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ORIGINAL ARTICLE

A Comparative Study of Clinical Profile and Relapse Patterns in TRIPLE-NEGATIVE and Non-Triple-Negative Breast Cancer Patients Treated with Curative Intent

Suryanarayana V. S. Deo[1] · Nootan Kumar Shukla[1] · Ajay Gogia[2] · Daya Nand Sharma[3] · Ashish Jakhetiya[1] · Dillip Kumar Muduly[1] · Pankaj Kumar Garg[1,4] · Sandeep R Mathur[5] · V. S. Reenivas[6]

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Abstract Molecular subtyping in breast cancer is recently emerging as an important determinant of treatment and outcomes, and triple negative breast cancer (TNBC) has been established as a distinct clinical entity with unique features and adverse outcomes. A retrospective analysis of a prospectively maintained computerized breast cancer database was performed, and all the non-metastatic female breast cancer patients undergoing potentially curative multimodality treatment between 2005 and 2012 were included for analysis. Patients with incomplete information regarding ER, PR, and HER2/neu status were excluded. All the eligible patients were divided into TNBC and non-TNBC group based on molecular subtyping. A comparative analysis between the two groups was performed to analyze the clinical spectrum and patterns of relapse. A total of 861 patients qualified for the final analysis and the proportion of TNBC was 254 (29.5%) and non-TNBC was 607 (70.5%). Patients in the TNBC group were slightly younger than the non-TNBC group (median age 46 vs. 49, p value = 0.006). TNBC group had a higher breast conservation surgery (BCS) rate, and there was no difference in the need for chemo and radiotherapy between two groups. The overall recurrence rates were significantly higher in TNBC group compared to non-TNBC group (26.8 vs. 19.3%, p value = 0.01). Local disease recurrences were significantly higher in TNBC compared to non-TNBC (7.9 vs. 3.1%, p value = 0.002). Both the regional and systemic recurrences were higher in TNBC group compared to non-TNBC, though the difference failed to attain statistical significance (for regional recurrences 2.4 vs. 1.5%, p value = 0.36; for systemic recurrences 23.2 vs. 17.8%, p value = 0.06). The brain metastasis was significantly higher in TNBC group (6.7 vs. 3.3%, p value = 0.02). In addition, time to relapse was also significantly less in TNBC cohort (16.1 vs. 22.1 months). TNBC accounts for almost one-third of the breast cancer patients with a relatively younger age at presentation, higher volume of disease burden and high breast conservation rates. Despite a standard multimodality therapy the local, systemic, and CNS recurrence rates are high in TNBC and majority relapse within first 2 years after completion of therapy.

Keywords Breast neoplasm · Molecular subtypes · Estrogen receptor · Progesterone receptor · Her2/neu receptor · Recurrence

✉ Suryanarayana V. S. Deo
svsdeo@yahoo.co.in

[1] Department of Surgical Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

[2] Department of Medical Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

[3] Department of Radiation Oncology, Dr BRA Institute Rotary Cancer Hospital, All India Institute of Medical Sciences, New Delhi 110029, India

[4] Department of Surgery, University College of Medical Sciences and Guru Teg Bahadur Hospital, University of Delhi, Delhi 110095, India

[5] Department of Pathology, All India Institute of Medical Sciences, New Delhi 110029, India

[6] Department of Biostatistics, All India Institute of Medical Sciences, New Delhi 110029, India

Introduction

Breast cancer continues to be the most common cancer among women worldwide [1–3]. Recent advances in the

field of breast cancer research have shown that breast cancer is a constellation of biologically diverse tumors with different clinical behaviors, response to treatment, and prognosis. Identification of key biomolecular and genetic markers during the last decade has facilitated in classifying breast cancer into different molecular subtypes. After extensive clinical validation molecular subtyping is now emerging as a major prognostic and predictive variable for breast cancer management. Apart from influencing decisions regarding systemic therapeutic options, it is also slowly making inroads in to surgical decision making as well. Based on the original gene expression profile work, four clinically important molecular subtypes of breast cancer were identified—ER positive/luminal-like, basal-like (cytokeratin 5/6 and 17 positive), normal breast-like (expression of basal epithelial genes with low expression of luminal epithelial genes), and ERB-B2 positive (Erb-b2 or Her2/neu positive). On further analysis, luminal types were classified into luminal A, B, and C depending upon levels of estrogen receptor expression and some other novel sets of genes. An important implication of this classification was that ER negative tumors have two distinct subtypes (basal-like and ErbB2 enriched) that should be treated as distinct disease [4, 5]. Triple negative breast cancer is further defined as ER negative, PR negative, HER2 negative, cytokeratin 5/6 positive and/or epidermal growth factor receptor positive for better understanding [4–6]. In the absence of widely available gene expression analysis, surrogate classification is widely used in clinical practice using immunohistochemical markers for ER/PR/Her2 receptors along with FISH in HER2 equivocal cases.

Among the various molecular-subtypes, TNBC has managed to generate significant interest among the oncology community due to its unique clinical behavior, adverse prognosis and management challenges [6]. Wide disparity has been reported in the frequency of TNBC in various racial groups. Though western literature suggests that TNBC accounts for 10 to 20% of invasive breast cancers a relatively higher frequency (30 to 35%) is reported in premenopausal African-American women [6, 7] and in studies from Asian countries [8–10]. Besides displaying a molecular heterogeneity, many studies have revealed that TNBC affects younger age group, displays more aggressive behavior, recurs more frequently, and results in poor survival [10]. Review of literature also showed few studies of TNBC reporting contrary outcomes [8, 9, 11]. Due to lack of specific therapeutic targets a combination of anthracycline and taxane based chemotherapy along with surgery with or without radiotherapy is the current standard of care for TNBC. This retrospective study was performed to evaluate the differences in clinical profile and patterns of relapse in TNBC patients in comparison to non-TNBC patients.

Methods

A retrospective analysis of the prospectively maintained computerized breast cancer database was performed to retrieve details of the all the breast cancer patients who had undergone surgical treatment as part of multimodality therapy during 2005 to 2012. The patients were included if they were female, aged more than 18 years, non-metastatic at presentation, and having histopathologically proven invasive ductal cancer with ER, PR and HER2/neu status availability. For the purpose of the study, TNBC was defined as tumors which were negative for all three receptors—ER, PR and HER2 (IHC 0, 1 + staining, or FISH negative in case of 2 + staining). Any ER/PR positivity or Her2/neu positivity (IHC 3+ staining or FISH positive in case 2+ staining) were labeled as non-TNBC tumors. Those patients who did not have complete information regarding clinical details or receptor status were excluded from the present study.

A consistent protocol-based treatment strategy was followed during the study period. Detailed history including clinical presentation, presence of risk factors, comorbidity, and family history was recorded for all patients. Apart from a detailed clinical examination local imaging including mammography was performed in all patients and MRI was performed when indicated. Core-needle biopsy was performed in all patients for histopathological confirmation of diagnosis and hormonal receptor and Her2/neu status estimation. Metastatic work-up included chest X-ray, ultrasonography or CT scan of abdomen and pelvis, bone scan, and other imaging including PET scan if clinically indicated. AJCC—2010 staging system based on tumor, node, and metastatic extent of lesions was used for staging purpose.

All the patients were treated with protocol based multimodality treatment. Early breast cancer (EBC) which included stage I and II were offered surgery upfront in the form of breast conservation surgery (BCS) in patients fulfilling standard selection criteria, and the remaining had modified radical mastectomy. Axillary lymph node dissection (ALND) was performed in patients with clinically palpable nodes in axilla while sentinel lymph node biopsy (SLNB) was performed in clinically node-negative axilla. Locally advanced breast cancer (LABC), stage III were divided into upfront operable and inoperable patients based on clinical assessment. Inoperable LABC was defined as having extensive ulceration/peu D'orange, presence of fixed axillary nodes or supraclavicular or infra-clavicular nodes, presence of arm edema, or inflammatory breast cancer. Operable LABC were managed with upfront surgery followed by chemotherapy and radiotherapy. Neo-

adjuvant systemic therapy followed by surgery and radiotherapy was used for inoperable LABC patients [12].

Surgical decisions were purely taken based on TNM staging, imaging findings, tumor breast ratio, and patients desire.

Systemic treatment decisions were taken as per standard NCCN guidelines including menopausal status, tumor size, axillary nodal, hormone receptor, and HER2 status. Standard anthracycline and taxane-based regimens were used in neo-adjuvant and adjuvant settings. Patients with hormone receptor positivity were prescribed tamoxifen for premenopausal and aromatase inhibitors for postmenopausal women. TNBC patients were not offered any hormonal therapy. Trastuzumab could not be given in majority of Her2/neu positive patients due to financial reasons.

Postoperative radiotherapy was given to all EBC patients who underwent BCS and all LABC patients. After completion of the treatment patients were followed at three monthly intervals for 2 years, at six monthly intervals till 5 years, and annually thereafter.

Data pertaining to clinical profile including demographics, clinical, and histopathological details, treatment profile and relapse patterns including time to relapse and patterns of relapse were extracted from the database for TNBC and non-TNBC groups, and a comparative analysis was performed using following statistical methods.

Statistical Analysis

Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) software (version 16, SPSS, Inc., Chicago, IL, USA). Parametric and non-parametric quantitative data was displayed as mean (standard deviation) and median (inter-quartile range) while qualitative data was represented as proportions/percentage [13–15]. Chi-square test and Mann Whitney *U* test was used to compare qualitative variables and for quantitative variables in non-TNBC and TNBC groups.

Results

There were a total of 1487 female patients of breast cancer underwent surgery during the study period. However 861 patients where information regarding all three receptor status was available fulfilled the inclusion criteria and were qualified for the final analysis. There were 254 breast cancer patients whose tumor tested negative for all three receptors (ER, PR and Her2,) comprising TNBC group and the remaining 607 were grouped as non-TNBC group. The frequency of TNBC and non-TNBC patients in the present study was 29.5 and 70.5%, respectively.

Table 1 displays the clinicopathological characteristics of the entire patient cohort. The TNBC patients were relatively younger compared to non-TNBC (median age 46 vs. 49 years, *p* value 0.006). Tumors were relatively larger in size (both clinical and pathological) in TNBC compared to non-TNBC patients. A higher number of patients had T3 and T4 tumors and relatively less number of patients had pathological axillary node positivity in TNBC group. There was no difference among margin status, extra-nodal spread, and skin involvement in both the groups. Among early breast cancer patients, a higher number of patients underwent breast conservation surgery (BCS) in TNBC group compared to non-TNBC group (40.4 vs. 22.1%, *p* value 0.001). As far as chemotherapy is concerned, there was no statistically significant difference in the need for chemotherapy including neo-adjuvant chemotherapy (NACT) in both the groups. In the TNBC group, pathological complete response (CR) rate among LABC patients who received NACT was 20/89 (22.8%) while it was 11/48 (22.9%) in the non-TNBC group. A slightly higher number of TNBC patients received radiotherapy due to high BCS rates (Table 1).

Table 2 shows patterns of relapse in both the groups. At a median follow-up of 32.4 months (IQR 19–52.9) higher number of disease recurrences were observed in TNBC compared to non-TNBC group (26.8 vs. 19.3%, *p* value 0.015). Median time to recurrence in TNBC groups was significantly shorter than in non-TNBC group (22.1 vs. 16.1 months, *p* value 0.00). Local disease recurrences were significantly higher in TNBC compared to non-TNBC group (7.9 vs. 3.1%, *p* value = 0.002). There was no significant difference in regional recurrences in two groups (2.4 vs. 1.5%, *p* value = 0.368). Though systemic recurrence were also observed in a higher number of TNBC patients compared to non-TNBC (23.2 vs. 17.8%), it failed to reach statistical significance (*p* value = 0.06). The frequency of brain metastasis were significantly higher in TNBC group (6.7 vs. 3.3%, *p* value = 0.025).

Discussion

Last three decades has witnessed a paradigm shift in the understanding of breast cancer biology and approach to management. There is a gradual transition from the traditional morphometric TNM staging system based on tumor size and extent of disease to the era of biology based molecular subtyping and precision medicine. High quality basic research and robust clinical validation has established the role of molecular subtyping in the prognostication, treatment planning and prediction of response to therapy in breast cancer patients. Among the various molecular subtypes TNBC has managed to generate significant interest due to its unique biology and challenges in management. As per published literature, TNBC constitutes 10–20% of all invasive breast cancer patients among North American and European population [7]. There is paucity of literature related to TNBC especially from developing countries. Few publications from Asia reported a relatively higher proportion of TNBC among Asian population [8, 9, 16, 17]. Even though majority of published literature indicate adverse outcomes in TNBC patients few studies have

Table 1 Clinicopathological characteristics and treatment profile of TNBC and non-TNBC groups

Clinical details		Total patients (n = 861)	Non-TNBC (n = 607)	TNBC (n = 254)	Non-TNBC vs. TNBC, p value[a]
Age					
	Mean (SD), in years	48.4 (11.4)	49.1 (11.1)	46.8 (12.0)	*0.006*
Tumor size					
	Mean (SD), in cm	4.8 (9.4)	4.8 (2.1)	5.4 (3.0)	*0.010*
Clinical stage					
	T1	70 (8.1%)	44 (7.2%)	26 (10.2%)	0.113
	T2	335 (38.9%)	253 (41.7%)	82 (32.3%)	
	T3	114 (13.2)	78 (12.9%)	36 (14.2%)	
	T4	342 (39.7%)	232 (38.3%)	110 (43.3%)	
Clinical *N* stage					
	N0	276 (32.0%)	200 (32.9%)	76 (29.9%)	0.362
	N1	385 (44.7%)	276 (45.5%)	109 (42.9%)	
	N2	170 (19.7%)	111 (18.3%)	59 (23.2%)	
	N3	30 (3.5%)	20 (3.3%)	10 (3.9%)	
Histopathological details					
Tumor size					
	Mean (SD), in cm	4.9 (9.4)	4.7 (9.7)	5.2 (8.9)	*0.007*
Margins					
	Negative	848 (98.5%)	599 (98.7%)	249 (98.0%)	0.527
	Positive	13 (1.5%)	8 (1.3%)	5 (2.0%)	
Pathological node status					
	pN0	376 (43.7%)	247 (40.7%)	129 (50.8%)	0.058
	pN1	220 (25.6%)	162 (26.7%)	58 (22.8%)	
	pN2	169 (19.6%)	126 (20.8%)	43 (16.9%)	
	pN3	96 (11.1%)	72 (11.9%)	24 (9.4%)	
Extracapsular spread					
	Absent	716 (83.2%)	497 (81.9%)	219 (86.2%)	0.120
	Present	145 (16.8%)	110 (18.1%)	35 (13.8%)	
Skin involvement					
	Absent	737 (85.6%)	526 (86.7%)	211 (83.1%)	0.172
	Present	124 (14.4%)	81 (13.3%)	43 (16.9%)	
Treatment details					
Surgery					
	BCS	EBC = 26.7%, (96/360) LABC = 8.2% (41 /501)	EBC = 22.1% (60/271) LABC = 8.8% (23 of 336)	EBC = 40.4% (36/89) LABC = 10.9% (18 /165)	For EBC–BCS vs. mastectomy *0.001*; For LABC–BCS vs. mastectomy 0.119
	Mastectomy	EBC = 73.3% (264/360) LABC = 91.8% (460/501)	EBC = 77.9% (211/271) LABC = 93.2% (313/336)	EBC = 59.6% (53/89) LABC = 89.1% (147/165)	
Chemotherapy					
	Yes	794 (92.2%)	553 (91.1%)	241 (94.9%)	0.068
	No	67 (7.8%)	54 (8.9%)	13 (5.1%)	
Neo-adjuvant chemotherapy					
	Yes	144 (16.7%)	91 (15.0%)	53 (20.9%)	0.090
Radiotherapy					
	Yes	285 (33.1%)	214 (35.3%)	71 (28.0%)	*0.038*
	No	576 (66.9%)	393 (64.7%)	183 (72.0%)	
Patterns of relapse and survival					
Time to recurrence	Median time (in months)	19.6 (10.0–28.6)	22.1 (12.6–32.9)	16.1 (8.0–24.0)	*0.000*

Table 1 (continued)

Clinical details		Total patients (n = 861)	Non-TNBC (n = 607)	TNBC (n = 254)	Non-TNBC vs. TNBC, p value[a]
Status of patients at last follow-up					
	Alive and disease free	680 (79.0%)	494 (81.4%)	186 (73.2%)	*0.011*
	Alive but with disease	75 (8.7%)	51 (8.4%)	24 (9.4%)	
Mortality	Died	106 (12.3%)	62 (10.2%)	44 (17.3%)	

[a] Chi-square test for qualitative variable and Mann-Whitney U test for quantitative variable

shown no significant difference in outcomes [8, 9, 11]. The current study is one of the largest retrospective cohort studies addressing the issue of clinical profile and patterns of relapse in TNBC and non-TNBC patients.

The reported wide variation in proportion of TNBC can be attributed to a number of factors including racial and ethnic factors, type of criteria adopted for defining receptor status, and technical issues related to processing of biopsy samples. In an analysis of 91,908 invasive breast cancers diagnosed in California between 2006 and 2009, Clarke et al. reported that African-American women had significantly higher rates of TNBC at all ages compared with White women [18]. Using the population-based California Cancer Registry data (6370 women of TNBC and 44,704 women with other breast cancers diagnosed between 1999 and 2003), Bauer et al. reported that TNBC affects younger women (for age < 40 years, odds ratio, 1.53), non-Hispanic black (odds ratio, 1.77), and Hispanics (odds ratio, 1.23) [6].

Reports from Asian subcontinent reported a relatively higher frequency (25 to 30%) of TNBC in comparison to western studies [9–11, 19]. In the current study, TNBC constituted 29.5% of all patients treated with a curative intent. Similarly, Nabi et al. [11] reported a 34.4% and Sharma et al. [16] reported 31.9% TNBC rates in North and Northeast Indian populations [16, 17]. In a previous publication from the same institution, Gogia A et al. [9] reported 21.0% TNBC in a different cohort of patients which included stage IV breast cancer patients with distant metastases. The present study corroborates the findings of these studies and highlights higher frequency of TNBC among Asian population.

As far as the clinical profile is concerned results of the current study shows that TNBC patients are younger than non-TNBC patients and tumor size and proportion of T3 and T4 tumors was higher in TNBC cohort. Other significant outcomes include relatively less frequency of axillary nodal involvement and higher breast conservation rates in TNBC patients. In general, TNBC present with well-circumscribed tumors and believed to grow in an expansile fashion and respond to neo-adjuvant therapy by concentric shrinkage with a higher pathological complete response rates [9, 20, 21]. Young age, good breast size and well-circumscribed nature of TNBC tumors might have facilitated more BCS in this group.

TNBC is considered an aggressive subtype affecting younger age group. The previous studies reported that majority of the TNBC patients are middle aged females in their 40s. Young age is considered a poor prognostic variable for disease recurrence in breast cancer; however, whether this notion holds true in TNBC compared to other molecular subtypes is not yet clear. In a retrospective analysis of two large databases of Korean breast cancer patients (n = 2474), Kim et al. reported that young age (<35 years) was an independent predictor of disease recurrence and poor cancer-specific survival in non-TNBC but not in TNBC [22]. In contrast to these findings, Cancello et al. reported that younger patients (<35 years) have

Table 2 Patterns of relapse in TNBC and non-TNBC groups

	Total (n = 861)	Non-TNBC (n = 607)	TNBC (n = 254)	p value[a]
Type of recurrence	185 (21.5%)	117 (19.3%)	68 (26.8%)	0.015
Local	39 (4.5%)	19 (3.1%)	20 (7.9%)	0.002
Regional	15 (1.7%)	9 (1.5%)	6 (2.4%)	0.368
Systemic	167 (19.4%)	108 (17.8%)	59 (23.2%)	0.066
Lung	73 (8.5%)	46 (7.6%)	27 (10.6%)	0.433
Liver	70 (8.1%)	50 (8.2%)	20 (7.9%)	0.859
Bone	62 (7.2%)	41 (6.8%)	21 (8.3%)	0.143
Brain	37 (4.3%)	20 (3.3%)	17 (6.7%)	0.025
Others	4 (0.5%)	2 (0.3%)	2 (0.8%)	0.368

[a] Chi-square test

a worse prognosis when compared with older patients with similar characteristics of disease irrespective of TNBC or non-TNBC status; though the highest risk of recurrence was observed in Her2 positive patients [20].

Aggressiveness of a particular subtype can be illustrated by early and frequent disease relapse following curative treatment. Results of the current study showed a significantly higher overall disease recurrence rates (26.8 vs. 19.3%) and shorter median time to recurrence (16.1 vs. 22.1 months) in TNBC patients. As far as the types of recurrence are concerned, TNBC cohort had higher local and systemic recurrences, and there was no difference in regional relapse rates. A number of studies have reported a significantly higher loco-regional recurrences following BCS or mastectomy in TNBC patients in comparison to luminal variants due to the intrinsic biology. In a study comprising 12,952 patients of breast cancer from Ireland [23], it was reiterated that TNBC patients are at higher risk of developing loco-regional recurrence following BCS or mastectomy: patients with luminal subtype tumors had a lower risk of LRR than TNBC following BCT (RR 0.38; 95% CI 0.23–0.61) or mastectomy (OR 0.61; 95% CI 0.46–0.79). The authors concluded that molecular subtype should be amalgamated in clinical decision while contemplating local control to identify those at increased risk of loco-regional recurrence, who may benefit from more aggressive local treatment. A study from MD Anderson Cancer Center also reported a higher chance of disease recurrence and poor survival in TNBC compared to non-TNBC within first 3 years of cancer diagnosis. The authors detected decreased 3-year progression-free survival (PFS; $p < 0.0001$) and 3-year overall survival (OS; $p < 0.0001$) rates for TNBC compared with non-TNBC [21]. Furthermore, Ribelles et al. suggested that presence of high Ki67 index in TNBC patients leads to early recurrence; TNBC patients with low Ki67 index display average recurrence risk [24]. In a previous study from the same institution, Gogia et al. [9] reported a decreased PFS among TNBC but no significant difference in overall survival outcomes between two groups.

Another interesting recurrence pattern in TNBC is predilection for brain metastasis. In the present study, brain metastasis was significantly higher in TNBC compared to non-TNBC subtype. A study conducted at Dana-Farber Cancer Institute to characterize the outcomes of patients with metastatic TNBC reported that 14% of TNBC were diagnosed with brain metastasis at the time of initial metastatic work-up, and 46% were diagnosed to have brain metastasis prior to death. The authors concluded that death as a direct consequence of CNS progression in the setting of controlled systemic disease is uncommon even though CNS relapse is common in TNBC. They further highlighted that high rate of CNS involvement is unlikely to be due to a sanctuary effect, but rather to the lack of effective therapies in general for TNBC [25].

Our study has some limitations. We included only non-metastatic patients where all three receptor statuses were available; data on histological grade was not available for all patients so grade was not included in any of the analysis.

Conclusion

Molecular subtyping of breast cancer is emerging as an important determinant of treatment outcomes in breast cancer. Results of the current study indicate that TNBC accounts for almost one-third of the breast cancer patients. TNBC patients are relatively young, present with a larger tumor size, higher proportion of T3 and T4 tumors and relatively higher breast conservation rates than non-TNBC patients. In addition, the overall and CNS relapse rates were higher in TNBC patients with a significantly shorter relapse-free interval.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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Retrospective Study For this kind of study, formal consent is not required. Complete anonymity is maintained for all included participants.

This article does not contain any studies with animals performed by any of the authors.

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