Prognostic Factors for Gastric Cancer with Cancer Cells in the Peritoneal Cavity

MINORU FUKUCHI, ERITO MOCHIKI, TORU ISHIGURO, TOSHIRO OGURA, JUN SOBAJIMA, YOUICHI KUMAGAI, KEIICHIRO ISHIBASHI and HIDEYUKI ISHIDA

Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, Saitama, Japan

Abstract. *Aim: To identify the prognostic factors for gastric cancer with positive peritoneal cytology (CY1) or peritoneal metastasis (P1). Patients and Methods: We retrospectively analyzed clinicopathological and survival data of 78 patients who had undergone gastrectomy and/or S-1 based chemotherapy for CY1 or P1 gastric cancer. Results: The median overall survival (OS) did not differ significantly between patients with CY1P0, CY0P1 and CY1P1 disease (24, 17 vs. 14 months, respectively). Among 12 clinicopathological factors, clinical N3 (odds ratio [OR]=2.18; 95% confidence interval [CI]=1.22-4.00; p=0.01) and gastrectomy not performed (OR=1.80; 95% CI=1.29-2.51; p<0.01) were significant independent prognostic factors. The median OS significantly differed between patients who had undergone gastrectomy plus chemotherapy versus chemotherapy alone (22 vs. 10 months, respectively; p<0.01). Conclusion: Gastrectomy and perioperative chemotherapy may both be indicated in CY1 or P1 gastric cancer patients with clinical N0-2.*

Gastric cancer is the most common type of cancer and the second leading cause of cancer-related mortality in Japan (1). The presence of cancer cells in the peritoneal cavity, evidenced by positive peritoneal cytology (CY1) or peritoneal metastases (P1), is a known significant poor prognostic factor in patients with gastric cancer (2). In both the TNM and Japanese Gastric Cancer Association classifications, CY1 and P1 are categorized as distant metastases (3, 4). Peritoneal metastasis is commonly present in patients with advanced gastric cancer and is associated with an extremely poor prognosis. As is true for overt peritoneal metastases, CY1 has been shown to predict peritoneal metastasis, and recurrence (5, 6).

Because gastric cancer with distant metastases such as by CY1 or P1 status is generally considered to be incurable, such patients usually do not undergo gastrectomy. The Japanese Guideline recommends treatment with chemotherapy, radiotherapy and palliative surgery (7). We previously reported that gastrectomy may be optimal for patients with CY1 gastric cancer because it has a favourable prognosis when perioperative chemotherapy is also administered (8). Moreover, several case series have suggested the possibility of cure in some carefully selected patients with CY1 or P1 gastric cancer treated with gastrectomy and perioperative chemotherapy with S-1 or S-1 plus cisplatin (9, 10). Although understanding the prognostic factors is helpful for determining the optimal treatment strategy for gastric cancer with cancer cells in the peritoneal cavity evidenced by CY1 or P1, only limited information is available from previous studies (5, 9, 10).

To evaluate the prognostic factors for gastric cancer with cancer cells in the peritoneal cavity, such as CY1 or P1 disease, we retrospectively examined the clinicopathological and survival data of patients who had undergone gastrectomy with/without S-1-based chemotherapy for this type of advanced cancer in the absence of other detectable metastatic disease.

Patients and Methods

Patients. A database of 78 patients with CY1 or P1 gastric cancer without other metastatic disease was retrospectively reviewed. All patients had undergone gastrectomy with/without S-1-based chemotherapy at the Saitama Medical Center of Saitama Medical University from January 2005 to December 2014. This study was approved by the Ethics Committee of Saitama Medical Center at Saitama Medical University (approval no. 613-II).

Tumour staging was performed according to the Union for International Cancer Control (seventh edition) pTNM staging guidelines, (3). Terminology defined by the Japanese Gastric Cancer

Correspondence to: Minoru Fukuchi, MD, Department of Digestive Tract and General Surgery, Saitama Medical Center, Saitama Medical University, 1981, Kamoda, Kawagoe, Saitama 350-8550, Japan. Tel: +81 492283619, Fax: +81 492228865, e-mail: mfukuchi@saitama-med.ac.jp

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Association was used to avoid unnecessary confusion (4). Peritoneal washing for cytological examination was performed during laparotomy or laparoscopic evaluation as described in a previous study (8). In addition, Eastern Cooperative Oncology Group performance status (PS) was evaluated in every patient upon admission. The median duration of follow-up was 15 months (range=1.2-64 months) after initial treatment by gastrectomy with/without chemotherapy.

Statistical analysis. Continuous variables are expressed as the median and range. Grouping of categorical and continuous variables was carried out using standard thresholds. Cox proportional hazard regression analysis was used to identify statistically significant independent factors for overall survival (OS). Factors with a *p*-value of less than 0.05 according to univariate analysis were assessed by multivariate analysis. In the univariate and multivariate analyses, odds ratios (ORs) with 95% confidence intervals (CIs) were calculated. Curves of survival after initial treatment were drawn by the Kaplan–Meier method and compared with the log-rank test. All statistical analyses were performed with JMP 5.0 software (SAS Institute, Cary, NC, USA). A *p*-value of less then 0.05 was considered statistically significant.

Results

Patients' characteristics. The characteristics of the 78 patients with gastric cancer with CY1 or P1 are presented in Table I. There were 49 male and 29 female patients with a median age of 67 years (range=33-86 years). Forty-three and 45 patients had a pre-treatment PS of 0 and 1-2, respectively. Forty-six and 60 patients had CY1 and P1, respectively. Fifty-six patients (72%) had undergone gastrectomy, whereas seven, five and three had undergone gastrojejunostomy, staging laparoscopy and exploratory laparotomy, respectively. Of the 69 patients (88%) who received S-1-based chemotherapy, 47 also underwent gastrectomy, whereas 22 did not (treated with chemotherapy alone).

Survival analysis. The 5-year OS rate of the entire cohort was 8% (median OS=18 months) after initial treatment. The median OS did not differ significantly between patients with CY1 alone (CY1P0) (n=18), P1 alone (CY0P1) (n=32) and CY1 and P1 (CY1P1) (n=28) (24, 17 and 14 months, respectively; $p=0.12$) (Figure 1A).

We selected the following 12 factors for univariate analysis: age (<67 *vs*. ≥67 years), sex (male *vs*. female), performance status (0 *vs*. 1, 2), tumours located throughout whole body (no *vs*. yes), macroscopic type (type 2 or 3 *vs*. type 4), histological type (G1 or G2 *vs*. G3), tumour depth (T2, 3 or T4a *vs*. T4b), nodal stage (N0-2 *vs*. N3), CY1 (no *vs*. yes), P1 (no *vs*. yes), gastrectomy (no *vs*. yes) and chemotherapy (no *vs*. yes). According to the univariate analysis, the following five factors were significantly associated with worse OS: tumours located throughout the body ($p=0.03$), macroscopic type 4 ($p=0.04$), T4b ($p=0.03$), N3 ($p=0.01$) and gastrectomy not performed ($p<0.01$). According to multivariate analysis, N3 (OR=2.18, 95% CI=1.22-4.00; $p=0.01$) and gastrectomy not performed (OR=1.80, 95% CI=1.29-2.51; $p<0.01$) were significant independent indicators for an unfavourable OS (Table II).

Table I. *Demographics of 78 patients with gastric cancer with positive peritoneal cytology or peritoneal metastasis*.

Characteristic	
Median age (range), years	67 (33-86)
Gender, n	
Male/female	49/29
Performance status,	n
0/1/2	43/21/14
Location,	n
U/M/L/whole body	19/18/29/12
Macroscopic type	
Type2/3/4	12/33/33
Histological grading, n	
G1/2/3	2/17/59
Tumor depth, n	
T2/3/4a/4b	2/5/54/17
Nodal stage, n	
N0/1/2/3	11/10/14/43
Peritoneal cytology, n	
Negative/positive	32/46
Peritoneal metastasis, n	
P0/1	18/60
Gastrectomy, n	
No/Yes	22/56
Chemotherapy, n	
No/Yes	9/69
S-1	39
S-1+Cisplatin	21
S-1+Paclitaxel	5
S-1+Docetaxel	4

The 5-year OS rate for the 47 patients treated with gastrectomy plus chemotherapy was 13% (median survival time=22 months). The 5-year OS rate for both the 22 patients treated with chemotherapy alone and the nine patients treated with gastrectomy alone was 0% (median survival times of 10 and 19 months, respectively). The median OS differed significantly between patients treated with gastrectomy plus chemotherapy and those treated with chemotherapy alone ($p<0.01$) (Figure 1B).

Discussion

We have clearly shown that clinical N0-2 and gastrectomy are independent favourable factors in patients with CY1 or P1 gastric cancer. Furthermore, our survival data show that gastrectomy plus S-1-based chemotherapy may have improved the prognosis of these carefully selected patients.

Table II. *Univariate and multivariate analysis in relation to overall survival.*

		Univariate		Multivariate	
Variable	N	Odds ratio (95% CI)	*p*-Value	Odds ratio (95% CI)	*p*-Value
Age; years					
<67	37	1			
≥67	41	1.25 (0.73-2.15)	0.41		
Gender					
Male	49	1			
Female	29	1.04 (0.78-1.36)	0.81		
Performance status					
0	43	1			
1, 2	35	1.56 (0.90-2.69)	0.11		
Location of whole body					
No	65	1		1	
Yes	13	1.49 (1.04-2.06)	0.03	1.40 (0.94-2.02)	0.09
Macroscopic type					
Type 2, 3a	47	1		1	
Type 4	31	1.33 (1.01-1.75)	0.04	1.01 (0.72-1.40)	0.94
Histological type					
G1, 2	19	1			
G3	59	1.23 (0.67-2.44)	0.52		
Tumor depth					
T2, 3, 4a	62	1		1	
T4b	16	2.07 (1.09-3.75)	0.03	1.64 (0.82-3.11)	0.16
Nodal stage					
N0-2	35	1			
N3	43	2.01 (1.16-3.56)	0.01	2.18 (1.22-4.00)	0.01
Positive cytology					
No	32	1			
Yes	46	1.03 (0.60-1.78)	0.92		
Peritoneal metastasis					
No	18	1			
Yes	60	1.83 (0.94-4.01)	0.08		
Gastrectomy					
No	22	1.93 (1.43-2.60)		1.80 (1.29-2.51)	
Yes	56	1	<0.01	1	<0.01
Perioperative chemotherapy					
No	9	1			
Yes	69	1.17 (0.48-3.88)	0.76		

CI: Confidence interval.

The presence of peritoneal metastases is generally considered a stronger prognostic factor than CY1 status; it is the factor that confers the poorest prognosis in patients with both P1 and CY1 (11). Lee *et al*. reported that the median OS of patients with CY1P1 is significantly worse than that of patients with CY0P1 (5). In the present study, there was a similar, but not statistically different/significantly (p=0.06), tendency for median OS of these two groups (data not shown). Aizawa *et al*. reported that 19.2% of patients with CY1P0 have new peritoneal metastases after chemotherapy and that it is impossible to determine whether this is attributable to a high rate of tumour progression during chemotherapy or to inaccurate assessment by staging laparoscopy (12). In the present study, we systematically treated patients with CY1 or P1 as having gastric cancer with cancer cells in the peritoneal cavity. As a result, the median OS did not differ significantly between patients with CY1P0, CY0P1 and CY1P1.

Previous studies have reported that poorer PS, clinical N3 and type 4 gastric cancer are independent unfavourable predictors of survival among patients with CY1P0 gastric cancer (5, 13-15). Although the primary focus of this study was the presence of CY1 or P1, multivariate analysis did identify clinical N3 disease as an independent unfavourable prognostic predictor, similarly to two previous studies for patients with CY1P0 gastric cancer (5, 15). In patients with

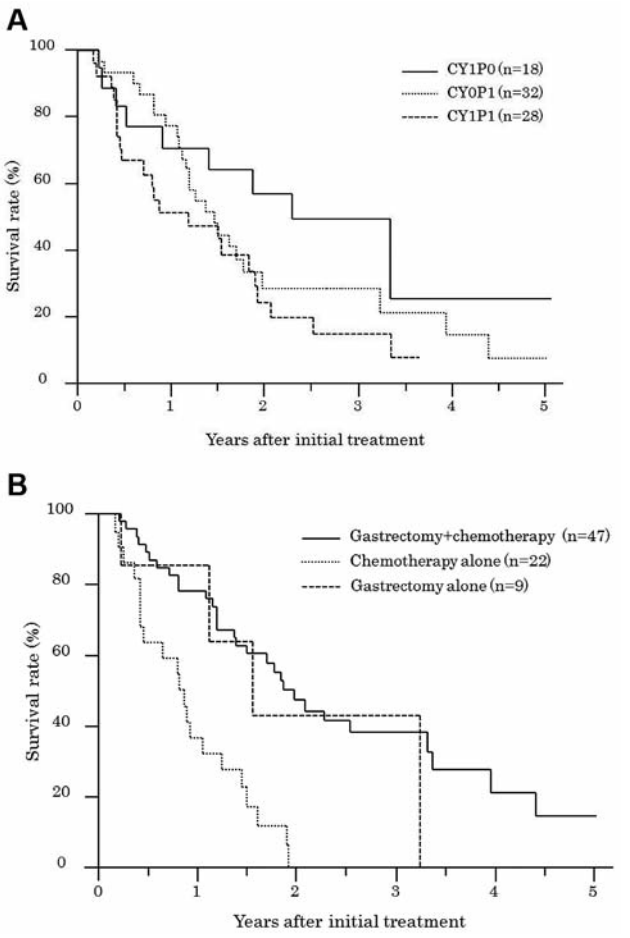

Figure 1. *Cumulative overall survival (OS) of 78 patients with positive peritoneal cytology (CY1) or peritoneal metastasis (P1) of gastric cancer. A: The median OS did not differ significantly between patients with CY1P0 (n=18), CY0P1 (n=32) and CY1P1 disease (n=28). B: The cumulative OS of 47 patients treated with gastrectomy plus chemotherapy was significantly better than that of 22 patients treated with chemotherapy alone (p<0.01).*

advanced gastric cancer, cancer cells released from the primary site may cause intraperitoneal metastases (16). However, those without serosal invasion may have CY1P0 disease, and such patients occasionally develop recurrences in both lymph nodes and the peritoneum (15, 17). These findings suggest that progression of both CY1 and P1 gastric cancer is associated with lymph node metastasis. Thus, it appears that the prognosis of patients with CY1 or P1 gastric cancer is determined by their nodal status. Therefore, further chemotherapy may be indicated in patients with clinical N3 disease.

However, some patients with CY1 or P1 gastric cancer do survive in the long-term (8). We, therefore, aimed to identify the optimal treatment strategy for these patients by analysing our survival data. Multivariate analysis identified gastrectomy as an independent prognostic factor in these patients. However, it is clear that selection bias was present in this study and the others discussed. Our analysis, thus, does not justify performing gastrectomy in all patients with CY1 or P1 gastric cancer; however, this procedure may be optimal for selected patients with CY1 or P1 gastric cancer.

Furthermore, the median OS of patients treated with gastrectomy plus chemotherapy was significantly longer than that of patients treated with chemotherapy alone in this study. In recent studies, perioperative chemotherapy with S-1 or S-1 plus cisplatin may have improved the prognosis of patients with CY1 or P1 gastric cancer treated with curative gastrectomy (9, 10). Other recent studies have demonstrated that intraperitoneal chemotherapy is safe and effective for patients with P1 disease; however, biomarkers for evaluating responses to this treatment and predicting outcomes have not yet been well characterised (18, 19). In the present study, patients who had undergone gastrectomy received first-line chemotherapy with S-1-based regimens. The expected prognosis of patients with CY1 or P1 gastric cancer depends on whether treatment includes both modern S-1-based chemotherapy and gastrectomy. Moreover, gastrectomy may facilitate continuation of oral S-1 intake by preventing tumour stenosis or bleeding if the surgery is reductive (8). However, because patients did not all receive the same chemotherapy regimens, its efficacy cannot be accurately evaluated here.

Although this retrospective study was performed at a single centre in a limited patient population and was therefore subject to selection bias, our findings should stimulate further inquiry into how to manage patients with CY1 or P1 gastric cancer. A prospective study with a larger series of patients is needed to clarify the optimal treatment strategy for this type of advanced cancer.

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