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CEA and CA 15-3 Serum Level in Metastatic Breast Cancer and its Correlation with Distant Metastasis

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ABSTRACT

The aim of this study was to investigate the correlation between cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA) tumor markers and different clinicopathological parameters of metastatic breast cancer and the site of distant metastasis. A total of 136 patients with metastatic breast cancer were included and the Radiotherapy and Oncology Database were used to determine their clinical and pathological variables along with the level of CEA and CA 15-3 at the time of diagnosis of distant metastasis. Univariate and multivariate analyses were used to investigate association between clinicopathological parameters, distant metastasis, and tumor marker levels. Increased serum levels of CA 15-3 and CEA at initial diagnosis of metastasis were seen in 59.5% and 44.9% of cases, respectively. Elevation of CA 15-3 and CEA did not correlate with grade, hormonal receptor and HER2 status but increased level of CA 15-3 was associated with tumor nodal status in multivariate analysis, with higher level of CA15-3 associated with more nodal involvement (P<0.001). CEA serum level had a significant correlation with breast cancer's pathological subtypes, with elevated CEA serum level seen more commonly in invasive ductal carcinoma (P= 0.01). Comparing the site of metastasis, the incidence of elevated CA 15-3 and CEA levels were most commonly seen in bone and liver solitary metastasis respectively, however, these differences were not statically significant. In metastatic breast cancer, elevated CA15-3 level was found in majority of cases, while increase in CEA level was seen in less than half of the population. Higher CA 15-3 level represented more frequent nodal involvement. Invasive ductal carcinoma demonstrated elevated CEA level more frequently compared with invasive lobular carcinoma. Tumor marker elevation did not differ regarding the first site(s) of metastasis.

Key words: Metastatic breast cancer, CA 15-3, CEA, Site of metastasis.

INTRODUCTION

Breast cancer is the most frequently diagnosed cancer among women worldwide, accounting for 25% of all cases. It is the leading cause of cancer death among females[1, 2]. During the past 30 years breast cancer incidence has increased steadily, however; due to screening methods and early detection of breast cancer, the mortality rate of this disease has remained stable[3, 4]. Regional and distant metastasis is a major threat to breast cancer patients, inappropriate prognostic event in the course of disease[5]. The use of tumor markers (TMs) in the management of patients with metastatic breast cancer has been investigated during the past two decades, however; their efficacy remains uncertain[6-8]. Developing new modalities for specific and targeted localised treatment of different cancers have necessitated the studies on TMs[9,10]. In breast cancer, the most widely used TMs

are cancer antigen 15-3 (CA 15-3) and carcinoembryonic antigen (CEA)[11]. The CA 15-3 (also known as MUC-1) represents sequences of mucins that are overexpressed in malignant cells[12]. CEA is a protein involved in cell adhesion but its serum level reportedly increases in certain kind of cancers[13]. Although according to the American Society of Clinical Oncology guidelines CEA and Ca 15-3 are not currently recommended as markers for breast cancer screening or early metastasis diagnosis[14], a number of studies have reported association between TMs elevation and the site of metastasis, prognosis, tumor size and axillary node metastasis[15, 16]. The present study was aimed to retrospectively evaluate the association between these TMs and clinicopathological parameters in metastatic breast cancer and their correlation with the site of distant metastasis.

MATERIALS AND METHODS

Participants

The medical records of 388 patients with metastatic breast cancer treated at the Department of Radiotherapy and Oncology of Ahvaz Golestan Hospital (Iran) between April 2005 and March 2013 were reviewed. Those patients whose TMs were recorded at the time of distant metastasis diagnosis and their complete clinicopathological data were available were included. Excluded cases were 196 cases without any TMs data recording, 41 cases with incomplete record of clinicopathological characteristics, 7 cases with synchronous cancers other than breast cancer, and 8 cases with bilateral breast cancer, respectively. A total of 136 patients were eligible to enter this study. Our institutional politics do not require the patients' approval for reviewing archived medical recording files. However, all private information including patients name and address were kept confidential and were not mentioned in any process of data collecting or analysis in this study.

Clinicopathological Parameters

All clinicopathological parameters including Estrogen Receptor (ER), Progesterone Receptor (PR), *human* epidermal growth factor receptor 2 (HER2), histopathology of tumor, nodal status, histological grade, and the site of distant metastasis were extracted from the patients' medical

Table 1: General characteristics of the study population

Characteristics	n	Percentage (%)
Sex		
Male	2	1.5
female	134	98.5
Age		
d”40	37	27.2
>40	99	72.8
ER		
Positive	73	53.7
Negative	63	46.3
PR		
Positive	69	50.7
Negative	67	49.3
HER2		
Positive	53	39
Negative	83	61
Histopathological subtype		
Invasive ductal carcinoma	119	87.5
Invasive lobular carcinoma	11	8.1
Others	6	4.4
Histological grade		
Grade 1	17	12.5
Grade 2	79	5.8
Grade 3	40	29.4
Nodal status		
N0	4	2.9
N1	49	36
N2	62	45.6
N3	21	15.4
CA 15-3		
Normal	55	39
Increased	83	61
CEA		
Normal	75	55
Increased	61	44.9
Site of metastasis		
Bone only	59	43.4
Liver only	19	14
Lung only	17	12.5
Solitary other than bone, liver and lung		
Multiple first site metastasis	10	7.4
	31	22.8

recordings archived in the Department of Radiotherapy and Oncology of Ahvaz Golestan Hospital (Iran).

Tumor Marker Analysis

The laboratory assessments and specific kits were used for the TMs. These assessments used the CA 15-3 and CEA reference ranges as <30 u/ml and <5ng/ml, respectively.

Data Analysis

The descriptive statistics were used to analyze the data. The frequency and percentage were used for qualification data and mean and Standard Deviation (SD) for the quantitative data. All data were analyzed with independent T-Test, Mann Whitney, Analysis of variance (ANOVA) and General Linear Model (GLM) tests using SPSS software version 20.

RESULTS

Data were first analysed with univariate analysis. Those with P-values less than 0.2 were entered in multivariate analysis and processed again. P-values less than 0.05 were considered statistically significant. General characteristics of 136 patients with metastatic breast cancer are

Table 2: Correlation between serum CA 15-3 level and clinicopathological parameters in study population with univariate analysis

	Mean±SD	Increased n (%)	Normal n (%)	P value
ER				
Positive	72.8±83.3	45 (61.7)	28 (38.4)	0.22
Negative	63.3±72.2	36 (57.1)	27 (42.9)	
PR				
Positive	74.7±85.4	42 (60.9)	27 (39.1)	0.21
Negative	62±72.1	39 (58.2)	28 (41.8)	
HER2				
Positive	73.5±84.9	32 (60.4)	21 (39.6)	0.43
Negative	65.2±75.5	49 (59)	34 (41)	
Histopathological subtype				
Invasive ductal carcinoma	67.2±78.4	71 (59.7)	48 (40.3)	
Invasive lobular carcinoma	48.37±60.1	4 (36.4)	7 (63.6)	0.04
Others	128.4±106	6 (100)	0 (0)	
Histological grade				
Grade 1	81.3±97.6	10 (58.8)	7 (41.2)	
Grade 2	53.3±60.2	48 (60.8)	31 (39.2)	0.6
Grade 3	82.9±100	23 (57.5)	17 (42.5)	
Nodal status				
N0	48.8±17.1	3 (75)	1 (25)	
N1	41.6±42.6	26 (53.1)	23 (46.9)	<0.001
N2	62.9±70.1	35 (56.5)	27 (43.5)	
N3	150.9±117.4	17 (81)	4 (19)	
Site of metastasis				
Bone only	68.8±75.3	39 (66)	20 (33.9)	
Liver only	66.8±88.4	10 (52.6)	9 (47.4)	
Lung only	50.5±46.9	9 (52.9)	8 (47.1)	0.82
Solitary other than bone, liver and lung				
Multiple first site metastasis	144.9±137.2	5 (50)	5 (50)	
	86.1±101	18 (58.1)	13 (41.9)	

summarized in Table 1. The median age of the patients was 48 years (range: 29-77 years). The age showed a negative ccorrelation c*oefficient with both CEA and CA 15-3 indicating these TMs decrease as age increases, but this relation was not statically significant for both CA 15-3 and CEA (P= 0.68 and P= 0.5, respectively).* Increased serum levels of CA 15-3 and CEA at initial diagnosis of metastasis were observed in 59.5% and 44.9% of the patients, respectively.

Table 2 and Table 3 show respectively the association between the serum level of CA 15-3 and CEA and patients' clinicopathological variables. Elevation of CA 15-3 and CEA did not correlate with grade, hormonal receptor and HER2 status, but increased levels of CA 15-3 were associated with tumor pathological subtypes and nodal status in univariate analysis (P= 0.044 and P <0.001, respectively). However, this correlation was only statistically significant for nodal status in multivariate analysis, with higher level of CA15-3 associated with more frequent nodal involvement (P <0.001).

The CEA serum level at the initial diagnosis of distant metastasis had a significant

Table 3: Corelation between serum CEA and clinicopathologiacal parameters in study population with univariate analysis

	Mean ± SD	Increased n (%)	Normal n (%)	P value
ER				
Positive	16.2±39	36 (49.3)	37 (50.7)	0.31
Negative	15.1±43	39 (61.9)	24 (38.1)	
PR				
Positive	14.3±36	35 (50.7)	34 (49.3)	0.67
Negative	17±45	40 (59.7)	27 (40.3)	
HER2				
Positive	13.6±26	26 (49)	27 (51)	0.36
Negative	17±47.9	49 (59)	34 (41)	
Histopathological subtype				
Invasive ductal carcinoma	17.2±43.3	54 (45.4)	65 (54.6)	
Invasive lobular	1.73±1.4	3 (18.2)	9 (8.8)	0.01
carcinoma	12±9.1	5 (83.3)	1 (16.7)	
Others				
Histological grade				
Grade 1	19.6±40.4	8 (47.1)	9 (52.9)	
Grade 2	15.2±44	35 (44.3)	44 (55.7)	0.49
Grade 3	14.9±33.1	18 (45)	22 (55)	
Nodal status				
N0	44.3±78.5	3 (75)	1 (25)	
N1	15.1±48.3	17 (34.7)	32 (65.3)	0.15
N2	14.8±36.8	28 (41.9)	36 (58.1)	
N3	14.1±20	15 (7.4)	6 (28.1)	
Site of metastasis				
Bone only	17.4±51	22 (37.3)	37 (62.7)	
Liver only	15.5±36.5	10 (52.6)	9 (47.4)	0.21
Lung only	16.9±45.9	6 (35.3)	11(64.7)	
Solitary other than bone, liver and lung				
Multiple first site metastasis	14±3.4	6 (60)	4 (40)	
	15.5±21.5	12 (38.7)	19 (61.3)	

relation with pathological subtypes of breast cancer in both univariate and multivariate analysis. Comparing invasive ductal and invasive lobular carcinoma, an elevated CEA serum level was more commonly observed in invasive ductal carcinoma (P= 0.01).

Table 4: Correlation between Histopathological breast cancer subtypes and Ln (CA15-3) with multivariate analysis

Histopathology		D	S.E	P value
IDC	ILC	0.34	0.27	0.27
	Other	-.086	0.36	0.17
ILC	Other	-1.21	0.44	0.03

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; d: Difference between Ln(CA 15-3) in the groups; S.E: Standard Error

Table 5: Correlation between nodal status and Ln (CA 15-3) with multivariate analysis

Nodal status		D	S.E	P value
N0	N1	0.48	0.45	0.72
	N2	0.09	0.45	0.99
	N3	-.074	0.47	0.39
N1	N2	-0.38	0.17	0.11
	N3	-1.22	0.23	<0.001
N2	N3	-0.84	0.22	0.001

d: Difference between Ln(CA 15-3) in the groups; S.E: Standard Error

Table 6: Correlation between histopathological subtypes of breast cancer and Ln(CEA) with multivariate analysis

Histopathology		D	S.E	P value
IDC	ILC	1.25	0.43	0.01
	Other	-0.51	0.59	0.97
ILC	Other	-1.76	0.71	0.10

IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; d: Difference between Ln(CEA) in the groups; S.E: Standard Error

In solitary first site metastasis, frequency of elevated and normal CA 15-3 level were almost equal; except for bone metastasis in which elevated CA15-3 serum level was 66% which was twice the normal range (33.9%) (Table 4). In multiple metastases, elevated serum level was observed in 58.1% of cases; however, none of these differences were statically significant (Table 5). The CEA serum level was merely increased in just over one third of all cases with solitary bone or liver metastasis and multiple first site metastases. However, CEA elevation was observed in about 50% of patients with solitary liver metastasis. It should be mentioned that these differences were not statically significant (P= 0.21) (Table 6).

CONCLUSION

In less developed countries breast cancer is still the most life threatening cancer diagnosed in women; however, in developed countries it has been surpassed by lung cancer to be the second most important cause of cancer deaths in females[2]. Due to heavy burden of breast cancer, numerous studies have been done to find early detectors and predictive factors to guide breast cancer management. In addition to traditional parameters, the use of TMs in breast cancer diagnosis and monitoring has recently spotlighted[15].

Several studies have reported association between CEA and CA 15-3 and metastatic breast cancer. Yerushalmi *et al.,.* and Molina *et al.,.* reported that CA 15-3 level in metastatic breast cancer is higher than CEA[17, 18]. In line with previous studies our findings showed elevated serum levels of CA 15-3 and CEA in 59.5% and 44.9% of all patients, respectively.

A number of studies such as Geng *et al.,.* and Yerushalmi *et al.,.* stated an association between different molecular subtypes of breast cancer and CEA and CA15-3 serum levels[11, 17]. In Geng *et al.,.* a higher percentage of elevated CEA and CA 15-3 were seen in breast cancer luminal subtype. In this study, CA 15-3 was more frequently elevated than CEA in patients with metastatic breast cancer regardless of histopathology of tumor. There was a significant correlation between CEA serum level and histopathology of cancer with increased

CEA level mostly found in invasive ductal carcinoma (P= 0.01) (Table 4).

In Lumachi *et al.,*. study positive nodes were seen more significantly in patients with elevated CEA and CA 15-3 serum level[19]. Our result declared a significant correlation between CA 15-3 and nodal status in metastatic breast cancer. While the serum level of CA 15-3 was almost equal in N1 and N2 groups, both of them had lower CA 15-3 serum level than N3 group (P<0.001).

Regarding the association between the TMs' levels and metastatic site(s), previous studies have shown controversial results. Some studies such as Yerushalmi *et al.,*.[17] did not identify significant difference in TMs levels considering different site(s) of metastasis. Contrary, other studies such as Geng *et al.,*.[11], Tampellini *et al.,*.[20] and Champion L *et al.,*.[5] reported elevated CA 15-3 level associating with bone, liver and multiple or visceral lesions metastasis, respectively. In the Wojtacki *et al.,*. study[21] highest mean values of CA15-3 were observed in patients with liver and multiple metastases with high sensitivity of the CA15-3 test in detecting bone metastases; however, they stated that their observation could not be conclusive due to small group of patients. In our results, CA 15-3 was more frequently elevated than CEA regardless of site(s) of metastasis. While CA 15-3 level did not differ among various site(s) of metastasis - except for bone in which increased level of CA 15-3 were twice as normal - CEA level varied based on site(s) of metastasis. For example, in solitary liver metastasis CEA was more often found to be elevated (52.6%). This percentage was 37.3% and 35.3% in solitary bone and lung metastasis, respectively. When multiple metastases were found at the initial diagnosis of metastasis, 58.1% and 38.7% of cases showed elevated CA 15-3 and CEA serum levels, respectively.

In conclusion, CA 15-3 is more often elevated in metastatic breast cancer than CEA. An elevated serum level of CA 15-3 correlated with more frequent nodal involvement. There was a significant correlation between CEA level and histopathological subtypes of tumor; increased CEA level more frequently found in invasive ductal carcinoma. Although there were some differences in TMs levels regarding initial site(s) of metastasis, none of these findings were statically significant.

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