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Prognostic Role of Gastrectomy in Patients With Gastric Cancer With Positive Peritoneal Cytology

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This retrospective study identified the optimal treatment strategy for patients with gastric cancer with positive peritoneal cytology. We analyzed clinicopathologic and survival data for 54 patients who had undergone gastrectomy and/or chemotherapy for treatment of gastric cancer with positive peritoneal cytology with (n = 40) or without (n = 14) metastatic disease. The median overall survival did not differ significantly between patients with gastric cancer with positive peritoneal cytology with and without metastatic disease (19 versus 13 months, respectively). Among 14 clinicopathologic variables, the lack of gastrectomy was the only significant independent unfavorable factor for survival (odds ratio, 1.64; 95% confidence interval, 1.04–2.57; $P = 0.03$). The median overall survival significantly differed among patients who had undergone gastrectomy plus chemotherapy, chemotherapy alone, and gastrectomy alone (25, 10, and 17 months, respectively; $P < 0.01$). Gastrectomy may be optimal for patients with (gastric cancer with positive peritoneal cytology), considering its favorable prognostic effect with respect to perioperative chemotherapy.

Key words: Peritoneal cytology – Gastric cancer – Gastrectomy

Stage IV gastric cancer is generally considered to be incurable, and affected patients are usually ineligible for surgical resection. Treatment options as recommended by the Japanese guidelines include chemotherapy, radiotherapy, palliative surgery, and palliative medicine.[1] However, several case series have suggested the possibility of cure in some carefully selected patients with stage IV gastric cancer, given the improvements in multimodal treatment.[2,3] Patients with cancer cells in the peri-

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toneal cavity (peritoneal cytology positive; CY1) could constitute such a population. A CY1 status is a predictor of peritoneal dissemination[4] and a poor prognostic factor in patients with gastric cancer.[5–8] However, the recent introduction of chemotherapy has changed the clinical picture to some extent. A phase 2 trial that explored the effect of D2 dissection followed by chemotherapy with S-1 reported a median overall survival (OS) of 24 months in patients with CY1 gastric cancer alone.[3]

However, few studies have investigated stratified treatments for patients with CY1 gastric cancer in the presence or absence of metastatic disease.[5,6] To evaluate the optimal treatment for these patients, we retrospectively examined the clinicopathologic and survival data for patients who had undergone gastrectomy and/or chemotherapy for this type of advanced cancer regardless of the presence of metastatic disease.

Patients and Methods

This study was approved by the ethics committee of Saitama Medical Center at Saitama Medical University. We retrospectively reviewed a database of 54 patients with CY1 gastric cancer in the presence or absence of metastatic disease. All patients had undergone gastrectomy and/or chemotherapy at the Saitama Medical Center of Saitama Medical University from January 2005 to December 2013. Peritoneal washing for cytologic examination was performed during laparotomy or laparoscopic evaluation. About 100 mL of sterile saline was instilled into the Douglas pouch, and a washing sample was then aspirated and collected. The Eastern Cooperative Oncology Group performance status was evaluated in every patient upon admission. The median follow-up duration was 12 months (range, 1.4–62.0 months) after initial treatment by gastrectomy and/or chemotherapy.

We performed tumor staging and histopathologic grading according to the seventh edition of the Union for International Cancer Control pTNM staging guidelines.[9] We described the tumor location, macroscopic type, and metastatic disease according to the definitions of the Japanese Gastric Cancer Association.[10]

Statistical analysis

Continuous variables are expressed as median and range. Grouping of categoric and continuous variables was carried out using standard thresholds. Cox proportional hazard regression analysis was used to identify statistically significant independent factors for survival. Factors with a P value of <0.05 in the univariate analysis were assessed by multivariate analysis. In the univariate and multivariate analyses, odds ratios with 95% confidence intervals were calculated. Survival curves were drawn by the Kaplan-Meier method and compared with the log-rank test. We performed all statistical analyses with JMP 5.0 software (SAS Institute Inc, Cary, NC). A P value of <0.05 was considered to be statistically significant.

Results

The characteristics of the 54 patients with CY1 gastric cancer are presented in Table 1. There were 34 male and 20 female patients, with a median age of 70 years (range, 26–86 years). Among 40 patients with metastatic disease (74%), 37, 9, and 17 had peritoneal (P1), hepatic (H1), and distant (M1) metastasis, respectively. A total of 32 patients (59%) had undergone gastrectomy, whereas 10, 7, and 5 patients had undergone gastrojejunostomy, staging laparoscopy, and exploratory laparotomy, respectively. Of the 51 patients (94%) who received chemotherapy, mainly with S-1–based regimens, 29 also underwent gastrectomy, whereas 22 did not undergo gastrectomy (they were treated with chemotherapy alone).

The median OS of the entire cohort was 17 months after initial treatment. The median OS did not differ significantly between patients with ($n = 14$) and without ($n = 40$) metastatic disease (19 versus 13 months, respectively; $P = 0.12$; Fig. 1A).

We selected the following 14 factors for the univariate analysis: age (<70 versus ≥70 years), sex (male versus female), performance status (0 versus 1, 2) tumors located throughout the whole body (no versus yes), macroscopic type (type 2 or 3 versus type 4), histologic type (G1 or G2 versus G3), tumor depth (T3 or T4a versus T4b), nodal stage (N0–N2 versus N3), P1 (no versus yes), H1 (no versus yes), M1 (no versus yes), number of metastatic organs (0–2 versus 3), gastrectomy (no versus yes), and chemotherapy (no versus yes). According to the univariate analysis, the following 3 factors were significantly associated with worse OS: H1 ($P = 0.03$), greater number of metastatic organs ($P = 0.05$), and lack of gastrectomy ($P < 0.01$). According to the multivariate analysis, lack of gastrectomy was the only significant independent

Table 1 Demographics of 54 patients with gastric cancer and positive peritoneal cytology

	Total
Age, y	
Median (range)	70 (26–86)
Sex	
Male	34
Female	20
Performance status	
0	28
1, 2	26
Location	
Upper third	11
Middle third	10
Lower third	24
Whole body	9
Macroscopic type	
Type 2	6
Type 3	28
Type 4	20
Histologic type	
Differentiated (G1, G2)	15
Undifferentiated (G3)	39
Tumor depth	
T3	6
T4a	40
T4b	8
Nodal stage	
N0	5
N1	10
N2	9
N3	30
Peritoneal metastasis	
No (P0)	17
Yes (P1)	37
Hepatic metastasis	
No (H0)	45
Yes (H1)	9
Distant metastasis	
No (M0)	37
Yes (M1)	17
No. of metastatic organs	
0	14
1	23
2	12
3	5
Gastrectomy	
No	22
Yes	32
Chemotherapy	
No	3
Yes	51

prognostic indicator for survival (odds ratio, 1.64; 95% confidence interval, 1.04–2.57; $P = 0.03$; Table 2).

The median OS for the 29 patients treated with gastrectomy plus chemotherapy was 25 months. The median OS times for both the 22 patients treated with chemotherapy alone and the 3 patients treated with gastrectomy alone were 10 and 17 months,

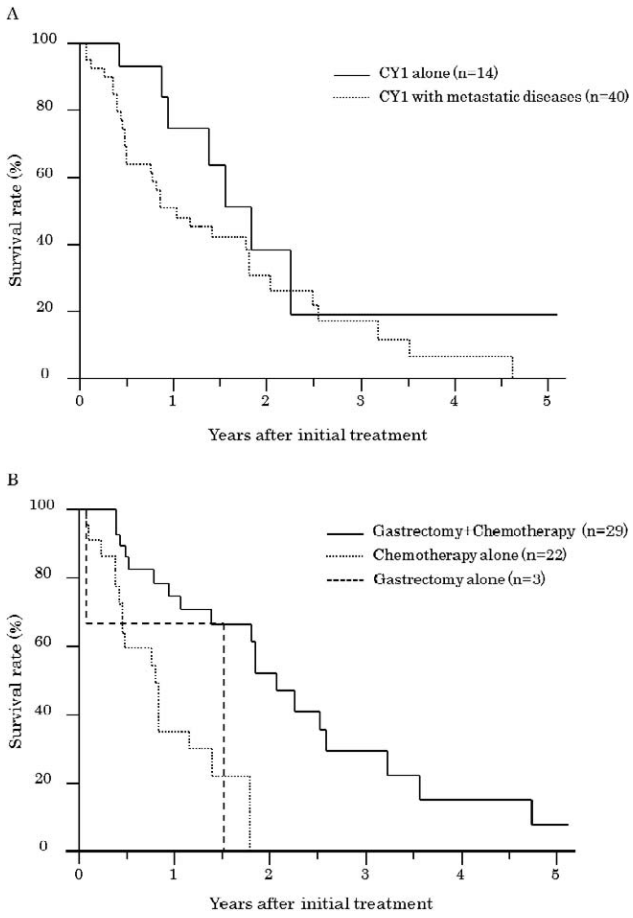

Fig. 1 Cumulative OS of 54 patients with CY1 gastric cancer. (A) The cumulative OS of 14 patients with CY1 gastric cancer alone was comparable with that of 40 patients with CY1 gastric cancer in the presence of metastatic disease ($P = 0.12$). (B) The cumulative OS of 29 patients treated with gastrectomy plus chemotherapy was significantly better than that of 25 patients treated with chemotherapy alone or gastrectomy alone ($P < 0.01$).

respectively. The median OS differed significantly between patients treated with gastrectomy plus chemotherapy and those treated with chemotherapy alone or gastrectomy alone ($P < 0.01$; Fig. 1B).

Discussion

We have clearly shown that gastrectomy is an independent favorable factor in patients with CY1 gastric cancer in the presence or absence of metastatic disease. Furthermore, we have shown that gastrectomy plus chemotherapy may improve the prognosis of these patients based on the survival data.

Table 2 Univariate and multivariate analyses in relation to overall survival

	Univariate		Multivariate	
Variables	Odds ratio (95% CI)	*P* value	Odds ratio (95% CI)	*P* value
Age, y				
<70 (n = 27)	1			
≥70 (n = 27)	1.30 (0.93–1.83)	0.13		
Sex				
Male (n = 34)	1.14 (0.59–2.25)	0.69		
Female (n = 20)	1			
Performance status				
0 (n = 28)	1			
1, 2 (n = 26)	1.59 (0.79–3.12)	0.19		
Location of whole body				
No (n = 45)	1			
Yes (n = 9)	1.68 (0.71–3.53)	0.22		
Macroscopic type				
Type 2, 3 (n = 34)	1			
Type 4 (n = 20)	1.32 (0.94–1.83)	0.10		
Histologic type				
G1, G2 (n = 15)	1			
G3 (n = 39)	1.65 (0.79–3.88)	0.19		
Tumor depth				
T3, T4a (n = 46)	1			
T4b (n = 8)	1.72	0.30		
Nodal stage				
N0–N2 (n = 24)	1			
N3 (n = 30)	1.78 (0.92–3.61)	0.08		
Peritoneal metastasis				
No (n = 17)	1			
Yes (n = 37)	1.44 (0.72–3.14)	0.31		
Hepatic metastasis				
No (n = 45)	1			
Yes (n = 9)	2.74 (1.14–5.93)	0.03[a]	1.07 (0.28–3.36)	0.91
Distant metastasis				
No (n = 37)	1			
Yes (n = 17)	1.23 (0.62–2.42)	0.51		
No. of metastatic organs				
0–2 (n = 49)	1			
3 (n = 5)	3.49 (1.00–9.37)	0.05[a]	1.89 (0.43–8.27)	0.38
Gastrectomy				
No (n = 22)	1.76 (1.21–2.58)	<0.01[a]	1.64 (1.04–2.57)	0.03[a]
Yes (n = 32)	1			
Perioperative chemotherapy				
No (n = 3)	1.55 (0.62–2.85)	0.29		
Yes (n = 51)	1			

CI, confidence interval.

[a]Significantly different.

It is well known that CY1 gastric cancer has a poor prognosis because it is associated with noncurative factors, such as P1, H1, and M1. In a large retrospective study, multivariate analysis indicated that CY1 was an independent predictor of prognosis in patients with locally advanced gastric cancer who were undergoing curative gastrectomy.[11] In recent studies, the median OS of patients with CY1 gastric cancer alone who underwent surgery was 12 to 24 months,[3,7,8,12] which is similar to that of our study (19 months). Moreover, previous studies have reported that noncurative gastrectomy, poorer performance status, clinical N3, and type 4 are independent unfavorable predictors of survival among patients with CY1 gastric cancer.[5–8] Some studies have suggested that CY1 alone does not increase the available prognostic information.[13,14] Therefore, the prognostic significance of CY1 alone remains controversial.

In the present study, the median OS (13 months) did not differ significantly between patients with and without metastatic disease. Moreover, we evaluated the optimal treatment strategy for these patients based on our survival data. The multivariate analysis showed that gastrectomy was the only independent prognostic factor among patients with CY1 gastric cancer with or without metastatic disease. However, it is clear that this study and the others discussed suffer from selection bias. In this study, gastrectomy does not seem to be sufficient to decide the therapeutic procedure for all patients with CY1 gastric cancer. It may still be optimal to perform gastrectomy for selective patients with CY1 gastric cancer.

Furthermore, the median OS of the 29 patients treated with gastrectomy plus chemotherapy was significantly longer than that of the patients treated with chemotherapy alone or gastrectomy alone in this study. Recent studies have shown perioperative chemotherapy with S-1 or S-1 plus cisplatin may improve the prognosis of patients with CY1 or P1 gastric cancer treated with curative gastrectomy.[3,5] The expected prognosis for CY1 gastric cancer, even with metastatic disease, seemed to be associated with the addition of modern chemotherapy, such as these regimens, to gastrectomy. Moreover, gastrectomy itself may contribute to the continuation of modern chemotherapy by preventing tumor stenosis or bleeding if the surgery is reductive.[15] In this study, 91% (29 of 32) of patients who had undergone gastrectomy received first-line chemotherapy, mainly with S-1–based regimens. However, because chemotherapy with these regimens was not treated equally with all patients, its efficacy cannot be sufficiently evaluated.

Although this retrospective study was performed at a single center in a patient population limited by selection bias, it stimulates further inquiry into how to manage patients with CY1 gastric cancer, even in the presence of metastatic disease. 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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