"A COHORT STUDY ON BREAST CANCER WITH SPECIAL EMPHASIS ON PROGNOSIS RELATED TO ER, PR, HER2 NEU RECEPTORS AND Ki67 INDEX STATUS AMONG PATIENTS ATTENDING BURDWAN MEDICAL COLLEGE AND HOSPITAL"

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ABSTRACT

Introduction: The most common cancer among women in the urban Indian population is breast cancer and it is second only to cancer of the cervix in the rural population. Currently, routine clinical management of breast cancer incorporates specific molecular markers; namely ER-Estrogen Receptor, PR-Progesterone Receptor, HER2-human epidermal growth factor receptor 2, that have been proven to provide therapeutic, predictive and prognostic value.

Aims: To detect the mean age of patients diagnosed with breast cancer (in early, locally advanced breast cancer (LABC) & metastatic and the ER, PR Her2 neu status and Ki67 indices among them. To observe whether different type of breast cancer among the different age group bears any correlation against receptors status and correlate the receptor status with the different histopathological type of breast cancer.

Materials And Method: This prospective observational study was conducted in CA breast patients attending General surgery OPD Burdwan Medical College Within 1 year 3 months period (May 2019-August 2020). 80 patients were included in this study.

Result: 80 cases of breast carcinoma were assessed for clinicopathological parameter and for expression of ER, PR, Her2 neu and Ki 67 index status. In our study it has been seen that younger age group patients are more susceptible for her2 neu receptor positivity. It has been seen that only 33.3% patients are her2 neu positive in 51-60 yrs age group, whereas the percentage is 64.3% in 31-40 yrs age group and we observed that, it has been noted that more of the ER, PR positive status were seen in lower grade tumors. As in the grade 1 tumors have 71.4% ER,PR positivity where as 27.3 % of grade 3 tumor shows Er positivity.In case of Her2 neu receptor status, more the higher grade more the chance of her 2 receptor positivity. As 90.9% of grade 3 tumor showed Positive result for Her2 neu receptor. We found a inverse correlation between ER, PR and Her2 neu receptor status.

Conclusion: Estrogen, Progesterone receptor positive tumors are common in post-menopausal women and Her2 neu receptor is common in pre-menopausal women. Her2 neu receptors are more prone to seen in grade 3 tumors than lower grade tumor. Her2 neu and er pr status has an inverse correlation with each other. The ki 67 index has proportionately seen in higher grade tumors. We have not found any correlation between ki67 index, age, receptor status. The survival of ER, PR positive tumors are more thant Receptor negative tumors.

Keywords: ER, PR, HER2 NEU receptors and Ki67 index

INTRODUCTION

The most common cancer among women in the urban Indian population is breast cancer and it is second only to cancer of the cervix in the rural population.[1]Breast cancer is a multifaceted disease having distinct biological subtypes with diverse natural history, presenting a varied spectrum of clinical, pathological and molecular features with different prognostic and therapeutic implications. Only about one half of patients with early breast cancer are treated and cured by local surgical excision alone. Therefore, it is important to identify the set of patients in whom the disease is destined to recur and which patients are likely to benefit from systemic chemotherapy.

Currently, routine clinical management of breast cancer incorporates specific molecular markers; namely ER-Estrogen Receptor, PR-Progesterone Receptor, HER2-human epidermal growth factor receptor 2, that have been proven to provide therapeutic, predictive and prognostic value.

About 80% of carcinomas that are ER and PR positive respond to hormonal manipulation. 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[2].

HER2/neu(c-erbB2)-HER2/neu over expression is associated with poorer survival[3], but its main importance is as a predictor of response to agents that target this transmembrane protein. (eg.Trastuzumab or herceptin/lapatinib/putuzumab). Histopathologic correlations with ER/PR expression in breast cancer was first described by Rosen.[4] Tumour types like lobular, tubular, mucinous and papillary carcinomas along with ductal carcinomas of good (low) nuclear grade tend to be ER positive.

The choice between hormonal therapy which has minimal side effects and chemotherapy with well-known morbidity and risks is a major responsibility. Studies have shown that in contrast to western literature, percentage of Estrogen and Progesterone Receptor (ER and PR) positive tumours in Indian subcontinent is persistently low.[5] There is a need to evaluate the expression of HER-2, Estrogen Receptor (ER) and Progesterone Receptors (PR) in breast carcinoma and to and to analyze it with the histomorphology.

Triple negative breast cancer is the worst in terms of prognosis at the present time and needs aggressive management based on receptor analysis, several trails and studies have done and ongoing on the role of receptor status on treatment of breast cancer (NSABP trail on raloxifene, tamoxifen).

Hence the present study is being undertaken to observe the trend and understand the histomorphology and immunohistochemistry of breast Cancer at our institute.

AIMS AND OBJECTIVES

1. To detect the mean age of patients diagnosed with breast cancer (in early, locally advanced breast cancer (LABC) & metastatic.

2. To detect the ER, PR Her2 neu status and Ki67 indices among them.
3. To observe whether different type of breast cancer among the different age group bears any correlation against receptors status.
4. Correlate the receptor status with the different histopathological type of breast cancer

MATERIALS AND METHODOLOGY

Study design – Prospective observational study
Study setting and time line- CA breast patients attending General surgery OPD Burdwan Medical College Within 1 year 3 months period (May 2019-August 2020).
Place of Study – Burdwan Medical College & Hospital
Period of Study – one year three months (May19- August 20)
Study population - Carcinoma of breast Patients attending General Surgery OPD, Burdwan Medical College and Hospital.
Sample size- 80
Inclusion criteria –
Histopathologically diagnosed breast malignancy in female of all age group whether undergone any surgery (modified radical mastectomy or breast conservative surgery) or not.
Exclusion criteria –
1. Patients in 1st trimester of pregnancy

RESULT AND DISCUSSION

Breast cancer accounts for 19.34%[85] of all cancer cases among nationally as per data from national and regional cancer registries. It is one of the commonest cancers and is the 2nd leading cancer among women[86]. The majority of patients go to seek medical attention while the disease is advanced. Early breast cancer is seen only among 30-40% in regional center and is quite high in developed countries.

There is a paucity regarding the breast cancer receptor status and its follow up survival in the developing world. Hence, individual should have the knowledge of various clinicopathological parameters of breast carcinoma specific for their region.

In this present study, 80 cases of breast carcinoma were assessed for clinicopathological parameter and for expression of ER, PR, Her2 neu and Ki 67 index status.

A. Out of 80 cases most of the patients are more than 40 years of age. Mean age at presentation was 45.82 years and median age of the patients is 48 yrs. Among the cases 53 cases were post-menopausal this is 66.25% of the patient population. And among the patients, 62 patients were more than 40 years of age while while 18 patients were less than 40 years age. The average of presentation of breast carcinoma in us is 61 years.[87,88] In the study done by **sunita saxena et al**[6] of new Delhi reported that median age at presentation is 47.8 years which is close to our study result. also there is a study done by **shabnam karangaden et a**l mean age is 47.65 also

correlate with our study. **Naeem et al,[7] su et al**, dang and nysorekar also showed almost similar result.

B. The commonest histological type in our study is invasive ductal carcinoma constitute 87.5% of the patient population it is 70 among the 80 patients. In the study by **Vinod Raina et al[8], Menaka DS lokuhetty[9], Lobana et al[10]** were 92.8%, 86.3% and 83.8% respectively. Our study is almost similar to their study.

C. Invasive ductal carcinoma was graded and we found most of the patients were presented with grade 2 tumor, among the 80 patients 62 patients presented with grade 2 tumor, which is 77.5% of the patient population. It is similar to the study done by **Lobana et al[10]**.

D. Estrogen, Progesterone receptor positive tumors tend to have a significantly longer disease-free survival than with receptor negative tumors.94,95,96 ER, PR expression in the study as follows we found 44 patients (55%) ER and 42 patients (52.5%) PR positive. The expression of both ER, PR receptor were seen in 42 patients (52.5%). Which is similar to study by **Bhagat et al[11]** showed 48.27% ER positive and 51.72% PR positive cases, another study done by **Sheth et al[12]** reported 53.9% ER and 46.1% PR positive cases in their study, another study done by **Allemani et al[13]** Showed 52% ER and 48% PR positive cases in their study. The result of this present study is almost similar to the above study.

E. In this study 38 patients (47.5%) were positive for Her2 neu receptor.

In other studies like a study by **A Himanshu R. Patel, Ankur Shrimal, Harsh P**. Trivedi showed 53.33% positive for her2 neu receptor, another study **Allemani et al[13]** reported 47% positive Her2 neu receptor in their study, A study by **Dutta et al[11]** reported 57.33% positive Her2 neu receptor in their study, Other studies like **Lal et al, Naeem et al** reported 15.65% and 45.9% her2 neu receptor positive in their study. In this present study results were almost same to the above studies.

F. in this study 56 patients showed ki 67value more than 12% which is considered positive. A study done by **Shandiz et al.** reported that 62.3% of patients were positive for Ki67, another study Hosein Kamranzadeh showed 69.16% patients positive for ki67 index.

G. In our study it has been seen that most of the older patients showed er pr positivity. In early age group only 14.3% patients showed positive er pr status where as in older ages it is gradually increasing. Its 83.3% in 51-60 yrs age group and 100% in more than 60 years age group.

A study done by **Col.V. Dutta et al [14] (2008)** studied about Estrogen, Progesterone receptor expression with the age. The results showed that receptor positivity increases with age. Young patients tend to have a high level of circulating estrogen and correspondingly low expression of receptors.

Nidal M Almasri et al [15] (2005) has reviewed 91 specimens of breast tumors during the period of 1995-1999. The author has found significant receptor expression in 58% patients older than 50 years.

A study by **R.D. puthiva** showed receptor status positivity of 77.77% in patients older than 50years age group.

The Increased immunoreactivity with advancing age is parallel to above mentioned studies.

H. In our study it has been seen that younger age group patients are more susceptible for her2 neu receptor positivity. It has been seen that only 33.3% patients are her2 neu positive in 51-60 yrs age group, whereas the percentage is 64.3% in 31-40 yrs age group.

I. in our study it has been noted that more of the ER, PR positive status were seen in lower grade tumors. As in the grade 1 tumors have 71.4% ER, PR positivity where as 27.3 % of grade 3 tumor shows Er positivity.

In case of Her2 neu receptor status, more the higher grade more the chance of her 2-receptor positivity. As 90.9% of grade 3 tumor showed Positive result for Her2 neu receptor. We found an inverse correlation between ER, PR and Her2 neu receptor status.

Rosen PP et al[4](1995) in his study correlated Estrogen, Progesterone receptor positivity with tumor size and histological grade. He concluded Estrogen, Progesterone receptor expressed more in low grade tumors and tumors of lesser diameter.

J. Buon et al found HER-2/neu receptor over expression in higher grade tumors. Hormone receptor positivity was seen 100% in grade I tumors, 76.30% in grade II tumors, and 41.18% in gradewe

III tumors. Their positivity tends to have an inverse relationship with tumor grade.

S.Goyle et al (2008) conducted a retrospective study in India. He has reviewed 131 patients and found that receptor and oncoprotein expression does not necessarily correlate with advanced tumors in our population.

We did not find any specific correlation between histological type and receptor status, as maximum of the patients we found were IDC NOS type.

In our study we did not find any death during this 1-year period, except some of the patients were lost to follow up.

But form some other studies like, a prospective cohort of breast cancer patients' done by Department of Epidemiology, University of Washington, USA and Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, USA, in which women with ER+/PR-, ER-/PR+, or ER-/PR- tumors experienced higher risks of mortality as compared to women with ER+/PR+ tumors.

In one more study by **Williams MR, et al,** the contribution of ER status to survival has been examined in those patients responding to therapy and compared to those progressing despite treatment.

However, in patients assessed as responding to therapy a significant difference did occur between these two groups. Patients assessed as responding to therapy with ER-positive tumours had a significant survival advantage over the small number of responding patients with ER-negative Primary tumours.

CONCLUSION

Breast carcinoma mainly seen in older age.

Most of the breast carcinoma are grade 2 tumor.

Estrogen, Progesterone receptor positive tumors are common in post-menopausal women. Her2 neu receptor is common in pre-menopausal women.

Her2 neu receptors are more prone to seen in grade 3 tumors than lower grade tumor. Her2 neu and er pr status has an inverse correlation with each other. The ki 67 index has proportionately seen in higher grade tumors. We have not found any correlation between ki67 index, age, receptor status. The survival of ER, PR positive tumors are more thant Receptor negative tumors. The study was complete and the result was more accurate if the duration of study is more and the number of patients is more.

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Table: Distribution of Histopathological Type distribution (n=80)

Histological type	No of patients
IDC NOS	70(87.5%)
Others	10(12.5%)

Table: Distribution of receptor status and ki 67 index according to age group

Age group	ER receptor positive		PR receptor positive		Her2 neu positive		Ki 67 index positive	
	no	%	no	%	no	%	no	%
21-30(n=4)	2	50	2	50	2	50	2	50
31-40(n=14)	2	14.3	1	7.1	9	64.3	5	35.7
41-50(n=41)	22	53.65	21	51.2	23	56.09	34	82.9
51-60(n=18)	15	83.3	15	83.3	3	16.6	14	77.7
>60(n=3)	3	100	3	100	1	33.3	1	33.3

Table: Distribution of receptor status among different histology type and grade.

Receptor status	Histology type						Histology grade					
	ILC(n=4)		IDC nos(n=70)		Others(n=6)		1(n=7)		2(n=62)		3(n=11)	
	no	%	No	%	no	%	no	%	no	%	no	%
ER positive	1	25	39	55.7	4	66.6	5	71.4	36	58.06	3	27.3
PR positive	1	25	38	54.2	3	50	3	42.9	36	58.06	3	27.3
Her 2 neu positive	3	75	34	48.5	1	16.6	1	14.3	27	43.5	10	90.9