Original Article

Elevated serum carcinoembryonic antigen and CA15-3 levels and the risk of site-specific metastases in metastatic breast cancer

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Background: To assess the relationship between serum carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) levels and the risk of site-specific metastases in metastatic breast cancer.

Methods: Clinicopathological characteristics of patients diagnosed with metastatic breast cancer at two academic centers between 1998 and 2013 were retrospectively analyzed. The association between serum CEA and CA15-3 levels at systemic recurrence and site-specific metastases was investigated by univariate and multivariate analyzes.

Results: A total of 305 patients were identified. One hundred and thirteen (37.0%) and 139 (45.6%) patients showed elevated serum CEA and CA15-3 levels, respectively. Serum CEA levels were less frequently elevated in patients with triple negative disease (P=0.030). Furthermore, elevated serum CEA (P=0.002) and CA15-3 (P<0.001) levels were significantly correlated with the number of metastatic organ sites. In multivariate analysis, abdomen/pelvis metastases [odds ratio (OR) 2.436; 95% confidence interval (CI), 1.446–4.104; P=0.001] and bone metastases (OR 2.414; 95% CI, 1.399–4.316; P=0.002) showed a strong correlation with elevated serum CEA levels. Elevated serum CA15-3 levels were significantly correlated with pleura metastases (OR 2.368; 95% CI, 1.093–5.133; P=0.029). Abnormal serum CA15-3 levels were a marginally predictive factor for bone metastases (OR 1.688; 95% CI, 0.992–2.874; P=0.054). Elevation of CEA and CA15-3 level was not significant association with the other sites of distant recurrence including lung/mediastina, axillary and/or neck lymph nodes, and other distant soft tissue.

Conclusions: Elevated serum CEA and CA15-3 levels may cause an increased risk of site-specific metastases in metastatic breast cancer. Further studies examining the role of serum CEA and CA15-3 levels in the organ-specific metastatic cascade are required.

Keywords: Breast cancer; metastases; tumor markers; carcinoembryonic antigen (CEA); cancer antigen 15-3 (CA15-3); subtype

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Introduction

The incidence of breast cancer in the United States and China has increased continuously over time, with more than 200,000 females newly diagnosed with the disease every year (1-3). Although significant progress has been achieved in the development of comprehensive therapy of breast cancer (4), distant metastases are still observed in about 20–30% of patients (5-7), resulting in approximately 40,000 deaths each year (1,3). Although the vast majority of breast cancer related deaths occur in patients with distant metastases, the unique patterns of distant metastases and mechanisms of disease progression have not been clearly elucidated.

Serum carcinoembryonic antigen (CEA) and cancer antigen 15-3 (CA15-3) are two of the most widely investigated tumor markers in breast cancer. CEA and CA15-3 are of limited use in the early diagnosis due to a lack of specificity and sensitivity (8,9). However, several studies have reported that elevated preoperative levels of CEA and CA15-3 can predict poor survival of breast cancer patients (10-12). The European School of Oncology-European Society for Medical Oncology (ESO-ESMO) suggests that the use of tumor markers for monitoring treatment response is reasonable for advanced breast cancer (13,14). However, data regarding differences in the risk of site-specific metastases between breast cancer serum tumor markers are limited and conflicting. In this study, we sought to clarify the possible relationship between the risk of site-specific metastases and serum CEA and CA15-3 levels in Chinese women with advanced breast cancer at two cancer centers.

Methods

Patients

We performed a retrospective analysis of breast cancer patients admitted to Sun Yat-sen University Cancer Center (SYSUCC) and the First Affiliated Hospital of Xiamen University [Xiamen Cancer Hospital (XMCH)] during the period from March 1998 to January 2013. The inclusion criteria for study enrollment were as follows: (I) female, unilateral invasive breast carcinoma, without distant metastases at the initial breast cancer diagnosis; (II) underwent surgical treatment (mastectomy or breast-conserving therapy) and axillary lymph node dissection; (III) complete resection of tumor without residual tumor observed in pathological examination; (IV) definite distant metastatic disease was found during the follow up period, with complete results of serum CEA and CA15-3 levels when confirmed with metastatic disease. The study was approved by the ethics committee of the First Affiliated Hospital of Xiamen University and SYSUCC (approval number of institutional review board, 2013B021800157).

Serum CEA and CA15-3 levels measurement and clinicopathologic parameters

Clinicopathologic characteristics including age, menopausal status, tumor size, nodal stage, estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor 2 (HER2) status, breast cancer subtype (BCS), serum CEA and CA15-3 levels were used to assess the risk of site-specific metastases. Hormone receptor (HR) positivity was defined as greater than 1% of cells demonstrating positive staining by ER or PR immunohistochemistry. HER2 positivity was defined as an immunohistochemical grade of 3+ before 2003, or 2+ with a fluorescence *in situ* hybridization test after 2003. Due to the majority of patients lacking Ki-67 data, we did not define the BCS according to the 14th St. Gallen International Breast Cancer Conference in 2015 (15), but instead defined four intrinsic BCS (16-18): HR+/HER2– (ER+ and/or PR+, HER2–), HR+/HER2+ (ER+ and/or PR+, HER2+), HR–/HER2+ (ER–, PR–, and HER2+) and HR–/HER2– (ER–, PR–, and HER2–).

Detection of CEA and CA15-3 was performed as described in our previous studies (10,19). The diagnostic cut-off point for serum CEA and CA15-3 levels was 5 ng/mL and 25 U/mL, respectively.

Sites of distant metastases

The sites of distant metastases in breast cancer patients were divided into seven regions according to a previous study (20), including abdomen/pelvis (liver, adrenal gland, lymph nodes, and other abdominopelvic organs), lung/mediastina (lung or pulmonary lymphangitic spread), brain, bone (skeletal system), pleura (pleura and/or pericardial effusion, pleural effusion and/or pleural effusion), axillary and/or neck lymph nodes, and other distant soft tissue.

Statistical analysis

Statistical analysis was performed using the SPSS version 16.0 (SPSS Inc., Chicago, IL, USA). A chi-square test or Fisher's exact test were performed to determine the differences

Table 1 Clinicopathologic characteristics of the 305 patients included in the study

Characteristic	N=305	SYSUCC	XMCH
Age (median) (years)	46.0	44.0	47.5
Menopausal status			
Premenopausal	203	118	85
Postmenopausal	102	54	48
Tumor size			
T1	88	51	37
T2	166	93	73
T3	38	20	18
T4	13	8	5
Nodal stage			
N0	96	68	28
N1	74	40	34
N2	64	29	35
N3	71	35	36
ER (n=299)			
Negative	133	83	50
Positive	166	89	77
PR (n=299)			
Negative	115	65	50
Positive	184	107	77
HER2 (n=277)			
Negative	179	99	80
Positive	98	60	38
Breast cancer subtype (n=277)			
HR+/HER2–	126	71	55
HR+/HER2+	57	34	23
HR–/HER2+	41	26	15
HR–/HER2–	53	28	25
CEA			
Normal	192	107	85
Elevated	113	65	48
CA15-3			
Normal	166	88	78
Elevated	139	84	55
Sites of distant metastases (n=489)			
Abdomen/pelvis	106	69	37
Lung/mediastinal	116	63	53
Pleura	31	13	18
Bone	153	74	79
Axillary and/or neck lymph nodes	35	13	22
Brain	33	15	18
Other distant soft tissue	15	5	10

SYSUCC, Sun Yat-sen University Cancer Center; XMCH, Xiamen Cancer Hospital; HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CEA, carcinoembryonic antigen; CA15-3, cancer antigen 15-3.

between groups for categorical variables. Univariate and multivariate logistic regression analyzes were performed to assess the relationship of patient clinicopathologic characteristics and serum CEA and CA15-3 levels for the risk of site-specific metastases. A P value <0.05 was considered significant in all analyzes.

Results

Patient and tumor characteristics

Patient clinicopathologic characteristics are summarized in *Table 1*. A total of 305 patients were identified in this study. Of these, 56.4% (172/305) of patients were from SYSUCC and 43.6% (133/305) of patients were from XMCH. The median age was 46.0 (range, 27–84) years at the initial breast cancer diagnosis. There were 113 (37.0%) and 139 (45.6%) patients with elevated serum CEA and CA15-3 levels, respectively. The median serum CEA and CA15-3 values in patients with elevated tumor marker levels were 16.9 (range, 5.1–3,515.0) ng/mL and 85.1 (range, 25.6–3,000.0) U/mL, respectively. The initial treatments after a diagnosis of metastatic breast cancer are shown in *Table 2*.

Sites of distant metastases

A total of 489 sites of distant metastases were identified in patients diagnosed with metastatic disease. One hundred

Table 2 The initial treatment after a diagnosis of metastatic breast cancer

Treatment	N (%)
Locoregional therapy	
Surgical intervention	31 (10.2)
Radiotherapy	52 (17.0)
Radiofrequency ablation	8 (2.6)
Systemic therapy	
Chemotherapy	285 (93.4)
Endocrine therapy	112 (36.7)
Targeted therapy	38 (12.5)
None	13 (4.3)

and seventy-six (57.7%) patients had single region metastases and 129 (42.3%) patients had multiple region metastases. The common sites of distant metastases were as follows: bone (31.3%), lung/mediastina (23.7%), abdomen/pelvis (21.7%), axillary and/or neck lymph nodes (7.2%), brain (6.7%), pleura (6.3%), and other distant soft tissue (3.0%; *Table 1*).

Patient clinicopathologic characteristics according to serum CEA and CA15-3 levels

Table 3 shows patient clinicopathologic characteristics according to serum CEA and CA15-3 levels. When classified according to normal or elevated serum tumor marker levels, serum CEA levels were less frequently elevated in patients with ER negative disease (P=0.001), PR negative disease (P=0.028) and HR–/HER2– subtype (P=0.030), while elevated serum CA15-3 levels were less commonly observed in PR negative disease (P=0.026). In addition, elevated serum CEA (P=0.002) and CA15-3 (P<0.001) levels were significantly correlated with the number of metastatic organs.

Association of serum tumor markers levels and the sites of distant metastases

Table 4 shows the metastatic characteristics according to serum CEA and CA15-3 levels. Univariate analysis showed that elevated serum CEA levels were more frequently associated with abdomen/pelvis and bone metastases in patients. Furthermore, elevated serum CA15-3 levels were frequently observed in abdomen/pelvis, pleura, and bone metastases.

In multivariate logistic regression analysis, abdomen/pelvis metastases [odds ratio (OR) 2.436; 95% confidence interval (CI), 1.446–4.104, P=0.001] and bone metastases (OR 2.414; 95% CI, 1.399–4.316, P=0.002) showed strong correlations with elevated serum CEA levels. Elevated serum CA15-3 levels were significantly correlated with pleura metastases (OR 2.368; 95% CI, 1.093–5.133, P=0.029). Abnormal serum CA15-3 levels were also a marginally predictive factor for bone metastases (OR 1.688; 95% CI, 0.992–2.874, P=0.054). Elevation of CA15-3 levels were not associated with abdomen/pelvis metastases (P=0.146) in multivariate analysis. Elevation of CEA and CA15-3 level was not significant association with the other sites of distant recurrence including lung/mediastina, axillary and/or neck lymph nodes, and other distant soft tissue.

Discussion

In this study, we explored the relationship between serum CEA and CA15-3 levels and the risk of site-specific metastases in metastatic breast cancer. Our results showed that patients with elevated serum CA15-3 levels were more likely to have abdomen/pelvis and bone metastases, while patients with elevated serum CA15-3 levels were more prone to pleura metastases.

Serum CEA and CA15-3 levels were elevated in 37.0% and 45.6% of patients in this study, respectively, which is similar to results in other studies (CEA: 36.0–50.7%; CA15-3: 36.4–55.6%) (21,22). As a special type of breast cancer classification, the prognosis of triple negative breast cancer (TNBC) is significantly worse than other BCS; however, our study found that the probability of elevated serum CEA levels in TNBC was significantly lower than the HR positive subtype (10.9% *vs.* 25.7–50.5%), which was similar to results from our previous research regarding preoperative tumor markers of breast cancer (10). In addition, Yerushalmi *et al.* found that tumor markers were less frequently elevated in TNBC (CEA: 31.3%; CA15-3: 68.4%) than luminal subtypes (CEA: 59.6–65.0%; CA15-3: 83.4–86.8%; P<0.001) (23). Kos *et al.* also showed that elevated tumor marker levels were less frequently observed in TNBC patients as compared to luminal groups (22). Therefore, monitoring of tumor marker levels in HR positive groups may be beneficial in determining early distant recurrence in breast cancer, while TNBC may have little value during follow up for timely detection of distant relapse.

Table 3 Clinicopathological characteristics according to serum CEA and CA15-3 levels

Characteristic	CEA		P value	CA15-3		P value
	Normal (%)	Elevated (%)		Normal (%)	Elevated (%)	
Age (years)			0.637			0.318
≤35	30 (15.6)	20 (17.7)		24 (14.5)	26 (18.7)	
>35	162 (84.4)	93 (82.3)		142 (85.5)	113 (81.3)	
Menopausal status			0.958			0.274
Premenopausal	128 (66.7)	75 (66.4)		106 (63.9)	97 (69.8)	
Postmenopausal	64 (33.3)	38 (33.6)		60 (36.1)	42 (30.2)	
Tumor size			0.816			0.854
T1	57 (29.7)	31 (27.4)		49 (29.5)	39 (28.1)	
T2	101 (52.6)	65 (57.5)		92 (55.4)	74 (53.2)	
T3	26 (13.5)	12 (10.6)		19 (11.5)	19 (13.7)	
T4	8 (4.2)	5 (4.5)		6 (3.6)	7 (5.0)	
Nodal stage			0.928			0.604
N0	60 (31.2)	36 (31.9)		54 (32.5)	42 (30.2)	
N1	46 (24.0)	28 (24.8)		44 (26.5)	30 (21.6)	
N2	39 (20.3)	25 (22.1)		33 (19.9)	31 (22.3)	
N3	47 (24.5)	24 (21.2)		35 (21.1)	36 (25.9)	
ER (n=299)			0.001			0.199
Negative	98 (51.6)	35 (32.1)		78 (47.9)	55 (40.4)	
Positive	92 (48.4)	74 (67.9)		85 (52.1)	81 (59.6)	
PR (n=299)			0.028			0.026
Negative	82 (43.2)	33 (30.3)		72 (44.2)	43 (31.6)	
Positive	108 (56.8)	76 (69.7)		91 (55.8)	93 (68.4)	
HER2 (n=277)			0.394			0.707
Negative	117 (66.5)	62 (61.4)		101 (65.6)	78 (63.4)	
Positive	59 (33.5)	39 (38.6)		53 (34.4)	45 (36.6)	
Breast cancer subtype (n=277)			0.030			0.556
HR+/HER2−	75 (42.6)	51 (50.5)		67 (43.5)	59 (48.0)	
HR+/HER2+	31 (17.6)	26 (25.7)		30 (19.5)	27 (22.0)	
HR−/HER2+	28 (15.9)	13 (12.9)		23 (14.9)	18 (14.6)	
HR−/HER2−	42 (23.9)	11 (10.9)		34 (22.1)	19 (15.4)	
Number of sites of distant metastasis			0.002			<0.001
Single	124 (64.6)	52 (46.0)		111 (66.9)	65 (46.8)	
Multiple	68 (35.4)	61 (54.0)		55 (33.1)	74 (53.2)	

HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CEA, carcinoembryonic antigen; CA15-3, cancer antigen 15-3.

Table 4 Serum CEA and CA15-3 levels associated with the sites of distant metastases

Site of distant metastasis	Univariate			Multivariate		
	OR	95% CI	P value	OR	95% CI	P value
Abdomen/pelvis						
CEA elevated *vs.* CEA normal	2.790	1.710–4.553	<0.001	2.436	1.446–4.104	0.001
CA15-3 elevated *vs.* CA15-3 normal	1.981	1.229–3.194	0.005	1.467	0.875–2.459	0.146
Lung/mediastinal						
CEA elevated *vs.* CEA normal	0.655	0.401–1.067	0.089			
CA15-3 elevated *vs.* CA15-3 normal	0.641	0.400–1.025	0.063			
Pleura						
CEA elevated *vs.* CEA normal	1.684	0.798–3.552	0.171			
CA15-3 elevated *vs.* CA15-3 normal	2.368	1.093–5.133	0.029	2.368	1.093–5.133	0.029
Bone						
CEA elevated *vs.* CEA normal	1.902	1.186–3.050	0.008	2.414	1.399–4.316	0.002
CA15-3 elevated *vs.* CA15-3 normal	1.727	1.096–2.723	0.019	1.688	0.992–2.874	0.054
Brain						
CEA elevated *vs.* CEA normal	1.698	0.821–3.511	0.153			
CA15-3 elevated *vs.* CA15-3 normal	1.140	0.553–2.350	0.722			
Axillary and/or neck lymph nodes						
CEA elevated *vs.* CEA normal	1.005	0.485–2.082	0.990			
CA15-3 elevated *vs.* CA15-3 normal	1.146	0.566–2.318	0.705			
Other distant soft tissue						
CEA elevated *vs.* CEA normal	1.140	0.395–3.292	0.808			
CA15-3 elevated *vs.* CA15-3 normal	1.387	0.490–3.926	0.538			

OR, odds ratio; CI, confidence interval; CEA, carcinoembryonic antigen; CA15-3, cancer antigen 15-3.

Studies of preoperative CEA and CA15-3 levels have shown that elevated serum tumor marker levels represent an increase in tumor burden, such as advanced tumor size and nodal stage (10,11,24,25). In this study, we also found that patients with multiple organ metastases were more prone to abnormal serum tumor marker levels, which suggests a relationship between elevated tumor marker levels and tumor burden in breast cancer with distant metastases.

ESO-ESMO guidelines recommend observing serum CEA and CA15-3 levels to monitor the therapeutic response in advanced breast cancer (13,14). However, the correlation between serum tumor marker levels and the risk of site-specific metastases has not yet been well established. Yerushalmi *et al.* found that CEA (P=0.17) and CA15-3 (P=0.2) levels did not correlate with the distant metastatic sites in metastatic breast cancer patients (23). Lee *et al.* found that elevated CEA was significantly correlated with liver metastases (P=0.002), and CA15-3 levels had a significant correlation with bone (P=0.021), liver (P=0.013), and multiple region metastases (P<0.001) (21). Caglar and colleagues also found that the mean CEA and CA15-3 levels in patients with bone metastases were significantly elevated compared to patients without bone metastases (P<0.001) (26). Furthermore, CEA and CA15-3 may be used as candidate biomarkers in diagnosing different causes of malignant pleural effusion (27). In a study of lung cancer, Lee *et al.* also found that bone metastases (P<0.001) and brain metastases (P=0.005) showed a significant correlation with elevated serum CEA levels; furthermore, CEA levels ≥100 ng/mL were correlated with abdominal/pelvic metastases (P<0.001) (20).

Our results found that patients with elevated serum CA15-3 levels were more prone to have abdomen/pelvis (P=0.001) and bone metastases (P=0.002), while CA15-3 levels were also potentially correlated with pleura (P=0.029) and bone metastases (P=0.054). Therefore, CEA and CA15-3 levels may serve as good biomarkers to assess the risk of site-specific metastases, especially the liver, bone and pleura metastases. The correlation between tumor marker levels and site of metastases requires further investigation, which may be of great value for the targeted therapy of breast cancer with organ-specific metastases.

CA15-3 is a member of the Mucin-1 (MUC-1) family (28). Previous studies have found that MUC-1 can be immunogenic and could be a suitable target for breast cancer immunotherapy (29,30). It was also found that targeting the MUC1-C oncoprotein inhibits the self-renewal capacity of breast cancer cells (31). Overexpress of CEA promotes the adhesion and metastatic processes in cancer cells (32). The oncofetal antigens include CEA, which may serve as a target for the active immune response against cancer. Our findings strongly support the feasibility of using an inhibitor targeting CEA, which may result in a delay of site-specific metastatic processes and prolonged survival in breast cancer (33,34). New cancer vaccines targeting both CEA and MUC-1 have also been developed (35-37). Our results provide a greater understanding for future investigative anti-CEA and CA15-3 targeting and intensive systemic assessment in advanced breast patients with site-specific metastases.

The American Society of Clinical Oncology does not recommend monitoring CEA and CA15-3 levels for routine surveillance of patients with breast cancer after primary therapy (38). However, the European Group on Tumor Markers has suggested routine measurement of tumor markers such as CEA and CA15-3 in patients with breast cancer since 2005 (39). In our previous studies, we have confirmed that preoperative serum CEA and CA15-3 levels can not only serve as prognostic factors in breast cancer patients (10), but they also have a potential impact on axillary treatment considerations (19). In this study, we further found that serum CEA and CA15-3 levels in metastatic breast cancer patients can predict the risk of site-specific metastases. Based on our results, we suggest that serum CEA and CA15-3 levels have potential clinical value in postoperative survival prediction and follow up monitoring of breast cancer patients.

There are several limitations in our study. First, retrospective studies have an inherent problem of selection bias. Secondly, CEA and CA15-3 levels may also be elevated in other benign conditions (40). In addition, the majority of patients with metastatic disease were diagnosed by clinical and imaging approaches and diagnosis was not confirmed by pathological examination. Furthermore, the molecular mechanisms between elevated serum tumor marker levels and the risk of site-specific metastatic affinity remain unclear.

Conclusions

In conclusion, elevated serum CEA and CA15-3 levels may cause an increased risk of site-specific metastase in metastatic breast cancer. Further experimental studies investigating the specific role of serum CEA and CA15-3 levels in the organ-specific metastatic cascade are required.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/tcr.2016.08.39). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the ethics committee of the First Affiliated Hospital of Xiamen University and SYSUCC (approval number of institutional review board, 2013B021800157) and individual consent for this retrospective analysis was waived.

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