patients was 668 days after surgical resection. Age less than 65 years (hazard ratio 0.463, 95% confidence interval 0.244–0.879) and pathologic nodal stage of N0–1 (hazard ratio 0.318, 95% confidence interval 0.160–0.635) were identified as significant independent prognostic factors for longer OS, whereas graded histologic response of primary tumor to NAC was statistically significant on univariate analysis, but not on multivariate analysis, as a prognostic factor.

Conclusions. Posttherapy nodal status, not graded histologic response, predicts survival after NAC for AGC and could serve as a reliable surrogate marker for OS in the course of exploring the most promising regimen for NAC.

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Gastric cancer is the second leading cause of cancer-related deaths worldwide, and the prognosis of advanced gastric cancer (AGC) remains poor, with 5-year survival rates of approximately 20–30% achieved with surgery alone in Western countries.[1–4] Because of this poor prognosis, preoperative chemotherapy and/or radiotherapy have been attempted to improve patient survival.[3–9] Because the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial provided strong evidence that preoperative chemotherapy followed by postoperative chemotherapy improved overall survival (OS) for patients with gastric cancer, neoadjuvant chemotherapy (NAC) has become increasingly used to treat potentially resectable AGC before resection in the Western world.[3]

In Japan, adjuvant chemotherapy with S-1 has become the standard of care in patients with stage II and III gastric cancer after curative resection.[10] However, by subset analysis, adjuvant S-1 has been proven to be unable to improve OS in patients with stage IIIB disease, suggesting the need for development of an effective NAC for these patients. There have been few generally accepted standard NAC regimens for the treatment of AGC. In the course of exploring the most promising regimen, a superior surrogate marker reflecting OS is necessary. Several potential indices have been explored, including progression-free survival, R0 resection rate, response rate by the Response Evaluation Criteria in Solid Tumors (RECIST), and histologic response. The prognostic significance of histologic response to chemotherapy and/or radiotherapy has been investigated for various malignancies, including pancreatic, rectal, and esophageal cancers, but the prognostic

value of this variable has been mixed and is still controversial, especially in AGC.[11–20]

This study was conducted to investigate prognostic factors in AGC patients who underwent NAC followed by gastric resection and to evaluate whether histologic response to NAC was predictive of survival in these patients.

PATIENTS AND METHODS

Patient Characteristics

Seventy consecutive patients with histologically proven gastric adenocarcinoma treated with NAC followed by surgical resection between Jan 1, 2000, and Dec 31, 2009, at Osaka National Hospital were identified from a prospective database; these patients corresponded to 5.2% of all 1354 patients undergoing gastrectomy during the same period. The clinical characteristics of these 70 patients are summarized in Table 1. Patients included 38 men and 32 women with a median age of 65 (range 35–81) years. In most cases, preoperative staging included chest X-ray, upper gastrointestinal series, abdominal computed tomography (CT) scan, endoscopy, and laparoscopy. All the patients had a performance status score of 1 or less on the Eastern Cooperative Oncology Group (ECOG) scale. The primary tumor was located in the proximal stomach in 28 patients, in the body of the stomach in 20 patients, and in the distal stomach in 16 patients. Six patients had a carcinoma involving the entire stomach, with linitis plastica in 24 patients. All patients had an advanced stage of primary gastric cancer in accordance with the guidelines of the Japanese Gastric Cancer Association, except for 2 patients with linitis plastica, who were classified as having stage Ib disease.[21] Patients who initially had noncurative factors such as hepatic metastasis, peritoneal metastasis, or distant metastasis were excluded from the present study. Operative procedures included total gastrectomy, distal gastrectomy, proximal gastrectomy, left upper abdominal evisceration, and pancreaticoduodenectomy in 55, 9, 1, 2, and 3 patients, respectively.

NAC was administered as prescribed by patient-enrolled protocols or according to these protocols after their completed accrual. Indications of NAC included para-aortic and/or bulky nodal metastases confirmed by contrast-enhanced CT scan, macroscopically large type 3 cancer, linitis plastica, and T4 and T3N2 tumor according to the Japanese criteria.[21] All patients completed at least one course of a planned NAC regimen, with 2 or more courses delivered in 62 patients. The combined chemotherapeutic regimen of S-1 (80 mg/m^2, days 1–21 orally) plus cisplatin (80 mg/m^2, day 8), repeated every 5 weeks, was administered to 47 patients (67%), of whom 39 underwent 2 courses and 1 completed 3 courses.[22] Alternative doublet regimens included 3 courses of S-1 (80 mg/m^2, days 1–14 orally) plus paclitaxel (50 mg/m^2, days 1 and 8), repeated every 3 weeks, in 10 patients, or 2 courses of irinotecan (70 mg/m^2, days 1 and 15) plus cisplatin (80 mg/m^2, day 1), repeated every 4 weeks, in 3 patients, one of whom received only 1 course.[23,24] As a triplet chemotherapeutic regimen, 9 patients received 2 courses of S-1 (80 mg/m^2, days 1–14 orally) in combination with paclitaxel (160 mg/m^2, day 1) and cisplatin (60 mg/m^2, day 14), repeated every 4 weeks, while 1 patient was provided 3 courses of S-1 (80 mg/m^2, days 1–14 orally) in combination with

TABLE 1 Patient and tumor characteristics

Characteristic	Value
No. of patients	70
Gender, male/female	38/32
Age, year, median (range)	65 (35–81)
Tumor location	
Proximal stomach	28
Body of stomach	20
Distal stomach	16
Diffuse/entire stomach	6
Initial disease stage	
Ib	2
II	7
IIIa	14
IIIb	21
IV	26
Type of resection	
Total gastrectomy	55
Distal gastrectomy	9
Proximal gastrectomy	1
Left upper abdominal evisceration	2
Pancreaticoduodenectomy	3
NAC regimen	
S-1 + cisplatin	47
S-1 + paclitaxel	10
Irinotecan + cisplatin	3
S-1 + cisplatin + paclitaxel	9
S-1 + cisplatin + docetaxel	1
Median no. of delivered courses (range)	2 (1–3)
Response to NAC	
Complete response	0
Partial response	34
Stable disease	34
Progressive disease	2
Adjuvant chemotherapy	
S-1	29
None	41

docetaxel (60 mg/m^2, day 8) and cisplatin (60 mg/m^2, day 8), repeated every 3 weeks.[25,26] No patients received neoadjuvant radiotherapy.

Response to NAC was assessed by endoscopy and abdominal CT scan based on the RECIST criteria. Overall response rate of 48.6% was obtained in this study with 34 having partial response, 34 stable disease, and 2 progressive disease. The overall response rate of 48.6% was comparable to that of 40–50% achieved with the preoperative administration of epirubicin, cisplatin, and 5-fluorouracil or cisplatin plus 5-fluorouracil.[3,4,9] This high overall response rate was attributed to the effective chemotherapeutic regimens used in the present study, all of which showed overall response rates of approximately 50% or more in the respective phase II/III studies.[22–26] Three to 6 weeks after the completion of NAC, 68 patients underwent a gastrectomy with D2 or more lymphadenectomy, whereas 2 patients received D1 gastrectomy with palliative intent. No patients required immediate surgery with cessation of planned NAC due to disease progression. Twenty-nine patients (41%) received adjuvant chemotherapy with S-1.

Table 2 depicts the pathologic characteristics of the resected tumors. Histologically, 20 patients had intestinal-type adenocarcinoma and 50 patients had diffuse-type adenocarcinoma according to Lauren's classification. Median tumor size was 70 (range 0–200) mm, with complete disappearance of primary tumor measured as 0 mm. Pathologic T stage and nodal involvement were classified according to the 6th edition of the Union for International Cancer Control tumor, node, metastasis system of staging. Most patients had advanced disease, as demonstrated by the 74% rate of serosal penetration (T3 + T4) and 80% incidence of nodal positivity, which was based on a sufficient median number of retrieved nodes of 53 (range 11–114). Curative resection (R0) was defined as removal of all visible disease and the associated nodal basin with negative surgical margins on microscopic analysis. Sixty-three patients (90%) underwent an R0 resection, whereas 7 patients underwent R1 or R2 resections (microscopically or grossly positive margins, respectively). In these 7 patients, positive peritoneal cytology was found in 6 patients and unresectable macroscopic peritoneal metastases were present in 2 patients at the time of resection. One patient had para-aortic metastasized lymph nodes left in the peritoneal cavity due to positive peritoneal cytology.

Graded histologic response of primary tumors was reported by 2 pathologists (M.M. and Y.K.), as shown in Table 2, based on the extent of residual tumor, fibrosis, and necrosis. Histologic response of gastric lesions to treatment was graded by the amount of residual viable carcinoma in relation to areas of fibrosis or fibroinflammation within the gross lesion according to the Japanese criteria.[21] Grade 3 (G3) response was defined as the complete absence of histopathologic evidence of malignancy. Grade 2 (G2) response was defined as <33.3% viable tumor cells observed on serial hematoxylin–eosin–stained sections, and grade 1b (G1b) as 33.3–66.6% viable cells. Tumors with 66.6% to less than 100% viable cells and those without any effect of chemotherapy on viable cells were scored as grade 1a (G1a) and grade 0 (G0), respectively. Two patients assessed as having progressive disease after NAC showed histologic response of G0.

TABLE 2 Pathologic features of resected specimens

Characteristic	Value
Lauren classification	
Intestinal	20
Diffuse	50
Tumor size (mm), median (range)	70 (0–200)
T stage	
T1	6
T2	12
T3	38
T4	14
N stage	
N0	14
N1	21
N2	12
N3	23
No. of nodes removed, median (range)	53 (11–114)
Resection type	
R0	63
R1	4
R2	3
Graded histologic response of primary tumor	
G3	1
G2	14
G1b	12
G1a	30
G0	13

Analyses of Prognostic Factors

The clinical course of each patient was followed until Dec 31, 2010. All patients either died during the observation period or had at least 1 year of follow-up, with 23 patients still alive at a median follow-up of 544 days (range 27–3,095 days; 337 days in 47 dead patients and 1,002 days in 23 alive patents) after surgical resection. OS was defined as the time from the date of surgical resection to the date of death from any cause or last follow-up. A univariate analysis was used to assess the association

between each clinicopathologic factor and OS. A multivariate analysis was performed to identify variables independently associated with survival.

Statistical Analysis

SAS statistical software 9.1 (SAS Institute Inc., Cary, NC) was used for all statistical analyses and a P value less than 0.05 was considered significant. The χ^2 test was used to evaluate differences in proportions. Survival rates were calculated according to the Kaplan–Meier method and differences were evaluated by the log rank test. Cox proportional hazards regression model was used to identify prognostic factors for survival.

RESULTS

OS and Prognostic Factors

Median survival time (MST) for all patients was 668 days, as shown in Fig. 1. There was 1 hospital death, which was caused by disease progression, carcinomatous meningitis, on postoperative day 27. The results of univariate and multivariate analyses of various clinicopathologic factors, such as gender, age, histology of primary tumor, pathologic tumor and nodal stage, resection type, and graded histologic response of primary tumor to NAC for OS are summarized in Table 3. In univariate analysis, T stage, N stage, resection type, and graded histologic response were significant prognostic factors, all of which showed reasonable correlation between MST and their stage/grade as follows: respective MST of >2,479, 867, 647, and 382 days in patients with T1, T2, T3, and T4 tumor ($P = 0.0049$), MST of 1,373, 1,282, 867, and 242 days in patients with N0, N1, N2, and N3 stage ($P < 0.0001$), and MST of >2,479, 624, 548, and 435 days

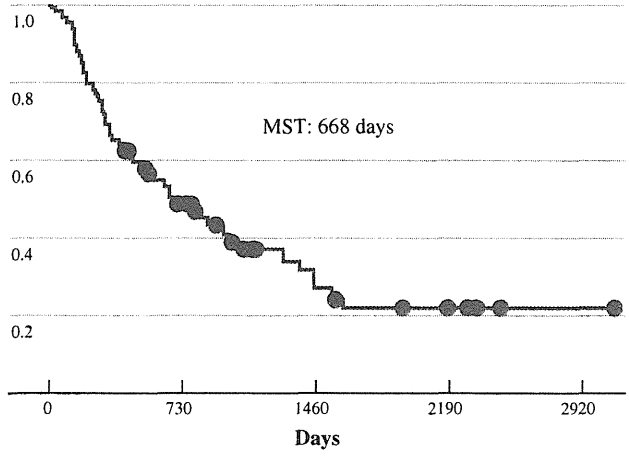

FIG. 1 OS of all patients

in patients with G3/2, G1b, G1a, and G0 response ($P = 0.0382$). Among these, age less than 65 years [hazard ratio (HR) 0.463, 95% confidence interval (CI) 0.244–0.879] and pathologic nodal stage of N0–1 (HR 0.318, 95% CI 0.160–0.635) were identified as significant independent prognostic factors for longer OS, while female gender and R0 resection demonstrated statistically marginal associations with prolonged OS. In contrast, graded histologic response was not a statistically significant predictor of OS in multivariate analysis.

Predictive Value of Histologic Response for Survival

To evaluate the potential role of graded histologic response as a prognostic marker, we conducted a subset analysis that was limited to patients with a pathologic nodal stage of N0–1. Of these 35 patients, graded histologic response was significantly associated with OS, as shown in Table 4. Specifically, MST for patients with a graded histologic response ≥G2 was not reached (>2,479 days) compared with that of 819 days for patients with a graded histologic response <G2 ($P = 0.0080$). When analyzing the 35 patients who had a pathologic nodal stage of N2–3, graded histologic response lost statistical significance as a prognostic marker (data not shown).

DISCUSSION

Given the generally poor long-term survival of <20–30% achieved with surgery alone, attempts in the Western world to improve survival of patients with AGC have so far employed chemotherapy and/or radiotherapy before surgery for locally advanced tumors.[3–9] On the basis of the recent results of the MAGIC study in particular, the treatment of patients with local AGC has evolved to include preoperative chemotherapy as a standard option.[3] However, despite the increasing use of preoperative chemotherapy for localized advanced disease, 5-year survival remains less than 40%, which underlines the need for exploration of more potent chemotherapeutic regimens.[3,4]

Indicators that optimally and independently reflect OS must be established for an efficient exploration of the most promising NAC regimens. Although the histologic response to chemotherapy and/or radiotherapy as a surrogate marker for OS has been investigated for various malignancies including pancreatic, rectal, and esophageal cancers, the prognostic value of histologic response is still controversial in these cancers.[11–16] Some have advocated a marked histologic response to preoperative treatment as a predictor of longer survival, while others deny the value of histologic grade of residual carcinoma. Posttherapy pathologic down-staging and the absence of positive lymph

TABLE 3 Prognostic factors for OS of all patients

Characteristic	Univariate analysis			Multivariate analysis		
	No. of patients	MST (d)	P	HR	95% CI	P
Gender						
Male	38	548	0.2582			0.0569
Female	32	867		0.505	0.250–1.02	
Age (median 65 year)						
65≤ year	35	530	0.0974			0.0186
<65 year	35	979		0.463	0.244–0.879	
Histology						
Intestinal	20	624	0.5400			0.4557
Diffuse	50	790		1.323	0.635–2.755	
T stage						
T1–2	18	2,479<	0.0034			0.9729
T3–4	52	530		1.019	0 339–3.067	
N stage						
N0–1	35	1,373	<0.0001			0.0012
N2–3	35	285		3.145	1.575–6.250	
Resection type						
R0	63	790	0.0367			0.0564
R1–2	7	178		2.695	0.974–7.463	
Graded histologic response						
G3, G2	15	2,479<	0.0037			0.0985
G1b, G1a, G0	55	624		2.726	0.829–8.962	

TABLE 4 Prognostic factors for OS of patients with pathologic nodal disease stage of N0–1

Characteristic	Univariate analysis			Multivariate analysis		
	No. of patients	MST (d)	*P*	HR	95% CI	*P*
Gender						
Male	18	1,282	0.5598			0.0188
Female	17	3,095<		0.232	0.069–0.785	
Age (median 65 year)						
65≤ year	19	790	0.2264			0.0994
<65 year	16	2,479<		0.372	0.115–1.206	
Histology						
Intestinal	8	1,282	0.8538			0.0609
Diffuse	27	1,605		4.878	0.929–25.64	
T stage						
T1–2	15	2,479<	0.2520			0.1470
T3–4	20	1,373		0.298	0.058–1.529	
Resection type						
R0	34	1,605	0.2578			0.3363
R1–2	1	–		2.976	0.322–27.78	
Graded histologic response						
G3, G2	10	2,479<	0.0343			0.0080
G1b, G1a, G0	25	819		17.24	2.103–141.3	

nodes have been noted to correlate with long-term survival in general, findings that have also been the case with AGC.[17–20] Ajani et al. identified histologic response as a predictor of survival in patients receiving preoperative chemoradiotherapy when assessed by univariate analysis.[5,6,8] However, multivariate analysis did not find

histologic response to be an independent predictor of OS. Likewise, Lowy et al. identified the response to preoperative therapy as the single most important predictor of OS after NAC for AGC.[17] However, in their study, patients were considered responders if they had either a clinical or a histologic response. It was therefore unclear whether histologic response alone could serve as a prognostic factor. In contrast, Mansour et al. found that although histologic response was associated with marked differences in OS, these associations did not persist in multivariate analysis.[19] Only pathologic lymph node status was independently associated with OS in patients treated with NAC. Gaca et al. also demonstrated that pathologic posttreatment nodal status independently predicted OS after neoadjuvant chemoradiation followed by surgical resection of gastroesophageal junction carcinoma.[20] In the present study, we assessed the prognostic value of various clinicopathologic factors for AGC including histologic response in the context of NAC. Although histologic response held statistical significance as a prognostic factor in univariate analysis, it did not maintain significance in multivariate analysis. Posttherapy nodal stage, but not histologic response, was an independent predictor of OS, as shown in Table 3, which is in line with the findings of other investigators.[19,20,27] Posttherapy nodal status may be superior to graded histologic response in reflecting the extent of metastatic tumor load that is resistant to chemotherapy.

Posttherapy nodal status would depend on at least two factors: the efficacy of the chemotherapy per se, and the nodal status before chemotherapy. The latter may weaken the value of posttherapy nodal status as a surrogate for the efficacy of NAC. However, when dividing the patients into two groups, 31 patients with a preoperative nodal stage of N0–1 and 39 patients with N2–3 according to the Japanese classification, age less than 65 years (HR 0.190, 95% CI 0.046–0.786) was identified as a single statistically significant prognostic factor for longer OS in patients with preoperative stage N0–1 cancer, and both age less than 65 years (HR 0.356, 95% CI 0.139–0.915) and posttherapy nodal status of N0–1 (HR 0.182, 95% CI 0.057–0.583) were identified as independent prognostic factors for durable OS in patients with preoperative stage N2–3 disease, whereas graded histologic response of primary tumor to NAC showed no statistical significance in either group on multivariate analysis.[21] Therefore, posttherapy nodal status, not graded histologic response, could be a good surrogate for the efficacy of NAC in AGC.

As for the threshold of graded histologic response associated with survival, the absolute difference in 3-year OS was 33.8% (63.6 vs. 29.8%) when patients were separated by the threshold of G2, which was greater than when patients were separated by the threshold of G1b (51.7 vs. 28.1%), as shown in Fig. 2. Graded histologic response was not associated with OS at the threshold of G1b in multivariate analysis (data not shown). Although there remains a possibility that graded histologic response correlates well with OS at the threshold of G3 (pathologic complete response) in multivariate analysis, the rate of G3 response after NAC for AGC is generally less than 5%.[17,19] In addition, lymph node metastasis has been reported to be an independent prognostic factor for OS even in patients with a pathologic complete response after preoperative chemoradiotherapy for esophageal cancer.[28]

In our series, 5 of 35 patients (14.3%) with stage N2–3 disease showed a graded histologic response of at least G2, whereas 10 of 35 patients (28.6%) with stage N0–1 cancer exhibited a response $\geq$G2. This correlation between advanced nodal status and decreased rate of histologic response may explain the lack of significance of graded histologic response in multivariate analysis. Similarly, a strong association between T stage and N stage (there were three stage N2–3 patients among 18 patients with stage T1–2, versus 32 stage N2–3 patients among 52 patients with stage T3–4, $P = 0.0021$ by the χ^2 test) could explain the lack of significance of T stage in multivariate analysis, in concordance with other reports.[19,20] R0 resection demonstrated statistically marginal associations with prolonged OS in Table 3. A moderate correlation between resection type and N stage (R0 resection rate was 97.1% (34 of 35) in stage N0–1 patients, versus 82.9% (29 of 35) in stage N2–3 patients, $P = 0.1110$ by the χ^2 test) might affect the status of R0 resection as a statistically significant prognosticator

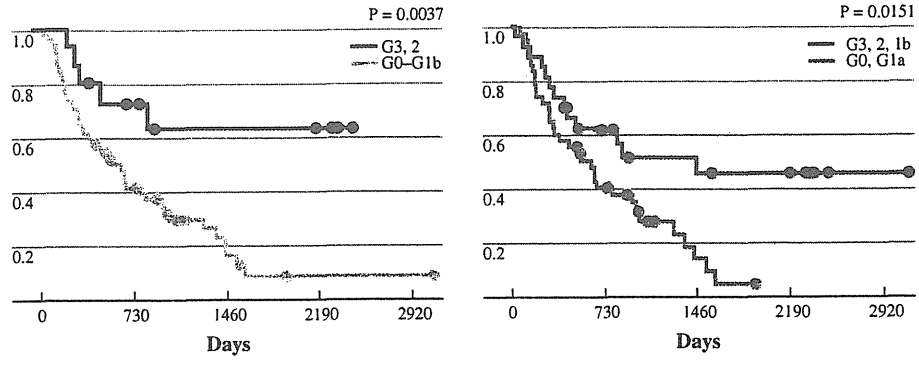

FIG. 2 OS by graded histologic response. *Open circle* indicates a censored case

in multivariate analysis. Linitis plastica was not a prognostic factor in univariate analysis with MSTs of 647 and 790 days in 24 patients with linitis plastica and the other 46 patients (data not shown), respectively ($P = 0.5302$), which could explain the lack of significance of diffuse-type in multivariate analysis.

Age less than 65 years was also identified as an independent prognostic factor for longer OS in the present study, which is in line with the results of other investigators demonstrating that age >65 years as well as postoperative nodal involvement were predictive of poor survival in multivariate analysis in patients with esophageal carcinoma.[29]

With respect to the impact of adjuvant chemotherapy with S-1 on outcomes, MSTs of 668 and 624 days were obtained in 29 patients with adjuvant S-1 and the other 41 patients without it, respectively ($P = 0.6049$). When incorporating adjuvant chemotherapy into multivariate analysis, posttherapy nodal status of N2–3 held its statistical significance as an independent prognosticator for shorter OS (HR 2.817, 95% CI 1.383–5.747, $P = 0.0043$), while graded histologic response was not a statistically significant predictor of OS (HR 3.483, 95% CI 0.907–12.33, $P = 0.0758$).

In conclusion, this study showed the statistically significant association of posttherapy nodal status with patient outcome as well as the absence of an independent association between OS and graded histologic response. Therefore, posttherapy nodal status could serve as a reliable surrogate marker in the course of searching for the most promising regimen for NAC. There are several limitations in the present study: a small-sized analysis performed at a single institution, long accrual for 70 patients, a highly selected group of patients with unusually high rate of linitis plastica, different chemotherapeutic regimens, and retrospective review of prospective database, which should be taken into account when considering the results of this study. An extremely poor prognosis in stage N2–3 patients (MST, 285 days) compared with that in stage N0–1 patients (MST, 1,373 days) after NAC followed by surgery warrants further investigation to develop restaging modalities after NAC in an attempt to identify those who have advanced nodal disease and would benefit the least from surgical resection.

CONFLICT OF INTEREST The authors indicated no potential conflicts of interest.

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