Pattern and Risk Factor Influencing Recurrence Pattern in Triple Negative Breast Cancer at Cancer Hospital in North India

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Abstract:
Background Commonest breast cancer in India among female is breast cancer. This is heterogeneous disease, one of subtype triple negative breast cancer defined as no expression of Estrogen and progesterone receptor and expression and amplification of Her2 neu. TNBC is more frequent and aggressive in younger age group. The aim of this study was to evaluate recurrence pattern and outcomes in cohort of younger age group diagnosed with TNBC.
Material and Methods- Medical record of 730 patients diagnosed with invasive breast cancer from January 2010 to December 2014 was retrieved. Cohort of 178 TNBC patients was included and analysed the clinical and pathological characteristic. DFS and OS curves were calculated using the Kaplan-Meier method.
Results- Mean age at the time of diagnosis was 43.91 years (range 22-72), a total of 82 patients developed recurrence/ metastasis during 6 years of observation. The median OS and DFS for the entire group are 22 months and 11 months respectively. In patients who develop metastasis OS is 22.64 months as compared to 26.11 months in those who do not develop metastasis (p =0.08). The most common site of the first recurrence was loco-regional followed by bone and lung
Conclusion- TNBC is an aggressive disease mainly involving younger age group. The peak risk of recurrence of the disease is between the first and third year following diagnosis, and that survival after recurrence is significantly shorter than that observed in patients with non-triple-negative. Taxane based chemotherapy improves the response rate but more clinical trials are required to established more effective regimen.

1. Introduction

Breast cancer is the most common cancer in women in India and is the most common cause of cancer death. [i] TNBC was defined as negativity for ER, PR and HER2/neu (IHC score 0 or 1+ or FISH non amplified).TNBC occur in about 10-24% of all breast cancer, it is more common in Asian countries. [ii] It is an aggressive disease of young age group associated with advanced stage and increased risk of metastasis with decrease survival after metastasis. [iii],[iv],[v]
The aim of this study was to analyse recurrence pattern in order to determine the prognostic factor of recurrence and overall survival in a group of TNBC patients treated in a tertiary canter in north India between the years 2010 and 2014.

2. Material and Methods

Medical record of 730 patients diagnosed with invasive breast cancer from January 2010 to December 2014 was reviewed. There were 209 TNBC patients (28.63% of total breast cancer).31 patients were lost to follow up so excluded from this study. Finally data of 178 TNBC patients were analysed. The last follow up of all patients was done in December 2015.
The clinic-pathological characteristics were determined by using descriptive statistics. Overall Survival (OS) was defined as the time period from diagnosis to death from any cause. Disease free survival was defined as the time period from diagnosis to first loco-regional or distant recurrence. Patients who did not experience any event/death or were lost to follow up were censored for survival analysis. DFS and OS curves were calculated using the Kaplan-Meier method. A p value(probability) less than 0.05 was considered significant.Corelation coefficient for continuous variable were corelated using the Pearsons corelation whereas the nominal and ordinal data were corelated using the spearmans corelation analysis.

3. Results

3.1. Patients
A total of 178 TNBC patients were reviewed. The mean age at the time of diagnosis was 43.91 years (range 22-72), although the number of cases ≤ 40 years is 94 as compared to 84 cases in above 40 group (Table 1). A total of 162 patients were diagnosed with Stage II and III (32% and 59% respectively) and 10 patients (5.6%) presented with metastasis at the time of diagnosis. Ductal cancer was the most common histological type (80.89%). 59% of patients received neo-adjuvant chemotherapy as more than 50% of the patients were locally advanced. Almost 46.6% patients received CAF and 51.7% received Taxane based chemotherapy. But pathological complete response was achieved in only 15.23% (16 patients) in this group of neo-adjuvant chemotherapy. Most common therapy used was 4 cycles Adria/Cyclophosphamide followed by 4cycles Docetaxal (more than 50%).

3.2. Recurrence
A total of 82 patients developed recurrence/ metastasis (including 10 patients which initially presented with metastasis) during 6 years of observation. Majority of these patients had metastasis in different sites. The most common site of the first recurrence was loco-regional followed by bone and lung. As subsequent metastasis, brain was most common site of metastasis followed by lung and bone.

Clinic-pathological characteristics	No. of patients(178)
Age at initial diagnosis, years	
Mean	43.91
Range	22-72
Initial clinical TNM stage	
I	6
II	57
III	105
IV	10
Systemic neo-adjuvant treatment	
Yes	105
No	66
Type of neo-adjuvant chemotherapy-regimen	
Adriamycin based	83
Taxol based	92
Others	3
Surgical treatment	
Mastectomy	164
Breast conservation	09
No	05
Adjuvant radiotherapy	
Yes	164
No	14
Systemic neo-adjuvant treatment	
Yes	105
No	66
Type of neo-adjuvant chemotherapy regimen	
Adriamycin based	83
Taxol based	92
Others	3
Surgical treatment	
Mastectomy	164
Breast conservation	09
No	05
Adjuvant radiotherapy	
Yes	164
No	14
Site of initial recurrence/ metastasis after start of treatment	75
Lung	13
Loco-regional	17
Brain	11

Bone	15
Liver	7
Others	12
Site of subsequent metastasis	
Brain	16
Lung	10
Bone	5
Liver	1
Locoregional recurrence	0
others	4
Second breast cancer	04
Other primary cancers	03

Table 1: Clinic-Pathological Characteristics, Treatment, and Pattern of Recurrence

3.3. Survivals

During 6 years of follow up 44 patients lost to follow up, 86 patients develop recurrence/metastasis, of which 24 patients are alive and 55 patients expired. 3 patients developed second primary cancer (1 thyroid, 1 ovary and 1 skin malignancy).

The survival after recurrence is different depending on the site of metastasis. Patients with brain metastasis survive least (median 5.89 months). The longest survival was after development of bone and loco-regional recurrence (10.47 months and 9.46 months respectively).The median survival after the development of liver metastasis was 5.77 months.

The median OS and DFS for the entire group are 22 months and 11 months respectively. The mean OS and DFS are 24.53 months and 14.86 months respectively. In patients who develop metastasis OS is 22.64 months as compared to 26.11 months in those who do not develop metastasis (p =0.08).

3.4. Factors Influencing DFS and OS

Use of NACT (r=0.315, p=0.007) in locally advanced breast cancer is positively correlated with DFS, while comparing both NACT regimen (CAF and taxane based chemotherapy), taxane based chemotherapy (r=0.018, p=0.880) is more positively correlated with DFS, whereas Stage of disease (r = -0.115) and tumour status (r = -0.146) was negatively correlated with DFS. While evaluating overall survival, use of NACT (r=0.226, p=0.004) is positively correlated with OS, preferable regimen was taxane based chemotherapy (r=0.099, p=0.192) whereas Stage of disease (r = -0.106) and tumour status (r = -0.147) was negatively correlated with OS.
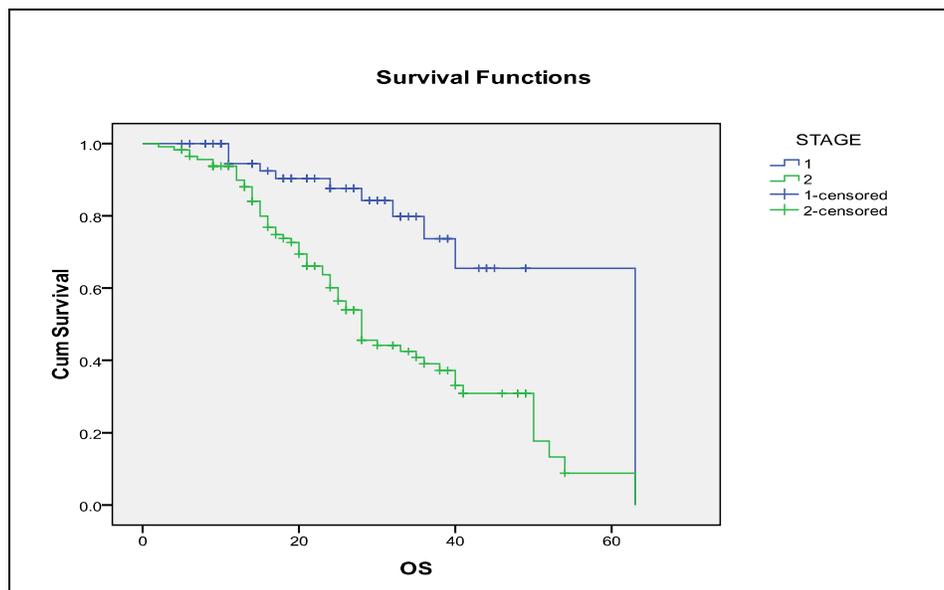

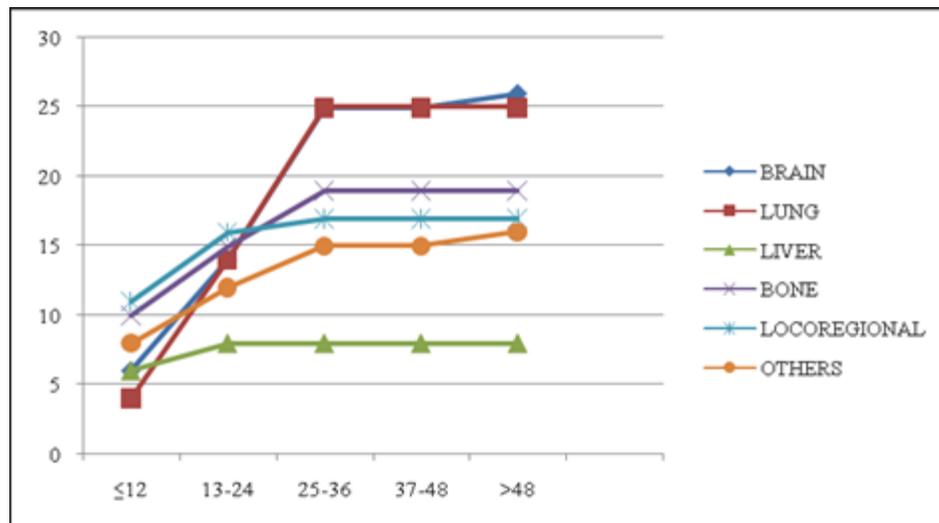*Figure 1: Kaplan Meire Curve of OS in Early Breast Cancer Vs LAB*

Figure 2: Kaplan Meire Curve of Recurrence Pattern in Triple Negative Breast Cancer

4. Discussion

Breast cancer is a heterogeneous disease. Subtypes of breast cancer have been identified with Gene expression studies using DNA micro arrays.[vi] As per ASCO guideline in triple-negative breast cancer (TNBC) there is no expression of Estrogen receptor(ER-negative), Progesterone receptor (PR-negative)and there is neither amplification nor expression of human epidermal growth factor receptor 2 (HER2-negative) in a tumour.[vii] TNBC is usually diagnosed at a younger age, In the present study the mean age is 43.91 years. Different Indian and western literature have also shown that TNBC is more frequent in young age. [2], [viii] It presents at a higher stage and larger size when compared to the other breast cancer molecular subtypes. The aggressive nature of TNBC can also be demonstrated as in the entire group 64.6% of the patients belong to Stage III/IV. In term of tumour status, 71.91% cases are T3/T4 and also the nodal positivity is 66.9% in the entire group. This is in consistent to other literature where TNBC is associated with advanced stage. [5], [8] The peak risk of recurrence of the disease is between the first and third year following diagnosis, and that survival after recurrence is significantly shorter than that observed in patients with non-triple-negative controls. [3], [4], [5] Additionally, TNBC has more than 20% greater incidence of visceral metastasis compared to the other breast cancer subtypes, which commonly metastasize to bone.[5],[ix]

 Studies have shown that there is increased pCR in TNBC patients who are treated with anthracycline and taxane based neoadjuvant chemotherapy.[8] In study by Pogada et al, there was pCR of 15 % and only two-third f the patients received anthracycline-taxane neoadjuvant chemotherapy.5 In this present study also, pCR was achieved in 15.23% of patients.

Pattern of recurrence is different in TNBC and non TNBC group. In a study by Dent et al , the risk of recurrence increases between 1-3 years from the date of diagnosis and then dropped.[9] Liedke C et al also demonstrated that the risk of relapse as higher for TNBC patients during first 3 years after diagnosis.[8]

Our study also showed that the recurrence/metastasis were more in initial 3 years of diagnosis. In addition, we also found that the sequence of metastasis which developed in different sites. In this study, 65% of locoregional metastasis and 50% of bone metastasis, developed in first year as compared to brain and lung metastasis in which their involvement in first year is only 23% and 17% respectively but by the end of 3 years almost 100% of brain and lung metastasis developed. The same pattern of metastasis was also found in the study by Pagoda et al the brain and lungs were the most common sites of recurrence and the risk of bone metastases declined from diagnosis.[5]

TNBC patients are usually associated with higher risk of brain and lung metastasis [3], [5],[8], [x] and so is in the present study. The metastasis to liver is less but this result is in consistent with the study by Pagoda et al. [5]

It has been found in the present study that the development of metastasis was 20.63% in early breast cancer as compared to 60 % in locally advanced breast cancer. These results are also in consistent to other study by Pagoda et al. [5] The estimated mean OS in the two groups are 51 months and 32.4 months respectively. (p>0.05).

5. Conclusion

TNBC is an aggressive disease mainly involving younger age group with higher stage. TNBC has unique pattern of metastasis, usually occur within first 3 years of diagnosis. Also they show good response Taxane based chemotherapy. More number of prospective randomized controlled trials is required to find out more effective therapy in TNBC patients to increase OS and DFS.

6. References

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