

Correlation of Hormone Receptor and Human Epidermal Growth Factor Receptor-2/neu Expression in Breast Cancer - A study at tertiary care hospital in Himachal Pradesh

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Abstract

Introduction: Female breast cancer has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases.¹ The main aim of our study was to study pattern of expression of Hormone receptor and Her2/neu in invasive breast carcinoma and to correlate ER PR status and Her-2/neu expression with various Clinicopathological aspects.

Method: The present study was carried out in the Department of Pathology, Indira Gandhi Medical College, Shimla, from the period of May 2019 to April 2021. Routine H&E staining for histological diagnosis and IHC analysis for ER, PR and Her-2/neu was carried out in all cases.

Results: This study includes 105 cases of IDC. Majority of patients, i.e., 80 (76.2%) cases were in the age group of 41years to 70 years. As per The Nottingham-Bloom Richardson Grading 66(62.8%) cases of IDC were diagnosed as grade II. The number of lymph nodes varied

from 01 to 29 and lymph node metastasis was found in 58(55.2%) cases. Lymph ovascular invasion was present in 74(70.4%) cases of IDC and absent in 31(29.6%) cases of IDC. 59 (56.2%) cases were ER positive; 54 (51.5%) cases were PR positive and 24(22.8%) cases were Her-2/neu positive. In our present study, 29 (27.6%) cases were triple negative while 8 (7.6%) were found to be triple positive.

Conclusions: Our study of ER, PR and Her-2/neu in IDC by IHC method indicates higher rates of positive expression correlated with various clinicopathological aspects. Higher number of grade 1 tumor showed ER, PR positivity as compared to grade 3 tumors. Inverse relationship was observed between Her-2/neu expression and ER, PR receptor status. Her-2/neu expression was increased with size and high grade of tumor. Her-2/neu expression did not show any significant correlation with age and lymph node status.

Keywords: breast cancer, immunohistochemistry, bloom Richardson grade, receptor status, estrogen receptor, progesterone receptor.

Introduction

Female breast cancer has now surpassed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases.¹ It is the fifth leading cause of cancer mortality worldwide, with 685,000 deaths. Among women, breast cancer accounts for 1 in 4 cancer cases and for 1 in 6 cancer deaths, ranking first for incidence in the vast majority of countries (159 of 185 countries) and for mortality in 110 countries.¹

According to National Cancer Registry Programme Report 2020, breast cancer estimated to contribute 2.0 lakhs (14.8%) new cases in india.² Breast cancer has ranked number one cancer among Indian females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women.²

Breast carcinoma has different prognostic and therapeutic modalities. The progesterone receptor (PR)/estrogen receptor (ER) status and expression of human epidermal growth factor receptor 2 (HER2/neu) are the three most beneficial investigations that influence the response to specific therapeutic agents toward breast cancer. A significant improvement in treatment regimens are vital for the survival of patients.³ HER2/neu expression is associated with poorer survival as it indicates high-grade tumor, and its status has become an important part of immunohistochemical evaluation of breast carcinoma to predict the response to monoclonal antibody therapy (e.g., herceptin), thereby to achieve favorable response to the treatment and hence survival. HER2/neu has prominent prognostic value than most currently used prognostic factors such as ER and PR status.^{4,5}

The main aim of our study was 1) to study pattern of expression of Hormone receptor and Her2/neu in invasive breast carcinoma. 2) to correlate ER PR status and Her-2/neu expression with various Clinico pathological aspects.

Materials and Methods

The present study was carried out in the Department of Pathology, Indira Gandhi Medical College, Shimla from a period of 2 years (May 2019 to April 2021), it included all cases of IDC (105). The study was approved by the Institutional Ethics Committee. Clinical characteristics of patients such as age, size of lump were documented from case files. All the modified radical mastectomy specimens were examined grossly to look for tumor size and nodal metastasis. All tissues were fixed in 10% buffered formalin immediately after resection. Representative sections were taken from tumor and submitted for processing, and routine H&E staining was performed for histopathological diagnosis. Tumors were graded according to Modified Bloom Richardson grading system.^{6,7}

Immunohistochemistry (IHC) for ER, PR, and her-2/neu was performed on bio genex fully automated processor using representative blocks of paraffin-embedded tumor tissue. Four micro meters thick sections were taken on poly-L-lysine-coated slides and submitted for IHC. Immunostainings were performed using the Streptavidin Biotin method. BiogenexTM monoclonal rabbit antihuman progesterone receptor, monoclonal rabbit anti-human c-erbB-2 oncoprotein, monoclonal rabbit antihuman ER were used for immunohistochemical staining, which was carried out manually by an experienced technical officer. Evaluation of the staining and assigning a score were performed by the author. The staining was evaluated on the invasive component only. Best-preserved and best-

stained areas of the sections were assessed. ER/PR positivity and HER-2/neu (score 3+) over expression were used as external control for sensitivity of immunoreactions.

Interpretation of IHC score

Immunoreactivity were evaluated semi quantitatively by two observers under 40X magnification. The results were noted as per the ALLRED scoring system for ER, PR and ASCO/CAP⁹ Guidelines for Her-2/neu.

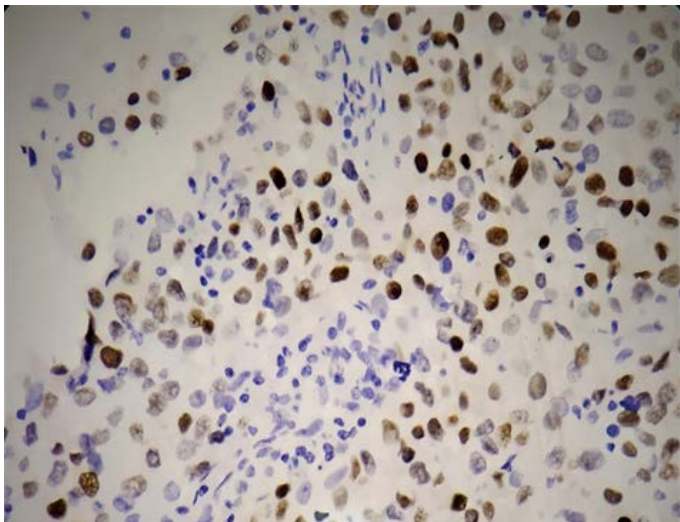


Figure 1: ER postivity showing Allred score of 4+3= in Infiltrating Duct Carcinoma, breast (x400).

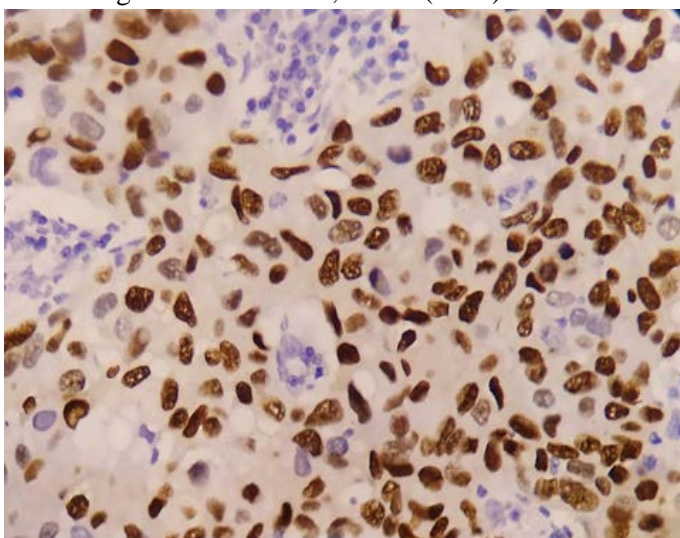


Figure 2: PR positivity showing Allred score of 3+3=6 in Infiltrating Duct Carcinoma , breast (x400).

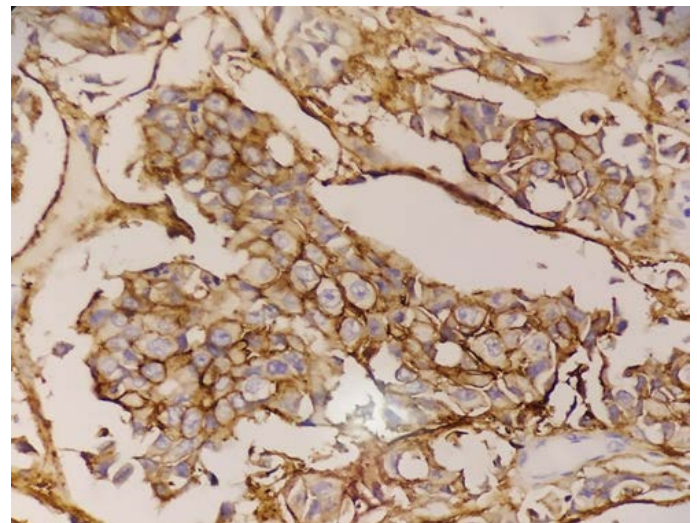


Figure 3: HER-2/NEU (3 +) staining in a case of Infiltrating Duct Carcinoma breast (x400)

Results

Table 1: Age wise distribution of 105 patients of IDC

The study group comprised of a total of 105 breast carcinoma patients. In our study, the youngest and oldest

Age group	No. of cases	Percentage
30-40	12	11.4
41-50	32	30.5
51-60	32	30.5
61-70	16	15.2
71-80	10	9.5
81-90	3	2.9
Total	105	100.0

patients were 31years and 85years old respectively. Majority of patients, i.e. 80 (76.2%) cases were in the age group of 41years to 70 years.

Table 2: Clinicopathological profile of IDC patients.

	Characteristics	No. of cases (%)
Age group	<40	12(11.4)
	>40	88(98.6)
Side	Left	55(52.4)
	Right	50(47.6)
Tumor	<2	15(14.3)

size(cm)		
	2-5	65(61.9)
	5	25(23.9)
NBRG	I	20(19.1)
	II	66(62.8)
	III	19(18.1)
Lymph node metastasis	Present	58(55.2)
	Absent	47(44.8)
Lymphovascular invasion	Present	74(70.4)
	Absent	31(29.6)

The left breast was slightly more commonly involved as compared to the right breast. No bilateral breast tumor was found in our study. Most 65(61.9%) cases fall in the stage pT2 with tumour size between 2-5 cm. As per The Nottingham-Bloom Richardson Grading 66(62.8%) cases of IDC were diagnosed as grade II, followed by Grade I and Grade III. The number of lymph nodes varied from 01 to 29 and lymph node metastasis was found in 58(55.2%) cases. Lymphovascular invasion was present in 74(70.4%) cases of IDC and absent in 31(29.6%) cases of IDC.

Table 3: Immunohistochemical profile of the study group.

	Status	n (%)
ER	Positive	59(56.2)
	Negative	46(43.8)
PR	Positive	54(51.5)
	Negative	51(48.5)
ERPR	ER+ PR+	50(47.6)
	ER- PR-	33(31.5)
	ER+PR-/ER-PR+	22(20.9)
HER2-neu	Positive (3+)	24(22.8)

	Negative (0,1+,2+)	81(77.2)
Triple marker	Triple Negative	29(27.6)
	Triple Positive	8(7.6)

Immunohistochemical profile of the study group as shown in Table 2 revealed 59 (56.2%) cases were ER positive, 54 (51.5%) cases were PR positive and 24(22.8%) cases were Her-2/neu positive. In our present study, 29 (27.6%) cases were triple negative while 8 (7.6%) were found to be triple positive.

50(47.6%) cases were positive for both ER and PR followed by ER-, PR- in 33(31.5%) cases. ER-, PR+ was observed in 10(9.5%) cases of IDC and only ER was positive in 12 (11.4%) cases.

Table 4: Hormonal receptor status and Her-2/neu expression according to size of tumor.

Tumor size	Cases (%)	ER+(59)	PR+(54)	Her2Neu+(24)
<2cm(pT1)	15(14.3)	7(11.8)	7(12.9)	3(12.5)
2-5cm(pT2)	65(61.9)	38(64.4)	36(66.6)	11(45.8)
>5cm(pT3)	25(23.8)	14(23.7)	11(20.3)	10(41.6)

ER and PR positivity was seen more frequently in grade I and II than grade III. Her2/neu positivity was seen more in tumors larger than 2cms in size.

Table 5: IHC positivity according to histological grade.

Grade	Cases (%)	ER+(59)	PR+(54)	Her2Neu+(24)
I	20(19.1)	15(25.4)	15(27.7)	2(8.3)
II	66(62.8)	38(64.4)	32(55.5)	19(79.1)
III	19(18.1)	6(10.1)	7(12.9)	3(12.5)

In our study ER and PR positivity was seen more frequently in grade I and II than grade III. Her-2/neu

positivity was correlated with grade of tumor. 8.3% of Grade I tumors, 79.1% of grade II and 12.5% of grade III tumors were positive for Her-2/neu.

Discussion

Our study comprised of 105 cases of IDC. The mean age in our study was found to be 53.9 years. The incidence in our study is similar to Ravi Kumar G et al¹⁰, Ambroise et al¹¹, Thakur et al¹² and Ali et al¹³.

The left side was more involved than the right side, which is in concordance with the studies of Tulinus et al¹⁴, Badru et al¹⁵, Sughrue et al¹⁶ and Lengare et al¹⁷.

In present study majority of our cases 61.9% (65) were between 2-5cm, similar findings were found in the studies done by Ravi Kumar G et al¹⁰, Sarkar Set al¹⁸, and Lengare et al¹⁷.

The most frequently observed histological grade was Grade II of IDC. In our study also, the most common grade was Grade II. However, Ortiz et al¹⁹ was in discordance to the present study where in grade III was the most common observed grade.

In our study 56.1% cases were ER positive, which is in concordance to studies done by El-Hafez et al²⁰, Yao C et al²² and Lengare et al¹⁷. Whereas Veda Shree et al²³ found comparatively lesser ER positivity in her cases.

51.4% cases showed PR positivity which is in concordance with the studies of Mohammadi Zadeh et al²¹, Sarkar Set al¹⁸ and Lengare et al¹⁷. Significant inverse association was found between hormonal receptor and histology grade.

Greater percentage of grade 1 tumors shows ER, PR positivity while compared to grade 3 tumors. The findings in study by Azizun Nisa et al showed similar results.²⁴

A significant number of cases in the present study comprised of TNBC cases, 27.6% cases belonged to this category. This observation was comparable to other studies conducted in India by Ghosh et al²⁵, Sharma et al²⁶, where the incidence of TNBC was 29.8% and 31.9% respectively.^{5,10.}

Hormone receptors in this study were found as follow: ER+/PR+(47.6%), ER+/PR-(11.4%), ER-/PR+(9.5%) and ER-/PR-(31.5%).

Her-2/neu positivity in various studies ranges widely from 7-63.3%. However in the present study expression of Her-2/neu was seen in 22.8% of cases which is in concordance to the studies of El Hafez et al²⁰(21.1%) and Tamanna et al²⁷(25%). Whereas Chan Yao et al²⁸ study found higher Her-2/neu positivity of 63.3%.

In our study Her-2/neu receptor revealed a significant inverse association with hormone receptor status. We found that ER and PR expression was increased in Her-2/neu negative tumors compared to Her-2/neu positive tumors. Similar results were found in study by Mona Rashed et al²⁹, Maha Arafah³⁰ and MS Al-Ahwal et al.³¹ There was no significant correlation was observed between lymph node status with ER, PR and Her-2/neu expression in present study. Studies by Azizun Nisa et al²⁴ and Muhammad Azam et al³² showed similar results. The results in our study do not show any correlation between age and Her-2/neu expression.

The triple negative breast carcinoma is characterized by lack of ER, PR and Her-2/neu expression. Our study showed 27.6% cases with Negative ER, PR and Her2/neu status. Study by Moses Embroise et al³³ showed 25% of triple negative cases respectively.

Conclusion

In the present study most of the cases of IDC, breast belonged to Grade II as per The Nottingham Bloom –

Richardson Grading. Majority of the low-grade tumours expressed the hormonal receptors. Her-2/neu was positive in only 22.8% of cases of IDC. Our results showed positive correlation between ER and PR accompanied by inverse correlation of them with HER-2/neu. In addition, we found significant correlation between ER and PR positive status and low-grade tumors. ER, PR status and Her-2/neu expression did not show any significant correlation with lymph node status. Her-2/neu expression did not show any significant correlation with age. These findings showed the importance of these biomarkers because they provide valuable prognostic information for best therapeutic decision.

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