Construction of a nomogram to guide prophylactic cranial irradiation in extensive-stage small cell lung cancer

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Abstract. Patients with extensive-stage small cell lung cancer (ES-SCLC) have a high risk of brain metastasis (BM). However, to the best of our knowledge, the risk factors for BM remain unclear. The present study aimed to investigate the risk factors and establish a prediction model for BM in patients with ES-SCLC. A total of 156 patients with ES-SCLC who had no BM and achieved a partial or complete response between January 2020 and March 2023 were included. Patients were randomly divided into training (n=109) and validation (n=47) cohorts. Factors associated with BM were assessed in the training cohort. Univariate and Cox multivariate analyses were performed to evaluate patients with ES-SCLC. Cox multivariate analysis identified oligometastasis [hazard ratio (HR), 0.35; 95% CI, 0.14-0.85; P=0.021], sex (HR, 2.48; 95% CI, 1.05-5.85; P=0.038) and baseline adrenal metastasis (HR, 2.85; 95% CI, 1.54-5.21; P<0.001) as independent risk factors for BM. A nomogram model was constructed to predict intracranial progression-free survival (iPFS). The areas under the receiver operating characteristic curves for the 9-, 12- and 18-month iPFS in the training cohort were 0.77, 0.74 and 0.75, respectively. The nomogram prediction and actual validation cohorts demonstrated good agreement. Among the high-risk factors for BM, the overall survival analysis demonstrated that non-oligometastasis and baseline adrenal metastasis were unfavorable prognostic factors. The present nomogram may aid risk assessment for BM in patients with ES-SCLC and guide prophylactic cranial irradiation.

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Introduction

Small cell lung cancer (SCLC) is a highly malignant neuroendocrine tumor with a 5-year survival rate of <5%. It accounts for 10-15% of all lung cancers, with more than two-thirds of cases classified as extensive-stage SCLC (ES-SCLC) (1). The brain is a common site of metastasis in ES-SCLC; >50% of patients with ES-SCLC develop brain metastases (BMs) within 2 years, and BMs are observed in up to 80% of patients at autopsy (2).

Immunological drugs can prolong patient survival but do not reduce the risk of BM (3). Once BM occurs, it markedly impacts patient survival and quality of life. As most chemotherapeutic drugs cannot cross the blood-brain barrier, there are limited options for preventing BM (4). Therefore, the role of prophylactic cranial irradiation (PCI) should not be overlooked.

Currently, there are controversies regarding the benefits of PCI in patients with ES-SCLC: A European Organization for Research and Treatment of Cancer study indicated that PCI is effective in reducing the risk of BM and prolonging the 1-year overall survival (OS) (5). However, a previous phase III clinical trial of patients with ES-SCLC without BMs used MRI to confirm PCI decreases the incidence of BM but does not increase survival (6). In addition, neurocognitive dysfunction associated with PCI may affect quality of life (7-9). The hypothesis that PCI using hippocampal avoidance decreases cognitive impairment is controversial (10-12). Regular MRI monitoring of BM combined with salvage stereotactic radiosurgery may replace PCI (6,13,14).

Therefore, it is essential to screen patients who are at high risk of BM for PCI to avoid overtreatment, which may lead to cognitive dysfunction and waste of medical resources (6,7).

The current National Comprehensive Cancer Network guidelines recommend PCI for patients with ES-SCLC who have an efficacy evaluations of partial/complete response (PR/CR) following standard treatment, provided they are under MRI surveillance (15). Nevertheless, it remains unclear which patients are likely to benefit from PCI, making the decision to perform this procedure challenging.

Previous studies (16,17) have evaluated the risk factors for the development of BM in patients with ES-SCLC; however, the enrollment population was all patients with ES-SCLC, and, to the best of our knowledge, few analyses (16-18) have been conducted separately for the population with PR/CR evaluation. A retrospective study in 2011 reported that weight loss, response to chemotherapy were independent predictors of BM in patients with ES-SCLC (16). Chung *et al* (17) demonstrated that extrathoracic metastasis, fluorodeoxyglucose positron emission tomography bone or splenic hypermetabolism and the neutrophil-to-lymphocyte ratio (NLR) are associated with the risk of BM in patients with ES-SCLC. However, neither of the aforementioned retrospective studies analyzed the risk factors for BM in patients exhibiting good efficacy.

The present study aimed to investigate the risk factors for BM in patients with MRI-confirmed baseline absence of BM in ES-SCLC, after achieving PR/CR as assessed by treatment efficacy. Furthermore, the study aimed to establish a nomogram model to facilitate decision-making for PCI.

Materials and methods

Study design and participants. The present retrospective study included patients newly diagnosed with ES-SCLC between January 2020 and February 2023 at Shandong Cancer Hospital (Jinan, China; Fig. 1). The inclusion criteria were as follows: i) SCLC verified by pathology; ii) ES-SCLC confirmed by imaging prior to treatment(MRI, ultrasound, Computed Tomography, Positron Emission Tomography/Computed tomography and Emission Computed Tomography), with no BM established by MRI; iii) receipt of at least four cycles of standard first-line platinum-based chemotherapy; and iv) CR or PR after 4-6 cycles. The exclusion criteria were as follows: i) Patients who had received antitumor therapy; ii) patients who had not undergone a brain MRI; iii) patients who had received PCI therapy; iv) patients with follow-up periods <9 months; and v) patients with a history of other primary malignant tumors. The clinical stage was classified according to the American Joint Committee on Cancer guidelines (8th edition) (19), and responses were evaluated using Response Evaluation Criteria in Solid Tumors (version 1.1) (20). Overall, 156 of 727 patients with ES-SCLC met the criteria, with a median age of 63 years (IQR, 56-68 years) and were randomly divided into training (n=109) and validation (n=47) cohorts in a 7:3 ratio using the sample function in R software version 4.0.3(r-project.org/). A prediction model was constructed for the training cohort, whereas the validation cohort was internally validated using receiver operating characteristic, calibration curves, and decision curve analysis. The requirement for ethics approval and informed consent was waived by the Ethics Committee of Shandong Cancer Hospital (Jinan, China).

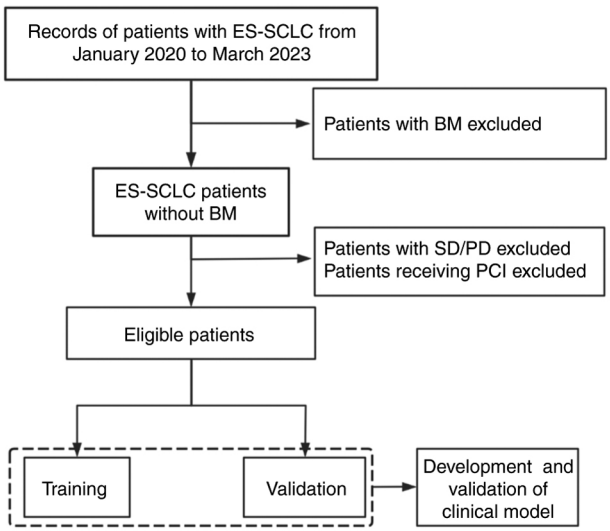

Figure 1. Flowchart of patient selection. ES-SCLC, extensive-stage small cell lung cancer; BM, brain metastasis; PCI, prophylactic cranial irradiation; SD, stable disease; PD, progressive disease.

Selection of potential predictors. Medical records of baseline clinical characteristics were retrieved and reviewed using an electronic medical record system. Patient demographics, including age, sex and smoking history, were also documented. Medical records contained information on hematological parameters, including carcinoembryonic antigen, neuron-specific enolase (NSE), pro-gastrin-releasing peptide, lactate dehydrogenase (LDH), NLR and platelet-lymphocyte ratio (PLR). Clinical characteristics, such as T, N and metastasis stage (19), were also extracted from medical records. Baseline metastatic status, specific parameters (NLR and PLR) and treatment status (mode of treatment, chemotherapy cycle and thoracic radiation therapy) were considered, and all unordered variables were transformed into categorical variables. All indicators were extracted from the initial diagnostic records.

Diagnosis of BM and definition of intracranial progression-free survival (iPFS). The occurrence of BM was the primary outcome of the present study. iPFS was defined as the interval from the initial pathological diagnosis (MRI was used to confirm lack of BM) to the occurrence of BM or the date of the last follow-up examination. iP was diagnosed based on imaging results (primarily brain MRI); however, if BM symptoms manifested before the imaging, the time of appearance was given precedence. Patients were instructed to undergo brain MRI (preferred) or computed tomography every 3-4 months following the conclusion of chemotherapy. From the second year onward, cranial imaging was performed every 6 months. The end point follow-up was May 2024 and the median follow-up time was 18.7 months (range, 4.8-41 months).

Statistical analysis. SPSS 27.0 software (IBM Corp.) was used to analyze the data. In the training cohort, univariate analysis was used to explore the relationship between the potential predictors and iPFS. The assessment of between-group differences was performed using χ^2 or Fisher's exact tests. Log-rank tests were used to compare different groups for univariate analyses. Factors with a P-value <0.05 were included in

Table I. Patient clinical and pathological characteristics.

Variable	Total, n (%) (n=156)	Training, n (%) (n=109)	Validation, n (%) (n=47)	χ^2	P-value
Sex				0.00	0.980
Female	33 (21.15)	23 (21.10)	10 (21.28)		
Male	123 (78.85)	86 (78.90)	37 (78.72)		
Age, years				0.13	0.717
>65	63 (40.38)	43 (39.45)	20 (42.55)		
≤65	93 (59.62)	66 (60.55)	27 (57.45)		
Smoking status				0.10	0.755
No	66 (42.31)	47 (43.12)	19 (40.43)		
Yes	90 (57.69)	62 (56.88)	28 (59.57)		
T classification				0.00	0.975
T1, T2	70 (44.87)	49 (44.95)	21 (44.68)		
T3, T4	86 (55.13)	60 (55.05)	26 (55.32)		
N classification				1.12	0.289
N1, N2	63 (40.38)	47 (43.12)	16 (34.04)		
N3	93 (59.62)	62 (56.88)	31 (65.96)		
CEA (ng/ml)				0.31	0.575
<5	91 (58.33)	62 (56.88)	29 (61.70)		
≥5	65 (41.67)	47 (43.12)	18 (38.30)		
NSE (ng/ml)				1.04	0.308
<17.5	23 (14.74)	14 (12.84)	9 (19.15)		
≥17.5	133 (85.26)	95 (87.16)	38 (80.85)		
Pro-GRP (pg/ml)				0.14	0.713
<50	13 (8.33)	8 (7.34)	5 (10.64)		
≥50	143 (91.67)	101 (92.66)	42 (89.36)		
D-dimer (mg/l)				2.31	0.129
<0.5	64 (41.03)	49 (44.95)	15 (31.91)		
≥0.5	92 (58.97)	60 (55.05)	32 (68.09)		
LDH (U/l)				0.96	0.328
<245	79 (50.64)	58 (53.21)	21 (44.68)		
≥245	77 (49.36)	51 (46.79)	26 (55.32)		
NLR				0.00	>0.999
<1.37	11 (7.05)	8 (7.34)	3 (6.38)		
≥1.37	145 (92.95)	101 (92.66)	44 (93.62)		
PLR				0.01	0.920
<121	39 (25.00)	27 (24.77)	12 (25.53)		
≥121	117 (75.00)	82 (75.23)	35 (74.47)		
Oligometastasis				0.07	0.789
No	54 (34.62)	37 (33.94)	17 (36.17)		
Yes	102 (65.38)	72 (66.06)	30 (63.83)		
Liver metastasis				0.01	0.921
No	102 (65.38)	71 (65.14)	31 (65.96)		
Yes	54 (34.62)	38 (34.86)	16 (34.04)		
Bone metastasis				0.00	0.963
No	100 (64.10)	70 (64.22)	30 (63.83)		
Yes	56 (35.90)	39 (35.78)	17 (36.17)		
Adrenal metastasis				0.43	0.514
No	128 (82.05)	88 (80.73)	40 (85.11)		
Yes	28 (17.95)	21 (19.27)	7 (14.89)		

Table I. Continued.

Variable	Total, n (%) (n=156)	Training, n (%) (n=109)	Validation, n (%) (n=47)	χ^2	P-value
Thoracic radiotherapy				0.66	0.418
No	92 (58.97)	62 (56.88)	30 (63.83)		
Yes	64 (41.03)	47 (43.12)	17 (36.17)		
Treatment mode				0.25	0.614
ChT-alone	39 (25.00)	26 (23.85)	13 (27.66)		
IO + ChT	117 (75.00)	83 (76.15)	34 (72.34)		
Chemotherapy cycles				0.74	0.389
4	18 (11.54)	11 (10.09)	7 (14.89)		
>4	138 (88.46)	98 (89.91)	40 (85.11)		
Immunotherapy cycles				0.34	0.561
<6	108 (69.23)	77 (70.64)	31 (65.96)		
≥6	48 (30.77)	32 (29.36)	16 (34.04)		
BM				2.15	0.209
No	77 (49.36)	58 (53.21)	19 (40.43)		
Yes	79 (50.64)	51 (46.79)	28 (59.57)		

NSE, neuron-specific enolase; Pro-GRP, pro-gastrin-releasing peptide; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ChT, chemotherapy; IO, immunotherapy; BM, brain metastasis.

multivariate Cox regression analysis to evaluate the independent risk factors influencing iPFS. A nomogram was constructed based on risk factors identified through multifactorial analysis by R software version 4.0.3 (r-project.org/). The total score was calculated for all individuals in the training cohort, and the data were quantitatively validated using the area under the receiver operating characteristic, calibration curve and decision curve. The Kaplan-Meier method was used to calculate OS. We performed univariate and multivariate analysis using the Cox proportional hazards models to identify possible predictors of prognosis. All tests were two-sided. P<0.05 was considered to indicate a statistically significant difference.

Results

Patient characteristics. A total of 156 patients were included in the present study. Analysis of the baseline characteristics is shown in Table I. Overall, 123 patients (78.85%) were male and 33 (21.15%) were female. The median age was 63 years, with 63 (40.38%) patients aged >65 years and 93 (59.62%) aged ≤65 years. A total of 54 patients (34.62%) exhibited non-oligometastatic status(extensive metastasis beyond oligometastasis), defined as the presence of >3 metastatic organs and >5 metastatic lesions. There was no significant difference in risk factors between the training and validation sets (all P>0.05). The median iPFS was 15.6 months (95% CI, 9.81-21.39 months), and the cumulative incidence of BM was 35% at 9 months, 44% at 12 months and 60% at 24 months. The median survival and follow-up times were 20.70 months (95% CI, 17.58-23.82 months) and 23.63 months (95% CI, 22.29-24.98 months), respectively (data not shown).

Factors influencing BM. Univariate analysis of the training cohort demonstrated that patients with non-oligometastases exhibited a heightened risk of BM compared with those with oligometastases [hazard ratio (HR), 0.35; 95% CI, 0.19-0.61; P<0.001; Table II]. Additionally, male patients had a higher risk of BM compared with female patients (HR, 2.62; 95% CI, 1.12-6.15; P=0.026). Furthermore, patients with liver metastases at baseline exhibited a heightened risk of BM compared with those without liver metastasis (HR, 1.98; 95% CI, 1.14-3.45; P=0.016). Patients with adrenal metastases at baseline also had a higher risk of BM compared with those without adrenal metastasis (HR, 3.03; 95% CI, 1.67-5.48; P<0.001). Cox multivariate analysis (Table III) demonstrated that absence of oligometastasis (HR, 0.35; 95% CI, 0.14-0.85; P=0.021), male sex (HR, 2.48; 95% CI, 1.05-5.85; P=0.038) and baseline adrenal metastasis (HR, 2.85; 95% CI, 1.54-5.21; P<0.001) were independent risk factors for BM.

Establishment of the nomogram. A nomogram was constructed using the three risk factors identified by Cox multifactorial analysis with P-values <0.05. This nomogram was used to predict the probability of iPFS at 9, 12 and 18 months in patients with baseline ES-SCLC without BM who achieved PR/CR efficacy on standard treatment and did not receive PCI. The risk associated with each factor was visualized in the nomogram (Fig. 2). The individual scores for the risk factors of each patient were summed to obtain an overall score, which corresponded to the likelihood of different iPFS outcomes. The areas under the receiver operating characteristic curve for the 9-, 12- and 18-month iPFS in the training cohort were 0.77 (95% CI, 0.67-0.87), 0.74 (95% CI, 0.65-0.84) and 0.75 (95% CI, 0.65-0.85), respectively (Fig. 3). Similarly, good results were obtained in the validation cohort, with the areas under

Table II. Univariate analysis predicting intracranial progression-free survival in patients without prophylactic cranial irradiation.

Variable	P-value	HR (95% CI)
Sex		
Female		1.00 (reference)
Male	0.026	2.62 (1.12-6.15)
Age, years		
>65		1.00 (reference)
≤65	0.558	1.19 (0.67-2.10)
Smoking status		
No		1.00 (reference)
Yes	0.064	1.73 (0.97-3.08)
T classification		
T1, T2		1.00 (reference)
T3, T4	0.856	0.95 (0.55-1.64)
N classification		
N1, N2		1.00 (reference)
N3	0.906	1.03 (0.60-1.78)
CEA (ng/ml)		
<5		1.00 (reference)
≥5	0.856	0.95 (0.55-1.64)
NSE (ng/ml)		
<17.5		1.00 (reference)
≥17.5	0.268	0.69 (0.35-1.34)
Pro-GRP (pg/ml)		
<50		1.00 (reference)
≥50	0.202	2.51 (0.61-10.32)
D-dimer (mg/l)		
<0.5		1.00 (reference)
≥0.5	0.113	1.57 (0.90-2.73)
LDH (U/l)		
<245		1.00 (reference)
≥245	0.173	1.46 (0.85-2.51)
NLR		
<1.37		1.00 (reference)
≥1.37	0.224	2.40 (0.58-9.88)
PLR		
<121		1.00 (reference)
≥121	0.222	1.54 (0.77-3.07)
Oligometastasis		
No		1.00 (reference)
Yes	<0.001	0.35 (0.19-0.61)
Liver metastasis		
No		1.00 (reference)
Yes	0.016	1.98 (1.14-3.45)
Bone metastasis		
No		1.00 (reference)
Yes	0.175	1.47 (0.84-2.56)
Adrenal metastasis		
No		1.00 (reference)
Yes	<0.001	3.03 (1.67-5.48)
Thoracic radiotherapy		
No		1.00 (reference)
Yes	0.157	1.48 (0.86-2.55)
Treatment mode		
ChT-alone		1.00 (reference)
IO + ChT	0.556	0.83 (0.45-1.53)
Chemotherapy cycles		
>4		1.00 (reference)
≤4	0.162	0.43 (0.14-1.40)
Immunotherapy cycles		
<6		1.00 (reference)
≥6	0.829	0.93 (0.50-1.73)

HR, hazard ratio; NSE, neuron-specific enolase; pro-GRP, pro-gastrin-releasing peptide; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ChT, chemotherapy; IO, immunotherapy.

Table III. Multivariate analysis predicting intracranial progression-free survival.

Variable	HR (95% CI)	P-value
Sex		
Female	1.00 (reference)	
Male	2.48 (1.05-5.85)	0.038
Oligometastases		
No	1.00 (reference)	
Yes	0.35 (0.14-0.85)	0.021
Liver metastasis		
No	1.00 (reference)	
Yes	1.00 (0.42-2.38)	0.997
Adrenal metastasis		
No	1.00 (reference)	
Yes	2.85 (1.54-5.21)	<0.001

HR, hazard ratio.

the curve for the 9-, 12- and 18-month iPFS being 0.65 (95% CI, 0.48-0.81), 0.75 (95% CI, 0.61-0.89) and 0.77 (95% CI, 0.64-0.90), respectively (Fig. 3). The calibration and decision curves of this nomogram in the training and validation cohorts demonstrated good agreement (Figs. 4 and 5).

Survival analysis. The univariate analysis revealed that age, N classification, oligometastasis, NSE, D-dimer and LDH levels, liver, bone and adrenal metastases, and thoracic radiotherapy, were significantly associated with OS (Table IV). These factors were included in the multivariate analysis, which demonstrated that oligometastasis (HR, 0.38; 95% CI, 0.18-0.81; P=0.012)

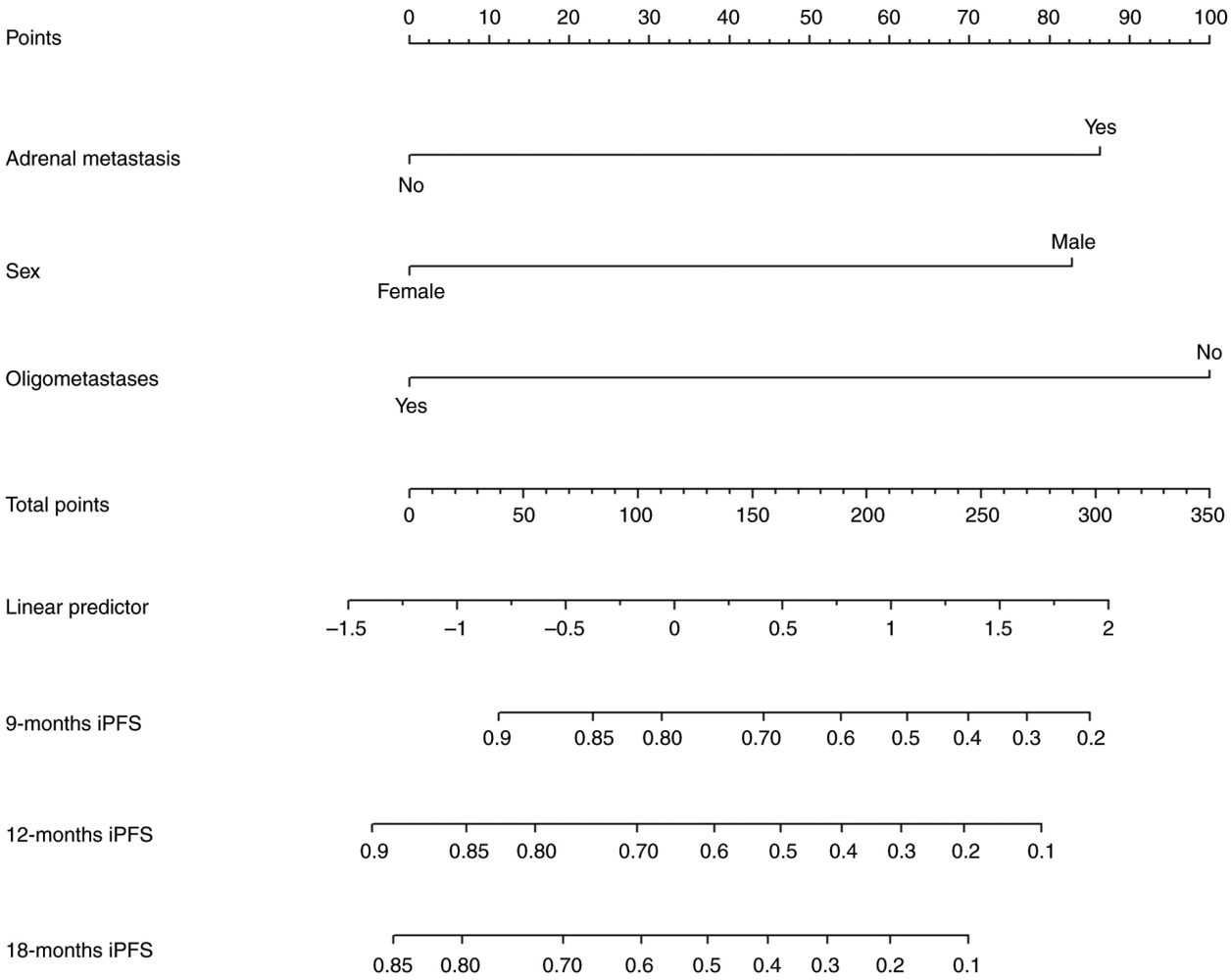

Figure 2. Nomogram to predict the probability of brain metastasis in patients with extensive-stage small cell lung cancer without prophylactic cranial irradiation. iPFS, intracranial progression-free survival.

was a favorable prognostic factor for OS. Conversely, higher N classification (HR, 2.08; 95% CI, 1.27-3.40; P=0.003) and adrenal metastases (HR, 1.80; 95% CI, 1.08-3.02; P=0.025) were unfavorable prognostic factors for OS.

Discussion

SCLC is aggressive and progresses rapidly, with a 2-year BM incidence of 60-80% (21). BM poses a notable burden to the patient and requires extensive care (22). Therefore, early intervention for BM is necessary. The current National Comprehensive Cancer Network guidelines recommend that only patients with good treatment efficacy are considered for PCI (14). Therefore, only patients with good efficacy ratings were included in the present study. However, the selection of PCI has been approached with caution in clinical practice; only 14 (4.7%) out of 297 patients with ES-SCLC without prior BM at Shandong Cancer Hospital received PCI during the present study period. An exploratory study by Ankolekar *et al* (23) analyzed the shared decision-making process among patients with ES-SCLC prepared to undergo PCI and the physician perceptions of its benefits, the results of the study revealed that most patients want better information to help make PCI decisions. Although prior research has addressed BM risk factors in SCLC, much focus has been on limited-stage SCLC (LD-SCLC) (18,24-28). Conversely, studies (15-16,27-29) targeting the ES-SCLC population have not examined those who were effectively treated and do not provide actionable guidance for patients recommended for PCI by the current guidelines. Consequently, the present study explored the BM risk factors in this subgroup to offer more tailored decision-making recommendations regarding PCI.

To the best of our knowledge, the present study was the first to assess risk factors for BM in ES-SCLC in patients with PR/CR following treatment and without PCI. Furthermore, a nomogram visualization model was developed. Male sex, non-oligometastatic status and baseline adrenal metastasis were independent risk factors for BM. The nomogram validation results demonstrated good concordance between the predicted and observed values, potentially aiding clinicians in deciding on PCI for patients with ES-SCLC. Patients with non-oligometastases were more susceptible to BM compared with those with oligometastases. This disparity may stem from the lower systemic tumor burden in oligometastatic patients, which may result in reduced recurrence and metastasis post-treatment, thereby diminishing the risk of BM (28). By contrast, patients with extensive metastasis (non-oligometastatic), despite achieving a favorable response to

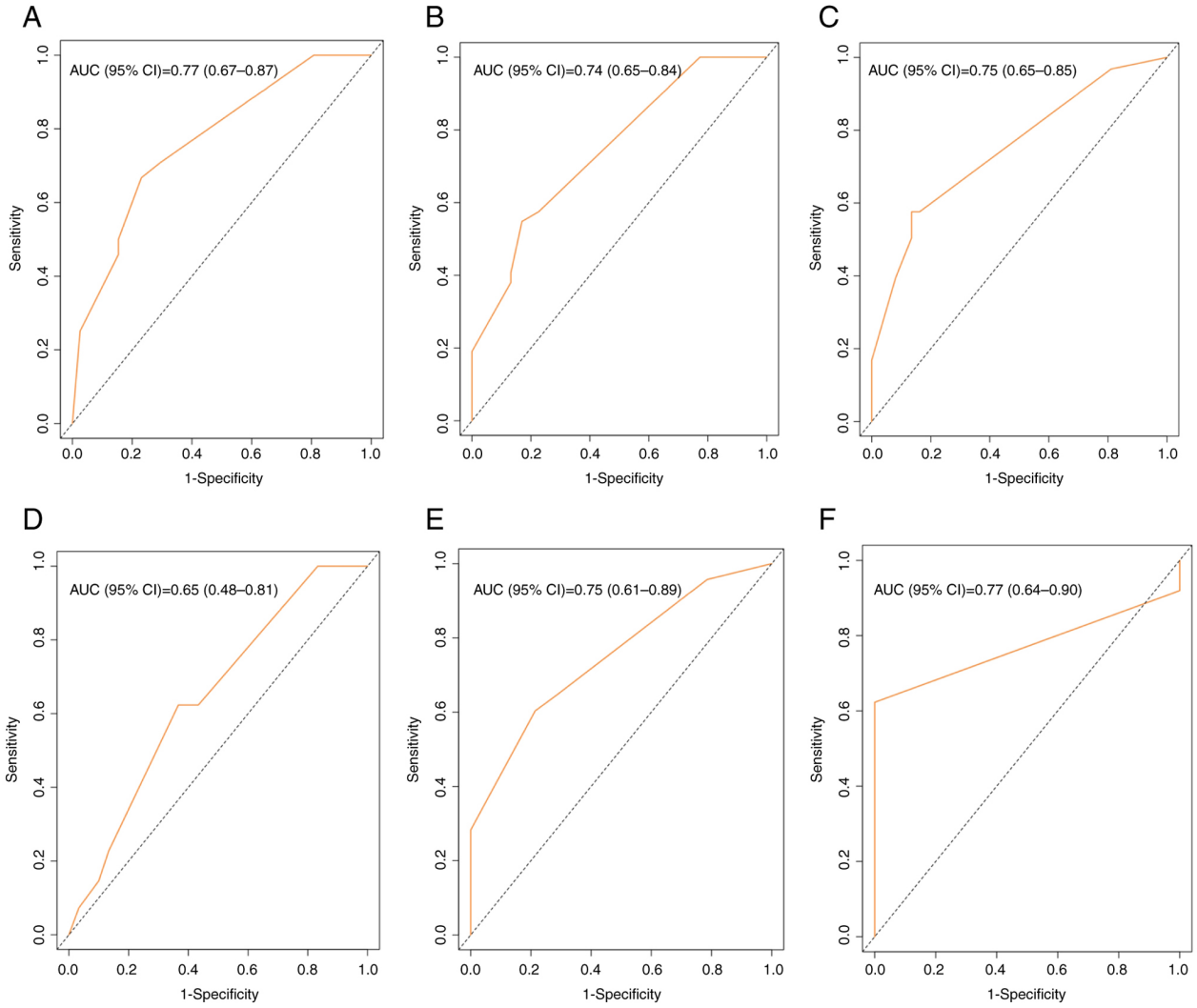

Figure 3. Receiver operating characteristic curves of the nomogram in the training cohort and validation cohort. iPFS of the training cohort at (A) 9, (B) 12 and (C) 18 months. iPFS of the validation cohort at (D) 9, (E) 12 and (F) 18 months. iPFS, intracranial progression-free survival; AUC, area under the curve.

antitumor therapy (with treatment efficacy reaching PR/CR), face a higher risk due to their inherent widespread metastatic burden. Therefore, the likelihood of recurrence and metastasis is higher in these patients (29). Chung *et al* (17) reached a similar conclusion, suggesting that extensive systemic metastases are linked to systemic inflammation and potentially associated with BM. A retrospective study by Oliver e*t al* (30) determined that the presence of ≥3 extrathoracic metastatic sites markedly increased the risk of developing BM in patients with ES-SCLC. Furthermore, Bang *et al* (29) identified extrathoracic metastasis as an independent predictor of a shorter iPFS. However, differing from the present study, the aforementioned studies did not evaluate the number of metastatic sites to assess oligometastatic status or vary the population selection, as both included patients with stable/progressive disease for efficacy assessment.

The present study demonstrated that the risk of BM varied based on baseline metastatic status, a finding not reported by previous studies (17,29-31). Patients with adrenal metastases before initial treatment exhibited a higher likelihood of developing BM compared with those without. In the analysis by Oliver *et al* (30), patients with baseline adrenal metastases had a non-significant tendency to develop BM in the Cox multivariate analysis (P=0.12). Potential reasons for these discrepancies include differing study populations, which could lead to varied outcomes. Additionally, the aforementioned study recorded only 10 cases (10.8%) of adrenal metastases before initial treatment, whereas the present study included 28 cases (17.95%), potentially influencing the results. Notably, in a study by Megyesfalvi *et al* (32), a higher co-occurrence of adrenal metastasis and BM was observed in patients with SCLC. The mechanism underlying this phenomenon remains poorly understood but may be associated with the homogeneity of metastatic sites (33), Furlan *et al* (34) suggested that mature adrenal glands have cells of nerve origin, the differentiation of peripheral glial stem cells forms chromaffin cells in the adrenal medulla during beginning of cell differentiation. Accordingly, it was hypothesized that similar 'metastatic hotbeds' may exist within the central nervous system alongside an abundant blood supply to the baseline adrenal metastasis site, potentially facilitating BM. These hypotheses require confirmation through further anatomical and histological studies.

Sex was also demonstrated to be an independent risk factor for the development of BM; Kim *et al* (35) noted that male sex

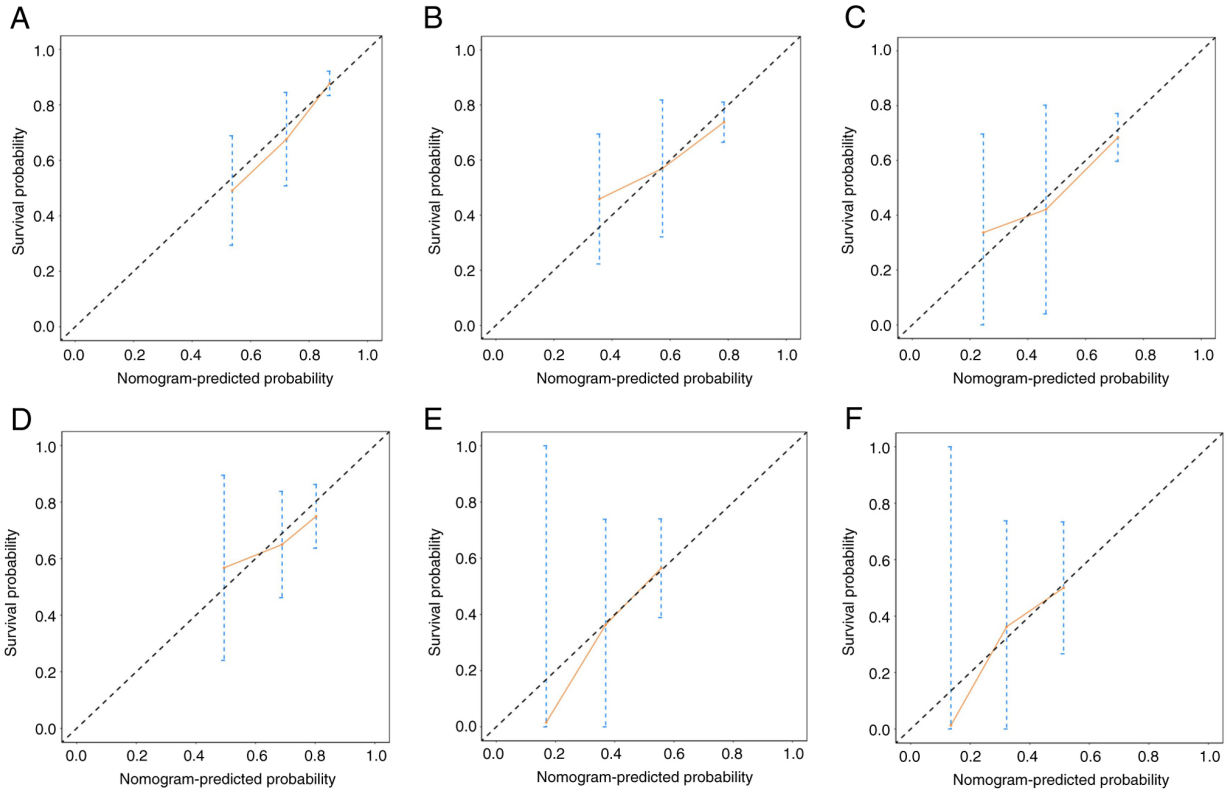

Figure 4. Calibration curves of the nomogram in the training and validation cohort. iPFS of the training cohort at (A) 9, (B) 12 and (C) 18 months. iPFS of the validation cohort at (D) 9, (E) 12 and (F) 18 months. iPFS, intracranial progression-free survival.

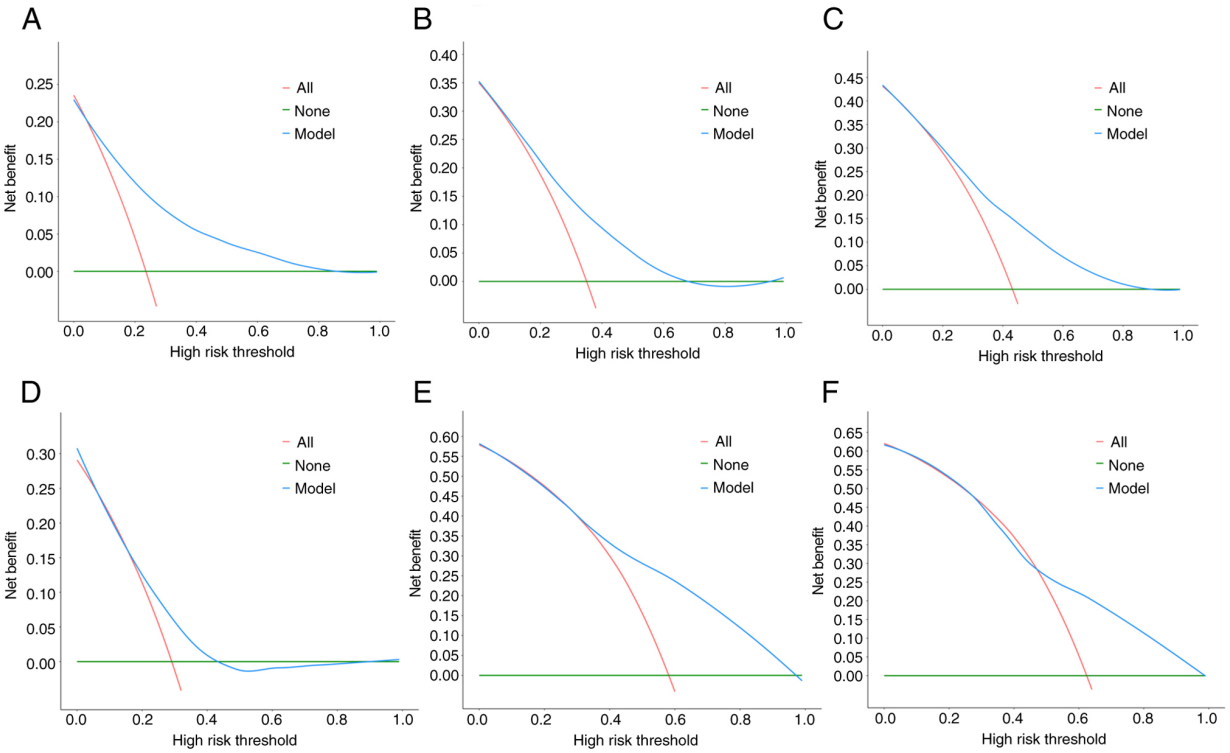

Figure 5. Decision curves of the nomogram in the training cohort and validation cohort. iPFS of the training cohort at (A) 9, (B) 12 and (C) 18 months. iPFS of the validation cohort at (D) 9, (E) 12 and (F) 18 months. iPFS, intracranial progression-free survival.

was associated with the risk of BM in LD-SCLC. A retrospective study by Reddy *et al* (36) also identified male sex as an independent risk factor for the development of synchronous BM in patients with SCLC. Additionally, male sex was included as a

Table IV. Multivariate analysis of factors influencing overall survival of all patients.

	Univariate analysis		Multivariate analysis	
Variable	χ^2	P-value	HR (95% CI)	P-value
Sex				
Female				
Male	0.28	0.600		
Age, years				
>65			1.00 (reference)	
≤65	4.84	0.028	0.65 (0.41-1.03)	0.066
Smoking status				
No				
Yes	1.74	0.187		
T classification				
T1, T2				
T3, T4	2.67	0.102		
N classification				
N1, N2			1.00 (reference)	
N3	8.12	0.004	2.08 (1.27-3.40)	0.003
Oligometastasis				
No			1.00 (reference)	
Yes	30.03	<0.001	0.38 (0.18-0.81)	0.012
CEA (ng/ml)				
<5				
≥5	0.50	0.482		
NSE (ng/ml)				
<17.5			1.00 (reference)	
≥17.5	6.06	0.014	1.95 (0.86-4.42)	0.108
Pro-GRP (pg/ml)				
<50				
≥50	0.84	0.360		
D-dimer (mg/l)				
<0.5			1.00 (reference)	
≥0.5	6.77	0.009	1.44 (0.90-2.29)	0.127
LDH (U/l)				
<245			1.00 (reference)	
≥245	5.82	0.016	1.00 (0.62-1.60)	0.999
NLR				
<1.37				
≥1.37	1.42	0.234		
PLR				
<121				
≥121	0.00	0.992		
Liver metastasis				
No			1.00 (reference)	
Yes	8.44	0.004	1.02 (0.56-1.85)	0.949
Bone metastasis				
No			1.00 (reference)	
Yes	9.50	0.002	1.12 (0.62-2.03)	0.711
Adrenal metastasis				
No			1.00 (reference)	
Yes	5.63	0.018	1.80 (1.08-3.02)	0.025

Table IV. Continued.

	Univariate analysis		Multivariate analysis	
Variable	χ^2	P-value	HR (95% CI)	P-value
Thoracic radiotherapy				
No			1.00 (reference)	
Yes	3.92	0.048	0.62 (0.38-1.00)	0.051
Treatment mode				
ChT-alone				
IO + ChT	0.06	0.808		
Chemotherapy cycles				
>4				
≤4	0.15	0.701		
Immunotherapy cycles				
<6				
≥6	1.08	0.299		

HR, hazard ratio; NSE, neuron-specific enolase; pro-GRP, pro-gastrin-releasing peptide; LDH, lactate dehydrogenase; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; ChT, chemotherapy; IO, immunotherapy.

risk factor in the nomogram for BM risk in patients with SCLC, developed by Li *et al* (18). This aligns with the present findings; however, the reason for this phenomenon remains elusive. Due to limitations of retrospective studies, such as small enrollment and single-center studies, a higher proportion of male patients may reduce the credibility of the conclusions. However, in the real world and clinical trials, the percentage of male patients is also high. In a retrospective study in Korea, the proportion of male patients among 9,994 patients with ES-SCLC was 86.4% (37). In the Chinese CAPSTONE-1 trial, the proportion of male patients was 80% (38). This is consistent with the present results. Therefore, it is necessary to expand the sample to validate the conclusions.

Certain risk factors for BM in patients with SCLC were not observed in the present study. A retrospective study demonstrated that weight loss is an independent risk factor for the development of BM (16); however, this factor was excluded due to the retrospective nature of the present study due to challenges in standardizing the timing of weight recordings and difficulty in determining precise weights. In patients with LD-SCLC, hematology-associated markers such as tumor markers, LDH and NLR are associated with the occurrence of BM (24,25,27); however, this association was not demonstrated in the present study. This may be attributed to the participants in the present study being patients with ES-SCLC who had developed extensive metastases (65% were oligometastatic) and having a high systemic tumor burden. Therefore, LDH and associated tumor markers were not risk factors for BM in patients with ES-SCLC.

Since the publication of phase III randomized controlled trials, such as IMpower133 and CASPIAN (39,40), immune checkpoint inhibitors combined with platinum-containing chemotherapy have been established as the standard first-line treatment for ES-SCLC, enhancing OS in patients with ES-SCLC (39). However, previous studies have not demonstrated that combination immunotherapy extends iPFS (3), and this observation has been reported only in patients with non-SCLC (41). The findings of the present study align with the aforementioned results, indicating that combination immunotherapy did not significantly increase iPFS compared with chemotherapy alone.

In the survival analysis of high-risk factors associated with BM, adrenal metastasis at baseline and non-oligometastasis were unfavorable factors for survival. More aggressive application of PCI may be more favorable for the prognosis of the patient.

The present study had limitations. Firstly, it was a single-center retrospective study with a limited sample size and not a randomized controlled trial, which may limit the generalizability of the data. Additionally, the nomogram established in the present study could only be validated through randomized internal validation and not with external data. Therefore, further large-scale, multicenter, prospective studies are required to confirm the validity of the present findings.

In conclusion, non-oligometastasis, baseline adrenal metastasis and male sex were significant risk factors for BM in patients with ES-SCLC who responded to standard treatment. Furthermore, the developed nomogram offered a personalized risk assessment for BM in patients with ES-SCLC who were free of BM at baseline and responded to standard treatment, thereby assisting clinicians in making informed decisions regarding PCI.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HL, FC, YJ and HZ conceived and designed the study. QX, HL, SL, JN, XZ and ZS analyzed data. YT, SL, YJ, ZS, JZ and JN interpreted data. Acquisition of funding by YT and HZ. HL, HZ, YT, JZ and SL revised the manuscript critically for important intellectual content. YT, YJ and HZ supervised the study. HL and FC wrote the manuscript. HL and HZ confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The present study did not require ethics approval as it was waived by the Ethical Review Committee of the Affiliated Cancer Hospital of Shandong First Medical University. Due to the retrospective nature of the present study, the requirement for informed consent to participate was waived.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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