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Original Article（Clinical Original）

Prognostic impact of CEA/CA19-9 at the time of recurrence in the patients with gastric cancer

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Key Words: CEA, CA19-9, recurrence, gastric cancer, prognosis

Abstract

Purpose: We evaluated the clinical impact of carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) values at the time of recurrence of gastric cancer in patients.

Methods: Among 790 patients with R0 resected gastric cancer without neoadjuvant therapy between 2004 and 2017, 89 recurrence cases were retrospectively evaluated. The clinical impact of CEA and CA19-9 values on recurrence sites and post-recurrent prognosis were evaluated using univariate and multivariate analysis.

Results: The positive rates of CEA and CA19-9 at recurrence were significantly higher than the preoperative positive rates (CEA, 56% vs 24%; CA19-9, 37% vs 15%). Although CA19-9-positive patients at recurrence exhibited poor survival, the difference was not significant. Positive rates of CEA at liver or lymph node recurrence were significantly higher than the preoperative positive rates. The positive rate of CA19-9 at peritoneal recurrence was significantly higher than the preoperative positive rate. CA19-9-positive patients at recurrence exhibited worse prognosis than CA19-9-negative patients, although the difference was not significant. At lymph node recurrence, CA19-9-positive patients exhibited significantly worse survival than CA19-9-negative patients.

Conclusion: In recurrent gastric cancer, the positive status of CA19-9 at recurrence might have a negative prognostic impact after recurrence, particularly in patients with lymph node recurrence.

Introduction

The overall survival of patients with recurrent gastric cancer is dismal, despite improvements in the multimodal treatment for gastric cancer [1]. Although various studies analyzed the clinical significance of preoperative biomarkers [2-4], only a few reports precisely analyzed the clinical significance of biomarkers at recurrence. An early diagnosis of the recurrence may improve its prognosis. Although computed tomography (CT) and ultrasonography are useful in detecting recurrent disease, these diagnostic tools cannot be used frequently for routine examination at every follow-up.

Carcinoembryonic antigen (CEA) and carbohydrate antigen 19-9 (CA19-9) tests are the most common and most convenient blood tests to monitor recurrence [5]; however, the clinical significance of these tumor markers has not been well analyzed in patients with recurrent gastric cancer. Various studies reported that preoperative CEA and CA19-9 may be used as prognostic factors, but their association with recurrent gastric cancer remains unclear. Several reports have examined the relationship between the positive rate of tumor markers measured before gastric cancer surgery and the prognosis [6-9]. Although the positive rates of tumor markers range from 20% to 30% before surgery, the positive rates at the time of recurrence have been reported to be approximately 50% or more [10]. However, only a few reports examine the relationship between recurrent gastric cancer and tumor markers [10,11]. There are no reports that evaluate the association between the positive rates of tumor markers at the time of recurrence, recurrence sites, and prognosis after recurrence.

Therefore, this study aimed to analyze the positive rates of tumor markers in recurrent gastric cancer to evaluate the clinical impact of CEA and CA19-9 at the time of recurrence and their association with prognosis after recurrence.

Methods

Patients

A total of 1130 patients with primary gastric cancers underwent gastrectomy between January 2004 and December 2017 at the Toho University Hospital. Among them, 790 patients were enrolled for subsequent analysis according to the following inclusion criteria: no double cancer, no preoperative treatment, R0 gastrectomy with standard lymphadenectomy performed according to the Japanese gastric cancer treatment guidelines, pathological stage I, II, or III gastric cancer according to the TNM Classification of Malignant Tumors, 8th edition, and sufficient data for analysis. After excluding 124 cases of unknown precise prognostic records, 666 cases were examined for the presence of recurrence. Eventually, 89 cases with recurrence were noted and analyzed in this study (Fig. 1).

Treatment and follow-up

The patients underwent a distal or total gastrectomy with standard lymphadenectomy according to the Japanese gastric cancer treatment guidelines. After surgery, patients were followed up every 3 months for 5 years or until the end of February 2019. Physical examinations and laboratory tests were performed during the follow-up. Enhanced CT (chest and abdominal cavity) examinations were performed every 6 months after surgery. Serum CEA and CA19-9 levels were measured before gastrectomy and at every follow-up visit after surgery. The cutoff values for CEA and CA19-9 were 5.0 ng/mL and 37 IU/mL, respectively. The positive rates of tumor makers were defined as the number of cases with higher than cutoff values divided by the total number of cases. Recurrence was determined based on CT findings and manifestations. The sites of initial recurrence were classified as peritoneal recurrence, liver recurrence, lymph node recurrence, and other recurrences. All

patients were followed up till the end of February 2019 or death.

Statistical analysis

Differences between the two groups were analyzed using Fisher's exact test for categorical variables. Survival curves for overall survival were obtained using the Kaplan–Meier method, and differences were assessed using the log-rank test. The overall survival was evaluated by univariate and multivariate analyses using the Cox proportional hazards model. $P < 0.05$ was considered statistically significant. All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions used frequently in biostatistics [12].

Results

Comparison of clinicopathological characters between nonrecurrent and recurrent gastric cancer cases

The comparison of clinicopathological characters between nonrecurrent and recurrent cases of gastric cancer in this study is presented in Table 1. There were 89 recurrent cases (13%) and 577 nonrecurrent cases (87%). The rates of recurrence were significantly higher in the tumors located at the upper location ($P = 0.009$), in total gastrectomy cases ($P < 0.001$), in T3T4 tumors ($P < 0.001$), and in N2 N 3 cases ($P < 0.001$) than in other cases. The preoperative positive rate of CEA was significantly higher in recurrent cases than in nonrecurrent cases ($P = 0.007$). The preoperative positive rate of CA19-9 was also significantly higher in recurrent cases than in nonrecurrent cases ($P = 0.03$). The preoperative positive rate of CEA and/or CA19-9 was significantly higher in recurrent cases than in nonrecurrent cases ($P = 0.005$).

Comparison of positive rates of CEA and CA19-9 before surgery and at the time of recurrence

Among the 89 recurrent cases, the CEA-positive rates increased significantly from 24% (21 of 89) before surgery to 56% (50 of 89) at the time of recurrence ($P < 0.001$); the CA19-9-positive rates also increased significantly from 15% (13 of 89) before surgery to 37% (33 of 89) at the time of recurrence ($P < 0.001$) (Fig 2).

Comparison of overall survival after recurrence according to the status of CEA and CA19-9

Regarding the preoperative CEA status, there was no significant difference in the prognosis between CEA-positive cases and CEA-negative cases ($P = 0.39$) (Fig 3a), and the relationship between the CEA status at the time of recurrence and prognosis was the same ($P = 0.79$) (Fig 3b). In contrast, regarding the preoperative CA19-9 status, there was no significant difference in the prognosis between CA19-9-positive cases and CA19-9-negative cases ($P = 0.81$) (Fig 3c). CA19-9-positive cases at the time of recurrence exhibited worse prognosis than CA19-9-negative cases, although the difference was not statistically significant ($P = 0.12$) (Fig 3d).

Comparison of overall survival according to the status of CEA and CA19-9 and recurrence sites

The comparison of positive rates of CEA and CA19-9 before surgery and at the time of recurrence is shown in Figure 4. According to the initial recurrence sites, the peritoneal recurrence cases were 33% (29 of 89), the liver recurrence cases were 29% (26 of 89), the lymph node recurrence cases were 22% (20 of 89), and the other recurrences cases were 16% (14 of 89). By peritoneal recurrence, the CEA-positive rates were 21% (6 of 29) before surgery and 48% (14 of 29) at the time of recurrence ($P = 0.05$) (Fig 4a). By liver recurrence, the CEA-positive rates were 8% (2 of 26) before surgery and 58% (15 of 26) at the time

of recurrence ($P < 0.001$). By lymph node recurrence, the CEA-positive rates were 35% (7 of 20) before surgery and 75% (15 of 20) at the time of recurrence ($P = 0.02$). Similarly, by peritoneal recurrence, the CA19-9-positive rates were 14% (4 of 29) before surgery and 41% (12 of 29) at the time of recurrence ($P = 0.03$) (Fig 4b). By liver recurrence, the CA19-9-positive rates were 23% (6 of 26) before surgery and 39% (10 of 26) at the time of recurrence ($P = 0.36$). By lymph node recurrence, the CA19-9-positive rates were 15% (3 of 20) before surgery and 35% (7 of 20) at the time of recurrence ($P = 0.27$).

The overall survival after recurrence according to the initial recurrence sites are shown in Figure 5. The CEA-positive cases showed worse prognosis than the CEA-negative cases with liver recurrence, although the difference was not statistically significant ($P = 0.4$) (Fig 5b); whereas the CA19-9-positive cases showed worse prognosis than CA19-9-negative cases with liver recurrence, although the difference was not statistically significant ($P = 0.06$) (Fig 5e). The CA19-9-positive cases showed worse prognosis than CA19-9-negative cases with lymph node recurrence, but the difference was statistically significant ($P = 0.005$) (Fig 5f). The overall survival curves with the other group did not indicate differences according to the status of the tumor markers (Fig 5a, c, d).

Univariate and multivariate analyses of prognostic variables in patients with recurrent gastric cancer

A univariate analysis was performed for age, gender, histological type, CEA status at the time of recurrence, and CA19-9 status at the time of recurrence, but no significant difference was observed (Table 2). Multivariate analysis also revealed no significant variables. However, CA19-9 showed a slight tendency to reduce overall survival ($P = 0.15$; hazard ratio, 1.45).

Discussion

The positive rates of CEA and CA19-9 at the time of recurrence were significantly higher than the preoperative positive rates. According to the sites of recurrence, the positive rate of CEA increased significantly with liver and lymph node recurrence, whereas the positive rate of CA19-9 increased significantly with peritoneal recurrence. The post-recurrent prognosis was significantly poor in CA19-9-positive patients with lymph node recurrence.

Previous reports showed only the relationship between the preoperative tumor markers' status and recurrence (Table 3) [6,7,10,11,13-18]. However, those reports did not indicate the clinical significance of the tumor markers' status at the time of recurrence. Ushigome et al. reported that CEA- and CA19-9-positive cases at recurrence of colorectal cancer showed significantly poor prognosis [19]. To the best of our knowledge, only a few reports have evaluated the impact of the tumor markers' status at the time of recurrence on the post recurrent prognosis of gastric cancer. Preoperative positive rates of tumor markers were reported to be approximately 30%, and the positive status was reported to be a poor prognostic factor in several papers [5-9,18]. In this study, the preoperative positive rate for both CEA and CA19-9 was also <30%, whereas the positive rates increased significantly at the time of recurrence, which is consistent with other reports [5,10,20]. We examined whether the status of the tumor markers at the time of recurrence reflected the post recurrent prognosis to evaluate the prognostic impact of tumor markers at the time of recurrence. Regarding the prognostic significance of the preoperative CEA and CA19-9 status, no statistical differences were observed in the overall survival between the positive and negative status, which can be partly explained by the patient selection in this study that was limited to recurrent cases. Therefore, the preoperative tumor marker status

predicts only the risk of recurrence, but not the post recurrent prognosis. Focusing on the CEA and CA19-9 status at the time of recurrence, the CEA status at the time of recurrence does not reflect the post recurrent prognosis, although CA19-9 at the time of recurrence might reflect the post recurrent prognosis.

Regarding the association of the CEA and CA19-9 status with recurrence sites, the characteristics of tumor markers in this study were compatible with a previous report [16]. Although the CEA-positive status at the time of recurrence indicated a slight negative impact on the prognosis after liver recurrence (Fig 5b), the CEA status overall had no significant impact on the prognosis according to recurrence sites, but the CA19-9 status had a negative impact on the prognosis after liver recurrence (Fig 5e) and lymph node recurrence (Fig 5f). Such differences between CEA and CA19-9 in the prognostic impact were partially explained by biological differences in the malignant potential of cancer cells between CEA- and CA19-9-positive cases.

Regarding peritoneal recurrence, CEA- and CA19-9-positive cases had a slightly better prognosis than negative cases (Fig 5a, 5d). One of the reasons was that CEA- and CA19-9-positive cases with peritoneal recurrence were detected earlier than imaging examinations. Peritoneal recurrence is usually difficult to detect by regular follow-up. The CEA- and CA19-9-positive cases at recurrence might be diagnosed earlier than both negative cases. Therefore, chemotherapy could be started early, suggesting that this may have positive effects on the prognosis after recurrence. Furthermore, even after the initiation of chemotherapy, the clear change in tumor markers makes it possible to easily evaluate the treatment response of chemotherapy and change the regimen appropriately [11].

CA19-9-positive cases at the time of recurrence tended to have poor prognosis (Fig 3d). This tendency was explained by subgroup

analyses that revealed poor prognosis in CA19-9-positive cases with lymph node recurrence or liver recurrence (Fig 5e, f). Although not statistically significant, multivariate analysis indicated that CA19-9-positive cases had poor prognosis (Table 2). Therefore, previous reports [20-22] suggested that the CA19-9-positive status at the time of recurrence might be a prognostic factor after recurrence owing to the malignant potential of CA19-9-positive cancer cells.

This study has several limitations. This was a retrospective analysis that involved a small number of cases examined as a single-center study. Although chemotherapy regimens should have a great impact on the prognosis after recurrence, we could not evaluate its effects on survival after recurrence. Finally, we excluded the patients with advanced tumors who received neoadjuvant chemotherapy because we intended to evaluate the status of tumor markers while eliminating the effects of preoperative treatment.

In conclusion, among the patients with recurrent gastric cancer, the positive status of CA19-9 at the time of recurrence might have a negative impact on prognosis after recurrence, particularly in patients with lymph node recurrence.

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Compliance with ethical standards

The ethical statement of this retrospective study was approved by the Ethics Committee of Faculty of Medicine, Toho University and the Ethics Committee of Toho University Omori Medical Center (Tokyo, Japan;A16035_A16001_26095_25024_24038_22047, M20196 19056 18002).

Conflict of Interest Statement

Jin Moriyama and the coauthors report no conflict of interest.

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Legends

Figure 1 Flowchart of patient selection

Figure 2 Positive rates of CEA/CA19-9 before surgery and at the time of recurrence. *P* value were analyzed by Fisher's exact test

Figure 3 Overall survivals according to the status of serum tumor markers before surgery and at the time of recurrence. (a) CEA status before surgery and months after recurrence. (b) CEA status at the time of recurrence and months after recurrence. (c) CA19-9 status before surgery and months after recurrence. (d) CA19-9 status at the time of recurrence and months after recurrence. *P* value were analyzed by Log-rank test

Figure 4 Positive rates of CEA/CA19-9 before surgery and at the time of recurrence by initial recurrence sites. (a) CEA (b) CA19-9. *P* value were analyzed by Fisher's exact test

Figure 5 Overall survivals according to the status of serum CEA/CA19-9 at the time of recurrence by initial recurrence sites. (a) Peritoneum recurrence (CEA) (b) Liver recurrence (CEA) (c) lymph node recurrence (CEA) (d) Peritoneum recurrence (CA19-9) (e) Liver recurrence (CA19-9) (F) lymph node recurrence (CA19-9). *P* value were analyzed by Log-rank test

Table 1 Comparison of clinicopathological characters between non-recurrent and recurrent gastric cancer cases

Variables	Non recurrence (n = 577)	Recurrence (n = 89)	*P* value[b]
Age			
≧65 years	369 (64%)	61 (69%)	0.47
< 65 years	208 (36%)	28 (31%)	
Gender			
Male / Female	391 (68%) / 186 (32%)	57 (64%) / 32 (36%)	0.54
Tumor location			
Upper	106 (18%)	29 (33%)	**0.009***
Middle	235 (41%)	27 (30%)	
Lower	236 (41%)	33 (37%)	
Type of gastrectomy			
Total / Partial	173 (30%) / 404 (70%)	52 (58%) / 37 (42%)	**< 0.001***
Histological type			
Diff[a] / Poorly Diff[a]	314 (54%) / 263 (46%)	45 (51%) / 44 (49%)	0.56
Pathological T			
T1	348 (60%)	11 (13%)	**< 0.001***
T2	67 (12%)	9 (10%)	
T3	104 (18%)	35 (39%)	
T4	58 (10%)	34 (38%)	
Pathological N			
N0	425 (74%)	17 (19%)	**< 0.001***
N1	82 (14%)	13 (15%)	
N2	48 (8%)	22 (25%)	
N3	22 (4%)	37 (41%)	
Pathological stage			
Ⅰ	382 (66%)	12 (13%)	**< 0.001***
Ⅱ	128 (22%)	20 (23%)	
Ⅲ	67 (12%)	57 (64%)	
Preoperative positive rates			
CEA	70 (12%)	21 (24%)	**0.007***
CA19-9	44 (8%)	13 (15%)	**0.03***
CEA and/or CA19-9	101 (18%)	27 (30%)	**0.005***

[a] Differentiation

[b] Fisher's Exact Test

Table 2 Univariate and multivariate analyses of prognostic variables in patients with recurrent gastric cancer

Variables	Univariate *P* value[a]	Multivariate *P* value[d]		
		H.R.[b]	95% CI[c]	*P* value
Age (year) (at recurrence)	0.76	0.91	0.50 - 1.65	0.76
≧65 / ＜ 65				
Gender	0.21	0.82	0.48 - 1.40	0.47
Male / Female				
Histological type	0.31	1.19	0.70 - 1.99	0.51
Poorly Diff[e] / Diff[e]				
TM status (at recurrence)				
CEA	0.79	1.01	0.62 - 1.63	0.96
Positive / Negative				
CA19-9	0.12	1.45	0.87 - 2.41	0.15
Positive / Negative				

[a] Log-rank test
[b] Adjusted hazards ratio
[c] Adjusted 95% confidence interval
[d] Cox proportional hazards model
[e] Differentiation

Table 3 Summary of recent reports which showed the significance of tumor marker status on the patients' prognosis.

References	Year	Patients (n)	Recurrence (n)	Stage	Tumor makers (TM)	Measurement of TM			Recurrence sites
						Before surgery	After surgery	At recurrence	
Takahashi et al. [10]	2003	321	120	Ⅱ/Ⅲ	CEA/CA19-9	Yes[b]	Yes	No[c]	Yes
Komatsu et al. [11]	2013	unknown	91	Ⅰ/II/Ⅲ	CEA/CA19-9	Yes	Yes	No	Yes
Lee et al. [14]	2014	1314	154	Ⅰ/II/Ⅲ	CEA/CA19-9	Yes	Yes	No	Yes
Zhou et al. [18]	2015	1075	NA[a]	Ⅰ/II/III/Ⅳ	CEA/CA19-9	Yes	No	No	No
Feng et al. [13]	2017	587	NA	Ⅰ/Ⅱ	CEA/CA19-9 /AFP/CA125	Yes	No	No	No
Wada et al. [16]	2017	1050	113	Ⅰ/II/Ⅲ	CEA/CA19-9	Yes	No	No	Yes
Wu et al. [17]	2017	299	188	Ⅰ/II/Ⅲ	CEA/CA19-9	Yes	Yes	No	Yes
Uda et al. [7]	2018	251	NA	Ⅰ/II/Ⅲ	CEA/CA19-9	Yes	Yes	No	Yes
Sawayama et al. [15]	2018	146	57	Ⅱ/Ⅲ	CA19-9	Yes	No	No	Yes
Suenaga et al. [6]	2019	998	NA	Ⅱ/Ⅲ	CEA/CA19-9	Yes	Yes	No	Yes
Present study	**2020**	**666**	**89**	**Ⅰ/II/Ⅲ**	**CEA/CA19-9**	**Yes**	**No**	**Yes**	**Yes**

[a] NA：Not applicable

[b] Yes：Measured or described

[c] No：Not measured or not described

Figure 1

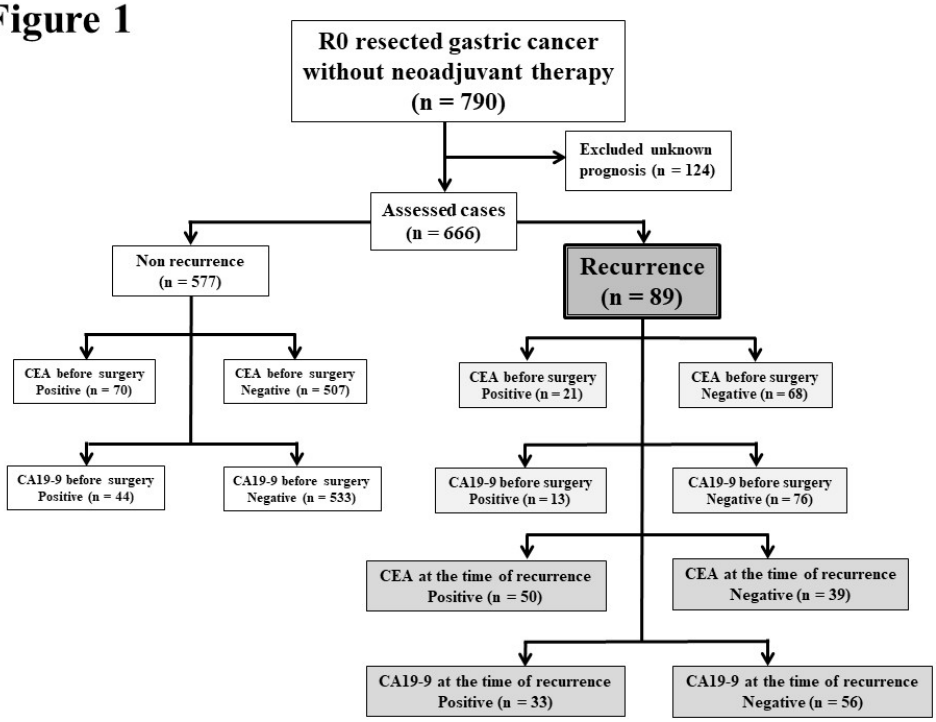

R0 resected gastric cancer without neoadjuvant therapy (n = 790)
Excluded unknown prognosis (n = 124)
Assessed cases (n = 666)
Non recurrence (n = 577)
Recurrence (n = 89)
CEA before surgery Positive (n = 70)
CEA before surgery Negative (n = 507)
CEA before surgery Positive (n = 21)
CEA before surgery Negative (n = 68)
CA19-9 before surgery Positive (n = 44)
CA19-9 before surgery Negative (n = 533)
CA19-9 before surgery Positive (n = 13)
CA19-9 before surgery Negative (n = 76)
CEA at the time of recurrence Positive (n = 50)
CEA at the time of recurrence Negative (n = 39)
CA19-9 at the time of recurrence Positive (n = 33)
CA19-9 at the time of recurrence Negative (n = 56)

Figure 2

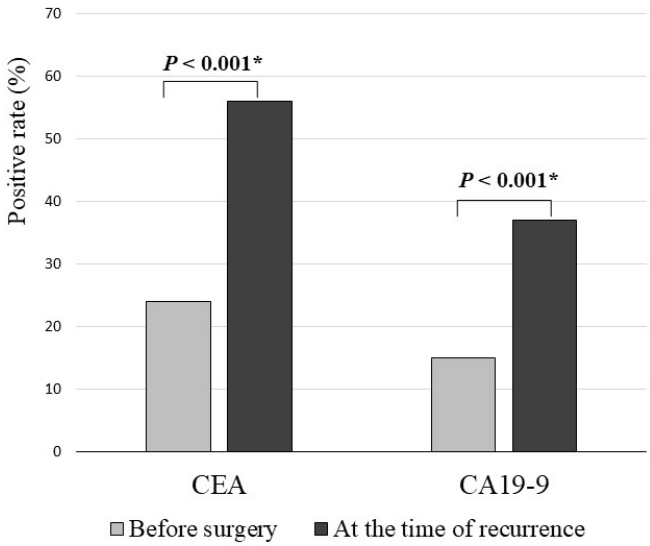

70
60
50
40
30
20
10
0
Positive rate (%)
P < 0.001*
P < 0.001*
CEA
CA19-9
Before surgery
At the time of recurrence

Figure 3

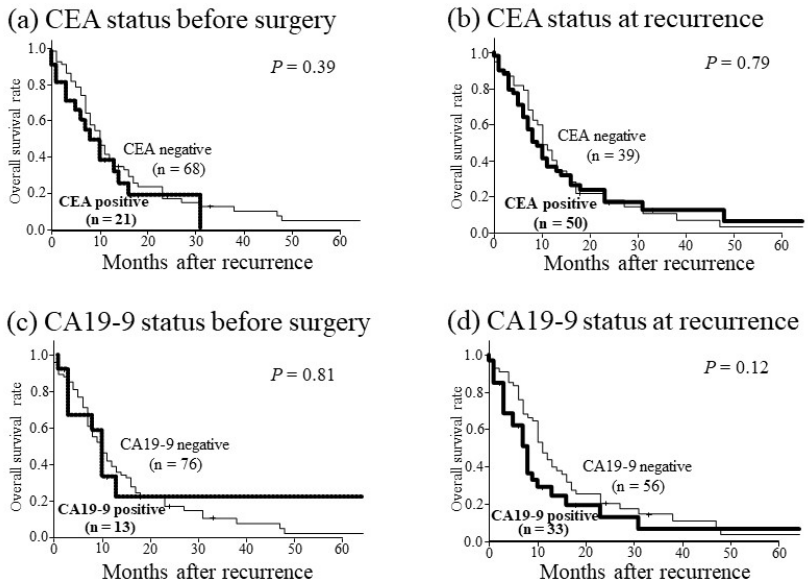

(a) CEA status before surgery
P = 0.39
CEA negative
(n = 68)
CEA positive
(n = 21)
Overall survival rate
Months after recurrence
(b) CEA status at recurrence
P = 0.79
CEA negative
(n = 39)
CEA positive
(n = 50)
Overall survival rate
Months after recurrence
(c) CA19-9 status before surgery
P = 0.81
CA19-9 negative
(n = 76)
CA19-9 positive
(n = 13)
Overall survival rate
Months after recurrence
(d) CA19-9 status at recurrence
P = 0.12
CA19-9 negative
(n = 56)
CA19-9 positive
(n = 33)
Overall survival rate
Months after recurrence

Figure 4

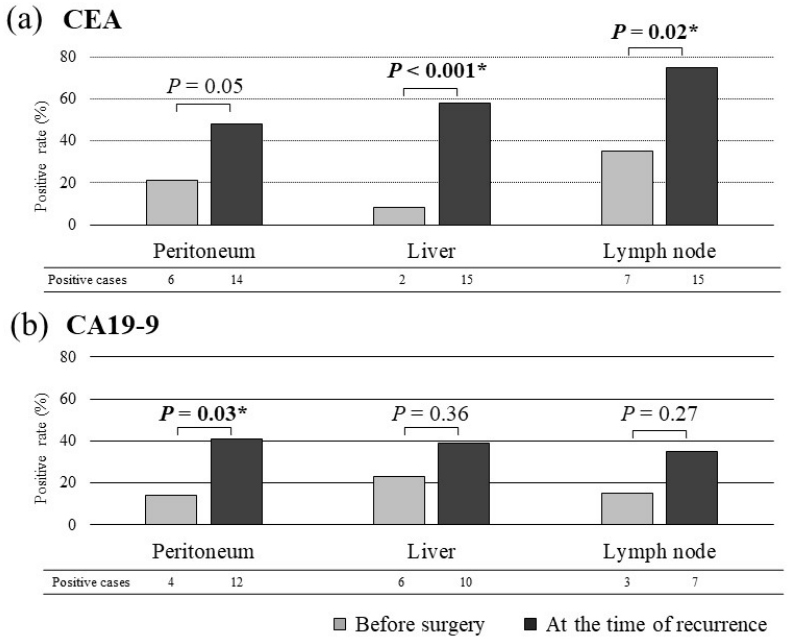
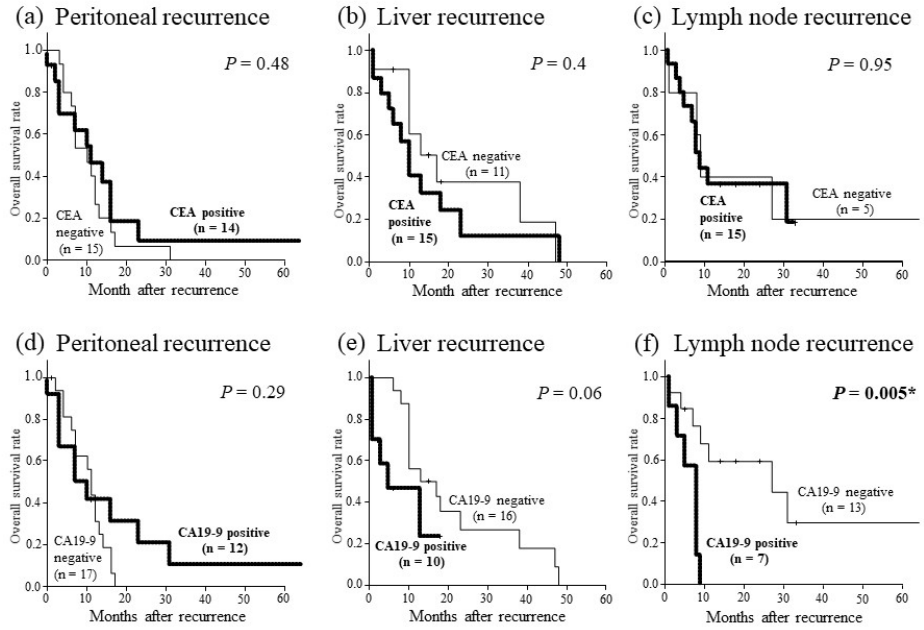

(a) CEA
P = 0.05
P < 0.001*
P = 0.02*
Positive rate (%)
80
60
40
20
0
Peritoneum
Liver
Lymph node
Positive cases 6 14 2 15 7 15
(b) CA19-9
P = 0.03*
P = 0.36
P = 0.27
Positive rate (%)
80
60
40
20
0
Peritoneum
Liver
Lymph node
Positive cases 4 12 6 10 3 7
Before surgery
At the time of recurrence

Figure 5


(a) Peritoneal recurrence
P = 0.48
CEA positive (n = 14)
CEA negative (n = 15)
(b) Liver recurrence
P = 0.4
CEA negative (n = 11)
CEA positive (n = 15)
(c) Lymph node recurrence
P = 0.95
CEA negative (n = 5)
CEA positive (n = 15)
(d) Peritoneal recurrence
P = 0.29
CA19-9 positive (n = 12)
CA19-9 negative (n = 17)
(e) Liver recurrence
P = 0.06
CA19-9 negative (n = 16)
CA19-9 positive (n = 10)
(f) Lymph node recurrence
P = 0.005*
CA19-9 negative (n = 13)
CA19-9 positive (n = 7)
Overall survival rate
Month after recurrence
Months after recurrence