Original Article

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Pathology Section

Role of Estrogen Receptor, Progesterone Receptor and HER2/neu Expression in Breast Carcinoma Subtyping

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ABSTRACT

Introduction: Breast cancer is rapidly emerging as the leading cause of cancer in Indian women. Diagnosis can be made on cytology and histopathology. The use of Immunohistochemistry (IHC) to assess the status of Estrogen receptor (ER), Progesterone receptor (PR) and HER2/neu (Human epidermal growth factor receptor 2) status, can provide information for the oncologist to plan the management protocol.

Aim: To assess the ER, PR, HER2/neu status in cases of carcinoma breast and its correlation with histological grade and other clinicopathological parameters.

Materials and Methods: This study was a prospective study conducted at MKCG MCH Brahmapur, Odisha, India of 82 cases for a period of one year and six months duration (June 2013-December 2014) where in all histopathologically diagnosed cases of breast carcinoma were included. BioGenex kit was used for IHC staining and Dako kit for HER2/neu. Allred scoring was used for ER & PR and Scaff-Bloom-Richardosn for HER2/neu. Statistical analysis was done with SPSS software version 20.0, Fisher's exact test, Chi-square test and student's t-test.

Results: In present study, the ER, PR and HER2/neu status were correlating significantly with histological grade. The grade II tumors had low ER/PR positivity, HER2/neu positive, while none of the grade I tumours were ER/PR negative, HER2/neu positive ($p<0.001$). Around 46 cases (56.6%) in the age group of 41-60 years with a mean age of 50.85 years were found. Infiltrating ductal carcinoma- No Special Type (IDC-NST) being the most common histologic type. Tumours with ER/PR negative, HER2/neu positive subtype was larger size (>5 cm), predominantly of higher histologic and high nuclear grade of modified Scarf-Bloom-Richardson (SBR) grading, with necrosis, vascular invasion and of clinical stage III.

Conclusion: In addition to the established prognostic parameters like histopathological grading and other clinicopathological parameters, hormone receptor status is also very useful and it also correlates well with the former ones. The present observation suggests for incorporation of IHC analysis in routine histopathology reports as they contribute in deciding the treatment protocol.

Keywords: Ductal carcinoma breast, Histopathological grading, Immunohistochemistry

INTRODUCTION

Breast carcinoma in the female is a ubiquitous disease that has high prevalence rate and causes high mortality rate in women all over the world. Hemlata P et al., observed that in recent years breast cancer has become the most common malignancy in Indian women, surpassing the cervical cancer [1]. Recent data from Indian Council of Medical Research (ICMR) has showed an estimated 1.62 lac (14% of all cancers in women) new cases, during 2018 accounting for number one cancer overall [2]. The management of diseases of breast and particularly breast cancer (both invasive and non-invasive) is a multidisciplinary endeavour dependent on the skill and expertise of an array of specialists. At the outset and often at later critical points, an accurate pathological diagnosis is the critical element for determining the course of treatment and for predicting prognosis [3]. The prognostic and therapeutic markers of breast cancer can be broadly grouped into three groups: i) Classical parameters that includes, variables such as histologic type and grade, tumour size, lymph node status, tumour necrosis and skin invasion; ii) IHC parameters like ER and PR of the tumour, and more recently HER2/neu; and iii) Molecular markers [2,3]. The classification of breast carcinoma based on IHC has both therapeutic and prognostic relevance which can be performed on routine paraffin blocks [4]. Breast cancer is rather a multifaceted disease having distinct biological subtypes with diverse natural history and a spectrum of clinical, pathological and molecular features which carry both prognostic and therapeutic information than a single disease entity [5]. The above facts re-assert the importance of studying the various prognostic factors especially the hormone receptor in breast cancer so that high risk patients with chances of recurrence can be picked up early and they can be managed well with targeted neoadjuvant chemotherapy with intense follow-up.

Present study assessed the IHC status of the following markers (ER, PR and HER2/neu status) in breast carcinoma. Correlation with modified Bloom-histological grading, various clinico-pathological parameters, IHC subtypes and histopathological grading was also done.

MATERIALS AND METHODS

The present prospective study was conducted in the Department of Pathology of a tertiary medical hospital (MKCG Medical College, Brahmapur, Odisha, India) for a period of one year and six months duration (June 2013-December 2014). All patients who had submitted the surgical samples in the laboratory were included in the study. However, in cases where the sample was not fixed properly or inadequate were excluded from the study. IHC evaluation of a total 82 patients was conducted who were confirmed to have breast carcinoma histologically. The study was done as per the Institutional Ethical policy and clearance for same was obtained prior to study (IEC No 37/12). The following parameters at the time of presentation were noted from the surgical pathology records: Age, sex, menstrual status, mode of presentation e.g., lump/nipple discharge, Investigation

findings (x-ray, ultrasonography of chest and mammography findings), side, site of tumour quadrant, procedure e.g., biopsy or mastectomy, tumour size on gross examination, histologic subtype of breast cancer and axillary nodal status. All the cases were routinely stained for Haematoxylin and Eosin (H&E), followed by IHC using ER alpha, clone ID5 (Mouse monoclonal, BioGenex Code No: M7047); Progesterone receptor, clone PgR (Mouse Monoclonal, BioGenex Code No: M3569); HER2/neu antibody (Polyclonal, BioGenex Code No: A0485) ready to use.

IHC Scoring System

ER and PR Allred scoring system: Allred scoring system has scores from 0-5 depending on proportion of cells positive stained (PS) and a score of 0-3 based on the intensity of staining for the cells (IS). The sum of PS and IS is the final Allred score (PS+IS=AS) [Table/Fig-1] [6].

Proportion score [PS]	Score	Intensity score [IS]
No cells are ER/PR positive	0	Negative
<1% of cells are ER/PR positive	1	Weak
1-10% of cells are ER/PR positive	2	Intermediate
11-33% of cells are ER/PR positive	3	Strong
34-66% of cells are ER/PR positive	4	--
67-100% of cells are ER/PR positive	5	--

[Table/Fig-1]: Allred scoring system [6].

HER2/neu Dako Hercep test score [7]: HER2/neu stains the membrane and its intensity of staining is scored in the range of 0-3. [Table/Fig-2].

Score	Stain pattern
0	Negative- No staining is seen or membrane staining is seen in <10% of tumor cells
1+	Negative- Faint/Barely perceptible membrane staining detected in >10% of tumor cells. The cells exhibit incomplete membrane staining.
2+	Weakly positive- Week to moderate complete membrane staining in >10% of tumor cells
3+	Positive- Strong complete membrane staining in >10% of tumor cells

[Table/Fig-2]: Dako hercep test score [7].

STATISTICAL ANALYSIS

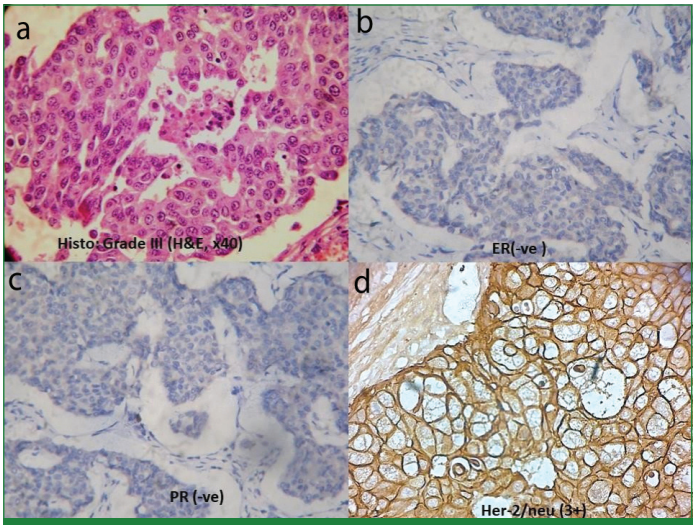
The statistical software namely Graph pad, SAS 9.2, SPSS 20.0, Stata 10.1 were used for the analysis of the data. Microsoft Word, Excel have been used to generate graphs, tables etc. A p-value of <0.05 was considered statistically significant.

RESULTS

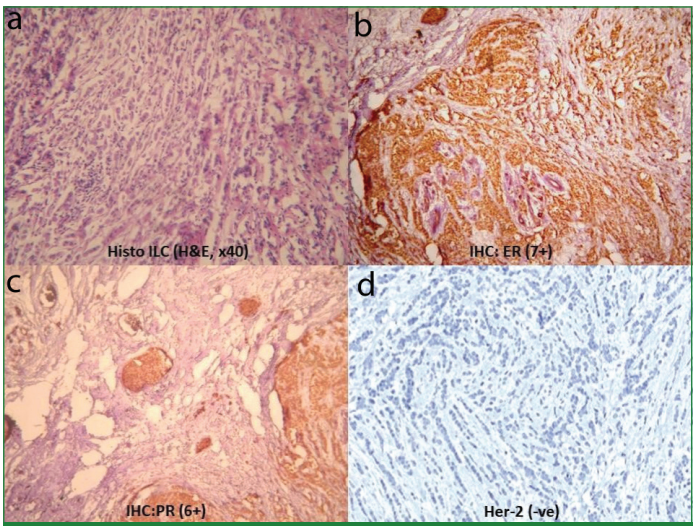
In the present study, 82 cases of carcinoma breast constituted the study group. The following demographic and clinical findings were observed: a) a wide age range at presentation with the mean being 50.85±12.04 years (28-84 years), 41-60 years being the most prevalent in 46 cases (56.1%) and no prepubertal patient; b) regarding menstrual status, 39 cases (47.5%) were post-menopausal; c) 11 cases (13.4%) had history of exogeneous Estrogen supplementation; d) family history of carcinoma breast was noted in 4 cases (4.87%) and 5 cases (6.1%) had recurrence; e) breast lump was the presenting symptom which was associated with pain in 75 cases (91%), skin fixity 4 cases (4.8%), nipple discharge 3 cases (3.6%) and ulceration 1 case (1.2% cases); f) bilaterality was noted in 1 case (1.2%) and left side was the predominant side in 61 (74.3%) cases; g) 4-6 months was the most common duration of illness at presentation in 31 cases (37.8%) followed by 24 cases (29.2%) with 7-9 months and only 5 cases (6.1%) had three months; h) for tumour location upper outer quadrant was the most common location in 51 cases (62%), in 13 cases (16%) it was upper inner quadrant and in 2 cases (2%) whole breast was involved.

About the nature of surgical procedures, 59 (72.1%) cases were Modified Radical Mastectomies (MRM) followed by 12 cases (14.6%) were lumpectomies, 7 cases (8.5%) were simple mastectomies, 3 cases (3.6%) small biopsies and 1 case (1.3%) quadrantectomies. The maximum tumour dimensions were highly variable with 2-5 cm size was commonest accounting for 49 (59.7%) cases.

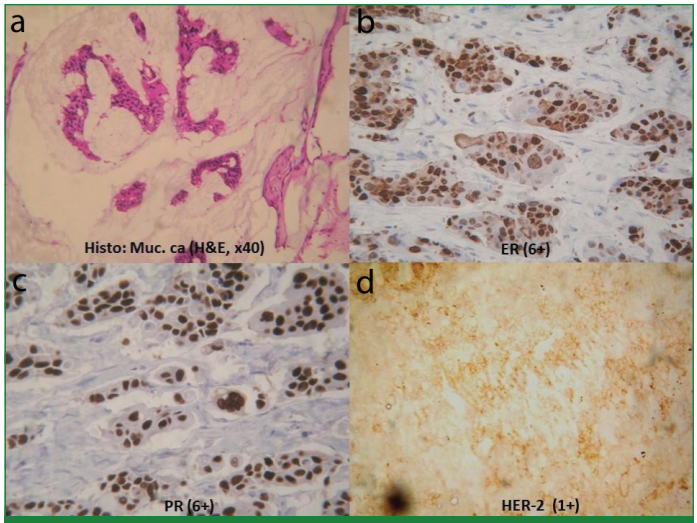
Histopathologically, 67 cases (81.7%) were diagnosed to be ductal carcinoma of breast NST [Table/Fig-3] followed by in decreasing order of occurrence lobular carcinoma 4 cases (4.87%) [Table/Fig-4], mucinous carcinoma [Table/Fig-5] and medullary carcinoma 3 cases each (3.66% each) [Table/Fig-6], metaplastic carcinoma [Table/Fig-7] and malignant phyllodes tumour (2.44% each) [Table/Fig-8] and a case of papillary carcinoma (1.22%). Of the 59 MRM specimens 67.8% cases had lymph node metastases. Paget's disease was noted in 12% cases. Fibrocystic changes in the adjacent breast parenchyma was the commonest associated change noticed (68%) followed by in-situ carcinoma (44%) and atypical ductal hyperplasia (15%). Of the in-situ carcinomas 33% were cribriform type, 28% comedo-carcinoma type, 25% mixed type and 14% solid type. The prevalence of associated features is desmoplastic stroma (84%), necrosis (66%), peritumoural retraction (55%), lympho-vascular invasion (41%), calcification (36%) and perineural invasion (15%). On SBR grading, Grade 2 was highest in incidence accounting for 42.6% cases. The most common Nottingham Prognostic Index (NPI) score was between 3.5-5.4 (moderate degree) in 39% cases.



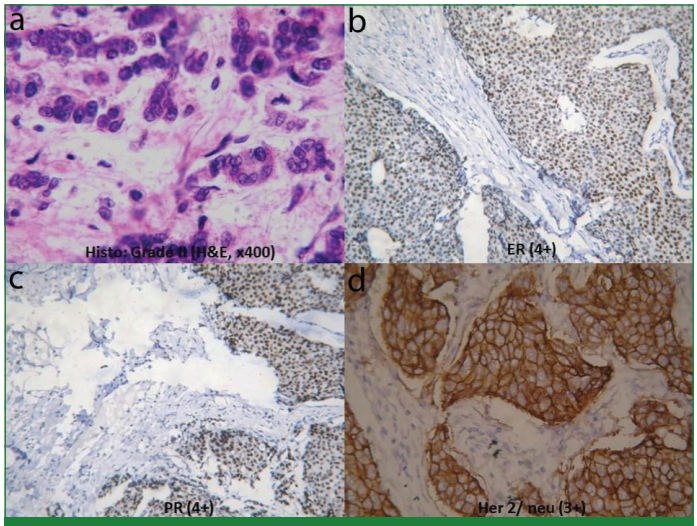
[Table/Fig-3]: (a) IDC (NOS) Grade III showing tumour cells in sheets and cords; (b,c) IHC negativity for estrogen and progesterone receptors; (d) Strong cytoplasmic membrane positivity for HER2/neu (H&E, x40; IHC, x40).



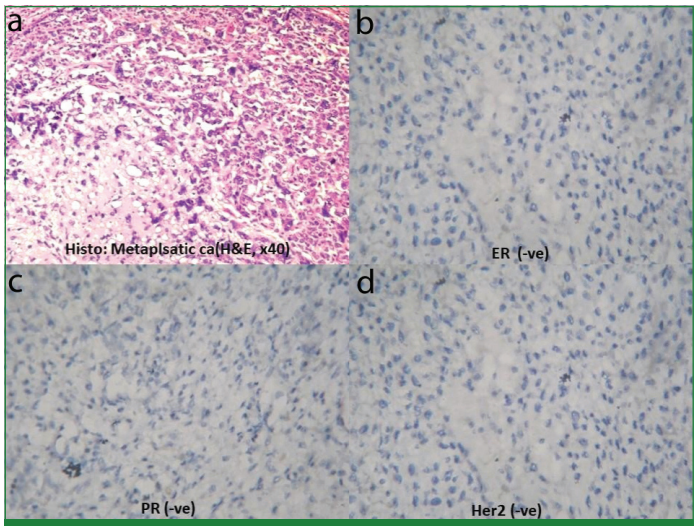
[Table/Fig-4]: (a) Invasive lobular carcinoma showing sclerotic stroma with Indian file pattern of ductal cells (b,c) IHC showing strong nuclear positivity ER/PR (7+/6+);(d) HER2/neu negative. (H&E, x40; IHC, x10, x40).



[Table/Fig-5]: (a) Mucinous carcinoma microscopy showing ductal cells in a pool of extracellular mucin; (b,c) IHC showing strong nuclear positivity for ER/PR 8+; (d) HER2/neu negative staining (H&E, x40; IHC, x40).

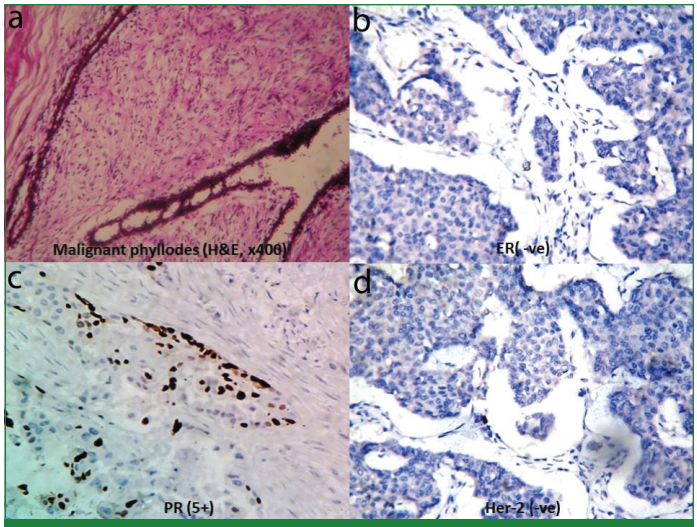


[Table/Fig-6]: (a) Medullary carcinoma microscopy showing syncytial growth pattern of pleomorphic tumour cells and dense lymphoplasmacytic infiltrate; (b,c) IHC showing ER, PR negative; (d) Strong cytoplasmic membrane positivity (3+) for HER2/neu (H&E, x40; IHC, x10, x40).



[Table/Fig-7]: (a) Metaplastic carcinoma microscopy showing sheets of spindle-shaped cells with no morphologic epithelial differentiation, foci of osseous and chondroid differentiation seen; (b,c) IHC showing nuclear negativity for ER, PR; (d) HER2/neu negative staining. (H&E, x40; IHC, x40).

Receptor status evaluation by IHC in the present study revealed that the overall ER, PR and HER2/neu positivity was 69.5%, 57.32% and 42.68%, respectively. The same in relation to the histologic subtypes is also noted [Table/Fig-9]. Of the total 82 cases 16 cases showed either ER or PR positivity and hence,



[Table/Fig-8]: (a) Malignant phyllodes microscopy showing stromal proliferation with marked nuclear pleomorphism and mitotic figure; (b,c) IHC showing negative for ER & strong nuclear positivity (5+) for PR; (d) Negative stain for HER2/neu. (H&E, x40; IHC, x40).

they were excluded from receptor status-based subtyping. Receptor based subtyping of the tumours revealed 46.9% (31 of 66 cases) were ER+PR+HER2/neu-, 25.7% (17 of 66 cases) were ER-PR-HER2/neu+, 19.7% (13 of 66 cases) were ER+PR+HER2/neu+ and 7.5% (5 of 66 cases) were ER-PR-HER2/neu- (Triple negative). ER+PR+HER2/neu-subtypes was found to be more in younger age group and the percentage of positivity decreases with the increasing grade as evident from the observation that, 54% of grade I, 42% of grade II and 4% of grade III tumours in the present study fall into this subtype, which was a statistically significant observation. Triple negative subtypes were found to be predominantly grade 3 accounting for 60% of cases in comparison to 20% of grade I and II tumours each. However, triple positive subtypes were mostly grade 2 tumours, 61% of cases and of the remaining, 23% were grade 1 and 16% were grade III. The correlation of receptor status with histologic grading revealed that, ER and PR positivity was low in grade III tumours, 8.7% and 8.5% respectively, which was statistically significant. In contrast, HER2/neu positivity was observed to be high (48%) in grade III tumours which was also a statistically significant observation.

S. No.	Histologic subtype	Total no. of cases	ER positivity	PR positivity	Her-2/neu positivity
1	IDC-NSO	67	51 (76.12%)	41 (61.19%)	32 (47.76%)
2	Lobular carcinoma	4	2 (50%)	2 (50%)	1 (25%)
3	Mucinous carcinoma	3	3 (100%)	2 (75%)	0
4	Medullary carcinoma	3	0	0	2 (75%)
5	Metaplastic carcinoma	2	0	0	0
6	Malignant phyllodes	2	0	2 (100%]	0
7	Papillary carcinoma	1	1 (100%)	1 (100%)	0

[Table/Fig-9]: Relationship between histologic subtypes and immunohistochemistry [9,10,11].

DISCUSSION

Breast carcinoma is a disease with a tremendous heterogenicity in its clinical behaviour. Clinical and pathological variables such as tumour size, histologic grade, histologic type, lymph node metastasis, vascular space invasion, tumour cell proliferation, tumour necrosis, extent of ductal carcinoma in situ, age are the predictors of prognosis and for the need of adjuvant therapy [8].

Biomarkers such as ER, PR and HER2/neu represent the most acceptable ones for predicting prognosis, response/resistance to treatment and in deciding the use of newer drugs such as transtuzumab in the case of HER2/neu over expression [9-11].

It has been indicated that younger age during menarche increases the risk of breast cancer by two times [12]. A worse risk profile was observed in younger women comared to the older women. Younger patients with breast cancers found to have large sized tumor with positive lymph nodes, negative hormone receptors status and higher tumor grade. Though some studies had reported early age of presentation of breast cancer in Indian women than Western countries [13,14]. In the present study, the age of presentation ranged from 28-84 years with a mean age of 50.85 years. Left upper outer quadrant 62% (51 cases) being the most common side of presentation, which was slightly higher compared to study by Meena SP et al., (54%) and Joshi K et al., (50%) [15,16].

Tumor size and lymph node involvement are the two most important clinical indicators for poor prognosis in breast cancer [17]. Pathological data of patients with breast cancer have shown that presence of lymph nodes involved by tumor cells can be seen in 30-50% cases and have a higher tumor size. Tumour size is one of the most powerful predictors of tumour behaviour in breast cancer. Larger the tumour size more poorer being the 5-year survival rate [18,19]. In the present study, 17.2% tumours were of size >5 cm with 12 cases negative for ER and PR and positive for HER2/neu in 10 cases. Similar were the findings in the study done by Yadav R et al., [11]. Studies have also confirmed that non-reactivity of hormone receptors increases with tumour size. Ontilo AA et al., and Huang JH et al., have shown that subjects with ER/PR+ HER2-subtypes were more likely to be older and post-menopausal when compared to pre-menopausal ones [5,20]. Present study also showed similar features.

In the present study, positive expression of ER, PR and HER2/neu was found to be 70%, 57%, and 42% respectively which correlate well with studies done by Yadav R et al., Lakmini KB and Kaul R et al., [11,21,22]. ER and/or PR expression is generally correlated inversely with HER2/neu overexpression (p=0.005) which is well correlated with other studies [11,23-25]. These results might reflect women who overexpress HER2/neu may be resistant to tamoxifen. However, a substantial number of HER2/neu+ tumours still expressed ER and PR. High ER, PR positivity with IDC (NOS), Lobular carcinoma and Mucinous carcinomas was also noted in studies done by Onitilo AA et al., Huang JH et al., Ayadi L et al., Perio G et al., and Lal P et al., [5,20,25-27]. In the present study, 81.7% (67 cases) were IDC (NOS). Similar observations were made by Ontilo AA et al., Zafarani B et al., [5,28]. Grade of any tumour is based on the fact that degree of malignancy of a tumour is reflected in their morphological structure. Present study showed: ER and PR association with Grade II tumours. But HER2/neu was more commonly associated with Grade III tumours in present study. Similar observation was made by Ontilo AA et al., Zafarani B et al., Doussal LV et al., [5,28,29].

None of the Grade I tumour were ER/PR negative in present study, whereas 82.3% grade III tumours were HER2/neu positive. This indicates that poorly differentiated tumours have less hormone receptors with increased HER2/neu expression. Stierer M et al., in their study correlated the histomorphology grading features i.e., degree of tubule formation, nuclear pleomorphism and mitotic count with the expression pattern of the ER and observed that, ER positivity strongly correlated with increased degree of nuclear pleomorphism and increased mitotic counts but not with the degree of tubule formation [30].

Large tumours of >5 cm with ER/PR positivity and HER2/neu negativity had less lympho-vascualr invasion (35.4%) when compared to the ER/PR-, HER2/neu+ subgroup (64.7%). These findings were comparable with the findings of Onitilo AA et al., and Peiro G et al., [5,26]. Hundred percent tumours with HER2/neu+ subgroups were in stage II and III. Similarly, 77% of tumours of tripple positive cases were in stage II and III this reflects the higher incidence of metastasis and aggressive biologic behaviour with HER2/neu overexpression. A correlation of various other studies is mentioned [Table/Fig-10] [5,11,31-35].

In the present study it was observed that, advanced stage breast cancer (i.e. Stage II, III and IV cancers) are common in middle aged patients. Socio-economic factors, lack of awareness among patients contribute for the advanced stage at presentation. Early detection will reduce the stage at presentation. Public health awareness needs to be implemented in more aggressive manner directed towards the societal influences impacting breast carcinoma progression.

Limitation(s)

The limitation of the study was it had a limited number of cases and the non-availability of Fluorescent in-situ hybridisation correlation in equivocal cases of HER2/neu.

CONCLUSION(S)

The advances in breast cancer diagnosis and management helps for early detection, effective management with targeted therapy and hence provide a better life to the patent. Targeted therapy has been the treatment of choice based on results obtained from IHC. The results of this study suggest for more research for more deep understanding of the relationship between the prognostic variables of breast cancer to utilise them in better patient management.

Availability of data and materials: All the data regarding the findings are available within the manuscript.

Paramaters	Bhaskar S et al., [35]	Negi M et al., [33]	Yadav R et al., [11]	Bansal C et al., [31]	Ontillo AA et al., [5]	Devi PU et al., [34]	Sarkar K et al., [32]	Present study
Age (Mean)	-	48 y	48 y	-	62.7 y	51.5 y	54.6 y	50.8 y
>40 y age	71%	40%	-	82.3%	-	53.6%	54.6%	57%
Tumour size >2 cm		-	60%	65.6%	27.8%	90.2%	82%	
Tumour location (UOQ*)	43%	-	-	26%	31%	46.3%	58%	62%
Post-menopausal	58.3%	52.2%	-	55.2%	-	46.3%	38%	47.5%
Left breast	47%	54.1%	-	47.7%	-	52%	52%	74.3%
Lymph node positive (LN +)	72%	-	-	54.2%	31%	46.3%		67.8%
IDC	96.7%	99.9%	92.3%	95.5%	72.7%	78.8%	86%	81.7%
SBR Gr II	39%	54%	51.5%	64%	38.4%	22%	28%	42.6%
Luminal A	57.3%	53.1%	42.3%	28.8%	68.9%	26.9%	50%	47%
Luminal B	-	17.2%	9.2%	8.8%	10.2%	19.6%	18%	20%
Her2/neu	15%	16.8%	43.8%	38.8%	7.5%	12.1%	22%	26%
Basal like	27.7	27.9%	4.7%	23.6%	13.4%	41.4%	10%	07%

[Table/Fig-10]: Correlation with recent researches [5,11,31-35].
*UOQ: Upper outer quadrant

Authors' contributions: TS carried out concepts and design, literature search, participated in clinical study. BB carried out data acquisition, data analysis. AKB carried out concept and design. MKP carried out data analysis, literature search, manuscript preparation and will stand as guarantor also. DPM participated in clinical study and manuscript review. All the authors have read and approved the final manuscript.

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