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CLINICOPATHOLOGICAL STUDY OF BREAST CARCINOMA WITH ESTROGEN RECEPTOR (ER), PROGESTERONE RECEPTOR (PR), HUMAN EIDERMAL GROWTH FACTOR RECEPTOR 2 NEU (HER2NEU) STATUS

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Abstract

Aims: The aim of this study is to evaluate the expression of Estrogen Receptor (ER) , Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 neu (HER2neu) in breast carcinoma and to compare it with other prognostic parameters such as patient's age, tumour size, lymph node metastasis, stage, histological type and grade of the tumour[2] and a follow up period of 6 months. **Materials and Methods:** This is a analytical study with proper diagnostic accuracy done among 50 adult patients both male and female presenting with breast lumps. Adult patients both male and female presenting with breast cancer to Vinayaka Mission's Kirupananda Variyar Medical College and Hospital from July 2020 to July 2022. **Results:** Among 50 patients, 10% belong to 31-40 years, 50% belong to 41-50 years, 30% belong to 51-60 years, 10% belong to 61-70 years. 2% are pre menopausal women, 12% are perimenopausal women and 86% are post menopausal women. 2% had positive history of breast cancer. 70% in upper outer region, 6% in upper inner region, 8% in lower outer region, 8% in lower inner region, 8% in central region. 98% are Intra Ductal carcinoma, 2% are Lobular carcinoma. In the study 66% of the study participants are ER positive, 66% of the study population are PR positive, 54% of the study population are HER-2 positive, 44% are ER/PR+HER2-, 22% are ER/PR+HER2+, 2% are ER/PR-HER2-, 32% are ER/PR-HER2+. Based on relationship between histological subtypes and ER,PR and HER-2 positivity, 33 cases of IDC are ER+ve, 33 cases on IDC are PR +ve, 27 cases of IDC are HER-2+ve. **Conclusion:** There has been outstanding advances in diagnosis and management of carcinoma breast over the last few decades in our country. Immunohistochemistry is used as a clinical tool as ER/PR and Her2 testing is widely available at a reasonable cost and serves as an informative classification of breast cancer based on immunopheno types, and is prognostic as well as predictive. Presence of hormone receptors correlates well with response to hormone therapy. Determination of ER, PR & HER2/neu status is essential in all cases irrespective of clinical staging and lymph node metastasis.

Keywords: Carcinoma, Immunohistochemistry, ER, PR & HER2/neu, Lobular Carcinoma.

INTRODUCTION

Breast carcinoma is the most common malignant tumor and the leading cause of carcinoma death in women. In our country, though the incidence of breast carcinomas is lower than the west yet it is the second most common malignant tumor in females comprising 16 to 21%. The first being carcinoma cervix. Breast cancers are diagnosed at a relatively advanced stage[1]

Breast carcinoma is a disease with a tremendous heterogeneity in its clinical behavior. It is the most common female cancer in the world with an estimated 1.67 million new cancer cases diagnosed in 2012. This represents about 12% of all new cancer cases and 25% of all cancers in women.[2]

Annual incidence of approximately 1, 44,000 new cases of breast cancers in India, it has now become the most common female cancer in urban India and the second commonest in the rural Indian women.[2]

Currently, routine clinical management of breast cancer incorporates specific molecular markers; namely Estrogen Receptor (ER), Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 (HER2) gene that have been proven to provide therapeutic, predictive and prognostic value. The triple negative breast cancer (ER/PR/HER-2/neu) has the worst overall survival.

The aim of this study is to evaluate the expression of Estrogen Receptor (ER), Progesterone Receptor (PR) and Human Epidermal Growth Factor Receptor 2 neu (HER2neu) in breast carcinoma and to compare it with other prognostic parameters such as patient's age, tumour size, lymph node metastasis, stage, histological type and grade of the tumour and a follow up period of 6 months.

MATERIALS AND METHODS

After obtaining consent, adult patients both male and female presenting with breast lumps undergo a complete triple evaluation consisting of clinical, pathological, and radiological examination. As part of the pathological examination, a core needle biopsy sample is taken3.

It is examined histopathologically for malignancy, and immunohistochemically for Estrogen receptor (ER), Progesterone receptor (PR), and Human Epidermal Growth Factor Receptor 2 neu(HER2neu) receptor expression4. Once malignancy is confirmed, receptor expression is compared against other components of the triple examination. Patients will be followed up for a period of 6months.

Inclusion Criteria

- Adult patients both male and female presenting with all types of biopsy proven breast cancer at all stages with Estrogen Receptor (ER) , Progesterone Receptor (PR), Human Epidermal Growth Factor Receptor 2 neu (HER2neu) status.

Exclusion Criteria

- Minors, benign breast disorders, patients previously treated for breast cancer, recurrent breast cancer, nonconsenting patients, medically unfit patients.

Statistical Analysis

Data Entry was done using Microsoft excel 2013 and analysis done using SPSS V 16. Qualitative data was expressed in frequencies and percentages and Quantitative data in mean and standard deviation.

Non Parametric tests include Chi square t test for intergroup comparison was used. Bar diagrams and pie chart were used to represent the data. p value of <0.05 was considered statistically significant.

RESULTS

Table 1: Age Distribution of Patients Studied

Age	No of patients	Percentage
31-40	5	10%
41-50	25	50%
51-60	15	30%
61-70	5	10%
>70	0	0%
Total	50	100.0

Table 1 shows distribution based on Age, 10% belong to 31-40 years, 50% belong to 41-50 years, 30% belong to 51-60 years, 10% belong to 61-70 years and 2% belong to >70 years.

Table 2: Menstrual Status of Patients Studied

Menstrual Status	No of patients	Percentage
Pre-menopausal	1	2.0
Peri menopausal	6	12.0
Post-menopausal	43	86.0
Total	50	100.0

Table 2 shows distribution based on Menstrual status, 2% are pre menopausal women, 12% are perimenopausal women and 86% are post menopausal women.

Table 3: Family History of Breast Cancer

Family history of Breast cancer	No of patients	Percentage
Absent	49	98.0
Present	1	2.0
Total	50	100.0

Table 3 shows distribution based on history of breast cancer, 2% had positive history of breast cancer

Table 4: Exogenous Oestrogen

Exogenous oestrogen	No of patients	Percentage
Yes	4	8.0
No	46	92.0
Total	50	100.0

Table 4 shows distribution based on Exogenous oestrogen, 8% had taken oestrogen

Table 5: Clinical Presentation

Clinical Presentation	No of patients	Percentage
Breast Lump	44	88.0
Breast Lump + Pain	5	10.0
Breast Lump + Skin Involvement	1	2.0
Total	50	100.0

Table 5 shows distribution based on Clinical presentation, 88% had Breast lump, 10% had Breast lump and pain, 2% had Breast lump and Skin involvement

Table 6: Duration Of Clinical Symptoms In Months

Duration in Months	No of patients	Percentage
0-3	25	50%
4-6	15	30%
7-9	10	20%
Total	50	100.0

Table 6 shwos distribution based on duration of clinical symptoms in months, 0-3 months in 50%, 4-6 months in 30%, 7-9 months in 20%.

Table 7: Side of Involvement

SIDE OF INVOLVED	No of patients	Percentage
Left Side	15	30.0
Right Side	35	70.0
Total	50	100.0

Table 7 shows distribution based on side of involvement, Right sided involvement in 70% and left side involvement in 30%.

Table 8: Locatıon of Tumor

Location Of Tumor	No of patients	Percentage
Upper Outer	35	70.0
Upper Inner	3	6.0
Lower outer	4	8.0
Lower Inner	4	8.0
Central	4	8.0
Total	50	100.0

Table 8 shows distribution based on location of tumour, 70% in upper outer region, 6% in upper inner region, 8% in lower outer region, 8% in lower inner region, 8% in central region.

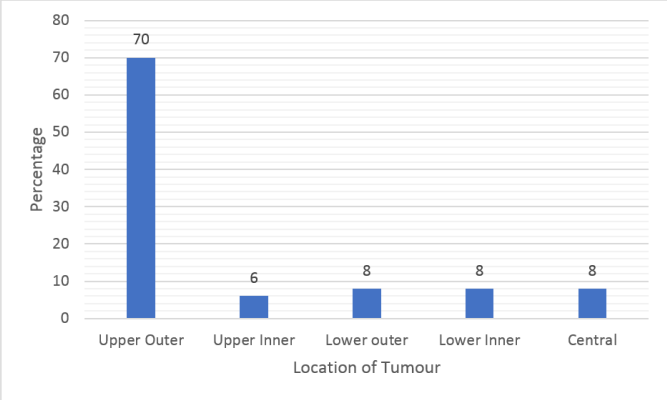

Figure 1: Distribution based on location of tumour

Table 9: Clinical Diagnosis

Clinical Diagnosis	No of patients	Percentage
Carcinoma	39	78.0
Fibroadenoma	4	8.0
Fibrocystic Disease	7	14.0
Total	50	100.0

Table 9 shows distribution based on clinical diagnosis, 78% were diagnosed clinically as Carcinoma, 8% with fibroadenoma, 14% with fibrocystic disease.

Table 10: Procedure

Procedures	No of patients	Percentage
Breast conservation surgery	7	14.0
MRM	43	86.0
Total	50	100.0

Table 10 shows distribution based on procedure done, Breast conservation surgery done in 14%, Modified radical mastectomy in 86%.

Table 11: Size of Tumor on Gross Examination

Size in CMs	No of patients	Percentage
<2	7	14.0
2-5	23	46.0
>5	20	40.0
Total	50	100.0

Table 11 shows distribution based on size of tumour on gross examination, 14% had size of tumour <2cm, 2-5 cm size in 46%, >5 cm in 40%.

Table 12: Scores of Histologic MBR Grade

	Histologic MBR grade		
	Score1	Score2	Score3
Tubule formation	6(12.0)	23(46.0)	21(42.0)
Mitotic Rate	10(20.0)	18(36.0)	22(44.0)
Nuclear Grade	10(20.0)	23(46.0)	17(34.0)

Table 12 shows distribution based on Histological MBR grade, Tubule formation Score 1 (12%), Score 2(46%), Score 3(42%)

Mitotic rate score 1 (20%), score 2 (36%), score 3 (44%)

Nuclear grade score 1(20%), Score 2(46%), score 3(34%).

Table 13: Histologic (MBR) Grade

Histologic MBR grade	No of patients	Percentage
Grade I	18	36.0
Grade II	15	30.0
GRADE III	17	34.0
Total	50	100.0

Table 13 shows distribution based on MBR Grade, Grade I in 36%, Grade II in 30%, Grade III in 34%.

Table 14: Final Histopathological Diagnosis

Final Diagnosis	No of patients	Percentage
IDC	49	98.0
Lobular Carcinoma	1	2.0
Total	50	100.0

Table 14 shows distribution based on Histopathological diagnosis, 98% are Intra Ductal carcinoma, 2% are Lobular carcinoma.

Table 15: Lymphnode Status

Lymphnode status	No of patients	Percentage
Metastasis	33	66.0
Reactive	17	34.0
Total	50	100.0

Table 15 shows distribution based on lymph node status, 66% had metastasis, 34% with reactive lymph nodes

Table 16: Involvement of Deep Surgical Margin

DSM	No of patients	Percentage
Involved	0	0%
Not Involved	50	100%
Total	50	100.0

Table 16 shows distribution based on involvement of Deep surgical margin, in all the patients no deep surgical margin involvement seen

Table 17: Pagets Disease

Paget's Disease	No of patients	Percentage
Present	1	2.0
Absent	49	98.0
Total	50	100.0

Table 17 shows distribution based on Pagets disease, 2% in the study had Pagets disease.

Table 18: ER

ER	No of patients	Percentage
Positive	33	66.0
Negative	17	34.0
Total	50	100.0

In the study 66% of the study participants are ER positive.

Table 19: PR

PR	No of patients	Percentage
Positive	33	66.0
Negative	17	34.0
Total	50	100.0

In the study, 66% of the study population are PR positive

Table 20: HER-2

HER-2	No of patients	Percentage
Positive	27	54.0
Negative	23	46.0
Total	50	100.0

In the study, 54% of the study population are HER-2 positive

Table 21: Immuno Histochemical Subtype

ER/PR and HER2	No of patients	Percentage
ER/PR+HER2-	22	44.0
ER/PR+HER2+	11	22.0
ER/PR-HER2-	1	2.0
ER/PR-HER2+	16	32.0
Total	50	100.0

Table 21 shows distribution based on Immunohistochemical subtypes, 44% are ER/PR+HER2-, 22% are ER/PR+HER2+, 2% are ER/PR-HER2-, 32% are ER/PR-HER2+

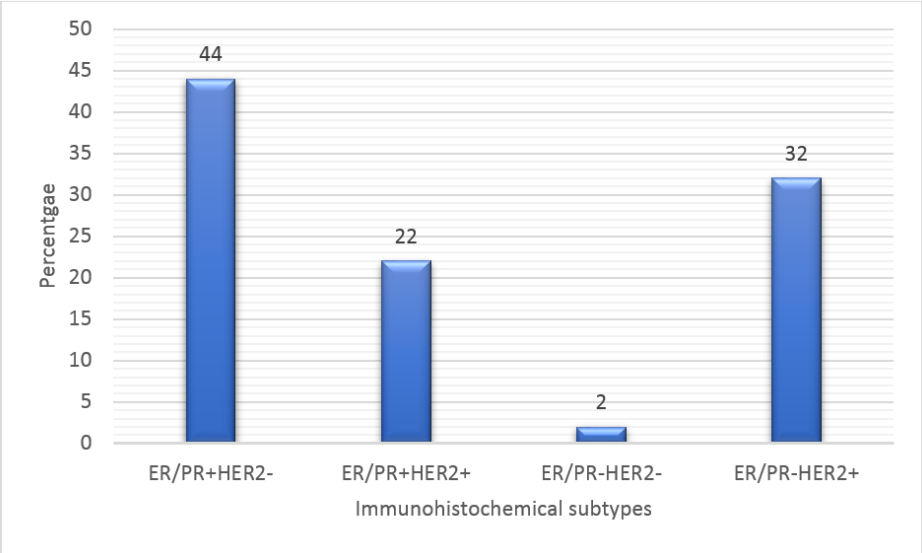

Figure 2: Distribution based on Immunochemical subtypes

Table 22: Relationship Between Histologic Subtypes And ER,PR, And HER-2 Positivity

Histologic subtype	ER+	PR+	HER-2-+
IDC	33	33	27
Lobular Carcinoma	0	0	0

Table 23: Relationship of ER to the Following Clinicopathological Features

Clinicopathological Features	ER		Chi-square value	P value
	Positive	Negative		
Menstrual Status				
Pre-menopausal	1(3.0)	0	1.52	0.6
Peri menopausal	5(15.2)	1(5.9)		
Post-menopausal	27(81.8)	16(94.1)		
Tubule Formation				
Score 1	4(12.1)	2(11.8)	3.28	0.2
Score2	18(54.5)	5(29.4)		
Score3	11(33.3)	10(58.8)		
Mitosis Grading				
Score 1	7(21.2)	3(17.6)	1.39	0.5
Score2	10(30.3)	8(47.1)		
Score3	16(48.5)	6(35.3)		
Nuclear Pleomorphism				
Score 1	6(18.2)	4(23.5)	1.26	0.5
Score2	14(42.4)	9(52.9)		
Score3	13(39.4)	4(23.5)		
Histologic Grading				
Score 1	16(48.5)	2(11.8)	7.09	**0.02***
Score2	7(21.2)	8(47.1)		
Score3	10(30.3)	7(41.2)		

Table 23 shows association between ER status and Clinicopathological features, in the study a statistically significant association observed with relation to histological grading and ER status as the p value calculated to be <0.05.

Table 24: Relationship of PR to the Following Clinicopathological Features

Clinicopathological Features	PR		Chi-square value	P value
	Positive	Negative		
Menstrual Status				
Pre-menopausal	1(3.0)	0	1.52	0.6
Peri menopausal	5(15.2)	1(5.9)		
Post-menopausal	27(81.8)	16(94.1)		
Tubule Formation				
Score 1	4(12.1)	2(11.8)	3.28	0.2
Score2	18(54.5)	5(29.4)		
Score3	11(33.3)	10(58.8)		
Mitosis Grading				
Score 1	7(21.2)	3(17.6)	1.39	0.5
Score2	10(30.3)	8(47.1)		
Score3	16(48.5)	6(35.3)		
Nuclear Pleomorphism				
Score 1	6(18.2)	4(23.5)	1.26	0.5
Score2	14(42.4)	9(52.9)		
Score3	13(39.4)	4(23.5)		
Histologic Grading				
Score 1	16(48.5)	2(11.8)	7.09	**0.02***
Score2	7(21.2)	8(47.1)		
Score3	10(30.3)	7(41.2)		

Table 24 shows association between PR status and Clinicopathological features, in the study a statistically significant association observed with relation to histological grading and PR status as the p value calculated to be <0.05.

Table 25: Relationship of HER-2 to the Following Clinicopathological Features

Clinicopathological Features	HER-2		Chi-square value	P value
	Positive	Negative		
Menstrual Status				
Pre-menopausal	0	1(4.3)	6.75	0.02*
Peri menopausal	6(22.2)	0		
Post-menopausal	21(77.8)	22(95.7)		
Tubule Formation				
Score 1	2(7.4)	4(17.4)	1.59	0.4
Score2	12(44.4)	11(47.8)		
Score3	13(48.1)	8(34.3)		
Mitosis Grading				
Score 1	4(14.8)	6(26.1)	1.04	0.7
Score2	10(37.0)	8(34.8)		
Score3	13(48.1)	9(39.1)		
Nuclear Pleomorphism				
Score 1	4(14.8)	6(26.1)	1.23	0.5
Score2	14(51.9)	9(39.1)		
Score3	9(33.3)	8(34.8)		
Histologic Grading				
Score 1	7(25.9)	11(47.8)	2.78	0.2
Score2	10(37.0)	5(21.7)		
Score3	10(37.0)	7(30.4)		

Table 25 shows association between HER-2 status and Clinicopathological features, in the study a statistically significant association observed with menstrual status and HER-2 status as the p value calculated to be <0.05.

Table 26: Clinicopathological Correlation Wıth Immuno Histochemical Subtypes

Clinical variable	ER/PR+HER2-	ER/PR+HER2+	ER/PR-HER2-	ER/PR- HER2+	P value
Age (Range) In Yrs	(38-71) 57.64±6.95	(39-63) 50.91±7.87	(55-55) 55±0	(47-68) 58.81±5.91	**0.03***
Tumor stage					
I	3(13.6)	0	0	1(6.3)	0.1
II	11(50.0)	1(9.1)	0	6(37.5)	
III	8(36.4)	10(90.9)	1(100.0)	9(56.3)	
Tumor Size					
<2cms	3(13.6)	4(36.4)	0	0	0.1
2-5cms	11(50.0)	4(36.4)	1(100.0)	7(43.8)	
>5cms	8(36.4)	3(27.3)	0	9(56.3)	
Lymphovascular Invasion					
Present	1(4.5)	1(9.1)	1(100.0)	5(31.3)	**0.01***
Absent	21(95.5)	10(90.9)	0	11(68.8)	
Cancer type					
IDC	22(100.0)	11(100.0)	0	16(100.0)	**0.02***
LOBULAR CARCINOMA	0	0	1(100.0)	0	
Histological Grade					
Grade I	11(50.0)	5(45.5)	0	2(12.5)	0.1
Grade II	4(18.2)	3(27.3)	1(100.0)	7(43.8)	
Grade III	7(31.8)	3(27.3)	0	7(43.8)	

Table 26 shows distribution based on correlation between immunohistochemical subtypes with clinicopathological findings, a statistically significant association observed with Age in years, Lymphovascular invasions and Cancer type variables with Immunohistochemical subtypes as the p value calculated to be <0.05

DISCUSSION

Hormone Receptors

Estrogen receptor (ER) and progesterone receptor (PR) tumor tissue assays[3]

- Consistently recommended by all guidelines for predicting response to endocrine therapy
- Recommended by most guidelines for prognosis

American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) 2010 guideline recommendations on immunohistochemical testing of ER and PR in breast cancer[4]

- Immunohistochemical test to determine ER and PR status used to identify patients likely to benefit from endocrine therapy
- Absence of benefit from endocrine therapy for women with ER-negative invasive breast cancers has been confirmed
- Testing recommended for
  - ✓ All invasive breast cancers
  - ✓ All breast cancer recurrences

- To ensure that prior results were not falsely negative
- To evaluate specimen for biologic changes since previous testing

No formal recommendation made for patients with ductal carcinoma in situ

- Testing of ER and PR commonly done and usefulness suggested by retrospective study published only in abstract form
- Validation studies appear unlikely to be done

Interpretation of test results

- Positive test defined as immunoreactivity (staining) in ≥ 1% of tumor nuclei
- Negative test defined as staining in < 1% of tumor cells in presence of appropriately stained extrinsic and intrinsic (normal breast epithelium) controls
- Percentage of stained tumor cells may be helpful with treatment decisions

Increased percentage of ER staining associated with improved

- Survival (overall, disease-free, recurrence-free and 5-year)
- Response to endocrine therapy
- Time to treatment failure
- Time to recurrence

Increased PR staining associated with improved

- Overall survival
- Response to endocrine therapy
- Time to treatment failure/progression
- Time to recurrence

Age Distribution

In the present study, 10% belong to 31-40 years, 50% belong to 41-50 years, 30% belong to 51-60 years, 10% belong to 61-70 years. A similar study was conducted by Narendra et al[5] where the Median age was 46 years (ranged from 28 to 66). Mean age of patients was 43.73 years (range: 32–63 years). The average age of breast cancer patients, at presentation, has been reported to be 50–53 years in various population-based studies conducted in different parts of the country while a significant proportion of Indian breast cancer patients are younger than 35 years of age.[6]

Mean age of the patient in the study by Abdel-Bary et al[7] was 42 years with range of 21–68 years whereas Swain et al[8]. found that mean age was 42 years. In a study conducted by Parmar et al on-breast conservation treatment in women with locally advanced breast cancer-experience from a single centre the maximum number of patients fell in pre-menopausal category with a mean age at presentation of 47.6 years.[9]

Menstrual Status

2% are premenopausal women, 12% are perimenopausal women and 86% are postmenopausal women.

History of Breast Cancer

2% had positive history of breast cancer

Clinical Presentation

88% had Breast lump, 10% had Breast lump and pain, 2% had Breast lump and Skin involvement

Duration of Clinical Symptoms in Months

Based on duration of clinical symptoms in months, 0-3 months in 50%, 4-6 months in 30%, 7-9 months in 20%.

Side of Involvement

Right sided involvement in 70% and left side involvement in 30%.

Location of Tumour

70% in upper outer region, 6% in upper inner region, 8% in lower outer region, 8% in lower inner region, 8% in central region.

Clinical Diagnosis

78% were diagnosed clinically as Carcinoma, 8% with fibroadenoma, 14% with fibrocystic disease.

Procedure Done

Breast conservation surgery done in 14%, Modified radical mastectomy in 86%.

Size of Tumour on Gross Examination

14% had size of tumour <2cm, 2-5 cm size in 46%, >5 cm in 40%.

Vasudevan et al[67] in their study reported that majority of the cases had a clinical size of 2 cm–5 cm at the time of presentation (66.7%), mean clinical size being 3.75 cm (with a standard deviation of 2.36). 11 cases (29.7%) had a tumor size of less than 5 cm preoperatively and only 9.1% had a tumor size of above 5 cm. Jadhav et al[10] in their study reported that 84.38% patients had lump size between 5–7.5 cm.

These data reinforce the importance of receptor status as well as tumor size, each of which might act as surrogates for tumor biology, in setting expectations for outcomes in patients who undergo NAC. Contemporary studies have addressed the role of breast conservation therapy following neoadjuvant chemotherapy for lesions greater than 5 cm. However, tumor size relative to breast size may be more important than exact measurements alone. Evaluation of breast size and discussion with the patient regarding postoperative expectations of her breast size is therefore critical to decide the best treatment course. Neoadjuvant chemotherapy has demonstrated comparable rates of disease-free survival and overall survival when compared with adjuvant therapy.

Histological MBR Grade

In the present study, Tubule formation Score 1 (12%), Score 2(46%), Score 3(42%)

Mitotic rate score 1 (20%), score 2 (36%), score 3 (44%)

Nuclear grade score 1(20%), Score 2(46%), score 3(34%).

The pre treatment clinical stage and post-treatment pathologic stage are the determinant of the progression of breast cancer patients undergoing neoadjuvant chemotherapy. Tumor size is easy to measure if there is no or minimal response to therapy. This assessment becomes challenging as tissue response to therapy makes the measurement of the actual isolated and clusters of residual tumor difficult.

Tumor cellularity can also be used as a measure of response to therapy. However, this assessment may be complicated by the presence of associated chemotherapy-induced tissue reaction resulting in overestimation of cellularity. Assessment of tumor cellularity requires access to tumor tissue prior to chemotherapy

MBR Grade

Grade I in 36%, Grade II in 30%, Grade III in 34%.

Histopathological Diagnosis

98% are Intra Ductal carcinoma, 2% are Lobular carcinoma.

Lymph Node Status

66% had metastasis, 17% with reactive lymph nodes.

The status of lymph nodes after therapy is the most important prognostic factor. This can be achieved clinically and by imaging. Performing sentinel lymph node biopsy after neoadjuvant chemotherapy for patients with clinically negative axilla at the time of diagnosis is an accep figure approach. As it has already been mentioned, clinically or radiologically suspicious lymph nodes should undergo minimally invasive sampling procedures such as ultrasound-guided fine needle aspiration biopsy prior to neoadjuvant chemotherapy.[11]

The degree of involvement of axillary nodes following neoadjuvant chemotherapy is the strongest predictor of subsequent relapse.[12] Hence, patients undergoing neoadjuvant therapy have, traditionally, proceeded to axillary clearance at the time of mastectomy or breast conservation. However, sentinel lymph node biopsy has become the axillary intervention of choice in breast cancer surgery and some 40% of axillae may convert from positive for disease to show a complete pathologically documented response following neoadjuvant therapy.

Suspicious axillary nodes seen on diagnostic imaging should undergo biopsy by fine-needle aspiration or core-needle biopsy to confirm metastatic involvement; however, a negative biopsy or the absence of suspicious nodes on ultrasound does not exclude axillary metastasis. Sentinel lymph node biopsy should be planned at the time of definitive surgical resection of the primary tumour in patients with a ‘negative’ axillary work-up on the original, prechemotherapy axillary assessment.

Some have advocated performing sentinel lymph node biopsy before the administration of neoadjuvant therapy; however, this approach remains controversial as clearance of involved axillary nodes with neoadjuvant therapy is a better prognostic indicator than response in the primary breast tumour alone and removal of the sentinel node does not allow for complete evaluation of pathologic response in the axilla[13]

Pagets Disease

2% in the study had Pagets disease.

Hormone Receptors

- In the study 66% of the study participants are ER positive.
- In the study, 66% of the study population are PR positive
- In the study, 54% of the study population are HER-2 positive

Immunohistochemical Subtypes

44% are ER/PR+HER2-, 22% are ER/PR+HER2+, 2% are ER/PR-HER2-, 32% are ER/PR-HER2+. Based on relationship between histological subtypes and ER,PR and HER-2 positivity, 33 cases of IDC are ER+ve, 33 cases on IDC are PR +ve, 27 cases of IDC are HER-2+ve.

Based on association between ER status and Clinicopathological features, in the study a statistically significant association observed with relation to histological grading and ER status as the p value calculated to be <0.05. Based on association between PR status and Clinicopathological features, in the study a statistically significant association observed with relation to histological grading and PR status as the p value calculated to be <0.05.

Based on association between HER-2 status and Clinicopathological features, in the study a statistically significant association observed with menstrual status and HER-2 status as the p value calculated to be <0.05. Based on correlation between immunohistochemical subtypes with clinicopathological findings, a statistically significant association observed with Age in years, Lymphovascular invasions and Cancer type variables with Immunohistochemical subtypes as the p value calculated to be <0.05

Biological markers that are routinely assessed in breast cancer specimens in pathology laboratories include estrogen (ER) and progesterone (PR) receptor expression, and HER-2/neu status. These markers can be assessed by several different techniques including immunohistochemical analysis and florescence in situ hybridization.

Although there are several concerns regarding the lack of formal, standardized processing protocols for many of the biological markers currently being used routinely in the clinic, much of the literature on these markers is consistent with the expected associated patient outcomes. The anticipation is that as more biological markers are characterized in terms of their prognostic or predictive abilities, they will be incorporated into the standard pathologic assessment and, thus, help facilitate a more refined molecular staging of disease.

This neoadjuvant approach is based on the finding that most breast tumors will decrease in size by at least 50% when exposed to 3 to 4 cycles of cytotoxic chemotherapy, thus permitting breast conserving surgery over mastectomy. Another potential benefit of neoadjuvant therapy is the ability to assess primary tumor response to the individual treatment, with the notion that agents could be adjusted depending on response.[14]

Androgen Receptor Expression

Based on systematic review[15] of 19 retrospective cohort studies evaluating association between androgen receptor expression and survival in 7,693 women with early breast cancer cutoffs for androgen receptor expression varied across studies 60.5% of

tumors expressed androgen receptor compared to tumors without androgen receptor expression, androgen receptor expression associated with increased.

- 3-year overall survival (odds ratio [OR] for death 0.47, 95% CI 0.39-0.58) in analysis of 14 studies
- 3-year disease-free survival (OR for recurrence 0.43, 95% CI 0.35-0.52) in analysis of 10 studies
- 5-year overall survival (OR for death 0.4, 95% CI 0.29-0.56) in analysis of 14 studies, results limited by significant heterogeneity
- 5-year disease-free survival (OR for recurrence 0.34, 95% CI 0.21-0.56) in analysis of 12 studies, results limited by significant heterogeneity

This study concluded that androgen receptor expression associated with increased survival in women with early breast cancer

Based on retrospective cohort study[16] 155,175 women > 30 years old with invasive breast carcinoma and known hormone receptor status from National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program were analysed.

Overall mortality by hormone receptor status

- 19.7% with estrogen receptor (ER)-negative/progesterone receptor (PR)-negative tumors
- 17.3% with ER-negative/PR-positive tumors
- 12.2% with ER-positive/PR-negative tumors
- 7.4% with ER-positive/PR-positive tumors

Compared to ER-positive/PR-positive tumors, increased mortality associated with

- ER-negative/PR-negative tumors (hazard ratio [HR] 2.3, 95% CI 2.2-2.4)
- ER-negative/PR-positive tumors (HR 1.8, 95% CI 1.6-1.9)
- ER-positive/PR-negative tumors (HR 1.4, 95% CI 1.3-1.5)

This study concluded that negative estrogen receptor and/or progesterone receptor tumor status associated with increased mortality in women with invasive breast cancer

HER2-neu

Overexpression of HER2-neu is associated with increased sensitivity to anthracycline regimens in the adjuvant setting. Present data on HER2-neu status and response to neoadjuvant anthracycline chemotherapy are conflicting.[17]

HER2 positivity1,3

Occurs in 15%-20% of breast cancers

May be associated with

- Increased response to anthracyclines and test should prompt strong consideration of anthracycline-based adjuvant therapy if chemotherapy indicated

- Poorer prognosis (increased mortality and recurrence) in absence of systemic therapy, but test not recommended by most groups for determining prognosis in early breast cancer
- Decreased benefit from non-anthracycline- and non-taxane-containing chemotherapy, but test not recommended to guide use of taxanes in adjuvant setting

Based on post hoc analysis of randomized trials

HER2 amplification tested in 639 tissue samples from 710 premenopausal women with node-positive breast cancer who were randomized to anthracycline-containing regimen (cyclophosphamide, epirubicin, and 5-flurouracil [CEF]) vs. non-anthracycline-containing regimen (cyclophosphamide, methotrexate, and 5-flurouracil [CMF])

628 tumors tested for HER2 amplification by fluorescent in situ hybridization (FISH) were included in analysis, of which 26% had HER2 amplification

HER2 amplification associated with

- Decreased overall survival (hazard ratio [HR] for death 1.62, 95% CI 1.24-2.11)
- Decreased relapse-free survival (HR for relapse 1.31, 95% CI 1.03-1.67)

Among tumors with HER2 amplification, CEF was superior to CMF in terms of

- Increased relapse-free survival (HR for relapse 0.52, 95% CI 0.34-0.8)
- Nonsignificant trend toward increased overall survival (HR for death 0.65, 95% CI 0.42-1.02)

No significant differences in overall or relapse-free survival comparing CEF vs. CMF in women with tumors not showing HER2 amplification.

This study concluded that HER2 amplification associated with decreased overall and relapse-free survival in premenopausal women with node-positive breast cancer.

HER2 levels considered high if ≥ 15 ng/mL, cutoff recommended by FDA-approved assay manufacturer

sHER2 levels ≥ 15 ng/mL associated with lower

- 3-year overall survival (hazard ratio 2.4, 95% CI 1.2-4.7)
- 3-year disease-free survival (hazard ratio 1.95, 95% CI 1.5-2.5)

This study concluded that in patients with early-stage HER2-positive breast cancer, soluble HER2 levels ≥ 15 ng/mL associated with lower 3-year overall survival.

Based on matched cohort study[18] 150 women with pT1a-b, pN0 and HER2-positive disease who had breast surgery were matched with controls and followed for median 4.6 years

- 79 HER2-positive, hormone receptor-positive patients matched to 158 HER2-negative, hormone receptor-positive patients
- 71 HER2-positive, hormone receptor-negative patients matched to 71 HER2-negative, hormone receptor-negative patients

HER2-positive disease associated with

- Decreased 5-year disease-free survival in patients with hormone receptor-positive disease (HR 5.2, 95% CI 1-25.9)
- Trend toward decreased 5-year disease-free survival
  - ✓ Overall (HR 2.4, 95% CI 0.9-6.5)
  - ✓ In patients with hormone receptor-negative disease (hazard ratio [HR] 1.2, 95% CI 0.3-4.7)

CONCLUSION

There has been outstanding advances in diagnosis and management of carcinoma breast over the last few decades in our country. Infiltrating duct cell carcinoma (NOS) type was the commonest type of carcinoma breast in our institute with significant group occurring in less than 45 years of age. Immunohistochemistry is used as a clinical tool as ER/PR and Her2 testing is widely available at a reasonable cost and serves as an informative classification of breast cancer based on immunophenotypes, and is prognostic as well as predictive. In this study an attempt was made to understand the correlation of ER, PR&HER-2 status with histopathological and clinicopathological parameters ER and PR positive expression was seen in grade 1 tumours and negative expression was seen with tumour size more than 2cm, positive lymph nodes and higher stage of disease. HER2/neu negative expression was seen in the post-menopausal age group, tumour size more than 2 cm, positive lymph nodes and higher stage of disease indicating bad prognosis. Triple negative cases were seen in 2% cases of infiltrating duct cell carcinoma indicating bad prognosis. In conclusion, ER, PR and HER-2 status correlates well with histopathological grading and other clinicopathological parameters. Presence of hormone receptors correlates well with response to hormone therapy. There is a significant decrease in mortality and tumour recurrences with hormone therapy. HER-2/neu has been found to be of significant because of its prognostic value since it can predict resistance to hormonal therapy. So, determination of ER, PR & HER2/neu status is essential in all cases irrespective of clinical staging and lymph node metastasis.

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