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Prognostic factors for postoperative survival in melanoma patients with bone metastasis

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Abstract

Melanoma can spread to the bone by metastasis and is relevant to a poor outcome. However, because of the rarity of melanoma patients with bone metastasis, the prognostic postoperative survival factors of them have not been elucidated. The aim of this special population-based cohort was to elucidate the prognostic factors associated with postoperative survival. The Surveillance, Epidemiology, and End Results database was used to extract postoperative survival data relating to patients with melanoma and bone metastasis at diagnosis between 2010 and 2016, along with data on a range of potential postoperative prognostic factors. We then investigated the potential postoperative prognostic roles of these factors using a Cox regression model and the Kaplan-Meier analysis. In all, the Surveillance, Epidemiology, and End Results database included 186 cases. Regarding overall survival, the 1-, 3-, and 5-year overall survival rates for the entire cohort were 36.2%, 15.4%, and 9.5%, respectively. Regarding cancer-specific survival, the 1-, 3-, and 5-year cancer-specific survival rates were 42.0%, 23.2%, and 16.6%, respectively. Within a cohort of melanoma patients with bone metastasis after surgery, our analysis showed that a smaller tumor size and the lack of metastases at other sites were predictors of survival.

Abbreviations: CSS = cancer-specific survival, OS = overall survival, RT = radiation therapy, SEER = Surveillance, Epidemiology, and End Results.

Keywords: bone metastasis, melanoma, prognosis, Surveillance, Epidemiology, and End Results (SEER), survival

1. Introduction

Melanoma, which is formed from melanocytes, is one of the most malignant cancers; although small in size (approximately 1 mm in diameter), these tumors are very aggressive.[1,2] Melanoma can affect many parts of the human anatomy, including the eyes, anus, and rectum,[3,4] but it most commonly affects the skin.[5] The demographic, epidemiological, and prognostic data for melanoma have been characterized extensively. The 5-year survival rate for patients with melanoma is closely related to the tumor stage, ranging from 91.4% to 24.6% among tumor stages I and IV.[6] Furthermore, a number of prognostic factors have been associated with melanoma, including age, race, sex, pathological pattern, tumor thickness, distant metastasis, systemic treatments, and radiation therapy (RT).[6–11] The prognosis of metastatic melanoma patients is pretty bad; the 5-year survival rate can be as low as 16% and the mean survival time is no more than 1 year.[12,13] In a recent study, Abdel-Rahman reported that different distant metastatic sites lead to distinctive prognoses.[14] Additionally, he found that the lack of surgery is a harmful prognostic factor for distant metastasis.[14] A complete surgical resection is crucial in metastatic melanoma. However, little is known about the precise prognostic factors for bone metastasis in melanoma patients after surgery.

To identify the prognostic indicators for this condition, we extracted data from a cohort of melanoma patients with bone metastasis after surgery between 2010 and 2016 from a cancer database compiled by the United States National Cancer Institute that is referred to as the Surveillance, Epidemiology, and End Results (SEER) database. Thus, this was a large population-based study of melanoma patients with bone metastasis after surgery that desired to identify potential independent postoperative survival determinants.

2. Methods

2.1. Patient population

We identified a total of 186 melanoma patients who were given a definite pathological diagnosis of bone metastasis after surgery between 2010 and 2016. We then used the case-listing session

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The datasets generated during and/or analyzed during the current study are publicly available.

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procedure to extract all suitable patient data from the SEER cancer database (www.seer.cancer.gov); this is a database that is open to the public, although patients remain anonymous. The study was approved by the Institutional Review Board of Taizhou Municipal Hospital.

First, we used histology codes provided by the International Classification of Diseases for Oncology, 3rd Edition (ICD-O-3), which contained melanoma patient data, to retrieve all individuals with melanoma (ICD-O-3 code 8720-8780). We then limited the patients to those with melanoma and bone metastasis. All of the patients included were diagnosed pathologically by positive histological examination, based on biopsy or surgical specimens. We extracted a range of information from the SEER database, including age at diagnosis, race, sex, tumor size, other metastatic sites (brain, lung, and liver), surgery, RT, chemotherapy, cause of death, and survival duration (months). In addition, surgery performed patients were singled out. Patients were excluded if the tumor size was unknown, whether there were other sites of metastasis (brain, lung, and liver) was unknown, and if the patient did not survive for longer than a month. Furthermore, tumor size refers only to the size of the primary site.

2.2. Statistical methods

Statistical analyses were carried out using SPSS (version 21.0) statistical software (IBM Corp., Armonk, NY) and Microsoft Excel 2016. We evaluated primary survival outcome as time in months by overall survival (OS) and cancer-specific survival (CSS); OS was considered as the time elapsed from diagnosis to death from any cause, while CSS was defined as the time between diagnosis and death specifically due to cancer. Survival curves for OS and CSS were created using the Kaplan-Meier method, while the log-rank test provided for comparative analysis of survival curves. Both the 1-, 3-, and 5-year OS and 1-, 3-, and 5-year CSS rates were calculated by life table method, respectively. Univariate analysis was initially used to discern possible independent postoperative prognostic factors for OS and CSS. Multivariate analyses were then showed to ascertain the independent survival determinants for prolonging postoperative survival of melanoma patients with bone metastasis. Race was not included into analyses because of its large disparities. Both univariate and multivariate analyses were based on a Cox proportional hazards regression model. We used hazard ratios along with the corresponding 95% confidence intervals (CIs) to demonstrate the effect of multiple factors on OS and CSS. Observations were censored if the melanoma patients with bone metastasis were still alive at the time of the last follow-up. In our cohort, differences were considered to be statistically significant if $P < .05$.

3. Results

3.1. Clinical data of the 186 melanoma patients with bone metastasis after surgery

Overall, 1317 melanoma patients were identified in the SEER registry, and 186 melanoma patients with bone metastasis were selected and their clinical data extracted from the SEER database (Table 1). Based on the median age at diagnosis, we divided the patients into two age groups: 83 of the patients (44.6%) were aged <65 years, while 103 (55.4%) were aged ≥65 years. For race, major patients were white (95.7%). The study involved 128 (68.8%) males and 58 (31.2%) females. When categorizing tumor sizes, we used the classification system used in previous research[15] and based on the median tumor size: 78 tumors (41.9%) were ≤2 cm, and 108 (58.1%) were >2 cm. About two-thirds of patients (76.9%) merged other parts of the metastasis. Approximate numbers of patients underwent RT (33.3%) and chemotherapy (35.5%). A total of 144 patients (77.4%) died. The 1-year OS and 1-year CSS rates for the overall cohort were 36.2% and 42.0%, respectively, while the 3-year OS and 3-year CSS rates were 15.4% and 23.2%, respectively, while the 5-year OS and 5-year CSS rates were 9.5% and 16.6%, respectively.

Table 1

Clinical characteristics of 186 patients with pathologically diagnosed melanoma patients with bone metastases after surgery in SEER database between 2010 and 2016.

Category	Value
Mean age at diagnosis (yrs)	67
Median age at diagnosis (yrs)	66.7
Age at diagnosis (yrs)	
<65	83 (44.6%)
≥65	103 (55.4%)
Race	
White	178 (95.7%)
Black	6 (3.2%)
Other	2 (1.1%)
Sex	
Male	128 (68.8%)
Female	58 (31.2%)
Tumor size	
Median tumor size (cm)	2.5
≤2 cm	78 (41.9%)
>2 cm	108 (58.1%)
Bone metastasis only	
Yes	64 (34.4%)
No	122 (65.6%)
Radiation therapy	
Yes	62 (33.3%)
No	124 (66.7%)
Chemotherapy	
Yes	66 (35.5%)
No	120 (64.5%)
Survival	
Yes	42 (22.6%)
No	144 (77.4%)
1-yr OS rate	36.2%
1-yr CSS rate	42.0%
3-yr OS rate	15.4%
3-yr CSS rate	23.2%
5-yr OS rate	9.5%
5-yr CSS rate	16.6%

CSS = cancer-specific survival, OS = overall survival, SEER = Surveillance, Epidemiology, and End Results.

3.2. Univariate analysis of variables associated with the OS and CSS of melanoma patients with bone metastasis after surgery

We evaluated a diverse range of factors using and Kaplan-Meier curves and univariate analysis (Figs. 1 and 2, Table 2,).

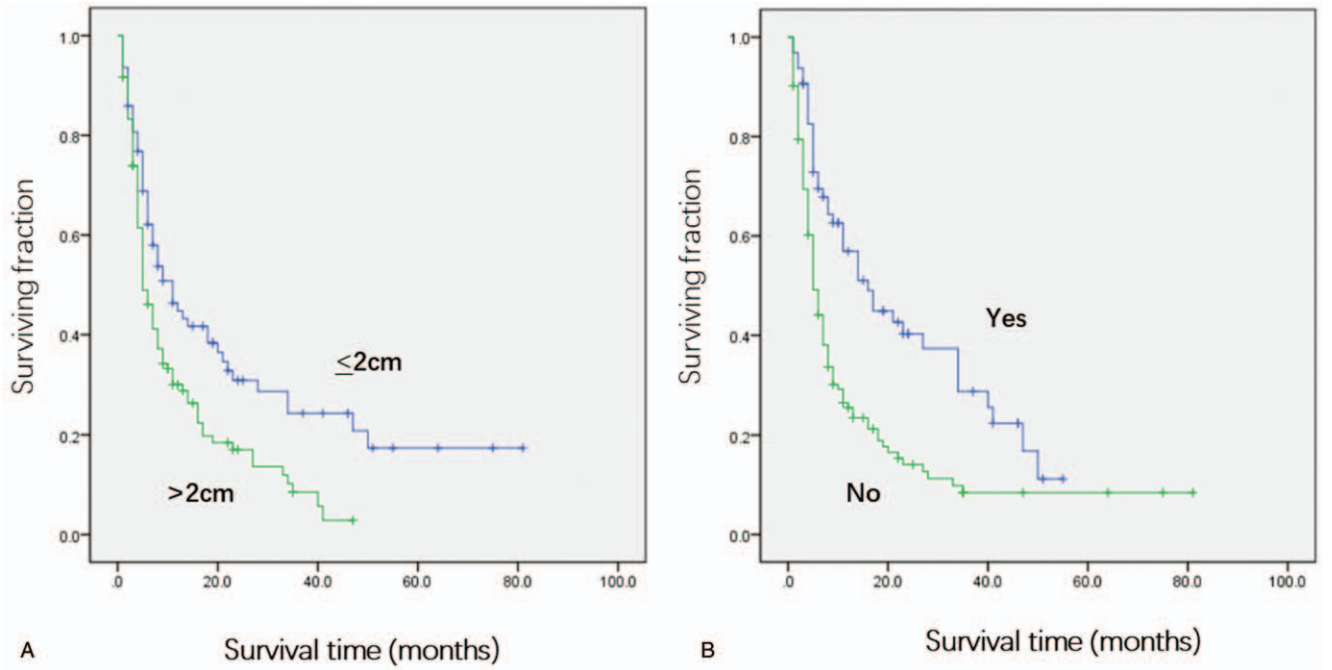

Figure 1. Kaplan–Meier method estimated overall survival in melanoma patients with bone metastasis after surgery stratified by (A) tumor size (cm) ($^{*}P = .002$), (B) bone metastasis only ($^{*}P < .001$). Note: *log-rank P value, $P < .05$, the statistically significant values.

In this study, neither age nor sex had statistically significant differences in OS or CSS. In terms of tumor size, having a smaller tumor size (≤2 cm) was an advantageous postoperative survival determinant for both OS and CSS (Figs. 1A and 2A, Table 2). Our analysis also clearly showed that having bone metastasis only (rather than metastases at additional sites) was significantly associated with both CSS and OS ($P = .002$ and $P < .001$, respectively) (Figs. 1B and 2B, Table 2). However, neither RT nor chemotherapy was significantly associated with OS or CSS.

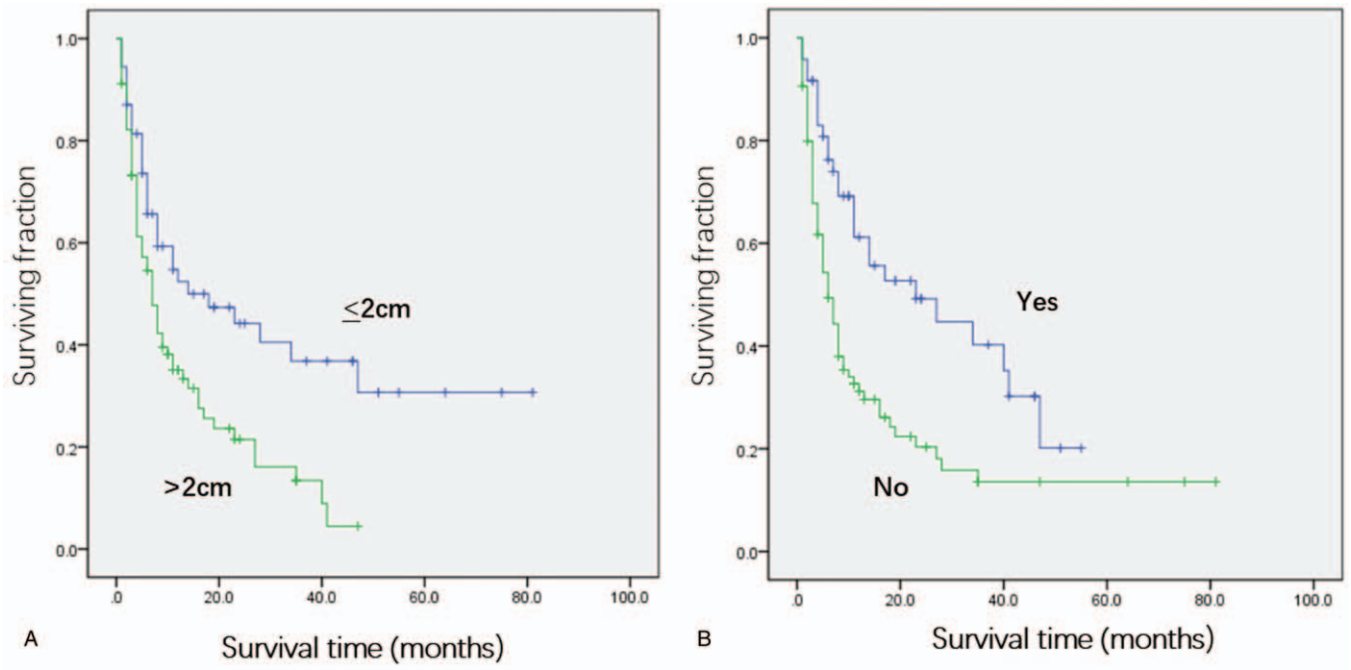

Figure 2. Kaplan–Meier method estimated cancer-specific survival in melanoma patients with bone metastasis after surgery stratified by (A) tumor size (cm) ($^{*}P = .003$), (B) bone metastasis only ($^{*}P = .001$). Note: *log-rank P value, $P < .05$, the statistically significant values.

Table 2

Using the univariate cox regression analysis of variables for melanoma patients with bone metastasis after surgery.

	Univariate cox regression analysis				Multivariate cox regression analysis			
	OS		CSS		OS		CSS	
Variable	Hazard ratio (95%CI)	*P*-value	Hazard ratio (95%CI)	*P*-value	Hazard ratio (95%CI)	*P*-value	Hazard ratio (95%CI)	*P*-value
Age at diagnosis (yrs)								
<65	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
≥65	1.225 (0.879–1.706)	.231	1.020 (0.675–1.542)	.923	1,252 (0.891–1.759)	.196	1.073 (0.702–1.639)	.745
Sex								
Male	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
Female	0.819 (0.569–1.181)	.285	0.794 (0.506–1.247)	.317	0.787 (0.544–1.138)	.203	0.782 (0.496–1.231)	.288
Tumor size								
≤2 cm	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
>2 cm	1.663 (1.179–2.347)	**.004**	1.910 (1.224–2.980)	**.004**	1.703 (1.207–2.403)	**.002**	1.869 (1.194–2.927)	**.006**
Bone metastasis only								
Yes	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
No	1.999 (1.389–2.877)	**<.001**	2.085 (1.318–3.299)	**.002**	2.167 (1.478–3.178)	**<.001**	2.263 (1.376–3.721)	**.001**
Radiation therapy								
Yes	1 (reference)		1 (reference)		1 (reference)	—	1 (reference)	
No	0.858 (0.610–1.206)	.378	0.746 (0.488–1.142)	.178	0.908 (0.639–1.291)	.593	0.755 (0.488–1.169)	.208
Chemotherapy								
Yes	1 (reference)		1 (reference)		1 (reference)		1 (reference)	
No	1.017 (0.727–1.422)	.924	0.922 (0.604–1.409)	.709	1.251 (0.868–1.803)	.229	0.702 (0.434–1.135)	.149

$P < .05$, the statistically significant values, marked in bold.
CSS = cancer-specific survival, OS = overall survival.

3.3. Identification of significant independent prognosis indicators of OS and CSS in melanoma patients with bone metastasis after surgery by multivariate analyzes

To validate these predictors, we performed the multivariate analysis. The results of the multivariate analyses were shown in Table 2. When assessed by multivariate analysis, several independent postoperative survival determinants for both OS and CSS, comprising tumor size and bone metastasis only, were identified.

4. Discussion

Melanoma is a rare form of cancer, and it can metastasize distally, to the bones, lungs, and brain. Unfortunately, metastatic melanoma is notoriously difficult to cure. Prognostic factors for melanoma of the skin and eyes have been reported in numerous studies.[3–5] Surgery is currently the recommended treatment for metastatic melanoma.[14] Abdel-Rahman[14] previously reported that metastatic melanoma patients who received surgery had significantly prolonged survival compared to those who did not receive surgery. However, due to its rarity, little is known about the prognostic factors associated with bone metastasis in melanoma patients after surgery. The SEER database, well-known for its large amount of data and excellent quality, is the best registry for cancer survival and epidemiology in the United States, and possibly, the world. The data analyzed in this study were extracted from the SEER database, which indicates the reliability and validity of the data. This study is the first to investigate postoperative prognostic factors for melanoma patients with bone metastasis using a large cohort extracted from the SEER database.

We also employed a variety of statistical analysis methods, including Kaplan-Meier curves, along with univariate and multivariate regression analyses, to investigate potential postoperative survival-related prognostic factors. In a previous study, Rockberg et al[6] found that 5-year OS rates varied from 85.3% for stage I to 12.9% for stage IV nonmetastatic melanoma patients. However, the 5-year OS rate (9.5%) of melanoma patients with bone metastasis after surgery in our study was lower. According to both OS and CSS data, we discovered that tumor size and bone metastasis only were significantly independently associated with postoperative survival. More precisely, a larger tumor size and the involvement of other metastasis sites were significantly independently associated with reduced postoperative survival rates.

A number of studies have reported survival rates according to melanoma patient age at diagnosis.[4,16,17] Ribero et al[16] demonstrated that younger age was associated with a lower melanoma mortality rate. However, we found that there was no significant difference between younger age and older age, as similar as the results of a previous study.[17] The reason for the different results remains unknown. A possible explanation is that surgery performed is not tolerated well in older patients due to poor body function. Some old patients who could not receive surgery may be not included in our cohort. Asian cancer patients usually have a better prognosis when compared to Caucasians, whereas Afro-Americans have the worst evolution.[18] Due to the limited sample size, we did not further analyze the differences of prognosis among different sub-ethnic groups. Perhaps as the sample size further increases, we can analyze it in the future. In our study, sex was not associated with prognosis. However, our study was dominated by males (with a ratio of approximately 2.2:1.0), which is consistent with the published data for melanoma overall.[19]

Tumor size is of great importance when predicting the postoperative prognosis of melanoma patients with bone metastasis. In our multivariate Cox regression analysis of OS that used ≤2 cm as the reference category, we found that the hazard ratios was 1.703 ($P = .002$) when tumors were >2 cm in

size. A previous study regarded baseline tumor size as an independent indicator of prognosis in patients with melanoma.[20] In another study, involving melanoma of the head and neck, a tumor size ≥43 mm was associated with a worse prognosis.[21] Our findings were similar to those published previously by Lee et al,[15] who reported that a smaller tumor size was deemed to be a preferable prognosis in patients with melanoma, potentially. In addition, another study showed that the smaller the tumor size, the lower the likelihood of metastasis of the melanoma.[22] Although the best categorization system regarding tumor size needs to be explored, the importance of tumor size for predicting the postoperative prognosis of bone metastasis in melanoma patients cannot be ignored. Postoperative patients with metastatic sites other than the bone tend to have a worse prognosis; this is expected because treatment has little effect if melanoma cells have already spread throughout the body to multiple sites.

With regards to RT, a good outcome after RT is reached in local or metastatic melanoma patients.[10,23] Indeed, some of the latest clinical trials have reported that RT conveys a survival advantage to these metastatic melanoma patients.[24,25] However, irrespective of whether we considered OS or CSS, postoperative patients undergoing RT appeared to have similar survival outcomes compared to those who did not undergo RT, thus indicating that RT may have little effect on prognosis, at least in our cohort. The results of our multivariate analysis of both OS ($P = .229$) and CSS ($P = .149$) suggest that chemotherapy does not help to prolong postoperative survival. Due to the vast range of adverse events associated with chemotherapy, such as lymphopenia, leukopenia, anemia, nausea, and fatigue, patients tend to only agree to take chemotherapy until they experience intolerable toxicity; consequently, chemotherapy is used cautiously in the clinic.[26] An extensive body of literature now exists on the safety and efficacy of different chemotherapeutics, as well as their impact on prognosis.[26–28] It is now crucial to explore the appropriate dosage and duration of chemotherapy drugs to improve prognosis.

Our research had several limitations that need to be considered. First, the SEER database did not include data relating to local recurrence that may have influenced the postoperative prognosis during follow-up. In addition, we were unable to extract data relating to chemotherapy dose and the lymph node status; these factors are also likely to be potential prognostic factors. Obesity, a known potential risk factor for malignancy, is associated with a high level of oxidative stress,[29,30] However, obesity data is not included in SEER database,[31] and the relationship between obesity and melanoma remains poorly studied. Obesity may be associated with the postoperative survival in melanoma patients with bone metastasis. Despite these deficiencies, our study provides a better understanding of bone metastasis in melanoma patients after surgery, and it highlights the fact that the SEER database makes it possible to study rare tumors, such as melanoma bone metastases, with great efficiency.

5. Conclusion

In summary, our analysis identified several significant independent predictors of the increased postoperative survival of melanoma patients with bone metastasis, including a smaller tumor size and the lack of metastasis at other sites. In contrast, our data revealed that age at diagnosis, sex, RT, and chemotherapy, were not significantly independently associated with the postoperative prognosis of these patients. Our data may provide the foundation for future research.

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