The Clinicopathological Features and Survival Outcomes of Patients with Different Metastatic Sites in Stage IV Breast Cancer

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Abstract

Background The features and survival of stage IV breast cancer patients with different metastatic sites are poorly understood. This study aims to examine the clinicopathological features and survival of stage IV breast cancer patients according to different metastatic sites. Methods Using the Surveillance, Epidemiology, and End Results database, we restricted our study population to stage IV breast cancer patients diagnosed between 2010 to 2015. The clinicopathological features were examined by chi-square tests. Breast cancer-specific survival (BCSS) and overall survival (OS) were compared among patients with different metastatic sites by the Kaplan-Meier method with log-rank test. Univariable and multivariable analyses were also performed using the Cox proportional hazard model to identify statistically significant prognostic factors. Results A total of 18,322 patients were identified for survival analysis. Bone-only metastasis accounted for 39.80% of patients, followed by multiple metastasis (33.07%), lung metastasis (10.94%), liver metastasis (7.34%), other metastasis (7.34%), and brain metastasis (1.51%). The Kaplan-Meier plots showed that patients with bone metastasis had the best survival, while patients with brain metastasis had the worst survival in both BCSS and OS ($p < 0.001$, for both). Multivariable analyses showed that age, race, marital status, grade, tumor subtype, tumor size, surgery of primary cancer, and a history of radiotherapy or chemotherapy were independent prognostic factors. Conclusion Stage IV breast cancer patients have different clinicopathological characteristics and survival outcomes according to different metastatic sites. Patients with bone metastasis have the best prognosis, and brain metastasis is the most aggressive subgroup.

Background

Breast cancer, one of the most frequently diagnosed cancer in women, is the second leading cause of cancer-related death among women worldwide. According to the 2018 cancer statistics, the estimate of the number of annually diagnosed breast cancer is 1.7 million, which accounted for 25% of all diagnosed cancer cases. In addition, 626,679 women are expected to die from this disease, making up 15% of all cancer deaths among females[1]. Despite the high morbidity of the disease, patients with breast cancer have a better prognosis compared to other aggressive cancers, with a 5-year survival rate of 91% and 10-year survival of 86%[2]. However, survival reduces greatly if patients develop distant metastases. The overall 5-year relative survival rate is 99% for localized diseases, 85% for regional diseases, and drops to 27% for distant-stage diseases[3].

It is estimated that 20-30% early stage BC will finally go on to develop metastatic disease, and approximately 6% of all women with breast cancer in the United States present with stage IV disease at the moment of initial diagnosis (called de novo metastatic breast cancer)[4]. These patients have a poor prognosis with a median survival time of 2-3 years[5], despite medical progress that has been made. Metastatic breast cancer is a heterogeneous disease with various prognoses[6], which are affected by many clinicopathological features of patients, such as age, race, marital status, performance status as

well as the tumor size, lymph nodes status, pathological or genotype characteristics, metastatic sites, number of metastatic sites, and medical treatments[7-9]. Therefore, the accurate estimation of survival of every patient may benefit patients significantly in all aspects of decision-making[10]. The TNM stage is the widely accepted tool to predict the prognosis of patients, but the factors included in this tool is very limited and it ignores patients specific conditions, pathological or genotype characteristics, and treatments[10]. Therefore, it is still difficult to make precise predictions on the individual prognosis of metastatic breast cancer by this tool. Among all the predictors of outcome mentioned above, the metastatic site may be the most important factor and have a significant impact on further treatment regimens.

Population-level estimates for prognosis among breast cancer patients with distant metastases are lacking, the relationship between clinically related factors and the exact patterns of distant metastasis is not well established. And thus, the purpose of this study was to use the Surveillance, Epidemiology, and End Results (SEER) database to investigate the clinicopathological features, treatment, and survival outcomes of stage IV breast cancer patients based on their metastatic sites at the time of cancer diagnosis on a population-based level.

Materials And Methods

Patients

The recent version of the Surveillance, Epidemiology and End Results (SEER) 18 registries Custom Data (with additional treatment fields) was used as the data source for the present population-based investigation. Maintained by National Cancer Institute, the SEER program is the largest publicly available cancer dataset in the world, which consists of 18 population-based cancer registries and covers approximately 26% of the US population across several geographic regions[11]. Patients diagnosed with female breast cancer as primary cancer from 2010 to 2015, with distant metastasis, were enrolled into the study. The tumors were classified based on their primary site of presentation and histology utilizing the International Classification of Disease for Oncology, Third Edition (ICD-O-3). Those patients with unknown metastatic sites and survival months were excluded. Of 19913 women with a diagnosis of stage IV breast cancer between the year 2010 and 2015 included into the SEER Registry, 18322 women were eligible for inclusion into the present study (Figure 1, consort diagram). Eligible patients were grouped according to the metastatic sites. All procedures performed in studies involving human participants were in accordance with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. It does not require informed patient consent due to the public access to the SEER database, and hence the study was deemed exempt from review by the Ethics Committee of the First Affiliated Hospital of Xian Jiaotong University.

Demographic and clinical variables

The relationship between metastatic sites and clinical characteristics, including age at diagnosis, year of diagnosis, race, marital status, tumor grade, tumor size, nodal status, subtype, and treatment was analyzed. Overall survival (OS) was calculated from the date of diagnosis to the date of death due to any cause, the date of last follow-up, or December 31, 2015. Breast cancer-specific survival (BCSS) was measured as the time from the date of diagnosis to the date of death attributed to breast cancer. Both overall survival and breast cancer-specific survival were used as endpoints.

Statistical Analysis

The baseline characteristics of patients and treatment were described using summary statistics, with continuous variables being shown as mean ± standard deviation. Differences between qualitative data and continuous variables were analyzed using $\chi 2$ statistics and analysis of variance, respectively. We used Kaplan-Meier plots to calculate survival curves and log-rank test to compare the differences of BCSS and OS between different metastatic groups. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated by univariate and multivariate Cox proportional hazard models to identify risk factors for patients' survival. All the tests above were 2-tailed, and a *p*-value of less than 0.05 was considered statistically significant. All statistical analyses were carried out using SPSS software version 20.0 (SPSS Inc.).

Results

Patient characteristics

According to the above inclusion and exclusion criteria, 18322 patients were enrolled in this study. Table 1 showed the demographic and clinicopathological characteristics of stage IV patients according to metastatic sites. Bone metastasis accounted for about 39.8% of patients (7292), followed by multiple metastasis (33.07%, 6059), lung metastasis (10.94%, 2005), liver metastasis (7.34%, 1346), other metastasis (7.34%, 1344), and brain metastasis (1.51%, 276). The median follow-up was 14 months. The mean age of liver metastasis (59.0 years) was the lowest and lung metastasis(66.2 years) was the highest among all the groups (range, 61.2-64.3 years). Liver metastasis was more frequent of poorly/undifferentiated tumor (48.66%), followed by lung metastasis (47.16%) and brain metastasis (42.39%). Bone was the predominant site of metastasis for the HR+/HER2- (64.4%) and HR+/HER2+ (11.76%) groups and the least common site in the HR-/HER2+ group (3.24%). Of patients in the brain, lung, and liver metastasis subgroups, 26.9%, 21.22%, and 14.42%, respectively, are the triple negative subtype. Patients with lung metastasis (50.69%) and multiple metastases (48.07%) tend to have larger tumors of T3-T4 at initial diagnosis. Furthermore, these two groups of patients also have a higher proportion of later N stage(N3), making up 29.48% and 33.94% respectively. The detailed patient characteristics are presented in Table 1.

Kaplan-Meier Survival analysis

Of all the 18322 patients finally recruited, 9880 patients were dead at the end of the last follow-up, and 7239 of them were dead of breast cancer specifically. The Kaplan-Meier plots were displayed in Figure 2 to show the survival of all population. Figure 2A shows the breast cancer-specific survival(BCSS) according to metastatic sites of stage IV patients. Brain metastasis had the worst survival: the 3-year BCSS rate was 2.1%. The 3-year BCSS rate of lung, liver, and multiple metastases were, 7.86%, 8.10%, and 6.95% respectively. Bone and other metastasis had better BCSS, for which the 3-year BCSS rate was 13.48% and 10.95%, respectively ($p < 0.001$). Figure 2B shows the overall survival (OS) according to metastatic sites of stage IV patients who were enrolled into the study. Similar to BCSS, patients with bone metastasis had the best survival, with 3-year OS rate of 4.7%, followed by patients with other metastasis, multiple metastases, and liver metastasis, and the OS rate was 4.33%, 3.70%, and 3.34% respectively. Patients with brain metastasis and liver metastasis had worse OS than other subgroups: the 3-year OS rate was 1.81%, and 2.89%, respectively ($p < 0.001$).

Cox regression analysis of survival

In order to further figure out the effect of multiple factors on BCSS and OS, the Cox proportional hazard model was applied in the analysis. In univariate analysis of BCSS and OS, unmarried status, race of black, higher grade, larger tumor size, later N stage, Her2 positive and triple negative subtypes, were proved to be risk factors for poor survival (hazard ratio [HR] > 1, $p < 0.001$). By contrast, married status, other race, chemotherapy, radiotherapy, and surgery were found to be protective factors for better survival (hazard ratio [HR] < 1, $p < 0.001$) (Table 2). As for metastatic sites, the results were consistent with those of Kaplan-Meier analysis. Patients with bone metastasis had the best BCSS and OS, followed by patients with other, liver, lung, and multiple metastases. Specifically, patients with brain metastasis exhibited the worst BCSS (hazard ratio [HR] =1.708, 95% confidence interval [CI] = 1.442-2.023, $p < 0.001$) and OS (hazard ratio [HR] = 2.492, 95% confidence interval [CI] =2.161-2.874, $p < 0.001$).

The variables mentioned above were enrolled in the multivariate Cox analysis subsequently. After adjusting for age, race/ethnicity, marital status, tumor grade, breast cancer subtype, tumor size, nodal status, surgery, radiotherapy, and chemotherapy in the analysis, metastatic sites remained an independent prognostic factor of BCSS and OS. The detailed results of Cox regression analysis of BCSS and OS are available in Table 3. Compared to patients with bone metastasis, the BCSS (HR 0.994, 95% CI 0.881–1.122, $p = 0.921$) and OS (HR 0.994, 95% CI 0.897–1.100, $p = 0.902$) of patients with lung metastasis were not significantly different. Patients with other metastasis had similar BCSS (HR 0.955, 95% CI 0.827-1.103, $p = 0.532$) as patients with bone metastasis, but worse OS (HR 1.127, 95% CI 1.001-

1.269, p = 0.048). Patients with liver (HR 1.384, 95% CI 1.208–1.586, p < 0.001; OS, HR 1.428, 95% CI 1.272–1.602, p < 0.001) and multiple metastases (BCSS, HR 1.475, 95% CI 1.361–1.599, p< 0.001; OS, HR 1.806, 95% CI 1.684–1.937, p< 0.001) had worse BCSS and OS than bone metastasis. Similarly, the multivariate analysis also indicated that those patients with brain metastasis had significant inferior BCSS (HR 1.975, 95% CI 1.551-2.514, p < 0.001) and OS (HR 2.307, 95% CI 1.862-2.859, p < 0.001) over other metastatic sites. Age, marital status, tumor grade, triple negative subtype, tumor size, surgery, chemotherapy were also the independent prognostic factors of survival outcomes.

Discussion

More and more patients suffer from cancer invasion and metastasis with the increase of cancer incidence worldwide. Tumor metastasis is complicated, and there are certain specificities during the process of tumor dissemination and invasion to distant organs. We hope to provide deep insights into a better understanding of the heterogeneity of metastatic breast cancer.

In the current study, we analyzed the clinicopathological characteristics and survival of de novo metastatic breast cancer according to metastatic sites using the SEER data. We also present prognostic factors and survival prediction of these patients. The results showed that patients with different metastasis had different clinicopathological characteristics and survival outcomes, indicating that advanced breast cancer can be divided into several distinct biological entities.

Metastatic breast cancer is widely known as incurable with poor prognosis compared to those without metastasis. Bone, liver, lung, and brain are common sites of distant metastasis in breast cancer[12]. There have been studies indicated that bone is the most common distant metastatic organ in breast cancer patients[13,14]. Consistent with previous studies, our results also showed that bone metastasis is the most prevalent subgroup among the studying cohort, accounting for 39.8% of the total patients. Recent studies suggest that biological subtypes of breast cancer may drive metastatic behavior towards specific organs, and it has also been demonstrated to have a different prognostic impact on different patterns of distant metastasis. In our study, we showed that the patients with bone metastasis are mainly composed of HR+/HER2- subtype (64.4%), which is supported by several studies that the patients with HR+ are more prone to develop bone metastasis[15,16]. Lung and liver metastases together are termed as visceral metastasis, both of which share similar clinicopathological features. In these two subgroups, tumors are more likely to be poorly differentiated or undifferentiated. But the predictive value and the relationship between visceral metastasis and breast cancer subtype are still controversial. A study by Kennecke et al demonstrated that compared with luminal A tumors, HER2-enriched tumors were associated with a significantly higher rate of liver metastases, and the patients with HR−/HER2+ had the highest probability of liver metastasis (23.3%) [7]. But some other studies reported that liver metastasis was not associated with breast cancer subtype[17]. In our study, HR+/HER2- and HR-/HER2+ tumors

exhibited high rates of liver metastasis of 33.4% and 21.3%, while HR+/HER2- and triple negative tumors exhibited high rates of lung metastasis of 38.7% and 21.2%, respectively. Brain has been previously described as a preferred site of metastasis among triple negative tumors. Martin, A. M et al previously reported on the incidence proportion of patients with breast cancer who were diagnosed as having brain metastases from 2010 to 2013[18]. They found that the incidence proportion of brain metastasis was highest among patients with HR-/HER2+ and triple-negative subtypes (11.37% and 11.45%, respectively) to any distant sites at diagnosis of breast cancer. Other incidence of brain involvement among patients with metastatic HER2 positive disease has been described to be 25% to 34%[19], which is significantly higher than the 3.4% and 1.9% rate for triple negative and HR-/HER2+ subtypes respectively in this study. The main reason for this is that the patients with brain metastasis enrolled in this study is very limited compared with other subgroups, accounting for only 1.51% of the whole cohort population, which makes it not as representative as other results. Further studies with more patients and prospective design are needed to better interpret the situation.

Breast tumors may favor metastasis to different biological features and also may be associated with varying survival probabilities according to their different organs. Some studies have shown that the survival of female breast cancer may be associated with different metastatic patterns[12,20]. However, these studies are controversial, and there's no population-based study focus on studying the survival differences in patients with different metastatic patterns. The study conducted by L. Gerratana et al showed the best prognosis was observed among patients with lung as the first site of distant metastasis (58.5 months), followed by those with first metastatic involvement of bone (44.4 months), liver (36.7 months) and brain (7.35 months)[12]. But the 5-year survival rate was significantly higher in patients with bone metastasis when compared with other types of distant metastasis in another study[20], which is consistent with our conclusion. In our study, the Kaplan–Meier curves showed that patients with bone metastasis had the best survival in both OS and BCSS, the 3-year BCSS and OS rate were 13.48% and 4.7%, respectively. Lung, liver and other metastasis had very similar survival according to Kaplan-Meier analysis, with 3-year BCSS rate of 7.9%, 8.1%, and 10.9% respectively. Multiple metastases are defined as distant metastasis of more than one organs in breast cancer patients. Women with multiple organs affected had worse survival than those with minimal metastatic disease, a finding confirmed in this study. The presence of brain metastasis was shown in our analysis as a poor prognostic factor compared to all the other distant metastases, and the survival of these patients was even worse than patients with multiple metastases. We got the same result in both Kaplan-Meier survival analysis and Cox regression analysis. Taking bone metastasis as the reference, univariate and multivariate analysis showed that patients with brain metastasis had the worst prognosis, the specific clinicopathological and molecular characteristics of each subtype could partly explain the differing reported outcomes. This result is in line with another study based on SEER database[18] as well as some retrospective studies[21,22]. However, our analysis differs in being on a much larger sample size which may give a more representative picture of the routine daily practice.

Historically, women diagnosed with metastatic breast cancer were not treated with surgery and received only systemic therapy[23]. It is believed that surgical resection of the primary tumor was palliative and performed only to relieve symptoms such as bleeding, infection, or pain. However, the value of local treatment of the primary in cases of a metastatic solid tumor has been shown for metastatic renal cell carcinoma, metastatic nonfunctioning pancreatic neuroendocrine tumors and hepatocellular carcinoma[24-26]. For breast cancer, there is no evidence-based consensus about whether and when to perform surgery in the setting of metastatic disease. The similar strategy is currently being explored in several ongoing studies for patients with metastatic breast cancer at initial presentation[27]. Some former retrospective data suggested no benefit from surgical resection to the primary tumor and synchronous metastases, since breast surgery may improve the control of local disease but it probably worsened control at distant sites. But more recent studies suggested that primary tumor resection following favorable response to systemic chemotherapy in stage IV patients may be considered in highly selected patients[28,29]. This is consistent with observations from our study describing a survival benefit for both BCSS and OS of the patients accepted surgery compared to those who did not undergo surgery. The conclusion is also true when it comes to radiotherapy and chemotherapy. Multivariate Cox proportional hazards model showed either radiotherapy or chemotherapy was significantly associated with improved survival of patients in this cohort. However, the study still carries the methodological defects of a retrospective analysis so that it is not enough to derive clear recommendations. Further randomized clinical trials are needed to reach conclusions on the benefits and risks of breast local treatment including surgery and radiotherapy with systemic treatment for women diagnosed with metastatic breast cancer. In this analysis, prognostic factors that influenced survival besides initial sites of metastases were age at diagnosis, race, marital status and tumor grade. This is in accordance with other studies investigating prognostic factors in metastatic breast cancer[8,30]. The current analysis showed that married patients have better overall and breast cancer-specific survival compared to unmarried patients. This difference may be explained by the social psychological support given by a partner, which benefits cancer patients a lot.

Inevitably, there are several limitations that should be admitted in this study. First, as a retrospective study rather than a prospective cohort study, inherent selection biases are unavoidable and could limit the external validity of this study. Second, information about disease recurrence or subsequent sites of disease involvement is not provided in the SEER database, so that the focus of this study is de novo metastatic breast cancer and we were unable to comment on patients who developed metastases later in their disease course. Third, the follow-up period was relatively short with the median follow-up time of only 14 months, as the data of HER-2 status were not available until 2010. Thus, we were only able to focus on the short-term prognosis of distantly metastatic breast cancer patients. These limitations may have contributed to study bias and undermine the power of analysis.

Conclusion

Despite these limitations, our results provide insight into the epidemiology, clinicopathological characteristics and survival outcomes of distant metastases in patients with newly diagnosed breast cancer in the United States. Even though patients with distant metastases are all defined as advanced cancer, the prognosis is much different according to the metastatic site. Patients with bone metastasis and other metastatic sites other than bone, liver, lung, or brain have an excellent prognosis, while brain metastasis is the most aggressive group and requires additional treatment options. Metastatic sites should be taken into consideration when making therapeutic strategies for patients with advanced cancer. Further studies are needed to confirm our results.

Abbreviations

BC: breast cancer; SEER: Surveillance, Epidemiology and End Results; BCSS: Breast cancer-specific survival; OS: overall survival; HR: Hazard ratio; CI: confidence interval

Declarations

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Availability of data and materials

The data were abstracted from an open database, the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov).

Authors' contributions

RW, JH and LN designed the study. XL and XL collected the data. RW and YZ analyzed the data. RW, YZ, and XL organized the manuscript. JH and LN reviewed the papers and revised the manuscript. All the authors (RW, YZ, XL, XL, JH and LN) have read and approved the final manuscript. All authors contributed

toward data analysis, drafting and revising the paper and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

This study used previously collected deidentified data, which was deemed exempt from review by the Ethics Committee of the First Affiliated Hospital of Xi'an Jiaotong University.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Due to technical limitations, tables 1 through 3 are only available as a download in the supplemental files section.

Figures

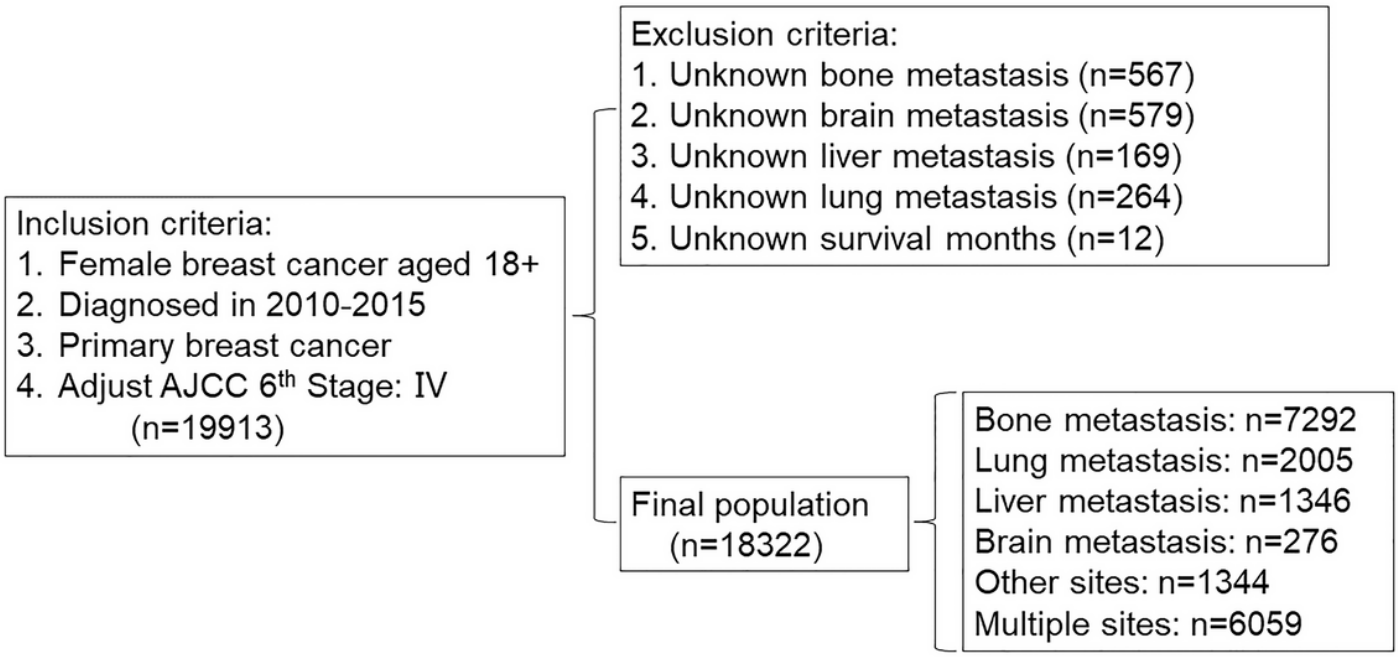

Figure 1

Flowchart for patients selection from the Surveillance, Epidemiology and End Results (SEER) database

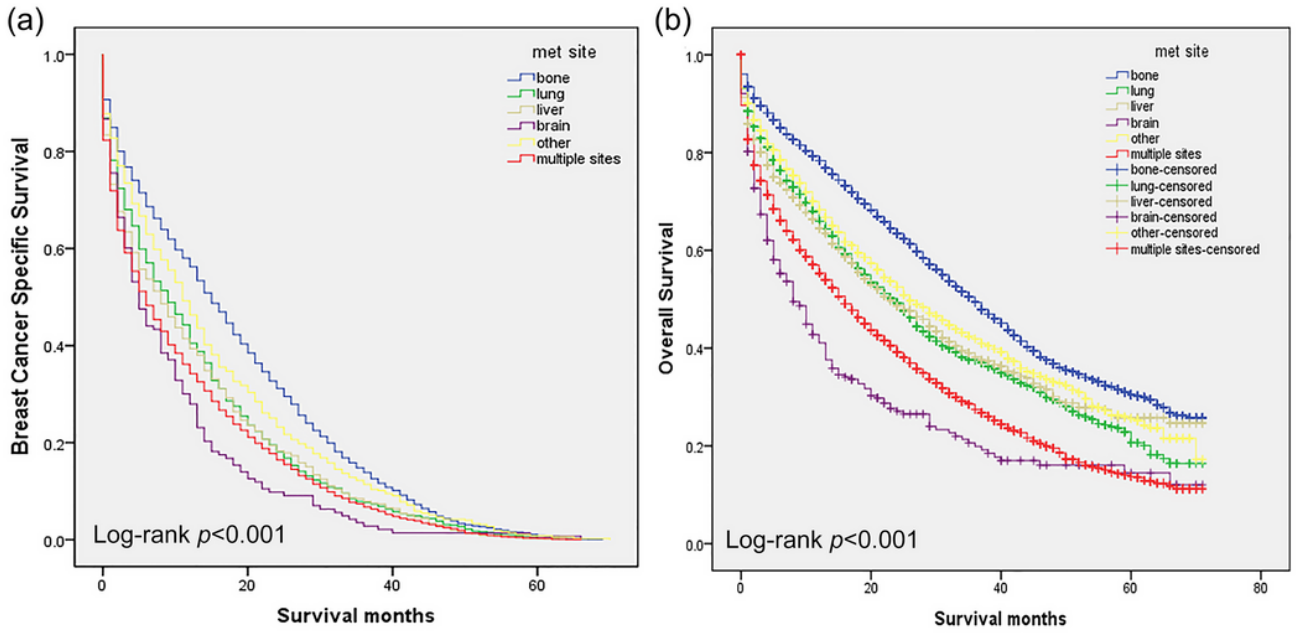

Figure 2

Survival curves with the log-rank tests of breast cancer-specific survival (BCSS, a, p<0.001) and overall survival (OS, b, p<0.001) based on metastatic sites for breast cancer patients

Supplementary Files

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- Table1.jpg
- Table2.jpg
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