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Clinico-Pathological Profile and Treatment Outcomein Patients with Triple-Negative Breast Cancer from a Cancer Care Centre in North–East India

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ABSTRACT

Introduction: Triple-negative breast cancer (TNBC) accounts for 12-17% of all breast cancers worldwide and is associated with a high risk of metastasis and poor survival. With limited long-term data evaluating the outcome of TNBC in the Indian population, we aimed to determine the clinicopathological profile and treatment outcome of patients with TNBC in a cancer care center from North-East India.

Methodology: A retrospective observational analysis was performed on medical records of patients with histologically proven breast cancer who tested negative for estrogen receptor (ER), progesterone receptor (PR), and HER2/neu by immunohistochemistry from January 2013 to December 2016. Data regarding demographic characteristics, clinical patterns, treatment details, and treatment outcomes were collected and analyzed.

Results: Our study evaluated seventy patients with TNBC with the mean age at presentation were 46.7 years (SD ±8.9 years). Infiltrating ductal carcinoma was the predominant histological pattern (92.9%), and Scarff Bloom Richardson grade III was seen in 52 (74.3%) patients. The majority of the patients presented with TNM stage III disease (50%) followed by stage II (34.3%), stage IV (11.5%), and bone was the commonest site of distant metastasis. Only 62.8% of patients had completed planned treatment. Fifty-eight patients (82.8%) received chemotherapy, amongst which 22 patients (37.9%) received a taxane-based regimen along with anthracycline. With a median follow-up duration of 35 months, loco-regional relapse was seen in 8 (11.4%), and distant relapse was seen in 24 (34.3%) patients. Median overall survival (OS) was 19±4.1 months, and median progression-free survival (PFS) was 18±2.4 months. Three-year OS and 3-year PFS were 31.7% and 25.5%, respectively, for the entire study population.

Conclusion: TNBC is an aggressive subtype associated with a poor prognosis, more distant failure, and limited therapeutic options. The addition of taxane to conventional anthracycline-based chemotherapy improves survival. In addition, treatment adherence and availability of newer therapeutic options can further enhance the overall outcome.

KEYWORDS: triple-negative, chemotherapy, taxane, survival, distant failure

I. INTRODUCTION

Breast cancer is the commonest cancer diagnosed worldwide (11.7%) and in India (13.5%) in both sex groups, according to the report of GLOBOCAN 2020. Breast cancer heterogeneity has been observed in histology and clinical outcome for a long time, and these differences have served as the basis for disease classification. Breast cancer is a heterogeneous disease with regard to biological behaviour, responses to treatment, and prognosis [1-2]. The traditional, mainly pathology-driven classification has been refined and, at times, replaced by molecular classifications, which have the potential to combine disease mechanisms with clinical outcome measures [3]. By gene-expression analysis, four breast cancer subtypes: Luminal (luminal A & B), HER2-enriched, normal breast-like, and basal-like have been identified with different clinical outcomes and responses to neoadjuvant chemotherapy [4]. Triple-negative breast cancer (TNBC) is a term that has been applied to cancers that lack expression of the estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor-2

(HER2). The ‘‘basal-like’’ category of tumours is mainly composed of ‘‘triple-negative’’ breast cancers. Some authors have established that the TNBC phenotype could reliably be a surrogate for the basal type [5]. The ER-negative genomic profile in TNBC includes multiple subtypes, such as basal-like, claudin-low 45, and interferon-rich 46, among others.

TNBC accounts for approximately 12-17% of all invasive breast cancers in Western populations [6]. The prevalence of TNBC in India is considerably higher compared with that seen in the Western population. The prevalence of TNBC in India ranged from 27% to 35% across studies, with a summary estimate of 31% [7].

Although gene expression profile (GEP) was initially used, it is neither economical nor practical in daily practice. Many investigators have used immunohistochemistry (IHC) based molecular classification to study invasive breast cancer and have shown predictive/ prognostic values comparable to GEP. Accurate IHC analyses for ER, PR, and HER2 are critical for IHC based molecular classification.

TNBC has been reported to be more aggressive and generally carry a poorer prognosis than luminal subtypes [8-10]. TNBC patients are usually younger, with higher-grade tumours and a higher risk of distant recurrence and death within the first 3 to 5 years after diagnosis [11]. Chemotherapy is the only systemic treatment option for TNBC, whereas patients with non-TNBC may benefit from both chemotherapy and endocrine therapy and HER2 directed therapy. Although the efficacy of chemotherapy for this disease has been higher, the prognosis of these patients remains suboptimal [12-13], with a poor long-term survival rate. This paradox is particularly evident in the neoadjuvant setting [14]. Unlike other breast cancer subtypes, there are no approved targeted treatments available, although immunotherapy is available for those with advanced TNBC that expresses programmed cell death ligand 1 (PD-L1) [15].

Limited long-term clinical data are evaluating the outcome of TNBC in the Indian population. The survival rate of Indian patients is lower than that of developed countries due to socioeconomic and logistics issues. In the current study, we aimed to determine the incidence, clinicopathological profile, treatment outcome, and survival of patients with TNBC in a cancer care center of North-East India retrospectively.

II. MATERIAL AND METHODS

A retrospective observational analysis was performed on medical records of histologically proven triple-negative breast cancer (TNBC) patients visiting Dr. B. Borooah Cancer Institute, Guwahati, Assam, from January 2013 to December 2016. Patients were followed up till December 2019. Data were collected retrospectively from individual medical case records.

The diagnosis was made by biopsy or histopathological examination of the surgical specimen. "Triple-negative" was defined according to American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines, as ≤1 percent expression of ER and PR as determined by immunohistochemistry (IHC), and that is either 0 to 1+ by IHC, or IHC 2+ with fluorescence in situ hybridization (FISH)-negative (not amplified) [16-17].

The medical records were reviewed for:
(i) Age at diagnosis (in years)
(ii) Tumour type
(iii) Tumour grade
(iv) Lymphovascular invasion (LVI)
(iv) Lymph nodal involvement
(v) Pathologic tumour size in centimeters
(vi) TNM staging [18]
(vii) Type of surgery (breast-conserving surgery or modified radical mastectomy)
(viii) Chemotherapy details
(ix) Radiation therapy details
(x) Duration of follow up
(xi) Location of recurrence (if present)
(xii) Survival (progression-free survival and overall survival)

Inclusion criteria: Adult patients (age ≥ 18 years) with triple-negative breast cancer attending Dr. B. Borooah Cancer Institute during the period from January 2013 to December 2016 was diagnosed by biopsy/histopathological examination and confirmed by immunohistochemistry.

Exclusion criteria: Patients younger than 18 years and patients who had synchronous other malignancy or were previously diagnosed and/or treated for other malignancy were excluded. Disease-free survival (DFS) was defined as the time interval between diagnosis and recurrence or death. Overall survival (OS) was defined as the time interval between diagnosis to last follow-up or time of death.

Statistical Methods: Patient and demographic characteristics were analyzed using median/centiles and mean. The effects of variables on recurrence and death were evaluated by univariate and multivariate cox-regression model analysis. The survival curve was estimated using the Kaplan-

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Meier method. Analyses were performed in SPSS 19.0 software. Two-tailed p-values less than 0.05 were considered statistically significant at a 95% confidence interval.

III. RESULTS

A. Demographic Characteristics

From January 2013 to December 2016, 70 patients of TNBC were included for the analysis, fulfilling the inclusion criterion.

Fifty-three patients (75.7%) were from a rural background, and seventeen (24.3%) were from the urban locality. Only one out of seventy patients were male, and the rest of the patients were female. The mean age of presentation was 46.7 years (Standard Deviation ± 8.9 years). Twenty-eight patients (40%) were below the age of 45 years [Table: 1]. Thirty-eight (54.2%) patients were post-menopausal.

Table 1: Demographic characteristics of TNBC patients

Variable		N=70 (%)	Mean
Mean age			46.7 Years (SD±8.9 years)
Residence	Rural	53(75.7%)	
	Urban	17(24.3%)	

B. Patient and Disease Characteristics

Forty-one (58.5%) patients presented with left-sided breast tumour, and 29 (41.5%) patients presented with right-sided tumour. The most common histological type was infiltrating duct carcinoma (n=65, 92.9%), followed by invasive lobular carcinoma (n=3, 4.3%). Scarff Bloom Richardson grade III was seen in 52 (74.3%) patients. Pathological tumour size was >5 cm in 29 (38.4%) patients. Pathological lymph nodal involvement was found in 55.7% of patients. The extra-capsular extension (ECE) and lymphovascular invasion (LVI) were seen in 26.9% and 30.1% of patients, respectively, in histopathological examination of the postoperative specimen. Majority of the patients presented with TNM stage III disease (n=35, 50%), followed by 24 patients (34.3%) with stage II and eight patients (11.5%) with stage IV disease [Figure: 1] [Table: 2]. Eight patients (11.5%) had distant metastasis at presentation, the bone being the most common site of presentation (50%), followed by liver (37.5%) and lung.

Table 2: Patient and disease characteristics of TNBC patients

Variables		N=70(%)
Histology	Infiltrating duct carcinoma	65(92.9%)
	Invasive lobular carcinoma	3(4.3%)
	Medullary carcinoma	2(2.9%)
Stage wise distribution(TNM)	Stage I	3 (4.2%)
	Stage II	24(34.3%)
	Stage III	35(50%)
	Stage IV	8(11.5%)
Breast Tumour	Left-sided	41(58.5%)
	Right-sided	29(41.5%)
Grade of tumour (Scarff Bloom Richardson's grade)	III	52 (74.3%)
	II	13(18.5%)
	I	5(7.2%)

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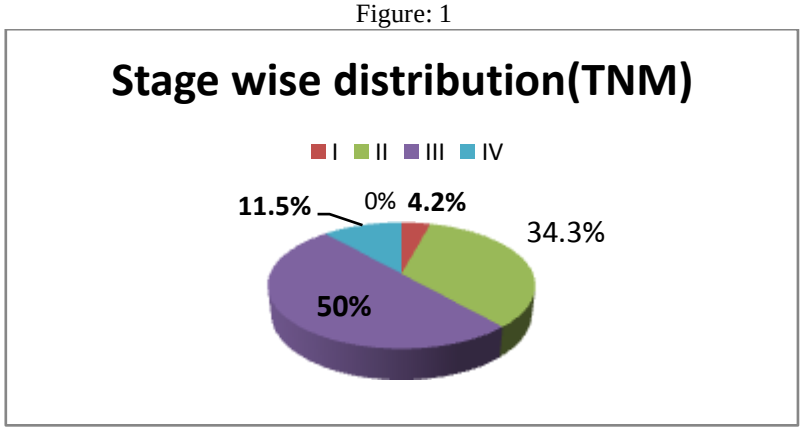
Figure: 1



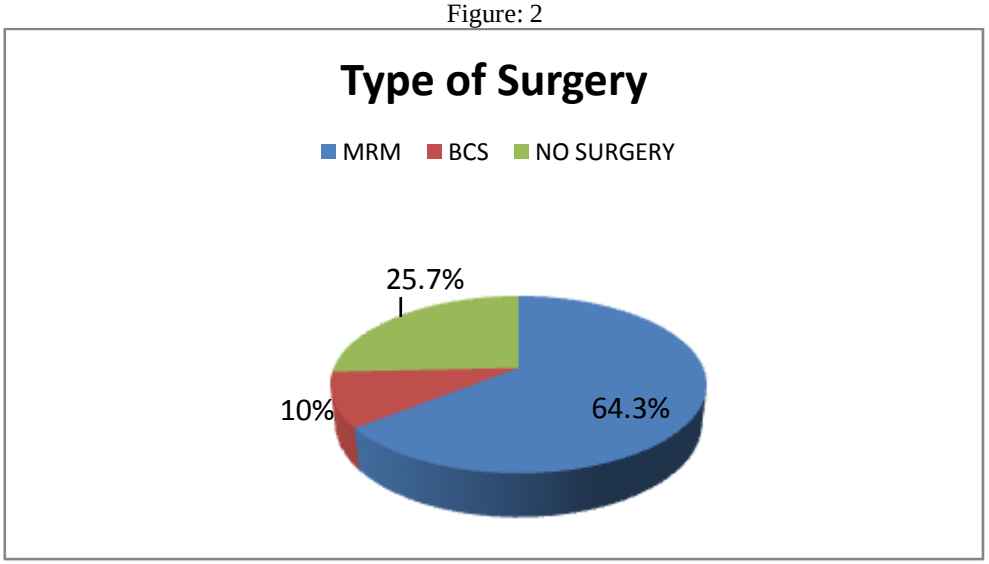
C. Treatment Characteristics

The majority of the patients underwent modified radical mastectomy (MRM) (n=45, 64.3%). Only seven (10%) patients underwent breast conservative surgery (BCS) [Figure: 2]. Upfront surgery was done in 34 (48.6%) patients. Thirty-two (45.7%) patients received adjuvant radiotherapy. Out of the total of 70 patients, 58 patients (82.8%) had received chemotherapy. Neoadjuvant chemotherapy (NACT) was received by 17 (24.3%) out of a total of 70 patients. All the patients have received anthracycline-based chemotherapy in neoadjuvant or adjuvant settings. Of these 58 patients who received chemotherapy, 22 patients (37.9%) received taxane, and four patients (6.8%) received platinum agents in addition to an anthracycline-based regimen. The average number of chemotherapy cycles received was 6 (range 1-8). [Table: 3]. The most commonly used chemotherapy regimen used was 5-FU, Epirubicin & Cyclophosphamide.

Table 3: Systemic therapy characteristics of TNBC patients

	Variables	N=58 (%)
Chemotherapy (n=58) [adjuvant and (neo)adjuvant setting]	Anthracycline-based alone	58(100%)
	Additional taxane	22(37.9%)
	Additional platinum	4(6.8%)
Average number of chemotherapy cycles received (n=58)	Any chemotherapy	6 cycles (range 1-8)

Figure: 2



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The most frequent toxicities that occurred due to chemotherapy were hematological toxicity, followed by gastrointestinal toxicity. The commonest hematological toxicity was neutropenia, with grade III neutropenia observed in 6 patients (10.3%) out of 58 patients who received any form of chemotherapy. Grade II nausea and vomiting were the commonest gastrointestinal toxicity observed. Forty-four patients (62.8%) out of a total seventy had completed planned treatment.

D. Treatment outcome and survival

With the median follow-up duration of 35 months (range 1 to 81 months), a total of 32 patients developed disease recurrence. Of the loco-regional relapse seen in 8 (n=8/70, 11.4%) patients, 5 patients (n=5/8, 62.5%) had chest wall relapse and 3 (n=3/8, 37.5%) patients had nodal relapse (ipsilateral axillary or supraclavicular nodal). Relapse at distant site were seen in 24 patients (n=24/70, 34.3%), with lung being the most common site (n=11/24, 45.8%), followed by bone (n=4/24, 16.7%) liver and brain (n=3/24 and 12.5% each) [Table: 4]. Twenty-two patients (n=22/32) received salvage therapy with either chemotherapy alone (18 patients) or combined chemotherapy and radiotherapy (7 patients).

Table 4: Pattern of failure in patients with TNBC

Disease Recurrence	N (%)
Local Relapse (n=8/70)	8 (11.4%)
Chest wall recurrence	5 (62.5%)
Nodal recurrence: Supraclavicular Ipsilateral Axillary	2 (25%) 1 (12.5%)
Distant Relapse (n=24/70)	24 (34.3%)
Lung	11 (45.8%)
Bone	4 (16.7%)
Liver	3 (12.5%)
Brain	3 (12.5%)
Others	3 (12.5%)

The median time to distant metastasis was 17.5 months. Median overall survival (OS) was 19±4.1 months, and median overall survival in stages II, III, and IV were 41±7.2, 19±3.5, and 4±2.3 months, respectively.

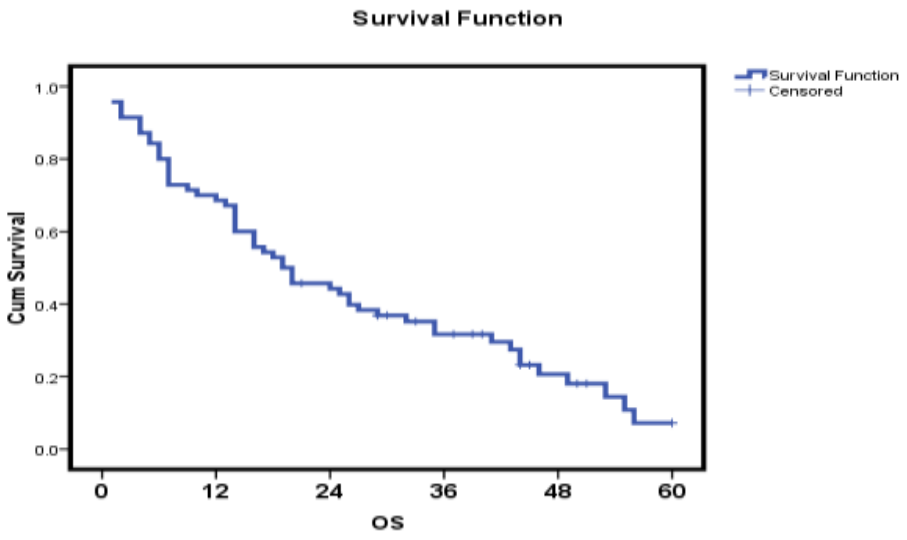

Figure 3: Kaplan Meier curve showing median overall survival (OS)

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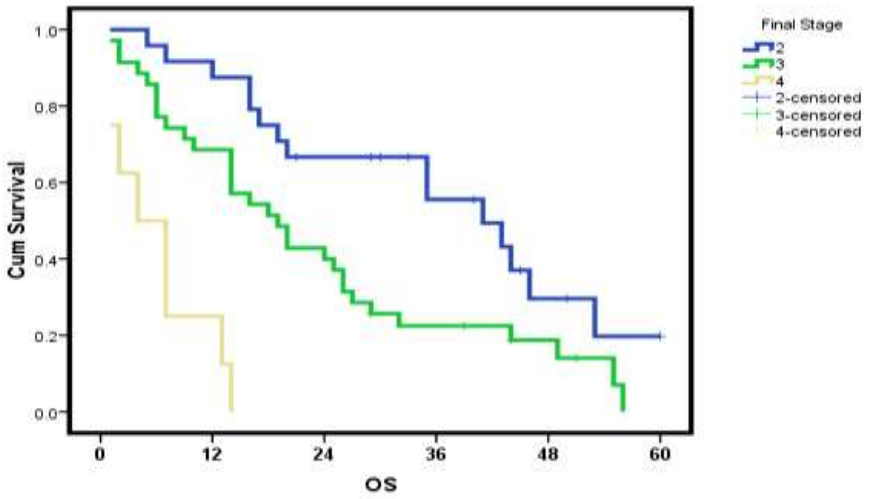

Figure 4: Kaplan Meier curve showing stage-wise distribution of overall survival (OS)

Median progression-free survival (PFS) was 18±2.4 months, and median PFS for stage II, III, and IV were 34±5.5, 14±4, and 2±1.8 months, respectively

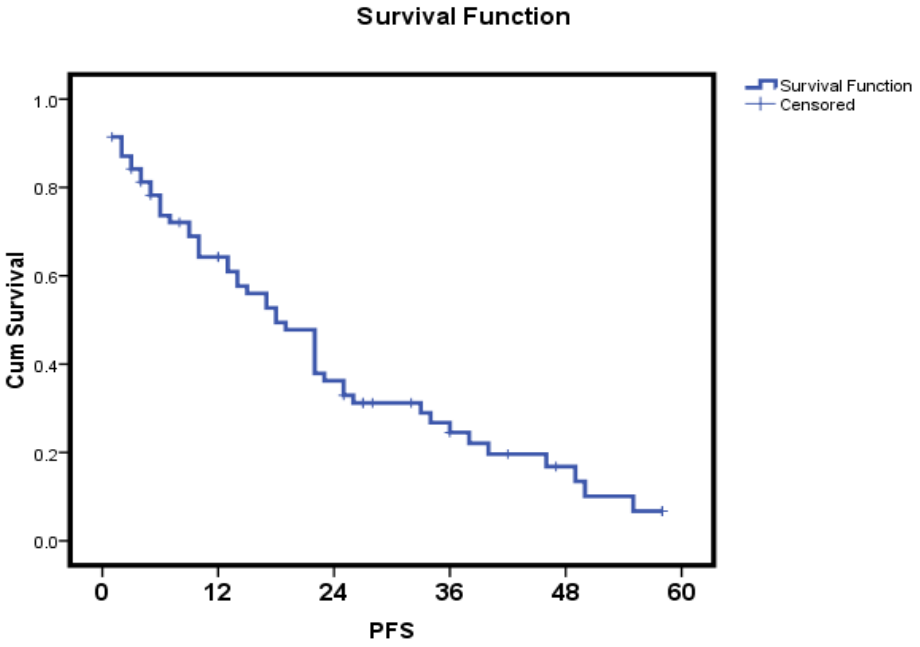

Figure 5: Kaplan Meier curve showing medianprogression free survival (PFS)

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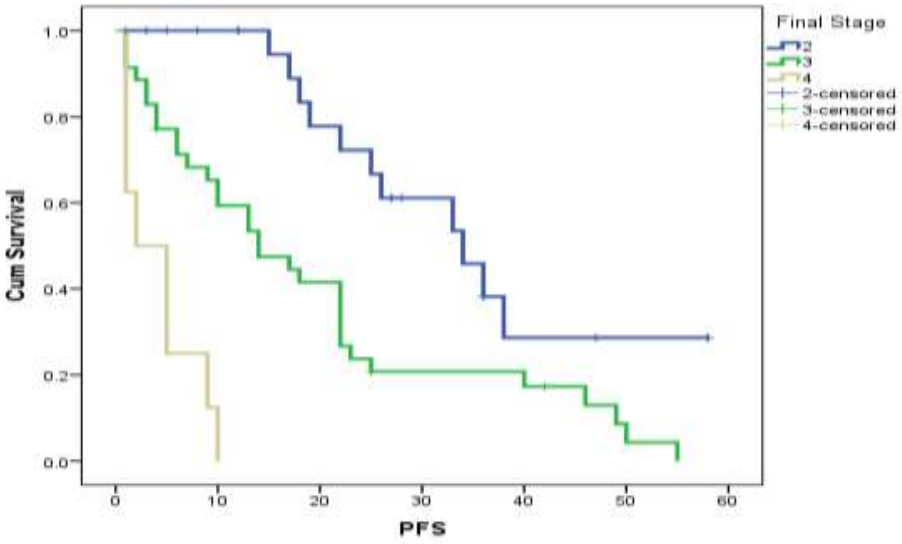

Figure 6: Kaplan Meier curve showing stage-wise distribution of progression free survival (PFS)

Three-year OS and 3-year PFS were 31.7% and 25.5%, respectively, for the entire cohort.
Additional taxane use to anthracycline-based chemotherapy regimen resulted in improved median survival (35.0 months vs. 17.0 months, P=0.033) [Figure: 7].

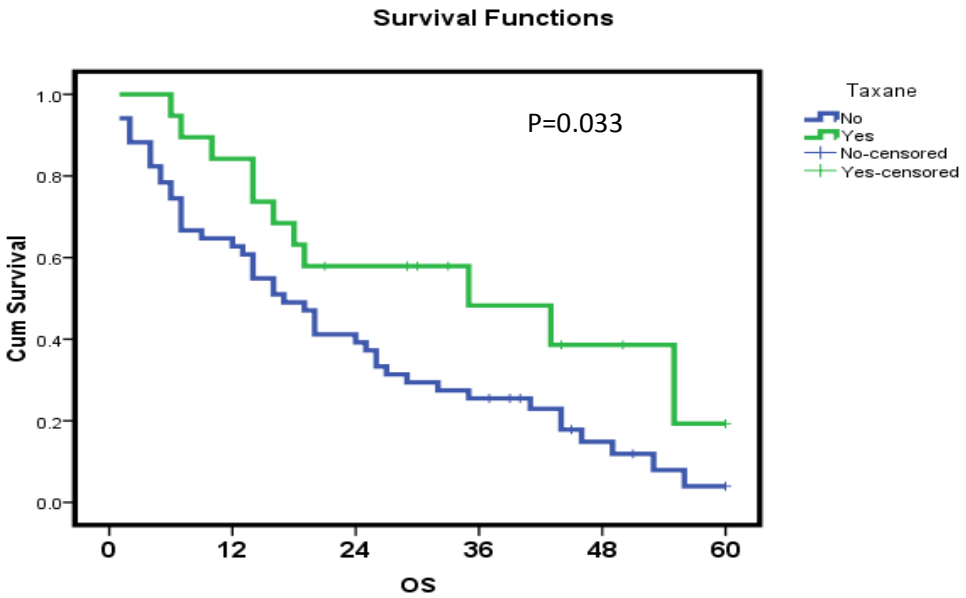

Figure 7: Kaplan-Meier curve showing overall survival (OS)with or without additional use of taxane-based regimen

Median OS was significantly better in patients who had completed the planned treatment (27.0 vs. 14.0 months P=0.002) [Figure: 8].

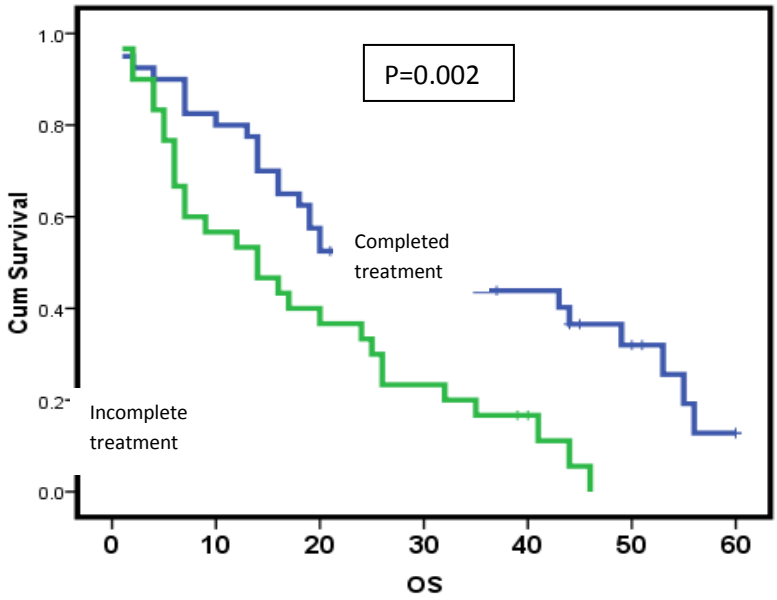

Figure 8: Kaplan-Meier curve showing improved OS for those who completed scheduled treatment

There is no significant correlation between distant relapse rate with higher T-stages (p=0.68), presence of lymphovascular space invasion (p=0.12), and node positivity (p=0.87).

IV. DISCUISSION

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is clinically negative for expressing estrogen and progesterone receptors (ER/PR) and HER2 receptor protein. It is characterized by its unique molecular profile, aggressive behaviour, distinct patterns of metastasis, lack of targeted therapies, and poorer overall survival. TNBC accounts for approximately 15% of breast cancers diagnosed worldwide [19]. Compared with hormone receptor-positive breast cancer, TNBC is more commonly diagnosed in women younger than 40 years. In this study, we have found that patients with TNBC present at a younger age which is comparable to other studies [20, 21]. Majority of our patients presented in the 5th decade of life with a mean age of 46.7 years, which is also similar to available worldwide data [22]. Infiltrating duct carcinoma (IDC) was the most common histopathological type in our study. IDC as the most common pathological sub-type has also been reported by Livasy et al. [23]. The less common histopathological types seen were invasive lobular carcinoma and medullary carcinoma, thus suggesting that the triple negativity can occur in all the histological subtypes of breast cancers [24, 25]. The majority of the patients with TNBC in our study had a high grade of the tumour (grade III in 74%), which correlated with the results obtained by Rakha EA et al. [26]. In our study, most of the patients presented with advanced stage of the disease (50% with TNM stage III and 12% with stage IV), and only 34% in stage II. Our findings were corroborated with another Indian study by Ajay et al. [27], where 45.3% of patients presented in stage III.

In contrast to our study, a Japanese study showed only 10.3% of patients with stage III disease [28]. This advanced presentation stage in developing countries like India could be due to lack of breast cancer awareness, belief in traditional medicine over western medicine, and poor access to health care. Approximately 12% of patients presented with metastasis, reflecting more biologically aggressive disease with early haematogenous spread. Visceral metastases are thought to be more common in TNBC [29]. However, we have found bone (50%) to be the most common site for metastasis at presentation, followed by liver (37%) and lung.

As TNBC lacks an obvious target, there remains a challenge in the optimal treatment strategy. A paradoxical finding is that triple-negative breast tumours often have a more profound initial response to chemotherapy than other phenotypes (i.e., ER and/or HER2 positive) despite poorer overall survival [30]. The inherent chemotherapy sensitivity of triple-negative breast cancer is not restricted only to the neoadjuvant setting. Although adding taxanes to adjuvant anthracycline-based regimens has been evaluated in various studies, the results in patients with TNBC are limited. In our study use of taxane added to

anthracycline-based chemotherapy resulted in significantly improved overall survival (P=0.033). In the adjuvant setting, a retrospective review of a subset of patients enrolled in the Cancer and Leukemia Group B (CALGB-9344) clinical trial indicated that the addition of a taxane (paclitaxel) to anthracycline-based chemotherapy provided the most significant benefit to patients with either HER2-positive or ER/HER2-negative breast tumours [31]. A subset analysis of several other studies showed the beneficial effect of adding taxane [32]. A meta-analysis of 12 randomized clinical trials also demonstrated that adjuvant docetaxel-based chemotherapy improves DFS and OS in TNBC compared with regimens without taxanes [33]. The association between BRCA1 dysfunction and triple-negative breast cancer has led to several neoadjuvant/adjuvant and metastatic studies evaluating platinum agents in the setting of triple-negative breast cancer [34].

The selection of surgical procedures depends on the extent of disease and patients' choice, social and cultural differences in the Indian population. Modified radical mastectomy was the commonest form of surgical procedure performed in patients with TNBC in most of the series, with 64% of patients underwent MRM in our study.

A limited number of studies have investigated the impact of treatment compliance on clinical outcomes. In the current study, we found improved survival in patients who had completed planned therapy with surgery, chemotherapy +/- radiotherapy in accordance with the stage of the disease (P=0.002). There appears to be a strong association between treatment compliance and improved survival. Likewise, Schwentner et al. [35] reported guideline-adherent adjuvant treatment associated with significantly enhanced survival parameters in TNBC patients.

In our study, distant recurrence was the most common pattern of failure affecting approximately one-third (34.3%) of patients with TNBC. This is in concordance with a study done by Dent et al. [9], which showed the incidence of distant metastasis was significantly higher in TNBC than non-TNBC. Compared to other breast cancer subtypes, metastatic TNBC disease tends to be more aggressive than metastatic non-TNBC subtypes and is more likely to have metastases in the viscera, particularly in the lungs and brain [36]. We observed lungs as the most common site of distant recurrence. We also observed an early distant failure with the median time to distant relapse at 17.5 months. The loco-regional failure rate in this study was 11.4% which was slightly more than that was found by Lori M et al. [37]. Both local and distant recurrences were more commonly seen during the first three years of the diagnosis. A similar type of recurrence pattern and time of recurrence was shown by Rebecca et al. [38]. However, we did not find any correlation between distant relapse rate with higher T-stages, lymphovascular invasion, node positivity, and additional use of taxane-based regimen.

Median overall survival (OS) was 19 months for the entire cohort, and median OS of metastatic disease was 4.2 months which was relatively lower than that found in a study done by Farrah et al. [39]. Median progression frees survival was 18 months, similar to the study done by Farrah et al. Three-year OS and 3-year PFS were 31.7% and 25.5%, respectively, for the entire study population. A study from the USA has shown a 3-year relapse-free survival (RFS) as 63% and overall survival as 71% [40]. Few European trials have shown 5-year RFS to be 68.2% and OS as 74.5% [41]. The difference in the survival outcomes across countries may be due to the differences in the stage of presentation (advance versus localized), treatment compliance (treatment adherent versus incomplete treatment), possible omission of metastatic disease from survival analysis, differences in the chemotherapy regimen used, and access to healthcare, etc.

The interpretation of these findings remains debatable due to the relatively small number of patients and the retrospective nature of this study. Being a retrospective one, unavoidable selection bias is a potential weakness of our study. Of note, our findings are consistent with the historical outcomes seen amongst the patients with TNBC in terms of poor prognosis. Randomized prospective studies are needed to improve prognosis further and to optimize treatment in patients with TNBC.

V. CONCLUSION

TNBC is an aggressive subtype of breast cancer associated with a higher grade of the tumour, and presented with advanced stage. Prognosis is poor, with an early peak of metastasis to visceral organs. TNBC subset of breast cancer is highly chemosensitive, and the addition of taxane to anthracycline-based regimens has a survival benefit compared to anthracycline-based regimens alone. The molecular typing of TNBC is necessary to understand the disease's complexity and develop therapies to improve survival further. Treatment adherence and availability of newer therapeutic options in resource restraint countries are needed to improve the survival in this subset of patients.

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