Brain Metastases in Triple Receptor-Negative Breast Cancer: Frequency, Risk Groups and Prognosis.

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Abstract: Objectives: The aim of this retrospective analysis is to determine the frequency, pattern, risk factors and survival of triple receptor-negative breast cancer (TNBC) focusing on brain metastases. **Methods:** From January 2001 to December 2007, a total of 123 patients with stage I through III TNBC were treated at the Department of Clinical Oncology, Tanta University Hospital. Patients were reviewed to define the frequency, risk groups , survival and prognosis of brain metastases in TNBC. Follow-up lasted until September 30, 2012.**Results:** The ages ranged from 30 to 70 years (mean, 48.87 years). Fifteen patients (12.20%) out of 123 patients developed brain metastasis and in 10 (8.13%) of them the brain was the first site of metastasis. Eleven (73.3%) out of this 15 patients developed brain metastases within 1 year of their primary diagnosis, and 8 patients out of these 11 patients developed brain metastases within the first 3 months. The incidence of brain metastases was significantly higher in premenopausal patients (p = 0.009), and patients who did not received postoperative radiotherapy (p <.001).There was a significant direct correlation between the developments of brain metastases overall or as the first site of recurrence and lymphovascular invasion, tumor size, nodal status, and tumor grade (all p <.001). Pathological type, regimen of chemotherapy and type of surgery were not statistically significant factors. Non-brain metastases occurred in 25 patients (20.33%). Disease-free survival for all patients with TNBC (n =123) at 2 and 5 years were 70% and 63%, respectively, while overall survival at 2 and 5 years were 85% and 70%, respectively. Median survival for the 15 patients who developed brain metastases was 3.03 months (95% CI 1.77 to 4.29 months) and for those 10 patients who developed brain metastases as the first site of recurrence was 3 months (95% CI 2.18 to 3.82 months). Median survival among those with distant metastases who did not develop brain metastases at all (25 patients) was 15.17 months (95% CI 0.97-29.36 months) (P = 0.01). **Conclusions:** TNBC patients have high risk of earlier brain metastasis with the highest incidence during the first year after diagnosis with poor prognosis.
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Key words: brain metastases, breast cancer, triple negative

1. Introduction

Breast cancer is increasingly recognized as a heterogeneous disease in which various subsets have distinctly different responses to treatment and outcomes **[1].** Genomic profiles have led to the discovery of molecular subtypes of breast cancer and significantly improved our ability to prognosticate in breast cancer patients **[2, 3].**

Triple-negative breast cancer(TNBC), defined as tumors that are negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor (HER)-2, represent a minority of breast cancers (10%-15%) **[4, 5, 6].**

Brain metastases from breast cancer result in high mortality and have become a major factor leading to the decline in survival [2].Symptomatic brain metastases account for 10% to 16% of all patients with breast cancer [3]. Identification of tumor characteristics associated with breast cancer brain metastases could help identify patients at risk **[4].** Research suggests that simultaneous negative expressions of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2), isa risk factor for breast cancer brain metastases **[5-12].**

Whole brain radiotherapy (WBRT), surgery, stereotactic radiosurgery (SRS), chemotherapy, and targeted therapy are the common treatments for brain metastases from breast cancer.

We conducted this retrospective analysis to determine the incidence, risk factors associated with the development of brain metastasis in 123 patients with non-metastatic TNBC, to provide a prognostic categorization of TNBC.

2. Patients and methods

Patients

We checked the medical record of all patients with non-metastatic triple receptor-negative breast cancer (TNBC) patients who had been seen at Clinical Oncology Department, Tanta University Hospital from January 2001 through December 2007.We obtained 123 TNBC patients from 1046 patients whose ER, PR, and HER-2 status were confirmed to be negative after exclusion of 35 patients either due to incomplete data or wrong marker result. Initial clinical stage of all patients was coded according to the staging criteria proposed by the 2003 sixth edition of the American

Joint Committee on Cancer [13]. Brain metastasis was diagnosed by clinical symptoms, signs, and cranial magnetic resonance imaging (MRI) or computer tomography scan (CT). Eligibility criteria for this analysis included female gender, an initial diagnosis of primary breast cancer without distant metastases, at least 2 months of follow-up information for disease recurrence. Male patients, patients with more than one primary and those who presented with de novo stage IV disease were excluded. Data extracted included the patients' demographic information, age at diagnosis, tumor histology, biological marker status, staging information and grade; treatment; survival status; and dates of initial diagnosis and work up, distant metastasis, brain metastasis, and death (if applicable).Follow up ended at September 30, 2012.

Pathology review and staging

Paraffin blocks of the all eligible patients were collected. Hematoxylin and eosin staining sections were prepared from all blocks and the sections were Histological classified and graded according to Tavassoli and Devilee in theWHO classification of breast and female genital system tumors [**14]** and modified Black's nuclear grading system [15], respectively.

Immunohistochemical (IHC) staining was carried out in order to evaluate levels of ER, PR and HER-2 with antibody retrieval (using immune DAKO system) stain for ER and PR. All the cases should express negative nuclear reaction for ER, PR with less than10% tumor cells with nuclear staining and expressed cytoplasmic staining< 10% of cell for her-2.

Treatment and Follow-Up

All patients received either preoperative or adjuvant chemotherapy and 98 (79.67%) patients received adjuvant radiation therapy to the chest wall and draining lymphatics following surgery. Seventy eight (63.41%) underwent modified radical mastectomy for their primary tumor, and 45 (36.59%) underwent a breast conserving surgery(BCS). Combination chemotherapy consisted of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) in 47 (38.21%) patients, 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) in 32 (26.02%) patients, sequential FEC with taxanes in 28 (22.76%) patients, or Cisplatin and taxanes in 16 (13.01%) patients. Regarding radiation therapy, patients received a median dose of 50 Gy in 2-Gy fractions delivered once daily to the chest wall and draining lymphatics, followed by a 10-Gy boost for those underwent breast conservative surgery (BCS), also in 2-Gy fractions delivered once daily, bringing the total dose to tumor bed to 60 Gy.

Patients were followed on a regular basis after completion of treatment through patients' clinic visits at the Clinical Oncology Department, Tanta University Hospital. Follow-up studies included physical examination, biopsy from any suspected lesion, mammography, breast and abdominopelvic sonography and/or computed tomography (CT) scan, as well as bone scan. Tests used for suspected distant metastasis (DM) included CT scanning, MRI of the brain, bone scanning, liver and kidney function tests, and alkaline phosphatase level measurements.

Statistical Analysis

Patients were followed up until September 30, 2012. At the time of analysis, the mean follow-up for the entire group was 55.36 months (range, 3.03 to 134.97 months). The primary endpoints in this study were the overall-survival (OS) and Disease-free survival (DFS) rates. Overall-survival (OS) rates were calculated from the time of diagnosis to the time of the last follow-up visit or death using the method of Kaplan and Meier [16]. Disease-free survival (DFS) was defined as the time from initial treatment to the earliest occurrence of an event, including locoregional, visceral and bone relapse. Those without any evidence of event were censored at the last date they were known to be alive. The variables analyzed were: age at diagnosis, TNM, menopausal status, lymphovascular invasion (present or absent), tumor nuclear grade (grade 3 versus grade 1–2),pathological type, regimen of chemotherapy, and adjuvant radiation therapy (yes versus no). SPSS Statistical package (version 12.0) was used for data analysis. Mean and standard deviation were estimates of quantitative data. Chi-square/ Fischer exact were tests of proportion independence. Kaplan-Meier method was used for estimating survival and log rank to compare curves [16]. Cox-regression analysis was used to estimate odds of recurrence & its 95% CI on univariate level and to evaluate independent prognostic variables affecting OS and disease-free survival (DFS). P value is significant at 0.05 levels.

3. Results

Patient characteristics:

The study included 123 female patients with TNBC diagnosed from 2001 to 2007. Their age ranging from 30–70 years at the time of diagnosis (mean 48.87 years; SD± 8.51). Their tumors size ranged from 1.5 cm to 15 cm. The majority of cases were T2 or greater, node positive, invasive duct carcinoma, and grade II. Seventy eight (63.41%) underwent modified radical mastectomy for their primary tumor, and 45 (36.59%) underwent a breast conserving surgery (BCS). A median of 15 lymph nodes were removed. All patients received either preoperative or adjuvant chemotherapy and 98 (79.67%) patients received adjuvant radiation therapy following surgery. The patients' and tumor characteristics as well as treatment modality were summarized in table (1).

Table (1): Patients' and tumor characteristics of the 123 patients with TNBC

Characteristic	No. patients (%)
Age (years)	
Mean	48.87 years
Range	(30-70)
SD	± 8.51
Metastatic site	
Lung	19 /40 (47.5%)
Brain	15 (37.5%)
Liver	12 (30%)
Bone	9 (22.5%)
Tumor status	
T1	12 (9.76%)
T2	53(43.09%)
T3	42 (34.15%)
T4	16 (13.01%)
Menopausal status	
Premenopausal	52 (42.28%)
Postmenopausal	71 (57.72%)
Tumor grade	
G1	12 (9.76%)
G2	56 (45.53%)
G3	55 (44.72%)
Pathological type	
Invasive duct carcinoma (IDC)	116 (94.31%)
Others	7 (5.69%)
Lymphovascular invasion	
Positive	35 (28.46%)
Negative	88 (71.54%)
Nodal status	
N0	35 (28.45%)
N1	66 (53.65%)
N2	20 (16.2%)
N3	2 (1.6%)
Adjuvant radiation therapy	
Yes	98 (79.67%)
No	25 (20.33%)
Type of surgery	
Breast conserving surgery (BCS)	45 (36.59%)
Modified radical mastectomy (MRM)	78 (63.41%)
Regimen of chemotherapy	
FAC	47 (38.21%)
FEC	32 (26.02%)
Sequential FEC with taxenes	28 (22.76%)
Cisplatin+ taxenes	16 (13.01%)

Development of brain metastases:

Table (2) summarizes the relation of the incidence of brain metastases to the patient and tumor characteristics, as well as to treatment data and mortality.

Fifteen patients (12.20%) out of 123 patients developed brain metastasis and in 10 (8.13%) of them the brain was the first site of metastasis. Eleven (73.3%) out of these 15 patients developed brain metastases within 1 year of their primary diagnosis, and 8 patients out of these 11 patients developed brain metastases within the first 3 months, and 4 patients were diagnosed with brain metastases after 1 year of their primary diagnosis. Thus the risk of brain metastases was the highest during the first year, progressively declining thereafter. The incidence of brain metastases was significantly higher in premenopausal patients ($p = 0.009$), and patients who did not receive postoperative radiotherapy ($p < 0.001$). There was a significant direct correlation between the developments of brain metastases overall or as the first site of recurrence and lymphovascular invasion, tumor size, nodal status, and tumor grade (all $p < 0.001$). Pathological type ($p = 0.865$), regimen of chemotherapy ($p = 0.671$) and type of surgery ($p = 0.063$) were not statistically significant factors for the development of brain metastases.

Nine (60%) out of the 15 patients with brain metastases had three or fewer lesions in the brain, and 6 (40%) had more than three brain lesions

All the 15 patients with brain metastases underwent whole-brain radiation therapy of 30 Gy in 10 fractions, 10(66.7%) patients of them as first line treatment of brain metastases and the reminder 5 patients start to receive whole-brain radiation therapy with the appearance of brain metastases while they were under systemic chemotherapy for non brain metastatic lesions.

Table (2): Incidence of brain metastases in relation to patient and tumor characteristics as well as to, treatment modality and mortality

		Brain metastases						
		Yes		No		Total		
		N	%	N	%	N	%	P-value
Menopausal status	**Premenopausel**	11	73.33	41	37.96	52	42.28	0.009
	Postmenopausel	4	26.67	67	62.04	71	57.72	
Tumor status	**T1**	0	0	12	11.11	12	9.76	<0.001
	T2	2	13.33	51	47.22	53	43.09	
	T3	5	33.33	37	34.25	42	34.15	
	T4	8	53.33	8	7.4	16	13.01	
Nodal status	**N0**	0	0	35	32.4	35	28.45	<0.001
	N1	4	26.7	62	57.4	66	53.65	
	N2	9	60	11	10.2	20	16.2	
	N3	2	13.3	0	0	2	1.6	
Tumor grade	**Grade I**	0	0	12	11.11	12	9.76	<0.001
	Grade II	5	33.33	51	47.22	56	45.53	

	Grade III	10	66.33	45	41.66	55	44.72	
LVI	**Positive**	11	73.33	24	22.22	35	28.46	<0.001
	Negative	4	26.67	84	77.78	88	71.54	
Type of surgery	**MRM**	11	73.33	67	62.04	78	63.41	<0.063
	BCS	4	26.67	41	37.96	45	36.59	
Pathological type	**IDC**	14	93.33	102	94.44	116	94.31	0.865
	Others	1	6.67	6	5.56	7	5.69	
Adjuvant RTh	**Yes**	4	26.67	94	87.04	98	79.67	<0.001
	No	11	73.33	14	12.96	25	20.33	
Regimen of chemotherapy	**FAC**	4	26.67	43	39.81	47	38.21	0.671
	FEC	5	33.33	27	25	32	26.02	
	Sequential FEC with taxenes	2	13.33	26	24.07	28	22.76	
	Cisplatin+ taxenes	4	26.67	12	11.11	16	13.01	

Overall survival (OS) and disease-free survival (DFS) estimates among all 123 patients with TNBC:

Maximal follow-up was 134.97 months with a mean of 55.365 months (range 3.03–134.970 months, SD± 22.938). Among 123 patients who had TNBC, distant metastases were diagnosed in 40 (32.52%) patients with an actuarial rate of DFS of 70% and 63% at 2 and 5 years, respectively, (Figure 1).

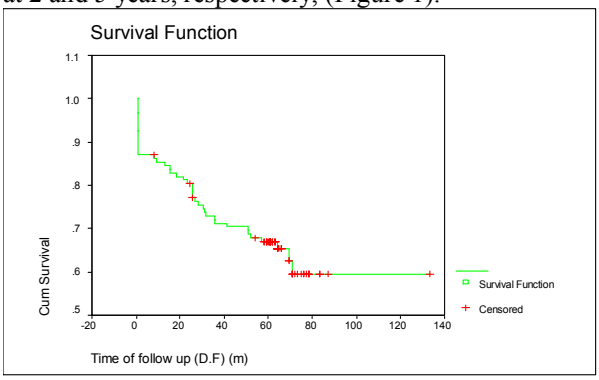

Figure 1. Disease free survival among all patients with triple receptor negative breast cancer (n=123)

In terms of OS, the two-year and five-year OS among all 123 TNBC patients entering the study were 85% and 70%, respectively, (Figure 2).

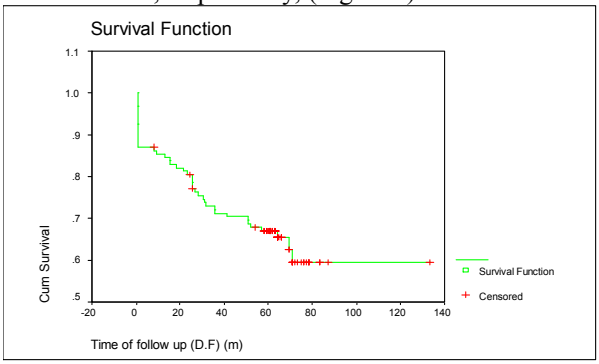

Figure 2.Overall survival among all patients with triple receptor negative breast cancer (n=123)

Median survival after onset of brain metastases was 3.03 months (95% CI 1.77 to 4.29 months), (Figure 3), which was statistically significant different from the median survival among those metastatic patients who did not develop brain metastases (n = 25); it was 15.17 months (95% CI 0.97-29.36 months), (P = 0.01).

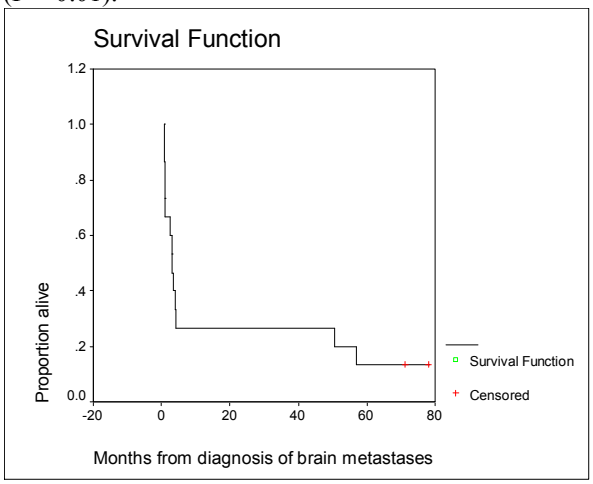

Figure 3. Kaplan–Meier survival among all patients who developed brain metastases (n=15).

4. Discussion

Triple receptor-negative breast cancer (TNBC) accounts for a disproportionate number of metastatic cases and breast cancer deaths compared with women with other subtypes of breast cancer[17-26].

In developed countries, there has been a remarkable improvement in mortality from breast cancer, but almost all of that benefit has occurred in the ER^+ and $HER\text{-}2^+$ subsets. At present, there is not a clear, proven effective single agent that targets a driving vulnerability in TNBC [27,28]. Triple-negative disease remains the biggest challenge moving forward, but clinicians may be are close to improved, treatment options and outcomes for these patients [27,28].

In our series TNBC represent 11.75% (123/1046) of all breast cancer patients in our

department and this consistantconsistent with that recorded in literature which ranged from 10 to 20% of all invasive breast cancers [29]. Fifteen patients out of these 123 patients(12.20%)TNBC developed brain metastasis in our series and this also concordance to 10.9% reported in review article by**Lim and Lin**. [30].

In a review article about BCBM in TNBC it was found that: From 25%-46% of patients with metastatic TNBC experiencing metastatic spread had brain metastasis [5,6, ,9,31]. This incidence agree with the results of our study, we observed that among women with TNBC, brain metastases occur in 37.5% (15/40) of those experiencing metastatic spread of disease.

In this study the incidence of central nervous system (CNS) metastases as first site of distant relapseis8.13% (10/123), which is associated with subsequent poor survival [32,33], and this agree with that incidence reported in literature in which it was ranged from 3.5%–14% of patients with TNBC [5,6].Several studies done to identify risk factors associated with the development of brain metastases has been primarily undertaken in an effort to identify subgroups of patients at high risk of developing brain metastases who would benefit from early detection and/or prevention measures [6]. In our study, the risk of brain metastases was particularly pronounced among premenopausal patients with lymphovascular invasion (LVI), larger tumor size, node positive disease, higher tumor grade and absence of adjuvant radiation therapy following surgery. In a single-institution study among 3193 patients, a significantly elevated risk of CNS metastases was found among patients with TNBC [31]; the risk of CNS metastases was particularly pronounced among young patients with node positive disease [31].

In our study, there was no statistical significance when looking at the effect of pathologic subtype or the type of chemotherapy on the development of brain metastases.

The aggressiveness of TNBC is indicated by the fact that the peak risk of recurrence occurs within the first 3 years after initial treatment of the disease with the majority of deaths occurring in the first 5 years [34, 35].

Importantly, diagnosis of central nervous system metastases among patients with TNBC compared with non-TNBC was followed by as shorter median survival of 3–5 versus 7–12 months, respectively [5,31, -38]. The findings of the present study point to a short median survival after onset of brain metastases (3.03 months) among TNBC patients. Evidence supporting such a hypothesis has been obtained from studies which found that, a diagnosis of CNS metastases among patients with TNBC was followed by as shorter median survival of 2.9–7 months [5,6,8,31,36,37,39].

Our results showed that survival times as low as 3 months in patients with brain metastases as the first site of distant relapse. Similar finding was reported by **Dawood et al.[6]** who found that central nervous system relapse in patients with TNBC showed survival times as low as 2.9 months in patients with CNS relapse as the first site of distant relapse [6].

In our study, median survival for the 15 patients who developed brain metastases was 3.03 months (95% CI 1.77 to 4.29 months). Median survival among those with distant metastases who did not develop brain metastases at all (25 patients) was 15.17 months (95% CI 0.97-29.36 months) (P = 0.01). **Dawood et al.[6]**reported that the median survival of women who developed brain metastases as a first site of recurrence was significantly lower compared with those who did not develop brain metastases as a first event (5.8 months versus 13.0 months, P < 0.0001).

A limitation of our study is its retrospective nature and consequent patient and treatment selection bias and variability in prognostic factors.

Our findings indicate that TNBC subtype consistently predicted a worse outcome. Secondly, our results indicate that brain metastasis is a frequent event in TNBC and it develops early in the course of the disease. This information may be useful in determining the aggressiveness of therapies aimed at controlling the disease. It also underscores the need to understand the biology underlying the aggressiveness of TNBC and to identify new molecular targets specific to TNBC. Thus, it is questionable whether the inclusion of this subgroup of TNBC patients into experimental cytostatic treatments is justified.

In conclusion we recommend further prospective randomized controlled studies that can help to further understand the risk factors, prognostic factors, and treatments for patients with TNBC brain metastases, and before trials that can investigate preventive and treatment strategies, much more needs to be learnt about the pathophysiology of brain metastases at a molecular level. In patients at high risk for brain metastases, whether routine brain screening should be used regularly and whether preventive treatment should be used to prevent or delay the occurrence of brain metastases and improve overall survival still needs further study.

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