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ORIGINAL ARTICLE

Clinical significance of CA125 and CA72-4 in gastric cancer with peritoneal dissemination

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Abstract
Background Serum tumor markers have been shown to correlate with the clinical status of patients with advanced gastric cancer. However, the clinical significance of each tumor marker in patients with peritoneal dissemination has not been fully verified.
Methods Four serum markers, carcinoembryonic antigen (CEA), carbohydrate antigen (CA) 19-9, CA125, and CA72-4, were periodically measured in 102 patients with peritoneal dissemination who received combination intravenous and intraperitoneal chemotherapy. The initial values at diagnosis and after treatment were analyzed in association with clinicopathological factors, response to chemotherapy, and overall survival.
Results The sensitivities of CEA, CA19-9, CA125, and CA72-4 for peritoneal metastasis at the initial diagnosis were 19, 36, 46, and 45%, respectively. The CA125 level was significantly correlated with the degree of peritoneal dissemination and the existence of malignant ascites. Patients with ovarian metastasis showed significantly higher levels of CA72-4. The median survival time of patients with an elevated CA125 level was significantly shorter than that of patients with a normal CA125 level (36.7 vs. 16.6 months, $p < 0.001$). Multivariate analysis showed that the degree of peritoneal metastasis and an elevated CA125 level were independent prognostic factors. Normalization of the CA125 level after 3 courses of chemotherapy was correlated with reduced ascites and improved survival.
Conclusions Serum CA125 and CA72-4 are clinically useful markers in diagnosis, evaluating the efficacy of chemotherapy, and predicting the prognosis of patients with peritoneal dissemination. From an academic point of view, periodic measurements of these markers are warranted in gastric cancer patients with possible peritoneal dissemination.

Keywords Tumor markers · Gastric cancer · Peritoneal dissemination · CA125 · CA72-4

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Introduction

Although the incidence and mortality rate of gastric cancer have decreased worldwide, it remains the fourth leading cause of cancer-related death [1]. Peritoneal metastasis is the most frequent and life-threatening form of metastasis and recurrence in patients with gastric cancer. Chemotherapy has been shown to prolong the survival of gastric cancer patients, but it has not achieved complete success yet. Recently, intraperitoneal chemotherapy has been shown to have a considerable positive effect on peritoneal dissemination [2, 3].

In clinical practice, the assessment of the efficacy of chemotherapy regimens is important for determining whether treatment should be continued or changed to another regimen. Computed tomography (CT) is commonly utilized to evaluate response in metastatic gastric cancer, and tumor markers, including carcinoembryonic antigen (CEA) and carbohydrate antigen (CA)19-9, are also taken into account as supplementary evidence of response [4, 5]. However, in patients with peritoneal metastases, tumor markers are often the only tool with which to evaluate the response to chemotherapy, because

individual peritoneal lesions are usually too small to be measured accurately by using CT scans.

In addition to the 2 common markers CEA and CA19-9, CA125 and CA72-4 have been reported to be elevated in advanced gastric cancer [6]. However, these markers are not all commonly measured, due to the lack of clinical evidence of their value. Serum CA125 levels are known to be elevated in peritoneal inflammation and in carcinomatosis, and are widely used in the diagnosis of ovarian cancer [7, 8]. A significant relationship between CA125 and gastric cancer with peritoneal dissemination has been reported [9–11]. However, in these studies, the number of patients with peritoneal metastasis was relatively small. Although serum CA72-4 has also been reported to be elevated in the advanced stages of gastric cancer [12–15], the clinical relevance of CA72-4 in peritoneal metastasis remains unclear.

In the present study, we retrospectively examined serum CEA, CA19-9, CA125, and CA72-4 levels in more than 100 gastric cancer patients with peritoneal dissemination, and re-investigated the clinical significance of these markers in gastric cancer with peritoneal metastasis.

Patients and methods

Patients and chemotherapy

A total of 102 consecutive gastric cancer patients with peritoneal metastasis who received combination chemotherapy between February 2005 and December 2010 at The University of Tokyo Hospital were enrolled in this study. Patients who also had distant metastasis other than ovarian metastasis were excluded. Patients with ovarian metastases were not excluded from the study because the frequency of co-existence of ovarian metastasis is high in peritoneal dissemination, and the relationship between CA125/CA72-4 and ovarian tumor has been pointed out. Patient characteristics are listed in Table 1. The chemotherapy regimen consisted of S-1, and intravenous and intraperitoneal paclitaxel, as described previously [2]. In brief, a peritoneal access port was implanted in the subcutaneous space of the lower abdomen, with a catheter placed in the pelvic cavity. S-1 was administered orally twice daily at a dose of 80 mg/m^2/day for 14 consecutive days, followed by 7 days' rest. Paclitaxel was administered intravenously at a dose of 50 mg/m^2, and intraperitoneally at 20 mg/m^2 on days 1 and 8. Paclitaxel was diluted in 1 liter of normal saline and administered through the implanted peritoneal access port over 1 h concurrently with intravenous infusion after standard premedication. Chemotherapy was repeated until disease progression or intolerable toxicity. This study was approved by the Ethics Committee of The University of Tokyo, and informed consent was obtained from all of the patients enrolled.

Table 1 Patient characteristics

Total no. of patients	102
Age (years)	
Median	57
Range	28–79
Sex	
Male	54
Female	48
Performance status (ECOG)	
0	73
1	28
2	1
Macroscopic type	
0	1
1	2
2	1
3	31
4	64
5	2
Histological type	
Intestinal	9
Diffuse	83
Mixed	10
Prior chemotherapy	
Yes	50
No	52
Prior gastrectomy	
Yes	22
No	80
Peritoneal metastasis	
P1	8
P2	25
P3	69
Ascites	
Present	73
Absent	29
Ovarian metastasis	
Present	16
Absent	32

ECOG European Cooperative Oncology Group

Measurement and assessment of tumor markers

Four serum tumor markers, CEA, CA19-9, CA125, and CA72-4, were measured before chemotherapy and monthly during treatment. CEA levels were investigated using a fluorescence-enzyme immunoassay (FEIA), while CA19-9 and CA125 levels were investigated using a chemiluminescent enzyme immunoassay (CLEIA); these assays were done at the Department of Clinical Laboratory, The

University of Tokyo Hospital. CA72-4 levels were investigated using an immuno-radiometric assay (IRMA) in a commercial laboratory (SRL, Tokyo, Japan). Levels at initial diagnosis and changes during treatment were analyzed in each patient. The cut-off values for CEA, CA19-9, CA125, and CA72-4 were defined as 5.0 ng/ml, 37 U/ml, 30 U/ml, and 4.0 U/ml, respectively. The sensitivity of the markers was calculated as the number of patients who showed elevated levels of each marker above the cut-off value divided by the total number of patients. The sensitivity of the combination of multiple markers was calculated as the percentage of patients who showed elevation in any of the combined markers.

The changes in each marker were evaluated in 93 patients in whom the markers could be measured after 3 courses of chemotherapy, and changes in the markers were evaluated in patients with levels of these markers above the cut-off value at the initial diagnosis.

Evaluation of patients' clinical status

The primary tumor and metastatic lesions were evaluated by gastroendoscopy and CT scan (contrast-enhanced, if possible). Peritoneal metastasis was also evaluated, by diagnostic laparoscopy, before chemotherapy and categorized into 3 groups according to the 12th edition of *The general rules for gastric cancer study* of the Japanese Research Society for Gastric Cancer [16] and the 1st edition of the *Japanese classification of gastric carcinoma* [17]: P1 (adjacent peritoneal involvement), P2 (a few scattered metastases to distant peritoneum), and P3 (many distant peritoneal metastases). The level of ascites was evaluated by CT scan and categorized into 4 groups; none, mild (limited pelvic involvement), moderate (over the pelvis), and severe (with marked abdominal distention requiring drainage). Tumor markers at the initial diagnosis were analyzed in relation to clinical status and overall survival. Univariate and multivariate analyses of prognostic factors for overall survival were also performed. Fourteen putative clinicopathological variables were selected, based on factors identified by previous studies [4, 15]. Patient-related factors included age, sex, and pre-treatment performance status according to the European Cooperative Oncology Group (ECOG). Tumor-related factors included macroscopic type, histological type, lymph node metastasis, degree of peritoneal metastasis (as mentioned above), peritoneal cytology, presence of ovarian metastasis, and the 4 tumor markers. The responses of the tumor markers were also analyzed in relation to the clinical response and overall survival.

Statistical analyses

Fisher's exact test was used for analyses of the sensitivity and positivity of each marker. The nonparametric Wilcoxon rank-sum test was used for the comparison of each original value of a tumor marker between 2 groups. Survival rates were calculated according to the Kaplan–Meier method, and differences were evaluated using the log-rank test. Cox's proportional hazards regression model was used to identify prognostic factors for survival. p values of <0.05 were considered statistically significant. All statistical analyses were performed using the JMP program version 8.0 (SAS Institute, Cary, NC, USA).

Results

Sensitivities of tumor markers for peritoneal metastasis

The sensitivities of the 4 markers and combinations of 2 of these markers for peritoneal metastasis are listed in Table 2. The sensitivities of CA125 and CA72-4 were 46.1 and 44.9%, respectively, which were higher than those of CEA and CA19-9. Of the combinations of 2 markers, CA125 and CA72-4 together showed the highest sensitivity (68.0%), while CEA and CA19-9 showed the lowest sensitivity (44.1%). The sensitivity was 78.4% for the combination of all 4 markers.

CA125 is correlated with the degree of peritoneal metastasis and level of ascites

The positivity of serum CA125 was significantly correlated with the presence of ascites (Table 3). The CA125 level was significantly higher where ascites was present (median 40.0 vs. 18.0 U/ml, $p < 0.0001$) and the CA125 level was significantly associated with the level of ascites (Fig. 1). The degree of peritoneal metastasis was also correlated with CA125 (Fig. 2). No significant correlation was observed between these factors and CEA, CA19-9, and CA72-4.

Table 2 Sensitivities of 4 serum tumor markers and combinations of 2 markers

	Sensitivity	Combination		
		CA19-9 (%)	CA125 (%)	CA72-4 (%)
CEA	18.6% (19/102)	44.1	52.9	51.0
CA19-9	36.3% (37/102)		62.7	60.0
CA125	46.1% (47/102)			68.0
CA72-4	44.9% (44/98)			

Each sensitivity value was calculated as the number of patients who showed an elevated level, above the cut-off value, of each marker divided by the total number of patients. The values for the combinations are the percentages of patients who showed elevated levels of either of the indicated markers

CEA carcinoembryonic antigen, *CA* carbohydrate antigen

Table 3 Correlation between the presence of ascites and tumor markers

	Ascites		OR	95% CI	*p*
	+	−			
CEA					
Elevated	16	3	2.43	0.65–9.08	0.14
Normal	57	26			
CA19-9					
Elevated	28	9	1.38	0.55–3.46	0.32
Normal	45	20			
CA125					
Elevated	42	5	6.50	2.23–18.94	<0.0005
Normal	31	24			
CA72-4					
Elevated	34	10	1.70	0.69–4.20	0.18
Normal	36	18			

CEA, CA19-9, and CA125 were measured in all the 102 patients, whereas CA72-4 was measured in 98 patients. OR is the ratio of the odds of the presence of ascites in the elevated-marker-level group to the odds of the presence of ascites in the normal-marker-level group

OR Odds ratio, *CI* Confidence interval

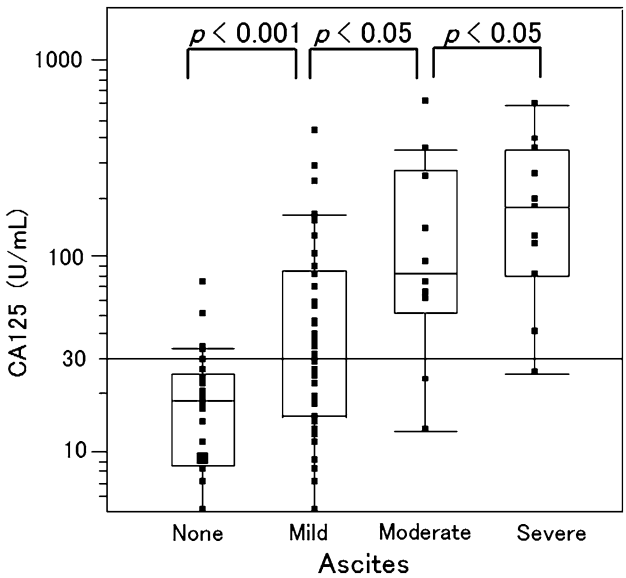

Fig. 1 Tukey's *boxplot* showing positive correlation between carbohydrate antigen 125 (*CA125*) levels and the level of ascites. Nonparametric multiple comparison tests (Wilcoxon rank-sum test) indicated serum CA125 levels were increased significantly according to the level of ascites. *Horizontal line* median value, *columns* interquartile ranges, *whiskers* from the ends of the columns to the outermost data points within the upper quartile + (1.5 × [interquartile range]) and lower quartile − (1.5 × [interquartile range])

CA72-4 is correlated with ovarian metastasis

The level of CA72-4 was significantly higher in patients with ovarian metastasis and its positivity was correlated with the presence of ovarian metastasis (Table 4). However, the other 3 markers, including CA125, were not correlated with ovarian metastasis.

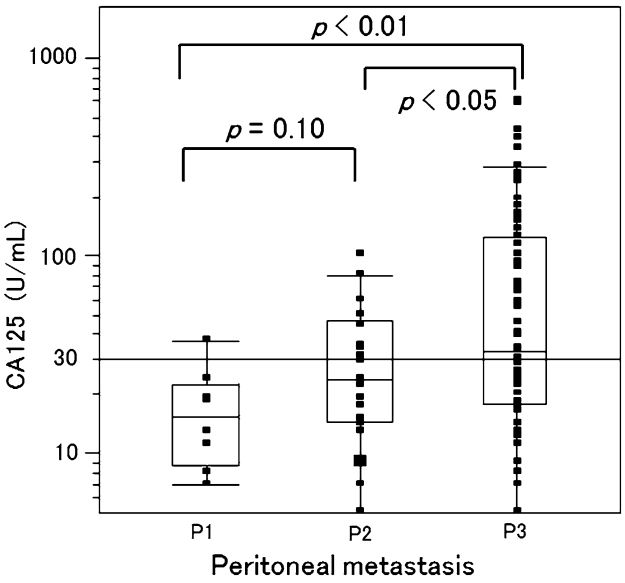

Fig. 2 Positive correlation between CA125 levels and the degree of peritoneal metastasis. Nonparametric multiple comparison tests (Wilcoxon rank-sum test) indicated serum CA125 levels were increased significantly according to the degree of peritoneal metastasis. *P1* metastases to the adjacent peritoneum, *P2* a few metastases to the distant peritoneum, *P3* numerous metastases to the distant peritoneum. *Horizontal line*, *whiskers*, and *columns*, as in Fig. 1

Correlation of tumor markers with other factors and clinical outcome

The correlations between the 4 tumor markers and other clinical factors, such as macroscopic type, histology, and lymph node metastasis, were analyzed, but no significant correlation was observed. The overall survival was significantly shorter in patients with elevated levels of CA125 (median survival time [MST]; 36.7 vs. 16.6 months, $p < 0.001$) (Fig. 3). However, the serum levels of the other markers were not associated with survival (data not shown).

The results of univariate and multivariate analyses of other prognostic factors for overall survival are shown in Table 5. Univariate analysis revealed that the degree of peritoneal metastasis, positive peritoneal cytology, presence of ascites, and elevated CA125 were significant prognostic factors. Multivariate analysis of these 4 factors showed that the degree of peritoneal metastasis and elevated CA125 were independent prognostic factors.

Changes in tumor markers and clinical factors

The tumor markers were assessed after 3 courses of combination chemotherapy, and the results are shown in

Table 4 Correlation between ovarian metastasis and CA72-4

CA72-4	Ovarian metastasis		OR	95% CI	*p*
	+	−			
Elevated	11	11	5.25	1.35–20.4	<0.05
Normal	4	21			
Median	6.8	3.2			<0.05

CA72-4 was measured in 47 women. OR is the ratio of the odds of the presence of ovarian metastasis in the CA72-4-elevated-level group to the odds of the presence of ovarian metastasis in the CA72-4-normal-level group

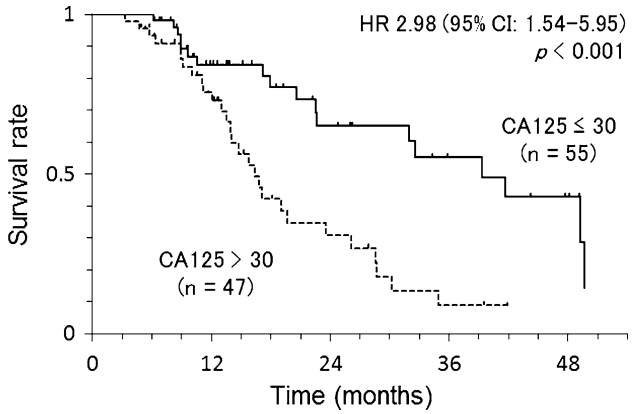

Fig. 3 Kaplan–Meier curves for overall survival showing a significant difference between patients with a normal level of serum CA125 (*solid line*) and those with an elevated level of serum CA125 (*broken line*; $p < 0.001$). *HR* hazard ratio, *CI* confidence interval

Table 6. In patients with elevated levels of each marker before chemotherapy, CA125 was reduced below the cut-off level in 74% of the patients, while CEA levels were normalized in only 18% of the patients. Interestingly, normalization of CA125 levels, but not normalization of the levels of the other 3 markers, showed a significant correlation with the level of ascites (Table 7). Moreover, as shown in Fig. 4, the normalization of CA125 levels was significantly correlated with improved survival (MST 17.0 vs. 9.5 months, $p < 0.001$).

Discussion

Tumor markers are commonly used in clinical practice. Baseline tumor marker levels are thought to provide prognostic information [18]. In gastric cancer, the levels of CEA and CA19-9 are widely used to predict prognosis and recurrence [4, 5, 19], but the clinical significance of these tumor markers remains unclear in terms of decision-making in the treatment of peritoneal metastasis. Previous reports have shown that the positivities of CA125 and CA72-4 were lower than those of CEA and CA19-9 in all stages of gastric cancer, but the sensitivities of CA125 and CA72-4 were relatively high in the advanced stages [19]. In our patients with peritoneal dissemination, CA125 and CA72-4 showed higher sensitivity than the other two tested markers.

Table 5 Univariate and multivariate prognostic analyses for overall survival

	HR	95% CI	*p*
Univariate analysis			
Age > 57 years	0.72	0.39–1.31	0.28
Female	1.08	0.60–1.95	0.79
PS1, PS2	1.68	0.90–3.04	0.10
Type 4	1.06	0.58–1.95	0.85
Diffuse	0.88	0.41–2.20	0.77
Lymph node metastasis	1.11	0.61–2.00	0.72
P2, P3	6.94	2.05–43.5	<0.001
Peritoneal cytology	2.19	1.05–5.17	<0.05
Ascites	3.18	1.58–7.14	<0.001
Ovarian metastasis	0.77	0.29–1.91	0.58
CEA > 5 (ng/ml)	1.54	0.69–3.08	0.27
CA19-9 > 37 (U/ml)	1.51	0.83–2.74	0.17
CA125 > 30 (U/ml)	2.99	1.61–5.74	<0.001
CA72-4 > 4 (U/ml)	1.24	0.67–2.29	0.48
Multivariate analysis			
P2, P3	5.88	1.45–40.0	<0.05
Peritoneal cytology	0.74	0.29–2.04	0.55
Ascites	2.00	0.88–4.97	0.10
CA125 > 30 (U/ml)	2.24	1.14–4.56	<0.05

PS performance status, *HR* hazard ratio

Table 6 The normalization of markers after chemotherapy in patients who were marker-positive at initial diagnosis

	CEA	CA19-9	CA125	CA72-4
Normalized	3 (18%)	13 (39%)	31 (74%)	12 (28%)
Unnormalized	14 (82%)	20 (61%)	11 (26%)	31 (72%)

Table 7 Correlation between CA125 response and change in the level of ascites

CA125	Ascites		OR	95% CI	*p*
	Increase/ no change	Decrease/ disappearance			
Normalized	9	20	5.93	1.27–27.7	<0.05
Unnormalized	8	3			

CA125 and the level of ascites were re-evaluated after 3 courses of chemotherapy. The level of ascites was divided into 4 categories, consistent with findings shown in Fig. 1, and the change was categorized into 2 groups: "increase or no change" and "decrease or disappearance". Of 42 patients with elevated CA125 levels at the initial diagnosis, 40 patients were assessed for changes in the level of ascites. OR is the ratio of the odds of increase or no change in the level of ascites in the CA125 unnormalized group to the odds of increase or no change in the CA125 normalized group

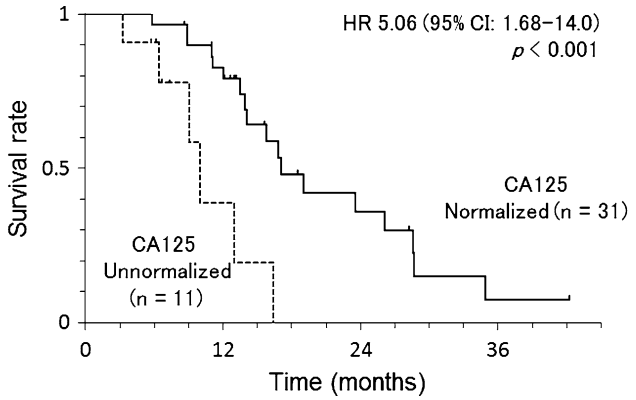

Fig. 4 Kaplan–Meier curves for overall survival showing a significant difference between the group in whom CA125 levels were normalized (*solid line*) and the group in whom CA125 levels remained elevated (*unnormalized*, *broken line*; $p < 0.05$)

Serum CA125 is commonly used, in combination with the guideline of the Response Evaluation Criteria in Solid Tumors (RECIST) Group, in ovarian cancer [7, 8]. CA125 is a large-molecule glycoprotein of transmembrane mucin named MUC16, and it has been shown to be aberrantly overexpressed in various malignancies, including ovarian cancer. Of note, the presence of ascites is a key determinant of CA125 at diagnosis in ovarian cancer [20, 21]. CA125 also exists in the mesothelial cells covering the peritoneum [22], which may explain CA125 elevation caused by peritoneal or endometrial inflammation other than cancer [9].

CA125 levels have been reported to be elevated in some gastric cancer patients. In previous studies, serum CA125 levels were shown to be elevated according to the degree of peritoneal dissemination with gastric cancer [9], and to be highly sensitive for predicting peritoneal metastasis [10, 11]. Moreover, in one of these studies [11], the level of CA125 was correlated with survival, although the number of patients in the study was relatively low. Our results on CA125 in more than 100 patients with gastric cancer are mostly consistent with those in previous studies, and suggest that serum CA125 reflects the status of peritoneal lesions of gastric as well as ovarian cancer.

Adachi and colleagues [23] reported that in ovarian cancer, the serum CA125 level could be influenced not only by CA125 production by the primary tumor but also by CA125 production in the mesothelium. They suggested that an increase in serum CA125 level in the CA125-positive tumor group might reflect tumor progression; in the CA125-negative tumor group, this might reflect the development of ascites or peritonitis carcinomatosa. Therefore, immunohistochemical analysis is warranted to distinguish these 2 different conditions. In fact, a previous study has shown that the production of CA125 by gastrointestinal tract cancer cells is infrequent [24]. Therefore, it may be more reasonable that an elevated level of CA125 is not derived from increased cancer cell volume but mainly reflects the severity of peritonitis caused by carcinomatosis.

One of the important clinical uses of tumor markers is for evaluating the efficacy of chemotherapy. Yamao et al. [6] reported that, in 26 patients with advanced gastric cancer, the survival time of responders assessed by the 4 tumor markers CEA, CA19-9, CA125, and CA72-4 was significantly longer than that of non-responders. In our study, the CA125 response showed an excellent correlation with the reduction of ascites and overall survival. We previously showed that the change in ascitic fluid volume was a useful predictor of the outcome of intraperitoneal chemotherapy in gastric cancer patients with peritoneal dissemination [25]. This finding is compatible with the finding that the CA125 response correlates with both reduction of ascites and longer survival. Moreover, in the present study, we showed that CA125 and the degree of peritoneal metastasis were significantly correlated, and both of these were defined as independent prognostic factors for overall survival on multivariate analysis. This finding suggests that CA125 may have biological relevance in the progression or reduction of the peritoneal lesions of gastric cancer. Indeed, it has been shown that CA125 on the cancer cell surface membrane contributes to the formation of metastasis to the peritoneum by initiating cell attachment to the mesothelial cells via binding to their cell-surface molecule mesothelin [26, 27]. Therefore, elevated CA125 may not simply be a result of disease progression, but may in fact have a causal relationship with the progression of peritoneal metastasis.

There have been several studies suggesting that CA72-4 is associated with advanced stages of gastrointestinal cancer and poor prognosis [12–15]. In our study, CA72-4 had the second highest sensitivity for peritoneal dissemination, following CA125. More interestingly, serum CA72-4 was significantly correlated with ovarian metastasis at initial diagnosis, while CA125 did not correlate with ovarian metastasis. CA72-4, a mucin-like glycoprotein compound with a molecular weight of greater than 1000 kDa, can be recognized by 2 monoclonal antibodies: B72.3, isolated using a cell membrane component of metastatic breast cancer to the liver, and CC49, isolated using the LS-174-T colon cancer cell line [28]. CA72-4 has been found to be elevated in a variety of adenocarcinomas with mucinous subtype malignancy, especially ovarian tumors [29]. In ovarian cancer, CA72-4 has been shown to have greater sensitivity for detecting mucinous cystadenocarcinoma, whereas CA125 was effective for the detection of serous cystadenocarcinoma [30]. In our series, positive expression of CA125 or CA72-4 did not correlate with the histological type of gastric cancer ($p = 0.73$, $p = 1.00$), although further study is required because the number of patients with the intestinal type was much smaller than that of patients

with the diffuse type. CA72-4 in metastatic ovarian tumors has not been reported previously, but our results indicate it may be considered a specific marker for the detection of malignant ovarian lesions, including metastasis from gastric adenocarcinoma.

In summary, serum CA125 and CA72-4 can now be considered valuable markers that reflect the quantitative volume of peritoneal dissemination in gastric cancer. Because peritoneal dissemination is the most frequent type of metastasis or recurrence in gastric cancer, the routine measurement of these 2 markers is warranted in patients with advanced gastric cancer with suspected peritoneal dissemination. More importantly, periodic monitoring of CA125 is critically important to determine the efficacy of chemotherapy against peritoneal lesions, as these lesions are rarely measurable by radiologic examinations.

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