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EPIDEMIOLOGY

Elevated levels of serum tumor markers CA 15-3 and CEA are prognostic factors for diagnosis of metastatic breast cancers

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Abstract To investigate the prognostic value of tumor markers, cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) levels at diagnosis of systemic recurrence. After primary treatments of locoregional breast cancers, serum CA 15-3 and/or CEA concentrations were regularly measured, and systemic recurrences were identified in 351 patients between January 1999 and December 2009. The association between tumor marker levels at systemic recurrence and survival were investigated by univariate and multivariate analyses. Elevated CA 15-3 and CEA levels were identified in 194 of 349 (55.6 %) and 111 of 308 (36.0 %) patients, respectively, at diagnosis of systemic recurrence. Elevated levels of CA 15-3 and CEA were correlated with visceral or multiple recurrences and elevated preoperative levels. Elevation of CA 15-3 was more prominent in younger patients and in primary node-positive tumors, while CEA was elevated in older patients at diagnosis and in estrogen receptor (ER)-positive tumors. Elevated tumor markers as well as ER negativity, short disease-free interval, and advanced stage at initial diagnosis showed independent prognostic significance on multivariate analysis. Among 306 patients for whom levels of both tumor markers at recurrence were available, 106 patients without elevation of either marker showed significantly better overall survival than those with elevated levels of either one or both markers, and the significance persisted in multivariate analysis. Elevated serum CA 15-3 and CEA levels at recurrence suggest increased tumor burden and may be prognostic for survival for metastatic breast cancer patients.

Keywords Breast carcinoma · CA 15-3 · CEA · Prognostic factors · Tumor marker · Systemic recurrence

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Introduction

Serum tumor markers have an important role in screening, early diagnosis of recurrence, and treatment of many malignancies [1]. In breast cancer, cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) are the two most widely used serum tumor markers in the clinical fields; however, the value of these markers remains unclear [2–4].

Although the limitation of low sensitivity and specificity preclude the use of serum tumor marker for the detection of early breast cancer, elevated preoperative tumor marker levels at initial presentation may predict poor outcome [5, 6]. Serial determination of tumor marker levels after primary treatment for breast cancer can be used to detect preclinical recurrence or metastatic disease with a lead time of 2–9 months, but the clinical value of this lead time remains to be determined [7–10]. Nevertheless, the majority of expert panels, except for the European Group on Tumor Markers (EGTM), disagree as to whether any serum tumor marker should be routinely used during postoperative follow-up periods in asymptomatic patients who had been treated for breast cancer [11–15].

We previously reported that elevated preoperative serum tumor marker levels are significantly associated with primary tumor burden and poor outcome, and serum tumor markers can be useful prognostic factors [6, 16]. Similarly, we hypothesized that patients with elevated serum tumor maker levels at the time of recurrence are associated with worse survival outcomes than those with normal levels.

The aim of this study was to evaluate the prognostic significance of serum tumor markers, CA 15-3 and CEA, at the time of systemic recurrence after primary treatment for locoregional breast cancers.

Materials and methods

Study population

During the period from January 1999 to December 2009, a total of 379 patients were diagnosed with systemic recurrences at our institution. Tumor marker levels were not studied in 26 patients, and two patients had incomplete medical records. After exclusion of 28 patients, 351 patients were finally included in the analysis. Among 351 patients, CA 15-3 and CEA levels at recurrence were available in 349 and 308 patients, respectively. Of these 351 patients, 306 (87.2 %) had available data for both tumor marker levels. All data were extracted from the Severance Hospital Breast Cancer Registry, which is a prospectively maintained database including clinical and pathologic information, treatment modalities, and details of outcome. This study was reported according to the Reporting Recommendations for Tumor Marker Prognostic Studies (REMARK) criteria [17].

Management after initial surgery was based on international guidelines and clinical follow-up was performed every 6–12 months, which included patient's history, physical examination, laboratory tests of CEA, CA 15-3, complete blood counts, and liver function test, chest radiography, mammography, breast and abdomino-pelvic ultrasonography, and bone scans. In addition, computed tomography (CT) scan or fluorine-18 fluorodeoxyglucose positron emission tomography (FDG PET)/CT scan was performed, if necessary.

Tumor marker analysis and pathologic parameters

We measured the concentration of serum tumor markers using an automated immunoanalyzer systems and chemiluminescent immunoassay for CEA (ADVIA Centaur, Bayer HealthCare LLC Diagnostic Division, NY) and CA 15-3 (VITROS ECi Immunodiagnostic System, Ortho-Clinical Diagnostics, Inc., NY). We defined the cut-off values for tumor markers as the 95th percentiles of healthy individuals, which was already used in our previous study (CA 15-3: 20.11 U/ml; CEA: 3.88 ng/ml) [6]. TNM staging was based on the criteria of the 6th American Joint Committee on Cancer. Tumors with $\geq$10 % nuclear-stained cells were considered positive for estrogen receptor (ER) and progesterone receptor (PR). Human epidermal growth factor receptor 2 (HER2) immunohistochemistry (IHC) was performed using the HercepTest^{TM} (DAKO, Glostrup, Denmark) and interpreted as 0, 1+, 2+, or 3+. HER2 was considered positive in cases with an IHC score of 3+.

The molecular subtypes were classified into four groups as follows: luminal A (ER+ and/or PR+ and HER2−), luminal B (ER+ and/or PR+ and HER2+), HER2 (ER−, PR−, and HER2+), and triple-negative breast cancer (ER−, PR−, and HER2−).

Statistical analysis

The difference between proportions was evaluated by the Chi square test. Survival time after recurrence was defined as the time from recurrence to death from any cause or final follow-up visit. Survival time after recurrence was estimated using the Kaplan–Meier method, and group differences in survival time were tested by the log-rank test. Multivariate Cox's proportional hazard analysis was performed to identify independent prognostic factors for survival time after systemic recurrence. All reported P values are two-sided, and a P value <0.05 was considered significant. SPSS for Windows (version 15.0) was used for all statistical analyses.

Results

At the median follow-up time of 18 months from the diagnosis of systemic recurrences (range; 0–134 months), 239 patients had died. CA 15-3 and CEA levels at the time of systemic recurrence were available in 349 and 308 patients, respectively. Median concentrations of CA 15-3 and CEA were 22.3 U/ml and 1.99 ng/ml, respectively.

Elevated CA 15-3 levels at the time of systemic recurrence were identified in 194 out of 349 patients (55.6 %) and elevated CEA levels were observed in 111 out of 308 patients (36 %). Clinicopathologic characteristics at the time of treatment of locoregional breast cancer are presented in Table 1 according to the levels of serum tumor markers at diagnosis of systemic recurrence. Elevation of CA 15-3 at recurrence was more prominent in younger patients ($P = 0.03$) or node-positive primary tumors ($P = 0.029$), while patients with elevated CEA levels frequently showed older age at diagnosis ($P = 0.031$) or ER-positive tumors ($P = 0.021$). A greater proportion of patients with preoperatively elevated tumor marker levels showed greater elevation of tumor markers at recurrence

Table 1 Correlation between tumor marker levels at recurrence and clinical prognositic factors

	CA 15-3 levels at systemic recurrence ($n = 349$)			CEA levels at systemic recurrence ($n = 308$)		
	Normal (%)	Elevated (%)	*P*	Normal (%)	Elevated (%)	*P*
Age						
≤35 years	14 (30)	33 (70)	0.030	31 (80)	8 (20)	0.031
>35 years	141 (47)	161 (53)		166 (62)	103 (38)	
Tumor size						
T1	63 (49)	66 (51)	0.203	81 (66)	42 (34)	0.573
≥T2	92 (42)	128 (58)		116 (63)	69 (37)	
Nodal status						
N0	55 (53)	48 (47)	0.029	65 (68)	31 (32)	0.357
≥N1	100 (41)	146 (59)		132 (62)	80 (38)	
TNM stage						
I	25 (49)	26 (51)	0.081	33 (66)	17 (34)	0.475
II	72 (49)	75 (51)		81 (66)	42 (34)	
III	58 (38)	93 (62)		83 (62)	52 (38)	
HG(307/272)						
I	8 (33)	16 (67)	0.107	13 (59)	9 (41)	0.259
II	77 (43)	102 (57)		98 (62)	59 (38)	
III	52 (50)	52 (50)		64 (69)	29 (31)	
ER(343/302)						
Negative	70 (49)	74 (51)	0.279	93 (72)	37 (28)	0.021
Positive	85 (43)	114 (57)		101 (59)	71 (41)	
PR(343/302)						
Negative	88 (46)	104 (54)	0.787	114 (67)	56 (33)	0.246
Positive	67 (44)	84 (56)		80 (61)	52 (39)	
HER2 (335/298)						
Negative	107 (45)	130 (55)	0.639	136 (64)	78 (36)	0.755
Positive	47 (48)	51 (52)		55 (65)	29 (35)	
Preop. level of CA 15-3 ($n = 230$)						
Normal	95 (52)	87 (48)	<0.001			
Elevated	8 (17)	40 (83)				
Preop. level of CEA ($n = 222$)						
Normal				130 (70)	57 (30)	<0.001
Elevated				11 (31)	24 (69)	
Molecular subtype (335/298)						
Luminal A	65 (43)	86 (57)	0.752	80 (60)	54 (40)	0.474
Luminal B	31 (46)	36 (54)		36 (64)	20 (36)	
HER2	16 (52)	15 (48)		19 (68)	9 (32)	
TNBC	42 (49)	44 (51)		56 (70)	24 (30)	
Status						
Alive	71 (63)	41 (37)	<0.001	78 (77)	24 (23)	0.001
Death	84 (35)	153 (65)		119 (58)	87 (42)	

TNM tumor-node-metastasis, *HG* histologic grade, *ER* estrogen receptor, *PR* progesterone receptor, *HER2* human epidermal growth factor receptor 2, *Preop*. preoperative, *CA 15-3* cancer antigen 15-3, *CEA* carcinoembryonic angigen, *TNBC* triple-negative breast cancer

than those without preoperatively elevated markers levels, but molecular subtypes were not associated with tumor marker levels. Table 2 shows the correlation between tumor marker level at recurrence and site of metastasis. Elevation of CA 15-3 level at recurrence was correlated with visceral plus bone ($P < 0.001$) or multiple recurrences ($P < 0.001$). Elevation of CEA level was associated with liver metastasis ($P = 0.002$).

Table 2 Correlation between tumor marker levels at recurrence and site of metastasis

	CA 15-3 levels at systemic recurrence ($n = 349$)			CEA levels at systemic recurrence ($n = 308$)		
	Normal (%)	Elevated (%)	*P*	Normal (%)	Elevated (%)	*P*
Site of recurrence						
Bone or soft tissue	38 (62)	23 (38)	<0.001	38 (72)	15 (28)	0.055
Viscera alone	76 (49)	77 (51)		91 (66)	46 (34)	
Viscera + bone	41 (30)	94 (70)		68 (58)	50 (42)	
Specific site of recurrence						
Bone						
(–)	84 (51)	81 (49)	0.021	99 (67)	49 (33)	0.303
(+)	71 (39)	113 (61)		98 (61)	62 (39)	
Soft tissue						
(–)	127 (43)	166 (57)	0.358	160 (62)	98 (38)	0.106
(+)	28 (50)	28 (50)		37 (74)	13 (26)	
Lung						
(–)	77 (47)	87 (53)	0.369	92 (64)	51 (36)	0.899
(+)	78 (42)	107 (58)		105 (63)	60 (37)	
Liver						
(–)	111 (49)	114 (51)	0.013	140 (70)	59 (30)	0.002
(+)	44 (35)	80 (65)		57 (52)	52 (48)	
CNS						
(–)	126 (46)	150 (54)	0.365	156 (64)	89 (36)	0.836
(+)	29 (40)	44 (60)		41 (65)	22 (35)	
Other viscera						
(–)	149 (45)	181 (55)	0.247	188 (65)	102 (35)	0.204
(+)	6 (32)	13 (68)		9 (50)	9 (50)	
Number of recurrence site						
Single	87 (55)	71 (45)	<0.001	96 (69)	44 (31)	0.124
Multiple	68 (36)	123 (64)		101 (60)	67 (40)	

Other viscera included adrenal gland, ovary, uterus, colon, kidney, and appendix

CA 15-3 cancer antigen 15-3, *CEA* carcinoembryonic angigen, *CNS* central nervous system

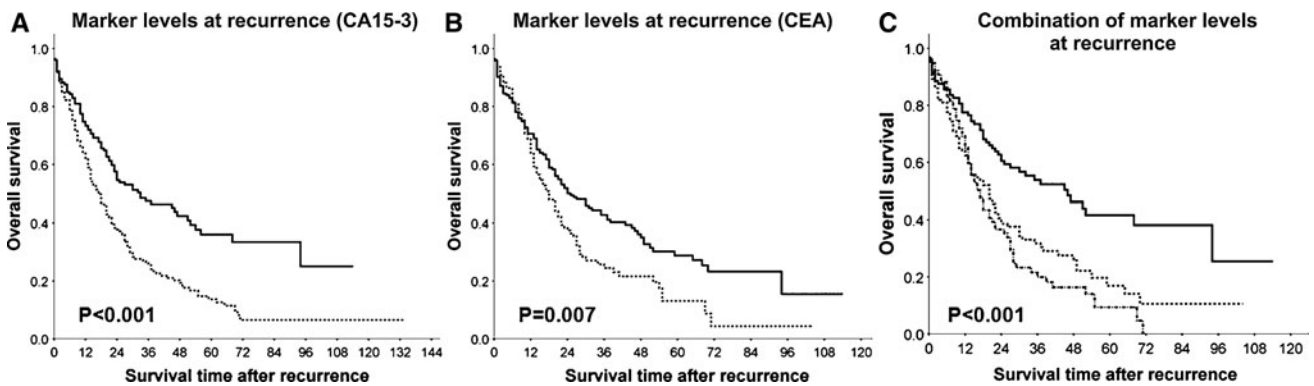

Fig. 1 Kaplan–Meier survival curve after recurrence according to levels of cancer antigen 15-3 (CA 15-3) at recurrence (**a**), carcinoembryonic antigen (CEA) (**b**), and combination of both markers (**c**). The *bold line* represents patients with normal levels, and *dotted line* represents patients with elevated levels (**a**, **b**). The *bold line* represents patients with normal levels of both markers, the *dotted line* represents patients with elevated levels of one marker, and the *chain line* represents patients with elevated levels of both markers (**c**)

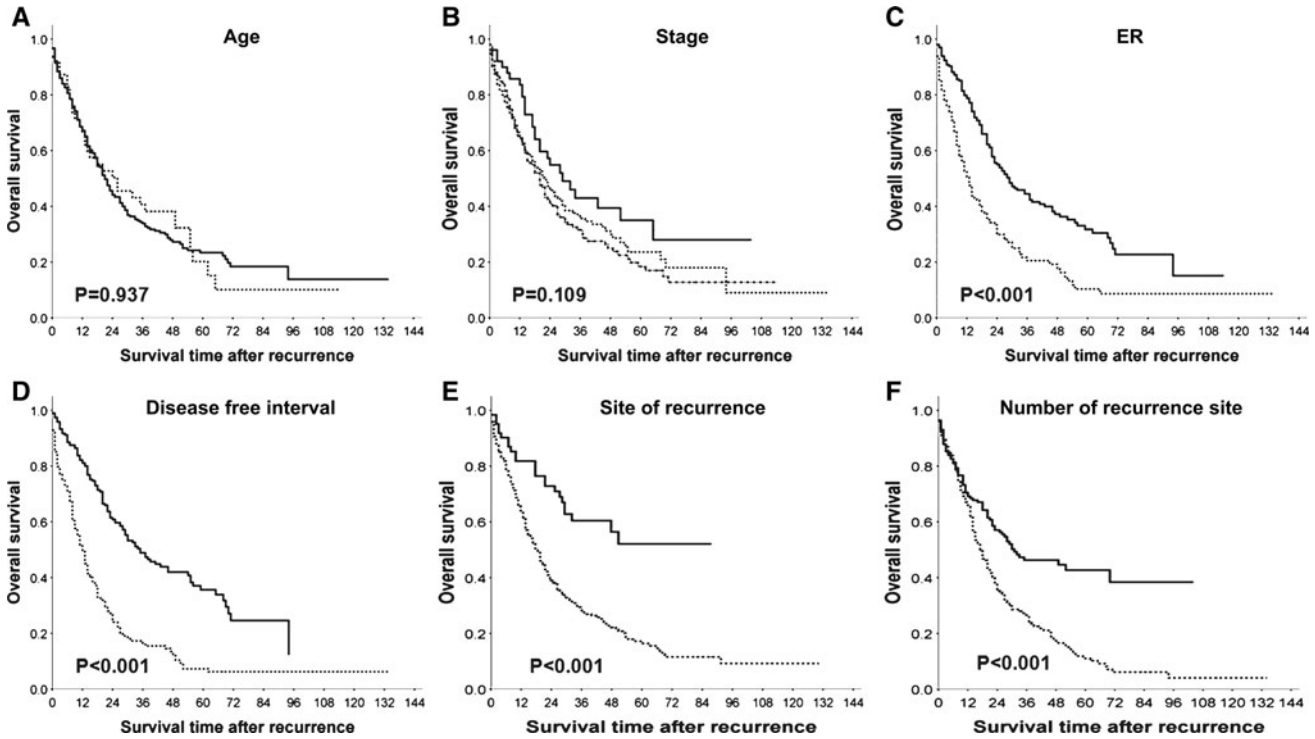

Fig. 2 Kaplan–Meier survival curve after recurrence according to age (**a**), stage (**b**), estrogen receptor status (**c**), disease-free interval (**d**), site of recurrence (**e**), and number of recurrence site (**f**). The *bold line* represents patients older than 35 years, the *dotted line* represents patients younger than 35 years (**a**). The *bold line* represents patients with stage I, the *dotted line* represents patients with stage II, and the *chain line* represents patients with stage III (**b**). The *bold line* represents patients with positive estrogen receptor, the *dotted line* represents patients with negative estrogen receptor (**c**). The *bold line* represents patients with disease-free intervals longer than 24 months, the *dotted line* represents patients with disease-free intervals of 24 months or less (**d**). The *bold line* represents patients with bone metastasis, the *dotted line* represents patients with visceral metastasis (**e**). The *bold line* represents patients with single metastasis, the *dotted line* represents patients with multiple metastases (**f**)

Kaplan–Meier survival curve after recurrence according to tumor marker levels at recurrence is shown in Fig. 1. Elevated CA 15-3 ($P < 0.001$) and CEA ($P = 0.007$) levels were significantly associated with worse survival outcome. In the analysis of the combination of both markers levels ($n = 306$), 106 patients (34.6 %) without elevation of either marker showed significantly better survival outcome than those with elevated level of either marker ($n = 123$, 40.2 %; $P < 0.001$) or both markers ($n = 77$, 25.2 %; $P < 0.001$).

The significance of various prognostic factors was also evaluated in a metastatic setting. ER negativity of primary tumor ($P < 0.001$), short disease-free interval of 24 months or less ($P < 0.001$), visceral recurrence ($P < 0.001$), and multiple site recurrences ($P < 0.001$) were associated with significantly poor survival outcomes, but patient age younger than 35 years or initial stage was not correlated with survival outcome after systemic recurrences (Fig. 2).

On multivariate analysis, after adjusting for clinicopathologic parameters, each tumor marker was entered into the model I, while combined tumor markers were considered in model II (Table 3). Elevated CA 15-3 and CEA levels at systemic recurrence were independent prognostic factors for overall survival after recurrence in model I. When considering the combination of both markers levels ($n = 306$), the highest risk of death was demonstrated in patients with elevated levels of both markers ($n = 77$), and there was a significantly increased risk in those with one marker elevated ($n = 123$) compared to those with no elevation of either marker ($n = 106$). Stage III at initial diagnosis, ER negativity, short disease-free intervals of 24 months or less, and multiple sites of metastasis were significant prognostic factors for survival after recurrence in models I and II.

Discussion

In the present study, CA 15-3 levels were elevated at systemic recurrence in 194 of 349 patients (55.6 %), and elevated CEA levels were observed in 111 of 308 patients (36 %), which is similar to results from other studies [CA 15-3; 54−80 %, and CEA; 30−50 % in metastatic breast cancer (MBC)] [9, 18–21]. However, CEA and CA 15-3 levels may be increased in other benign conditions such as diverticulitis, gastritis, gastric ulcer, bronchitis, cholangitis, and liver abscess in cases of CEA and chronic hepatitis,

Table 3 Multivariate analysis of prognostic factors for survival time after recurrence using Cox proportional hazards model

Model I				Model II			
Variables	HR	CI	*P*	Variables	HR	CI	*P*
Stage				Stage			
I	1			I	1		
II	1.458	0.933–2.277	0.098	II	1.484	0.949–2.322	0.084
III	1.625	1.042–2.535	0.032	III	1.670	1.073–2.599	0.023
Estrogen receptor				Estrogen receptor			
Positive	1			Positive	1		
Negative	1.723	1.278–2.324	<0.001	Negative	1.697	1.256–2.291	0.001
DFI				DFI			
>24 months	1			>24 months	1		
≤24 months	2.341	1.728–3.171	<0.001	≤24 months	2.366	1.748–3.202	<0.001
Site of recurrence				Site of recurrence			
Bone	1			Bone	1		
Viscera	1.666	0.976–2.845	0.062	Viscera	1.674	0.979–2.861	0.060
Number of recur sites				Number of recur sites			
Single	1			Single	1		
Multiple	1.431	1.028–1.992	0.034	Multiple	1.427	1.024–1.988	0.036
CA 15-3 at recurrence				Combination of marker levels			
Normal	1			Both normal	1		
Elevated	1.729	1.275–2.345	<0.001	One elevated	1.761	1.238–2.504	0.002
CEA at recurrence				Both elevated	2.389	1.631–3.499	<0.001
Normal	1						
Elevated	1.374	1.021–1.849	0.036				

HR hazard ratio, *CI* confidence interval, *CA 15-3* cancer antigen 15-3, *CEA* carcinoembryonic angigen, *DFI* disease-free interval

liver cirrhosis, tuberculosis, sarcoidosis, and systemic lupus erythematosus in cases of CA 15-3 [3].

No correlation between tumor markers and age has been established; however, Fletcher et al. [22] reported that CEA might be elevated in the elderly and smokers. Therefore, we should be cautious in drawing a definite conclusion about the clinical value of measuring tumor markers levels to detect recurrences to avoid unnecessary additional examinations and psychological tension when the elevation is due to causes other than true cancer recurrence. Nevertheless, elevated tumor marker levels are more frequently observed in MBC patients than in primary breast cancer patients, and patients with elevated maker levels at recurrence showed worse outcomes than those with normal levels [23–27]. Patients who had elevated tumor marker levels before surgery also showed more frequent elevation at recurrence. Since markers are relatively easy and inexpensive to measure, regular measurement of serum tumor marker levels could provide useful information for earlier detection of recurrence or accurate prediction of outcomes after recurrence.

As shown in our previous studies [6, 16] and in other studies [27–29], higher preoperative tumor marker levels represent tumor burden and are associated with worse survival in early breast cancer. Significantly elevated tumor markers levels were observed in multiple metastasis, bone and visceral recurrence or visceral metastasis, which suggests an association of elevated tumor marker level with recurrent tumor burden (Table 2).

The correlation between tumor marker levels and metastatic sites is not very well established. The prospective study by Tampellini et al. [27] reported that CA 15-3 levels were more frequently elevated in liver metastasis, but the diagnostic value of CEA levels has not been investigated. In addition, elevated CA 15-3 levels were more frequently observed in patients with multiple metastases, but statistical significance was not observed by the Chi square test ($P = 0.1$). Yerushalmi et al. [26] investigated the correlation between tumor marker and breast cancer subtype, sites of metastasis and prognosis in their large cohort study, and there was no relationship between tumor marker and metastatic site. The present study showed that CA 15-3 was significantly elevated in patients with bone or liver metastasis. On the other hand, CEA was frequently elevated in those with liver metastasis. The correlation between tumor marker levels and site of metastasis needs to be further investigated.

In terms of association with survival outcome, Insa et al. [30] in their analysis with 439 recurrent breast cancers, reported that primary tumor size, axillary lymph node status, hormone receptor negativity, adjuvant chemotherapy, disease-free interval, location of recurrence, and number of metastatic sites were associated with survival in univariate analysis and site of recurrence, axillary nodal status, ER status, and disease-free interval remained significant in multivariate analysis. Largillier et al. [31] analyzed prognostic factors in 1038 MBC patients and showed that older age, axillary node positivity, tumor size greater than 2 cm, hormone receptor negativity, short disease-free interval, and site of metastasis are the most relevant factors for predicting survival. However, serum tumor markers have been incorporated into studies of MBC patients on a limited basis. On univariate analysis in the present study, elevation of either CA 15-3 or CEA level, elevation of both marker levels at recurrence, stage III at initial diagnosis, ER negativity, short disease-free intervals, and multiple metastatic sites showed significantly worse survival outcomes, and these factors remained independent prognostic factors on multivariate analysis.

In summary, our study suggests that tumor markers CA 15-3 and CEA may be prognostic for survival for MBC and elevated levels at the time of recurrence are associated with poor outcomes.

Conflict of interest The authors have declared no relevant conflicts of interest.

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