Original Research Article

Breast carcinoma histopathological correlation with molecular classification: A comparative study

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A B S T R A C T

Background: Breast cancer is the most common malignancy in females. It isroutinely classified according to the WHO classification. However, molecular classification can be more powerful than histopathology as a predictive factor for the different treatment strategies.

Aims: This study gives an insight to overall prognosis, role of molecular markers, various molecular subtypes and better categorization of triple negative breast cancer cases.

Setting and Design: This was a cross sectional study conducted in the department of pathology over a period of 2 years.

Material and Methods: In this study, 500 cases of breast carcinoma were included. Molecular phenotype was determined using expression of estrogen receptor, progesterone receptor, HER2/neu, Ki67, epithelial growth factor receptor (EGFR), and cytokeratin 5/6.

Statistical Analysis Used: Correlation of molecular subtypes with histological grade, prognostic and predictive factors done by using chi square test. Using software Medcalc version 12.2.1.0.

Results: Of the 500 cases, maximum number of cases 38.20% were luminal A. Most common histological subtype in all category were Infiltrating duct carcinoma (Not Otherwise Specified) {IDC (NOS)} with higher grade of IDC (NOS) in her2neu and basal type. Unclassified category includes both low grade tumors and high grade tumors. Statistically significant association of molecular subtype was found with histological subtype, tumor necrosis, lymphocytic response and lymphovascular invasion. (P ≤ 0.001)

Conclusion: Molecular classification would result in less frequent use of chemotherapy in breast carcinoma and have its considerable advantages in reducing toxicity and costs.

Key message: In view of increasing awareness, younger age of presentation and occasional family history various screening program should be popularized.

1. Introduction

Worldwide breast cancer is the most common cancer diagnosed in women.[1] Various published reports from different cancer registries in India indicate rising trends in breast cancer incidence.[2]

Majority (approx. 80%) of breast cancer are categorized as Infiltrating Duct Carcinoma, not otherwise specified, but their behaviour is not uniform.[3]

In this context currently attempt is made for molecular classification of breast cancer. This is primarily based on gene profile. Molecular classification can be more powerful than histopathology as a predictive factor for the different treatment strategies. This would results in less frequent use of chemotherapy, so reduces toxicity and costs.[4]

An effort has been made with the use of panel including antibodies to ER, PR, Her2neu, Ki67, CK 5/6 and EGFR to classify breast cancer into various molecular subtypes.

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2. Materials and Methods

The present study was conducted after obtaining ethical approval from ethical review committee.

This was cross sectional study of breast carcinoma cases during the period from January 2013 to Jan 2015, in the Department of Pathology. 500 numbers of patients of primary breast cancer were evaluated, during this period.

A detailed history regarding age, sex, parity, family history, menstrual history, lactation history, mammography, metastatic workup were reviewed in all cases. For metastatic workup bone scan, chest X-Ray and Ultra- sonography abdomen of patients were taken under consideration.

In present study we received three types of sample. Trucut biopsy were received in bouin's fluid fixed for 6-8 hrs and processed. Mastectomy and Breast Conservative Surgery specimens received were properly sliced and fixed in 10% formalin for 18-20 hours. Detailed gross examination was done. The tissue sections stained with H&E and detailed histopathological examination was done as per CAP protocol. Sections from tumor were subjected for Immunohistochemistry (IHC) staining.

2.1. Immunohistochemistry (IHC)

ER, PR and Her2neu in all 500 cases, Ki67 in 266 selected cases, EGFR and CK 5/6 in 176 selected cases.

The clone of antibody used for ER was SP-1 mouse species, PR was SP-2 mouse species, Her2neu was EP-3 mouse species, EGFR was EP 38Y rabbit species, CK5/6 was D5/16B4 mouse species and for Ki67 was MIB-1 mouse species.

2.2. ER/PR reporting

Nuclear positivity was assessed in tumor cells and percentage of tumor cells showing positivity, Staining intensity (graded as 1+ = weak staining, 2+ = moderate staining and 3+ as strong staining) were noted (Figures 1 and 2).

Her2neu reporting was done according to Hercep test guidelines (Figure 3).[5]

Correlation of ER/PR with Her2neu done by using ch isquare test. Using software Medcalc version 12.2.1.0.

2.3. Ki67 Labeling Index

The percentage of positive nuclei was expressed as a "Ki-67 labeling index" which is the percent of cells expressing Ki-67 determined by counting 1000 cells/slide. Ki67 index of 14% or more positive tumor nuclei taken as cut off point (Figure 4).

2.4. EGFR reporting

Positive staining was defined as positive membrane staining, and was scored according to the criteria originally developed for HER2neu as negative, 1+, 2+ and 3+, using 10% staining of tumor cells as the cut off point (Figure 5). [6]

CK5/6 Reporting: Positive staining was defined as cytoplasmic staining with perinuclear enhancement. A staining intensity index was used, defined as the product of staining intensity (0-3) and proportion of immunoreactive cells (less than 10% =1, 10-50% = 2, more than 50% = 3) (Figure 6).

Specimens with staining indices 1-9 were defined as positive, those with a staining index of 0 were defined as negative. [7]
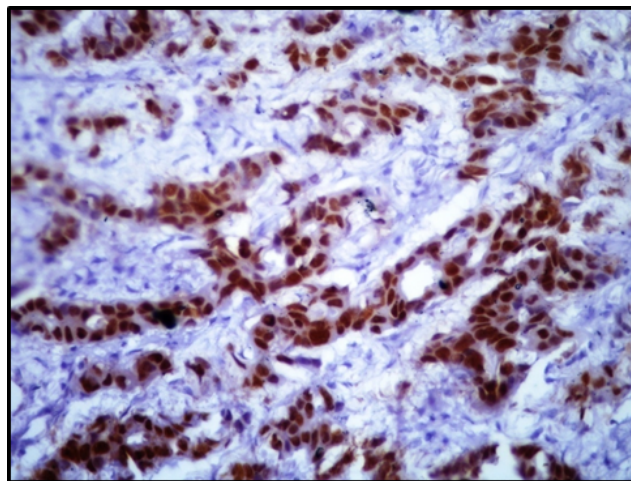

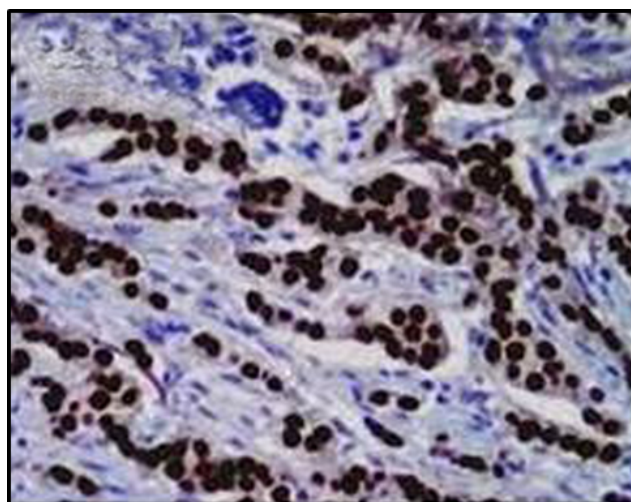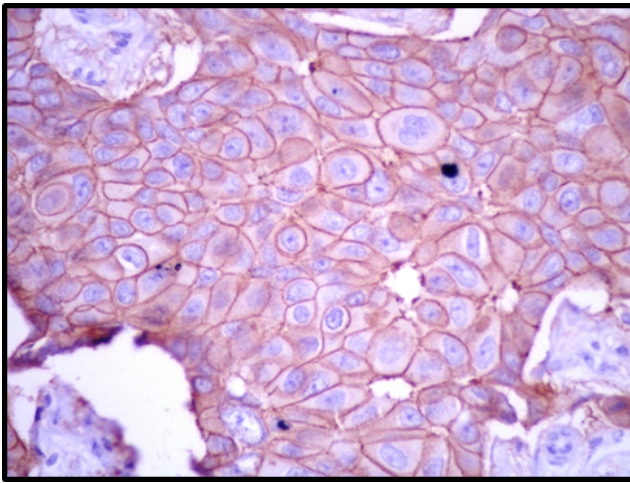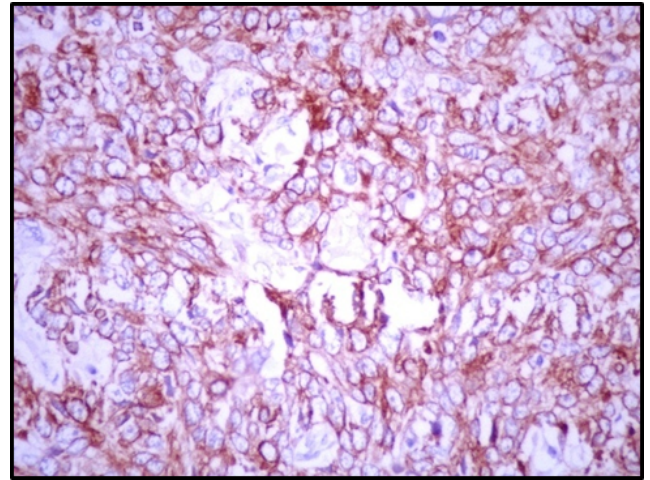**Fig. 1:** IDC (NOS) MD 40x showing ER positivity

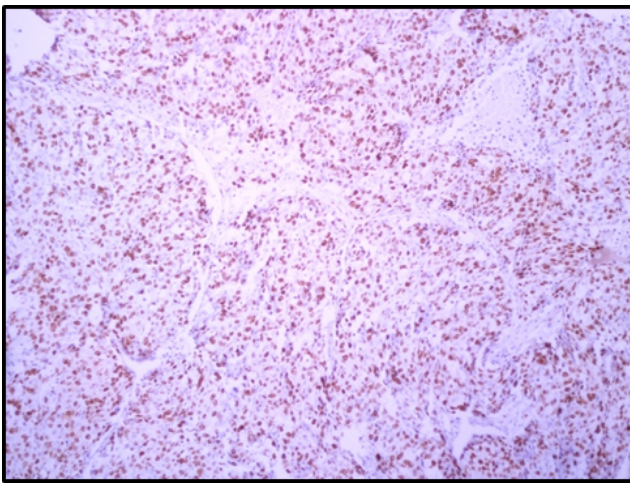**Fig. 2:** Invasive lobular carcinoma showing PR positivity 40x

2.5. Statistics

Correlation of molecular subtypes with histological grade, prognostic and predictive factors done by using chi square test, using software Medcalc version 12.2.
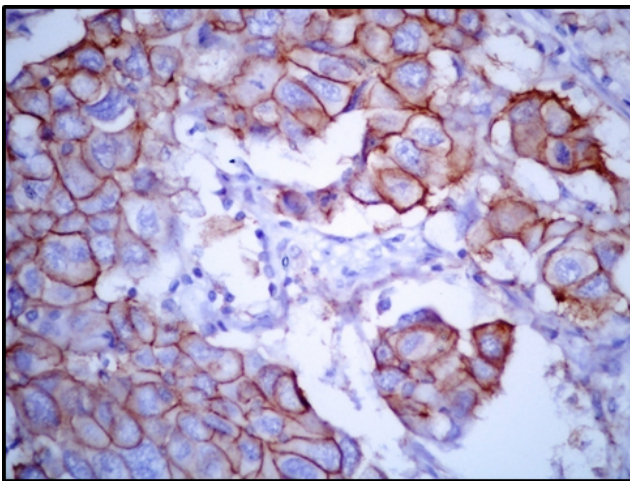
Fig. 3: Her2neu (3+) 40x

Fig. 4: Ki67 index >14%

Fig. 5: EGFR positivity 40x

Fig. 6: CK 5/6 positivity 10x

3. Results

Commonest histological subtype is IDC (NOS) grade II followed by lobular carcinoma. Coexisting intraductal component with IDC was seen in 22.26%. Necrosis was found in 46.15% of cases. Lymhovascular invasion was found in 32.36% of cases. Perineurial invasion seen in 6.10% of cases. Lymph node metastasis was found in 55.23% of cases.

Incidence of ER, PR positivity in study population was 40.20% and 40.40% respectively. Her2neu over expression was seen in 21.80%. Triple negative cases constituted 35% of total cases.

Lobular, mucinous and tubular tends to be ER/PR positive and medullary, metaplastic and adenoid cystic carcinoma tends to be triple negative. Intraductal carcinoma tends to be Her2neu positive.

Molecular classification based on ER, PR, Her2neu, Ki67 Index, EGFR and CK5/6, 38.20% cases were luminal A followed by unclassified type 18.20%. Basal like 17%, Her2neu type 14.80% and luminal B 11.80% cases. Commonest molecular class was Luminal A.

Most common histological subtype in luminal A category was infiltrating duct carcinoma (grade II) followed by invasive lobular carcinoma. In Her2Neu category majority of cases were IDC Grade II and III followed by intraductal carcinoma. Most common histological subtype in basal category was infiltrating duct carcinoma(grade III and II) followed by medullary and metaplastic carcinoma. Unclassified category includes both low grade and high grade tumors (Table 1).

Ki67 was low <14% in Luminal A and >14% in Luminal B. EGFR / CK5/6 positivity was found in basal like and few cases of Her2neu type.

Statistically significant association of molecular subtype was found with histological subtype, tumor necrosis,

Table 1: Percentage of various histological subtypes in each molecular class

Histologic Subtype	Luminal A	Luminal B	Her2neu Type	Basal Like	Unclassified
IDC	78.01%	96.61%	85.13%	84.69%	91.20%
Lobular	11.52%	1.69%	0.00%	0.00%	4.40%
Intraductal	1.05%	0.00%	8.11%	0.00%	1.10%
Tubular	4.71%	0.00%	0.00%	0.00%	0.00%
Papillary	1.05%	0.00%	1.35%	0.00%	0.00%
Mucinous	2.09%	1.69%	1. 35%	0.00%	0.00%
Medullary	0.00%	0.00%	2.71%	8.24%	1.10%
Metaplastic	0.00%	0.00%	0.00%	3.53%	0.00%
Others	1.57%	.01%	1.35%	3.54%	2.20%

lymphocytic response and lymphovascular invasion.

4. Discussion

In this study WHO classification was followed. Percentage of various histological subtypes was as follows - IDC (NOS) 84.80%, invasive lobular carcinoma 5.40%, medullary carcinoma 2%, tubular carcinoma and Intraductal carcinoma 1.80% each, invasive mixed lobular and duct carcinoma 1% each, mucinous carcinoma 1.20%, metaplastic carcinoma and invasive papillary carcinoma 0.60% each, invasive micropapillary carcinoma, sebaceous carcinoma and adenoid cystic carcinoma 0.20% each. Incidence of various histologic types were comparable with various studies done by Saxena et al.,[8] Omar Hameed et al.[9] and Dixon JM.[10]

In 316 cases of IDC histological grade was assessed by RB score, 90 cases (28.48%) of grade I (RB score 3-5), 181 case (57.29%) were of grade II (RB score 6-7), and 45 cases (14.23%) were of grade III (RB score 7-8). HL Kishan Prasad et al.[11] demonstrated 44.4% cases of grade I tumors, 39.7% cases of grade II tumors and 15.9% cases of grade III tumors.

IHC profile included ER, PR, Her2neu, Ki67 index, EGFR and CK5/6.

In our study ER positivity was in 40.20% cases and PR positivity was in 40.40% cases. The cases with both ER and PR positivity were 30.40%, only ER positive were 9.80% and only PR positive were 10% cases. HL Kishan Prasad et al.[11] have reported ER positivity in 36.5% cases and PR positivity in 31.7% cases. The result of study are comparable with this study. Ghosh et al.[12] studied receptor status in 2001 cases of breast cancer. ER and/ or PR expression was positive in 51% of cases. Shet et al.[13] from TMH institution documented both ER and PR positivity in 41.8% only ER positivity in 7% cases and only PR positivity in 3.4% of cases. Desai et al.[14] have reported the estrogen, progesterone status of breast carcinoma in India. There receptor status was determined by IHC in 798 tumors out of which 32.6% were ER positive and 46.1% were PR positive. Thus incidence of hormone receptor non reactivity in breast carcinoma in India is high. Till date, no definite

explanation of low ER/PR positivity in Indian population can be ascertain. The results of our study was comparable with studies in Asia population.

Payne et al.[15] stated that PR may be detected in cases that appear ER negative, which may be due to false negative ER assay, very low levels of ER or to variants of ER not recognized by the antibody but still capable of stimulating PR expression. The predictive value of PR positivity in the absence of ER is controversial, with some reports suggesting that positive PR, even in the absence of ER, identifies a patient group more responsive to hormonal therapy, but this finding is not universal.

Possible reason for low expression of ER/PR in our study population can be younger age of presentation as compare to western world. As tumor associated with younger age tends to be ER/PR negative. Pre-analytic factors such as prolonged ischemic time, prolonged fixation also affects the positivity.

Review blocks which were processed outside in rural area may have prolonged ischemic time and improper processing responsible for receptor negativity.

According to ASCO/CAP guidelines over 1% immune reactive cells of tumor cell are considered positive these can be missed during assessment of ER/PR evaluation as they are not computer assisted reporting.

In present study Her2neu was assessed by IHC is in all 500 cases. On IHC Her2neu was positive (3+) in 21.80% of cases, equivocal in 9.20% of cases and negative in (0 or 1+) in 69% of cases. In this study equivocal results were also considered negative. Results of our study was also comparable with Lal et al.[16] and Muddawa et al.[17] studies.

In our study triple negativity observed in 35% of cases. Triple positivity observed in 20 cases (4.00%). Megha et al.[18] observed triple negativity in 36% of cases in study conducted at Karad, India. Kakarala M et al.[19] studied breast cancer histology and receptors status characterization in Asia (Indians/Pakistani) women in US. They observed that ER/PR negativity was higher in Asia women as compare to Caucasias.

Thus the results of our study are comparable with results of study conducted by Kakarala et al.[19] and Megha et al.[18]

We studied inverse relationship between ER and PR with Her2neu expression. ER and PR expression was decreased significantly in Her2neu positive tumors as compared to Her2neu negative tumors. This association was statistically significant for both ER and PR (P value <0.05) same as Lal et al.[16] studies.

Hormone receptor positivity was also correlated with histological subtypes. In our study ER/PR positivity for IDC (NOS) was 36.36% and 33.64% respectively and Her2neu positivity was 27.27%. Lobular carcinoma accounts 5.40% of total cases. ER and PR positivity was 74.07% and 81.48% respectively. ER/PR positivity was more as compared to IDC (NOS).

Garau et al.[20] conducted a study of 975 cases of invasive lobular carcinoma also observed high ER and PR positive expression 83% and 69% respectively. Findings of our study correlated with studies of Garau et al.[20] and Cristafanill et al.[21]

All cases of tubular carcinoma had ER positivity and 77.78% cases had PR positivity and had negative expression for Her2neu. In mucinous carcinoma ER/PR expression was observed in 83.33% and Her2neu expression was observed in 16.67%. All medullary carcinoma were triple negative. Diab et al.[22] also observed high rate of ER/PR positivity in 91% and 92% of cases in tubular and mucinous carcinoma. Intraductal carcinoma observed in 9 cases (1.8%) with ER and PR positivity in 22.22% and 11.11% respectively and Her2neu expression was observed in 66.67%.

Desai et al.[14] also described that lobular carcinoma and mucinous carcinoma are more frequently ER/PR positive where as high grade IDC(NOS), ductal carcinoma in situ and medullary carcinoma were predominantly ER and PR negative. Results of our study were comparable with studies of Diab et al. and Desai et al.[14]

In 66.67% cases of metaplastic carcinoma showed no lymph node involvement, all were triple negative and showed positivity for EGFR and CK5/6. Yanni Song et al.[23] studied cases of 55 patients with metaplastic breast carcinoma presenting between 1991 and 2006 and compared to the cases of 767 age-matched patients with invasive ductal carcinoma from the same time period, observed that metaplastic breast carcinoma presented with a higher percentage of triple-negative cases, compared with the group of patients with invasive ductal carcinoma and triple-negative invasive ductal carcinomas. D. Rayson et al.[24] studied 27 patients with metaplastic carcinoma and 23 patients had information available on nodal, ER and PR status. Twenty patients (87%) were node negative and ER/PR negative.

In 66.67% cases of Invasive papillary carcinoma ER/PR positivity seen and Her2neu over expression seen in 33.33% of case.

All other histological variants were triple negative.

Tumors classified as ER positive and HER2 negative by IHC would include a mixture of luminal A and luminal B subtypes that might be distinguished by Ki67 index.

Out of 266 cases 191 cases showed ki67 index <14% and were ER and/ or PR positive, classified as luminal A and 59 cases showed Ki67 index >14%, out of these 59 cases 34 cases were ER+/PR+/Her2neu+ and remaining 25 cases were only ER and/or PR positive. Remaining 16 cases randomly selected from Her2neu, basal like and unclassified category. All showed Ki67 index >14%. In Luminal A out of 191 cases ER+ and PR+ were 62.83%, ER+ and PR - were 19.90%, and ER - and PR + were 17.28%. All cases were Her2neu negative. In Luminal B out of 59 cases ER+ and PR+ cases were 50.85%, ER+ and PR - were 18.64%, and ER - and PR+ were 30.50%. Her2neu positivity was 57.62% of all cases.

In Her2neu Type all 74 cases showed Her2neu positivity and negative for ER and PR.

Remaining 176 cases were triple negative. Out of 176 triple negative cases, 85 cases showed EGFR and/or CK5/6 positivity and remaining 91 cases were EGFR and CK5/6 negative termed as unclassified type. All Luminal A (5 cases) and Luminal B (8 cases) cases were EGFR and CK5/6 negative.

Dalal M. AL Tamimi (2010)[25] studied 231 patients, luminal A cases were 3.9%, Luminal B were 16%. Our findings were more similar to Maggie CV Cheang et al.[26] who found 38.2% cases of luminal A and 19%, 28% & 17% of luminal B, basal like and Her2neu respectively. But the results differ from other studies like Xiaohong R. Yang et al.[27]

In Her2neu type, 2 cases showed EGFR and CK5/6 positivity and remaining 3 cases were both EGFR and CK5/6 negative. Bhargava R et al.[28] showed CK5/6 and EGFR immunoreactivity in Her2neu tumors with apocrine differentiation.

Histological subtyping was done in all five molecular categories (Table 1). Our results were similar to study done by Danae Pracella et al.[29] Dezheng Huo et al.[30] and Xiaohong R. Yang et al.[27]

In Basal Like category 85 cases were included, most common histological type observed was IDC (NOS) in 83.51%, maximum with Grade II and III followed by medullary carcinoma in 8.24% and metaplastic carcinoma in 3.53% of all cases. Adenoid cystic carcinoma, high grade spindle cell carcinoma and invasive mixed lobular and duct carcinoma seen in 1.18% of cases each. Our results were similar to study done by Dezheng Huo et al.[30] and Danae Pracella et al.[29]

In Unclassified type out of total 91 cases, 91.40% cases were of IDC (NOS), maximum with Grade II followed by 4.40% cases of invasive lobular carcinoma. Intraductal carcinoma, medullary carcinoma, micropapillary carcinoma and sebaceous carcinoma was 1.10% each. Dezheng Huo et

al.,[30] observed 83% cases of IDC type in which maximum cases were of grade II followed by 8% of Metaplastic carcinoma in unclassified category.

Correlation of various prognostic factors were studied with molecular subtypes.

Statistically significant association of molecular subtypes was found with histological subtype, lymphocytic response, tumor necrosis, lymphovascular invasion. (P value ≤ 0.001)

No statistically significant association of age, tumor size, lymph node status and desmoplasia with molecular subtypes was found (P value ≥ 0.001). Review of literature reveals variable association of various prognostic factors with molecular subtypes.

In study done by Danae Pracella et al.[29] found significant associations between molecular subtypes and age at diagnosis, histological type, tumor grade, lymph node involvement, tumor stage. Dezheng Huo et al.[30] observed, no significant association of molecular subtype with tumor size and age.

5. Conclusion

In present study total 500 cases were studied. Commonest molecular class was Luminal A. 38.20% cases were luminal A followed by unclassified type 18.20%. Basal like 17%, Her2neu type 14.80% and luminal B 11.80% cases.

Most common histological subtype in luminal A category was infiltrating duct carcinoma (grade II) followed by invasive lobular carcinoma. In Her2Neu category majority of cases were IDC Grade II and III followed by Intraductal carcinoma. Most common histological subtype in basal category was infiltrating duct carcinoma (grade III and II) followed by medullary and metaplastic carcinoma. Unclassified category includes both low grade and high grade tumors.

Low grade tumors tends to be more ER/PR positive and high grade tumors tend to be ER/PR negative. Lobular, mucinous and tubular tends to be ER/PR positive and medullary, metaplastic and adenoid cystic carcinoma tends to be triple negative. Intraductal carcinoma tends to be Her2neu positive. Ki67 was low <14% in Luminal A and >14% in Luminal B. EGFR / CK5/6 positivity was found in Basal Like and few cases of Her2neu Type.

Statistically significant association of molecular subtype was found with histological subtype, tumor necrosis, lymphocytic response and lymphovascular invasion.

6. Recommendation

1. In view of increasing awareness, younger age of presentation and occasional family history various screening program should be popularized.
2. Histological classification along with various prognostic factors still remains the gold standard for reporting particularly in developing countries like India. ER PR and Her2neu should be included in every histopathological report.
3. Equivocal results of Her2neu should be confirmed by FISH.
4. To optimize result of IHC, pre-analytic variable should be strictly controlled.
5. Molecular classification needs further evaluation particularly in relation to histological subtypes and various prognostic factors, for it to be established as standard classification.

7. Source of Funding

None.

8. Conflict of Interest

None.

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