ER & PR Status, Tumour Recurrence in Breast Carcinoma Patients- A Prospective Cohort Study

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ABSTRACT

Introduction: Breast cancer occurs in middle and elder age group people but this is the most common carcinoma in women (22%), which is more than twice the prevalence of cancers in women at any other site. Breast cancer patients with tumours that are estrogen receptor (ER) positive and/or progesterone receptor (PR) positive have lower risk of mortality compared to women with ER and/or PR negative disease. In breast cancer the average incidence of estrogen receptor and progesterone receptor positivity is 77% and 55% respectively as shown in the studies. However lower rates of positive estrogen and progesterone receptor breast cancers are found in Indian population from the western literature. Prognosis and management of breast cancer are influenced by the classic variables such as histological grade, tumour size, lymph node status, status of hormone receptors (ER and PR) of the tumour and Her-2 Neu status.

Objective: To study the Estrogen and Progesterone receptor status of carcinoma Breast patients in various age groups, stages of disease, Grades of disease and axillary lymph node status

Association between joint hormone receptor status and breast cancer disease free survival (DFS) risk within categories of diagnosis age, stage of disease, grade of disease, Axillary lymph node status.

Materials and Method: All patients with tissue biopsy proven carcinoma breast registered to the department of Radiotherapy at Govt. T.D medical college Alappuzha will be taken into cohort. The period of recruitment was 3 years after ethics clearance. The Estrogen and Progesterone receptors in the tumour cells of these patients will be assessed using Immunohistochemistry method.

The patients will be categorized into four groups according to their joint ER/PR status: ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR-.The association between the joint hormone receptor status and the variables in breast cancer viz age of patient, stage of disease, grade of disease, axillary lymph node status will be studied. Disease free survival among the various groups will be studied using the Cox Proportional hazard model.

Result: A total of 158 patients who fulfilled the inclusion criteria were enrolled in the study. Out of these patients 102 (64.56%) were ER+/PR+; 18 (11.39%) were ER+/PR-; 3 (1.9%) patients were ER-/PR+; and 35 patients (22.15%) were ER-/PR-. The majority of the patients were ER+/PR+.

Age group of the patients. The maximum number of patients (50 patients) come under 50-59 years age group and this age group had the maximum number of patients with ER+/PR+ (45 patients). It was also noted that ER-/PR+ was the least in all age groups whereas ER-/PR- was relatively high in patients less than 49 years of age.

Depending on stage of the disease it was found that the majority of patients presented with stage 3 disease (48.10%). The majority of patients with stage 3 disease were ER+/PR+. Of the 3 patients with ER-/PR+ disease 2 patients had stage 4 disease. ER-/PR- was most frequently seen in Stage 2 disease.

Grade of the tumour was classified as Grade 1, Grade 2 and Grade 3. Out of 158 patients there were 6 with Grade 1 disease, 105 with Grade 2 and 47 patients had Grade 3 disease. It was observed that maximum number of patients had Grade 2 disease and this group had the most number of ER+/PR+ and ER-/PR- patients 58

and 30 respectively. Whereas ER+/PR- and ER-/PR+ was mostly seen with Grade 2 disease 15 and 2 respectively.

Axillary lymph node status was categorized as 0 nodes, 1-3 nodes, and 4 or more nodes. 63 (39.87%) patients had 0 nodes. 68 (43.04%) patients had 1-3 nodes and 27 (17.09%) patients had >4 nodes positive. It could be observed that majority of patients had 1-3 lymph nodes and most of the patients in this group had ER+/PR+ disease. It was also observed that ER-/PR- was mostly seen in patients with more than 4 nodes positive.

The study period was 3 years post ethics clearance. 158 patients had average follow up period of 1.8 months. During this period it was observed that total of 24 patients had disease progression. Out of the 24 patients, 18 had local recurrence whereas 6 patients had systemic recurrence. The 18 patients with local recurrence 1 was ER+/PR+; 6 ER+/PR-; 10 ER-/PR+; and 1 ER-/PR-. Out of the 6 patients with systemic recurrence 0 were ER+/PR+; 2 ER+/PR-; 3 ER-/PR+; and 1 ER-/PR-.

Multivariable Cox proportional hazards regression analysis showed that patients with ER+/PR- (hazard ratio [HR], 1.55; 95% CI, 1.52-1.58) and ER-/PR+ (HR, 1.68; 95%CI, 1.62-1.74) tumors had worse Disease Free survival (DFS) than patients with the ER+/PR+ subtype. The DFS was statistically significantly worse in patients with ER-/PR+ tumors than in patients with ER+/PR- tumors (HR, 1.16; 95% CI, 1.12-1.21).

INTRODUCTION

Breast cancer occurs in middle and elder age group people but this is the most common carcinoma in women (22%), which is more than twice the prevalence of cancers in women at any other site. It ranks second among cancer deaths in adult females. The incidence of breast cancer varies from 3.9/100,000 in Mozambique to as high as 101.1/100,000 in the US. Breast cancer patients with tumours that are estrogen receptor (ER) positive and/or progesterone receptor (PR) positive have lower risk of mortality compared to women with ER

and/or PR negative disease. However, few studies have evaluated variations in the risks of breast cancer specific mortality across ER/PR status by either demographic or clinical characteristics.

The determination of estrogen receptor (ER) and progesterone receptor (PR) activity in breast cancer is a standard medical practice nowadays. It is an important predictor of response to hormone therapy and overall prognosis of the patient. The tumours that are estrogen receptor (ER) positive and / or progesterone receptor (PR) positive have lower risks of recurrence and mortality after their diagnosis as compared to women with ER and ./ or PR negative disease. Clinical trials have also shown that the survival advantage for women with hormone receptor positive tumours is enhanced by treatment with adjuvant hormone and / or chemotherapeutic regimens. In breast cancer the average incidence of estrogen receptor and progesterone receptor positivity is 77% and 55% respectively as shown in the studies. However lower rates of positive estrogen and progesterone receptor breast cancers are found in Indian population from the western literature. The frequency of negative estrogen receptor and progesterone receptor is much common in India 46.5% than in the West (10%). Breast cancer patients of Indian origin tend to be younger, tumours are often large when first diagnosed, and of a high grade as compared to western series.

During the past two decades the mortality rate has been decreased significantly due to early detection of disease and the use of aggressive multimodality treatment leading to improved clinical outcomes. Further decline in the breast cancer recurrence and mortality is expected as a result of the tremendous advance in the understanding of the biology of the disease and its associated risk factors. Increasingly, women identified as being at high risk for breast cancer can take advantage of risk reducing intervention that are potentially lifesaving.

Prognosis and management of breast cancer are influenced by the classic variables such as histological grade, tumour size, lymph node status, status of hormone receptors (ER and PR) of the tumour and Her-2 Neu status.

MATERIALS AND METHODS

All patients with tissue biopsy proven carcinoma breast registered to the department of Radiotherapy at Govt. T.D medical college Alappuzha were taken into this cohort. The period of recruitment was 3 years after ethics clearance. The Estrogen and Progesterone receptors in the tumour cells of these patients will be assessed using Immunohistochemistry method. The present study used a cut off of more than 1% of tumour cells with nuclear staining to define ER PR positivity.

Separate proforma was filled for each patients and all those patients who fulfilled the inclusion criteria were categorized into four groups according to their joint ER/PR status: ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR-.The association between the joint hormone receptor status and the variables in breast cancer viz age of patient, stage of disease, grade of disease, axillary lymph node status will be studied. Disease free survival among the various groups will be studied using the Cox Proportional hazard model.

Disease free survival was calculated in months by using the subject's date of completion of Chemotherapy and or Radiotherapy and one of the following (a) clinical evidence of loco-regional recurrence (b) clinical and or radiological evidence of systemic recurrence of disease

Statistical Methods

Patients were categorized into four groups according to their joint ER/PR status: ER+/PR+, ER+/PR-, ER-/PR+, and ER-/PR-.The association between the joint hormone receptor status and the variables in breast cancer viz age of patient, stage of disease, grade of disease, axillary lymph node status will be studied. Disease free survival among the various groups will be

studied using the Cox Proportional hazard model.

RESULT

A total of 158 patients who fulfilled the inclusion criteria were enrolled in the study. Out of these patients 102 (64.56%) were ER+/PR+; 18 (11.39%) were ER+/PR-; 3 (1.9%) patients were ER-/PR+; and 35 patients (22.15%) were ER-/PR-. The majority of the patients were ER+/PR+.

Total number of Patients = 158
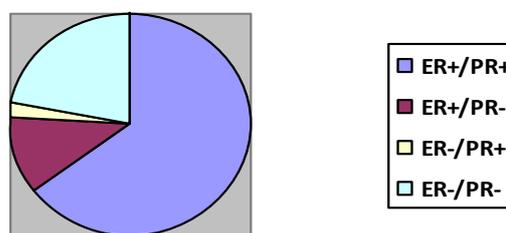
Age group of the patients <30years-total of 9 (5.69%) patients- 1 (11.11%) patient ER+/PR+; 2 (22.22%) patients ER+/PR-; 0 patients were ER-/PR+; and 6 (66.67%) patients ER-/PR-. 30-39 years-total 33 (20.89%) patients- 20 (60.61%) patient ER+/PR+; 2 (6.06%) patients ER+/PR-; 1 (3.03%) patient were ER-/PR+; and 10 (30.3%) patients ER-/PR-. 40-49 years- 42 (26.58%) patients- 23 (54.76%) patient ER+/PR+; 8 (19.05%) patients ER+/PR-; 1 (2.38%) patients were ER-/PR+; and 10 (23.81%) patients ER-/PR-. 50-59 years- 50 (31.65%) patients- 45 (90%) patient ER+/PR+; 3 (6%) patients ER+/PR-; 0 patients were ER-/PR+; and 2 (4%) of patients ER-/PR-. 60-69 years- 16 (10.13%) patients- 7 (43.75%) patient ER+/PR+; 3 (18.75%) patients ER+/PR-; 1 (6.25%) patients were ER-/PR+; and 5 (31.25%) patients ER-/PR-. >70 years- 8 (5.06%) patients-6 (75%) patient ER+/PR+; 0 patients ER+/PR-; 0 patients were ER-/PR+; and 2 (25%) patients ER-/PR-. The maximum numbers of patients come under 50-59 years age group and this age group had the maximum number of patients with

ER+/PR+ (45 patients). It was also noted that ER-/PR+ was the least in all age groups whereas ER-/PR- was relatively high in patients less than 49 years of age.

**ER/PR Status in Different Age group**
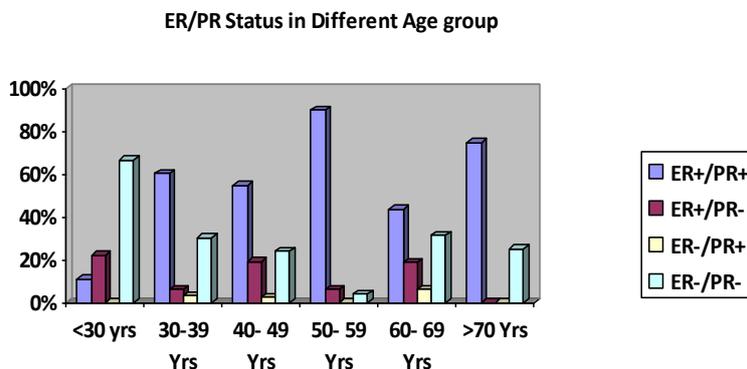
Depending on stage of the disease it was found that 19 (12.03%) patients had Stage 1 disease. Of these 6 (31.58%) were ER+/PR+; 4 (21.05%) ER+/PR-; 0 ER-/PR+; and 9 (47.37%) ER-/PR-. 55 (34.81%) patients with Stage 2 disease- 35 (63.64%) were ER+/PR+; 5 (9.09%) ER+/PR-; 0 ER-/PR+; and 15 (27.27%) ER-/PR-. Stage 3 disease in 76 (48.10%) patients- 58 (76.32%) were ER+/PR+; 7 (9.21%) ER+/PR-; 1 (1.32%) ER-/PR+; and 10 (13.15%) ER-/PR-. Stage 4 disease in 8 (5.06%) patients- 3 (37.5%) were ER+/PR+; 2 (25%) ER+/PR-; 2 (25%) ER-/PR+; and 1 (12.5%) ER-/PR-. The majority of patients presented with stage 3 disease (48.10%). The majority of patients with stage 3 disease were ER+/PR+. Of the 3 patients with ER-/PR+ disease 2 patients had stage 4 disease. ER-/PR- was most frequently seen in Stage 2 disease.

Grade of the tumour was classified as Grade 1, Grade 2 and Grade 3. Out of 158 patients there were 6 (3.8%) with Grade 1 disease, 105 (66.45%) with Grade 2 and 47 (29.75%) patients had Grade 3 disease. Out of 6 patients with Grade 1 disease- 5 (83.33%) patients had ER+/PR+ and 1 (16.67%) patient ER+/PR-. In grade 2 disease- 58 (55.24%) were ER+/PR+; 15 (14.28%) ER+/PR-; 2 (1.9%) ER-/PR+; and 30 (28.58%) ER-/PR-. Out of 47 patients with Grade 3 disease- 39 (82.98%) were ER+/PR+; 2 (4.25%) ER+/PR-; 1 (2.13%) ER-/PR+; and 5 (10.64%) were ER-/PR-. It was observed that 66.45% patients had Grade 2 disease and this group had the most number of ER+/PR+ and ER-/PR- patients 55.24% and 28.58% respectively. Whereas ER+/PR- and ER-/PR+ was mostly seen with Grade 2 disease 14.28% and 1.9% respectively.

ER/PR Status with Grade

Percentage of ER/PR with Stage of Disease
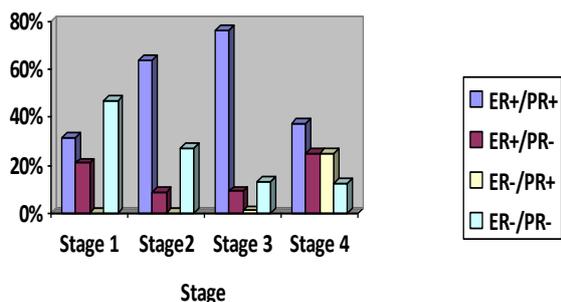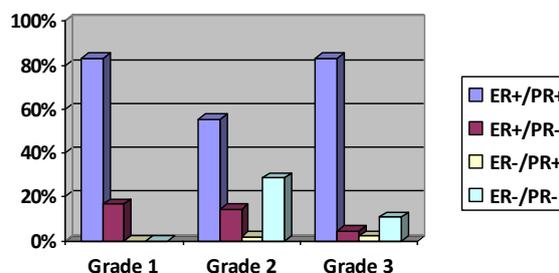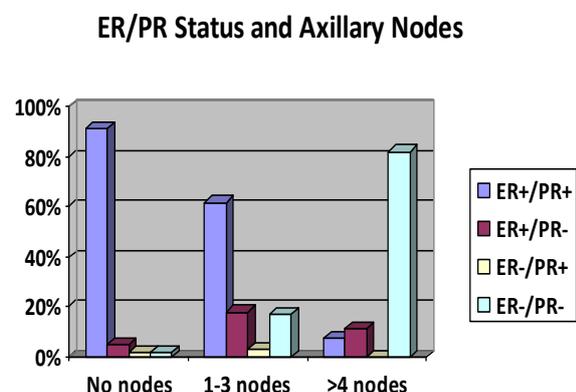

Axillary lymph node status was categorized as 0 nodes, 1-3 nodes, and 4 or more nodes. 63 (39.87%) patients had 0 nodes. 68

(43.04%) patients had 1-3 nodes and 27 (17.09%) patients had >4 nodes positive. Of the 63 patients with 0 nodes- 58 (92.06%) were ER+/PR+; 3 (4.76%) ER+/PR-; 1 (1.59%) ER-/PR+; and 1 (1.59%) ER-/PR-. In patients with 1-3 nodes- 42 (61.76%) were ER+/PR+; 12 (17.65%) ER+/PR-; 2 (2.94%) ER-/PR+; and 12 (17.65%) ER-/PR-. Of the 27 patients with >4 nodes- 2 (7.41%) were ER+/PR+; 3 (11.11%) ER+/PR-; 0 ER-/PR+; and 22 (81.48%) ER-/PR-. It could be observed that 43.04% of patients had 1-3 lymph nodes and most of the patients in this group had ER+/PR+ disease. It was also observed that ER-/PR- was mostly seen in patients with more than 4 nodes positive.

ER/PR Status and Axillary Nodes

The study period was 3 years post ethics clearance. 158 patients had average follow up period of 1.8 months. During this period it was observed that total of 24 patients had disease progression. Out of the 24 patients, 18 had local recurrence whereas 6 patients had systemic recurrence. The 18 patients with local recurrence 1 was ER+/PR+; 6 ER+/PR-; 10 ER-/PR+; and 1 ER-/PR-. Out of the 6 patients with systemic recurrence 0 were ER+/PR+; 2 ER+/PR-; 3 ER-/PR+; and 1 ER-/PR-.
Multivariable Cox proportional hazards regression analysis showed that patients with ER+/PR- (hazard ratio [HR], 1.55; 95% CI, 1.52-1.58) and ER-/PR+ (HR, 1.68; 95%CI, 1.62-1.74) tumors had worse Disease Free survival (DFS) than patients with the ER+/PR+ subtype. The DFS was statistically significantly worse in patients with ER-/PR+ tumors than in patients with ER+/PR- tumors (HR, 1.16; 95% CI, 1.12-1.21).

DISCUSSION

There were 158 patients enrolled in this study and all the patients were females. The diagnosis was confirmed by Trucut biopsy or Incision/Excision biopsy. Most of the patients underwent Modified Radical Mastectomy with Axillary clearance. The receptor testing was done by Immunohistochemistry using tissue sample. 64.56% patients were found to be ER+/PR+. The study by Jalal Poorolaja et al also showed about 70.8% of the patients were ER+, 66.6% were PR+. This had also studied the Her2Neu receptor which was not done in our study. In another study by Shet T et al, she states that there has been an upward trend in the number of ER+/PR+ breast cancer.

The youngest patient was 24years of age and the mean age was 49.2 years. This was comparable with the age incidence as in the study by Jalal Poorolaja et al. In this study the mean (SD) age of patients at diagnosis was 48.59. This is much younger age compared to the western population. In our study, 48.1% of patients presented as Stage 3 disease. In a study by Jignasa et al, it shows that in an Indian context patients are diagnosed in advanced stage which could be attributed to the socioeconomic background.

Stage of the disease was divided into four from 1 to 4. In our study there was stage 3 disease in 76 (48.10%) patients and 55 (34.81%) patients with stage 2 disease. In the study by Gulam Nabi Sofi et al. he found 62.9% patients with T2 disease. It was comparable with the stage of disease as in the study by Jalal Poorolaja et al, where he got 43.5% and 23.8% of patients with stage 2 and 3 respectively.

In our study 66.45% of patients had Grade 2 disease and only 3.8% patients with Grade 1 disease. In a study by Gulam Nabi Sofi et al there 52.1% cases with grade II and 40.3% cases were Grade 3 disease. The

number of patients with Grade 1 disease was only 7.6% in this study. But in the study by Jalal Poorolajal et al most of the patients (54.3%) presented with grade 2 disease.

The nodal status of the patients were studied and found that 63 (39.87%) patients had 0 nodes. 68 (43.04%) patients had 1-3 nodes. In the study by Gulam Nabi Sofi et al. he found 34.8% patients with no nodes and 25% with 1-3 nodes positive. Paul L. Nguyen et al study showed only 22.7% patients with 1-3 nodes.

Multivariable Cox proportional hazards regression analysis showed that patients with ER+/PR- (hazard ratio [HR], 1.55; 95% CI, 1.52-1.58) and ER-/PR+ (HR, 1.68; 95%CI, 1.62-1.74) tumors had worse Disease Free survival (DFS) than patients with the ER+/PR+ subtype. This was comparable with the results of the study by N. Wu et al which clearly states that tumours with ER+/PR- and ER-/PR+ are associated with a poor prognosis even with endocrine therapy. These two types of tumours require a more aggressive therapeutic strategy. To improve the survival of patients with these two types of tumours, further investigation focusing on the most appropriate endocrine therapy strategy or the development of targeted agents can benefit these patients warrant investigation.

CONCLUSION

It was observed that the patient population was much younger when compared to the western population. They also presented at a more advanced stage of the disease. Overall the hormone receptor positivity was high in the study population. The Disease free survival was much better in the ER+/PR+ subgroup of study population. Hormone receptor negative patients should be put on more aggressive treatment regimen. At the same time all measures should be intensified to pick up carcinoma breast patients at an early stage. This would include promoting health education and widespread use of screening measures.

Conflict of Interest

Authors have declared no conflicts of interest

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