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Clinico-Pathological Characteristics of Breast Carcinoma in Young Patients-A Study from A Tertiary Institute

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ABSTRACT

Background: Breast cancer is the most common cancer among women world-wide. An early age onset with breast cancer is considered to be a woman younger than 40. Young age is an independent poor prognostic factor. This study aims at describing the histopathological and immunohistochemical features of invasive breast carcinoma in young women <40 years of age.

Methods: A total of 188 cases of invasive carcinoma breast were obtained from the pathology records of tertiary cancer hospital, south India, from January 2022 to January 2024. Of these 42 cases are < 40 years of age.

Result: A total of 42 cases of invasive carcinoma breast (22.3%) is in the <40 years age group. Tumor size is ≤2cm seen in 2.4%, 2-5cm in 57.1 % and >5cm in 40.5%of cases. 37 cases are Duct cell carcinoma NST, 1 lobular carcinoma, 4 with other types of invasive ductal carcinoma. multicentric in 18 cases (42.8%), 15 cases (35.7%) show lymph node metastasis. LVI seen in 12 cases (28.6%). 10 cases (25%) were triple negative (ER-, PR-, HER2/neu), 11 cases (26.1%) are HER2/neu positive, 24 (57.1%) were Luminal A (ER+ and PR+) and 21 (50 %) were Luminal B (ER+, PR+, HER2/neu +). Triple negative cases and only for HER2/neu positives are mostly grade III tumors. Ki 67 index is >25% seen predominantly in Her 2 Positive (72.7%) cases and in most of these tumors are in grade III (70.5%) and one tumor is in grade II (4.1%)

Conclusion: The main poor prognostic factors in <40 yrs with carcinoma breast are negative estrogen receptor status, multicentric position, higher histologic grade, triple-negative tumors, and higher Ki-67 index. In possible cases study of BRCA 1 germline mutation is necessary in patients with a family history of breast or ovarian carcinomas.

Key Words: *Young women, Invasive ductal carcinoma, Estrogen receptor (ER), progesterone receptor (PR), Her2/neu receptor and Ki 67 index.*

INTRODUCTION:-

Breast cancer is the most common cancer among women world-wide. As with most epithelial tumors, the incidence of breast cancer increases rapidly with age but It has been suggested that early age onset breast carcinomas may be different from those that occur in older women and early age is an independent poor prognostic factor and has a more aggressive disease subtype [(1,2)]. An early age onset with breast cancer is considered to be a woman younger than 40. Breast cancer in the young women usually is of a higher histologic grade, unfavorable hormonal status, higher risk of relapse and higher mortality rate when compared with breast cancer occurring in older populations.[(3)] This study aims at describing the histopathological and immunohistochemical features of invasive breast carcinoma in young women <40 years of age.

Materials and Methods:-

A total of 188 cases of invasive carcinoma breast were obtained from the pathology records of Great Eastern Medical School and Hospital, Srikakulam, India, from January 2016 to January 2020. Of these 188 reported cases of invasive carcinoma breast 42 cases are young females < 40 years of age. The patient's clinical details in comparison with clinical examination, mammogram and ulstrasonograms are studied. Lumpectomy and mastectomy specimens in a young patient (<40 years) with the diagnosis of carcinoma breast are included in the study. Clinico-pathological data were recorded for age, focality of the tumor, tumor size, tumor grade, lymph node status (LN), lympho-vascular invasion (LVI) of tumor and Hormone receptor status and Ki 67 index.

One to two paraffin blocks were available from each case. The tissue is fixed in buffered formalin was studied. The carcinomas of breast were classified and graded according to histologic classification of ovarian tumors by the World Health Organization (WHO).

These neoplasm's were studied using Estrogen Receptor (ER, monoclonal; DAKO, Denmark) ,Progesterone receptor concentrate(PR, monoclonal; DAKO, Denmark), c-erbB-2 Oncoprotein (polyclonal,HER2/Neu, DAKO), Ki-67 Antigen (Concentrate, monoclonal MIB-1;DAKO).

Four to five micron paraffin-embedded tissue sections taken on glass slides (Biogenex optiplusTM microscope slides) coated with 0.1% poly-D-lysine. The tissue sections were immunohistochemically stained using an avidin-biotin peroxidase complex (ABC) method. Antibodies are utilized at a dilution of 1:50 in buffer.

The sections were rehydrated by sequential immersion in xylene, graded concentrations of ethanol, and tap water. Slides were kept in a citrate buffer (pH 9) and two cycles of heat retrieval were done in the oven at 99ºC for ten and five minutes, respectively. Slides were washed in the Tris buffer (pH 7.8). All tissue sections were incubated with hydrogen peroxide for 10 minutes to eliminate endogenous peroxidase activity. Sections were washed thrice in Tris buffer, followed by 30 minutes incubation with primary antibodies. Secondary antibody (Dako REALTM EnvisionTM) was added after washing with the Tris buffer for 40 minutes. At the end, chromogen diaminobenzidine (DAB) was added for 10minutes, followed by counterstaining with hematoxylin for two minutes, sequential immersions in xylene and alcohol and mounting with distyrene plasticizer xylene (DPX).

To rule out instability of reagents, positive and negative controls were run simultaneously with the patient's specimen. If unexpected staining was observed, which cannot be explained by variations in laboratory procedures and a problem with the antibody was suspected, the test was discarded and a new test was performed again with a new kit.

Histopathological examination and immunohistochemical characterization were done by two pathologists, individually, to reduce observer bias. The scoring was performed by counting a minimum of 500 invasive tumor cells. Based on the intensity of color produced and proportion of cells stained ER,PR was scored (ALLRED scoring system- **Fig 1**) and The interpretation analysis for Her-2/neu was performed according to the American Society of Clinical Oncology/CAP guidelines (**Fig 2**) **[(4)].** Ki 67 was done in all cases. The immunohistochemical analysis of Ki-67 was conducted following recommendations from the International Ki-67 in Breast Cancer Working Group **[(5)].** A range of Ki-67 index values were then assigned to three groups (<10, 10-25 and ≥25%). Data were entered in SPSS version 21 and correlations were investigated using Chi-square and Fisher's exact test. A p-value of <0.05 was considered statistically significant.

Results:-

Clinico-Pathological Features of Breast Cancer:-

Of the 188 breast cancers that were investigated, 42 cases (22.3%) are in <40 years age group.

In the present study out of 42 cases, 28 (66.7%) are mastectomy specimens and 14(33.3%) are lumpectomy specimens. Tumor size is ≤2cm seen in 1 (2.4%) case, 2-5cm in 24 (57.1 %) cases and 17 (40.5%) cases show >5cm. Histologically, 37 cases (88%) are Duct cell carcinoma NST, 1 case (2.3%) of lobular carcinoma, 4 cases(9.5%) are other types of Ductal carcinoma, which includes one case each of invasive carcinoma NST with medullary features, encapsulated papillary carcinoma, metaplastic carcinoma and mucinous carcinoma. Examination of lymph nodes resected during mastectomy showed that 15 cases (35.7%) tumors with metastasis. LVI seen in 12 cases (28.6%). Neoadjuvant therapy was taken in 8 cases (19%) **(Table 1)**

Hormone receptor status in Breast cancer:-

Of the 42 invasive carcinoma breast that we investigated, a total of 10/42 (25%) were triple negative (ER-, PR-, HER2/neu), 11/42 (15%) showed only HER2/neu expression, 24/42 (57.1%) were Luminal A (ER+ and PR+) and 21/42 (50 %) were Luminal B (ER+, PR+, HER2/neu +). Triple negative cases and only for HER2/neu positive cases are mostly grade III tumors. **(Table 2)**

Of these 42 breast carcinomas in young adults most of the estrogen and progesterone positive tumors show Ki 67 index <10% seen in 76% of cases. Ki 67 index is >25% seen predominantly in Her 2 Positive (72.7%) cases and in most of these tumors are grade III(70.5%) and one tumor is grade II(4.1%) (**Table 3)**

Table 1 -clinico pathological characteristics in 42 young patient <40 years age diagnosed with invasive carcinoma Breast

Parameter	Number (%) (n=42)
1.SIZE OF THE TUMOUR	
<2 cms	21(50%)
2-5 cms	18 (42.8%)
>5 cms	03 (7.14%)

2.GRADE OF THE TUMOUR	
Grade 1	01(2.4%)
Grade 2	24(57.1%)
Grade 3	17(40.5%)
3.HISTOLOGICAL TYPE	
Ductal	37(88%)
Lobular	1(2.3%)
Others	4(9.5%)
4. MULTIFOCALITY OF TUMOUR	18 (42.8%)
5.POSITIVE LYMPH NODES	15(35.7%)
6.LYMPHOVASCULAR INVASION	12(28.6%)
7.NEOADJUVANT THERAPY	8(19%)
8.SURGERY TYPE	
Mastectomy	28(66.7%)
Lumpectomy	14(33.3%)

Table 2 - Correlation of Receptor status (ER, PR, HER2/NEU) in different grades of Breast Carcinoma.

GRADE OF THE TUMOUR	Grade - 1	Grade - 2	Grade - 3	p-value
ER Positive	1/1(100%)	18/24(75%)	06/17(29.4%)	
PR Positive	1/1(100%)	17/24(70.8%)	06/17(29.4%)	
HER2/NEU Positive	0/1	02/24(8.3%)	09/17(64.7%)	
p-value				

Table 3 - Correlation of Ki 67 index with hormone receptor positivity and grade of the tumour.

Ki 67 Index	ER Positive (n=25)	PR positive (n=24)	Her -2 positive (n=11)	Grade 1 (n=01)	Grade 2 (n=24)	Grade 3 (n=17)
<10%	19/25 (76%)	19/24 (76%)	02/11 (18.1%)	01/01	19/24 (79.1%)	00/17
10-25%	06/25 (24%)	05/24 (20.8%)	01/11 (9%)	00/01	04/24 (16.7%)	05/17 (29.4%)
>25%	00/25	00/24	08/11 (72.7%)	00/01	01/24 (4.1%)	12/17 (70.5%)
p-value						

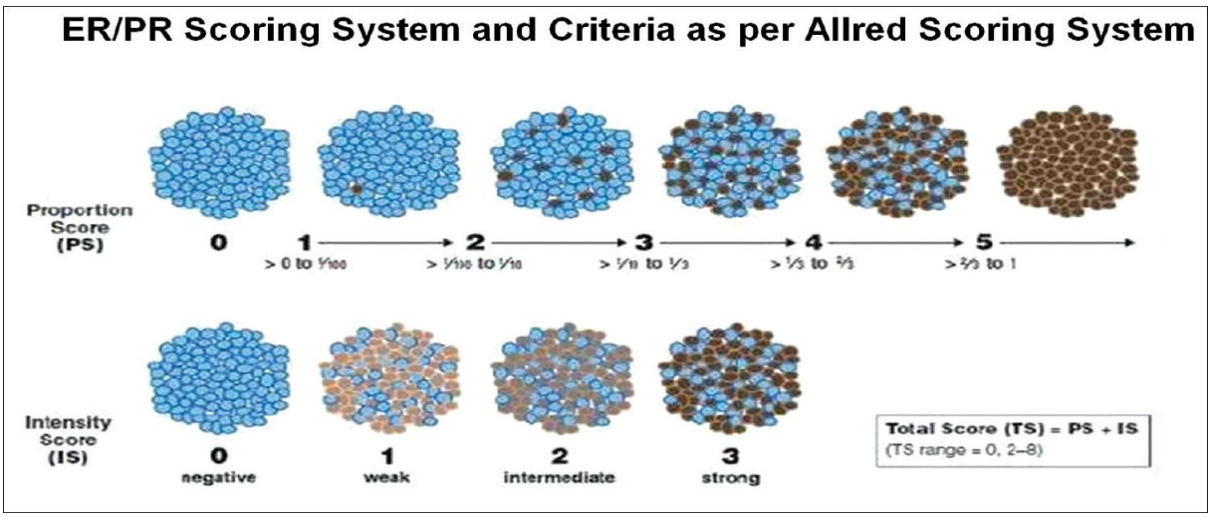


Fig-1 - show Allred scoring system for hormone receptor status

Score	Interpretation
0	No staining
1+	Weak, incomplete membranous staining in any proportion of tumor cells
2+	Complete membrane staining that is either no uniform or weak in intensity but with obvious circumferential distribution in at least 10% of cells
3+	Uniform intense membrane staining of at least 10% of invasive tumor cells

Fig 2 - show interpretation of Her 2 Receptor Membrane positivity in IHC according to the American Society of Clinical Oncology/CAP guidelines

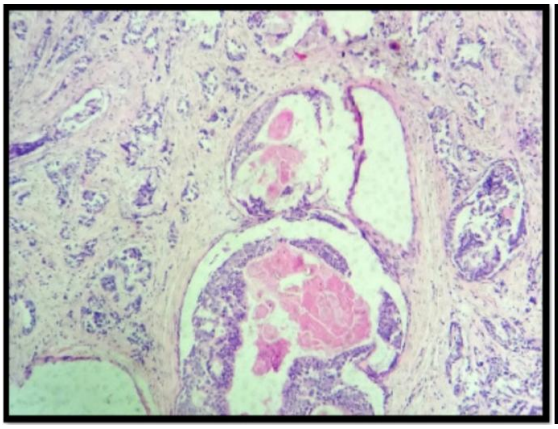


Fig 3 - IDC grade II with DCIS (H&E 100x).

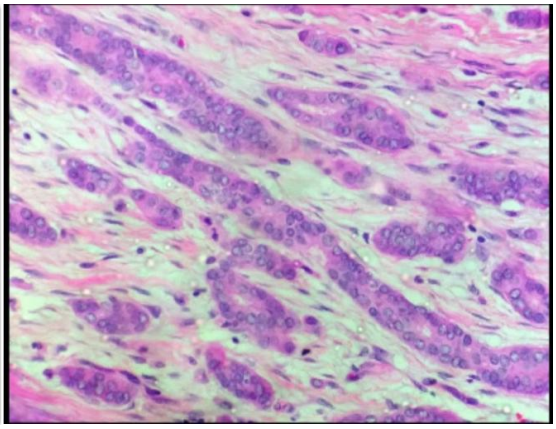


Fig 4 - IDC grade II (H&E 400x).

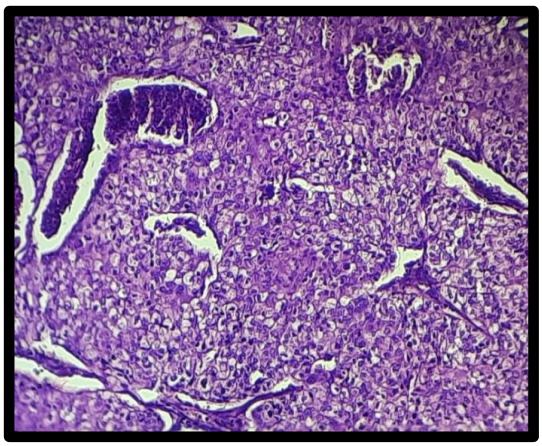


Fig 5 - IDC grade III with medullary features (400x).

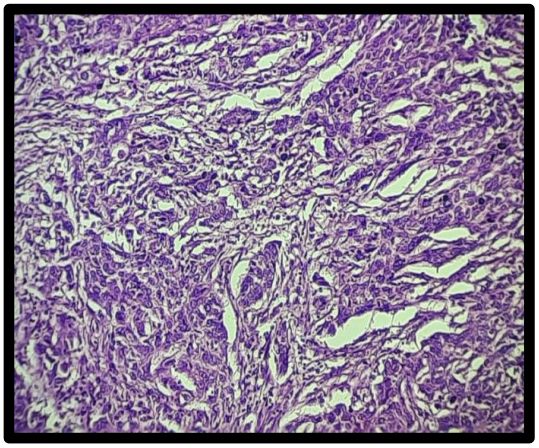
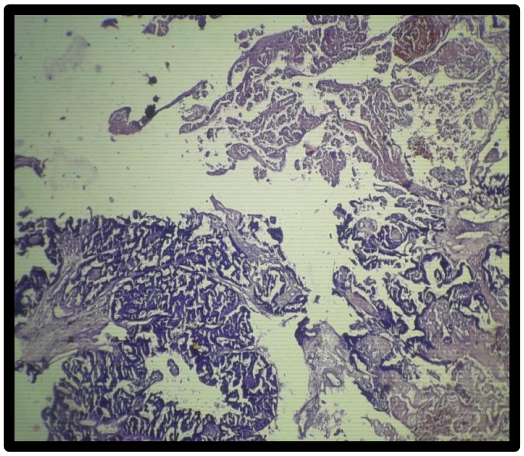


Fig 6 - IDC Grade III(100x)



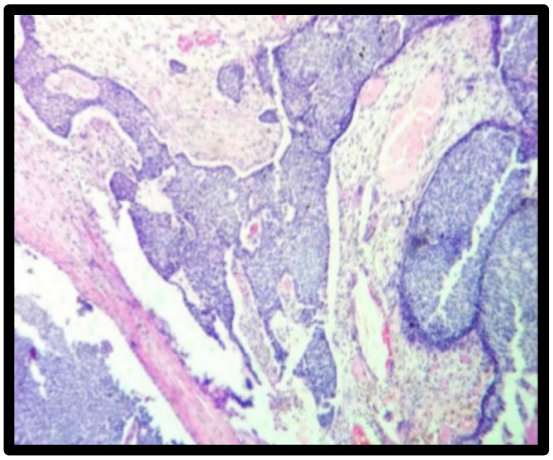
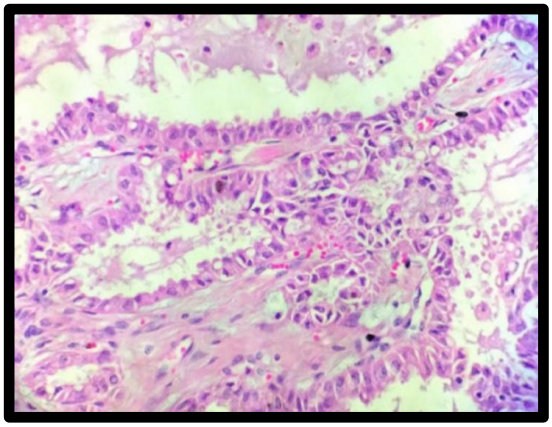


Fig 7-Encapsulated papillary carcinoma breast (100x).
Fig 8 - Encapsulated papillary carcinoma breast (400x).



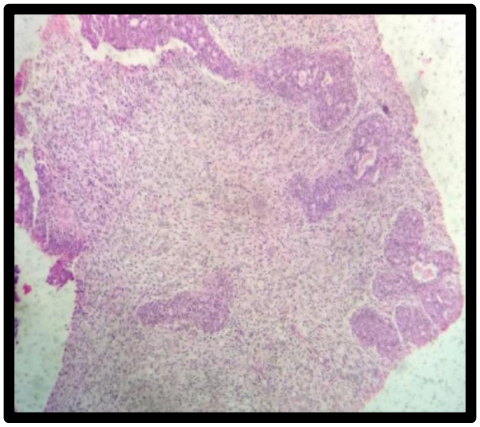
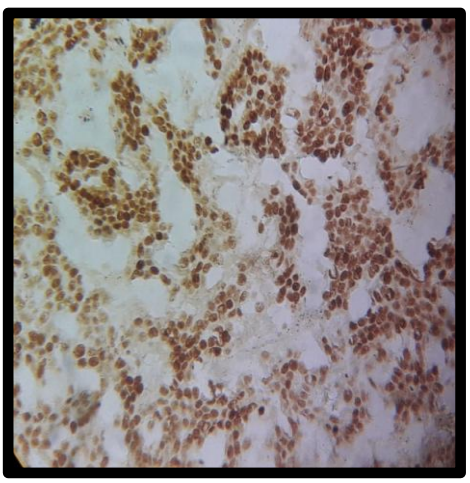


Fig 9-Mucinous carcinoma breast (400x). **Fig 10- Metaplastic carcinoma breast (100x).**



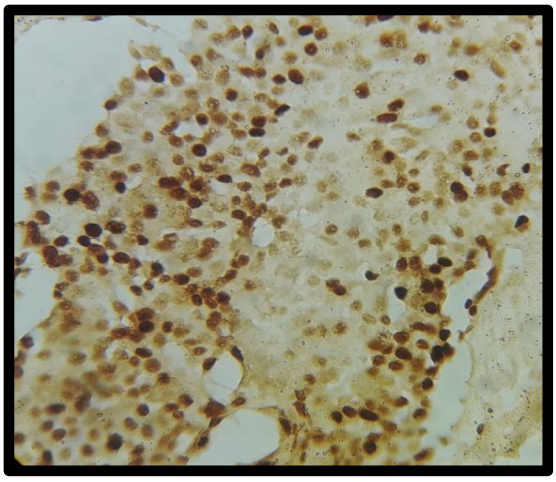
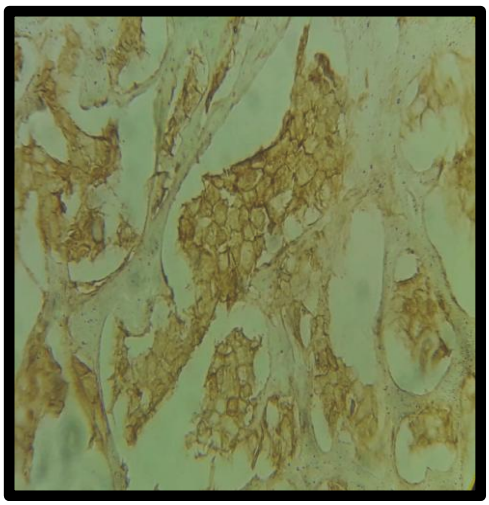


Fig 11, 12 -Hormone receptor with ER,PR -Positive (400x) in grade II tumor



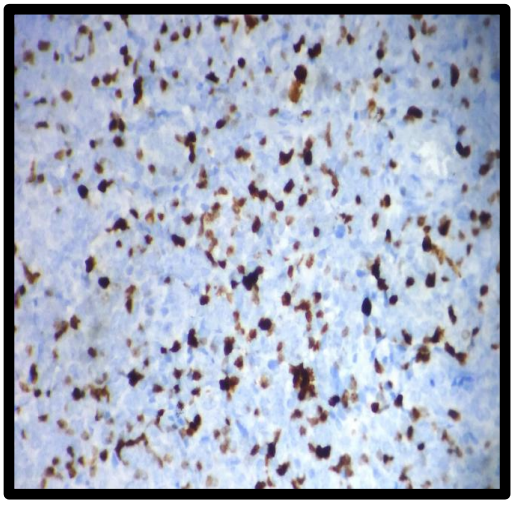


Fig 13 - Her 2 membranous positive(400x) in grade III tumor

Fig - Ki 67 index >25% (400x) in grade III tumor

DISCUSSION-

In developed countries, 5%-7% of all patients with breast cancer are younger than 40 years of age [(2)]. Early age breast cancer is considered to be different from older patients. Early age breast carcinoma has a more aggressive biologic behavior, higher tumor grade with more vascular invasion than found in older women [(6)]. In young patients, the disease has worse prognosis in terms of overall survival and disease recurrence [(7)]**.** Some studies found that young age as an independent factor of poor disease prognosis [(8,9)] .The Early age (≤40 years), type of tumor, tumor size ,Grade III, LVI, negative Hormone Receptor ,HER-2 positivity are poor prognostic factors associated with high expression levels of Ki-67.[(10)]

The present study was done in young patients (<40) diagnosed with carcinoma breast. Invasive ductal carcinoma was the most frequent histologic type of tumor(88%)(Fig 3,4,6), 4 cases (9.5%) are other types of Ductal carcinoma, which includes one case each of invasive carcinoma NST with medullary features (Fig 5), encapsulated papillary carcinoma (Fig 7,8), metaplastic carcinoma (Fig 10) and mucinous carcinoma (Fig 9),1 case (2.3%) of lobular carcinoma. Similar to other studies, invasive ductal carcinoma is one of the most frequent cancers in general and among women under 40 years of age [11, 12]. The tumor is multifocal in 42.8% of cases and mastectomy was done in these cases, tumor size <2cm found in 50% cases, Lymph Node metastasis is found in 15 cases (35.7%) and LVI is found in 12 cases(28.6%) in contrast to the study done by Gajdos C,et al and they found that younger patients had larger tumors with more nodal involvement [13] . but the results were on par with the study done by Colleoni et al.[14] and Ivan Eric et al [15], Multicentric tumors being recognized as highly significant predictors of reduced survival, increased local relapse, and distant metastases. With adjuvant chemoradiotherapy, there is no difference in survival between mastectomy and breast-sparing resection like lumpectomy [16]

In this study one case is reported as grade I tumor, which is positive for estrogen and progesterone receptors.

This study has found that most of the grade II tumors are estrogen and progesterone receptor positive in 75% and 70.8% respectively (Fig 11,12) . 8.3% patients are Her 2 positive. Histology shows grade II followed by grade III was significantly more frequent in the group of young patients. Similar results are found in the study by Gnerlich et al. [17]

In the present study Grade III tumors found positive estrogen and progesterone receptor status in 29.4% cases, but Her2 positivity seen in 64.7% cases (Fig 13). These characteristics are usually associated with more aggressive behavior, poorer prognosis, and linked with Her2/neu overexpression. Her2/neu overexpression has been reported in tumors developing at a younger age and considered to be part of aggressive immunophenotype in breast cancer, especially with lymph node metastases [18]. Anders et al. found that Her2/neu status did not prove to be an independent factor of poor prognosis in young patients with cancer [19]. We found triple-negative tumors (25%) in the YW group. Triple-negative tumors were overrepresented among young women with breast cancer with a rate of 25% study by munzone et al [20]. The possible mechanism being these carcinomas, particularly in younger women, are supposed to be associated with BRCA 1 germline mutations and represent the most aggressive phenotype that is linked to poor prognosis [21]. In our study Ki 67 index of >25% found in 72% of Her2 positive cases(Fig 14) , most of them are grade III (70%) cases, which is a high value pointing to poor prognosis of the disease. Many studies have suggested that Ki-67 is a predictive factor of the disease outcome in hormone positive tumors [22]. Ki-67 index predicts the response to chemotherapeutic treatment and with disease prognosis in hormone negative patient groups [23].

Conclusion:-

In general 5%-7% of all patients with breast cancer are younger than 40 years of age. The main poor prognostic factors are negative Hormone receptor status, multicentric position, higher histologic grade, triple-negative tumors, and higher Ki-67 index. These are the key factors for aggressive disease with increased probability of poor disease-free survival. In possible cases study of BRCA 1 germline mutation is necessary in patients with a family history of breast or ovarian carcinomas.

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To the Editors,
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