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The Clinical Significance of CA19-9 and Tumor Size Ratios for Predicting Prognosis After Conversion Surgery in Patients With Stage IV Gastric Cancer

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Abstract. *Background/Aim: The clinical benefit of conversion surgery (CS) after chemotherapy remains unclear for stage IV gastric cancer (GC) patients. This study aimed to investigate the prognostic factors used to determine whether CS is a promising therapeutic strategy. Patients and Methods: We retrospectively analyzed data from 156 patients diagnosed with unresectable stage IV GC who underwent chemotherapy as the initial treatment, including 40 patients who had R0 resection in CS. Results: The median survival time of the CS patients was significant longer than that of patients who underwent chemotherapy alone. A multivariate analysis identified only pN3 as an independent prognostic factor in CS patients. Among the differentiated tumor type patients, carbohydrate antigen 19-9 (CA19-9) levels were significantly higher in pN3 patients than in pN0-2 patients before chemotherapy. Among undifferentiated tumor type patients, pN3 patients had a significantly lower tumor size ratio (before chemotherapy/before surgery) than pN0-2 patients. Conclusion: Although it is clinically difficult to diagnose lymph node metastasis using preoperative examinations, CA19-9 levels and tumor size ratios may be preoperative indicators for predicting pN3, which is associated with a poor prognosis in CS.*

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Gastric cancer (GC) is the fourth most common malignancy worldwide and the most common in eastern Asia (1). Patient outcomes have improved since gastrectomy and D2 lymph node dissection became the standard procedure for GC worldwide. Although the recent development of systemic chemotherapy has considerably improved the prognosis of patients with unresectable GC, the median survival time (MST) of 6-14 months remains poor (2). The REGATTA trial – a randomized, controlled trial of reduction surgery plus chemotherapy versus chemotherapy alone for stage IV GC with a single noncurative factor – failed to show any survival benefit of reduction surgery (3).

Recently, several studies have reported that surgery combined with perioperative chemotherapy may increase the odds of survival in cases with advanced GC (4-8). Several investigators have reported clinical utility of conversion surgery (CS) after chemotherapy among patients with colorectal, pancreatic, esophageal, and gastric cancers (9-12). CS is another treatment strategy for patients who initially respond to chemotherapy; it aims to achieve R0 resection after chemotherapy for tumors that were either initially unresectable or marginally resectable for technical or oncological reasons (13, 14). However, because stage IV GC patients have different metastasis patterns and heterogeneous backgrounds, it is difficult to predict whether CS will be successful before starting chemotherapy. Although CS could potentially improve clinical prognoses among patients with initially unresectable GC, it is unclear which indicators are important for successful and curative CS. It still remains controversial who should be recommended for CS and when CS should be performed.

The present retrospective study was conducted to evaluate the clinicopathological characteristics of unresectable stage IV GC patients and examine which predictive factors provide a survival benefit following CS.

Table I. *Patient characteristics at diagnosis (n=40).*

		Patients (n=40)
Gender	Male/Female	28/12
Age	<70/≥70	19/21
cT status before chemotherapy	cT0- 3/cT4	9/31
cN status before chemotherapy	cN0-2/cN3	28/12
Histological type	Differ/Undiffer	25/15
Peritoneal dissemination before chemotherapy	0/1	23/17
Liver metastasis before chemotherapy	0/1	29/11
Distant lymph node metastasis before chemotherapy	0/1	25/15
Number of distant metastatic sites	1/≥2	34/6
cT status before conversion surgery	cT0- 3/cT4	22/18
cN status before conversion surgery	cN0-2/cN3	39/1
Operation procedure	TG/DG/PG	23/13/4
Depth of tumor invasion	pT1-3/ pT4	30/10
Lymph node metastasis	pN0-2/pN3	31/9
CEA (ng/ml) before chemotherapy	<5.68/≥5.68	31/9
CA19-9 (U/ml) score before chemotherapy	<37.0/≥37.0	30/10

TG: Total gastrectomy; DG: distal gastrectomy; PG: proximal gastrectomy; Differ: differentiated tumor types; Undiffer: undifferentiated tumor types; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Patients and Methods

Patients and staging. We retrospectively collected the data of 156 patients who were diagnosed with unresectable stage IV GC and underwent chemotherapy as the initial treatment between January 2010 and March 2020 in the Department of Digestive Surgery, Kagoshima University.

Before starting chemotherapy, all patients underwent a blood test, esophagogastroduodenoscopy, fluoroscopy, and computed tomography (CT). After excluding patients who underwent R1 and R2 resection and had incomplete data, 40 patients who had undergone CS were enrolled in the study. Table I summarizes the clinicopathological features of the patients included in analyses. Patients were grouped and staged based on the tumor-node-metastasis classification of gastric carcinoma established by the American Joint Committee on Cancer (15).

Before chemotherapy and surgery, we used CT and ultrasonography to diagnose clinical node staging. Regional lymph nodes were considered to be metastasized if they had a short-axis diameter >8 mm (16). Clustered nodes were categorized as cN2 or cN3, according to the number of nodes estimated on the images. We used CT, positron emission tomography, or staging laparoscopy to determine whether the patient had peritoneal dissemination. Levels of carcinoembryonic antigens and carbohydrate antigen 19-9 (CA19-9) were considered to be elevated at ≥5.68 ng/ml and ≥37.0 U/ml, respectively. This retrospective study was approved by the Ethics Committee of Kagoshima University (approval numbers: 190200 and 200014). Written informed consent was obtained from all patients.

Chemotherapy. Among the 40 patients included in this study, 24 received taxane-based chemotherapy and 16 received platinum-based chemotherapy, including intra-peritoneal paclitaxel therapy. Additionally, 10 patients whose GC was positive for human epidermal growth factor receptor 2 received trastuzumab along with chemotherapy. We assessed the response to chemotherapy using CT and esophagogastroduodenoscopy every 2-6 chemotherapy cycles, using the Response Evaluation Criteria in Solid Tumors (17).

Conversion surgery. CS was clinically indicated for patients with a performance status of at least 0-2 and full curative R0 resection. Therefore, patients underwent a staging laparoscopy that assessed noncurative factors, such as peritoneal dissemination and positive peritoneal cytology; patients with these findings were not considered for CS. Total gastrectomy, proximal gastrectomy, or distal gastrectomy was selected according to the location and the size of the tumor.

Pathological assessments in resected specimens. Following CS, the resected tumor specimens were pathologically examined and categorized according to the Japanese Classification of Gastric Carcinoma (16). Surgical resection was classified as R0, R1, or R2 based on the presence or absence of residual tumors after CS.

Statistical analysis. Statistical analyses of group differences were performed using the χ^2 test and Student *t*-test. We used the Kaplan–Meier method for a survival analysis, and examined differences in survival using the log-rank test. Prognostic factors were assessed using univariate and multivariate analyses (Cox's proportional hazard regression model). All statistical calculations were performed using SAS statistical software (SAS Institute, Inc., Cary, NC, USA). A *p*-value of <0.05 was considered to be statistically significant.

Results

Patient characteristics at diagnosis and conversion surgery. We retrospectively analyzed 40 patients who underwent R0 resection for CS. Total, distal, and proximal gastrectomy were performed in 23, 13, and 4 patients, respectively.

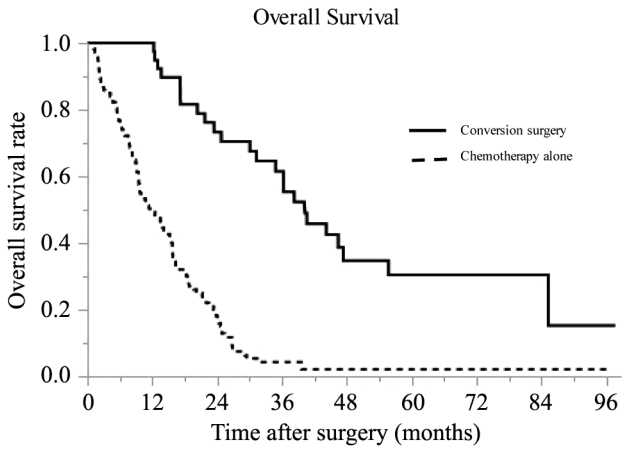

Figure 1. *Kaplan–Meier curves for overall survival of patients who underwent conversion surgery or chemotherapy alone.*

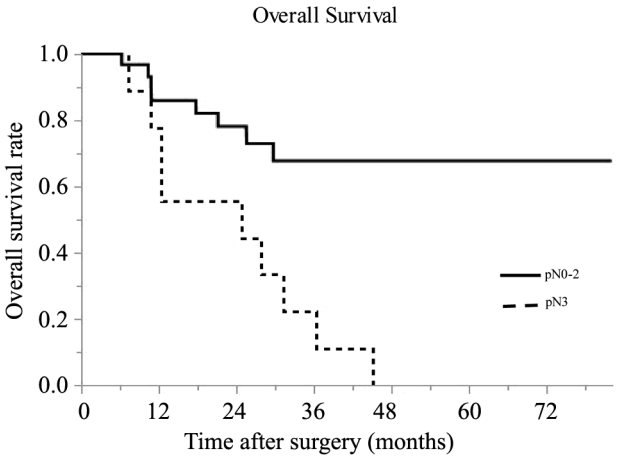

Figure 2. *Kaplan–Meier curves for overall survival of patients with pN0-2 and pN3 who underwent conversion surgery.*

Before chemotherapy, peritoneal dissemination, liver metastasis, and distant lymph node metastasis were found in 17, 15, and 11 patients, respectively. Among 15 patients with liver metastasis, metastasis was not detected before CS in 9 patients. However, liver metastases were found in 6 patients and were removed with CS. Out of 11 patients with distant lymph node metastasis, 7 patients were not detected with metastasis before CS, and 4 patients with lymph node metastasis underwent lymph node dissection. The MST of the CS patients was significantly longer (40.8 months) than that of patients who received chemotherapy alone (12.0 months; $p<0.0001$, log-rank test; Figure 1). Among the 40 CS patients, 24 patients had disease recurrence, 13 had peritoneal dissemination, 7 had liver metastasis, 6 had lymph node metastasis, and 3 had lung metastasis.

Relationship between conversion surgery and survival outcomes. A univariate analysis showed that overall survival (OS) rates in CS patients were significantly associated with peritoneal dissemination ($p=0.007$), distant lymph node metastasis ($p=0.020$), and pre-chemotherapy pN status ($p=0.003$). A multivariate analysis identified pN3 status as the only significant independent predictor of a poor OS rate ($p=0.028$; Table II). Among the 40 CS patients, the patients with pN3 had a 3-year OS rate of 22.2%, while those with pN0-2 had a 3-year OS rate of 74.2% ($p=0.0008$; Figure 2).

Clinicopathological features in patients with pN3. Table III summarizes the clinicopathological factors of patients with pN3. In the 9 patients with pN3, 4 were diagnosed with differentiated tumor types and 5 with undifferentiated tumor types. All 9 patients with pN3 had disease recurrence: 8 had peritoneal dissemination, 2 had lymph node metastasis, and 1 had liver metastasis. Of the 9 pN3 patients, 3 were diagnosed with cN3 before chemotherapy and 1 patient was diagnosed with cN3 before surgery. Out of 25 total patients with differentiated tumor types, CA19-9 levels were higher in the 4 patients with pN3 than in the 21 patients with pN0-2 before chemotherapy and surgery ($p=0.002$; Figure 3A and Table IV).

In the 15 patients with undifferentiated tumor types, the tumor sizes were larger in the 5 patients with pN3 than in the 10 patients with pN0-2 before chemotherapy and surgery and at pathological diagnosis (Table V). The tumor size ratio was defined as the tumor size before chemotherapy to the tumor size before surgery. The tumor size ratio was significantly lower in pN3 patients than in pN0-2 patients ($p=0.032$; Figure 3B).

Discussion

Previous studies reported that CS induced long-term survival in selected patients with stage IV unresectable GC (18-20). Although CS has been proposed for patients who respond to initial chemotherapy, the clinical indications for curative and successful CS remain unclear. Yoshida *et al*. (13) suggested new classifications for those patients with stage IV GC who may benefit from surgery after induction chemotherapy. In this biological categorization system, the presence or absence of macroscopic peritoneal metastasis is an important factor in planning CS (13). In the present study, we examined the clinical data of initially unresectable stage IV GC patients and assessed the clinical indications for success and long-term survival after CS.

We retrospectively examined 40 patients who underwent R0 CS after chemotherapy. The MST of the CS patients was significant longer (40.8 months) than that of patients who

Table II. *Univariate and multivariate analyses of OS of CS patients (n=40).*

	Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*p*-Value	Hazard ratio (95%CI)	*p*-Value
Age		0.051		
≤70 years	Reference			
>70 years	0.35 (0.09-1.01)			
cT status before chemotherapy		0.229		
cT1-3	Reference			
cT4	2.26 (0.63-14.3)			
cN status before chemotherapy		0.525		
cN0-2	Reference			
cN3	1.41 (0.44-3.84)			
Histological type		0.110		
Differentiated	Reference			
Undifferentiated	2.18 (0.83-6.01)			
Peritoneal dissemination before chemotherapy		0.007		0.132
Absent	Reference		Reference	
Present	3.77 (1.42-11.0)		2.29 (0.78-7.41)	
Liver metastasis before chemotherapy		0.462		
Absent	Reference			
Present	0.48 (0.14-1.97)			
Distant lymph node metastasis before chemotherapy		0.02		0.285
Absent	Reference		Reference	
Present	0.26 (0.06-0.82)		0.48 (0.10-1.77)	
CEA (ng/ml) before chemotherapy		0.402		
<5.68	Reference			
≥5.68	1.59 (0.50-4.33)			
CA19-9 (U/ml) score before chemotherapy		0.081		
<37.0	Reference			
≥37.0	2.61 (0.87-7.17)			
pT status		0.458		
pT1-3	Reference			
pT4	1.47 (0.50-3.87)			
pN status		0.003		0.028
pN0-2	Reference		Reference	
pN3	4.47 (1.69-11.9)		3.12 (1.12-8.82)	
Number of distant metastatic sites		0.445		
1	Reference			
≥2	1.46 (0.53-3.82)			

CI: Confidence interval; CEA: carcinoembryonic antigen; CA19-9: carbohydrate antigen 19-9.

Table III. *Patient characteristics with pN3 (n=9).*

	Histological type	cN status before chemotherapy	cN status before surgery	CA19-9 before chemotherapy	CA19-9 before surgery	Tumor size before chemotherapy	Tumor size before surgery
Case 1	Differentiated	3a	1	2,671	912.7	40	40
Case 2	Differentiated	3a	2	3,314	152.1	103	92
Case 3	Differentiated	3a	0	3,140	181.7	80	50
Case 4	Differentiated	2	2	3,198	201.0	250	230
Case 5	Undifferentiated	2	0	5.6	4.4	110	65
Case 6	Undifferentiated	1	3a	7.2	9.6	170	170
Case 7	Undifferentiated	1	0	24.4	19.2	150	145
Case 8	Undifferentiated	0	1	2.7	5.0	88	84
Case 9	Undifferentiated	1	1	17	17.2	75	75

CA19-9: Carbohydrate antigen 19-9.

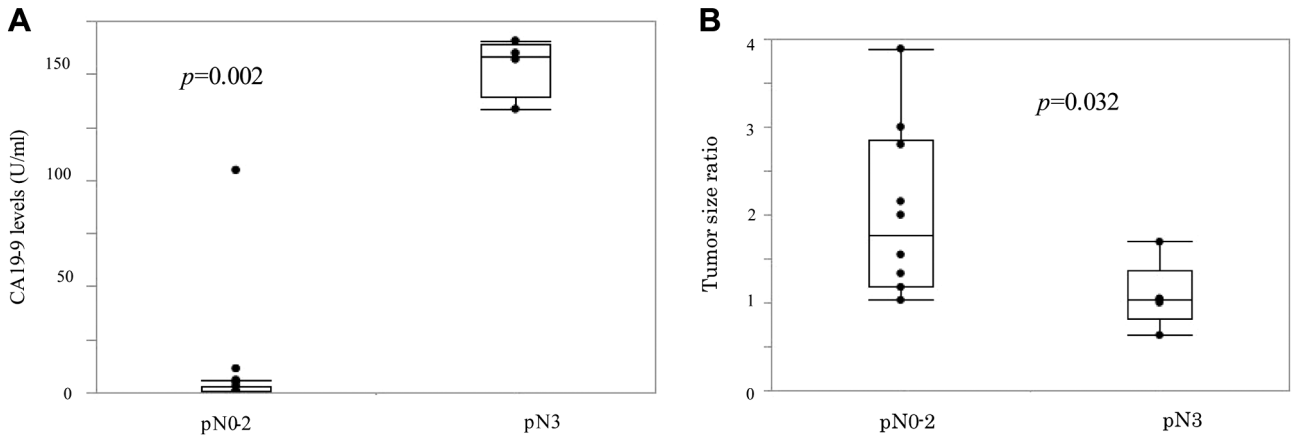

Figure 3. *A. CA19-9 levels before chemotherapy in patients with pN3 and pN0-2. B. Tumor size ratios in patients with pN3 and pN0-2.*

Table IV. *Mean levels of CA19-9 in differentiated tumor types (n=25).*

	CA19-9 before chemotherapy	CA19-9 before surgery	CA19-9 after surgery
pN0-2 (n=21)	136.5 (0.9-2097)	31.2 (0.9-329.5)	10.4 (0.9-30.2)
pN3 (n=4)	3080.7 (2671-3314)	361.8 (152.1-912.7)	218.6 (10.6-453.3)

CA19-9: Carbohydrate antigen 19-9.

Table V. *Mean levels of tumor size in undifferentiated tumor types (n=15).*

	Tumor size before chemotherapy	Tumor size before surgery	Pathological tumor size
pN0-2 (n=10)	53.2 (20-150)	33.2 (9-68)	29.8 (0-70)
pN3 (n=5)	118.6 (75-170)	107.8 (65-170)	129 (70-170)

underwent chemotherapy alone (12.0 months; $p<0.0001$). A multivariate analysis identified only pN3 as an independent prognostic factor in CS patients ($p=0.028$). In patients with differentiated tumor types, pN3 patients had higher CA19-9 levels before chemotherapy than pN0-2 patients ($p=0.006$). In patients with undifferentiated tumor types, pN3 patients had significant larger tumor size ratios than patients with pN0-2 ($p=0.032$).

Morgagni *et al*. reported that the MST was 50 months for patients who had chemotherapy plus surgery compared with 14 months for those who had chemotherapy alone and 3 months only for those who received supported care (21). Kanda *et al*. (22) showed that the MST was 29 months for stage IV GC patients with secondary gastrectomy after S-1-based chemotherapy. Fukuchi *et al*. reported that patients with unresectable GC undergoing R0 and R1/R2 resections had 5-year OS rates of 49 and 15%, respectively (19). Hence, the MST in this study was comparable to those of other investigations.

Recently, several studies have demonstrated the clinical importance of R0 resection in patients undergoing CS (23, 24). However, while CS could potentially improve the clinical prognosis in cases of initially unresectable GC, important indicators for successful and curative CS have been unclear.

In our analysis, we found that pN3 was the only independent prognostic factor in CS patients. Our results showed that pN3 patients have a poor prognosis and should be carefully evaluated for surgery or continued chemotherapy. Although preoperative node staging is essential for the best treatment planning, 3 pN3 patients were diagnosed with cN3 before chemotherapy and only 1 patient was diagnosed with cN3 before surgery in this study. Ohashi *et al*. (25) reported

46.3% overall accuracy of preoperative node staging using contrast-enhanced multi-detector row CT. Fukagawa *et al*. (26) reported a sensitivity of 62.5% and a specificity of 65.7% for contrast-enhanced CT in diagnosing lymph node metastasis. The low positive predictive value (77.7%) and sensitivity (62.5%) were similar to those from precious reports (27, 28). Lymph node assessment by size alone has limitations.

A recent meta-analysis showed that serum CA19-9 levels are associated with disease-free survival of GC patients (29). Several studies reported that elevated CA19-9 levels were also associated with lymph node metastasis in GC (30). Sawayama *et al*. (31) reported that a high preoperative serum CA19-9 level was associated with early recurrence, suggesting that patients with high CA19-9 levels might be candidates for stronger perioperative therapies. In this study, among the patients with differentiated tumor types, CA19-9 levels before chemotherapy were significantly higher in pN3 patients than in pN0-2 patients. Few previous reports have shown associations between the CA19-9 levels and histological type in GC patients. This may be due to higher clinical N stages of patients with differentiated tumor types than in those with undifferentiated tumor types. Our results indicate that CA19-9 levels and tumor size ratio could be important predictors for CS in differentiated and undifferentiated tumor types, respectively.

The present study had several limitations. This preliminary study consisted of a retrospective analysis of a small population (n=40) from a single institution, which may have resulted in bias. Therefore, larger validation studies are needed to strengthen the present results.

Conclusion

Although pN3 was a significant independent prognostic factor in CS patients with initially unresectable GC, a precise preoperative diagnosis of lymph node metastasis was difficult. The CA19-9 levels before chemotherapy and the tumor size ratio may be indicators for successful CS.

Conflicts of Interest

None of the Authors have any financial conflicts of interest regarding the present study.

Authors' Contributions

Conception and design: Keishi Okubo, Takaaki Arigami, Yoshikazu Uenosono, Takao Ohtsuka. Administrative support: Takaaki Arigami, Yoshikazu Uenosono. Provision of study materials or patients: Takashi Kijima, Daisuke Matsushita, Ken Sasaki, Hiroshi Kurahara. Collection and assembly of data: Masahiro Noda, Shigehiro Yanagita, Shinichiro Mori. Data analysis and interpretation: Keishi Okubo, Daisuke Matsushita, Yusuke Tsuruda. Manuscript writing: Keishi Okubo, Takaaki Arigami, Takao Ohtsuka. Final approval of manuscript: All Authors.

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