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Predictors for survival in patients with bone metastasis of small cell lung cancer

A population-based study

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Abstract

The objective of the current study is to analyze the clinical and demographic characteristics of patients with bone metastasis of small cell lung cancer (SCLC) and explore their survival predictors.

We retrospectively extracted patients with bone metastasis of SCLC from the Surveillance, Epidemiology, and End Results database. We applied Cox regression analyses to identify independent survival predictor of overall survival (OS) and cancer-specific survival (CSS). Only significant predictors from univariable analysis were included for multivariable Cox analysis. Kaplan–Meier method was used to evaluate survival differences between groups by the log–rank test.

A total of 5120 patients with bone metastasis of SCLC were identified and included for survival analysis. The 1-year OS and CSS rates of bone metastasis of SCLC were 19.8% and 21.4%, respectively. On multivariable analysis, gender, age, radiotherapy, chemotherapy, liver metastasis, brain metastasis, insurance status, and marital status independently predicted OS and CSS. There was no significant difference of OS and CSS in terms of race and tumor size.

Independent predictors of survival were identified among patients with bone metastasis of SCLC, which could be valuable to clinicians in treatment decision. Patients with bone metastasis of SCLC may benefit from radiotherapy and chemotherapy.

Abbreviations: CSS = cancer-specific survival, NSCLC = nonsmall cell lung cancer, OS = overall survival, SCLC = small cell lung cancer, SEER = Surveillance, Epidemiology, and End Results.

Keywords: bone metastasis, characteristics, prognosis, small cell lung cancer, survival predictor

1. Introduction

Small cell lung cancer (SCLC) is a highly invasive neuroendocrine tumor, accounting for about 10% to 15% of all lung cancer patients.[1] Bone, as one of the common metastatic sites of SCLC,[2] is also one of the main reasons for treatment failure.[3,4] Among all lung cancer types, SCLC has the worst prognosis, which has not changed much in the past few decades.[5,6] Additionally, the prognosis of patients with bone metastasis of SCLC was worse than that of nonsmall cell lung cancer (NSCLC) type.[7] To date, chemotherapy and radiotherapy are still the main treatments for SCLC, which are beneficial for prolonging survival.[8,9] Surgery for SCLC remains controversial and is only considered for patients with early stage SCLC.[10] We can't help wondering whether these treatments will also prolong the prognosis of patients with bone metastasis of SCLC. Currently, evidence on appropriate treatments for them is lacking.

Rational therapeutic strategies of bone metastasis of SCLC depend on the patients' prognosis. At present, there are few studies on exploring prognostic risk factors among patients with bone metastasis of SCLC. Therefore, we sought to further determine the clinical predictors of survival among patients with bone metastasis of SCLC, which may result in treatment improvement. We applied the Surveillance, Epidemiology, and End Results (SEER) database in the present study, due to its popularity in survival analysis of cancer patients.

2. Methods

2.1. Study population

In this retrospective study, we extracted bone metastasis of SCLC cases from the SEER database using SEER* Stat Version 8.3.6 (https://seer.cancer.gov/). As a large-scale, population-based database, the SEER represents approximately one-third of the US population and covers 20 geographic areas in the US, which provides a free tool for clinical study of malignant tumors. This database does not contain any patient identification information and approval by institutional research ethics committee was not applicable to this study.

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The datasets generated during and/or analyzed during the current study are not publicly available, but are available from the corresponding author on reasonable request.

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According to the International Classification of Diseases for Oncology, Third edition, we identified primary SCLC by histological subtype codes: 8002, 8041, 8043, 8144, 8145. The database only records bone metastasis information after 2010, so we only included patients diagnosed with SCLC with bone metastasis from 2010 to 2016. Additionally, patients who lacked information about pathological diagnosis, tumor size, treatment, survival time, and metastatic status were excluded. Clinical and pathological data were retrieved, including race, gender, continuous age, tumor size, radiotherapy, chemotherapy, metastatic status, survival time, insurance status, and marital status. In our study, radiotherapy refers to the local treatment of primary SCLC.

2.2. Statistical analyses

We performed all statistical analyses by using SPSS v22.0 (Chicago, IL). Cancer-specific survival (CSS) was defined as the time from diagnosis till death due to SCLC. We performed Cox regression analysis to identify independent survival predictor of overall survival (OS) and CSS. Only significant predictors from univariable analysis were included for multivariable Cox analysis. During Cox regression analyses, we also calculated hazard ratios along with 95% confidence interval to show the impact of predictors on survival. Kaplan–Meier method was used to evaluate survival differences between groups by the log–rank test. Variables with bilateral $P < .05$ were considered to be statistically significant.

Table 1

Baseline characteristics of 5120 patients with bone metastasis of small cell lung cancer.

Race	
White	4550 (88.9%)
Black	387 (7.6%)
Others	183 (3.6%)
Gender	
Female	2319 (45.3%)
Male	2801 (54.7%)
Age (yr)	
<60	1122 (21.9%)
60 to 69	1938 (37.9%)
70 to 79	1539 (30.1%)
≥80	521 (10.2%)
Tumor size (cm)	
<3	1208 (23.6%)
3 to 5.9	1946 (38.0%)
6 to 8.9	1268 (24.8%)
>9	698 (13.6%)
Radiotherapy	
Yes	2092 (40.9%)
No	3028 (59.1%)
Chemotherapy	
Yes	3768 (73.6%)
No	1352 (26.4%)
Brain metastasis	
No	4087 (79.8%)
Yes	1033 (20.2%)
Liver metastasis	
No	2241 (43.8%)
Yes	2879 (56.2%)
Insurance status	
Insured	4201 (82.1%)
Any Medicaid	770 (15.0%)
Uninsured	149 (2.9%)
Marital status	
Married	2755 (53.8%)
Others	2365 (46.2%)

3. Results

3.1. Baseline characteristics

The entire cohort comprised 5120 patients with bone metastasis of SCLC. Clinical and demographic characteristics for these patients were listed in Table 1. Of these patients, more than 3 quarters of patients (88.9%) were white and over half of patients (54.7%) were male. Approximately 21.9% of the cases were aged <60 years, 37.9% were 60 to 69 years, 30.1% were 70 to 79 years and 10.2% were ≥ 80 years. Tumor size was also classified into 4 categories, including <3 cm (n = 1208, 23.6%), 3 to 5.9 cm (n = 1946, 38.0%), 6 to 8.9 cm (n=1268, 24.8%), and >9 cm (n= 698, 13.6%). Radiotherapy was performed for 2092 (40.9%), and chemotherapy was performed for 3768 (73.6%). Brain metastasis accounted for 20.2%, and liver metastasis accounted for 56.2%. Most patients (82.1%) were insured and over half of the patients (53.8%) were married. In all patients, the 1-year OS and CSS rates were 19.8% and 21.4%, respectively.

3.2. Univariable Cox regression analysis

Univariable Cox regression analysis could be seen in Table 2. On univariable analysis, female, younger age, radiotherapy, chemo-

Table 2

Univariate Cox analysis of variables in patients with bone metastasis of small cell lung cancer.

	OS		CSS	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Race				
White	1		1	
Black	0.946 (0.849–1.055)	.322	0.955 (0.844–1.081)	.467
Others	0.899 (0.769–1.052)	.185	0.892 (0.747–1.066)	.208
Gender				
Female	1		1	
Male	1.097 (1.035–1.162)	.002	1.117 (1.046–1.193)	.001
Age (yr)				
<60	1		1	
60 to 69	1.104 (1.021–1.194)	.013	1.123 (1.031–1.223)	.008
70 to 79	1.322 (1.219–1.434)	<.001	1.295 (1.183–1.419)	<.001
≥80	1.771 (1.587–1.975)	<.001	1.656 (1.455–1.885)	<.001
Tumor size (cm)				
<3	1		1	
3 to 5.9	1.034 (0.958–1.115)	.392	1.043 (0.956–1.138)	.344
6 to 8.9	1.012 (0.931–1.100)	.782	1.020 (0.927–1.122)	.687
>9	1.051 (0.953–1.160)	.321	1.067 (0.954–1.193)	.257
Radiotherapy				
Yes	1		1	
No	1.417 (1.336–1.504)	<.001	1.384 (1.295–1.480)	<.001
Chemotherapy				
Yes	1		1	
No	3.722 (3.475–3.985)	<.001	3.889 (3.597–4.205)	<.001
Brain metastasis				
No	1		1	
Yes	1.207 (1.124–1.297)	<.001	1.274 (1.176–1.381)	<.001
Liver metastasis				
No	1		1	
Yes	1.372 (1.294–1.455)	<.001	1.411 (1.320–1.509)	<.001
Insurance status				
Insured	1		1	
Any Medicaid	1.044 (0.963–1.131)	.298	1.052 (0.961–1.151)	.272
Uninsured	1.304 (1.102–1.544)	.002	1.332 (1.112–1.596)	.002
Marital status				
Married	1		1	
Others	1.157 (1.083–1.235)	<.001	1.157 (1.083–1.235)	<.001

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival.

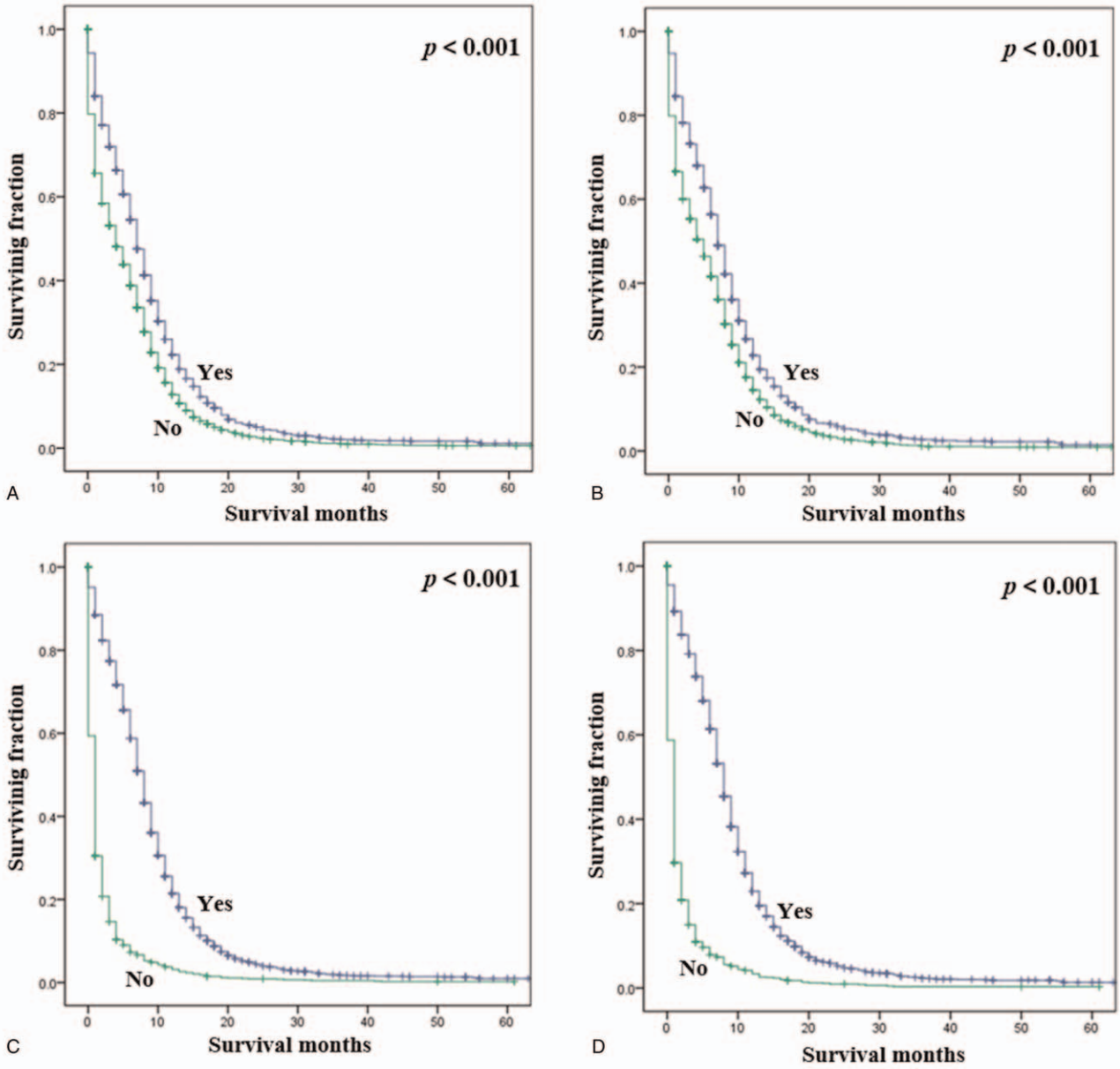

Figure 1. Kaplan–Meier method estimated OS and CSS in patients with bone metastasis of small cell lung cancer stratified by treatment methods. (A) OS stratified by radiotherapy; (B) CSS stratified by radiotherapy; (C) OS stratified by chemotherapy; (D) CSS stratified by chemotherapy. (CSS = cancer-specific survival, OS = overall survival).

therapy, no brain and liver metastasis, insured status, and married status were significant predictors for increased OS and CSS. Race and tumor size had no obvious effect on survival time. Patients who received radiotherapy had better OS and CSS than those who did not receive radiotherapy (Fig. 1A and 1B, $P < .001$). Similarly, patients treated by chemotherapy experienced significantly prolonged OS and CSS than those who did not receive chemotherapy (Fig. 1C and 1D, $P < .001$). The survival curves showed that patients with brain or liver metastasis experienced significantly poorer prognosis (Fig. 2, $P < .001$).

3.3. Multivariable Cox regression analysis

Table 3 showed the results of multivariable Cox regression analysis. On multivariable analysis, gender, age, radiotherapy, chemotherapy, liver metastasis, brain metastasis, insurance status, and marital status were significant independent predictors of both OS and CSS.

4. Discussion

With the increase in the overall incidence of bone metastasis due to lung cancer, this field has gradually become one of the hotspots of clinical research.[11] Although there have been many reports on bone metastasis of lung cancer recently, the research population is mainly patients with bone metastasis of NSCLC. SCLC is an aggressive neuroendocrine malignancy prone to metastasis, which is different from NSCLS.[12] To date, SCLC remains an important challenge for the clinicians. Therefore, it is necessary and crucial to separately explore different subtypes of lung cancer with bone metastasis. In the present study, we first analyzed the

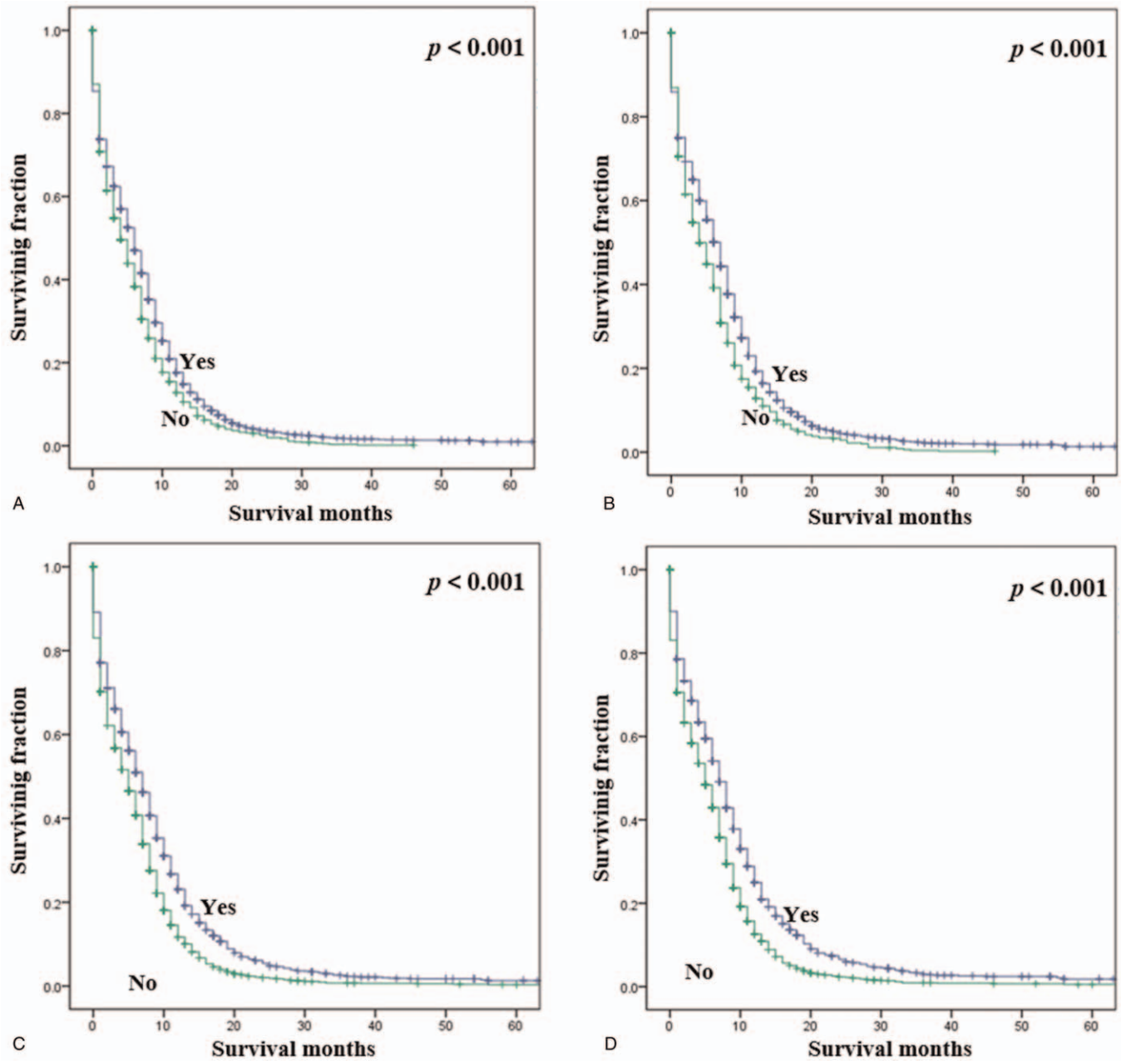

Figure 2. Kaplan–Meier method estimated OS and CSS in patients with bone metastasis of small cell lung cancer stratified by distant metastasis. (A) OS stratified by brain metastasis; (B) CSS stratified by brain metastasis; (C) OS stratified by liver metastasis; (D) CSS stratified by liver metastasis. (CSS = cancer-specific survival, OS = overall survival).

clinical and demographic characteristics of bone metastasis of SCLC based on the SEER database. Furthermore, we determined several independent predictors of survival, in an attempt to make better clinical decisions.

The 1-year OS and CSS rates of bone metastasis of SCLC were 19.8% and 21.4%, respectively, indicating a quite poor prognosis. No difference was observed in OS and CSS by race, which was consistent with 1 previous study about bone metastasis of all lung cancers.[3] However, some researchers found that white race could predict poor OS and CSS of bone metastasis of NSCLC.[13,14] Our mutivariable analysis showed that gender was significantly correlated with OS and CSS, which was congruent with many previous studies.[3,15,16] This study found that older age independently predicted a poorer OS and CSS, which was consistent with others.[3,17,18] There was no difference in OS and CSS by tumor size in our study. However, some researchers reported significant relationships between tumor size and survival in lung cancer with bone metastasis.[3,19] Further researches are needed to confirm this finding. Distant metastasis was usually recognized as an important predictor of worse survival of lung cancer.[15,19,20] Our study identified that brain and liver metastasis were independent prognostic factors for bone metastasis of SCLC, suggesting that treating both of these metastases may prolong survival.

Another feature of this study is that marital and insurance status had an impact on the prognosis of SCLC with bone

Table 3

Multivariate Cox analysis of variables in patients with bone metastasis of small cell lung cancer.

	OS		CSS	
Variable	**HR (95% CI)**	***P***	**HR (95% CI)**	***P***
Gender				
Female	1		1	
Male	1.132 (1.067–1.202)	<.001	1.138 (1.064–1.218)	<.001
Age (yr)				
<60	1		1	
60 to 69	1.137 (1.050–1.232)	.002	1.167 (1.070–1.274)	.001
70 to 79	1.264 (1.161–1.376)	<.001	1.238 (1.126–1.362)	<.001
≥80	1.430 (1.275–1.604)	<.001	1.369 (1.196–1.568)	<.001
Radiotherapy				
Yes	1		1	
No	1.229 (1.153–1.310)	<.001	1.211 (1.127–1.302)	<.001
Chemotherapy				
Yes	1		1	
No	3.465 (3.226–3.721)	<.001	3.655 (3.369–3.965)	<.001
Brain metastasis				
No	1		1	
Yes	1.347 (1.249–1.453)	<.001	1.382 (1.269–1.504)	<.001
Liver metastasis				
No	1		1	
Yes	1.400 (1.319–1.486)	<.001	1.436 (1.342–1.537)	<.001
Insurance status				
Insured	1		1	
Any Medicaid	1.089 (1.000–1.185)	.049	1.102 (1.002–1.212)	.046
Uninsured	1.418 (1.193–1.686)	<.001	1.445 (1.201–1.739)	<.001
Marital status				
Married	1		1	
Others	1.102 (1.036–1.171)	.02	1.095 (1.022–1.173)	.01

CI = confidence interval, CSS = cancer-specific survival, HR = hazard ratio, OS = overall survival.

metastasis. Similarly, Huang et al[16] reported that marital status was an independent prognostic factor of lung adenocarcinoma with brain metastases. Reddy et al[21] reported that lack of insurance was the strongest predictor of mortality for SCLC with brain metastasis. This suggests that clinicians need to pay attention to the economic level and marital status of patients with advanced cancers.

In terms of treatment methods, radiotherapy and chemotherapy are common treatment methods for SCLC.[22,23] However, few studies have explored whether the above methods are equally effective for SCLC patients with bone metastasis. Radiotherapy is usually considered as a palliative local treatment, mainly used for symptomatic treatment.[24,25] However, this study is the first to find that radiotherapy was one of the important independent risk factors affecting the prognosis of SCLC patients with bone metastasis. Interestingly, of all risk factors, chemotherapy showed the greatest effect on prognosis in patients with bone metastasis of SCLC. Additionally, Cho et al[7] found that surgical treatment for bone metastasis was a positive independent predictor of survival among lung cancer patients. Putatively, treatment of bone metastasis may be helpful in prolonging outcomes in patients with bone metastasis of SCLC.

Although the SEER database contains a large amount of information on lung cancer patients from different regions and provides a useful tool for oncologist, there are several limitations in this study. First, bias may occur due to the retrospective nature of the study. Second, we do not obtain other potential clinical predictors in the SEER database, such as molecular markers and target therapy. Third, the SEER database does not provide detailed bone metastasis information.

5. Conclusions

This is the largest study to identify independent prognostic factors for patients with bone metastasis of SCLC. Gender, age, radiotherapy, chemotherapy, liver metastasis, brain metastasis, insurance status, and marital status were recognized as independent survival predictors. Better understandings of these survival predictors in patients with bone metastasis of SCLC could help clinicians with better treatment decision. However, further studies are needed to confirm our findings.

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