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Distant metastasis in triple-negative breast cancer

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Triple-negative breast cancer (TNBC) relapses more frequently than hormone receptor-positive subtypes and is often associated with poor outcomes. This retrospective study reviewed the pattern of distant metastasis with regard to survival in patients with TNBC. A total of 205 TNBC patients were analyzed. TNBC patients with lung metastases had the longest median post-metastatic OS (with 95% confidence interval) of 16.6 (10.3-22.9) months, followed by the bone, 16.3 (11.7-20.8) months, the liver, 8.9 (3.5-14.4) months, the pleura, 7.5 (2.8-12.3) months, and the brain, 4.3 (0.6-8.0) months. Kaplan-Meier plots indicated that TNBC patients with metastatic spread to brain, liver, and pleural had poorer post-metastatic OS rate than patients with lung metastases ($p = 0.001$, 0.004, and 0.029, respectively). Moreover, brain and liver metastases correlated significantly with poorer post-metastatic OS as compared to bone metastasis ($p = 0.004$ and 0.011, respectively). Route of first metastasis correlated significantly with survival of TNBC patients with brain metastases being the poorest survival indicator, followed by metastases to liver, pleura, bone, and lung.

Key words: triple-negative breast cancer, metastasis, survival

Breast cancer is the most prevalent cancer and ranks second in cancer mortality in women affecting approximately a million worldwide. Breast cancer is a highly heterogeneous disease consisting of various subtypes each carries a distinct molecular and pathologic profile [1-4]. Triple-negative breast cancer (TNBC) is a subtype of breast cancer that lacks the expression of estrogen and progesterone receptors (ER/PR), and lacks overexpression or amplification of HER2/NEU gene. TNBC often share similar biological features with basal-like carcinomas and is associated with poor clinical outcome, high rates of recurrence following chemotherapy, and metastasis [5-9]. Although novel targeted agents, including hormonal and HER2-directed therapies, are ineffective in this setting, an array of chemotherapeutic agents is suitable for use in patients with TNBC [10-12]. Anthracycline and taxane (AT) are the preferred first-line treatment for TNBC in Taiwan. Despite of the treatment, however, most TNBC patients relapse and progress quickly on subsequent line palliative therapy [13, 14].

The gene expression and differentiation of breast carcinoma have been shown to correlate with the sites to which tumors metastasize [15-19]. A higher incidence of visceral metastases was reported in patients with TNBC as compared with non-TNBC patients [8, 20]. Moreover, it has been reported that the excess risk of distant metastases in TNBC is attributed to high incidence of visceral metastases [21].

The aim of this study was to investigate the pattern of metastatic spread of TNBC patients with regard to survival.

Patients and methods

Patients diagnosed with TNBC between January 1, 2001 and December 31, 2006 were selected and analyzed from Cancer

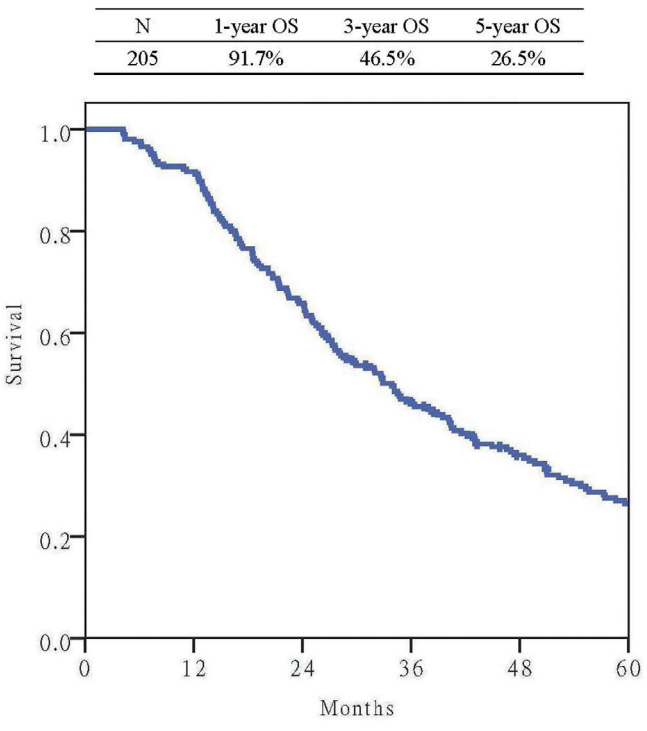
registry database of four medical centers (National Taiwan University Hospital, Chang Gung Memorial Hospital Linkou Branch, Veterans General Hospital Taipei, and Kaohsiung Medical University Hospital) in Taiwan. This study was approved by the Institutional Review Board of the four medical centers. Written informed consent was waived due to the retrospective nature of the investigation. Distant metastasis was defined as clinical evidence of distant disease based on clinical and/or radiographic findings. Overall survival (OS) was calculated from the time of initial diagnosis to death of any cause. Post-metastatic OS was defined as the date of first distant metastasis to death of any cause. Patients still alive at the end of the study were censored at the date of last follow-up. Data from medical charts were retrieved, and the patients' outcomes were followed until June 30, 2008 or date of death, whichever occurred first. Cases which lacked survival data or complete treatment history were excluded from the analysis. The 95% confidence interval was calculated using the Clopper-Pearson method. Post-metastatic OS were assessed by Kaplan-Meier analysis using log-rank test. All statistical calculations were done using SPSS version 17.0 for windows (SPSS, Inc., Chicago, IL). $P < 0.05$ was considered significant.

Table 1. Triple negative breast cancer patients' demographics and disease characteristics.

Characteristic	Number of Subjects	
	N=205	%
Age (years) at first breast cancer diagnosis		
Mean(SD)	49.3(11.3)	
(min, median, max)	(25,48,81)	
Age (years) at first distal metastasis		
Mean(SD)	51.5(10.9)	
(min, median, max)	(26,51,82)	
Stage		
I	9	4.4
II	63	30.7
III	108	52.7
IV	25	12.2
Lymph Node		
Positive	128	62.4
Negative	43	21
Unknown	34	16.6
Distal Metastasis Site		
Bone	47	22.9
Lung	41	20
Brain	14	6.8
Liver	28	13.7
Pleura	18	8.8
Mixed	37	
Bone+Brain	3	1.5
Bone+Lung	4	2
Bone+Liver	7	3.4
Bone+Pleura	1	0.5
Bone+Others	1	0.5
Bone+Lung+Brain	1	0.5
Bone+Lung+Liver	5	2.4
Bone+Lung+Pleura	1	0.5
Bone+Liver+Pleura	1	0.5
Lung+Liver	7	3.4
Lung+Pleura	1	0.5
Lung+Others	1	0.5
Lung+Pleura+Others	1	0.5
Liver+Pleura	3	1.5
Others	8	3.9
No	12	5.9

Results

A total of 205 patients who were diagnosed with TNBC at the four medical centers in Taiwan were analyzed. The disease characteristic that includes the first site(s) of distant metastasis is listed in Table 1. The median OS was 33.9 months for all 205 TNBC patients; OS rates for 1-year, 3-year, and 5-year were 91.7%, 46.5%, and 26.5%, respectively (Figure 1). 193 of 205 (94.1%) patients presented with distant metastases. The most common site for the first metastasis to occur was the



N	Number of deaths (%)	OS (month)	
		Median	95%CI
205	179(87.3%)	33.9	27.6,40.1

Figure 1. Kaplan-Meier analysis for overall survival of the 205 patients with triple-negative breast cancer.

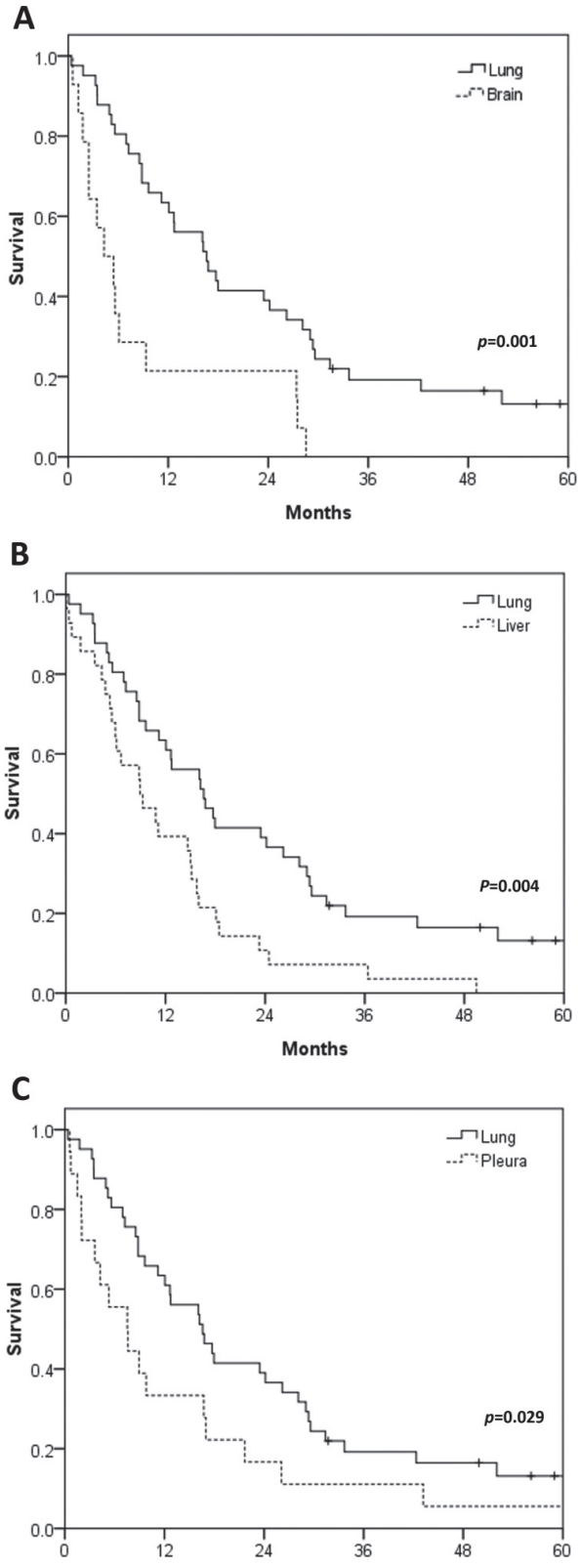


Figure 2. Kaplan-Meier overall survival (OS) curves for triple-negative breast cancer patients as a function of first metastatic site. A) lung versus brain B) lung versus liver C) lung versus pleura.

bone (22.9%), followed by lung (20.0%), liver (13.7%), pleura (8.8%), and brain (6.8%). Thirty-seven patients (18.0%) had evidence of synchronous metastases of multiple sites at time of initial metastasis. We calculated and compared the post-metastatic OS of TNBC patients according to the five most common first-metastatic site which included the bone, lung, liver, pleural, and brain. For the purpose of elucidating the site of metastases with regard to survival, the 37 cases with multiple metastatic sites were not included in the survival analyses. TNBC patients with the lung as the first metastatic site had the longest median post-metastatic OS (with 95% confidence interval) of 16.6 (10.3-22.9) months, followed by the bone, 16.3 (11.7-20.8) months, the liver, 8.9 (3.5-14.4) months, the pleura, 7.5 (2.8-12.3) months, and the brain, 4.3 (0.6-8.0) months (Table 2). Kaplan-Meier survival analysis indicated that patients with metastatic spread to the brain, liver, and pleura exhibited poorer post-metastatic OS than patients with lung metastases (Figure 2). On the other hand, brain and liver metastases correlated significantly with poorer post-metastatic OS as compared to bone metastasis. There was no significant difference in post-metastatic OS between bone and either lung or pleura metastases (Figure 3).

Table 2. Overall survival of triple negative breast cancer patients by the first site (organ) of metastasis.

Organ	N=148	Number of deaths(%)	Post-Metastatic OS (month)		
			Median	95%CI	*p*
Bone	47	39(83.0%)	16.3	(11.7,20.8)	
Lung	41	36(87.8%)	16.6	(10.3,22.9)	
Brain	14	14(100%)	4.3	(0.6,8.0)	0.001*
Liver	28	28(100%)	8.9	(3.5,14.4)	
Pleura	18	18(100%)	7.5	(2.8,12.3)	
Bone	47	39(83.0%)	16.3	(11.7,20.8)	0.732
Lung	41	36(87.8%)	16.6	(10.3,22.9)	
Bone	47	39(83.0%)	16.3	(11.7,20.8)	0.004*
Brain	14	14(100%)	4.3	(0.6,8.0)	
Bone	47	39(83.0%)	16.3	(11.7,20.8)	0.011*
Liver	28	28(100%)	8.9	(3.5,14.4)	
Bone	47	39(83.0%)	16.3	(11.7,20.8)	0.081
Pleura	18	18(100%)	7.5	(2.8,12.3)	
Lung	41	36(87.8%)	16.6	(10.3,22.9)	0.001*
Brain	14	14(100%)	4.3	(0.6,8.0)	
Lung	41	36(87.8%)	16.6	(10.3,22.9)	0.004*
Liver	28	28(100%)	8.9	(3.5,14.4)	
Lung	41	36(87.8%)	16.6	(10.3,22.9)	0.029*
Pleura	18	18(100%)	7.5	(2.8,12.3)	
Brain	14	14(100%)	4.3	(0.6,8.0)	0.397
Liver	28	28(100%)	8.9	(3.5,14.4)	
Brain	14	14(100%)	4.3	(0.6,8.0)	0.492
Pleura	18	18(100%)	7.5	(2.8,12.3)	
Liver	28	28(100%)	8.9	(3.5,14.4)	0.773
Pleura	18	18(100%)	7.5	(2.8,12.3)	

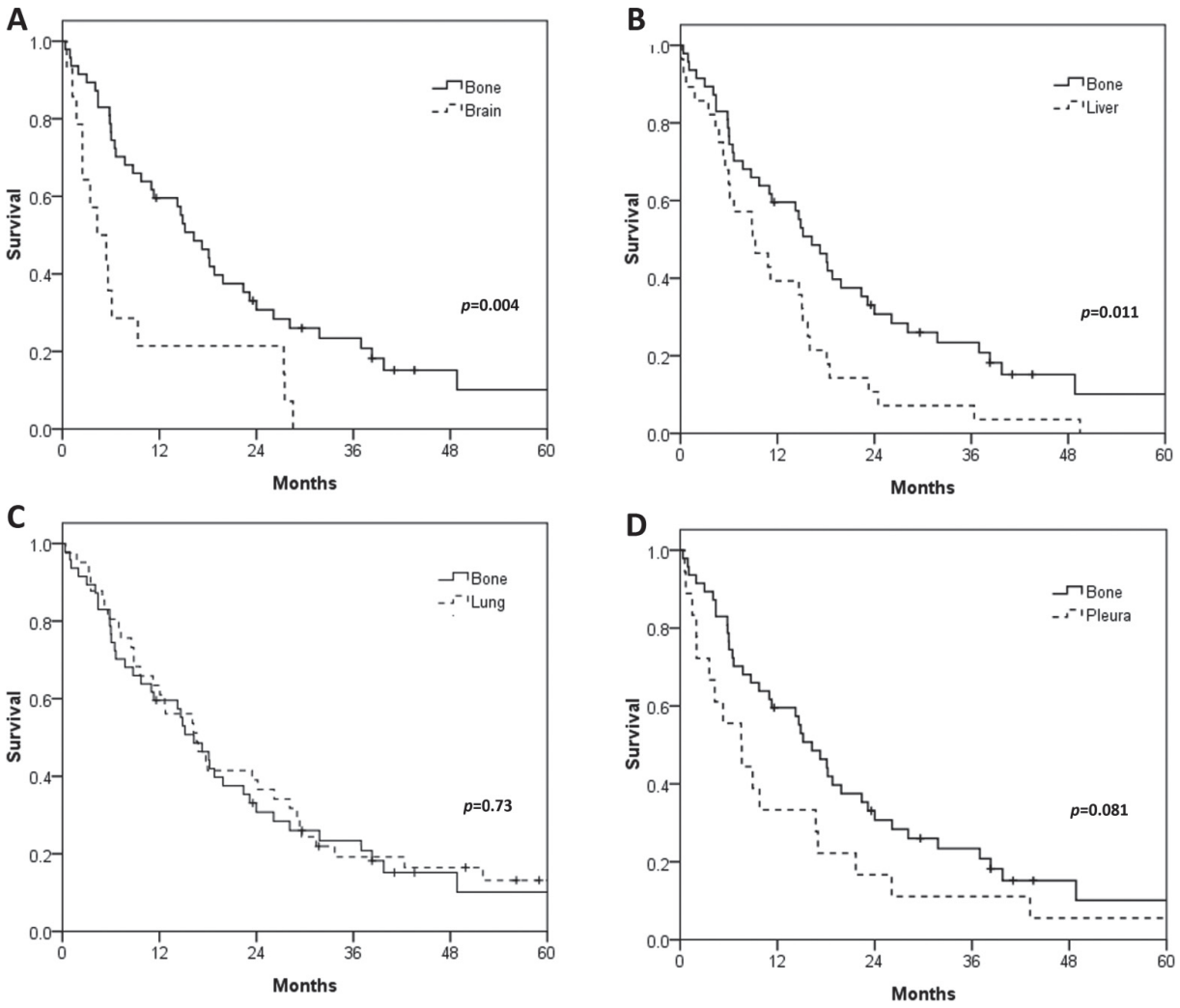


Figure 3. Kaplan-Meier overall survival (OS) curves for triple-negative breast cancer patients as a function of first metastatic site. A) bone versus brain B) bone versus liver C) bone versus lung D) bone versus pleura.

Discussion

Breast cancer of the triple-negative phenotype is associated with poor survival [5, 7, 8, 20, 22, 23]. The adverse prognosis of TNBC is in large part the result of the excess risk of developing visceral metastases [7, 21]. It has been reported that while the rate of bone metastases was comparable for TNBC and for the other breast cancer subtypes, TNBC patients are four times more likely to develop visceral metastases than patients with non-TNBC subtypes [21]. It is thought that once a patient develops distant metastatic disease, variables other than the number of organ sites and the location involved have no bearing on outcome and that patients with visceral disease generally have a poor outcome. The current investigation focused on the survival differences in patients with different first metastatic organ. The analysis on this cohort of TNBC patients revealed that, of the first-affected organs, patients with brain metastases had the shortest median post-metastatic OS of 4.3 months. Survival rates of patients after the first distant metastatic spread were comparable for bone and lung. TNBC patients with brain and liver metastases had poorer survival than those with bone and lung metastases. Pleural metastases in patients were also associated with unfavorable survival outcome compared to lung metastases. There was a trend toward poorer survival in patients with pleura compared with bone metastases, though statistical significance was not reached. Taken together, these data indicated that the route of first metastasis correlated significantly with survival of TNBC patients with distant metastases to the brain being the poorest survival indicator, followed by liver, pleura, bone, and lung.

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