Original Article

Validation of a novel prognostic index: BMS-Score for patients with brain metastases of small cell lung cancer

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Background: A new disease-specific prognostic score (Disease-specific Prognostic Score for Patients With Brain Metastases From Small-cell Lung Cancer termed BMS-Score) was published to clarify the prognosis of patients with brain metastasis (BM) of small cell lung cancer (SCLC) treated with whole brain radiotherapy (WBRT). The purpose of the present study was to validate the prognostic value of the newly proposed BMS-Score through comparison with three other previously published prognostic indices.

Methods: In total, 451 patients with BM of SCLC treated with WBRT at the Shanxi Province Cancer Hospital from January 2010 to December 2019 were included. The clinical characteristics of all patients were recorded and follow-up was through April 2020. Overall survival (OS) was calculated by Kaplan-Meier analysis, and univariate and multivariate analyses were used to calculate the prognostic cofactors. The concordance index (C-index) was used to assess the prognostic value of the following four prognostic systems: recursive partitioning analysis (RPA), diagnosis-specific graded prognostic assessment (DS-GPA), basic score for brain metastases (BSBM), and the newly proposed BMS-Score.

Results: The independent factors affecting the prognosis of SCLC patients with BM included the Karnofsky performance score (KPS), number of brain metastases, extracranial metastases (ECM) state, and whether treatment had been received before BM. RPA, BSBM, DS-GPA, and BMS-Score log-rank test P values were all less than 0.001 among each group ($P<0.001$). The C-indices of the four groups were 0.554, 0.584, 0.588, and 0.643, respectively.

Conclusions: The four prognostic scoring systems exhibited medium predictive value for SCLC. The BMS-Score had the best applicability compared with the other three prognosis indices.

Keywords: Prognostic index; small cell lung cancer (SCLC); brain metastases; whole brain radiotherapy (WBRT); survival

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Introduction

Lung cancer has the highest morbidity and mortality of all malignancies worldwide (1). Small cell lung cancer (SCLC) accounts for approximately 15–20% of lung cancers (2). SCLC patients have a particularly high propensity to develop brain metastases (BMs), with 10–20% SCLC patients harboring brain metastasis at initial diagnosis and 50–80% developing brain metastasis during the treatment process (3-5). Due to the propensity for multiple brain metastases (2), the median survival times (MSTs) of patients with BMs is approximately 1–2 months without

treatment, while the standard treatment with WBRT can improve survival to 3–6 months (6-8). WBRT is the first-line treatment, with a recommended dose of 30 Gy in 10 fractions or 40 Gy in 20 fractions (9,10). However, most patients exhibit significant heterogeneity after receiving WBRT (11). To individualize patient treatment, stratified-specific prognostic indices are needed for this cohort.

Previous studies focused mainly on BMs, and specific studies on the prognosis in SCLC with BM are few. Several prognostic index systems were previously published including 1997, Gaspar *et al.* created recursive partitioning analysis (RPA), in 2004, basic score for brain metastases (BSBM) proposed by Lorenzoni *et al.* and Sperduto *et al.* Constructed the revised diagnosis-specific graded prognostic assessment (DS-GPA) in 2010; however, these index studies enrolled a small number of SCLC patients (12-14). In 2018, Bernhardt *et al.* developed a new prognostic evaluation system specifically for SCLC BM treated with WBRT: the BMS-Score, this is the first prognostic index for small cell lung cancer with brain metastases and it includes three factors: KPS, synchronous BM or metachronous BM, and ECM state (15). These three factors are assigned a different weight points: 2 points for KPS ≥70, 1 point for synchronous BM, 1 point for ECM state stable, the scores of each patient was the sum of points in each factor. The purpose of the present study is to validate the prognostic value of the newly proposed BMS-Score by comparing it with the RPA, BSBM, and DS-GPA prognostic indices.

We present the following article in accordance with the MDAR reporting checklist (available at http://dx.doi.org/10.21037/apm-20-1819).

Methods

Study inclusion criteria

The present study was carried out at a single institution, the Shanxi Province Cancer Hospital. We retrospectively collected the records of patients (n=801) with histologically confirmed SCLC with BM from January 2010 to December 2019, BMs newly diagnosed within 3 months and confirmed by enforced computed tomography (CT) and/or magnetic resonance imaging (MRI), and those treated with WBRT. Patients treated with prior cranial radiotherapy (PCI, n=43), only palliative chemotherapy (n=301), stereotactic radiosurgery (SRS, n=3), or prior surgery (n=3), were excluded. All of the patients had complete and detailed clinical data and dates of death or follow-up examinations. Ultimately, 451 patients were eligible for analysis. Patient characteristics are listed in *Table 1*.

WBRT was performed in all patients. Of these, 294 patients were treated with 30 Gy in 10 fractions, 134 patients were treated with 40 Gy in 20 fractions, and 23 patients did not complete the full treatment course due to deterioration of their general condition. Furthermore, 33.7% of the patients received an additional dose (WBRT-add) of 10–20 Gy in 2 doses/day depending upon the individual BM. All patients received appropriate chemoradiotherapy for their primary disease and extracranial metastases (ECM) according to their condition.

All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived. This study was approved by the Shanxi Provincial Cancer Hospital ethics committee.

Analysis of prognostic factors and stratification

In this study, clinical characteristics included the following: gender, age, Karnofsky performance score (KPS) at the time of BM diagnosis, time of BM, number of BMs, smoking history, synchronous BM, metachronous BM, with or without ECM, ECM state, control of the primary tumor, and whether the patient had received first-line chemotherapy and radiation prior to BM. Synchronous BM was defined at the time of initial diagnosis of the primary tumor, including BMs that were newly diagnosed within 3 months. ECM state at the time of diagnosis of brain metastasis (BM) [stability or progress were measured according to the Response Evaluation Criteria in Solid Tumors (RECIST) standard based on the latest CT scan] (16). Synchronous BM was defined as progressive disease, and those without ECM were considered stable. Stratification was performed according to the RPA, BSBM, DS-GPA, and BMS-Score indices.

Statistics

The endpoint of the study was overall survival (OS), which was estimated from the first day of discovery of BMs to the time of death or last date of follow-up. Kaplan-Meier survival curves were created to estimate OS, and the log-rank test was used for univariate analysis to compare the difference among the subgroups. Multivariate Cox proportional-hazard ratios were applied to assess the independent factors. $P<0.05$ was considered statistically

Table 1 Characteristics of 451 SCLC BM patients treated with WBRT

Variables	MSTs (months)	Number of patients	%
Gender			
Female	13.43	82	18.20
Male	11.40	369	81.80
Age group			
<50	13.43	79	17.50
50–60	12.30	188	41.70
>60	10.30	184	40.80
KPS group			
<70	6.63	62	13.70
70–80	12.60	280	62.10
90–100	13.90	109	24.20
No. BM group			
1	14.77	146	32.40
2	14.83	51	11.30
3	9.90	6	1.30
Multiple	9.70	239	53.00
Unknown	12.93	9	2.00
Smoking history			
No	12.70	120	26.60
Yes	11.80	331	73.40
Synchronous/metachronous BM			
Synchronous	12.93	116	25.70
Metachronous	11.47	335	74.30
ECM			
No	16.90	58	12.90
Yes	11.00	393	87.10
ECM state			
Stable	17.00	160	35.50
Progress	9.90	291	64.50
Control of primary tumor			
Progress	10.87	230	51.00
Stable	13.07	221	49.00
Treatment before BM			
No	13.07	117	23.90
Yes	11.37	343	76.10
Total	11.87	451	100

SCLC, small cell lung cancer; WBRT, whole brain radiotherapy; KPS, Karnofsky performance score; No. BM, number of brain metastases; BM, brain metastases; ECM, extracranial metastases; MSTs, median survival times.

significant. The concordance index (C-index) was used to compare the predictive values of the four existing systems. Generally, a C-index greater than 0.50 is statistically significant, with values closer to 1 indicating greater accuracy. All of the analyses were performed using SPSS 26.0 (except for the C-index, which was calculated using R version 3.6.3 and R Studio-1.2.5033).

Results

Patient characteristics

A total of 451 patients with BMs were eligible for this study. Most of the patients (81.8%) were male, 82.5% were older than 50 years, 73.4% had a history of smoking, and 86.3% were in good general condition (KPS ≥70). Overall, 25.7% of BMs were identified as synchronous with the primary tumor and 53.0% of patients had multiple BMs. Of the 451 included patients, 393 (87.1%) had BMs occurring simultaneously with extracranial lesions, with 64.5% of ECMs progressing and less than half of the patients (49.0%) with BMs having stable primary tumors. Most of the patients (76.1%) received first-line chemotherapy and radiation for primary lung lesions before BMs. Details are shown in *Table 1*.

OS and prognoses

At the last follow-up date, a total of 340 patients had died, with an OS maturity rate of 75.4%. The MST for the whole series was 11.87 months [95% confidence interval (CI), 10.611–13.129], with 1-, 2-, and 3-year survival rates of 49.4%, 21.5%, and 12.1%, respectively. The prognostic factors that influenced survival in the univariate analysis were gender, age, KPS, number of BMs, smoking history, with or without ECM, ECM state, and control of the primary tumor. Multivariable analysis showed that a higher KPS (KPS ≥70), fewer number of BMs, stable ECM, and receiving treatment before BM were statistically significant survival factors (*Table 2*).

Prognostic indices

A comparison of the prognostic value of the four indices is shown in *Table 3* and *Figure 1*. In the RPA, BSBM, DS-GPA, and BMS-Score indices, survival curves demonstrated excellent separation among each group (log-rank test, P<0.001). According to RPA, most of the patients (82.5%)

Table 2 Results of the univariate and multivariate analysis of cofactors associated with overall survival

Variables	Univariate analysis (P)	Multivariate analysis		
		Risk ratio	95.0% CI	P
Gender	0.005	–	–	–
Age group	0.042	–	–	–
KPS group	<0.001	0.463	0.339–0.633	<0.001
No. BM group	<0.001	1.124	1.039–1.216	0.004
Smoking history	0.048	–	–	–
Synchronous BM	0.917	–	–	–
ECM	0.001	–	–	–
ECM state	<0.001	2.351	1.823–3.032	<0.001
Control of primary tumor	0.003	–	–	–
Treatment before BM	0.628	1.511	1.162–1.965	0.002

KPS, Karnofsky performance score; No. BM, number of brain metastases; BM, brain metastases; ECM, extracranial metastases.

Table 3 Log-rank analyses of four scoring systems

Group	Patients	MSTs (months)	95% CI		Log-rank P
			Low	High	
RPA					<0.001
I class	18	16.900	11.686	22.114	
II class	372	12.830	11.577	14.083	
III class	61	5.930	3.709	8.151	
BSBM					<0.001
Zero-point	83	7.470	5.839	9.101	
One-point	181	12.700	10.741	14.659	
Two-point	164	13.630	10.204	17.056	
Three-point	23	17.430	5.498	29.362	
DS-GPA					<0.001
0–1.0	186	9.070	7.751	10.389	
1.5–2.0	191	13.600	11.906	15.294	
2.5–3.0	70	14.900	11.687	18.113	
3.5–4.0	4	17.430	14.293	20.567	
BSM-Score					<0.001
Group one	57	5.700	3.942	7.458	
Group two	167	9.400	6.604	12.196	
Group three	227	16.200	14.466	17.934	
Total	451	11.870	10.611	13.129	

The median survival times of the four prognostic index and log rank-test were all less than 0.001 among each group (P<0.001). MSTs, median survival times; RPA, recursive partitioning analysis; DS-GPA, diagnosis-specific graded prognostic assessment; BSBM, basic score for brain metastases.

were in class II, 4% were in class I, and 13.5% were in class III. We found that MSTs following WBRT were 16.9 months in class I, 12.83 months in class II, and 5.93 months in class III. For the BSBM group, the MST of the zero-point group was 7.47 months, 12.7 months for the one-point group, 13.63 months for the two-point group, and 17.43 months for the three-point group. The MSTs for all of the DS-GPA groups were 9.07, 13.6, 14.9, and 17.43 months, respectively. The BMS-Score revealed that the MST was 5.7 months in group one (0–1 points), 9.4 months in group two (2 points), and 16.2 months in group three (3–4 points). The number of patients with a BMS-Score of 0 to 1, 2, 3, and 4 points was 57, 167, 224, and 3, respectively. In the 4-points group, only two patients had an outcome, so those with three and four points were merged into Group 3.

Patients in the worst groups of the four systems (RPA: class III, BSBM: zero points, DS-GPA: 0–1 points, and BMS-Score: Group One) had MSTs of 5.93, 7.47, 9.07, and 5.7 months, respectively. In addition, MSTs in the best groups of these systems (RPA: class I, BSBM: three points, DS-GPA: 3.5–4.0 points, and BMS-Score: Group Three) were 16.9, 17.43, 17.43, and 16.2 months, respectively. Moreover, due to a deterioration of general condition, 23 patients did not complete the full course of WBRT. In this subgroup, the MST was only 4.4 months, and all of the four prognostic grading systems were able to predict poor survival in this subgroup.

The C-index was calculated to compare the predictive values of each scoring system. The C-index values for RPA, BSBM, DS-GPA, and BMS-Score were 0.554, 0.584, 0.588, and 0.643, respectively. These results suggested that the four scoring systems had medium predictive value for SCLC BMs treated with WBRT. The BMS-Score exhibited the best applicability (*Table 4*).

Discussion

Patients suffering from SCLC with BM have a poor prognosis following treatment due to the heterogeneous nature of the disease (11). The reported median survival

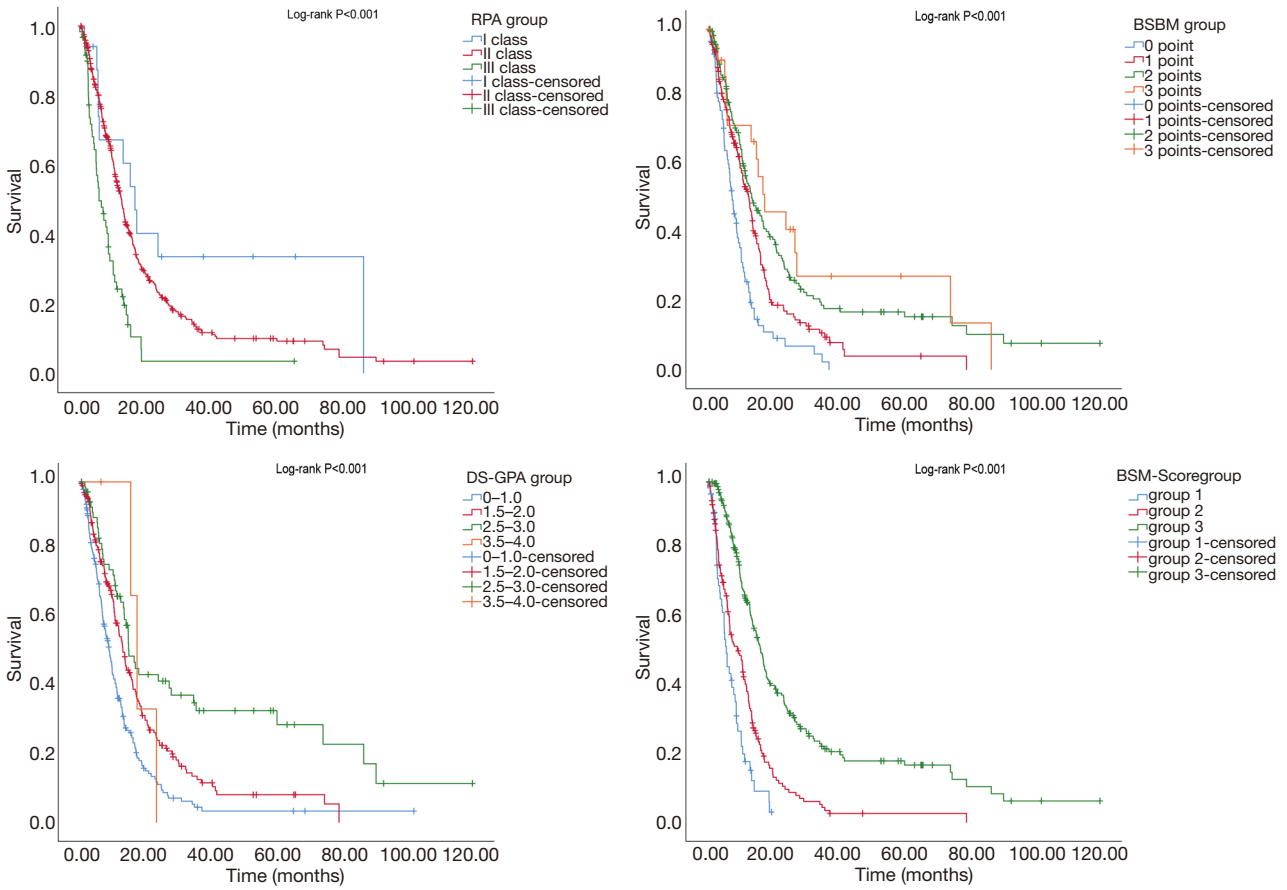

Figure 1 Kaplan-Meier curves showing SCLC BM patient survival using the RPA, BSBM, DS-GPA, and BMS-Score prognostic indices, respectively. SCLC, small cell lung cancer; BM, brain metastasis; RPA, recursive partitioning analysis; BSBM, basic score for brain metastases; DS-GPA, diagnosis-specific graded prognostic assessment.

Table 4 The predictive value of the four prognostic systems (C-index)

Score	Group	Number of patients	C-index
RPA	I/II/III	18/372/61	0.544
BSBM	Zero/one/two/three	83/181/164/23	0.584
DS-GPA	0–1/1.5–2/2.5–3/3.5–4	186/191/70/4	0.588
BMS-Score	One/two/three	57/167/227	0.643

RPA, recursive partitioning analysis; DS-GPA, diagnosis-specific graded prognostic assessment; BSBM, basic score for brain metastases.

for these patients ranges from 1 to 14 months (3,10). An accurate stratified benefit-risk evaluation based on prognosis is generally a clinically efficacious tool for making individualized and precise treatment decisions (4). Recently, Bernhardt *et al.* developed a new prognostic evaluation system specifically for SCLC BM called the BMS-Score (15). In this study, we initially enrolled 451 patients to validate this novel index. Through calculating the C-index value, we found the BMS-score index to have medium predictive ability, although it did exhibit better predictive value compared with the previously published RPA, BSBM, and DS-GPA indices. However, we identified some drawbacks to this predictive system that require further revision.

The original work for the prognostic study only went back to 1997, Gaspar *et al.* collected the data from 1,200 BM patients with various cancer types in three WBRT clinical trials by the Radiation Therapy Oncology Groups (RTOG) between 1979 and 1993, and published the first prognostic system (RPA), which included four factors: age,

KPS, control of the primary tumor, and with or without ECM (12). Among all of these BM patients, only 4% (n=51) had SCLC. In 2004, the BSBM score system was proposed by Lorenzoni *et al.* based on 110 BM patients who were divided into three levels based on the sum of the score (zero or one points) from three main variables: KPS, primary tumor control, and presence or absence of ECM (13). Since these indices included incomplete independent prognostic factors, Sperduto *et al.* developed the GPA system in 2008 based on 1,960 patients from four RTOG (17). Furthermore, to specify the prognostic index for different cancer types, Sperduto *et al.* constructed the updated DS-GPA, which was based on 5,067 patients from 11 institutions between 1985 and 2007. This system has been widely validated and includes four factors (age, KPS, number of BMs, and presence or absence of ECM) (14). However, SCLC BM patients were grouped with non-SCLC (NSCLC) patients, and only a small number of SCLC patients were included.

There are two SCLC BM-specific prognostic score systems: the Rades-SCLC and the BMS-Score (15,18). In 2013, Rades *et al.* proposed the Rades-SCLC scoring system, which was based on 117 SCLC BM patients treated with WBRT. The score of each independent prognostic factor (including KPS, number of BMs, and ECM) acquired points based on their weight on prognosis, with the sum of three factors in each patient constituting his/her final score. Patients were then grouped into three prognostic stratifications according to their total points (18). However, this system is complex and has limited predictive ability, and is thus not often used in clinical practice (19,20). In 2018, Bernhardt *et al.* proposed a novel index called the BMS-Score, which consists of only three factors: KPS, synchronous BM or metachronous BM, and ECM state (15). This novel SCLC BM-specific prognostic index was easier to be used compared with the previous ones, even by simple clinical examinations, a relatively accurate assessment for the patients' prognosis can be made from three easier-to-measure variables. Then patients will be divided into different prognostic categories.

To further validate the BMS-Score system and confirm its prognostic value for SCLC BM patients treated with WBRT, we retrospectively enrolled 451 patients and analyzed the predictive capability of the four prognostic scoring systems. The C-index values for RPA, BSBM, DS-GPA, and BMS-Score were 0.554, 0.584, 0.588, and 0.643, respectively, indicating that they have medium predictive value. Furthermore, the BMS-Score exhibited the best predictive ability, suggesting its potential prognostic value. However, it was derived from a relatively small sample size (n=221), and the only treatment option was WBRT. In fact, there are numerous treatment modalities for SCLC BM in routine clinical practice. For example, In recent years, mounting evidence has shown that immunotherapy may be a promising method for this cohort of patients .IMpower-133 study shows that the first-line randomized trial for Extensive stage small cell lung cancer comparing etoposide + carboplatin + placebo with etoposide + carboplatin + atezolizumab, the median overall survival was 12.3 months in the atezolizumab group and 10.3 months in the placebo group (hazard ratio for death, 0.70); another research named CASPIAN study also showed positive results. Comparing with the chemotherapy alone, the median survival of durvalumab combined chemotherapy group was improved 2–7 months. However, efficacy in the subgroup of brain metastases further reform is needed (21-23). In the era of multidisciplinary treatment, the optimal prognostic index should consider all therapeutic options. Additionally, a concern regarding WBRT is the long-term risk of cognitive decline (24,25). This may also have an effect on survival and quality of life. Thus, to further optimize this index, such factors should be incorporated into future updates.

In the present study, the MST was 11.87 months, which is relatively better than in previous reports (14,20). This was mainly due to the retrospective design and an inherent selection bias. Also, most patients in this study presented with a favorable performance state, with 86.3% of KPS scores greater than 70 points. Moreover, the longer survival might be related to the fact that BMs tend to be detected early by more sensitive imaging systems such as MRI, and patients were treated in the recent decade. In the present study, the main independent predictive factors associated with OS were KPS, number of BMs, ECM state, and receipt of treatment before BM, which is consistent with previous studies (14,15,18,26). However, in contrast to Bernhardt *et al.* (15), there was no significant statistical difference between synchronous and metachronous BM. According to national guidelines, SCLC with BM should be treated with WBRT at a recommended dose of 30 Gy in 10 fractions, supported by diffuse intracranial disease features (27,28). In our institution, 30 Gy in 10 daily fractions is generally adopted, with some patients being treated with a 40 Gy dose in 20 fractions due to edema present around large tumors. Borgelt *et al.* compared the first two randomized national Phase III trials carried out by the RTOG and showed that differing radiation doses and

fractionation schemes did not make a substantial difference to OS (29,30). Thus, the two dose patterns did not affect the experimental results in this study.

In conclusion, this study showed that the four prognostic scoring systems exhibit medium predictive value for SCLC prognosis. Compared with the RPA, BSBM, and DS-GPA prognosis indices, the BMS-Score had the best applicability for SCLC BM treated with WBRT. More importantly, it provides a basis for further studies of BM in SCLC. In future, it is necessary to update the prognostic index via a large multicenter trial, and more potential independent prognostic factors and multi-treatment options should be considered.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants were in accordance with the Declaration of Helsinki (as revised in 2013). Individual consent for this retrospective analysis was waived. This study was approved by the Shanxi Provincial Cancer Hospital ethics committee.

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