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Original Research Article

Incidence of Molecular Subtypes in Breast Cancer & its Association with Axillary Nodal Involvement

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Abstract:

Immuno-histochemical staining is used as a surrogate marker instead of gene expression analysis for classification of Breast Cancer Subtypes(BCS) and depending on these subtypes treatment is planned . Data correlating BCS & axillary nodal involvement is limited.

Objective: To know the distribution pattern of Breast Cancer Subtypes and to find the correlation between Breast Cancer Subtypes & axillary nodal involvement and other clinicopathological features.

Methodology: All breast cancer patients who underwent primary breast surgery (MRM or BCS) in the Surgical Oncology Department at Amrita Institute of Medical Sciences, Kochi (Kerala) from October, 2010 to march, 2013 were included in the study. As per institutional protocol all the specimens were submitted for histopathological examination & immunohistochemical staining which included ER, PR, HER-2/neu and Ki-67. Tumors with 1% or more positively nuclear-stained cells were considered positive for ER and PR expression. Cut-off value of nuclear Ki-67 expression was set at ki-67=<14% as low & with ki-67 = >14 as high. HER2 results were considered positive in cases with 3+ membranous staining of IHC or gene amplification by fluorescence in-situ hybridization (FISH).

Results: The study cohort consisted of 503 patients(luminal A= 21.5%; luminal B= 46.5%; Triple negative=19.3% & Her2Type=12.7%) of which 270 patients(53.8%) were node positive. Significant association (P value= 0.001) was noted between luminal B type and nodal positivity where as significant association (P value= 0.028) was also noted between luminal A type and Triple negative with nodal negativity.

Conclusions: Most common molecular subtype found in our study was luminal B followed by luminal A, triple negative and HER2 type in the descending order. Nodal involvement was found more with luminal B and less with Luminal A & Triple negative. Node negative cancers are more associated with low ki-67 & node positive cancers are more associated with high ki-67.

Introduction

In India breast cancer has ranked number one cancer among females with age adjusted rate as high as 25.8 per 100,000 women and mortality 12.7 per 100,000 women [1]. Breast cancer is no longer considered a single entity, but is instead a heterogeneous disease composed of distinct biological subtypes with diverse clinical, pathological, molecular, and genetic features and different therapeutic responsiveness and outcomes.[2] Gene-expression profiling studies have led to an innovative molecular classification of breast cancer into four distinct subtypes: the basal-like subtype, which is estrogen receptor (ER)-negative and HER2-negative; the HER2 subtype, characterized by increased expression of HER2 and of genes mapping to the HER2amplicon; and two luminal ER-positive subtypes: luminal A, characterized by high levels of ER and ER-related genes, and luminal B [3] characterized by lower ER levels and high expression of genes implicated in the proliferation process(table no 1). These newly defined molecular subgroups have distinct clinical outcomes. [4-6]

Gene expression profiling using DNA microarray is a very expensive technique and cannot be used on formalin-fixed, paraffin embedded samples. Recently studies have established that similar subtypes can be identified using immunohistochemical specific markers as surrogate tool for DNA microarray.[7]

The precise prevalence and clinico-pathological characteristics of these molecular subtypes of invasive breast tumors are not extensively studied in Indian population. The aim of this study was to identify and define the precise prevalence of molecular subtypes of invasive breast carcinoma using immunohistochemistry (IHC) in Indian population and to correlate with the morphological features and prognostic parameters. The morphological features and prognostic parameters such as age, tumor size, tumor grade, and lymph node status of invasive breast carcinoma of each molecular subtype were compared.

Methodology

All breast cancer patients who underwent primary breast surgery(Modified Radical Mastectomy or Breast Conserving Surgery) in the Surgical Oncology Department at Amrita Institute Of Medical Sciences, Kochi (Kerala) from October, 2010 to march, 2013 were included in the study. Patients with pure in-situ carcinoma, history of receiving neoadjuvant cancer therapy, recurrent or metastatic disease were excluded. Data regarding patient demographics, & morphological features were retrospectively obtained by reviewing medical records.

As per institutional protocol all the specimens were submitted for histopathological examination & immunohistochemical staining which included ER, PR, HER-2/neu and Ki-67. Tumors with 1% or more positively nuclear-stained cells were considered positive for ER and PR expression[8]. To distinguish between subtypes luminal A and B, a cut-off value of nuclear Ki-67 expression was set at 14%, as suggested by a previous study[9]. HER2staining was scored by counting the number of cells positively

stained on the membrane and expressed as a percentage of total tumor cells according to the American Society of Clinical Oncology(ASCO) and the College of American Pathologists (CAP) guidelines[10].

using the following categories: group 0, no immunostaining; group 1, weak incomplete membranous staining in any proportion of tumor cells; group 2, complete membranous staining, either non-uniform or weak in at least 10% of tumor cells; and group 3, uniform intense membranous staining in >30% of tumor cells. HER2 results were considered positive in cases with group 3 membranous staining of IHC or gene amplification by fluorescence in-situ hybridization (FISH).

Based on IHC or FISH findings of ER, PR, HER2, and Ki-67expression, our study population was divided into four subtypes: luminal A (ER +and/or PR +, HER2 - and Ki-67 <14%); luminal B(ER +and/or PR +, HER2 - and Ki-67 _14% or ER +and/or PR +andHER2 + irrespective of Ki-67 expression); HER2-enriched (ER -, PR -and HER2 +); and triple-negative breast cancer (TNBC) (ER -, PR -and HER2 -) (Table 1).

Table 1: Immunohistochemical criteria for defining molecular subtypes.

Subtypes	ER	PR	HER2	Ki-67
Luminal A	ER positive and/or PR positive		Negative	<14%
Luminal B	ER positive and/or PR positive		Negative	>14%
	ER positive and/or PR positive		Positive	Any
HER 2 -enriched	Negative	Negative	Positive	Any
TNBC	Negative	Negative	Negative	Any

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth
factor receptor type 2; TNBC: triple-negative breast cancer.

Statistical Analysis

All data were analyzed using the SPSS statistical software (version 17.0). The x2 test was used for categorical variables to compare the distribution of clinicopathological characteristics among BCSs. The relationship between patient characteristics and axillary lymph node metastases was examined by univariate and multivariable logistic regression analyses. Factors that were statistically significant in univariate analysis were entered into multivariable logistic regression analysis. A P value<0.05 was considered significant in all analyses.

Results

Out of 504 patients, 108 (21.5%), 234 (46.5%), 64

(12.7%), and 97 (19.3%) were luminal A, luminal B, HER2-enriched, and TNBC subtypes, respectively as shown Fig.1. Patient and tumor characteristics of the 504 cases are summarized in Table No 2. The median age at diagnosis of all patients was 54.2 years (range,22-88). There were 54% of patients had nodal positivity. Expression of ER, PR, HER2, and Ki-67 (> 14%) was observed in 56.5%, 54.6%, 25.4% and 74.2% of patients, respectively. The characteristics of the evaluable patients by molecular subtypes are given in Table 3. Patients with triple negative and Her-2 subtype had a higher grade disease and higher T stage. High Ki-67 values were detected more significantly in Luminal B subtype, while low Ki-67 values

were detected more significantly in Luminal A subtype (P value=0.001)

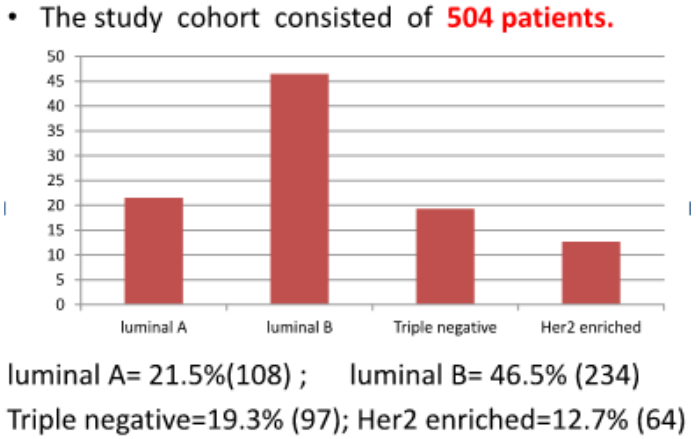

Figure 1: Showing distribution pattern of Breast Cancer Subtypes

Table 2: Clinicopathological Characteristics of Patients

Variable	Population (n = 504)
Age (mean in yrs)	54.37
T status (%)	
T1	23.7
T2	59.8
T3	12.6
T4	3.7
Nodal status(%)	
No	45.8
N1	25.5
N2	13.7
N3	14.9
Node positive (%)	54.1
Metastasis (%)	3.1
Receptor status (%)	
ER positive	57.5
PR positive	54.6
HER-2 positive	25.4
Ki-67 positive	74.2
MBR Grade (%)	
Grade 1	34.9
Grade 2	37.0
Grade 3	26.9
Molecular breast subtypes (%)	
Luminal A	21.4
Luminal B	46.4
HER-2 enriched	12.9
Triple negative	19.2

Table 3: Showing characteristics of the evaluable patients by molecular subtypes.

Characteristic	Luminal A	Luminal B	HER-2 Type	Triple negative	P value
Age					
<40yrs	8(7.4%)	25(10.7%)	14(21.5%)	11(11.3%)	0.039
>40 yrs	100(92.6%)	209(89.3%)	51(78.5%)	86(88.7%)	
Tumour Size					
T1	43(31.8%)	60(44.4%)	15(11.1%)	17(12.6%)	0.019
T2	53(18.3%)	130(44.8%)	39(13.4%)	68(23.4%)	
T3	9(14.8%)	35(57.4%)	7(11.5%)	10(14.6%)	
T4	3(16.7%)	9(50%)	4(22.2%)	2(11.1%)	

Nodal status					
Node Negative(N0)	60(26%)	88(38.1%)	29(12.6%)	54(23.4%)	0.002
Node Positive(N1/N2/N3)	48(17.6%)	146(53.7%)	36(13.2%)	42(15.4%)	
MBR Grade					
Grade 1	61(56.4%)	91(38.9%)	11(16.9%)	25(25.8%)	0.001
Grade 2	40(37%)	90(38.5%)	26(40%)	27(27.8%)	
Grade 3	7(6.5%)	53(22.6%)	28(43.1%)	45(46.4%)	
Ki-67					
Low Ki-67	102(79.1%)	6(4.7%)	11(8.5%)	10(7.8%)	0.001
High Ki-67	6(1.6%)	228(60.8%)	54(14.4%)	87(23.2%)	

Cross-tabulation between molecular subtypes and Ki -67 against node positivity is shown in Table 4. Significant association (P value= 0.001) was noted between luminal B type and nodal positivity where as significant association was also noted between luminal A type and Triple negative with nodal negativity. Node negative cancers are more associated with low ki-67 & node positive cancers are more associated with high ki-67

Table 4: Cross-tabulates between molecular subtypes& Ki-67 with node positivity.

Molecular subtypes	Node negative	Node positive	P value
Luminal A	60(26%)	48(17.6%)	0.024
Luminal B	88(38.1%)	146(53.7%)	0.001
Triple negative	54(23.4%)	42(15.4%)	0.022
HER-2 enriched	29(12.6%)	36(13.2%)	0.761
Low Ki-67	72(55.8%)	57(44.2%)	0.009
High Ki-67	159(42.4%)	215(57.5%)	

Univariate logistic regression analyses was examined between patient characteristic and axillary lymph node metastases as shown in Table 5. PR+, HER-2+, High Ki-67, Tumour size (T4 & T3) and Luminal B were associated with a higher risk of lymphnode metastases with significant P value. Younger age, Lower tumour size(T1), Luminal A and Triple negative subtype were associated with a lower risk of lymph node metastases with significant P value. Those factors which were significant on univariate logistic regression analysis were subjected to multivariate logistic regression analysis as shown in Table 6. Only high tumour size(T4) was associated with a higher risk of lymph node metastases with significant P value while younger age and lower tumour size(T1) was associated with a reduced risk of lymph node metastases with significant P value.

Table 5: Showing univariate logistic regression analysis

Characteristics	B coefficient	P value	Odds ratio	95% Confidence Interval	
				Lower	Upper
Age (40yrs)	-0.020	0.008	0.980	0.965	0.995
ER positive	0.235	0.268	1.265	0.835	1.916
PR positive	0.422	0.050	1.525	1.001	2.323
her2 positive	0.467	0.034	1.594	1.037	2.451
ki67 positive	0.603	0.005	1.828	1.202	2.781
Tumour size -T4	0.492	**0.009**	1.636	1.130	2.368
Tumour size -T3	0.296	**0.003**	1.344	1.104	1.636
Tumour size -T2	0.077	0.393	1.080	0.905	1.290
Tumour size -T1	-0.895	**0.001**	0.409	0.272	0.614
Luminal A	-0.495	**0.024**	0.610	0.397	0.936
Luminal B	0.626	0.001	1.870	1.308	2.672
Triple negative	-0.515	**0.025**	0.598	0.382	0.936
HER2- type	0.100	0.711	1.105	0.652	1.875
MBR Grade	0.183	0.108	1.200	0.960	1.500

Table 6: Showing multivariate logistic regression analysl

Characteristics Characteristics	B coefficient	P value	Odds ratio	95% Confidence Interval	
				Lower	Upper
Age	-0.021	0.011	0.979	0.964	0.995
PR status	0.413	0.157	1.512	0.853	2.679
her2	0.266	0.408	1.305	0.695	2.448
ki67	-0.099	0.628	0.906	0.608	1.350
T4	0.454	0.019	1.574	1.077	2.300
T3	0.197	0.063	1.218	0.990	1.499
T1	-0.778	0.001	0.459	0.296	0.712
Luminal A	-0.371	0.493	0.690	0.239	1.991
Luminal B	0.243	0.581	1.276	0.538	3.024
Triple negative	-0.202	0.664	0.817	0.329	2.028

Discussion

Breast cancer is a heterogenous disease & is traditionally classified based on histopathology. A newer method of classification is molecular subtypes of breast cancer, based on ER, PR, HER-2 receptor & Ki-67 status which can predict/influence the prognosis and response to hormonal and targeted therapies. The distribution of subtypes among our study cohort was luminal A (21.5%), luminal B (46.5%), HER2-enriched (12.7%), and TNBC (19.3%), which was similar to previous studies [11-14].

Mean age at the time of diagnosis was 53.47years and patients below 40 years were 11.5%. However, in the European population only 2.7% were below 35 years of age [15]. In terms of morphological grading, the groups differed significantly in terms of tumor grade (p value =0.001). The maximum numbers of cases with grade III morphology were TNBC (46.4%) and least was in Luminal A group (6.5%).Regarding size of tumour in our study,T4 was associated more commonly with Luminal B and smaller size was associated more commonly with Luminal A and Luminal B.

Ki-67 is the factor that suggests the proliferative activity of the tumour. In our study, high Ki-67 values were detected more significantly in Luminal B subtype, while low Ki-67 values were detected more significantly in Luminal A subtype, which suggests that this subtype is less aggressive. Node negative cancers are more associated with low ki-67 & node positive cancers are more associated with high ki-67. These findings are on par with previous studies [16-21].

In the present study, we assessed the clinical value of BCS for predicting axillary lymph node metastasis in breast cancer patients and the results showed there is significant association (P value= 0.001) was noted between luminal B type and nodal positivity where as significant association was also noted between luminal A type and Triple negative with nodal negativity. This observation is similar to the results of previous studies [22-24]. A study by Ugras et al [22] investigated 11,596 patients with breast cancer and found that nodal metastases were least frequent in TNBC as compared with other subtypes .Danish Breast Cancer Cooperative Group database that included 20,009 patients observed that TNBC patients had a reduced risk of axillary lymph node involvement than other BCSs when adjusted for other risk factors [23]. In a Surveillance, Epidemiology, and End Results study with 7,274 patients, luminal B subtype had higher rate of lymph node metastasis than the TNBC [24]. However, the value of BCS for predicting axillary lymph node status remains controversial. In a Korean study, TNBC patients had a higher risk of nodal positivity (OR 2.09) [25]. In addition, Wiechmann et al [26] reviewed the records of 6,042 patients and reported that TNBC tumors did not have involved lymph nodes more often than non-TNBC. Furthermore, Gangi et al [27] investigated 2,967 patients and multivariate analysis failed to show a significant difference in the lymph node status among patients with Breast cancer subtypes. Racial differences, selection bias, or heterogeneity within the same molecular subtype might also contribute to unclear associations between molecular subtypes and axillary involvement.

Axillary lymph node status is an important prognostic factor in breast cancer patients. Many studies from Western countries showed that age, tumor location, tumor stage, grade, and LVI could be used to evaluate the axillary lymphnode status [28-32] Univariate logistic regression in our study showed PR+, HER-2+, High Ki-67, Tumour size(T4 & T3) and Luminal B were associated with a higher risk of lymph node metastases with significant P value. Younger age, Lower tumour size(T1), Luminal A and Triple negative subtype were associated with a lower risk of lymph node metastases with significant P value. But on multivariate regression analysis only tumour size was significant i.e. high tumour size(T4) was associated with a higher risk of lymph node metastases with significant P value while younger age and lower tumour size(T1) was associated with a reduced risk of lymph node metastases with

significant P value. Study conducted in Korea showed similar findings [33]. In addition, racial differences, sample size variation across studies, selection bias, or heterogeneity within the same molecular subtype might also contribute to unclear associations between axillary involvement& molecular subtypes Asaxillary lymph node metastasis is the most significant prognostic factor in primary breast cancer, further investigation is necessary to understand the relationship between molecular subtypes and regional nodal metastasis.

Conclusions

Most common molecular subtype found in our study was luminal B followed by luminal A, triple negative and HER2 type in the descending order . Nodal involvement was found more with luminal B and less with Luminal A & Triple negative. Node negative cancers are more associated with low ki-67 & node positive cancers are more associated with high ki-67. Our results show that BCS as determined by ER, PR, HER2 and Ki-67status can predict axillary lymph node metastasis in breast cancer. Although TNBC is more aggressive, a lower risk for axillary lymph node metastasis compared to patients with other Breast cancer subtypes. In conclusion, detecting the subtype of breast cancer is important for disease prognosis, but also for determining and providing an adequate therapy. Hence, the molecular subtype of breast cancer needs to be determined in a routine histopathological assay.

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