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IMPACT OF PROGNOSTIC FACTORS ON SURVIVAL PATTERN OF BREAST CANCER PATIENTS: 5 YEAR SURVIVAL STUDY

Radiotherapy

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ABSTRACT

Background:- Breast cancer is heterogeneous disease with various prognostic factors which play significant role in deciding plan of management and further prognosis in terms of overall survival (OS) and disease free survival (DFS). The aim of this study was to assess the impact of tumor stage, tumor grade, molecular subtypes and lymph node metastasis on survival of carcinoma breast patients. **Methodology:-** Retrospective data of 216 post treatment breast cancer patients was collected from hospital records and analyzed. These patients were treated at Department of Radiation Oncology at B.Y.L. Nair Ch. Hospital, Mumbai. Tumor stage, tumor grade, molecular subtypes including immunohistochemical (IHC) parameters like hormonal receptor status and lymph node metastasis were observed. For statistical analysis, chi square test and Kaplan Meier tests were used for significant correlation and survival analysis respectively. **Results:-** Among 216 patients , majority of patients (45.59%) belong to pathological stage II with predominant T2 stage, 93.51 % patients diagnosed with IDC (Invasive Ductal Carcinoma) as common histological type. Most common subtype on basis of immunohistochemistry (IHC) was basal (TNBC) subgroup with 62 (29%) patients. Overall survival was 68.51% with 148 patients survived at end of 5 years and 68 (31.48%) patients died. Stage wise 5 year overall survival rates were 79.41%, 75%, 57.77% for stage I, Stage II, and stage III respectively. **Conclusion:-** Tumor Stage, Nodal Stage and molecular subtypes of Breast Cancer were having statistically significant impact on 5 year survival of patients. Multidisciplinary treatment modalities played important role in complete cure of breast cancer patients which is considered as very complex disease.

KEYWORDS

Breast Cancer, Hormonal Receptor Status, Molecular Subtypes, 5 year survival

INTRODUCTION

Female breast cancer has now crossed lung cancer as the leading cause of global cancer incidence in 2020, with an estimated 2.3 million new cases, representing 11.7% of all cancer cases. It is the fifth leading cause of cancer mortality worldwide, with 6,85,000 deaths [1, 2].

According to Globocan 2020 observatory, in India Breast Carcinoma stands on 1st position (1,78,361 cases out of 13.24 lakhs new cases) when incidence of new cases considered for all ages and most deadliest (90,408 out of 8.51 lakhs cancer related deaths) form of cancer in 2020 [3,4]. As per ICMR – PBCR data, breast malignancy is the commonest malignancy among females in urban registries of Delhi, Mumbai, Ahmadabad, Kolkata and Trivandrum and it accounts for more than 30% of all cancers in females [5].

Prognosis of breast cancer patients depends on various key factors like tumor stage , tumor grade, histological type, lymph node involvement, hormonal receptor status, LVI (lymphovascular invasion) and PNI (perineural invasion) .

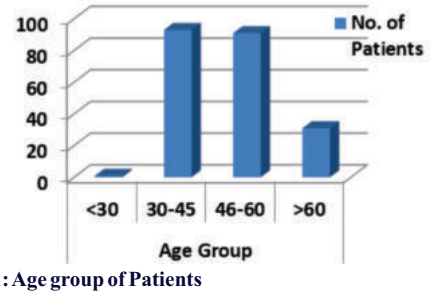
Currently Breast Carcinoma is treated with multimodality approaches like surgery, neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiotherapy and hormonal therapy. The purpose of this study was to assess the impact of tumor stage, tumor grade, hormonal receptor status with molecular subtypes and lymph node metastasis on overall survival of breast cancer patients which will guide us for deciding further plan of appropriate management in future.

MATERIAL & METHODS

Retrospective data of 216 histopathologically proven breast cancer patients who received complete treatment was collected from hospital records. The tumor characteristics in terms of clinicopathological & IHC parameters were recorded which includes age , gender, tumor laterality, tumor stage, tumor grade, hormonal receptor status (ER-Estrogen receptors/PR-Progesterone receptors/HER), type of surgery, histopathological type, number of positive axillary lymph nodes, treatment received in form of neoadjuvant and adjuvant chemotherapy, adjuvant radiotherapy, hormonal therapy. Overall survival was considered and calculated in months from date of diagnosis. 5 year survival was taken into consideration from follow up records of patients and telephonic follow up was carried out for patients who have lost to follow up in person in our oncology clinic. Statistical analysis was done to evaluate the difference in impact of tumor stage, nodal stage, molecular subtypes and tumor grade on survival of patients using chi square test and calculation of 'P' value for significance test. The Kaplan Meier survival plot was used to compare and evaluate overall survival among groups.

RESULTS

Age of cancer patients in our study ranged from 25-83 years. The median age was 48 yrs. Majority of the breast cancer patients represented from 30-45 yrs age group with 93 patients (43 %) (Graph 1).



Graph 1: Age group of Patients

As shown in Fig. 1, among 216 patients, only 3 (1%) were male patients and 213 (99 %) were female patients.

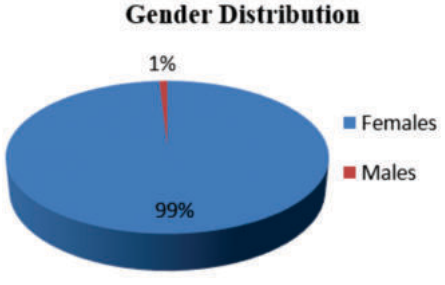


Fig 1: Gender distribution

In context to laterality, 107 (49.53%) patients had right sided breast carcinoma and 109 (50.46 %) patients had left sided breast carcinoma. Among 216 patients, 177 patients underwent MRM (Modified Radical

mastectomy) and 39 patients underwent BCS (Breast Conservation Surgery). In context to nodal involvement, 146 patients were node positive and 70 patients were node negative. In our study, most common histopathological type was Invasive Ductal Carcinoma (IDC). 202 of total patients had IDC and 14 patients were diagnosed with Lobular carcinoma. Grade III was predominant grade of the tumor in our study with 156 (72.22%) patients.

Table 1: Clinicopathological and IHC Parameters

Parameter	Group	No. of Patients (%)
Age (in yrs)	<30	1 (0.46)
	30-45	93 (43)
	46-60	91 (42.12)
	>60	31 (14.35)
Gender	Females	213 (99.07)
	Males	3 (1)
Laterality	Right	107 (49.53)
	Left	109 (50.46)
Surgery	MRM	177 (81.94)
	BCS	39 (18.05)
Stage	I	34 (15.74)
	II	92 (45.59)
	III	90 (41.66)
Lymph Node Involvement	Positive	146 (67.59)
	Negative	70 (32.40)
Histology	Ductal	202 (93.51)
	Lobular	14 (5.09)
Hormonal Receptor Status	Luminal A (ER +/PR+/HER-)	54 (25.0)
	Luminal B (ER +/PR +/Her+)	14 (6.48)
	HER2 Rich (ER-/PR-/HER +)	33 (15.74)
	Basal (ER -/PR-/HER-)	62 (29)
	Nonclassified	53 (24.53)
Tumor Grade	Grade I (MRBS 3-5)	4 (1.85)
	Grade II (MRBS 6-7)	56 (25.92)
	Grade III (MRBS 8-9)	156 (72.22)
Chemotherapy	Neoadjuvant Chemotherapy	99 (45.83)
	Adjuvant Chemotherapy	197 (91.20)
RT	Adjuvant Radiotherapy	216 (100%)
Hormonal Therapy	Tamoxifen	65 (30.09)
	AI	48 (22.22)
	No HT	103 (47.68)

Neoadjuvant chemotherapy, adjuvant chemotherapy, adjuvant radiotherapy and hormonal therapy received by 45.83 %, 91.20 %, 100 % and 52.31 % patients respectively.

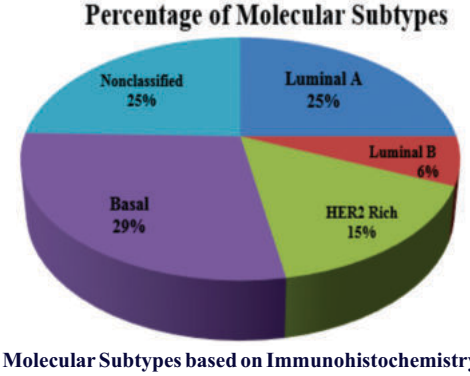


Fig 3: Molecular Subtypes based on Immunohistochemistry

In our study, Basal (triple negative breast cancer-TNBC) type was most common 62 (29 %) molecular subtype and Luminal B was least common subtype with 14 (6.48%) patients (Fig 3).

Table 2: Correlation of Prognostic factors with 5 year survival

Sr. No.	Parameter	5 Year Survival		Death	P Value
1	Tumor Stage	Stage I	27	7	p=0.0144 χ^2=8.47
		Stage II	69	23	
		Stage III	52	38	
2	Nodal Stage	N0	58	12	p<0.0001 χ^2=30.19
		N1	42	14	
		N2	38	19	
		N3	10	23	
3	Molecular Subtype	Luminal A	42	12	p=0.0017 χ^2=17.17
		Luminal B	12	2	
		HER 2 Rich	24	9	
		Basal Type	30	32	
		Nonclassified (NC)	40	13	
4	Tumor Grade	Grade I	3	1	p=0.9001 χ^2=0.210
		Grade II	38	16	
		Grade III	107	51	

Table 2 clearly shows that Stage of the disease was having statistically significant impact on 5 year survival of patients (p=0.0144).

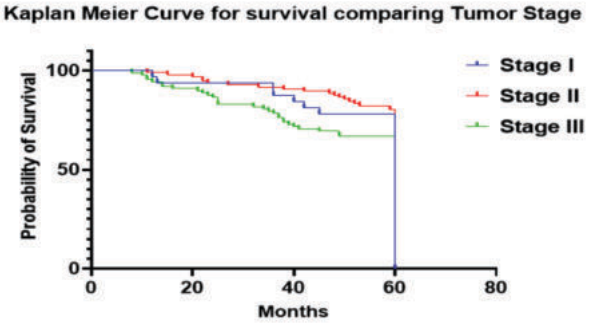


Fig. 4 Kaplan Meier Curve for Survival Analysis comparing Tumor Stage

The Kaplan Meier curve plotted for overall survival analysis of cancer patients comparing stage of tumor shows that 5 year survival rate was highest for stage II breast cancer patients. Significant mortality was observed in stage III breast cancer patients. (Fig.4).

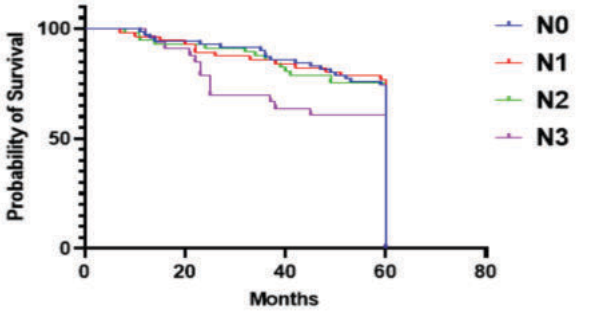


Fig 5 Kaplan Meier Curve for Survival Analysis comparing Nodal Stage

As shown in Table 2, Lymph node stage has very significant impact on survival of breast carcinoma patients (p<0.0001). As nodal stage shifts from N0 to N3, survival of patients significantly decreases. Significant mortality rate was observed in N3 stage (Fig. 5).

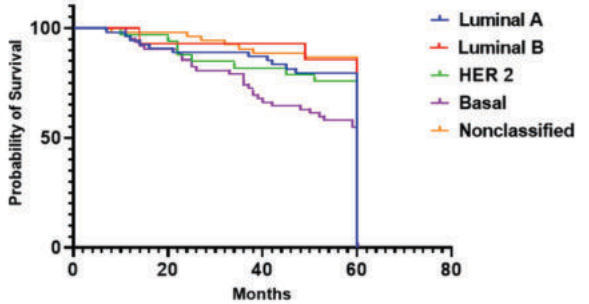


Fig. 6 Kaplan Meier Curve for Survival Analysis comparing Molecular Subtypes

As shown in Table 2, the 5-year survival rate for Luminal A type is 28.37 % among survivors followed by nonclassified (NC) subtype with 27.02 % of survivors. Highest mortality was seen in Basal molecular subtype as 47.05 % of total patients died during observation period which found to be statistically significant (p=0.0017). The Kaplan Meier curve was plotted to assess the association between molecular subtypes and overall survival of cancer patients which clearly shows that Basal subtype is poor prognostic group, as group specific mortality was significant (Fig. 6).

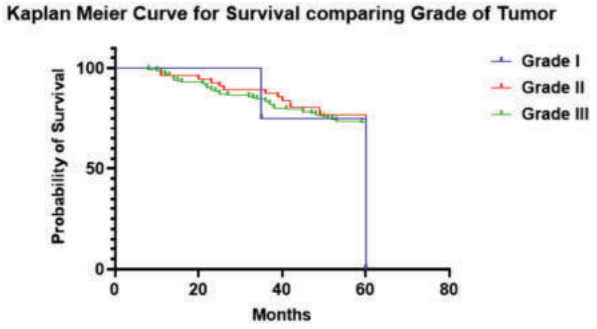


Fig 7 Kaplan Meier Curve for Survival Analysis comparing Tumor Grade

As shown in Table 2 and Fig. 7, Grade of the tumor was proved to be statistically insignificant prognostic factor deciding survival of breast cancer patients in our study.

DISCUSSION

Breast cancer is a heterogeneous disease with varied morphological appearances, molecular features, behavior, and response to therapy. Currently plan of management is decided by team of multidisciplinary faculties as breast cancer is complex disease when we consider various predictive and prognostic factors. Stage of the disease, axillary nodal status, and hormone receptor status showed statistically significant association with overall survival in breast cancer. Among these, the stage of disease and axillary nodal status are established prognostic factors for carcinoma breast.

In contrast to earlier studies, most of the breast cancer patients at our institute have been presented with pathological stage II, which is being considered as better trend as patients in past used to present in advanced stages of tumor. First presentation in breast oncology clinic at advanced stage itself leads to poor prognosis which affects the further survival. In addition to this, over the years, it has been observed that more young ladies are affected by breast cancer. The average age of patients with breast cancer has shifted from 50–70 years old to 30–50 years old [6].

The stage of the disease is one of the most important factors influencing the overall survival. A study conducted at SGPGIMS Lucknow found that the 5-year overall survival rate was 62%. The 5-year actuarial survival has been 90% for stage I patients, 78% for stage II, 57% for stage III, and 22% for stage IV, though the survival data is available based on the follow up information for only 75% of patients [7].

TMH study done by Ganesh B et al included 1,866 cases of breast cancer. Results observed that prognosis is poorer for late-stage disease patient (T3), compared to those diagnosed in early stage T1. The survival rates were 84%, 75% and 60% for T1, T2 and T3 stage respectively. The difference in survival rates between T1 and T3 was statistically significant (p=0.0002) [8].

Axillary lymph node status has repeatedly been shown to be the single most important predictor of disease-free survival and overall survival in breast cancer [9, 10, 11].

Tonellotto F et al conducted retrospective cohort study of node-positive stage II and III breast cancer patients consisting 628 women with node-positive breast cancer. Results showed hazard of death of pN2 and pN3 patients was 2.17 and 2.41 respectively ($p<0.001$) and the hazard of intermediate (0.21–0.65) and high-risk (>0.65) lymph node ratio patients was 1.70 and 2.74 respectively ($p\leq0.001$). In women with node-positive breast cancer, the number of positive lymph nodes (pN) and lymph node ratio (LNR) are important prognostic factors of disease-free survival and overall survival. [12]

Carey LA et al conducted a trial consisting 496 incident cases of invasive breast cancer from the Carolina Breast Cancer Study , the basal-like breast cancer subtype was more prevalent among premenopausal African American women (39%) compared with postmenopausal African American women (14%) Breast cancer–specific survival differed by subtype (*P*.001), with shortest survival among HER2/ER- and basal-like subtypes [13].

Dunnwald LK et al performed observational study including 175 women at least 30 years old with a primary diagnosis of invasive breast carcinoma. Greater differences were observed in analyses stratified by grade; among women with low-grade lesions, ER-/PR- patients had a 2.6-fold to 3.1-fold increased risk of mortality compared to ER+/PR+ patients, but among women with high-grade lesions, they had a 2.1-fold to 2.3-fold increased risk. Compared to women with ER+/PR+ tumors, women with ER+/PR-, ER-/PR+, or ER-/PR- tumors experienced higher risks of mortality [14]. This data was consistent with our study findings as basal type (ER-/PR-/HER2-) is predominant molecular subtype and was having statistically significant mortality.

Sharma JD et. al. conducted a study with analysis of 336 breast cancer patients, they significantly found that hormone receptors with positive (ER/PR+) status have 13.6% higher survival rate than those who were with negative hormonal status (ER/PR-). The overall survival for ER/PR positive is 72.1% compared to 58.5% of ER/PR negative (*P* = 0.1290) [15].

Histological grade is an important determinant of prognosis that also allows risk stratification within a given tumor stage [16, 17, 18, 19]. Our study findings and analysis was inconsistent with the established conclusion that tumor grade is significant prognostic factor. Henson et al proved that as breast tumors increased in size, the histological grade also increased. The study results suggested that in linking histological grade with stage of disease, the staging system should be considered. Histological grade when used in conjunction with stage of disease can improve the prediction of treatment outcome. A prognostic index can be created for breast cancer using a combination of stage of disease and histological grade [16].

CONCLUSION

Tumor stage, nodal stage and molecular subtypes had statistically significant influence on 5 year overall survival (OS) of breast cancer patients. Higher tumor stage, N3 nodal stage and basal subtype were proved to be poor prognostic group as they were having statistically significant mortality. Hence aggressive multimodality treatment and follow up screening plan should be offered for this subgroup of patients.

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