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Original Research Article

Study of correlation of ER, PR, HER2 receptor status in breast cancer at a single tertiary care hospital with emphasis on clinical utility of PR receptor

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ABSTRACT

Background: The receptor status of breast cancer, including ER, PR and HER 2, play a crucial role in the development of treatment plan of breast cancer. Clinical utility of ER as a predictive biomarker to identify patients likely to benefit from hormonal therapy is well established, added value of PR is less defined. This study aim to know the demography of breast cancer and to document the status of ER, PR and HER 2 status in the north Indian population, as catered by single tertiary care hospital in Lucknow, Uttar Pradesh.
Methods: All the patients of breast cancers where surgery or core biopsy was performed for invasive breast carcinoma followed by evaluation of ER, PR and HER 2 status were included in the study from January 2014 to June 2018. Cases were analyzed retrospectively for documentation of ER, PR and HER2 status, using American society of Clinical Oncology/College of American Pathologists (ASCO/CAP) interpretation guidelines.
Results: 112 patients were included in the study with mean age of 53.70±12.47. Most common histological type was invasive carcinoma of no special type. 43.75% cases were ER+/PR+, 5.35% were ER+/PR-, and 50.89% were ER-/PR-. ER-/PR+ status was seen in none of our cases. Correlation of ER and PR with HER 2 was possible in 90 cases and triple negative breast cancer (TNBC) status was observed in 32.2% of cases.
Conclusions: Demography and ER positivity and incidence of TNBC is not different from rest of India, however the clinical utility for evaluation of PR receptor is to be further investigated.

Keywords: Breast carcinoma, Estrogen, Progesterone, HER 2 receptor

INTRODUCTION

Breast cancer which is considered universal worldwide is the most common cancer in female, representing approximately 25% of all cancers. It is also ranked number one cancer among Indian females with age adjusted incidence rate of 25.8 per 1,00,000 women and mortality 12.7 per 1,00,000 women.[1]

Treatment of breast cancer includes combined therapy; surgery, radiotherapy, chemotherapy, endocrine therapy, and targeted therapy and so forth. Hormone therapy can be started before surgery (as neoadjuvant therapy) or used after surgery (as adjuvant therapy) or as a prophylactic treatment of high risk populations as in BRCA mutation carriers. Evaluation of hormone receptor on surgically resected specimen or core biopsy material is essential to

assess the utility of hormone therapy and thus the College of American Pathologists and American Society of Clinical Oncology recommend ER and PR testing for all newly diagnosed cases of invasive breast cancer and breast cancer recurrences.[2]

The biologic, predictive, and prognostic importance of assessment of estrogen receptor (ER) expression in breast cancer is well established. The added value of assessment of progesterone receptor which is surrogate marker of estrogen receptor activity assessment remains controversial.[3,4]

Hence a hospital based study was carried out to determine the hormonal status of breast cancer cases attending the tertiary care hospital in Lucknow, Uttar Pradesh to know various hormonal spectrum of breast cancer in the northern part of India and also to evaluate the clinical utility of PR assessment in breast cancers.

METHODS

The patient population comprise of all the cases underwent surgery or core biopsy for invasive breast cancers between January 2014 to June 2018 at Sahara Hospital, a tertiary care referral hospital. The inclusion criteria were: cases who (1) had undergone mastectomy or breast conservation (2) core biopsy to start chemotherapy and hormone therapy before surgery (3) had complete immunohistochemistry data for ER, PER and HER 2. Study was performed at Department of Laboratory Medicine, Sahara Hospital, Lucknow.

Data include age, size of tumor, histopathological typing and grade. All cases are subjected to immunohistochemistry for ER, PR, HER 2 on formalin fixed, paraffin embedded breast tumor sections by using ready to use monoclonal antibody and HRP polymer detection system with 3'-3' diaminobenzidine hydrochloride (DAB) as the chromogen. Adequate tissue fixation in 10% buffered formalin for 6-24 hrs was ensured and thin paraffin (3-4 µ thickness) sections with maximum invasive tumor component was selected for IHC. Both H&E and IHC slides were reviewed by two independent pathologists and results were interpreted with positive and negative controls. For ER and PR results were interpreted as positive when more or equal to 1% of tumor cells showed positive nuclear staining as per the ASCO/CAP interpretation guidelines 2010.

Initial immunohistochemistry for HER 2 was carried out in all cases and HER 2 scoring was categorized as 0, 1+, 2+, 3+. Result was considered as positive for HER2 (score 3+) if uniform intense membrane staining of >30% of invasive tumor cells was seen. Test was considered negative if there was no staining (score 0) or incomplete membrane staining that is faint/barely perceptible and within >10% of the invasive tumor cells (score 1+). Equivocal results (score 2) was labeled when circumferential membrane staining that is incomplete and/or weak/moderate and within >10% of the invasive tumor cells; or complete and circumferential membrane staining that is intense and within ≤10% of the invasive tumor cells was noticed as per ASCO–CAP HER2 Test Guideline 2013 Recommendations. In all equivocal results (score 2) reflex test as confirmation by fluorescence in situ hybridization (FISH) was advised. Due to financial constraints and loss of follow up for FISH testing the correlation in 22 cases with HER 2 (score 2+) could not be performed. The data were prepared on Excel sheet and analyzed manually for interpretation of results.

RESULTS

Table 1: Pathological spectrum of breast carcinoma.

Pathology	No of cases (N=112)	Percentage (%)
Invasive carcinoma of no special type	100	89.02
Invasive lobular carcinoma	4	3.57
Carcinoma with neuroendocrine carcinoma	1	0.89
Mucinous carcinoma	4	3.57
Secretory carcinoma	1	0.89
Metaplastic carcinoma	2	1.78

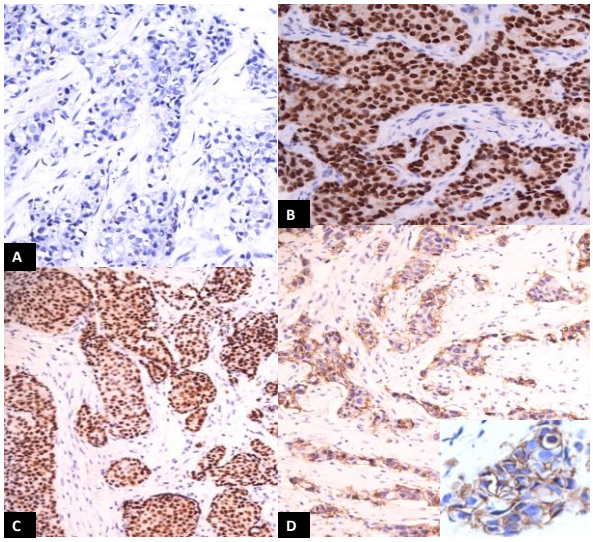

Figure1: (A) Negative staining for ER/PR, 10X (B) strong nuclear staining for ER, 20X (C) strong nuclear staining for PR, 20X; (D) HER 2 –Score 3,10X and inset showing complete membranous staining, 40X.

Over the period of four and half years, 112 patients with invasive breast carcinoma were analyzed. The mean age of patients was 53.70±12.47 with range of 35 to 80 years. Most of the tumors belong to histological grade II. Pathological spectrum of breast carcinoma is shown (Table 1). The maximum 89.02% cases belong to

invasive carcinoma of no special type (NST) also known as invasive ductal carcinoma or ductal NOS. ER, PR and HER 2 receptor were evaluated by immune-histochemistry in all cases (Figure 1). Results are as follows (Table 2). Out of 112 Breast cancer cases, 49 cases (43.75%) were ER/PR positive and 57 cases were negative for both ER and PR (50.89%). None of case identified as ER-/PR+, while ER+/PR- cases were only 6 (5.35%).

Table 2: Results of ER/PR/HER 2 Receptor of Breast carcinoma.

Parameter	Number	Percentage (%)
ER		
Positive	55	49.1
Negative	57	50.89
PR		
Positive	49	43.75
Negative	63	56.25
Combined hormone receptor sensitivity		
ER+ PR+	49	43.75
ER+ PR-	6	5.35
ER- PR+	0	0
ER-PR-	57	50.89
HER 2		
Positive	33	29.46
Negative	57	50.89
NA	22	19.64

Table 3: Correlation of ER, PR and HER2 receptor.

ER/PR/HER2 status	No. of patients (N=90)	Percentage (%)
ER positive/PR positive/HER2 positive	9	10
ER negative/PR negative/HER 2 negative	29	32.22
ER positive/PR positive/HER2 negative	24	26.66
ER negative/PR negative/ HER2 positive	22	24.44
ER positive/PR negative/ HER2 negative	4	4.44
ER positive/PR negative/ HER2 positive	2	2.22

Cases with equivocal HER 2 (IHC 2+) where FISH could not be performed were excluded for further correlation. Therefore, correlation of ER, PR and HER 2 was possible in 90 cases only (Table 3). Reasons identified in these 22 patients were financial constraints and loss of follow up.

Out of 90 cases triple negative cases constitute major bulk of 29 cases (32.2%), while triple positive cases were only 9 (10%).

DISCUSSION

Breast cancer is the most common cancer in women worldwide and is a major health concern especially in developing countries where majority of cases are being diagnosed in late stages. Global cancer rates in general are estimated to rapid rise from 14 million in 2012 to 20 million over the next two decade, thus making breast cancer a significant health emergency.[5]

In India, it is also the most common cancer among women and affects them one decade earlier than women in western countries suggesting that breast cancer occur at a younger premenopausal age in India. The mean age of cases in our study was 53.70±12.47 which was similar to other studies from India.[6,7]

The prognosis of breast cancer depends on several factors including ER/PR/HER 2 status. The biologic, prognostic and predictive importance of assessment of estrogen receptor (ER) expression in breast cancer is well established that ER positive tumors are associated with better overall survival compared to ER negative tumors.[8] There is a direct correlation between the levels of expression and response to hormone therapies, and even tumors with very low levels (≥1% positive cells) have a significant chance of responding. Western literature showed that by immunohistochemistry, about 70-80% of invasive breast carcinoma express nuclear ER in a proportion ranging from ≥1% to 100% positive cells and like ER, PR is expressed in the nuclei of 60-70% of invasive breast cancers, with expression that varies in continuum ranging from 1% to 100% positive cells.[9,10]

In our study only 49.1% of cases showed ER positivity and 43.75% showed PR positivity. Studies from other regions of India have also documented lower positivity for both the receptors. Desai et al from India have documented low ER positivity of 32.6% only while PR positivity was seen in 46.1% of their breast cancer cases.[11] Another study from South India showed 46.87% ER positivity and 43.75% PR positivity.[12] Similarly, Mudduwa, in a study from Sri Lanka documented a prevalence of 45.7% ER-positive and 48.3% PR-positive tumours.[13] Thus prevalence of hormone receptor-positive breast cancer in Asian countries has been found to be lower than the western world and reasons for low positivity should be searched.

Another interesting finding in our study is that we have none of the case expressing PR but not ER (ER-/PR+). Low percentage of ER-/PR+ cases was described in previous study from India and Kaul et al in their study also from north India revealed 0% ER-/PR+ cases.[14,15]

Added clinical benefit of PR evaluation in breast cancers is uncertain and debate is going among western

researches whether ER-/PR+ tumors are actually exist. Role of PR status in the management of breast cancer remains controversial and to date relatively few studies have been performed to find an association between PR status and prognosis of breast cancer.

In a study by Hefti et al by incorporating gene expression profiling data, clinical and immunohistochemistry data across two large and diverse datasets found PR expression at low level in ER- breast cancer. They clearly mentioned that ER-/PR+ breast cancers are not a reporoducible subtype and PR expression is not associated with prognosis in ER- breast cancer.[3]

Similarly Olivotto et al in their study observed that with modern IHC method most breast tumors that are ER− are also PR−. They concluded that as PR testing is no longer useful in clinical decision-making and it is time to stop progesterone receptor testing in breast cancer management.[4]

In clinical practice, it is very complex to use PR as a biological marker. Despite progress in understanding the structure and function of PR, it is still not widely used as either a predictive or prognostic marker in the treatment of cancer. However data from the large ATAC (Arimidex, Tamoxifen, Alone or in combination) adjuvant trial, a worldwide clinical trial comparing the efficacy of tamoxifen with that of the aromatase inhibitor showed that patients with ER+/PR+ tumors had a lower recurrence rate than those with ER+/PR- tumors (7.6% vs. 14.8%, respectively).[16] Yao et al in their study found that patients with ER positive invasive breast cancers with low PR expressing tumors have a worse prognosis than those with high PR expressing tumors.[17]

Further research is also needed to investigate the Role of Tamoxifen in ER-/PR+ tumors and clear guidelines are essential when to evaluate PR receptor in invasive breast carcinoma. In developing countries, finances used for PR receptor evaluation can be better utilized for management in breast cancer patients.

Percentage of triple negative breast cancers (TNBC) in our study was 32.2**%** while triple positive breast cancers constitute only 10%. This percentage is considerably higher compared with that seen in Western populations, where TNBC accounts only 12% to 17% of all invasive breast cancers.[18] Another study from one tertiary care centre in India revealed 22.7% triple negative cases.[19] And one large study by Sandhu et al by combining the data from seventeen studies from India involving 7,237 breast cancer patients found 31% incidence of TNBC.[20] This finding is also alarming because the targeted therapy to ER, PR, HER2 receptor are of no use in TNBC causing lower disease free survival and overall survival. Extensive research is needed not only to understand the determinants of TNBC in India but also in finding newer and better treatment options.

CONCLUSION

This single institutional study of 112 cases of breast cancer patients from North India suggest that mean age of breast cancer patient is 53.70±12.47 with ER positivity of 49.1%, not grossly different from rest of the country but significantly lower than western studies.

ER-/PR+ tumors was not identified in this study and on analyzing the various research data we have an opinion that PR testing is highly unlikely to alter therapeutic decisions, the resources could be saved or better allocated. We encourage others to question the value of continuing a test, initiated for good reasons, but which today has little use in guiding therapy decisions.

Further studies are also required in larger group taking into account various clinical parameters along with molecular study and survival pattern analysis to substantiate these immunohistochemical findings.

Similarly with high incidence of triple negative breast cancers an additional research is needed to understand the determinants of TNBC in India for future better outcome in these patients.

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REFERENCES

1. Malvia S, Bagadi SA, Dubey US, Saxena S. Epidemiology of breast cancer in Indian women. Asia Pac J Clin Oncol. 2017;13(4):289-95.
2. Hammond ME, Hayes DF, Dowsett M, Allred DC, Hagerty KL, Badve S, Fitzgibbons PL, et al. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Clin Oncol. 2010;28:2784-95.
3. Hefti MM, Hu R, Knoblauch NW, Collins LC, Haibe-Kains B, Tamimi RM, et al. Estrogen receptor negative/progesterone receptor positive breast cancer is not a reproducible subtype Breast Cancer Res. 2013;15(4):68.
4. Olivotto IA, Truong PT, Speers CH, Bernstein V, Allan SJ, Kelly SJ, et al:Time to stop progesterone receptor testing in breast cancer management. J Clin Oncol. 2004;22:1769-70.
5. Stewart BW, Wild CP. In:Bernard W.Stewart, Christopher P.Wild eds. World cancer report 2014.

6. Chopra B, Kaur V, Singh K, Verma M, Singh S, Singh A. Age shift:Breast cancer is occurring in younger age groups-is it true? Clin Cancer Investig J. 2014;3:526-9.
7. Sandhu DS, Sandhu S, Karwasra RK, Marwah S. Profile of breast cancer patients at a tertiary care hospital in north India. Indian J cancer. 2010;47(1):16-22.
8. Dunnwald LK, Rossing MA, Li CI. Hormone receptor status, tumor characteristics, and prognosis: a prospective cohort of breast cancer patients. Breast Cancer Res. 2007;9(1):6.
9. Harvey JM, Clark GM, Osbome CK, Allred DC. Estrogen receptor status by immunohistochemistry is superior to ligand binding assay for predicting response to adjuvant endocrine therapy in breast cancer. J Clin Oncol. 1999;17:1474-84.
10. Horii R, Akiyama F, Ito Y, Iwase T. Assessment of hormone receptor status in breast cancer. Pathol Int. 2007;57:784–90.
11. Desai SB, Moonim MT, Gill AK, Punia RS, Naresh KN, Chinoy RF. Hormone receptor status of breast cancer in India:a study of 798 tumours.Breast.2000;9(5):267-70.
12. Suvarchala SB, Nageswararao R. Carcinoma breast-Histopathological and hormone receptors correlation. J Biosci Tec. 2011;2:340-8.
13. Mudduwa LK. Quick score of hormone receptor status of breast carcinoma:Correlation with the other clinicopathological prognostic parameters. Indian J Pathol Microbiol. 2009;52:159–63.
14. Chatterjee K, Bhaumik G, Chattopadhyay B. Estrogen receptor and progesterone receptor status of breast cancer patients of eastern India: A multi-institutional study. South Asian J Cancer. 2018;7(1):5–6.
15. Kaul R, Sharma J, Minhas SS, Mardi K. Hormone receptor status of breast cancer in the himalayan region of northern India. Indian J Surg. 2011;73(1):9-12.
16. Dowsett M, Cuzick J, Wale C, Howell T, Howell T, Houghton J, Baum M, Retrospective analysis of time to recurrence in the ATAC trial according to hormone receptor status :an hypothesis –generating study. J Clin Oncol. 2005;23:7512-7.
17. Yao N, Song Z, Wang X, Yang S, Song H. Prognostic Impact of Progesterone Receptor Status in Chinese Estrogen Receptor Positive Invasive Breast Cancer Patients. J Breast Cancer. 2017;20(2):160–9.
18. Foulkes WD, Smith IE, Reis-Filho JS. Triple-negative breast cancer. N Engl J Med. 2010;363:1938–48.
19. Patnayak R, Jena A, Rukmangadha N, Chowhan AK, Sambasivaiah K, Venkatesh B, et al. Hormone receptor status (estrogen receptor, progesterone receptor), human epidermal growth factor-2 and p53 in South Indian breast cancer patients:A tertiary care center experience. Indian J Med Paediatr Oncol. 2015;36(2):117–22.
20. Sandhu GS, Erqou S, Patterson H, Mathew A. Prevalence of Triple-Negative Breast Cancer in India:Systematic Review and Meta-Analysis. J Glob Oncol. 2016;2(6):412–21.

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