ORIGINAL ARTICLE

EFFECT OF AGE ON PROGNOSIS IN DIFFERENT MOLECULAR SUBTYPES OF FEMALE BREAST CARCINOMA

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ABSTRACT

Background: Breast carcinoma is one of the ten commonest worldwide malignancies. The objective of the current study was to correlate the significance of prognostic markers and molecular subtypes with patients' age in carcinoma of female breast.

Material & Methods: A descriptive study was conducted at Department of Pathology, Peshawar Medical College, Peshawar and Pakistan Institute of Medical Sciences, Islamabad. Sixty mastectomy specimens were selected using a non-probability sampling method from 1st January, 2012 to 31st December, 2013. Histological type, tumor size, tumor grade and lymph node status were determined. Estrogen receptor (ER), progesterone receptor (PR) and Her-2/neu expression were evaluated immunohistochemically.

Results: Among these 60 patients, the mean age was 50.5±14.4 years. There were 26 (43.3%) patients with age more than 50 years while 24 (40%) were between 40 and 50 years. Ten (16.7%) patients had age less than 40 years. Luminal A molecular subtype was observed in 50% in age groups 40 to 50 and above 50 years. The age group above 50 years had more cases of luminal B (58%) and non-luminal (42%) types. Triple negative molecular subtype is more common in age group between 40 and 50 years i.e. 57.1%.

Conclusions: It was concluded that age is an important factor in determining the aggressiveness of female breast cancer along with other markers like, ER, PR and HER2/neu receptor status.

KEY WORDS: Invasive ductal carcinoma; Estrogen receptor; Progesterone receptor

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INTRODUCTION

Breast carcinoma is one of the ten commonest worldwide malignancies. Every year more than one million women are diagnosed with breast malignancies. Approximately 14% of female cancer deaths are due to this disease.[1] It is the most common (25%) of all female malignancies in Pakistan.[2]

The breast carcinoma incidence peaks among women in their forties in Asian countries as compared to United States and Europe where it commonly involves women in their sixties.[3]

The variables which influence the prognosis and management of breast cancer include histological type, grade and stage of the tumor, along with ER, PR and Her-2/neu status.[4] These biomarkers provide guidelines for treatment, its associated outcomes and about aggressiveness of the lesion. Their combined expression also represents surrogates for the four major molecular subtypes: Luminal A, Luminal B, HER2 positive (Non-Luminal), and triple negative (or basal-like).[5] These molecular types have significant correlation with prognosis and response to chemotherapy of the disease.[6]

Studies have shown that breast cancer at a younger age showed more aggressive biological behavior and more unfavorable prognosis as compared with older patients.[7]

The objective of the current study was to correlate the significance of tumor size, lymph node involvement, histological grade and molecular subtypes with patients' age in carcinoma of female breast.

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MATERIAL AND METHODS

A retrospective descriptive study was carried out at the Department of Pathology, Peshawar Medical College, Peshawar and Pakistan Institute of Medical Sciences, Islamabad from 1st January 2011 to 31st December 2013.

Mastectomy specimens of female patients from its affiliated teaching hospitals, belonging to Khyber Pakhtunkhwa province with diagnosed breast carcinoma were included. Patients who had received neo-adjuvant chemotherapy before mastectomy were excluded. The sample size was 60. Patients were grouped as below 40, 40 to 50 and above 50 years. Samples were received in 10% buffered formalin. Tumor size was measured on gross examination and classified as < 2 cm, 2 – 5 cm and > 5 cm. Representative sections of the tumor and lymph nodes were submitted for paraffin embedding after formalin fixation; 3-4 μm thick sections of the tissue were made and stained with hematoxylin and eosin (H&E) for subsequent microscopy. Histological typing of the tumor and detection of lymph node metastases were performed. Histological tumor grading was done using modified Bloom and Richardson scoring system.[8] Lymph nodes were grouped as 1-3, 4-9 and >9 according to number of lymph nodes showing metastases. The parameters were recorded according to TNM staging for breast carcinoma. Representative sections with tumor and the adjacent normal breast tissue (internal control) were processed for ER, PR and HER-2/neu immuno-histochemical staining. ER and PR positivity were assessed by using H-scoring system taking nuclear staining with a score >50% as positive. For HER-2/neu staining, a score 3+ was taken as positive.[9,10]

Molecular Types	Immunohistochemical Stain Reaction
Luminal A	ER+ /PR+ HER2-
Luminal B	ER+ /PR+ HER2+
Non luminal	ER- PR- HER2+
Triple Negative	ER- PR- HER2-

Data was entered in SPSS version 19.0 and statistical analysis was done to determine frequency of ER, PR and other morphological prognostic parameters along with different molecular subtypes.

RESULTS

During this study a total of 60 mastectomy specimens of female breast cancer were included. Morphologically all the cancers were invasive ductal carcinoma (NOS). The mean age was 50.5 ±14.4 ranging from 21 to 85 years. There were 26 (43.3%) patients with age more than 50 years while 24 (40%) were between 40 and 50 years. Ten (16.7%) patients had age less than 40 years. The right breast was more commonly involved (58%). The tumor size ranged from 1 cm to 26 cm. Four (6.7%) cases were multifocal. ER and PR were positive in 29 (48.3%) and 21 (35%) cases respectively while HER-2/neu was positive in 17 (28.3%). (Fig. 1)

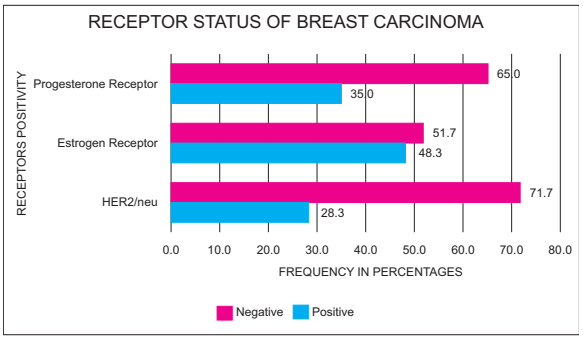

Figure 1: Receptor status of breast carcinoma.

The age group status was compared with tumor grade, size, lymph node involvement and immunohistochemical stain reaction. Histological grade II was the most common in all the three age groups. In age group below 40 years, 50% cases belonged to grade II and grade III each. Out of 24 cases between age of 40 and 50 years, 13 (54.2%) were grade II. Similarly 18 (69.2%) cases of age above 50 years had histological grade II. Tumor size of more than 5 cm was common in all age groups. The patients with age above 50 years had greater number of lymph nodes with no metastases (57%). In age groups, below 40 years 60% cases and between 40 to 50 years, 62.55% cases were positive for lymph node metastases. (Table 1)

Table 1: Age group status by tumor grade, size, lymph node involvement and immunohistochemistry.

Features		Age group		
		Under 40 n=10	40 to 50 n=-24	Above 50 n=26
Histological Grade	Grade I	0 (0.0)	3 (12.5%)	5 (19.2%)
	Grade II	5 (50%)	13 (54.2%)	18 (69.2%)
	Grade III	5 (50%)	8 (33.3%)	3 (11.5%)
Tumor size	<2cm	2 (20%)	3 (12.5%)	0 (0.0)
	2-5cm	2 (20%)	9 (37.5%)	12 (46.2%)
	>5cm	6 (60%)	12 (50%)	14 (53.8%)
Lymph mode	None	4 (40%)	9 (37.5%)	15 (57.7%)
	1-3	1 (10%)	8 (33.3%)	5 (19.2%)
	4-9	3 (30%)	5 (20.8%)	3 (11.5%)
	>9	2 (20%)	2 (8.33%)	3 (11.5%)

Luminal A molecular subtype was observed 50% in age group between 40 and 50 and above 50 years each. The age group above 50 years had more cases of luminal B and non-luminal types i.e. 58% and 42% respectively. Triple negative molecular subtype was more common in the age group between 40 and 50 years i.e. 57.1%. (Table 2)

Table 2: Age with molecular subtypes of breast cancer.

Age of patients in years	Luminal A n=20	Luminal B n=12	Non luminal n=14	Triple Negative n=14
<40	0 (0.0)	3 (25%)	4 (28.6%)	3 (21.4%)
40-50	10 (50%)	2 (16.7%)	4 (28.6%)	8 (57.1%)
>50	10 (50%)	7 (58.3%)	6 (42.9%)	3 (21.4%)

DISCUSSION

The present study comprised of referred cases from allied teaching hospitals of Peshawar Medical College for which hormonal and Her-2/neu receptors were requested by the clinicians.

A large number of studies show 20% to 38% regional variations of this disease in Pakistan including Khyber Pakhtunkhwa Province.[11,12]

The present study was designed to determine the association of patients' age with histologic grade, tumor size, lymph node metastases, reactivity pattern of estrogen receptor (ER), progesterone receptor (PR) and HER-2/neu in invasive ductal carcinoma NOS of female breast in district Peshawar of Khyber Pakhtunkhwa.

In this study, all the cases belonged to histological type invasive ductal carcinoma NOS which is most commonly observed throughout the world.[13]

In our study the HER2/neu receptor was positive in 28.3% cases which is slightly higher than other studies from Northern America (22.2%)[14] and Europe (13.0%)[15]. Her2/neu positivity in our study is almost identical to other regional studies conducted by Mostafa et al,[16] Pinjawani et al[17] and Keyhani et al[18]. The overall ER expression was positive in 29 (48.3%) cases which is lower than the findings of studies by Anderson et al[19] and Chung et al[20] i.e. 64.9% and 61% respectively. Our findings were different from other national studies by Kamil et al[21] (32%) and Sharif et al[22] (74%). Similarly, our findings of positive PR expression i.e., 21 cases (35%) was less than other international studies by Aprino et al[23] (57%) and Chung et al[20] (51.9%). Regarding studies in Pakistan, our findings were almost similar to Kamil[21] et al (29.68%) but lower than Sharif et al[22] (67%). These variation may be due to pattern of referred cases at different centers in our country.

Majority of the tumors were histological grade II in all the three age groups. In patients with age above 50 years there were only 3 cases (11.5%) with grade III tumor which is much lower than 59.3% by Rakha et al[24] and 61.4% Albrekten et al[25]. In contrast to this some national studies have findings identical to us[26-28]. It may highlight regional and geographical differences.

The tumor size of more than 5 cm was common in all the age groups being 60%, 50% and 53.8% respectively. However, Sharif et al26 found 30.6%, 22.2% and 21.4% cases with the same tumor size in the identical age groups. This variation at national level indicates the type of biopsy used for diagnosis. However, Bertrand et al[29] found 64.9% cases with tumor size up to 2 cm in age group above 55 years. This may point at the age of the patient at which she seeks consultation.

In this study, relatively younger patients i.e., under 40 years, were more positive (60%) for lymph node metastases than the older patients having age above 50 years (42.3%). These finding are almost consistent with Sharif et al[26] who found lymph node metastases 69% and 67% respectively in patients with the same age groups. However, this finding is also consistent with Wildiers et al[30] suggesting in his study that axillary lymph node involvement decreases with increasing age up to approximately 70 years. This is because in younger age group breast cancer is likely to be more aggressive.[31]

In our study triple negative molecular subtype is more common in age group below 50 years i.e. 78.5% which is comparable to Sajid et al[32] with 65.88% in the same age group. Similarly in another study performed at Karachi, the identical molecular subtype was detected in 60% cases in the above age group.[33] In contrast to this, results from foreign population based studies show a lesser number of triple negative subtypes of female breast carcinoma in younger age group. Lund et al[34] and Clark et al[35] identified 30.2% and 28.8% cases of triple negative subtypes respectively in patients below age 50 years. The above two studies were carried out in United States of America. This shows racial and geographic variations.

In our study Luminal A molecular subtype was observed in 50% in age groups 40 to 50 and above 50 years. The age group above 50 years had more cases of luminal B (58%) and non-luminal (42%) types. Almost similar frequencies were found for Indian subjects residing in United States in the study by Sing et al.[36] This indicates hereditary and genetic predisposition in spite of environmental and geographic differences.

CONCLUSION

It was concluded that age is an important factor in determining the aggressiveness of female breast cancer along with other markers like, ER, PR and HER2/neu receptor status.

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CONFLICT OF INTEREST
Authors declare no conflict of interest.
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None declared.