

Analysis of Patterns of Recurrence & Survival In Triple Negative Breast Cancer Patients In A Rural Based Medical College Hospital of West Bengal, India : A Retrospective Study

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Abstract

Introduction: Breast cancer is a heterogeneous disease with different morphological features and clinical behavior ^[1]. One of its subtypes is Triple Negative Breast Cancer (TNBC) which means no expression of Estrogen & Progesterone receptor and Her 2- neu status. ^[2,3]

Aim of this study is to evaluate recurrence pattern & survival in patients diagnosed with TNBC from April 2010 to March 2015 in a rural medical college of West Bengal. Total no of patients included in this study (n) was 239. Disease free survival (DFS) and overall survival (OS) were calculated using the Kaplan – Meier method.

Results - Median age at the time of diagnosis was 40 yrs(range 22-72 yr) . Majority of patients were in stage II and stage III disease. After 3 yrs total 84 patients (35.14%) developed recurrence of which most common was visceral metastases (68.36%) . DFS at 3 yrs was 64.43%) and OS was 75.73%). After 5 yrs metastases occurred in 41.42% .The highest risk of recurrence was during first 3 yrs after primary treatment. 5 yr DFS 61.08% and Os 71.54%.

Conclusion: TNBC is an aggressive disease involving younger & pre menopausal patients with higher stage. TNBC has a unique pattern of metastasis usually occur in first 3 years of diagnosis & it is mostly visceral. More no. of prospective randomized controlled trials are required to find out more effective treatment to increase survival (DFS & OS) in TNBC patients.

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I. Introduction

According to ASCO guidelines and the latest St Gallen consensus triple negative breast cancer (TNBC) only if there is no expression estrogen and progesterone receptor and there is neither expression nor amplification of human epidermal growth factor receptor 2 in a tumor. ^[2] TNBC accounts for about 15.25% of all breast cancers. ^[3,4] TNBC patients have poorer prognosis compared with other molecular subtypes of breast cancer. ^[5] They are at higher risk of early recurrence mainly in lungs, brain and soft tissue. ^[6,9,14,15,16] The highest risk of relapse is between the first and third year after primary treatment. ^[19,22] In case of recurrence survival is shorter than in non TNBC patients. ^[23] However, TNBC is more sensitive to chemotherapy. ^[11,13] The rate of pathological complete response (p CR) after neoadjuvant chemotherapy is higher than in other subtypes. ^[13] Method of treatment in TNBC group is limited due to lack of molecular targets. Adjuvant treatment is usually recommended in TNBC and should include anthracyclines, taxanes and an alkylating agent. The aim of our study was to analyze pattern of recurrence and survival in a group of consecutive 239 TNBC patients treated at Bankura Sammilani Medical College, West Bengal, India between the years 2010 and 2015.

II. Material & Methods

1. Type of study : Retrospective study.
2. Place of study : Bankura Sammilani Medical College and hospital, West Bengal, India.
3. Study duration : April 2010 –March 2015.
4. Study population : Carcinoma breast patients who are triple negative (i.e ER, PR & HER2 negative)

2.1 Inclusion Criteria : Female patients with carcinoma breast (stage I, II, III, IV) who are triple negative .

2.2 Exclusion Criteria : i) patients who are unwilling to undergo chemotherapy.

ii) patients who had dearranged liver function tests , severe cardiac problems or some other severe medical diseases.

2.3 Study Variables : Menopausal status of patient, tumor type, nodal status, stage of the disease at diagnosis, surgical treatment, systemic neoadjuvant treatment, adjuvant radiotherapy , recurrence and survival.

2.4 Statistical Methods : The pattern of recurrence and survival in TNBC was determined using descriptive statistics. Disease free survival (DFS) , defined as the time from diagnosis of TNBC to first locoregional or distant metastasis or recurrence. Overall survival (OS) , defined as the time from diagnosis of TNBC to death. DFS and OS curves were calculated using the Kaplan- Meier method.

Recurrence rates were presented by cumulative hazard rate and annual hazard rate.

III. Results

1. Total number of patients taken for the study (n) was 239.
2. Median age of patients at diagnosis was 47 yrs. (Range 22 yr- 72 yrs)
3. Majority of patients were diagnosed were diagnosed with stage II & III (29.28% &62.76% respectively) and only 10 patients (4.1%) had evidence of distant metastasis at initial diagnosis.
4. 160 patients (66.94%) had positive axillary lymph node at presentation.
5. The most common histological type was infiltrative duct carcinoma (89.95%).
6. Systemic neoadjuvant chemotherapy was given to 160 patients (66.94%) due to locally advanced breast cancer.
7. Modified radical mastectomy was the most common type of surgery , performed in 224 patients (93.72%).
8. 210 patients (87.86%) received adjuvant chemotherapy.

IV. Recurrence

During the 5 years of observation metastatic disease occurred in one third of all TNBC patients. Majority of patients had metastasis in different sites. Visceral metastasis was more common. The highest risk of recurrence was during first 3 years after primary treatment. Then during the next 2 years of observation it did not change significantly. (i.e. plateau after 3 years). (FIGURE 1). Cumulative hazards of metastasis are presented in Table 2. The risk of new metastasis after 3 years from primary treatment was very low.

V. Survival

1. During the first 3 years of observation, 58 patients died while during the next 2 years 10 patients died.
2. During the first 3 years DFS & OS were 64.43% & 75.73% respectively.
3. After 5 years DFS & OS were 61.08% & 71.54% respectively. (Table 3).

Table 1:-

PATIENTS & TUMOR CHARACTERISTICS	NO. OF PATIENTS	%
MENOPAUSAL STATUS		
Pre & peri menopausal	143	60.3%
Post menopausal	96	39.7%
TUMOR TYPE		
Invasive duct carcinoma	215	89.95
Invasive lobular carcinoma	7	2.94
Others	17	7.11
NODAL STATUS		
Positive	130	58.15
Negative	109	33.06
SURGICAL TREATMENT		
Modified radical mastectomy	224	93.72
Breast conserving surgery	12	5.02
Palliative mastectomy	3	1.26
TNM STAGING AT DIAGNOSIS		
I	9	3.77
II	70	29.29
III	150	62.76
IV	10	4.18
SYSTEMIC NEO – ADJUVANT THERAPY GIVEN :-		
YES	160	66.94
NO	79	33.06
ADJUVANT THERAPY (RT)		

GIVEN	210	87.86
YES	29	12.14
NO		
TYPES OF NEO- ADJUVANT TREATMENT :-		
DOXORUBICIN BASED	73	45.62
TAXOL+ DOXO BASED	85	53.13
OTHERS	2	1.25

Table 2: Recurrence

After 3 Years –

Local relapse – 6

Distant metastasis -73 (Excluding 10 patients who had metastasis at initial diagnosis).

Death -58

After 5 Years –

Distant metastasis – 14

Death -10

Distribution Of Recurrence	After 3 Years	After 5 Years
Local Relapse Only	6 (7.59%)	Nil
Visceral	54 (68.36%)	10 (71.42%)
Bones Only	11(13.93%)	2 (14.28%)
Soft Tissue Only	6 (7.59%)	1(7.14%)
Soft Tissue + Bones	2 (2.53%)	1 (7.14%)

TABLE 3: - Survival

AFTER 3 YEARS –

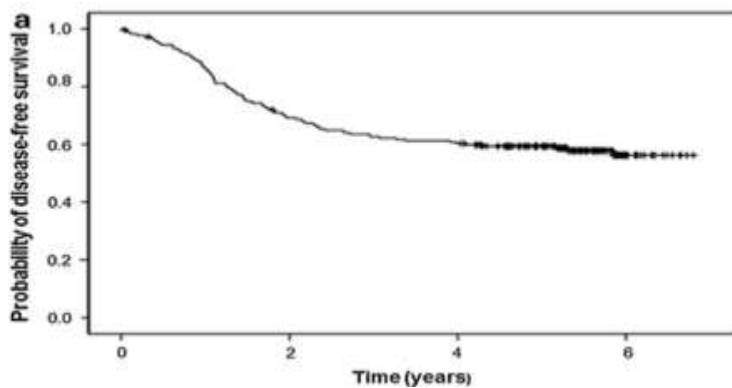
DFS = 64.43%

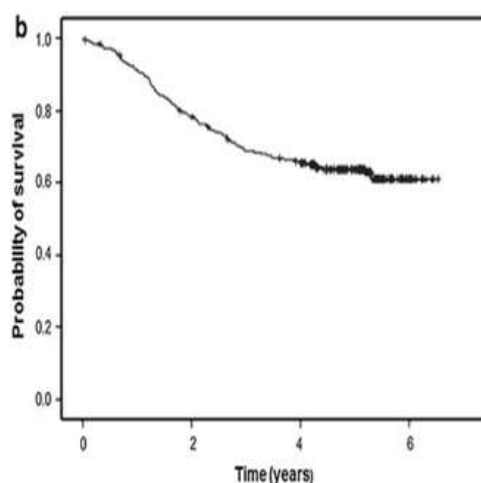
OS = 75.73%

AFTER 5 YEARS –

DFS = 61.08%

OS = 71.54%





a Disease-free survival (DFS) and b overall survival (OS) in triple-negative breast cancer patients

VI. Discussion And Summary

The incidence of TNBC in our study was 18.3%, which is within range as world criteria (15.25%). In recent studies TNBC reported to be the most common molecular subtype in India mainly in North India. (Akhter et al 2015, Nigar J et.al 2014). Ranpranam et.al respectively analyzed 636 patients and incidence of TNBC was 24.4%. In our study we have included 257 patients but 18 patients lost to follow up. So total 239 patients were studied (n= 239). 10 patients presented with distant metastasis. Median age at presentation was 40 years. Predominant age group was pre menopausal (60.3%) & most of the patients presented with locally advanced stage (stage III - 81.5%).

TNBC usually diagnosed at younger age. In present study median age at diagnosis 40 yrs. Different Indian & Western literatures have also shown that TNBC is more frequent at young age.^[8] It also presents with higher stage compared to other molecular subtypes.^[32] In our study total 62.76% patients presented in stage III. Nodal positivity was 58.15%. This is consistent with literature where TNBC is associated with higher stage. The features of nodal involvement at diagnosis in TNBC patients differ in various studies with conflict results.^[31,33,34] Lin et.al demonstrated recently that TNBC patients were less likely to be lymph node positive. But in our study nodal positivity was 58.15% which is consistent with 54.4% reported in other studies. The risk of recurrence in TNBC patients is highest in first 3 years after treatment & additionally 20% greater incidence of visceral metastasis compared to other subtypes of breast cancer which commonly metastasize to bone.^[24,25] In our study recurrence in first 3 years was 34.5% of which 68.36% had visceral & 13.93% had bone metastasis.

Dent et. al. reported that rise of recurrence rose sharply from the time of diagnosis & maximum during first 3 years & then falls. Similarly in another study the risk of relapse was strongly time dependent & dramatically highest during first 3 years after diagnosis.^[22,26,30] Dent et. al. (2007) found that TNBC patients had more likely hood of distant recurrence & death from breast cancer within 5 years of diagnosis. The same phenomenon occurred in our study. Maximum recurrence (Total 79 & 34.5%) had developed in first 3 years of which maximum was distant recurrence. 6 patients had local relapse whereas 73 patients had distant recurrence in first 3 years. In distant recurrence most common was visceral (68.36%).

Liedtke et.al. (2008) also reported similar findings in recurrence. Regarding survival they also reported that death rate is higher only in first 3 years & reaching plateau after that period. In our study we noted a similar significant drop in OS & DFS in the first 3 years. In 3 years DFS – 64.43% & in 5 years DFS- 61.08%. OS in our study was 75.73% after 3 years & 71.54% after 5 years.^[19,22]

There are conflicting reports about local recurrence rates in TNBC while some report showed a very low incidence of loco regional relapse in TNBC of 3 -8% (Freedamn et.al, Ngnyim et.al 2008, Solin et.al 2009). But other studies showed this to be in the range of 10 -20%. (Dent et.al 2007, Abdul karim et.al 2011, Hafftus et. al 2006, Vedic et.al 2010).^[9,14] In our study all the local recurrences occurred in first 3 years & it was 7.59% & in 5 years there was no local recurrence. Metastatic behavior of TNBC also is quite distinct compared to other subtypes. TNBC tends to metastasize more commonly to viscera compared with hormone receptor positive cancers. TNBC has been reported to have lung metastasis compared with other sites. It also has a lower rate of bone involvement (Anders & Careus 2009, Fonkes et al 2010, ragails et al 2011). Similarly in our study most common site of recurrence is visceral (68.36%) at 3 years & 71.42% at 5 yrs. In bones it is 11% at 3 years and 2% at 5 years. In Kennecke et. al^[24] bone metastasis is 16.6% & visceral metastasis was 55.9%. In our study bone metastasis is similar to reported by Kennecke et. al. and visceral metastasis is slightly greater, probably that is due to increased no. of patients in Stage III in our study.^[29,30]

Our study has several limitations including it is an observational design, paucity of information regarding surgical management & access to long term follow up care also was not available for our analysis. However our study is a large data set including only triple negative subtype. Nonetheless the factors affecting failure patterns & survival outcome have a complex relationship & future research is needed to better understand our results.^[35]

VII. Conclusion

TNBC is an aggressive disease involving younger & pre menopausal patients with higher stage. TNBC has a unique pattern of metastasis usually occur in first 3 years of diagnosis & it is mostly visceral. More no. of prospective randomized controlled trials are required to find out more effective treatment to increase survival (DFS & OS) in TNBC patients.

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