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Features of human epidermal growth factor receptor-2 and hormonal receptors in tissues of women with breast cancer

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Abstract

Introduction: Cancer of the Breast is the most common cancer in women in India and accounts for 14% of all cancers in women. For post mastectomy treatment of breast cancer, HER2/neu and Hormonal receptors assessment is required as it influences the treatment and predict treatment outcome and prognosis. In this study HER-2 and hormonal receptors status was assessed in biopsies of breast cancer at SPMC, Bikaner Hospital. So this study attempts to explain the pattern of HER-2, PR, and ER expression as well as associated factors among women with breast cancer at SPMC, Bikaner Hospital.

Material and Methods: A longitudinal study of female breast incisional biopsies confirmed to be carcinoma at the Histopathology division of SPMC, Bikaner Hospital. (Sept 2018–August 2019).

Exclusion criteria was morphologically poor tissue blocks, blocks without tumor, and male patients. Immunohistochemistry for estrogen (ER), and progesterone (PR) receptors and HER2 were done preceded by routine staining.

Results: A total of 176 cases were confirmed to be carcinoma including 112 meeting inclusion criteria. Age ranged 21–73 years and the mean age was 43.22 years. 59.82% of the patients were in the 40–55 years age group. Invasive ductal carcinoma was seen in the majority of women (74.1%), 42.8% were of intermediate grade. Quite a few (36.6%) were of stage three.

Immunostaining for hormones was done in 110/112 patients.

Conclusions: Pattern of HER2 and Hormonal receptors expression was similar to expression in SAARC countries but somewhat different to Caucasians and African races. As far as triple negative breast carcinomas (TNBC) is concerned it's incidence was found to be similar to the rest of the Indian reports, the majority of them were luminal. Over-expression of HER2 is relatively common. It is strongly recommended that receptor status assessment be made routine for breast cancer patients at all centers doing Breast cancer treatment.

Keywords: Breast cancer, HER2/neu, PR/ER, Hormone receptors.

Introduction

Breast cancer is the most common cancer in urban females and second most common in rural India. 1 Its incidence is 25.8 per 100,000 women and mortality is 12.7 per 100,000 women inindian subcontinent. Presence of ER,PR and HER2 have impact on prognosis of patients and these are predictive markers as well. 2 Indian women show lesser hormone receptor positivity in comparison to western world. 3 In recent years the incidence of triple negative and aggressive breast cancer is also increasing especially in younger age group in India. 4 The present study is conducted to see the pattern of these markers in breast cancer patients at a regional cancer centre in North West India and to compare it with other studies.

Material and Methods

This was a longitudinal study done from September 2018–August 2019 in the department of pathology at Sardar Patel Medical College, Bikaner, a tertiary care teaching hospital in northwestern India. All the female breast tissues sent to our department and found positive for breast cancer were analyzed.

Inclusion criteria

1. Female breast cancer patients
2. Tissue with good morphology
3. The tissues on which IHC was applied.

Exclusion criteria

1. Male breast
2. Benign conditions of breast
3. Tissue with poor morphology

Routine histological procedure was followed and slides were stained with H&E. Histological typing of the malignant cases was done and tumors were graded. The histological grading of invasive breast cancer was performed using the Elston-Ellis modification of Scarff-Bloom-Richardson system which scores the amount of glandular formation, nuclear pleomorphism and mitotic index of the tumor cells. Each of these features were scored from 1 to 3, and then scores were added to get total scores which ranged from 3 to 9 according to the grading system. Total final score of 3–5 was graded as low grade (grade 1) and score of 6–7 was graded as intermediate grade (grade 2) and score of 8–9 was graded as high grade tumor (grade3). The cases positive for primary breast carcinoma were selected for immunohistochemical staining for ER,PR and HER2and it was performed at Prakash Lab, Bikaner with an automated IHC machine (BenchMark XT, Roche).ER, PR evaluation: Any tumor with >1% of cells showing nuclear staining was considered as positive. ER and PR scoring for all cases was done using Allred scoring. ER and PR were considered positive for cases which scored 3+ or more on Allred score.HER2 scoring- was done according to the ASCOCAP 2013 guidelines. Age, histological type, histological grade and status of receptors in breast cancer were noted in a proforma. Data was tabulated in Microsoft Excel 2013 and analysed by using Statistical Package for Social Sciences (SPSS) Version 21. For all statistical analysis, P value < 0.001 was considered as significant.

Observation and Result

112 cases were studied in one year period and the mean age of presentation was 43.22 year. Majority of our patients were in the 40-55 year age group. (table 1)

Table 1: Number of patients in different age groups.

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Age groups at diagnosis (years)	Number of patients	Percentage
< 40	19	16.96%
40–55	67	59.82%
>55	26	23.21%
Total	112	100%
Mean age	43.22 ± 0.5 years	

Most of the cases were of infiltrating ductal carcinoma (74.1%) type followed by invasive lobular carcinoma (11.6%) and others.(Table 2)

Table 2: Histological type of tumors

Histological Type	No. of Patients	Percentage
Invasive ductal carcinoma	83	74.1
Invasive lobular carcinoma	13	11.6
Medullary carcinoma	10	8.9
Others	6	5.3
Total	112	100

Majority of our patients presented with grade 3 tumor (36.60%) followed by grade 2 tumor(42.80%). (Table 3)

Table 3: Histological grading of tumors

Histological Grading	No. of cases	Percentage
High grade	41	36.6
Intermediate grade	48	42.8
Low grade	23	20.5

ER,PR and HER2 staining pattern matched with other Indian studies. ER+ 39.28%, PR+ 26.78%and HER2+ 16.07% was found in our study. Majority of our cases were receptor negative i.e.46.42% which was in contrast to western studies. (Table 4,5)

Table 4: Receptor status of tumors

Receptor Status	No. of patients	Percentage
ER +	44	39.28
PR +	30	26.78
HER-2 +	18	16.07
Triple +	2	1.78
Triple -	52	46.42

Table 5: Comparison of different Indian studies.

Indian study groups	ER%	PR%	HER2%
Desai et al[4]	32.6	46.1	-
Dutta et al[5]	24	30	46.3
Ambroise et al.[2]	59	51	27.10
Kumar et al.[6]	48		15
This study	39.28	26.78	16.07

In infiltrating ductal carcinoma, total 28% cases were ER positive, 44% were PR positive and55% were HER2 positive while in case of lobular carcinoma it was 64%, 70%, and 10%respectively. (Table 6)

Table 6: Receptor status in different histological types.

Type	Total	ER (%)	PR (%)	HER 2(%)
IDC	83	28	44	55
ILC	13	64	70	10
Medullary carcinoma	10	35	45	5

Hormonal receptor positivity increased with age i.e. 50% were ER + and 56.66% were PR + in>55 year age group while for HER 2, the positivity was more in younger age group i.e. 50% in<40 year age group.(Table 7)

Table 7: Receptor status correlation with age

Age (years)	ER (n=44)	%	PR(n=30)	%	HER2 (n=18)	%
<40	10	22.72	5	16.66	9	50
41-55	12	27.27	8	26.66	7	38.88
>55	22	50	17	56.66	2	1.11

ER positivity was seen maximally in grade 1 tumors (68.42%) while majority of grade 2 and 3tumors were ER negative. (Table 8)

Table 8: Histological grade and ER receptor status correlation.

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Histological grade	ER positive	ER negative
I	13 (68.42%)	6 (31.58%)
II	20 (48.78%)	41 (78.84%)
III	11 (21.16%)	41 (78.84%)

The chi-square statistics is 15.4789. The p- value 0.000435. The result is significant at p <0.01.PR positivity was seen in grade 1 tumors maximally (42.10%) while grade 2 and 3 tumors show decreased positivity for PR. (Table 9)

Table 9: Histological grade and PR receptor status correlation.

Grade	PR positive	PR negative
I	8 (42.10%)	11(57.89%)
II	15 (36.58%)	26 (63.41%)
III	7 (12.96%)	47 (87.03%)
The chi-square statistics is 9.6382. The p - value is 0.008074. The result is significant at $p <$ 0.01.		

Her 2 positivity increased with tumor grade, it was maximum in grade 3 tumors (17.30%). Mostof the grade 1 tumor (89.47%) were Her 2 negative. (Table 10)

Table 10: Histological grade and HER2 receptor status correlation.

Grade	HER2 positive	HER2 negative
I	2 (10.53%)	17 (89.47%)
II	7 (17.07%)	34 (82.93%)
III	9(17.30%)	43 (82.70%)

Figure 1 showing a case of infiltrating duct carcinoma at 10x H&E. Next images are of ER, PRand HER-2 staining of the same case.

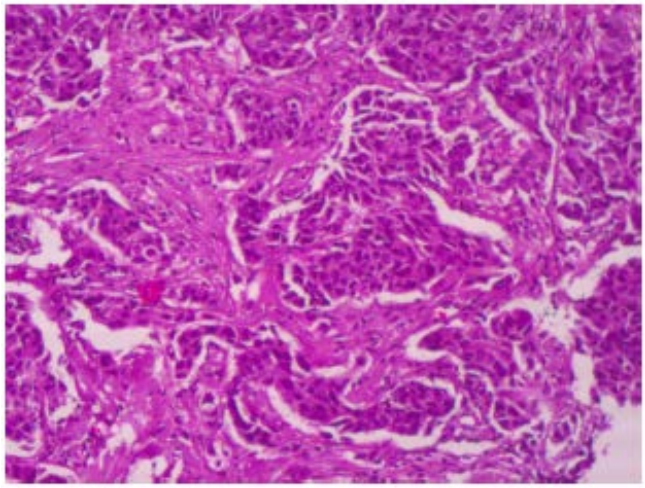

Fig 1: Infiltrating duct carcinoma

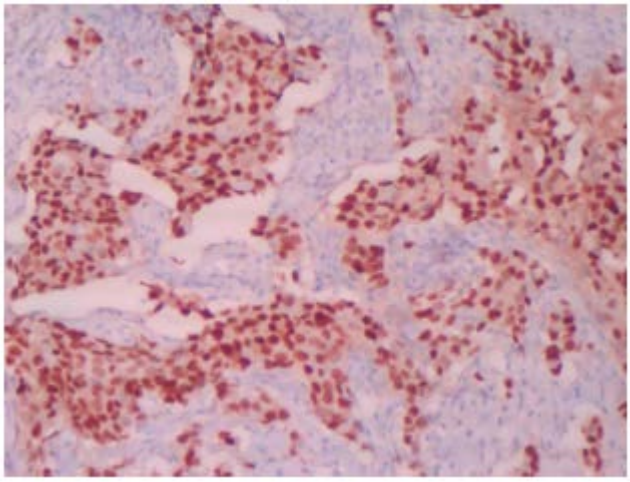

Fig 2: ER (SP-1) Allred score 8

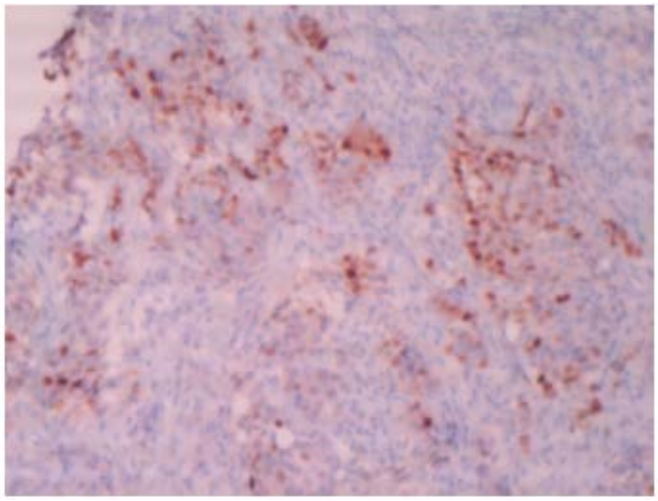

Fig 3: PgR (1-E-2) Allred score 5

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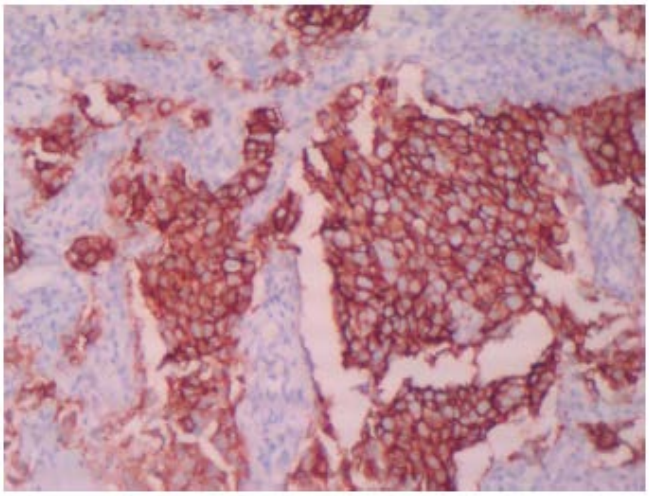

Fig 4: Her-2/neu (4-B-5) Score 3 +

Discussion

Breast carcinoma is the most common malignant tumor and the second most common cause of carcinoma death in women worldwide. The incidence is high in western world and low in a Sian and African countries but it is rising rapidly in recent years in india. More Indian females are diagnosed with breast cancer even at a younger age in comparison to west. Median age at diagnosis is between 48-53 years in India while it is in seventh decade in USA. Our patients presented at median age of 43.22 years. Younger patient generally have more aggressive type of tumor. Breast cancer have many Histologic subtypes, invasive Ductal carcinoma being the most common one, others are invasive lobular ca, medullary ca and tubular ca etc. Most of our patients have IDC (74.10%). Histologic grading of breast carcinoma is done according to Nottingham modification of Bloom- Richardson grading system. Most of our patients presented with intermediate and high grade cancer. Higher grade presentation in our country suggests that the biological behavior of breast cancer in the Indian population may be different besides delayed presentation to hospitals due to ignorance, poor access and/or initial consultation of traditional healers. A crucial development in treatment of breast cancer is recognition of the fact that presence of hormone receptor i.e. estrogen and progesterone receptors in malignant breast tissue correlates with response to hormone therapy and chemotherapy. In fact ER is one of the most powerful predictive markers in breast cancer management while PR is a weaker one. The measurement of HER2/Neu protein over expression by immunohistochemistry or HER2/neu gene amplification by fluorescence in situ hybridization(FISH) currently has an established role indecision making regarding patient management, particularly in the selection of patients for treatment with trastuzumab (Herceptin), a monoclonal antibody that targets the HER2/neuprotein and for other chemotherapy as well. Any degree of HR positivity makes the patient suitable for hormone therapy which is safe and administered orally on an outpatient basis. By the use of complementary DNA microarray profiling, breast cancer has been divided into six molecular subtypes: Luminal A, Luminal B, basal-like, HER2-like, normal epithelial-like, and claudin-low. The IHC surrogates for the molecular subtypes are: 1. Luminal A (ER + or PR + orboth, HER2 neu negative) 2. Luminal B (ER + or PR + or both, HER2 neu+) or (ER+, low PR+,HER2 neu−, high Ki67), 3. HER2 neu enriched (ER−, PR−, HER2 neu+) 4. Basal-like (ER−,PR−, HER2 neu±) However, the molecular sub typing was not done in our study and ki-67 was also not done for all cases. The hormonal receptor positivity increases with age and these patients respond very well with hormonal therapy despite their age. Our study has reported a high proportion of receptor negative cases (46.42%). Indian patients present a decade earlier than the western world and generally with higher grades as was also found in our study. These features make these groups of patients unsuitable for targeted therapy and

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compel us to focus on early screening and molecular diagnosis of these patients.

Conclusion

Hormonal receptors and her2 status in our study matched with other Indian researches but not with the western pattern. Indian patients generally present at younger age and with high grade. Many of our patients were found triple negative. This highlights the need of early screening and diagnosis in these patients to reduce the morbidity and mortality.

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