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RETROSPECTIVE ANALYSIS OF ER, PR & HER 2/ NEU RECEPTOR STATUS IN RELATION TO PROGNOSTIC OUTCOME OF BREAST CARCINOMA PATIENTS.

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ABSTRACT The study was done retrospectively on 50 patients of breast cancer to establish association between ER, PR status, HER2/neu overexpression, clinical features and tumour histopathology, and to effectively use these parameters to prognosticate and treat breast cancer patients. We found that ER, PR combined is a good prognostic indicator for carcinoma breast while HER2/neu cannot be used individually for prognosticating the outcome in women with carcinoma breast. But when HER2/neu is combined with ER and PR, we found worst outcome in women having triple negative (ER -, PR -, HER2/neu -) status and best outcome is seen in women with triple positive (ER +, PR +, HER2/neu +) status.

KEYWORDS : ER, PR, HER2/neu, Carcinoma breast, prognosis.

INTRODUCTION

Breast carcinoma is the most common malignant tumour and the leading cause of carcinoma death in women, with more than 10,00,000 cases occurring worldwide annually. The usual surgical procedure for carcinoma breast is radical mastectomy. The outcome after surgery varies widely. Prognostic information is important in counseling patients about the likely outcome of their disease and planning further management. Apart from clinical parameters like age, menopausal status and disease presentation, important prognostic indicators in histopathology are tumour sizeand extent, histologic type, histologic grade and lymph node status. [1] In addition, there are other factors which not only are predictive of outcome, but also direct therapies against particular molecular targets. Some of these factors are: Estrogen and progesterone receptors (ER, PR): The presence of these nuclear hormone receptors is correlated with a better outcome and is an important predictor of response to hormonal (anti-estrogen) therapy. About 80% of carcinomas that are ER and PR positive respond to hormonal manipulation, whereas only about 40% of those with either ER or PR alone respond. [2] ER positive cancers are less likely to respond to chemotherapy. Conversely cancers that fail to express ER or PR have a less than 10% likelihood of responding to hormonal therapy but are more likely to respond to chemotherapy. HER2/neu(c-erbB2): HER2/neu overexpression is associated with poorer survival, but its main importance is as a predictor of response to agents that target this transmembrane protein (eg. Trastuzumab or herceptin). Proliferative rate: In addition to mitotic counts as part of histologic grading proliferation can be measured by immunohistochemical detection of cellular proteins produced during the cell cycle, e.g. Ki-67. Carcinomas with high proliferation rates have a poorer prognosis but may respond better to chemotherapy. Thus current therapeutic approaches for breast carcinoma consist of combinations of surgery, postoperative radiation, hormonal treatment and chemotherapy. The choice between hormonal therapy which has minimal side effects and chemotherapy with well-known morbidity and risks is a major responsibility of the clinician. Accurate and reliable assessment of the ER, PR and HER2/neu status of breast cancers by the pathologist is therefore crucial. Our institute has started doing ER, PR & HER2/neu status since 2012. There has not been any study so far on its prognostic and survival outcome in our institute. Hence the present study was undertaken to establish association between ER, PR status, HER2/neu overexpression, clinical features and tumour histopathology, and to effectively use these parameters to prognosticate and treat breast cancer patients.

Purpose And Significance

Retrospective analysis of ER, PR & HER2/neu receptor status in relation to prognostic outcome of breast carcinoma patients in our hospital.

The present study was conducted with the following objective to establish association of expression patterns of ER, PR & HER2/neu with survival outcome of breast carcinoma patients. We have done the study on a time bound basis where our basic concern was to see the incidence of survival. Other parameters like disease free interval and survival with disease, locoregional recurrence, distant metastasis were not evaluated.

The present study of retrospective analysis of ER, PR & HER2/neu receptor status in relation to prognostic outcome of breast carcinoma patients was undertaken at the Dept. of General Surgery & Oncosurgery in Choithram hospital & Research Centre, Indore from July 2012 to December 2015 on women with carcinoma breast.

Place Of Study

Department of General Surgery & Oncosurgery, Choithram Hospital & Research Centre, Indore.

Study Design

Retrospective & Prospective, non interventional, observational study.

Duration Of Study: July 2012 – December 2015

Study Population

All women with known history of carcinoma breast who had visited CH & RC during study period.

Sample Size & Sampling Technique

In a study done by **Nikhra et al (2014)**[5] they had included 43 women with breast neoplasm in their study. Accordingly we have included 50 women in our study, thus, justifying our sample size. Convenient sampling was done.

Inclusion Criteria

All women of any age group with confirmed diagnosis of Carcinoma breast.

Exclusion Criteria

- Women whose present survival status could not be traced.
- Data of those women who do not allow her records to be used for analysis.

METHODOLOGY

All the data required for the study was obtained from Medical Records Department (MRD) of our institute, after getting permission to use these records.

Data files were retrieved from the medical records department of women with carcinoma breast who had visited Department of General Surgery & Oncosurgery between July 2012 to December 2015.

Every woman was called and enquired about her ER, PR & HER2/neu receptor status, histopathology status of lump/tumour and the survival status. During the telephonic conversation with the woman and/or her legally acceptable representative, verbal consent for using her data for study purpose was obtained. Then analysis of data was done.

Data Collection
This was a survival/death based study via telephonic conversation. All were telephonically contacted and none by post. Data was collected on a pre-designed customized proforma.

Outcome Measures
ER, PR & HER2/neu receptor status, histopathology results and survival results were taken as outcome parameters.

Statistical Analysis
The demographic data and non-parametric data was represented in the form of number & percentage. The association between two variables was carried out using Pearson's Chi square test. A p value of < 0.05 was taken as statistically significant. The final data was presented in the form of tables and graphs.

Financial Inputs / Funding
Present study was not funded by any pharmaceutical company.

Ethical Considerations
After getting Ethics committee & Scientific committee approval, the study was initiated in the institute. A written permission to look into the records of the institution was obtained from MRD of CH & RC.

OBSERVATIONS & RESULTS

Table No. 1 Survival outcome in relation to treatment given (N=50)

Treatment	Death	Survived	Total
BCS + Chemotherapy + RT	0	1	1
BCS + RT + Chemotherapy	0	1	1
BCS + Tamoxifen + Chemotherapy	0	4	4
BCS + Tamoxifen + RT	0	13	13
BCS + Tamoxifen + RT + Chemotherapy	0	3	3
BCS + Tamoxifen + RT + Chemotherapy + Trastuzumab	0	1	1
Chemotherapy alone	1	2	3
MRM + Chemotherapy	1	3	4
MRM + Chemotherapy + RT	0	1	1
MRM + RT	0	2	2
MRM + RT + Chemotherapy	2	10	12
MRM + RT + Tamoxifen	0	1	1
MRM + RT + Tamoxifen + Chemotherapy	0	1	1
MRM + Tamoxifen	0	1	1
MRM + Tamoxifen + RT	0	1	1
MRM + Tamoxifen + RT + Chemotherapy	0	1	1
Total	4	46	50

In our study, 1 woman who received chemotherapy alone, 1 woman who received MRM + chemotherapy and 2 women who received MRM + RT + chemotherapy had expired.

Table No. 2 Survival outcome in relation to histopathological grading (N=50)

Histopathological Grading	Death		Survived		Total	
	No.	%	No.	%	No.	%
Infiltrating duct carcinoma	2	50.0	38	82.6	40	80.0
Intraductal carcinoma	1	25.0	7	15.2	8	16.0
Lobular carcinoma	1	25.0	1	2.2	2	4.0
Total	4	100.0	46	100.0	50	100.0

In the present study, there were 40 women with infiltrating duct carcinoma, 8 were having intraductal carcinoma and 2 were having lobular carcinoma. There were 50% deaths in women with infiltrating duct carcinoma, 25% each deaths in woman with intraductal carcinoma and lobular carcinoma. More number of deaths were seen in women with infiltrating duct carcinoma.

Table No. 3 ER status, PR status and HER2/neu Status combined in Relation to Survival Outcome (N=50)

ER, PR and HER2/neu Status	Death	Survived	Total
ER-, PR-, HER2/neu Negative	4	9	13
ER-, PR-, HER2/neu Positive	0	4	4
ER-, PR+, HER2/neu Positive	0	2	2
ER+, PR-, HER2/neu Negative	0	6	6
ER+, PR+, HER2/neu Negative	0	11	11
ER+, PR+, HER2/neu Positive	0	14	14
Total	4	46	50

2=12.375, df=5, P value = 0.030, Significant

The above table shows the survival outcome in relation to ER, PR and HER2/neu status. All the deaths (4) occurred in women with ER, PR and HER2/neu negative status, while maximum survival (14) was seen in women with ER, PR and HER2/neu positive status. Statistically significant association was seen between survival outcome and the ER. PR and HER2/neu status (P<0.05).

Table No. 4 Triple Negative and Triple Positive Status in Relation to Survival Outcome (N=50)

ER, PR and HER2/neu Status	Death		Survived		Total	
	No.	%	No.	%	No.	%
ER-, PR-, HER2/neu Negative	4/13	30.8	9	69.2	13	100.0
ER+, PR+, HER2/neu Positive	0/14	0.0	14/14	100.0	14	100.0
Z value	2.248					
P value	0.024*					

Z test for two sample proportion.
P value < 0.05 will be taken as statistically significant

The above table shows the survival outcome in women with triple negative and triple positive status. In triple negative women (ER-, PR- and HER2/neu Negative) there were 4 (30.8%) deaths while in triple positive women (ER+, PR+, HER2/neu Positive), there were no deaths reported. The proportional comparison of death between triple negative and triple positive women was found to be statistically significant (P<0.05), with a higher proportion of deaths in triple negative women.

DISCUSSION

ER / PR Status
In our study we found both ER,PR positive were 50% and ER,PR negative were 34% in total patients. **Bhagat et al (2012)**[3] had found ER+PR+ in 36.20% cases and ER- PR- in 48.27% cases. **Goyanas et al (2008)**[4] had found ER, PR positive in 38% cases and ER,PR negative in 28% cases.

ER / PR AND HER2/neu STATUS
In our study we found ER, PR, HER2/neu positive cases were 28% and ER, PR, HER2/neu negative cases were 26%. Similar result was found by **Bhagat et al (2012)**[3] in which 25.8% cases were triple negative. **Nikhra et al (2014)**[5] found triple positivity in 9.3% cases and triple negativity in 32.5% cases.

In our study HER2/neu expression increased from 8% to 26% in ER -, PR – cases to ER +, PR + cases respectively. ER, PR expression was more 28% in HER2/neu positive cases than HER2/neu negative cases 22%. This was contradictory to the inverse relationship found between ER, PR and HER2/neu by **Farzami et al (2008),**[6] **Bhagat et al (2012),**[3] **Nikhra et al (2014)**[5] **and Yadav et al (2016).**[7]

Histopathological Finding
In our study we found 80% cases were infiltrating ductal carcinoma, 16% were intraductal carcinoma, 4% were lobular carcinoma. Similar results were obtained by **Ozmen et al (2015)**[8] in which 81% cases were Infiltrating duct carcinoma. **Nikhra et al (2014)**[5] had found 95.34% cases to be Invasive Ductal carcinoma. **Bhagat et al (2012)**[3] had found 94.82% cases to be IDC. **Goyanas et al (2008)**[4] had shown a predominance of invasive duct carcinomas (IDC) (73.9%) and invasive lobular carcinomas (ILC) (10%). Special-type invasive carcinomas (medullary, mucinous, tubular and papillary carcinomas) accounted for 5% of the sample, while special clinical varieties, such as inflammatory carcinoma and Paget's disease, represented less than 1%.

Triple Negativity And Triple Positivity
In triple negative women (ER-, PR- and HER2/neu Negative) there were 4 (30.8%) deaths while in triple positive women (ER+, PR+, HER2/neu Positive), there were no deaths reported. We have a very poor outcome in women with triple negative status.

In a study done by **Onitilo et al (2009)**[9] they had also found that triple negative subtype (ER/PR−, HER2−) had the worst overall survival (hazard ratio, 1.8; 95% CI, 1.06–3.2), and worst disease-free survival (hazard ratio, 1.5; 95% CI, 0.8–3.0).

Thus, our study results corroborate with the findings of study done by **Onitilo et al (2009).**[9]

Summary

We found that very good outcome was seen in women with both ER and PR positive, while worst outcome was seen in women with both ER and PR negative status. Statistically significant association could be seen between the survival outcome and ER/PR status, showing that survival outcome in women with breast carcinoma is dependent on ER/PR status.

Whereas, no statistically significant association could be seen between the survival outcome and HER2/neu status, showing that survival outcome in women with breast carcinoma is independent of the HER2/neu status.

There were 2 (50%) deaths in women with infiltrating duct carcinoma, (25%) each death in woman with intraductal carcinoma and lobular carcinoma.

In our study we found that statistically significant association was seen between survival outcome and the ER, PR and HER2/neu status. Higher proportion of deaths were seen in triple negative women in comparison to triple positive women.

CONCLUSION

- In our study, we found that ER, PR combined is a good prognostic indicator for carcinoma breast while HER2/neu cannot be used individually for prognosticating the outcome in women with carcinoma breast.
- But when HER2/neu is combined with ER and PR, we found worst outcome in women having triple negative (ER -, PR -, HER2/neu -) status and best outcome is seen in women with triple positive (ER +, PR +, HER2/neu +) status.

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