Original Paper

Perioperative Serum Carcinoembryonic Antigen Levels Predict Recurrence and Survival of Patients with Pathological T2-4 Gastric Cancer Treated with Curative Gastrectomy

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Abstract

Background/Aims: Whether serum carcinoembryonic antigen (CEA) and carbohydrate antigen (CA) 19-9 levels serve as prognostic indicators in patients with gastric cancer (GC) have long been disputed. The aim of the present study was to evaluate the significance of perioperative serum levels of CEA and CA19-9 for predicting recurrence and long-term survival after patients with pT2-4 GC undergo curative gastrectomy. ***Methods:*** This study included 251 patients with radically resected pT2-4 GC without preoperative treatment. Associations between the preoperative and postoperative serum levels of CEA or CA19-9 and postoperative long-term outcomes and recurrence patterns were evaluated. ***Results:*** Preoperative CEA >5.0 ng/ml was an independent prognostic factor of overall survival. Elevation of both preoperative CEA and CA19-9 levels showed no synergistic adverse effect on prognosis. Preoperative levels of these markers achieved superior predictive performance compared with the postoperative values. Adverse prognosis significantly associated with persistent elevation of CEA levels before and after gastrectomy. Elevation of CEA levels, particularly at postoperative measurement, were significantly associated with hematogenous recurrence. ***Conclusion:*** Determination of perioperative CEA levels facilitated predictions of recurrence patterns and prognosis among patients with pT2-4 GC who underwent curative gastrectomy.

Introduction

Serum biomarkers that accurately identify cancer patients who are at risk of recurrence have consistently been target of research [1-3]. Diagnostic value of carcinoembryonic antigen (CEA), a membrane glycoprotein serving as a tumor-associate colon adenocarcinoma antigen, was first reported by Gold and Freeman in 1965 [4]. Since then, CEA has been broadly utilized as a serum tumor marker in various malignancies including gastric cancer (GC) [5-7] . Similarly, carbohydrate antigen 19-9 was identified by Koprowski et al. as an anti sialyl-Lea sugar chain antigen in 1979 and has been used extensively as a serum tumor marker among digestive organ cancers [8,9].

Whether serum CEA and CA19-9 levels contribute as prognostic indicators for patients with GC have long been discussed, but the results have been rather mixed [10,11]. Inconsistencies in the criteria used for patient inclusion and analyses and different variables (e.g. early detection or prognostic factors) are cited as possible explanations of the conflicting data [12-14]. In addition, advances in measurement technology, increased prevalence of early-stage GC and changes in standard of care such as application of adjuvant therapies may also have caused changes in clinical significance of serum CEA and CA19-9 over time [15-17]. Moreover, most published studies focus only on preoperative values of serum tumor markers [6,14]. Thus, there may be room for further evaluating relevance of these tumor markers using data from the modern era which include serum values obtained during the

postoperative follow up.

We asked therefore if the combined postoperative levels of CEA and CA19-9 during the perioperative period provides more meaningful prognostic information compared with that acquired using only the preoperative level of each tumor marker. For this purpose, correlations between the tumor marker information and long-term outcome and recurrence patterns were evaluated in T2-4 (pT2-4) GC underwent curative gastrectomy after 2001.

Methods

Ethics

This study conforms to the ethical guidelines of the World Medical Association Declaration of Helsinki–Ethical Principles for Medical Research Involving Human Subjects. Patients provided written informed consent for surgery and use of clinical data as required by the Institutional Review Board of Nagoya University [18].

Patients

We evaluated medical records of 1,083 patients who underwent surgery for GC at the Department of Gastroenterological Surgery, Nagoya University between March 2001 and September 2016. Demographics, perioperative findings, pathological findings, and

postoperative course were retrospectively collected from our prospectively compiled medical database. The inclusion criteria, which were met by 251 patients, were as follows: pathologically confirmed gastric adenocarcinoma; no preoperative treatment; histologically confirmed R0 resection; pT2-4 according to the TNM Classification of Malignant Tumors, 7th Edition [19]; and integrity of data.

Perioperative management

Patients underwent gastrectomy with D2 lymphadenectomy according to the Japanese Gastric Cancer Treatment Guidelines [20], and the reconstruction method was determined at the surgeon's discretion. Postoperative adjuvant chemotherapy was administered according to the evidence available at the time of surgery, the patient's physical condition, and with the patient's consent. Since 2007, adjuvant chemotherapy using S-1 (an oral fluoropyrimidine derivative) has been administered to all patients unless contraindicated by the patient's condition [21,22]. Chemotherapy given after recurrence was decided at the discretion of the treating physician. Patients received postoperative follow-up that included physical examinations, laboratory tests, and enhanced computed tomography (chest and abdominal cavity) once every 6 months for 5 years or until death [23].

Evaluation of perioperative tumor markers

Preoperative serum levels of CEA and CA19-9 were measured within 14 days before gastrectomy. Postoperative measurement of CEA and CA19-9 levels was usually performed at the outpatient clinic 6–10 weeks after surgery and before administration of adjuvant chemotherapy. The cutoff values of CEA and CA19-9 were set at the upper limit of the normal value for each tumor marker at our institution and were as follows: CEA, 5.0 ng/ml; CA19-9, 37 IU/ml. Patients were classified into two groups for each tumor marker according to these cutoff values.

Statistical analysis

Continuous variables were presented by the mean value when normal distribution was exhibited. Otherwise, the median values were presented. Overall survival and disease-free survival were estimated using the Kaplan–Meier method. The differences in survival, hazard ratios, and 95% confidence intervals were calculated using Cox proportional hazards models. Variables with a p value <0.05 were entered into the final model of multivariable regression analysis. The χ^2 test was used to evaluate associations between levels of CEA and the prevalence of postoperative recurrence. Statistical analysis was performed using JMP 10 software (SAS Institute Inc., NC, USA). A p value <0.05 was considered statistically significant.

Results

Patients' characteristics

Demographics and perioperative clinical characteristics of the 251 patients are summarized in Table 1. Median preoperative levels of CEA and CA19-9 were 2.4 ng/ml and 12 IU/ml, respectively. Total gastrectomy was performed to treat 91 patients (36%); and 55, 45, 45, 32, 38, and 36 patients were classified as TNM stages IB, IIA, IIB, IIIA, IIIB, and IIIC, respectively. Median postoperative levels of CEA and CA19-9 were 2.2 ng/ml and 9 IU/ml, respectively. The patients were followed for a median of 39.6 months (range 6-174 months) or until death.

Prognostic significance of preoperative serum levels of CEA and CA19-9

Preoperative CEA >5.0 ng/ml was significantly associated with preoperative CA19-9 >37 IU/ml and pathological lymph node metastasis ($p = 0.0406$ and $p = 0.0341$, respectively), but not with other clinicopathological factors including age, sex, tumor location, differentiation and pathological tumor depth. The overall survival rates of patients in the CEA >5.0 ng/ml group were significantly shorter after curative gastrectomy compared with those in the CEA ≤5.0 ng/ml group (5-year survival rates 42% and 83%, respectively, $p = 0.0012$) (Fig. 1a). In contrast, the difference in overall survival between the preoperative CA19-9 >37 IU/ml and ≤37 IU/ml groups was not significant (5-year survival rates were 63% and 80%, respectively)

(Fig. 1b). Multivariable analysis using a stepwise regression model identified preoperative CEA >5.0 ng/ml as an independent prognostic factor for overall survival (hazard ratio 2.51, 95% confidence interval 1.18–5.05, p = 0.01771) (Table 2). When patients were categorized according to the serum levels of CEA combined with those of CA19-9, there was no significant difference in survival between patients with elevation of both CEA and CA19-9 compared with those with elevation of either of the tumor markers (Fig. 1c). Similar trends were observed when analyzing disease-free survival for preoperative CEA (Fig. 2a), CA19-9 (Fig. 2b), or these markers combined (Fig. 2c).

Significance of postoperative levels of CEA and CA19

The number of patients with elevated levels of CEA and CA19-9 decreased after surgery compared with those before surgery (CEA, 15 vs 36 patients; CA19-9, 25 vs 39 patients) (Table 1). The prognostic values of CEA and CA19-9 levels before and after surgery are shown in Table 3. Overall, the predictive performance of the preoperative levels of the markers was superior compared with that of the postoperative values.

Patient survival and time course of changes in CEA levels

Among patients with preoperative CEA >5.0 ng/ml, the CEA levels of 26 patients (72%) decreased to the normal range after resection. In contrast, 10 patients (28%) with persistently

elevated CEA levels experienced significantly shorter overall survival ($p = 0.0338$) (Fig. 3a) and disease-free survival ($p = 0.0395$) (Fig. 3b) compared with those whose CEA levels decreased. Further, prognosis varied gradually according to the time course of changes of serum CEA levels.

Association between perioperative CEA levels and recurrence patterns

The prevalence of overall recurrence in the preoperative CEA >5 ng/ml group was higher compared with that of the CEA ≤5 ng/ml group (42% and 16%, respectively, $p = 0.0011$). The CEA >5 ng/ml group had a significantly higher prevalence of liver metastasis as initial recurrence compared with that of the CEA ≤5 ng/ml group (14% and 3%, respectively, $p = 0.0106$), whereas the frequencies of peritoneal, lymph node, and lung metastases were not significantly different (Fig. 4a). Moreover, patients with postoperative CEA >5 ng/ml experienced initial recurrences only via the hematogenous routes, including liver and lung, and they had a 10-fold higher prevalence of liver recurrence compared with that of the CEA ≤5 ng/ml group (33% and 3%, respectively, $p < 0.0001$) (Fig. 4b).

Discussion

CA19-9 is expressed in faint amounts on the surface of normal epithelial cells of various organs including the stomach, colon, rectum, pancreatic duct, bile duct, bronchus and

endometrium [8,24,25]. Malignant transformation of the epithelial cells can cause abnormal production of CA19-9 and release the secretory CA19-9 into the circulation [26,27]. With respect to CEA levels in GC, we (Y.K.) reported in the early 1990s that CEA mRNA level in GC tissues is detectable but is significantly lower than that of colon cancer, especially in the poorly differentiated phenotype, and does not correlate directly with the serum CEA level [28]. As for possible explanations of the gap of CEA levels between GC tissues and the sera, there have been several reports that the amount of CEA released into the circulation does not depend mainly on the tissue CEA level, but distribution patterns within the cancerous tissues, tumor differentiation and lymphovascular invasion [29-31]. Hamada et al. conducted immunohistochemical analysis and found that the appearance of CEA in the surrounding stroma led to the elevation of blood CEA levels due to abnormal distribution of CEA on the basolateral plasma membrane of colorectal cancer cells [32]. Although previous studies demonstrated that CEA-producing GC and CA19-9-producing GC have different characteristics in morphology, histopathology and metastatic preference, the prognostic values of serum CEA and CA19-9 are still under debate [5,6,9,14].

Here we focused on evaluating the prognostic significance of perioperative CEA and CA19-9 levels for patients with pT2-4 GC who underwent curative gastrectomy since 2001. We found that preoperative CEA levels had higher predictive significance compared with those of preoperative CA19-9, and we identified the former as an independent prognostic

factor for recurrence and overall survival of patients with pT2-4 GC. The findings indicate that the CEA level was more informative than CA19-9 for patients with pT2-4 GC and therefore was the focus of the analyses that follow. The univariate analysis identified pathological tumor depth and lymph node metastasis as prognostic factors, while multivariable analysis did not. In many studies, they were found to be independent prognostic factors among the similar populations. We have two speculations for this controversial results. One is the alteration of prognostic factors by administration of adjuvant S-1 in resectable GC. We reported that macroscopic tumor size was the only significant prognostic factor for the S-1 adjuvant group, whereas high preoperative CEA, total gastrectomy, vessel invasion, pathological tumor depth were identified as significant prognostic factors in the surgery alone group [21]. Because of the long study period, the patient cohort included those before and after standardization of adjuvant S-1 in this study. This might influenced on prognostic impact of pathological tumor depth and lymph node metastasis. In addition, the confounding between each potent prognostic factors including tumor size, total gastrectomy, vessel invasion might decreased statistical significance of pathological tumor depth and lymph node metastasis in the model of multivariable regression analysis. Our observation of simultaneous elevation of both CEA and CA19-9 levels has no mechanisms involving a synergistic adverse effect on survival. In this study, administration of adjuvant chemotherapy was not found to be prognostic factor. The possible reason was the inclusion of patients before standardization of

S-1 adjuvant. In the early 2000s, adjuvant chemotherapy was selectively administered to worrisome patients for recurrences due to more advanced disease stages [33,34].

Since there have been numerous studies addressing the prognostic significance of preoperative blood tumor markers, lack of novelty regarding the data for the significance of preoperative CEA levels is one of the shortcomings of the present study. However, little is known about the significance of postoperative levels of CEA and CA19-9 of patients with GC who undergo curative gastrectomy [12,35]. Thus, we evaluated postoperative levels of the markers and perioperative changes in CEA levels to update our knowledge and to provide added values of measurement of serum tumor markers of GC. We found that the hazard ratios of overall survival and disease-free survival associated with postoperative levels of CEA and CA19-9 were smaller compared with those of preoperative levels. However, when we analyzed the CEA levels before and after gastrectomy, the survival curves for overall and disease-free survival were stratified by the patterns of changes in CEA levels, indicating that risk of adverse prognosis can be stratified more precisely than using a single measurement. Normalization of postoperative level of CEA or CA19-9 after curative gastrectomy is a strong prognostic factor for GC, suggesting that preoperative levels as well as the time course of changes of serum CEA levels can help physicians to more precisely stratify patients at risk and then implement a management strategy that includes postoperative surveillance and adjuvant therapy [36]. Although physicians have to consider that serum CEA levels can be

influenced by other factors including smoking and diabetes mellitus [6,12], patients with persistent elevation of CEA levels before and after gastrectomy may be candidates for intensive examinations and combination chemotherapy.

A striking finding of the present study was the strong association between perioperative levels of CEA and hematogenous recurrences. Consistent with a previous study, preoperative CEA levels served as a sensitive marker for predicting liver recurrence [37,38], and we found that patients with high postoperative CEA levels experienced initial recurrences only via hematogenous metastasis to the liver or lungs. This difference was more apparent in the postoperative levels of CEA, indicating that postoperative evaluation of CEA levels is useful for predicting recurrence patterns. These results offered valuable insights for both postoperative surveillance and treatment strategies. The influences of implementation of adjuvant S-1 monotherapy should be considered because the long-term results of the randomized phase III trial (ACTS-GC trial) suggested that S-1 adjuvant contributed to reduction of peritoneal recurrences rather than hematogenous recurrences (hazard ratio 0.69 and 0.78, respectively) [22]. Combination adjuvant chemotherapy, such as capecitabine plus oxaliplatin [39], might be advisable for patients who had high perioperative serum CEA levels. Moreover, intensive postoperative surveillance (including gadolinium ethoxybenzyl diethylenetriamine pentaacetic acid-enhanced magnetic resonance imaging of the liver, bone scintigraphy, and positron emission tomography) for early detection of hematogenous

metastasis may be advisable for patients with elevated CEA levels, paying particularly close attention to the postoperative levels [40].

The limitations of this study include its retrospective nature and the limited number of subjects from a single institute. Further, exploring optimal cutoff values of CEA and CA19-9 levels specific to patients with pT2-4 GC may maximize the prognostic value of these markers and will likely stimulate further research on the molecular pathological events that determine CEA and CA19-9 levels. Nevertheless, our findings provide updated evidence to support the clinical utility of conventional blood tumor markers for managing patients with pT2-4 GC. More specifically, we summarized the expected clinical application of our findings as follows. Measurement of preoperative CEA levels is recommended for patients with resectable GC because it has predictive values for postoperative prognosis and recurrence patterns. Additionally, not only before surgery, but also postoperative measurement of CEA levels is advisable because it enables physicians to more precisely stratify patients at risk of adverse prognosis and hematogenous recurrences, leading to improvement of management strategy including intensive postoperative surveillance and adjuvant therapy.

In conclusion, measurement of perioperative CEA levels can improve prediction of recurrence and prognosis of patients with pT2-4 GC. Intensive surveillance that focuses of hematogenous recurrence is advisable for patients with persistent elevation of CEA levels after curative gastrectomy.

Disclosure Statement

The authors declare that they have no competing interests. No financial support was received.

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Table 1. Demographics and perioperative clinical characteristics of patients included in the study

Variables	Values
Age, median (range)	67 (20-91)
Sex (male/female)	192/59
Diabetes mellitus (%)	44 (18%)
Preoperative symptom (%)	105 (42%)
Preoperative body mass index, mean ± SD	22.3 ± 3.4
Preoperative CEA (ng/ml), median (range)	2.4 (0.1-1737)
≤5.0 ng/ml	215
>5.0 ng/ml	36
Preoperative CA19-9 (IU/ml), median (range)	12 (1-6300)
≤37 IU/ml	212
>37 IU/ml	39
Tumor location	
Entire	6
Upper third	76
Middle third	86
Lower third	83
Tumor size (mm), mean ± SD	47.6 ± 27.7
Type of gastrectomy	
Total gastrectomy	91
Partial gastrectomy	160
Splenectomy (%)	50 (20%)
Dissected lymph nodes, mean ± SD	36.8 ± 17.6
Operative time (min), mean ± SD	240 ± 58
Intraoperative blood loss (ml), median (range)	282 (1-2450)
Differentiation	
Differentiated	92
Undifferentiated	159
UICC pT factor	
pT2	87
pT3	78
pT4	86
UICC pN factor	
pN0	102
pN1	51
pN2	40

pN3	58
UICC stage	
IB	55
IIA	45
IIB	45
IIIA	32
IIIB	38
IIIC	36
Postoperative CEA (ng/ml), median (range)	2.2 (0.3-64)
≤5.0 ng/ml	236
>5.0 ng/ml	15
Postoperative CA19-9 (IU/ml), median (range)	9 (1-876)
≤37 IU/ml	226
>37 IU/ml	25
Adjuvant chemotherapy (%)	122 (49%)
Median postoperative follow-up (month)	39.6

The study's inclusion criteria were met by 251 of 1,083 patients. SD, standard deviation; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9; UICC, Union for International Cancer Control.

Table 2 Prognostic factors for overall survival

Variables	Univariate			Multivariable		
	Hazards ratio	95% CI	*P* value	Hazard ratio	95% CI	*P* value
Age (≥65 years)	1.27	0.66 – 2.49	0.4783			
Male sex	1.12	0.53 – 2.63	0.7793			
Preoperative symptoms	1.17	0.61 – 2.23	0.6397			
Preoperative body mass index (≥22)	1.06	0.55 – 2.03	0.8679			
Preoperative CEA (>5 ng/ml)	3.52	1.70 – 6.89	0.0012	2.51	1.18 – 5.05	0.0177
Preoperative CA19-9 (>37 IU/ml)	2.08	0.88 – 4.36	0.0894			
Postoperative CEA (>5 ng/ml)	2.93	0.99 – 6.90	0.0506			
Postoperative CA19-9 (>37 IU/ml)	1.81	0.68 – 4.04	0.2166			
Tumor location (lower third)	0.71	0.33 – 1.41	0.3353			
Tumor size (≥50 mm)	4.80	2.36 – 10.8	<0.0001	2.88	1.32 – 6.82	0.0071
Total gastrectomy	2.96	1.54 – 5.90	0.0011	2.32	1.15 – 4.83	0.0183
Operative time (≥240 min)	1.61	0.82 – 3.40	0.1736			
Intraoperative blood loss (≥200 ml)	1.90	0.95 – 4.13	0.0712			
Postoperative complication	2.20	0.98 – 4.50	0.0565			
Undifferentiated tumor	1.10	0.56 – 2.27	0.7865			
Lymphatic involvement	2.91	0.89 – 17.9	0.0841			
Vessel invasion	4.93	2.28 – 12.3	<0.0001	4.20	1.87 – 10.8	0.0003
Invasive growth	1.23	0.64 – 2.35	0.5354			
Pathological tumor depth (pT4)	2.95	1.54 – 5.80	0.0011	1.66	0.84 – 3.38	0.1437
Pathological lymph node metastasis	5.00	2.13– 14.7	<0.0001	2.30	0.91 – 7.08	0.0803
Adjuvant chemotherapy	0.92	0.48 – 1.77	0.8053			

CI, confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Table 3 Prognostic significance of preoperative and postoperative levels of CEA and CA19-9

	Preoperative levels						**Postoperative levels**					
	Overall survival			Disease-free survival			Overall survival			Disease-free survival		
	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*	HR	95% CI	*P*
CEA (>5 ng/ml)	3.52	1.70 – 6.89	0.0012	2.99	1.58 – 5.38	0.0012	2.93	0.99 – 6.90	0.0506	2.73	1.04 – 5.93	0.0423
CA19-9 (>37 IU/ml)	2.08	0.88 – 4.36	0.0894	2.03	1.02 – 3.78	0.0456	1.81	0.68 – 4.04	0.2166	1.80	0.78 – 3.63	0.1551

HR, hazard ratio; CI, confidence interval; CEA, carcinoembryonic antigen; CA19-9, carbohydrate antigen 19-9.

Fig. 1. Overall survival curves of 251 patients categorized according to their preoperative levels of (**a**) CEA, (**b**) CA19-9, and (**c**) CEA combined with CA19-9.

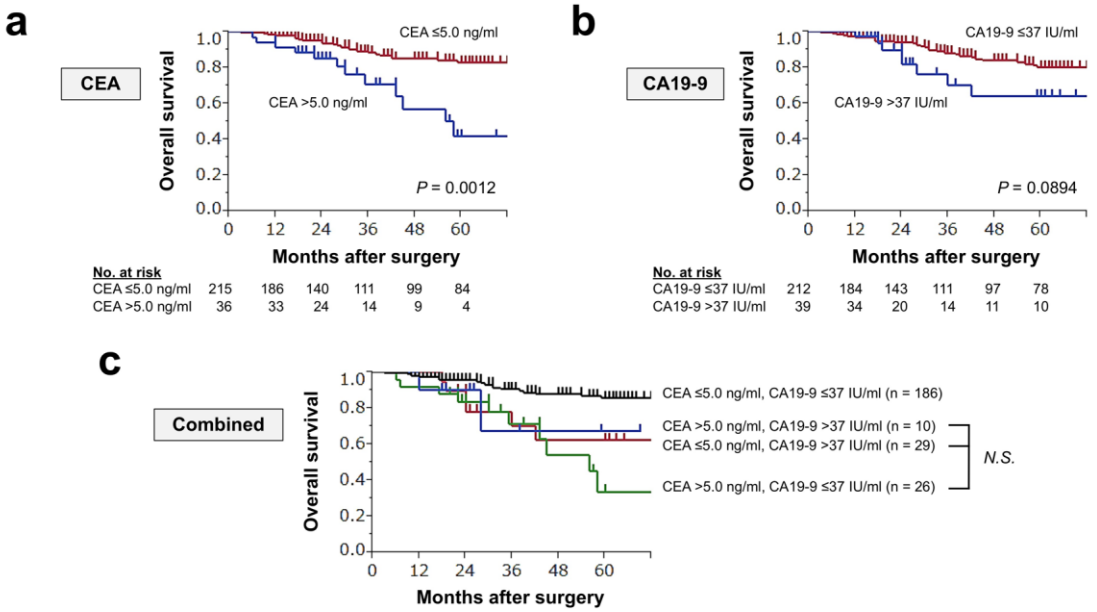

Fig. 2. Disease-free survival curves of 251 patients categorized according to their preoperative levels of (**a**) CEA, (**b**) CA19-9, and (**c**) CEA combined with CA19-9.

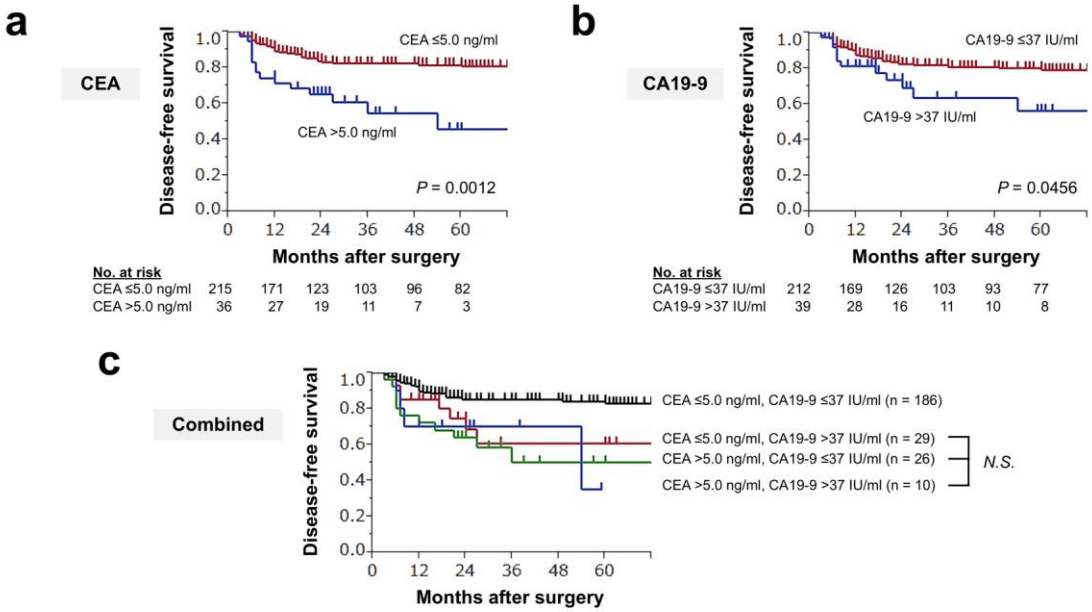

Fig. 3. Influence of changes in CEA levels over time on (**a**) overall survival and (**b**) disease-free survival.

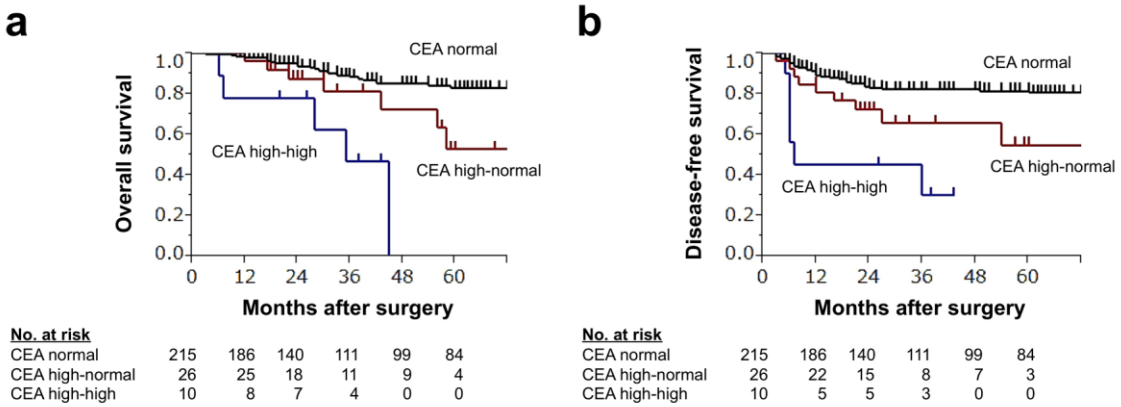

Fig. 4. Prevalence of the site of initial recurrence according to (**a**) preoperative and (**b**) postoperative CEA levels.