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Clinical outcome for small cell lung cancer patients with bone metastases at the time of diagnosis

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ABSTRACT

Objectives: The characteristics and prognostic factors of small-cell lung cancer (SCLC) patients with bone metastases at first diagnosis have scarcely been reported. This study aimed to analyze the prognostic factors of these patients and to develop a scoring system for survival to provide evidence for clinical treatment decisions.
Materials and Methods: The records of 102 SCLC patients with bone metastasis at the time of diagnosis who were seen in our hospital between May 2010 and May 2015 were retrospectively reviewed. The log-rank test and multivariate Cox regression analysis were used to evaluate potential clinical predictors of survival. A scoring system was developed based on the hazard ratios of significant independent prognostic factors.
Result: The most common site of bone metastases was the spine (64.7%), and 26 patients (25.6%) had a single bone metastasis. The median survival was 10.4 months, and the 2-year survival rate was 10.3%. Age, number of bone metastases, and occurrence of extraosseous distant metastases were significant independent prognostic factors for overall survival. Based on their scores, patients were divided into three groups. The median survival times of the three groups were 6.4 months, 8.5 months and 12.4 months, and the 2-year survival rates were 0%, 2.9%, and 19.3% (p = 0.000). Twenty-six patients (25.5%) developed skeletal-related events (SREs), and the most common SREs were radiation to the bone (22.5%) and spinal cord compression (11.8%).
Conclusion: This study includes preliminary clinical data of SCLC patients with bone metastases at the time of diagnosis, and more studies are needed.

1. Introduction

Small-cell lung cancer (SCLC) accounts for approximately 15-20% of lung cancer, which is highly malignant, prone to distant metastasis, and has a poor survival rate [1]. During the past 30 years, the survival of SCLC patients has not improved significantly. Until recently, it had been reported that the addition of immunotherapy may lead to a significant survival benefit in the treatment of extensive SCLC [2]. However, survival is still poor, especially for extensive SCLC. For extensive SCLC, the skeletal system is one of the most common sites for metastases, and approximately two-thirds of patients with SCLC have bone metastases at diagnosis. Once bone metastases occur, they may produce considerable morbidity, such as substantial bone pain, pathologic fracture, and spinal cord compression, which have a negative impact on the quality of life. The choice of treatment method for bone metastases should be based on patient life expectancy [3,4]. Therefore, predicting

the survival time of SCLC patients with bone metastases is of great clinical significance. Many studies have reported the natural history of NSCLC patients with bone metastases [5–10]. However, the prognostic factors and characteristics of SCLC have scarcely been reported, and there is no scoring system for life expectancy in SCLC. This study aimed to examine the characteristics and prognostic factors of SCLC patients with bone metastases at initial diagnosis and to develop a scoring system to guide physicians in estimating the survival time of these patients.

2. Materials and Methods

2.1. Study population

We retrospectively reviewed 103 patients with SCLC and bone metastases at the time of diagnosis at our hospital between May 2010

Table 1
Characteristics of SCLC patients with bone metastases at initial diagnosis.

Subgroups	Number of patients (%)
Gender	
Female	20 (19.6)
Male	82 (80.4)
Age	
< 65	71 (69.6)
≥65	31 (30.4)
Smoke	
Yes	83 (81.4)
No	19 (18.6)
KPS	
< 80	12 (11.8)
≥80	90 (88.2)
Coexisting with extraosseous metastases	
No	47 (46.1)
Yes	55 (53.9)
Number of bone metastases	
Single	26 (25.5)
Multiple	76 (74.5)
Appendicular bone metastases	
Yes	45 (44.1)
No	57 (55.9)
Number of vertebra metastases	
< 3	68 (66.7)
≥3	34 (33.3)
T stage	
T1	5 (4.9)
T2	78 (76.5)
T3	15 (14.7)
T4	4 (3.9)
N stage	
N0	2 (2.0)
N1	8 (7.8)
N2	56 (54.9)
N3	36 (35.3)
Supraclavicular lymph nodes metastases	
Yes	34 (33.3)
No	68 (66.7)
Location of extraosseous metastases	
Liver	25 (24.5)
Brain	11 (10.8)
Adrenals	7 (6.9)
Abdominal lymph node	4 (3.9)
Skin	1(1.0)
Pleural/chest wall	8 (7.8)
Pancreas	2 (2.0)
Contralateral lung	8 (7.8)
LDH level	
Normal	47 (46.1)
Elevated	55 (53.9)
ALP level	
Normal	87 (85.3)
Elevated	15 (14.7)

Abbreviations: LDH = lactate dehydrogenase; ALP = alkaline phosphatase

and May 2015. We excluded one patient because of incomplete information. Thus, in our study, 102 patients were analyzed. All patients were diagnosed with typical clinical indicators and an assessment of histopathological results. Chest and abdominal computed tomography (CT), radionuclide bone scan, and brain magnetic resonance imaging (MRI) or integrated positron emission tomography (PET)-CT were undertaken to assess tumor stage. Thus, radionuclide bone scan or PET-CT was performed routinely to stage bone metastases. If the radionuclide bone scan or PET-CT manifested suspicious bone lesions, especially a single suspicious bone lesion, magnetic resonance imaging, CT or radiography was mandatory to determine whether bone metastases were present. At least one radiologist and one physician confirmed the diagnosis. The imaging was reviewed for this report. In regard to the number of bone metastases, the patients with two adjacent vertebral metastases were classified into the multiple metastases group. There was one patient with two adjacent vertebral metastases, and that

patient was classified into the multiple metastases group. The patient characteristics are summarized in Table 1. Twenty (19.6%) patients were female, and eighty-two (80.4%) patients were male. The median age was 60 years (range 42-85 years).

The following potential prognostic factors were evaluated: sex (male vs female), age (< 65 vs ≥65), smoking status (yes vs no), coexisting extraosseous metastases (yes vs no), number of bone metastases (single vs multiple), appendicular bone metastases (yes vs no), number of vertebral metastases (< 3 vs ≥3), T stage (T1/T2 vs T3/T4), N stage (N0/N1/N2 vs N3), LDH level (normal (≤250 U/L) vs elevated (> 250 U/L)), and ALP level (normal female (≤120 U/L) and male (≤132 U/L) vs elevated female (> 120 U/L) and male (> 132 U/L)). Because there were only 12 patients with a KPS < 80, the KPS was not analyzed in this study. Tumor response was assessed as described in the Response Evaluation and Criteria in Solid Tumors (RECIST).

2.2. Treatment

All patients underwent chemotherapy, and all patients received EP (30 mg/m2 cisplatin from days 1 to 3; 100 mg etoposide from days 1 to 5), CE (500 mg carboplatin for day 1; 100 mg etoposide from days 1 to 5) or platinum-based chemotherapy as the first-line treatment. Patients received a median of six cycles of chemotherapy. Forty-nine patients received TRT, and TRT started after at least 2 cycles of chemotherapy. The total dose administered was 40 to 60 Gy delivered at 1.8 to 2 Gy per fraction or 30 to 45 Gy delivered at 3 Gy per fraction. Only three patients (2.9%) received prophylactic cranial irradiation. Eighty-seventeen patients received treatment with bisphosphonate, of whom 12 patients received zoledronic acid and 75 patients received pamidronate disodium.

2.3. Statistical Analysis

The primary outcome was overall survival (OS), which was defined as the time from the first day of treatment to the date of death or last follow-up. Patients were followed up until death, and surviving patients were censored at the time of their last follow-up. The Kaplan–Meier method was used to estimate the distribution of time to death. Multivariate Cox regression analysis was performed to determine the significant factors associated with longer survival. An adjusted hazard ratio with a 95% confidence interval was reported for each factor. All statistical tests were 2-sided, and a result was considered statistically significant at $p < 0.05$. The statistical software SPSS version 18.0 was used for statistical analysis.

The scoring system was made according to the hazard ratios of significant prognostic factors in the multivariate analysis. The score of a factor was 2 or 0 when the hazard ratio was < 0.5. The score of a factor was -2 or 0 when the hazard ratio was > 2. The score of a factor was 1 or 0 when the hazard ratio was > 0.5 and < 1. The score of a factor was -1 or 0 when the hazard ratio was > 1 and < 2. The prognostic score was calculated by adding the scores for individual factors.

3. Results

3.1. Distribution of skeletal metastases

There were 26 patients (25.6%) with a single bone metastasis and 76 patients (74.5%) with multiple bone metastases. There were 68 patients with less than 3 vertebral metastases and 34 patients with more than three vertebral metastases. Sixty-six (64.7%) patients were found to have spine metastases, which was the most common site of bone metastases. Other common bone metastasis sites included the ribs (48%), pelvis (36.3%) and femur (14.7%) (Fig 1).
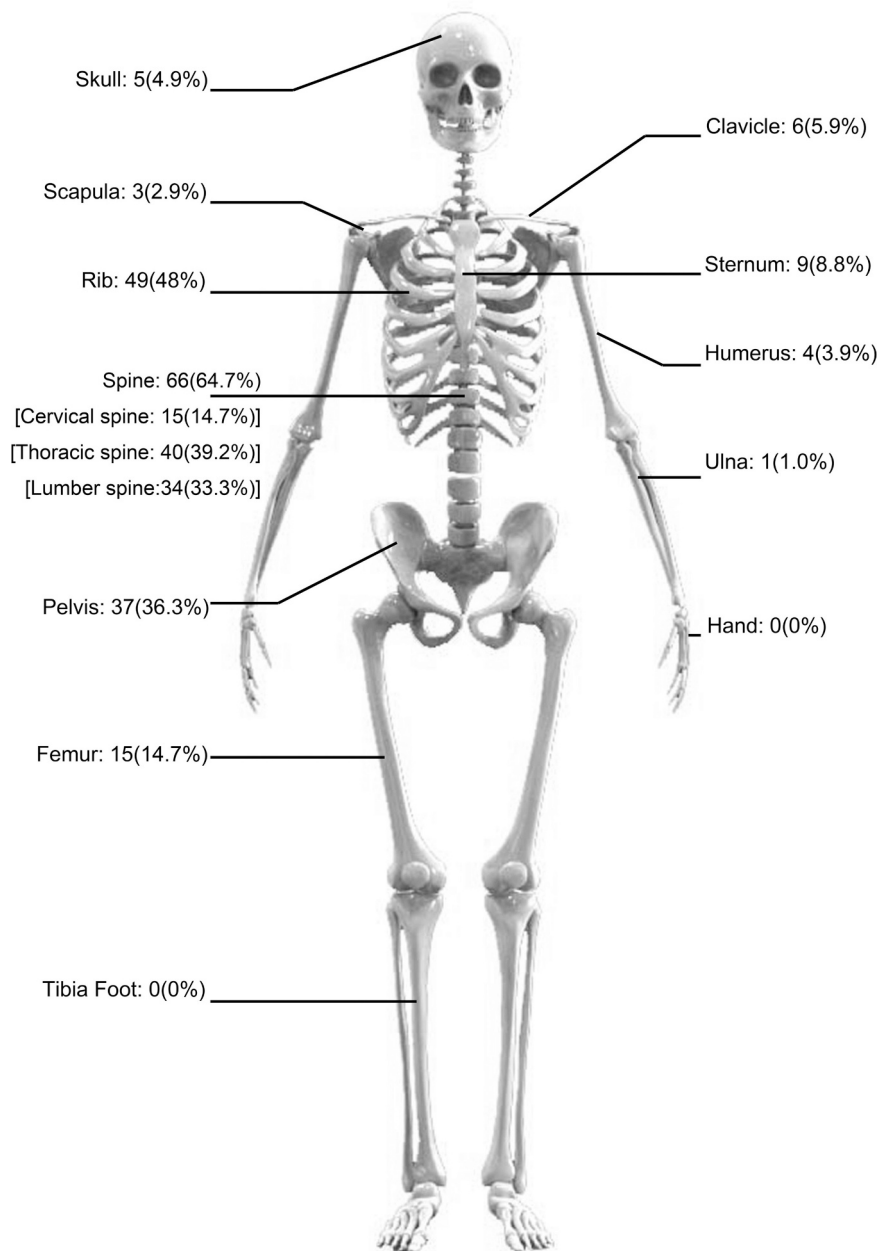
Skull: 5(4.9%)

Clavicle: 6(5.9%)

Scapula: 3(2.9%)

Rib: 49(48%)

Sternum: 9(8.8%)

Humerus: 4(3.9%)

Spine: 66(64.7%)
[Cervical spine: 15(14.7%)]
[Thoracic spine: 40(39.2%)]
[Lumber spine:34(33.3%)]

Ulna: 1(1.0%)

Pelvis: 37(36.3%)

Hand: 0(0%)

Femur: 15(14.7%)

Tibia Foot: 0(0%)

Fig 1. Distribution of bone metastases in patients with small cell lung cancer at initial diagnosis. The most common sites of bone metastases were spine (64.7%).

3.2. Survival and prognostic factors of survival

The median survival time was 10.4 months, and the 2-year survival rate was 10.3%. Seventeen patients (16.6%) with only a single bone metastasis and no extraosseous distant metastases had a median survival of 17.8 months and a 2-year survival rate of 38%. Age, sex, smoking, coexistence of extraosseous distant metastases, number of bone metastases, appendicular bone metastases, number of vertebral metastases, T stage and N stage, LDH level and ALP level were included in the univariate analysis. The results showed that age, coexistence of extraosseous distant metastases, number of vertebral bone metastases, number of bone metastases, N stage, and LDH level were significant prognostic factors in the univariate analysis (see Table 2). Multivariate analysis showed that age, coexisting with extraosseous distant metastases, and number of bone metastases were significant prognostic factors for overall survival (see Table 3). The median survival time was 11.5 months and the 2-year survival rate was 28.3 months in the single bone metastasis group, while the median survival time was 9.3 months

and the 2-year survival rate was 5.3% in the multiple bone metastases group (p = 0.026). Patients with coexisting extraosseous distant metastases had a median survival time of 8 months and a 2-year survival rate of 2.1%, while for patients without coexisting distant metastases, the median survival time was 12.2 months, and the 2-year survival rate was 17.7% (p = 0.000).

3.3. Scoring system for survival

We developed a scoring system according to three of the significant factors identified from the multivariate analysis according to their hazard ratios. Patients with age ≥ 65 years received -1 point, and other patients received 0 points. Patients with multiple bone metastases received -1 point, and those with a single bone metastasis received 0 points. Patients with coexisting extraosseous distant metastases received -2 points, and other patients received 0 points (see Table 4). To verify the validity of the survival score, we divided patients into 3 groups according to the score (see Table 5). The median survival times

Table 2
Univariate analysis of survival in SCLC patients with bone metastases at initial diagnosis.

Subgroup	Median Survival (months)	2-year survival rate (%)	p Value
Gender			
Male	10.4	7.2	0.226
Female	10.3	23.7	
Age			
< 65	10.9	13.1	0.002
≥65	9.1	3.4	
Smoke			
Yes	13.0	8.5	0.103
No	10.3	18.9	
Coexisting extraosseous metastases			
Yes	8.0	2.1	0.000
No	12.2	17.7	
Number of bone metastases			
Single	11.5	28.3	0.026
Multiple	9.3	5.3	
Appendicular bone metastases			
Yes	9.3	10.6	0.992
No	10.5	9.7	
Number of vertebra metastases			
< 3	10.9	14.5	0.01
≥3	8.67	2.9	
T stage			
T1/T2	10.0	8.9	0.231
T3/T4	10.6	15.4	
N stage			
N0/N1/N2	66	15.8	0.009
N3	36	0	
LDH level			
Normal	11.5	16.0	0.048
Elevated	8.8	5.2	
ALP			
Normal	10.4	10.1	0.832
Elevated	10.3	13.3	

Abbreviations: LDH= lactate dehydrogenase; ALP= alkaline phosphatase

Table 3
Multivariate analysis of survival in SCLC patients with bone metastases at initial diagnosis.

Potential prognostic factor	Hazard Ratio	95%CI	P
Age	1.847	1.159-2.942	0.010
Coexisting with extraosseous metastases	2.324	1.475-3.661	0.000
Number of bone metastases	1.776	1.040-3.034	0.036
N stage	1.046	0.628-1.744	0.832
Number of vertebrate bone metastases	1.165	0.718-1.891	0.449
LDH level	0.731	0.469-1.137	0.136

Abbreviations: LDH= lactate dehydrogenase

Table 4
Score of significant survival factors in patients with bone metastases of small cell lung cancer

Potential prognostic factor	Subgroup	Score	Hazard Ratio
Age	< 65	0	1.847
	≥65	-1	
Coexisting with extraosseous distant metastases	No	0	2.324
	Yes	-2	
Number of bone metastases	Single	0	1.776
	multiple	-1	

of the three groups were 6.4 months, 8.5 months and 12.4 months, respectively, and the 2-year survival rates were 0%, 2.9%, and 19.3%, respectively (p=0.000) (Fig 2).

Table 5
Score and survival of different groups

Subgroup	No. patients	Score	Survival Median survival (months)	Two-year survival rate (%)
Group 1	16	-4	6.4	0
Group 2	35	-2/-3	8.5	2.9
Group 3	51	-1/0	12.4	19.3
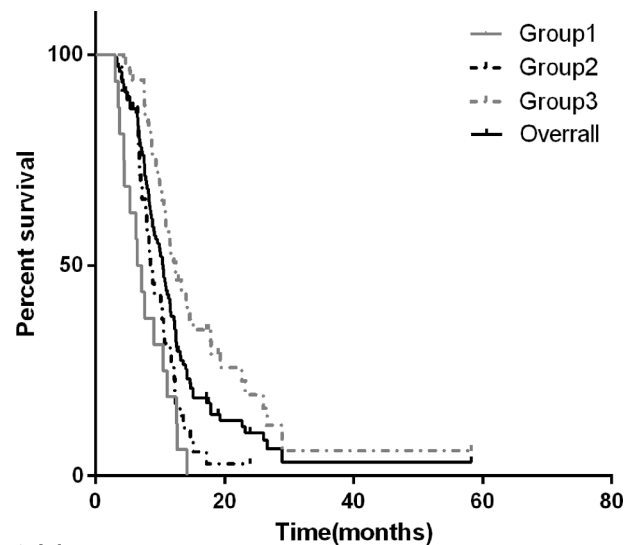
No. at risk				
Overall	102	18	13	0
Group1	16	0	0	0
Group1	35	34	0	0
Group1	51	17	12	0

Fig 2. Survival curves of different groups. The median survival time of the whole group and three subgroups were 10.4 months, 6.4 months, 8.5 months and 12.4 months, respectively (p=0.000).

3.4. Characteristics of SREs

At initial diagnosis, pathological fractures occurred in 2 patients, and spinal cord compression syndrome occurred in 5 patients. Hypercalcemia was observed in 1 patient. Seven patients underwent bone radiotherapy, including 5 patients with spinal cord compression syndrome and 2 patients with pathological fracture. In the course of treatment, there were 7 patients with spinal cord compression syndrome and 2 patients with pathological fracture. Sixteen patients underwent bone metastasis radiotherapy, including 6 patients with spinal cord compression and 2 patients with pathological fracture. One patient underwent surgical treatment for spinal cord compression. Therefore, 26 patients (25.5%) experienced skeletal-related events (see Table 6). A total of 41 SREs were observed in the whole group, and the skeletal morbidity rate was 0.88.

For patients who were treated with bisphosphonate, 23 patients (26.4%) had bone-related events. For the fifteen patients who did not

Table 6
Characteristics of SREs in SCLC patients with bone metastases at diagnosis and during treatment

SREs	Number of patients (n)	Percentage (%)
Radiation to bone	23	22.5
Spinal cord compression	12	11.8
Pathologic fracture	4	3.9
Hypercalcemia	1	1.0
Surgical stabilization	1	1.0

Table 7

Results of SCLC with bone metastases in previous studies

Year/Country/Author	Study population	No. SCLC with BM	Findings of SCLC with BM Survival	Incidence of SREs
2016 Korea Kang EJ et al [12].	ES-SCLC	61 (BM at initial diagnosis)	Median:4.13m; Poor prognostic factors: PS ≥ 2; higher ALP	34.4%
2012, Japan K. Nakazawa et al [18]	LS-SCLC + ES-SCLC	46 (BM at initial diagnosis);	1 yr: 25% (without extraosseous metastases)	NR
2018,Thailand Pruksakorn D et al.[8]	SCLC + NSCLC	30 (BM at initial diagnosis)	1 yr: 10.7%	NR
2019, Brazil Silva GT et al [31]	SCLC + NSCLC	22 (BM at initial diagnosis /follow up)	Median: 2.13m (with SREs), 8.57m (without SREs) p = 0.146	63.6%
2014, Danish Cetin K et al.[32]	SCLC + NSCLC	340 (BM at initial diagnosis /follow up)	NR	50%.
2014, Japan N. Katakami et al.[24]	SCLC + NSCLC	47 (BM at initial diagnosis /follow up)	NR	8.5%
2016, Swiss (Conen K et al.) [33]	SCLC	92 (BM at initial diagnosis /follow up)	NR	18.4% (total) 8.7%(initial diagnosis)

Abbreviations: BM = bone metastases; NR = not reported; m = months.

use bisphosphonate, 3 of them (20.0%) had bone-related events. Patients with SREs had a two-year survival rate of 5.2% and a median survival time of 10.5 months, while patients without SREs had a two-year survival rate of 9.6% and a median survival time of 10.4 months (p = 0.490).

4. Discussion

The skeletal system is the most common metastasis site for several types of cancer, such as breast cancer, prostate cancer, and lung cancer. Small-cell lung cancer is more prone to metastasis and has a poorer survival than breast cancer and prostate cancer. The median survival time of extensive SCLC ranges from 5 to 10 months [5,10,11]. In addition, the effects of systemic therapy on each primary site are different, so it is important to analyze the prognosis and characteristics of SCLC alone. This study retrospectively analyzed the clinical characteristics and prognostic factors of 102 SCLC patients with bone metastasis at initial diagnosis and developed a scoring system to predict survival.

Little information on ES-SCLC with bone metastases has been reported in previous studies, and we summarized what has been reported in Table 7. To our knowledge, only one study has reported prognostic factors in SCLC patients with bone metastases at initial diagnosis [12]. Kang EJ et al. analyzed 61 SCLC patients with bone metastases at initial diagnosis. The median survival time was 4.13 months, and poor PS and high ALP (two times above the upper normal limit) were poor prognostic factors. In our study, the median survival time of SCLC patients with bone metastases was 10.4 months, and there were three significant beneficial prognostic factors: age < 65; single bone metastasis; and no extraosseous metastases. We think that there are several reasons for the difference in median survival time between the two studies. First, in the former study, 26 patients (42.6%) had a PS ≥ 2, and 23 patients (22.5%) did not receive chemotherapy; in our study, only 11.8% of patients had a KPS less than 80, and all patients received chemotherapy. Second, in the former study, the disease stage was more advanced, and there were only two patients (3.3%) without extraosseous metastasis, while in this study, there were 47 patients (46.1%) without extraosseous metastasis. In our study, elevated ALP (above the upper normal limit) was not a prognostic factor, which is consistent with the findings of Kang EJ's study. However, there were only 2 patients with high ALP (two times higher than the upper normal limit), which may be another reason for the better survival in our study than in the other study. Primary site, PS, presence or absence of metastases to organs, and number of bone metastases have been reported as important prognostic indicators in patients with bone metastases from various cancers [13–15]. Several studies have demonstrated that there

is a significant difference in survival between ED-SCLC patients with different numbers of organs with metastases [16–18]. The results of this study agree with a previous study showing that the state of organ metastases is a significant prognostic factor and plays the most important role in ED-SCLC with bone metastases.

Our study confirmed that multiple bone metastases were much more common than a single bone metastasis (74.5% vs 25.5%). It has been reported that lung cancer patients with a single bone metastasis have a better survival than lung cancer patients with multiple metastases [6,19], while some studies have found no significant difference in survival expectations between patients with a single bone metastasis or multiple bone metastases [8]. In this study, patients with a single bone metastasis had a longer survival than patients with multiple bone metastases. The number of bone metastases was a significant prognostic factor in univariate and multivariate analyses. However, when radiotherapy and chemotherapy response status were analyzed in the multivariate analysis at the same time, the number of bone metastases was not a significant prognostic factor. This suggests that patients with multiple bone metastases may benefit from radiotherapy and chemotherapy. Furthermore, in this study, seventeen patients with a single bone metastasis and no coexisting distant metastases had good survival, with a median survival time of 17.8 months and a 2-year survival rate of 38%, suggesting that a more aggressive treatment approach may be needed.

Several scoring systems have been developed to predict the survival of patients with bone metastases after palliative surgery or radiotherapy, and they are based on the study of various primary tumors [15,20–27]. To our knowledge, this study is the first to develop a scoring system for SCLC with bone metastases. The scoring system was derived from the three significant factors identified using the hazard ratio method, and according to the score, patients were classified into three groups. Different groups had significantly different survival rates. Patients with low scores had a short life expectancy. For those patients, surgical intervention and long-course radiotherapy should be avoided; however, noninvasive ablation for pain control and short-course radiotherapy are recommended. Patients with a high score had a good prognosis; therefore, surgical intervention and long-course radiotherapy are recommended.

The incidence of SREs in non-small-cell lung cancer ranges from 40% to 65% [28–30], and it ranges from 8.5% to 63.5% in SCLC according to reported studies [12,30–33] (see Table 7). In a study by Katakami N et al., the incidence of SREs in SCLC was lower than that in NSCLC, and the incidence of SREs in extensive small-cell lung cancer was only 8.5% [30]. Kang EJ et al. [33] reported an SRE incidence of 34.4% in 61 SCLC patients with bone metastases at diagnosis. In this

study, SREs occurred in 26 patients (25.5%), which is consistent with the findings of a previous study. We speculate that the low incidence of SREs is due to the short survival time of small-cell lung cancer patients and the lack of timely bone-related examinations after disease progression in many patients. In the present study, the most common SREs were radiation to the bone (22.5%) and spinal cord compression (11.8%), which is consistent with the findings of other studies [32]. Many studies have reported that SREs are prognostic factors for survival, while some studies have not found that the occurrence of SREs affects survival [7,31,32,34]. In our study, there was no significant difference in the 2-year survival rate and median survival time between those patients with and without SREs. The role of SREs in survival requires further investigation.

In conclusion, this study reported the clinical features and prognostic factors of survival in SCLC patients with bone metastases at the time of diagnosis and developed a simple scoring system for predicting survival, which can provide important evidence for clinical treatment decisions in these patients. However, there are some limitations of this study. First, this study was based on the experience of a single institution and had a small number of patients. Second, most patients in this study had good performance. The scoring system still requires further validation.

Acknowledgements

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