Bone metastases at initial diagnosed breast cancer — A retrospective study based on SEER database

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Research article

Keywords: breast cancer, metastatic bone, molecular subtype, survival

Posted Date: July 3rd, 2019

DOI: https://doi.org/10.21203/rs.2.10918/v1

Abstract

Background To explore the features of incidence proportions and long-term survivals of breast cancer patients with bone metastasis when first diagnosed. Methods Data were extracted from the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute. Stratifications were made according to molecular subtype, age, sex, race and other factors. We performed multivariable logistic and Cox regression analysis to detect predictors of occurrence of bone metastasis at first diagnosis and factors related to all-cause mortality. Results We identified 310789 patients with breast cancer within the study period. Approximately 3.6% patients were diagnosed as bone metastasis within the entire cohort and 50.5% of the metastasis cohort. The highest incidence was from the cohorts of HR+/HER2+ (5.0% of the entire cohort). N3, metastases to brain, lung and liver were associated with higher possibility of developing bone metastases. For survival, HR+/HER2+ experience the longest survival time (41 months) and triple-negative patients had the shortest survival period (10 months). lymph node status other than N0 and distal metastasis to brain, lung and liver as possible factors which were associated with higher all-cause mortality. Conclusions We recommend routine bone screen at first diagnosis within high risk patients.

Background

Breast cancer is one of the most common malignancy in female and nearly 12% of diagnosed breast cancer is metastatic (1-3). Bone metastases is a common site for metastases among breast cancer patients and counts for approximately 70% of disease specific death according to previous study (4-6). However, population-based study of robust estimates relating to the incidence of bone metastases at diagnosis of breast cancer is lacking, partly due to the International Classification of Diseases (ICD) coding system did not label out metastases subtype of cancer patients. In previous autopsy studies, 74% of patients were found to have bone metastases, part of these patients was not clinically apparent prior to death(7).Because of lacking existed evidence, there is no recommendation for routine assessment or continued reassessment of bone metastases(8, 9). Thus, most patients with bone metastases are diagnosed by symptoms which usually necessitating interventions to prevent further adverse events(10). Studies of population-based for prognosis among patients with newly diagnosed bone metastases are currently lacking .Hence, the present study used the Surveillance, Epidemiology, and End Results(SEER) database to investigate the incidence proportion of bone metastases in breast cancer as main goal. The second aim of this study is to estimate survival data and find sociodemographic and clinical predictors relevant to poorer survival.

Methods

Data of cancer incidence, treatment and survival of nearly 30% of the US population from 20 cancer registries was included in the SEER database. We downloaded the data from 2010 to 2014 through SEER stat. We extracted data of patients of invasive breast cancer with confirmed bone metastases at initial diagnosed. Further screening was conducted to exclude bone metastases by autopsy or death certificate

as well as patients without complete follow-up records. We studied the data by stratifying breast cancer by molecular subtype; hormone receptor-positive human epidermal growth factor receptor-2 negative (HR +/HER2-), HR+/HER2+, HR-/HER2+ and triple-negative breast cancer (TNBC). Calculation was made among exact number and incidence proportions after stratification by age, race and gender. Two kinds of incidence proportion were calculated, bone metastases divided by total breast cancer as the first and bone metastases divided by all metastases as the second. Multivariable logistic regression was performed to investigate the relevant influential factors of presence of bone metastases if there were available from SEER. By using Kaplan-Meier method, survival estimates were conducted. To identify covariates associated with mortality, multivariable Cox regression was performed. All data was obtained using SEER*Stat Software version 8.3.4 (https://seer.cancer.gov/seerstat/). Statistical analyses were performed by SPSS statistical software version 21. All P values were two-sided, and $P \leq 0.05$ was considered significant.

Results

Incidence We identified 310789 patients with breast cancer diagnosed from 2010 to 2014. Stratified by molecular subtype, there were 61.7%,9.5%,4.1%,10.4%, 8.9% patients molecularly tested as HR+/HER2-, HR+/HER2+, HR-/HER2+, TNBC and unknown respectively. Among metastases to any site patients, there were 50%, 14%,7.6%,11% and 17.4% tested as HR+/HER2-, HR+/HER2+, HR-/HER2+, TNBC and unknown respectively. Within all included patients, 11300 had bone metastases which took up 3.6% of the entire cohort and 50 .5% of metastases patients. The highest incidence proportion was from the HR+/HER2+ (5.0%)and HR-/HER2+ (4.5%) cohort. (Shown in Table1). Based on our multivariable logistic regression analysis, HR+/HER2+ compared with HR+/HER2- (OR, 1. 19; 95% CI, 1. 06 -1. 35; P = 0. 003), N3 compared withN0 (OR, 2.76; 95% CI, 1.66-4.60; P < 0.01), metastases to brain compared with None (OR,4.03; 95% CI, 2. 67 -6. 09; p<0. 01), to lung compared with None (OR, 27.31 ; 95% CI, 20.06-37.17; p<0.01) and liver compared with None (OR, 10.45; 95% CI, 4.63-23.59; p<0. 01) were associated with higher possibility of developing bone metastases. Triple-Negative was associated with lower risk of bone metastases at diagnosis compared with HR+/HER2- (OR, 0. 72; 95% CI, 0. 64 -0. 82; P <0. 01). Other factors such as age, gender and marital status were not significantly related to developing bone metastases.(Shown in Table 2)

Survival According to eligible data, patients stratified by molecular subtype with follow-up during the study time were summarized in Table 1. As shown in Figure 1, among patients with bone metastases at diagnose, HR+/HER2+ experienced the longest survival time (41 months) and triple-negative patients had the shortest survival period (10 months). Figures comparing bone metastases (median survival 30 months) with lung (21 months), brain (11 months) and liver (19 months)was shown as Figure 2, Figure 3 and Figure 4. Comparing with other distal organ metastases, bone metastases had longer survival time. By performing Cox Regression Analysis, we identified age between 61 to 80 (vs. age 18-40; hazard ratio[HR],1. 79; 95% CI, 1. 68-1.91, p<0.01) and older than 80 (vs. age 18- 40; HR,5.32; 95% CI, 4.99-5.67,

p<0.01), black race (vs. white; HR ,1. 35; 95% CI, 1. 30 -1. 39, p<0.01), molecular subtype as HR−/HER2+ (vs. HR+/HER2−; HR, 1. 55; 95% CI, 1. 48 -1. 63; p<0. 01) and Triple-negative (vs. HR+/HER2−;HR, 2. 60; 95% CI, 2. 52 -2. 68; p<0.01), lymph node statusN3(vs. N0; HR, 3. 21; 95% CI, 3. 09 -3. 35; p<0.01) , N2(vs. N0; HR, 2. 42; 95% CI, 2. 31 -2. 54; p<0.01) , N(vs. N0; HR, 1. 75; 95% CI, 1. 69 -1. 80; p<0.01), distal metastases to brain (vs. None; HR, 2. 22; 95% CI, 2. 07 -2. 40; p<0. 01), lung (vs. None; HR, 1. 97; 95% CI, 1. 88 -2. 07; p<0. 01) and liver (vs. None; HR, 2. 78; 95% CI, 264-2.92; p<0.01) as possible factors which were associated with greater all-cause mortality. Detailed data was shown in Table3. Briefly, increased mortality and poorer survival were associated with more extent distal metastases and specific molecular subtype. Moreover, we also identified married (vs. unmarried, HR, 0. 67; 95% CI, 0. 65 -0. 69, p<0. 01) and insured (vs. uninsured, HR, 0. 67; 95% CI, 0. 62 -0. 72, p<0. 01) status as protective factor of all-cause mortality.

Discussion

In this study, we describe that the incidence of identified bone metastases among patients with newly diagnosed breast cancer and characterize the subsequent survival of such patients. We found that patients with HR+/HER2+ has the highest incidence proportion of bone metastases while triple-negative sub-types the lowest. Moreover, the effect of black race, insurance status and marital status on bone metastases rate is not obvious. Patients in the bone metastases cohort were likely diagnosed as a result of kinetic system symptoms given that guidelines for breast cancer patients do not recommend screening imaging of the bone. So, the true incidence of breast cancer with bone metastasesis is likely underestimated by the results in the study. We also found that HR+/HER2+ experience the longest survival time (41 months) and triple-negative patients had the shortest survival period (10 months) among patients with bone metastases at diagnose. The development of bone metastases is multifactorial. Metastases through blood is very common in distant metastases in breast cancer. It increases the risk of cancer metastases that breast cancer transfers through the abundant blood flow of vertebral-venous plexus to bone (11) . Otherwise, bone is suggested to be a large repository of growth-stimulating factors including fibroblast growth factors, platelet-derived growth factors, and bone morphogenetic proteins. These factors could promote tumor growth and provide a basic ground for tumor metastases (12, 13). It is reported that skeletal metastases often occur in HR+/HER2- patients with breast cancer when it recurrences. As is shown in our research, the HR+/HER2+ patients has the highest incidence proportion of bone metastases. Previous reports showed that dissemination of breast cancer cells took place long before the detection of breast cancer metastases. Under many circumstances, these cells die during dissemination. Unfortunately, parts of these cancer cell might survive and exist in a dormant state in bone marrow (14, 15). And the dormant cells with HR+ could be reactivated by steroid hormone. As a result, they subsequently develop metastases in bone as they can hijack normal biological processes concerning bone remodeling(16). We found the outcome of bone metastases patients was better than those with other organ like the brain, liver, or lung metastases and HR+/HER2+patients experienced the longest survival time (41 months). HR+ patients with breast cancer are sensitive to targeted therapy, endocrine therapy can remit the tumor and improve the survival of patients. HER2+

patients are sensitive to anti-HER2 therapy (17, 18). Thus, that is probably why patients with HR+, HER2+ status have better outcome. Breast cancer patients are closely associated with bone metastases (19). Previous research found that 62.5% of patients with initial metastases breast cancer were diagnosed with bone metastases (20). However, Current National Comprehensive Cancer Network(NCCN), American Society of Clinical Oncology, and European School of Oncology-Metastatic Breast Cancer guidelines for breast cancer do not include the use of routine bone screening in breast cancer patients, based on a lack of demonstrated survival advantage in existed nonrandomized retrospective studies(21). In spite of the progress of treatments, a great number of female under high risks of bone metastases was still undetected. A study by Jensen and its colleagues (22), reported that bone metastasis occurred in 4% of 35912 female patients, with an average follow-up of 3.9 years. A further study in Japan reported that 690 patients out of 5023(13.7%) developed bone metastases within 10 years after breast cancer surgery(23). Our study revealed that HR+/HER2+ (5%), N3 stage (22%) and other organs metastases (60%) took up the largest proportion when stratified by molecular subtype, lymph node stage and organ metastases. Therefore, we suggest that routine bone staging should be recommended in HR+/HER2+, N3 or other organs metastases breast cancer patients. Bone metastases can lead to bone resorption. This can lead to several skeletal-related events like bone pain, pathological fracture, spinal cord compression.(24). The current American Society of Clinical Oncology (ASCO) evidence-based clinical practice guidelines recommended the use of bisphosphonates in breast cancer if any sign of metastatic bone destruction was shown for preventing further destruction and skeletal-related events(25). Our analysis have identified HR+/HER2+,N3 and other organs metastases as poor prognostic factors. We firmly believe that early bone scanning and standardized treatment with bisphosphonates for these patients can reduce the incidence of skeletal-related events hence prolong their survival. There are some limitations in our study. Due to the nature of retrospective study, selection bias and missing data are inevitable. Another limitation was that we were only accessible to the data of presence of bone metastases at initial diagnosis which means patients who developed bone metastases in later process were excluded in our study. Despite these limitations, our study provides insight into the epidemiology of bone metastases in patients with newly diagnosed breast cancer.

Conclusions

It gave physicians another thought when evaluating the utility of bone screening among patients with high risk of bone metastases. We recommend that routine bone staging be used in HR+/HER2+, N3 or other organs metastases breast cancer patients.

Abbreviations

HER2, human epidermal growth factor receptor 2

HR, hormone receptor

TNBC, triple-negative breast cancer. + ,positive; − ,negative

OR, Odds ratio

CI, confidence interval

HR, hazard ratio

NCCN, National Comprehensive Cancer Network

Declarations

Ethics approval and consent to participate

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

Consent for publication

Not applicable

Availability of data and material

The datasets used or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The study no grant Conflicts of interest All authors declared they have no potential conflicts of interest.

Funding

The study was not funded by any fund

Authors' contributions

The article was mainly written by Zheng Wang and Xiaoli Tang and they contributed equally to the study. Qi Zhang, Xiaoqing Wu, Meiyuan Yang and Zhixiang Jin helped with date analyzing and paper editing. The whole study was instructed by Daorong Wang.

Acknowledgements

Not applicable

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Tables

Table1. Incidence of breast cancer with initial bone metastasis by the molecular subtype

molecular Subtype	With Breast Cancer	With Metastastic Disease	With Bone Metastases	Among Entire Cohort	Among Subset With Metastastic Disease	Survival Among Patiens With Bone Metastases Midian Month
HR+/HER2−	208405	11159	6516	3.1%	58.4%	34
HR+/HER2+	29431	3164	1478	5.0%	46.7%	41
HR−/HER2+	12769	1707	577	4.5%	33.8%	27
TNBC	32462	2476	896	2.8%	36.2%	10
Unknown	27722	3867	1833	6.6%	47.4%	18
All subtypes	310789	22373	11300	3.6%	50.5%	30

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor; TNBC, triple-negative breast cancer.

Table2. Multivariable Logistic Regression for the Presence of Bone Metastases at Diagnosis of Breast Cancer

Variable	Patients	with bone metastases	Among Entire Cohort	
	N=310789	N=11300	OR(95%CI)	P Value
Age at diagnosis				
18-40	14420	683	1[Reference]	NA
41-60	121261	4195	0.98(0.92-1.05)	.53
61-80	139968	5003	1.00(0.94-1.06)	.96
>80	35140	1419	NA	NA
Sex				
male	2463	130	1[Reference]	NA
female	308326	11170	NA	NA
Race				
White	246328	8747	1[Reference]	NA
Black	34532	1723	1.11(0.87-1.42)	.38
Other	27399	782	1.06(0.83-1.36)	.62
Unknown	2530	48	NA	NA
Marital status				
Unmarried	126952	5895	1[Reference]	NA
Married	164497	4761	1.01(0.92-1.10)	.82
Unknown	19340	644	NA	NA
Median household income	310789	11300	NA	NA
High school education	310789	11300	NA	NA
Insurance status				
Uninsured	5578	505	1[Reference]	NA
Insured	296862	10527	1.09(0.96-1.26)	.18
Unknown	8349	268	NA	NA
Subtype				
HR+/HER2−	208405	6516	1[Reference]	NA
HR+/HER2+	29431	1478	1.19(1.06-1.35)	.003*
HR−/HER2+	12769	577	0.95(0.79-1.12)	.51
Triple-negative	32462	869	0.72(0.64-0.82)	<0.01*
Unknown	27722	1833	NA	NA
Lymph node status				
N0	201597	2540	1[Reference]	NA
N1	65219	3617	1.45(0.87-2.42)	.15
N2	15031	907	1.49(0.89-2.50)	.13
N3	12828	2881	2.76(1.66-4.60)	<0.01*
NX Adjust	15668	1349	1.73(1.04-2.89)	.04
NA	446	6	NA	NA
Brain metastases				
None	302684	444	1[Reference]	NA
Yes	1268	800	4.03(2.67-6.09)	P<0.01*
Metastases of lung				
None	299688	2271	1[Reference]	NA
Yes	5379	2982	27.31 (20.06-37.17)	P<0.01*
Metastases of liver				
None	298602	1692	1[Reference]	NA
Yes	4426	2626	10.45(4.63-23.59)	P<0.01*

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor. + Denotes positive; − denotes negative; *****, *Only significant results presented (P < .05).*

Table3. Multivariable Cox Regression for All-Cause Mortality Among Patients With Bone Metastases

Variable	Patients	with bone metastases	All-Cause Mortality	
	N=310789	N=11300	HR(95%CI)	P Value
Age at diagnosis				
18-40	14420	683	1[Reference]	NA
41-60	121261	4195	1.04(0.97-1.01)	.28
61-80	139968	5003	1.79(1.68-1.91)	<0.01*
>80	35140	1419	5.32(4.99-5.67)	<0.01*
Sex				
male	2463	130	1[Reference]	NA
female	308326	11170	NA	NA
Race				
White	246328	8747	1[Reference]	NA
Black	34532	1723	1.35(1.30-1.39)	<0.01*
Other	27399	782	0.80(0.77-0.85)	<0.01*
Unknown	2530	48	0.27(0.22-0.35)	<0.01*
Marital status				
Unmarried	126952	5895	1[Reference]	NA
Married	164497	4761	0.67(0.65-0.69)	<0.01
Unknown	19340	644	0.78(0.75-0.863	<0.01*
Median household income	310789	11300	NA	NA
High school education	310789	11300	NA	NA
Insurance status				
Uninsured	5578	505	1[Reference]	NA
Insured	296862	10527	0.67(0.62-0.72)	<0.01*
Unknown	8349	268	0.97(0.89-1.07)	.61
Subtype				
HR+/HER2−	208405	6516	1[Reference]	NA
HR+/HER2+	29431	1478	1.03(0.99-1.08)	.19
HR−/HER2+	12769	577	1.55(1.48-1.63)	<0.01*
Triple-negative	32462	869	2.60(2.52-2.68)	<0.01*
Unknown	27722	1833	1.91(1.85-1.97)	<0.01*
Lymph node status				
N0	201597	2540	1[Reference]	NA
N1	65219	3617	1.75(1.69-1.80)	<0.01*
N2	15031	907	2.42(2.31-2.54)	<0.01*
N3	12828	2881	3.21(3.09-3.35)	<0.01*
NX Adjust	15668	1349	2.97(2.84-3.10)	<0.01*
NA	446	6	NA	NA
Brain metastases				
None	302684	444	1[Reference]	NA
Yes	1268	800	2.22(2.07-2.40)	P<0.01*
Metastases of lung				
None	299688	2271	1[Reference]	NA
Yes	5379	2982	1.97 (1.88-2.07)	P<0.01*
Metastases of liver				
None	298602	1692	1[Reference]	NA
Yes	4426	2626	2.78(2.64-2.92)	P<0.01*

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hormone receptor. + Denotes positive; − denotes negative. * *Only significant results presented (P < .01).NA, not available.*

Figures

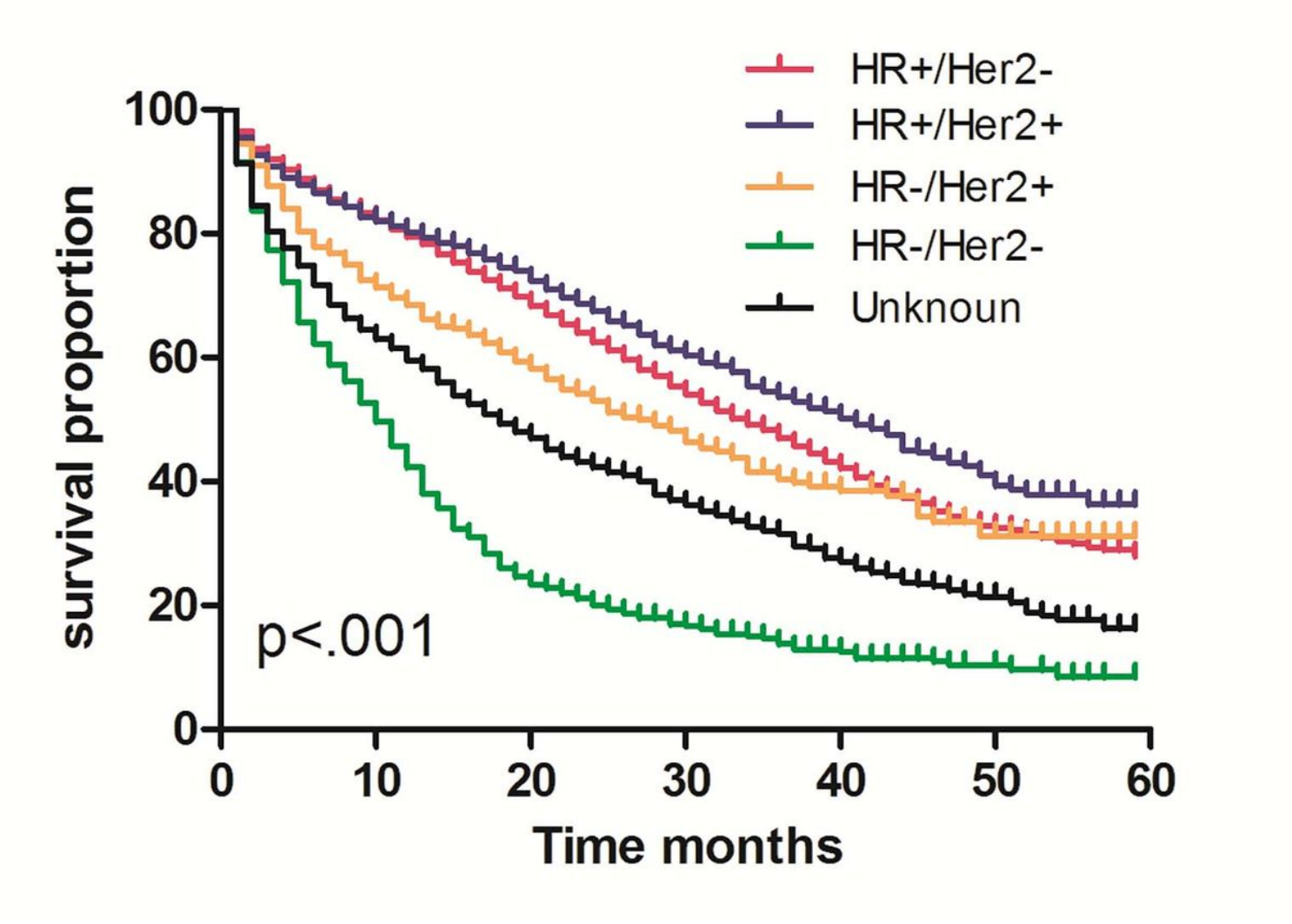

Figure 1

Survival analysis among patients with initial bone metastases stratified by subtype

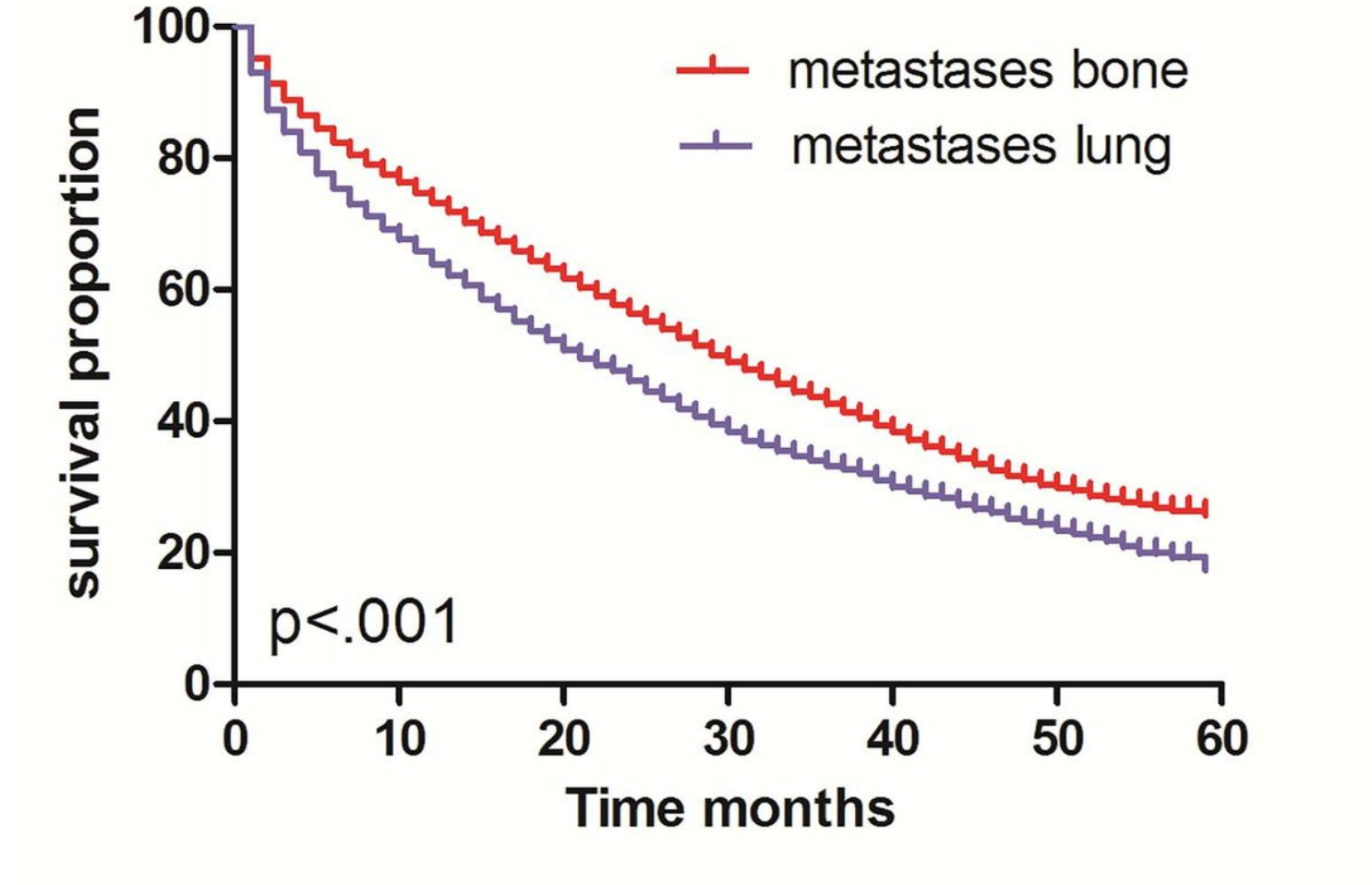

Figure 2

Survival metastatic bone and lung

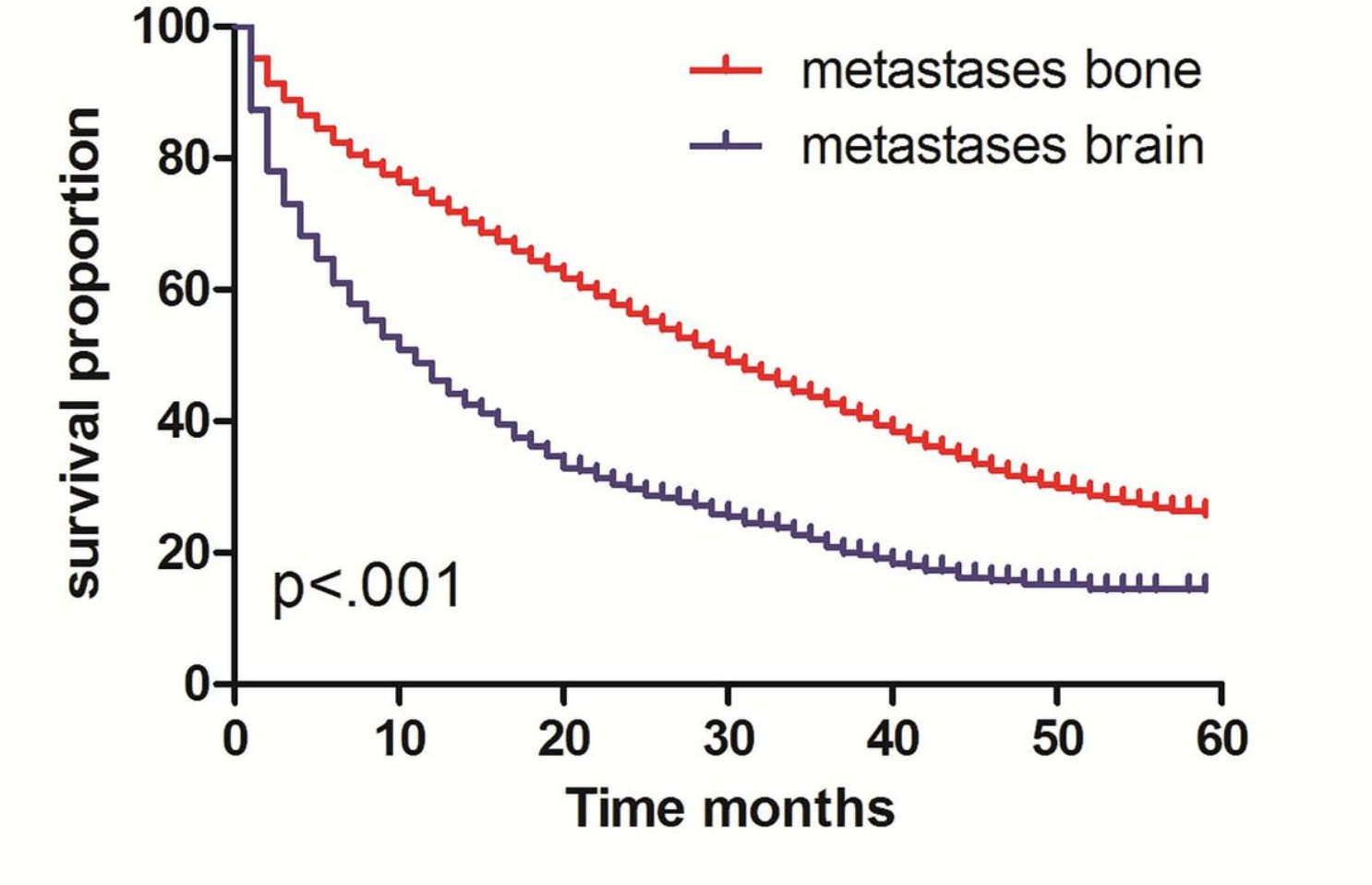

Figure 3

Survival metastatic bone and brain

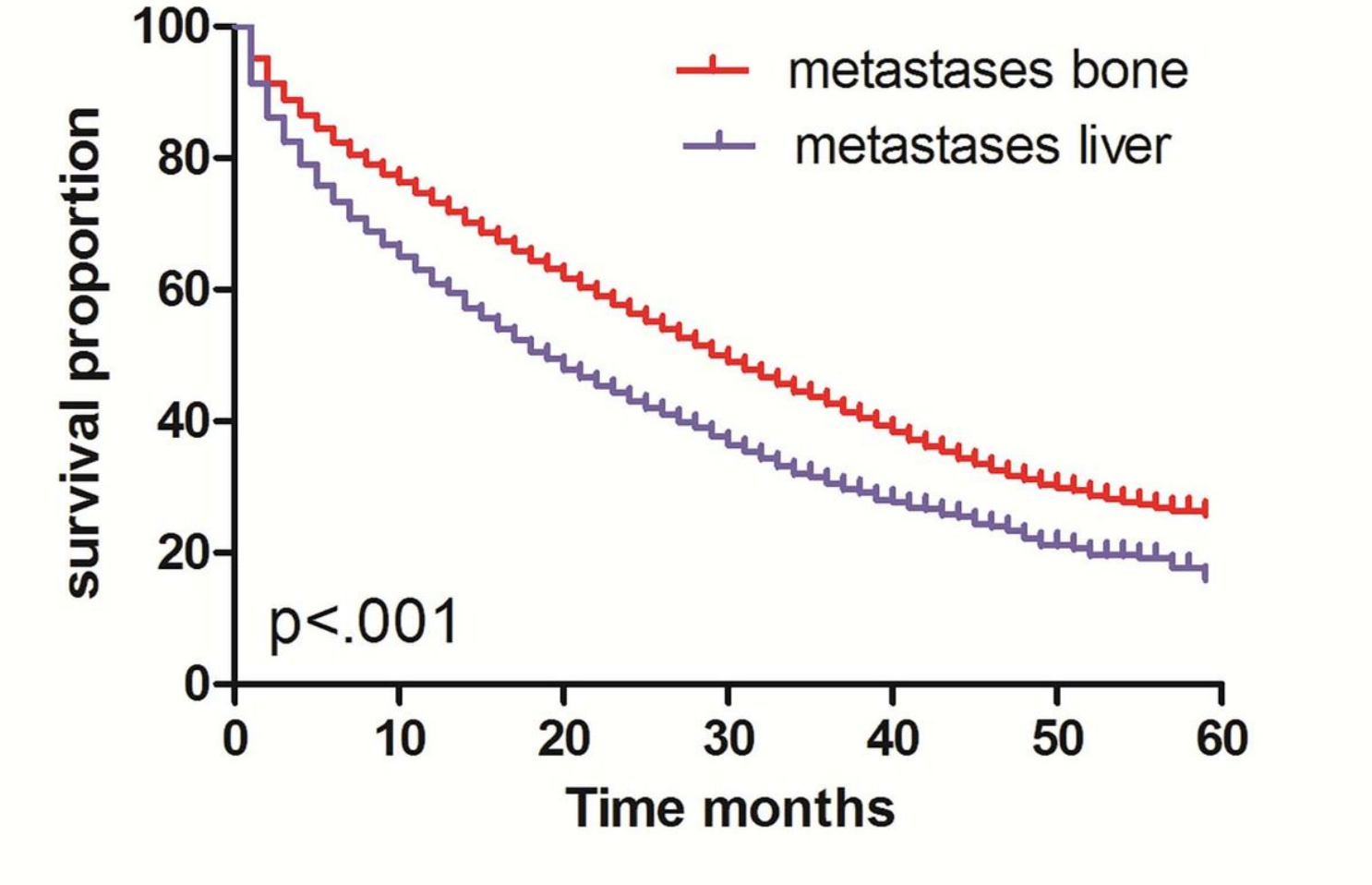

Figure 4

Survival metastatic bone and liver