ORIGINAL ARTICLE
SIGNIFICANCE OF CA15-3 IN CARCINOMA OF THE BREAST WITH VISCERAL METASTASES

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Background: The most common malignancy and second most common cause of death is breast cancer among women. About 2.09 million fatalities from breast cancer happened in 2018. The objective was to evaluate the elevated CA15-3 in breast cancer patients with visceral metastases presenting at the tertiary care hospital of Karachi. **Methods:** It was a cross-sectional study conducted at the Department of Oncology of Jinnah Postgraduate Medical Center from 15th December 2018 to 15th November 2019. Female patients aged 26–80 years diagnosed with visceral metastatic (defined as metastasis to lung, liver, brain and adrenal glands) breast cancer were included in the study. The diagnosis of breast cancer was confirmed on histopathology whereas the metastatic sites were evaluated using physical examination and imaging. The serum CA15-3 concentration was assessed using assay kits. The serum CA15-3 level of 0-32 U/ml was taken as normal range for all the patients whereas CA15-3 level greater than 32 U/L was considered as elevated CA15-3. SPSS version 23 was used to enter and analyze data. **Results:** A total of 139 females were included in the study. The mean age & BMI of the patients were reported as 46.5 years & 26.69 kg/m². In the majority of the patients' metastases were detected in the liver (n=54), 92 in the lungs+ parenchymal disease, 20 in adrenal glands, 12 in pleural effusion and 10 in the brain. Out of 139 patients with visceral metastases, 52(37.4%) had normal CA15-3 level whereas 87 (62.6%) had elevated serum CA15-3 levels (>32 U/L). **Conclusion:** The serum CA15-3 tumour marker is elevated significantly in visceral metastases and can be used as a prognostic marker in metastatic breast cancer patients.

Keywords: Tumour marker; Elevated CA15-3; Metastases; Metastatic breast cancer; Visceral metastases; Invasive ductal carcinoma

INTRODUCTION

The most common malignancy and second most common cause of death is breast cancer among women. About 2.09 million fatalities from breast cancer happened in 2018.[1] Nearly 12% of women in the US are at risk of developing breast cancer throughout their lifetime.[2] This malignancy is prevalent in elderly women in the West (after 60 years), while it is more prevalent in younger women in Pakistan.[3]

The survival rate of breast cancer has increased in past years due to early detection and advances in treatment. The five-year survival rate is reported as 90% with invasive breast cancer whereas 83% survive for ten years.[4] Approximately up to 10% of the females had stage IV or metastatic at the time of diagnosis, whereas 20–30% had metastatic recurrence in previously treated cases.[5] The metastatic breast cancer patients usually have extensive visceral disease including pleura, lungs, liver, and brain. The metastasis to visceral organs has been reported as 41% in breast cancer patients.[6] The median survival time in these patients is approximately one to two years with an estimated survival rate of 20% and they usually have poor prognoses.[7]

"Cancer antigen 15-3 (CA15-3)" is the most reliable and commonly used serum tumour marker for breast cancer diagnosis [(8)]. It provides prognostic information regarding the efficacy of treatment, metastatic to distant organs and disease recurrence in breast cancer.[9] The increased level of CA15-3 is reported in 19% of breast cancer patients at the time of primary diagnosis and is strongly associated with metastatic disease.[10–12] Approximately 84% of metastatic breast cancer patients have elevated CA15-3 level.[10] Hence this research aimed to evaluate the elevated CA15-3 in breast cancer patients with visceral metastases presenting at the tertiary care hospital of Karachi. This tumour marker would be helpful for oncologists in the early detection and management of breast cancer patients with visceral metastases.

MATERIAL AND METHODS

It was a cross-sectional study conducted at the Department of Oncology of Jinnah Postgraduate Medical Center from 15th December 2018 to 15th November 2019. The sample size was estimated using the Open Epi online sample size calculator by taking statistics for elevated CA15-3 as a 10%[13] margin of 5% and 95% confidence level, the calculated sample size came out as 139. Women aged 26–80 years diagnosed with visceral metastases (defined as metastasis to lung, liver, brain and adrenal glands) breast cancer, having stage 4 tumours were included in the study. The diagnosis of breast cancer was confirmed on histopathology whereas the metastatic sites were evaluated using physical examination and appropriate imaging. Women with malignancy other than breast cancer, bone metastasis, renal dysfunction, liver, bone & and lung diseases, neoplastic disorders and pregnancy were excluded from the study. The non-probability consecutive sampling technique was applied to select the samples.

The approval from the ethical review committee was sought out before the conduct of the study. The written and verbal informed consent was taken from all the eligible females before the initiation of data collection. The data regarding demographics, medical & and treatment history along with physical examination findings were noted in pre-designed proforma by the researcher herself. The serum CA15-3 concentration was assessed using assay kits. The serum CA15-3 level of 0–32 U/ml was taken as normal range for all the patients whereas CA15-3 level greater than 32 U/L was considered as elevated CA15-3.

SPSS version 23 was used to enter and analyze data. Mean & SD was reported for all quantitative variables whereas frequencies & and percentages were reported for all qualitative variables. Chi-square test was applied to see the significant difference concerning effect modifiers. $p \le 0.05$ was taken as statistically significant.

RESULTS

A total of 139 females were included in the study. The mean age & BMI of the patients were reported as 46.5 years & and 26.69 kg/m^2. Forty-six percent of the females were Urdu speaking & 74.8% of the females were from low socioeconomic status (monthly income<15,000 rupees) and 61.9% were multiparas (parity more than 2). About 52.5% of the females had pre-menopausal status and 53.2% had intermediate grade tumours. About 127 females showed no family history of breast cancer and 79.5% had positive nodal status. In 75 females' the right side of the breast was involved and the most common pathological type of breast tumour was

invasive ductal (91.4%). The hormonal status such as ER, PR, and Her 2 Neu were found positive in 58.3%, 59.7% and 25.9% of patients respectively. Of all of the patients (100%) received palliative setting 62.5% had undergone surgery and 61.1% had chemotherapy exposure. (Table-1)

In the majority of the patients, metastases were detected in the liver (n=54) shown in Figure 1. Out of 139 patients, 87 (62.6%) had elevated serum CA15-3 level (>32 U/L). The categories of CA15-3 levels are displayed in figure 2.

Patients of age more than and equal to 35 years of age had a frequency of elevated CA15-3 as compared to patients of age less than 35 years and the relationship was statistically significant ($p<0.05$). Patients affected with the right side of the breast had a comparatively high frequency of elevated CA15-3 as compared to patients with the left and bilateral affected site and the relationship was statistically significant ($p<0.05$). A statistically significant difference was observed in the frequency of elevated CA-15-3 levels concerning the ductal pathological type of tumour ($p<0.05$). The site of metastases such as liver, Lung + Parenchymal disease, brain and pleural effusion showed statistically significant differences between normal and elevated CA15-3 ($p<0.05$). (Table 2)
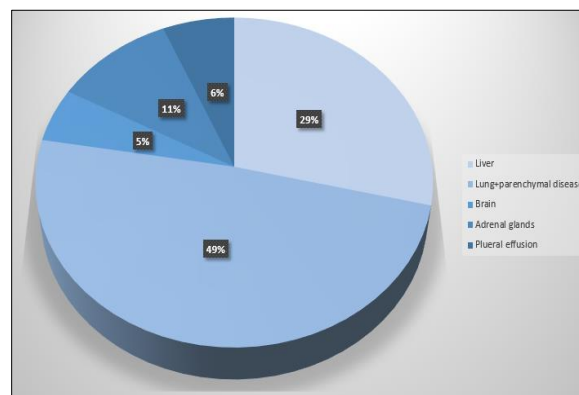

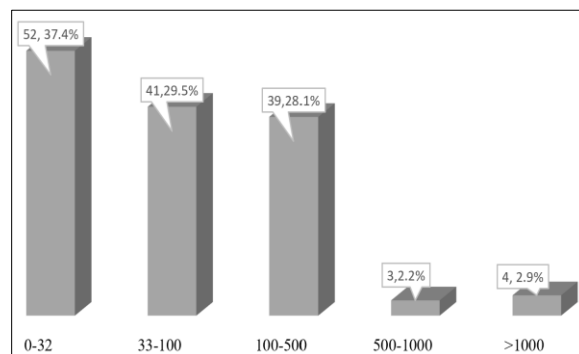**Figure-1: Frequency of breast cancer with visceral METS**

Figure-2: Frequency distribution of serum CA15-3 concentration (U/L

Table-1: Baseline characteristics of study variables (n=139)

Quantitative variables	Mean	SD	Qualitative variables	n	%
Age (yrs.)	46.50	10.88	**Family History of breast cancer**		
BMI (kg/m^2)	26.69	4.47	Yes	12	8.6
Qualitative variables	**n**	**%**	No	127	91.4
Ethnicity			**Nodal status**		
Urdu	64	46.0	Yes	70	79.5
Sindhi	25	18.0	No	18	20.5
Punjabi	22	15.8	**Site of breast**		
Pushtoo	11	7.9	Right	75	54.0
Balochi	17	12.2	Left	55	39.6
Socioeconomic status			Bilateral	9	6.5
Low (<15,000 rps)	104	74.8	**Pathological type of tumour**		
Middle (15000-30000 rps)	33	23.7	Ductal	127	91.4
High (>30000 rps)	2	1.4	Inflammatory	2	1.4
Parity			Lobular	6	4.3
Null	42	30.2	Undifferentiated	2	1.4
1	5	3.6	Others	2	1.4
2	6	4.3	**Hormonal status**		
More than 2	86	61.9	ER +ve	81	58.3
Menstrual Status			PR +ve	83	59.7
Pre menopause	73	52.5	HER 2 NEU +ve	36	25.9
Post menopause	66	47.5	**Type of treatment**		
Grade of tumour			Surgery	87	62.5
Low	20	14.4	Chemotherapy	85	61.1
Intermediate	74	53.2	Radiotherapy	43	30.9
High	45	32.4	Hormonal therapy	23	16.5

Table-2: Stratification of elevated CA15-3

Variables	Elevated CA15-3 (>32 U/L)		Total	*p*-value
	Yes (n=87)	No (n=52)		
Age groups				
< 35 years	11	1	87	0.024
≥ 35 years	76	51	52	
Parity				
Null	26	16	42	0.484
1	3	2	5	
2	2	4	6	
More than 2	56	30	86	
Menstrual Status				
Pre menopause	49	24	73	0.245
Post menopause	38	28	66	
Grade of tumour				
Low	10	10	20	0.412
Intermediate	49	25	74	
High	28	17	45	
Family History of breast cancer				
Yes	9	3	12	0.353
No	78	49	127	
Nodal status				
Yes	85	48	133	0.13
No	2	4	6	
Site of breast				
Right	43	32	75	0.043
Left	35	20	55	
Bilateral	9	0	9	
Pathological type of tumour				
Ductal	77	50	127	0.049
Inflammatory	2	0	2	
Lobular	6	0	6	
Undifferentiated	2	0	2	
Others	0	2	2	
Hormonal status				
ER +ve	55	26	81	0.247
PR +ve	55	28	83	0.276
HER 2 NEU +ve	24	12	36	0.646
Site of metastasis				
Liver	50	4	54	0.001
Lung + Parenchymal disease	42	45	87	0.001
Brain	10	0	10	0.011
Adrenal gland	15	5	20	0.215
Pleural effusion	12	0	12	0.005

DISCUSSION

Breast carcinoma is the most prevalent malignancy among females globally, accounting for twenty-five percent of all cancers.[14] The tumour marker, i.e., CA15 -3 plays a significant part in the early diagnosis, treatment response, early metastasis diagnosis and recurrence of disease in breast cancer patients.[8,9] In the current research we evaluated the elevated CA15-3 in breast cancer patients with visceral metastases.

In the present research majority of the patients with visceral metastases had elevated CA15-3 (62.6%). The most common site of metastases was liver (29%), followed by lungs (25%) and pulmonary nodule (24%). A statistically significant relationship was found between elevated CA15-3 and lung, liver, brain, and pulmonary nodule pleural effusion metastases ($p<0.05$). Laessig D *et al.* found similar results in their research, 71.8% of the patients with metastasis disease had CA15-3 level above the 95th percentile and 19.3% had liver metastasis.[11] In the research by Berruti *et al.* visceral metastases have significantly higher level CA15-3 as compared to soft tissues and bone involvement and the sensitivity of CA15-3 was reported higher for pleural effusion [15]. In another research by Taghizadeh A *et al.* also observed that 65% of the patients with visceral metastases had elevated CA15-3 concentration. The most frequent sites of metastasis except bone were liver (n=59) and lung (n=51), in addition, the elevated CA15-3 showed a statistically significant relationship with lung metastasis. [16] In the research conducted by H et al. the elevated CA15-3 was found in 35.5% of the patients with lymph node metastases, whereas bone metastases were significantly higher than live, brain and lung metastases ($p<0.05$).[13] In research conducted by Ali HQ *et al.* found higher mean CA15-3 levels among patients with breast cancer as compared to controls ($p<0.05$), whereas no correlation was found between CA15-3 concentration and lymph node metastases ($p>0.05$).[17] In the retrospective analysis by Nieder C *et al.* of 118 females with metastases breast cancer 84% of them had raised serum CA15-3 level. [18] Bahrami-Ahmadi A *et al.* also found a significant association between metastases and elevated CA15-3, i.e., the mean CA15-3 level was significantly higher among the metastases group (52.72±27.09) as compared to non-metastases group (27.58±13.46) ($p<0.05$).[9] In the study by Fatima H *et al.* elevated CA15 was frequent among females with visceral metastases and the most common sites were the lung and liver, whereas the liver showed a nearly statistically significant relationship with elevated CA15-3 ($p=0.06$). [19]

The average age of patients in the current research was recorded as 46.5 years varying from 26 to 80 years. The case-control study conducted by Fejzic H *et al.* found the mean age of the breast cancer patients as 55.3 years, in which the mean age of the cases (patients with metastases) and controls were reported as 54.74±8.41 and 55.8±7.94 years respectively and found an insignificant difference between them ($p>0.05$).[13] The average age of breast cancer participants was recorded in the research undertaken by Shao Y et al. as 50 years varying from 16 to 78 years, most of them had tumour stage 2 (46.5%) & 90% of the patients were of age more than 35 years. Further, the age showed an insignificant difference with elevated CA15-3 ($p>0.05$).[20] In another study conducted by Taghizadeh A et al., it was found that the average age of metastatic breast cancer patients was 48.39 and most of them were over 35 years of age (86%), but the relationship with abnormal CA15-3 (p>0.05) was insignificant.[16] Similar results have been noted in the current study that the majority of the patients were in the age group of ≥35 years (91.4%) but the relationship with elevated CA15-3 was statistically significant ($p<0.05$).

In the present research, the majority of the patients had the right site of breast involvement (n=75), followed by a left site (n=55) and only 9 patients presented with bilateral involvement. The patients with right site involvement have a high frequency of elevated CA15-3 as compared to left and bilateral sites and the relationship was statistically significant ($p<0.05$). The study conducted by Osman AMA *et al.*, observed the same proportion of right and left sites of the breast, i.e., 50% of breast cancer patients had the right site involvement and 50% had the left site involvement.[21] In the present study, most of the patients with visceral metastases had invasive ductal pathological type (91.4%) wherein 77 patients had elevated CA15-3 and showed statistically significant difference ($p<0.05$). Similarly in the study conducted by Darlix A et al., the most frequent pathological subtype was ductal carcinoma (82.9%) in females with metastasis breast cancer and 60.3% of the females had elevated CA15-3, furthermore, CA15-3 was independently associated with poor outcome ($p<0.05$).[22] In another study conducted by Hosseini SM *et al.* also found 87.5% of the patients with metastases had invasive ductal histopathological type among them 59.7% of the patients had elevated CA15-3 concentration, hence the difference between the pathological type and elevated CA15-3 was statistically significant ($p<0.05$).[23]

The present study has certain limitations, it was a cross-sectional study and didn't include the

follow-up, single centre and had a smaller sample size. In future multi-center, comparative studies such as cohort or case-control with larger sample sizes shall be conducted.

CONCLUSION

The serum CA15-3 tumour marker is elevated significantly in visceral metastases and can be used as a prognostic marker in metastatic breast cancer patients.

AUTHORS' CONTRIBUTION

Bhunisha: Conception and design of the study, developed the methodology. GH: Review it critically for important intellectual content and make the final changes. ZS: Literature review and data collection. PM: Analysis and interpretation of data. AS: Literature review and data collection. RR, PK, SB, JP: Data collection and interpretation.

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