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Original Article

Surgery Section

A Comparison of Clinical Features, Pathology and Outcomes in Various Subtypes of Breast Cancer in Indian Women

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ABSTRACT

Background: Breast cancer is often classified into subtypes using immunohistochemical markers. These subtypes have distinct biological behaviour. This study was conducted with the aim of estimating the distribution of various subtypes of breast cancer in Indian population based on immunohistochemistry markers and to determine the clinical features, pathology and outcomes of these subtypes of breast cancer.

Materials and Methods: A retrospective study was undertaken and all patients of breast cancer over a 5 year period were included. These patients were divided into 4 subgroups depending on the presence or absence of immunohistochemical markers: i) Luminal A (ER/PR+, Her 2 neu–); ii) Luminal B (ER/PR+, Her 2 neu+); iii) Her 2 enriched (ER-/PR-, Her 2 neu+) and; iv) Triple negative (ER-,PR-, Her2 neu-). Clinical and pathological features and survival were compared between patients in the 4 subgroups.

Results: Luminal A subgroup had majority of patients (43.8%). Patients in Luminal B, Her 2 enriched, and Triple negative subgroups were 14.8%, 16.1% and 25.3%. Median follow-up of patients was for 34 months. Luminal A subgroup patients were more likely to be postmenopausal and have smaller and lower grade (I/II) tumours with better survival (OS-91.06%). Patients in the Triple negative subgroup were more likely to be premenopausal (p-value 0.036, odds ratio 0.611, CI 0.394-0.949), have larger and higher grade (III) tumours with worse overall survival (OS-88.46%, odds ratio 1.32, 95%CI 0.602-2.39). Her 2 enriched group patients had bad prognostic features like larger size of tumour and higher grade of tumour and worst survival among all the subgroups (OS-85.07%, odds ratio 1.78, 95% CI 0.767-4.163). However, these outcomes were not statistically significant for the subgroups.

Conclusion: A retrospective study was undertaken of breast cancer patients in India, according to subtypes based on immunohistochemistry. Luminal A had prognostic features and survival which was better as compared to other subgroups (Luminal B, Her 2 enriched and Triple negative). Incidence of patients with Triple negative breast cancer was higher in the premenopausal period. Patients with Her 2 enriched breast cancer had the worst survival among all the subgroups.

Keywords: Estrogen receptor, HER2, Immunohistochemistry, Triple negative

INTRODUCTION

Breast cancer is a heterogeneous disease with diverse natural history, which can be classified based on clinical and pathological parameters. This helps in prognostication and prediction of response of various types of breast cancers to therapy.

In the last decade, significant research has focused on developing molecular classification of breast cancer [1,2]. This classification of breast cancer into molecular subtypes based on gene expression profile is considered as the gold standard. However the use of gene expression profiling is still limited, especially in developing countries, due to the expense and lack of technical availability. Hence a surrogate method of classification of molecular subtypes based on immunohistochemistry has been proposed which can act as a reliable indicator of the molecular subtypes [3]. This immunohistochemistry (IHC) classification is inexpensive, easily available and gives prognostic and therapeutic information.

AIM

Demonstrate the distribution in Indian patients of the different subtypes of breast cancer based on IHC markers and determine their associations with clinical and pathological features and their outcomes.

MATERIALS AND METHODS

This is a retrospective study of 521 breast cancer patients who presented to a tertiary cancer care centre from January 2007 to December 2012. Male patients with breast cancer, patients with non-Indian nationality and patients with metastatic disease were excluded. Data was collected from medical case records and histopathological records. Follow up information was collected by directly contacting the patients and consent was taken for the study. The last cut off date for follow up was taken as three months after the end of the study period. The study was approved by the institutional ethical committee.

Estrogen receptor (ER), Progesterone receptor (PR) and Her 2 neu status data was collected for all the patients. Based on IHC, the breast cancer patients in this study were classified into four groups. Patients were classified into Luminal A subgroup when either ER or PR or both were present, but Her 2 neu was absent. Patients were classified into Luminal B subgroup when Her 2 neu was present along with either ER or PR or both. Patients were classified into Her 2 enriched subgroup when only Her 2 neu was present. In the absence of ER, PR and Her 2 neu, patients were classified to triple negative subgroup. Thus the four subgroups were-

i) Luminal A= ER/PR+, Her2- = ER+/PR+, Her2-; ER-/PR+, Her2-; ER+/PR-, Her2-;

ii) Luminal B = ER/PR+, Her2+ = ER+/PR+, Her2+; ER-/PR+, Her2+; ER+/PR-, Her2+;

iii) Her 2 enriched = ER-/PR-, Her2+;

iv) Triple negative = ER-/PR-, Her2–.

ER and PR were estimated by antigen retrieval method from the tumour blocks. For this study, ER/PR was considered positive, if staining of more than 10% of nuclei was present [Table/Fig-1] [4].

IHC scoring for Her 2 neu was done according to [Table/Fig-2] [5]. Basal markers like cytokeratin 5/6 and EGFR (epidermal growth factor receptor) were not done in this study.

STATISTICAL ANALYSIS

Differences in subjects and tumour characteristics between the

1. Review Internal/ External Controls
- If not as expected: Repeat Testing
2. Receptor +ve/ -ve or uninterpretable
3. Positive if > 10 % Nuclear Positivity of any intensity
4. Negative if < 10 % Nuclear Positivity of any intensity
5. Not interpretable if Internal /External Controls –Not satisfactory
6. If Cytoplasmic staining- Repeat assay/ another block

[Table/Fig-1]: Interpretation of ER/PR Assay

Score 3
Uniform intense membrane staining of more than 30% of invasive tumour cells
Score 2
Complete membrane staining that is non-uniform or weak but with obvious circumferential distribution in at least 10% of cells, or intense complete membrane staining in 30% or less of tumour cells
Score 1
Weak, incomplete membrane staining in any proportion of invasive tumour cells, or
Weak, complete membrane staining in less than 10% of cells.
Score 0
No staining is observed in invasive tumour cells.

[Table/Fig-2]: IHC Scoring Criteria for Her 2 neu

various breast cancer subtypes were analysed using Chi-square test or Fisher's exact test for categorical variables. Overall survival was measured from the date of diagnosis to the date of death from any cause. Disease-free survival was measured from the date of diagnosis to the date of first relapse. Each breast cancer subtype was compared with the most common reference group of Luminal A subtype.

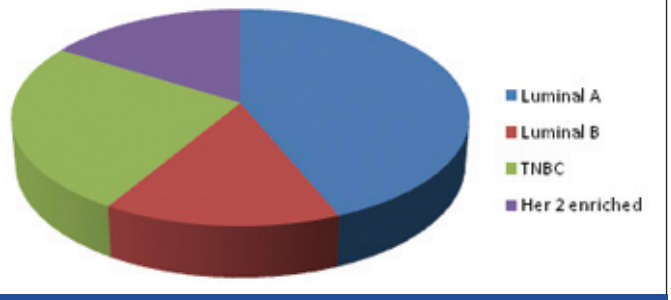
SPSS 17.0 statistical software was used for all analysis. A p-value of <0.05 was considered statistically significant.

RESULTS

A total of 521 patients who had complete data about their ER, PR and Her 2 neu status were analysed for this study. Median follow up was 34 months. 37.8% patients were premenopausal, while 62.2% were postmenopausal. The median age was 47 years (min 18 years and max 65 years). All of the 521 patients underwent complete treatment, as per the recommended guidelines according to their stage. 63.6 % underwent mastectomy and 36.4% underwent breast conservation surgery. Infiltrating duct carcinoma was the most common pathological subtype.

Majority of the tumours were T2 (63.4%) with median tumour size being 3 cms. 20.3% patients were lost to follow up. Of the remaining patients, the disease free survival was 71.1% and the overall survival was 89.2%.

Based on ER, PR and Her 2 neu reports, the patients were subdivided into 4 groups- Luminal A, Luminal B, Her 2 enriched and triple negative. Majority (43.8%) of the patients were in luminal A subgroup. Luminal B patients were 14.8%, Her 2 enriched group were 16.1% and triple negative patients were 25.3% [Table/Fig-3].



[Table/Fig-3]: Incidence of various subtypes.

These four subgroups were further analysed with respect to their pathological characteristics and survival as seen in [Table/Fig-4]. Luminal A was taken as reference group and the other subgroups were compared as seen in [Table/Fig-5]. Patients in Luminal A subgroup were more likely to be postmenopausal, have smaller size tumours, have grade I/II tumours and have better survival (OS-91.06%). Premenopausal patients (p-value 0.036, odds ratio 0.611, CI 0.394-0.949), larger and grade III tumours and worse overall survival (OS-88.46%, odds ratio 1.32, 95% CI 0.602-2.39) was observed in triple negative subgroup of patients. Bad prognostic features like larger size of the tumour, higher grade of the tumour and worst overall survival (OS-85.07%, odds ratio 1.78, 95% CI 0.767-4.163) were observed in Her 2 enriched subgroup of patients. However the difference in outcomes did not reach statistical significance for all the subgroups as shown in [Table/Fig-6]. In the outcome analysis 20.3% patients were lost to follow up. The curve for overall and disease free survival is shown in [Table/Fig-7,8].

DISCUSSION

In the last decade, characteristic patterns of gene expression profiling have emerged which reflect the molecular differences between the various subtypes of breast cancer. These subtypes

		Luminal A	Luminal B	Triple negative	Her 2 neu enriched	p-value
Menopausal status	Pre	39.09%	13.71%	30.46%	16.75%	
	Post	46.60%	15.43%	22.22%	15.74%	0.159
Type of surgery	BCS	44.25%	19.54%	22.99%	13.22%	
	MRM	41.78%	12.50%	27.96%	17.76%	0.099
Type of chemotherapy	Anthrax based	36.68%	11.32%	29.25%	20.75%	
	Taxane + Anthra based	36.97	14.29	29.41	19.33	0.932
Tumor size in cm	Less than 2	54.55	12.12	21.21	12.12	
	2-5	46.52	13.52	27.27	12.83	
	More than 5	28.57	9.52	33.33	28.57	0.065
Outcome	Alive without disease	44.41	15.59	24.75	15.25	
	Alive with disease	42.67	16.0	25.33	16.0	
	Death	35.56	15.56	26.67	22.22	0.924
Grade of tumour	I	71.43	17.86	3.57	7.14	
	II	51.19	11.95	22.87	13.99	
	III	23.21	16.96	39.29	20.54	<0.001

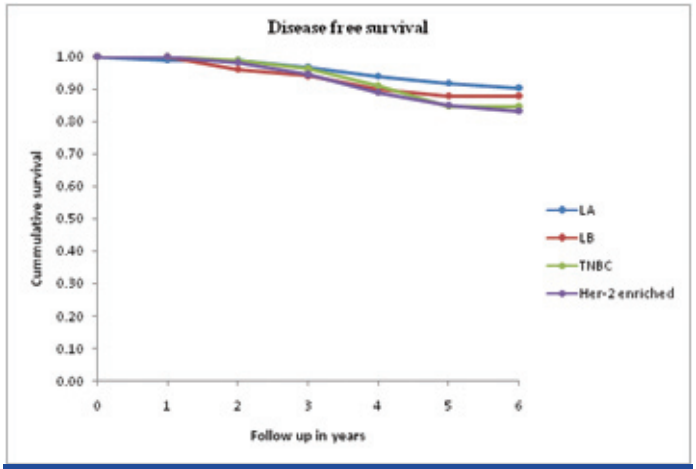
[Table/Fig-4]: Clinicopathological characteristics and outcome according to breast cancer subtypes

Outcome	Luminal A	Luminal B	Triple negative	Her 2 enriched	p-value
Disease Free Survival	73.18%	70.76%	70.19%	67.16%	0.926
Overall Survival	91.06%	89.23%	88.46%	85.07%	0.598

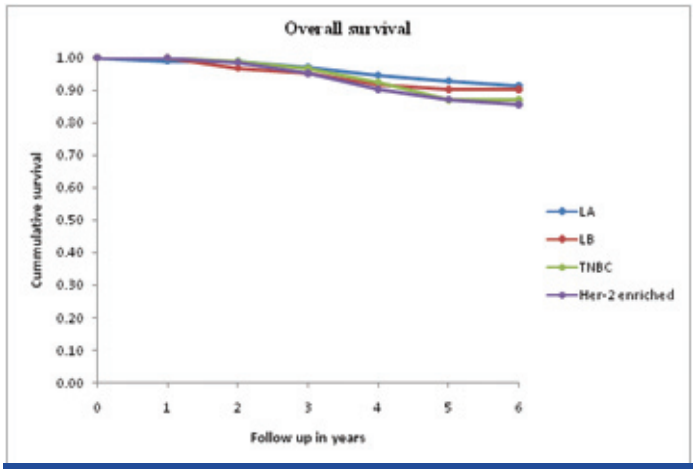
[Table/Fig-5]: Outcomes of various subgroups

Characteristics	Luminal B			Triple negative			Her 2 enriched		
	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI	p-value	Odds ratio	95% CI
Menopausal status	0.945	0.944	0.548 - 1.624	0.036	0.611	0.394-0.949	0.44	0.788	0.470- 1.321
Type of surgery	0.24	0.677	0.393 -1.165	0.348	1.28	0.80-2.062	0.275	1.42	0.809-2.502
Type of chemotherapy	0.671	1.32	0.562 - 3.09	0.992	1.052	0.552 - 2.003	0.909	0.974	0.472 - 2.007
Tumour size	0.799			0.086			0.007		
Outcome (OS)	0.853	1.22	0.481 - 3.13	0.617	1.32	0.602 - 2.390	0.259	1.78	0.767 - 4.163

[Table/Fig-6]: Comparision of Luminal A and other subgroups



[Table/Fig-7]: Disease free survival curves for various subgroups



[Table/Fig-8]: Overall survival curves for various subgroups

correlate well with clinical subtypes of breast cancer based on immunohistochemical markers.

Breast cancer has been classified into the following subtypes on the basis of IHC: i) Luminal A; ii) Luminal B; iii) Her 2 enriched and; iv) Triple negative breast cancer.

The incidence of these subtypes varies in different series as shown in [Table/Fig-9]. The incidence of Luminal A in our study was almost similar to the British Columbia randomised trial (BCRT) [6] and the Carolina breast cancer study (CBCS) [7], while it was almost half the incidence demonstrated by others [8-11]. The incidence of Luminal B subgroup in our study was similar to that demonstrated in BCRT, CBCS and another large cohort study [12] while it is almost double that of some other studies [8-11]. The incidence of Her 2 neu enriched subgroup was the most dissimilar when compared to other series of patients. As with Luminal A and Luminal B, the incidence of Her 2 neu enriched subgroup was almost similar to that demonstrated by BCRT while the other series had almost half or even less incidence of these patients [7-12]. The incidence of triple negative subgroup in our study was similar to the BCRT and the CBCS while it was two to five times the incidence demonstrated in other studies [8-12].

Overall, the incidence of subgroups in our study was similar to patients in the BCRT and CBCS but differed quite extensively from other studies. Our study showed a lower percentage of Luminal A and higher percentage of triple negativity as compared to other studies mentioned in [Table/Fig-9]. This could be due to ethnicity. Triple-negative cancers are known to occur more frequently in young black and Hispanic women than in young Caucasian women [13]. This relatively high incidence of TNBC may be partly explained by the fact that the risk factors for TNBC, like- high parity, young age at the time of first birth [14,15], lower socioeconomic status [16], younger age at diagnosis i.e. < 50 years [13,17] are commonly

Study	Luminal A	Luminal B	Her 2 enriched	Triple negative	Total no of patients
British Columbia Cancer Agency [4,5]	71%	6 %	7 %	15 %	3348
Mayo Clinic Breast Cancer study [6]	86 %	9 %	2 %	4 %	256
Vancouver General Hospital study [7]	78 %	4 %	6 %	12 %	246
University of British Columbia [8]	42 %	15 %	17 %	26 %	365
Carolina breast cancer study [9]	51.4 %	15.5 %	6.6%	26.4%	496
Dawood et al., [10]	65.8 %	14.3 %	4.9 %	15 %	1945
Our study	43.8%	14.8 %	16.1 %	25.3%	521

[Table/Fig-9]: Incidence of various subtypes in different series

seen in Indian population [18-20]. Moreover, there is a difference in the breast cancer epidemiology in Indian women when compared to Caucasian women. Indian women are younger at diagnosis, with a larger proportion of high grade tumours and higher proportion of triple negative tumours as compared to Caucasian women [21,22].

Many of the studies mentioned in [Table/Fig-9], had subdivided the triple negative group into 2 subgroups- core basal (ER-, PR-, Her 2 neu -, cytokeratin 5/6 + and EGFR +) and unclassified or negative phenotype (ER -, PR -, Her2 neu -, cytokeratin 5/6 - and EGFR -). Since cytokeratin 5/6 and EGFR were not done in this study, we have not used this subclassification. However, this subtyping of triple negative cancers into basal and non basal is important prognostically due to the difference in survival in both the subgroups [23].

In our study, the triple negative cancers were more common in younger premenopausal women. Triple negative breast cancer seems to be more predominant in younger age groups [7,13,17].

This could be due to partial overlap of triple negative breast cancer group with patients of BRCA 1, 2 mutations which tend to present earlier. BRCA 1, 2 testing was not performed in this study.

The clinicopathological features of different subtypes correlates with survival [Table/Fig-4]. In our study, the patients in Luminal A subgroup were more likely to be postmenopausal, have smaller size tumours, have grade I/II tumours and have better survival than other subgroups.

Patients in Her 2 enriched group had the worst prognostic features like larger tumour size, higher grade, and worst overall survival. The triple negative subgroup had more premenopausal patients and worse prognostic factors than Luminal A and poor survival. This study supports other studies [7,24] which have shown both the Her 2 enriched and triple negative subgroups to have poorer clinical and pathological features and prognosis.

The survival estimates (in percentages) of different phenotypes in various series is given in [Table/Fig-10]. Patients with Luminal A, Luminal B and Triple negative had better survival as compared to patients with Her 2 enriched breast cancer. This is in accordance with other studies [7,12]. In an analysis of data consisting of 10159

Study	Luminal A %	Luminal B %	Her 2 enriched %	Triple negative %	Median Follow up in years	Survival	p-value
Dawood et al., [10]	96	88	81	89	15	5 y DFS	<0.0001
Carey et al., [5]	84	87	52	75	11.2	BCSS	<0.001
Blows et al., [23]	72	58	53	63		OS	
Our study	91.06	89.23	85.07	88.46	2.8	OS	0.598

[Table/Fig-10]: Estimated survival of different phenotypes in various series
DFS- Disease Free Survival; BCSS- Breast cancer specific survival; OS- Overall Survival

cases from 12 studies, Blows et al., [25] have demonstrated survival rates much less than other studies as shown in [Table/Fig-10]. But case studies included by Blows et al., contained patient data from 1974 up to 2005. With the improvement in survival rates from all types of cancer improving over the past 40 years, pooling of such data is bound to yield lower survival rates [26]. The period of time that has elapsed after the diagnosis will determine the survival rate and the prognosis with the mortality rates being determined by the subtype of breast cancer [25]. The follow-up period is almost a decade in the series published by Carey et al., [7] while it is 15 years in the series published by Dawood et al., [12]. The follow-up period of our study is 2.8 years and the curves reflecting the survival (overall and disease free) have just started separating as shown in [Table/Fig-7,8]. So, even though there is no statistically significant difference in the survival of different subgroups in our study at present, a follow- up study after a few years will present more insights.

This study indicates that these subtypes of breast cancer based on immunohistochemical profiling have distinct biological characteristics that are associated with differences in survival.

Since this is a retrospective study with small number of patients and short follow up, many of these differences have not been evident to be statistically significant. However, the findings of clear differences in the behaviour of the immunohistochemically classified subtypes suggests that the use of these markers for routine clinical practice would be beneficial and could improve the targeting of adjuvant therapies for the breast cancer patients.

CONCLUSION

In this retrospective study of breast cancer patients at a tertiary cancer care hospital in India, according to the IHC subtypes, Luminal A had better prognostic features and survival compared to other subgroups. Mainly premenopausal women had Triple negative breast cancer.

Patients in the Her 2 enriched subgroup had the worst prognostic features and the worst survival amongst all subgroups. However the survival differences among all subgroups were not statistically significant. A follow-up study after a few years is warranted to document further differences in survival, if any.

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