

Analysis of prognostic factors influencing brain metastasis in EGFR-mutant lung adenocarcinoma and comparison of prognostic assessment models

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Abstract. Patients with EGFR-mutant lung adenocarcinoma are at risk for brain metastasis (BM), which worsens prognosis. The present study aimed to investigate the prognostic factors affecting the prognosis of patients with locally advanced lung adenocarcinoma with epidermal growth factor receptor (EGFR) mutations following the development of brain metastases (BM) after radical radiotherapy and chemotherapy. The present study also aimed to evaluate four scoring systems: Recursive partitioning analysis (RPA), diagnosis-specific graded prognostic assessment (DS-GPA), basic score for BM (BSBM) and lung cancer-associated molecular (Lung-mol) GPA, for their predictive roles. A retrospective analysis was performed on the clinical data of 260 patients with lung adenocarcinoma with BM and EGFR mutation admitted to the Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine-Hebei Province (Cangzhou, China), from January 2016 to December 2022. The Cox proportional hazard model identified statistically significant prognostic factors. The log-rank test assessed the predictive effect of the four prognostic scoring systems on survival. Receiver operating characteristic (ROC) curves

were constructed and the area under the curve (AUC) of each system was calculated. Among the 260 patients analyzed, the median survival time was 28.7 months. Independent prognostic risk factors included a Karnofsky Performance Status (KPS) score of <80 [hazard ratio (HR)=2.706; 95% CI, 1.825-4.012; P<0.001], extracranial metastases (HR=2.296; 95% CI, 1.543-3.418; P<0.001) and treatment with first- or second-generation EGFR-tyrosine kinase inhibitors (TKIs; HR=7.155; 95% CI, 4.950-10.344; P<0.001). All four scoring systems (RPA, DS-GPA, BSBM and Lung-mol GPA) were significant predictors of 1-, 2- and 3-year survival (P<0.001). ROC curve analysis revealed that the Lung-mol GPA system had the highest AUC, significantly outperforming the other three systems (P<0.05). In conclusion, KPS score, the presence of combined extracranial metastases and the generation of EGFR-TKIs administered are key independent prognostic factors in patients with BM secondary to radical radiotherapy for EGFR-mutated lung adenocarcinoma. Among the RPA, BSBM, DS-GPA and Lung-mol GPA models, the Lung-mol GPA model demonstrated notably increased predictive accuracy in patient prognosis.

Introduction

Lung cancer is the leading cause of cancer-associated morbidity and mortality globally, with ~2.1 million new cases and 800,000 mortalities annually (1). Non-small cell lung cancer (NSCLC) accounts for ~85% of all lung cancer cases (2). Despite recent advancements in early detection techniques (low-dose computed tomography screening) and treatment options, survival rates have only slightly improved and the overall prognosis for patients with metastatic lung cancer remains poor (3-6). Brain metastases (BM) are a common metastatic pattern in lung cancer; at initial diagnosis, 10% of patients with lung cancer present with BM and during the course of the disease, 40-60% of patients with lung adenocarcinoma will develop BM (7). BM poses a notable clinical challenge, as it often leads to rapid neurological deterioration and markedly impacts the quality of life of patients (8). The presence of BM in patients with lung adenocarcinoma markedly complicates treatment decisions and therapeutic outcomes.

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Abbreviations: AUC, area under the curve; BM, brain metastases; BSBM, basic score for BM; DS-GPA, diagnosis-specific graded prognostic assessment; EGFR, epidermal growth factor receptor; TKIs, tyrosine kinase inhibitors; KPS, Karnofsky Performance Status; Lung-mol GPA, lung cancer-associated molecular graded prognostic assessment; NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; RPA, recursive partitioning analysis; ROC, receiver operating characteristic

Key words: cancer, lung adenocarcinoma, brain metastasis, prognostic scoring system, EGFR-TKIs

Patients with epidermal growth factor receptor (EGFR) mutations are at a cumulative risk of BM as high as 70% (9). This risk is particularly pronounced in EGFR-mutant lung adenocarcinoma, where resistance to first- and second-generation EGFR-tyrosine kinase inhibitors (TKIs; such as gefitinib/erlotinib and afatinib/dacomitinib, respectively) often results in disease progression and the development of BM. The molecular mechanisms underlying this progression are not fully understood; however, they are considered to involve a combination of tumor heterogeneity, blood-brain barrier penetration and changes in treatment response (10-12).

BM markedly impacts both quality of life and prognosis. Common symptoms, including headaches, seizures, cognitive dysfunction and motor deficits, complicate symptom management and survival prediction (13,14). The present study aimed to stratify the prognosis of patients with lung cancer with BM and compare the predictive accuracy of various prognostic models in a specific cohort: Patients with locally advanced lung adenocarcinoma, EGFR mutations and BM development following radical radiotherapy. In this cohort, accurate prediction of patient outcomes is key to tailoring treatment plans and improving survival rates. The use of prognostic models incorporating clinical, molecular and radiological factors can potentially guide clinical decisions and enhance patient care in the future.

Patients and methods

Patients. A retrospective analysis was performed on patients with lung adenocarcinoma with BM admitted to Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine-Hebei Province (Cangzhou, China), between January 2016 and December 2022. The inclusion criteria were as follows: i) Pathologically confirmed lung adenocarcinoma; ii) locally advanced stage (inoperable or surgery-intolerant at diagnosis, re-staged according to the 8th edition of the AJCC TNM, IIIA, IIIB, IIIC) with initial treatment consisting of radical radiotherapy (either synchronous or sequential) (15); iii) BM diagnosed via magnetic resonance imaging (MRI) of the brain, with the brain as the first site of distant metastasis recurrence after completion of radical radiotherapy. At initial diagnosis (prior to radical treatment), no evidence of distant metastasis (M0 stage) was present in any patient (16); iv) exon 19 deletion (19DEL) or exon 21 point mutation (L858R mutation) identified by genetic testing; and v) complete medical records. The exclusion criteria were as follows: i) Patients lost to follow-up; and ii) Patients with other primary malignant tumors. A total of 340 patients with lung adenocarcinoma and BM were initially screened for eligibility during the present study period. The patient selection process is detailed in Fig. S1. Briefly, 80 patients were excluded for the following reasons: i) 32 had other EGFR mutation types or were EGFR wild-type; ii) 25 had other primary malignant tumors; iii) 15 had incomplete medical records or were lost to follow-up; and iv) 8 did not receive radical radiotherapy as initial treatment. In total, 260 patients met all inclusion criteria and constituted the present study cohort for analysis.

Definition of key variables and molecular testing

Synchronous and metachronous BM. BM detected at the initial diagnosis of lung adenocarcinoma or within 6 months thereafter were classified as synchronous. BM developing >6 months after the initial diagnosis were classified as metachronous (17).

Adjudication of primary tumor control. ‘Primary tumor control’ was defined as the absence of progression (for example, complete response, partial response or stable disease) at the primary pulmonary site, assessed via contrast-enhanced CT of the chest. This assessment was performed at the time of BM diagnosis, referencing baseline imaging obtained prior to the initiation of radical radiotherapy (18).

Determination of EGFR mutation status. EGFR mutation status (19DEL and exon 21 L858R point mutation) was determined from tumor tissue samples obtained via biopsy at initial diagnosis. Mutations were identified using a commercially available and clinically validated Amplification Refractory Mutation System PCR kit (AmoyDx® EGFR Mutation Detection Kit). All genetic testing was performed in the central laboratory of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine-Hebei Province (Cangzhou, China) prior to the administration of any EGFR-TKI therapy.

Timing of EGFR-TKI therapy associated with BM. The majority of patients (95%) initiated EGFR-TKI therapy after BM diagnosis. The timing of TKI initiation (before or after BM diagnosis) was recorded and included as a binary covariate in the initial univariate survival analysis. As it was not significantly associated with overall survival (OS; $P > 0.1$), it was not included in the final multivariable model.

Classification of EGFR-TKIs. In the present study, EGFR-TKIs were categorized by generation. First-generation TKIs included gefitinib and erlotinib, second-generation TKIs included afatinib and third-generation TKIs referred to osimertinib. The term ‘first- or second-generation TKIs’ refers to the group of patients who did not receive third-generation TKI as part of their initial treatment regimen. The timing of TKI therapy associated with cranial radiotherapy was categorized. Concurrent therapy was defined as TKI initiation within 30 days before or after the start of radiotherapy.

Brain metastasis scoring system model. The recursive partitioning analysis (RPA) scoring system (19) classifies patients into three groups: i) Grade I for patients ≤ 65 years old, with a Karnofsky Performance Status (KPS) score ≥ 70 , controlled primary tumor and no extracranial metastases (20); ii) grade III for patients with a KPS score < 70 ; and iii) grade II for all others. The basic score for BM (BSBM) system (21) utilizes three prognostic factors: KPS score (50-70 and 70-100), primary tumor control and presence or absence of extracranial metastases, assigning values of 1 and 0, respectively. The total score ranges from 0 (worst) to 3 (best). The Diagnosis-Specific Graded Prognostic Assessment (DS-GPA) system (22) incorporates four factors: Age (> 60 , 50-60 and < 60), KPS score (< 70 , 70-80 and > 80), extracranial metastases (present and absent) and number of BM (> 3 , 2-3 and 1), with values assigned as 0, 0.5 and 1, respectively, yielding a total score between 0 and 4. The lung cancer-associated molecular (Lung-mol) GPA system (23) includes five factors: i) Age (≥ 70 and < 70 years); ii) KPS score (< 70 , 80 and 90-100);

iii) extracranial metastases (present and absent); iv) number of BM (>4 and 1-4); and v) genetic status (EGFR/anaplastic lymphoma kinase (ALK)⁻, EGFR/ALK⁺). These factors are assigned values of 0, 0.5 and 1, respectively, with total scores ranging from 0 to 4. All 260 patients were scored using the RPA, BSBM, DS-GPA and Lung-mol GPA systems, followed by survival comparisons to evaluate the predictive accuracy of each model.

Treatment after brain metastasis. Upon diagnosis of BM, treatment strategies were individualized based on a multidisciplinary team discussion. The primary approach involved systemic therapy with EGFR-TKIs and local intracranial treatment. Local treatment for BM included stereotactic radiosurgery (SRS) for patients with limited (1-4) metastases or whole-brain radiotherapy (WBRT) for those with more extensive or diffuse metastases. Supportive care, including corticosteroids for peritumoral edema, was administered as clinically indicated. The use of corticosteroids (primarily dexamethasone) adhered to a standardized institutional protocol to manage symptomatic BM or notable peritumoral edema, with a rapid tapering strategy following clinical and radiological improvement (24). The KPS score used in all analyses was assessed after the initial stabilization of cerebral edema and neurological symptoms, typically at the first planned follow-up visit (4-6 weeks after BM diagnosis), to best reflect the baseline functional status of the patient independent of acute interventions. Following progression on first-line EGFR-TKIs, subsequent treatment lines were administered at the discretion of the physician, which could include switching to a third-generation EGFR-TKI (if not initially used) based on repeat genetic testing, combination chemotherapy or continued local therapy for new lesions. Data on the type of intracranial radiotherapy (SRS vs. WBRT) and subsequent systemic therapy lines were collected and analyzed. In the present study cohort, the majority of patients (177/260, 68.1%) received concurrent EGFR-TKI therapy and cranial radiotherapy (Table I).

Follow-up and evaluation. Patients were followed up via telephone or outpatient review from August 1, 2023. Follow-up occurred every 3 months for the first 2 years and every 6 months thereafter. At each visit, patients underwent neurological assessments, brain MRI and routine blood tests to monitor disease progression and treatment-related side effects (such as rash, diarrhea, fatigue and radionecrosis). OS was recorded from the diagnosis of BM to mortality or the follow-up cut-off. Progression-free survival (PFS) was also assessed, with a focus on changes in BM and extracranial progression.

Statistical analysis. Statistical analysis was performed using SPSS (version 27.0; IBM Corp.) and GraphPad Prism software (version 8.0; Dotmatics), with AUC comparisons for each scoring system performed using MedCalc software (version 23.0; MedCalc Software Ltd.). The present study endpoint was OS, defined as the time from BM diagnosis to mortality from any cause. The median follow-up time was calculated using the reverse Kaplan-Meier method (25). Survival analysis was performed using the Kaplan-Meier method and log-rank test. Categorical data are presented as frequencies (percentages),

Table I. Baseline characteristics of the present study cohort (n=260).

Characteristic	Number of patients (%)
Age, years	
<60	152 (58.5)
≥60	108 (41.5)
Sex	
Male	122 (46.9)
Female	138 (53.1)
KPS	
<80	98 (37.7)
≥80	162 (62.3)
Smoking history	
No	140 (53.8)
Yes	120 (46.2)
EGFR mutation type	
Exon 19 deletion	139 (53.5)
L858R	121 (46.5)
EGFR-TKIs	
Generation I/II	136 (52.3)
Generation III	124 (47.7)
BM, n	
1-3	188 (72.3)
>3	72 (27.7)
Extracerebral metastasis	
No	162 (62.3)
Yes	98 (37.7)
Primary tumor control	
No	172 (66.2)
Yes	88 (33.8)
Cranial RT	
No	41 (15.8)
Yes	219 (84.2)

RT, radiotherapy; BM, brain metastases; TKI, tyrosine kinase inhibitor; EGFR, epidermal growth factor receptor; KPS, Karnofsky Performance Status.

and continuous data were presented as mean ± standard deviation or median (interquartile range). Variables for the multivariable Cox regression model were selected based on two criteria: i) Established clinical relevance as prognostic factors in lung cancer with BM, and ii) a significance level of P<0.1 in the univariate analysis. This approach aimed to minimize the risk of overfitting while reducing the omission of potential clinical confounders. The candidate variables meeting these criteria were age, KPS score, EGFR-TKI generation, presence of extracranial metastases and primary tumor control.

The 'Enter' method was used, wherein all selected variables were simultaneously entered into the model to avoid the instability associated with stepwise selection. Multicollinearity

among the included variables was assessed using the variance inflation factor (VIF), with all VIF values being <2.0 , indicating no significant collinearity. The proportional hazards (PH) assumption for all variables in the final model was analyzed using Schoenfeld residuals (global test $P=0.124$). Furthermore, the scaled Schoenfeld residuals for each variable were visually inspected and indicated no clear pattern over time, confirming that the PH assumption was not violated. Therefore, no corrective measures, such as stratification or time-dependent covariates, were necessary.

Due to the retrospective nature of the present study, a pre-hoc sample size calculation was not performed and the cohort included all consecutive eligible patients during the present study period. However, a post hoc power analysis was conducted using G*Power software (version 3.1.9.7; Heinrich Heine University) for the primary multivariable Cox model. With a sample size of 260, α level of 0.05 and the observed hazard ratio (HR) for EGFR-TKI generation (HR=7.155), the achieved statistical power was $>99\%$, indicating sufficient power to detect this clinically significant effect. The Cox proportional hazards regression model was used for multifactorial analysis to identify statistically significant prognostic factors. The AUC for each scoring system was derived from receiver operating characteristic (ROC) curves. The predictive capabilities of the four scoring systems for survival were compared at 1, 2 and 3 years in patients with BM. Statistical significance of differences in the AUC between the Lung-mol GPA and other models was analyzed using the DeLong test. The calibration of the prognostic models was assessed with calibration plots and quantitatively using the Hosmer-Lemeshow goodness-of-fit test (26). To quantify the incremental predictive benefit of the Lung-mol GPA over other models, the present study calculated the Continuous Net Reclassification Improvement (NRI) (27). Between-group comparisons of categorical baseline characteristics in Table SI were performed using χ^2 test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Clinical characterization. The present study included 260 patients, with 108 aged ≥ 60 years and 152 aged <60 years. Of these, 122 were men and 138 were women. The basic characteristics of the 260 patients are detailed in Table I.

Baseline characteristics stratified by first-line TKI generation. To assess the comparability of key patient groups, baseline characteristics were stratified according to the generation of the first-line EGFR-TKI administered. As detailed in Table SI, the 136 patients who received first- or second-generation TKIs and the 124 patients who received third-generation TKIs were well balanced across all recorded prognostic factors, including age, sex, KPS score, smoking history, EGFR mutation type, number of BM, presence of extracranial metastases, primary tumor control status and receipt of cranial radiotherapy (all $P>0.05$). This balance strengthens the validity of comparing outcomes between these treatment strategies.

Analysis of factors influencing prognosis. As of the follow-up cut-off date, the median follow-up time for the entire cohort, calculated using the reverse Kaplan-Meier method, was

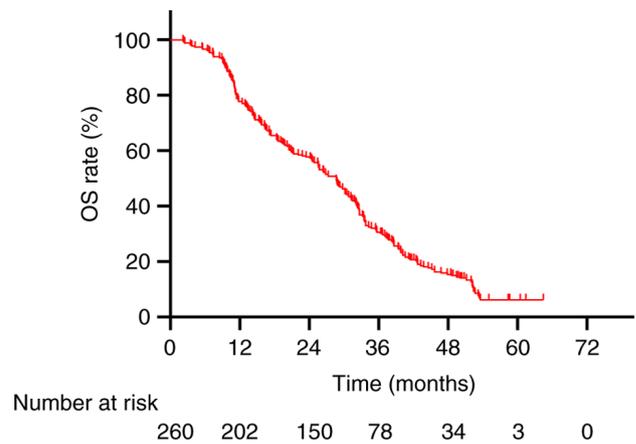


Figure 1. Survival curves of 260 patients with brain metastases from epidermal growth factor receptor-mutated lung adenocarcinoma. OS, overall survival.

58.0 months (95% CI, 54.2-61.8). The median OS for the 260 patients was 28.7 months (95% CI, 26.0-31.4). The 1-, 2- and 3-year OS rates were 77.7, 57.7 and 30.0%, respectively (Fig. 1). Univariate analysis demonstrated that age, KPS score, type of EGFR-TKIs used, presence of extracranial metastasis and primary tumor control were significantly associated with patient prognosis ($P<0.05$; Table II). The multivariate Cox analysis identified a KPS score <80 , treatment with first- or second-generation EGFR-TKIs and the presence of extracranial metastases as independent prognostic risk factors for patients with BM secondary to radical radiotherapy for EGFR-mutated lung adenocarcinoma (Table II).

Sensitivity and subgroup analyses for post-BM treatments. Acknowledging that subsequent therapies may influence survival analysis, additional statistical evaluations were performed. First, a sensitivity analysis was performed by incorporating 'Radiotherapy_type' (SRS vs. WBRT) as a covariate into the primary multivariable Cox model for the entire cohort. The results confirmed that the three key independent prognostic factors: KPS <80 (HR, 2.706; 95% CI, 1.825-4.012; $P<0.001$), presence of extracranial metastasis (HR, 2.296; 95% CI, 1.543-3.418; $P<0.001$) and use of first-/second-generation EGFR-TKIs (HR, 7.155; 95% CI, 4.950-10.344; $P<0.001$) remained highly significant, with minimal change in their HRs (Table II). Second, to isolate the prognostic effect of clinical factors from the influence of first-line third-generation TKI use, a subgroup analysis was performed. A separate multivariable Cox regression was performed exclusively for the 136 patients treated with first-/second-generation TKIs. As shown in Table III, within this subgroup, KPS <80 (HR, 5.415; 95% CI, 1.269-9.640; $P<0.001$) and presence of extracranial metastasis (HR, 3.484; 95% CI, 0.813-5.747; $P<0.001$) remained strong independent predictors of worse survival, whereas the number of BM and age were not retained in the final model. Recognizing that subsequent treatment lines could confound the survival analysis, the patterns of subsequent systemic therapy between the first-/second-generation and third-generation TKI groups were compared. Patients in the first-/second-generation TKI group received a greater

Table II. Univariate and multivariate Cox regression analysis for overall survival.

Characteristic ^a	Number of patients (%)	Univariate analysis			Multifactorial Cox analysis		
		HR	95% CI	P-value	HR	95% CI	P-value
Age, years							
<60	152 (58.5)	1.000	-	-	1	-	-
≥60	108 (41.5)	1.614	1.238-2.104	<0.001 ^b	1.154	0.854-1.557	0.351
Sex							
Male	122 (46.9)	1	-	-	-	-	-
Female	138 (53.1)	1.002	0.773-1.299	0.986	-	-	-
KPS							
≥80	162 (62.3)	1	-	-	1	-	-
<80	98 (37.7)	6.845	4.967-9.434	<0.001 ^b	2.706	1.825-4.012	<0.001 ^b
Smoking history							
No	140 (53.8)	1	-	-	-	-	-
Yes	120 (46.2)	1.11	0.857-1.439	0.429	-	-	-
EGFR mutation type							
Exon 19 deletion	139 (53.5)	1	-	-	-	-	-
L858R	121 (46.5)	1.129	0.871-1.463	0.364	-	-	-
EGFR-TKIs							
Generation III	124 (47.7)	1	-	-	1	-	-
Generation I/II	136 (52.3)	10.277	7.407-14.258	<0.001 ^b	7.155	4.950-10.344	<0.001 ^b
BM, n							
1-3	188 (72.3)	1	-	-	-	-	-
>3	72 (27.7)	1.283	0.950-1.734	0.104	-	-	-
Extracerebral metastasis							
No	162 (62.3)	1	-	-	1	-	-
Yes	98 (37.7)	6.436	4.644-8.920	<0.001 ^b	2.296	1.543-3.418	<0.001 ^b
Primary tumor control							
Yes	88 (33.8)	1	-	-	1	-	-
No	172 (66.2)	1.45	1.093-1.923	0.01 ^b	1.021	0.757-1.378	0.889
Cranial RT							
Yes	219 (84.2)	1	-	-	-	-	-
No	41 (15.8)	1.068	0.753-1.515	0.711	-	-	-
Radiotherapy type							
SRS	158 (60.8)	1	-	-	-	-	-
WBRT	61 (23.4)	1.228	0.865-1.908	0.137	-	-	-
Receipt of any subsequent systemic therapy							
Yes	201 (77.3)	1	-	-	-	-	-
No	59 (22.7)	1.196	0.769-2.014	0.283	-	-	-

^aFor all categorical variables, the group with the more favorable prognosis was set as the reference category (HR=1.0). An HR >1 indicates increased risk of mortality associated with the reference group. ^bP<0.05. HR, hazard ratio; KPS, Karnofsky Performance Status; SRS, stereotactic radiosurgery; RT, radiotherapy; WBRT, whole-brain RT; BM, brain metastases; EGFR, epidermal growth factor receptor.

median number of subsequent therapy lines (2 vs. 1) and were more likely to receive at least one subsequent line of treatment (85.3 vs. 68.5%; P<0.001), with the majority (71.3%) receiving a third-generation TKI upon progression (Supplementary Table SII). A sensitivity analysis adjusting for 'Receipt of any subsequent systemic therapy' in the multivariable Cox

model confirmed that the association between first-line TKI generation and OS remained robust.

Predictive role of brain metastasis scoring systems. Survival curves for the four scoring systems are presented in Figs. 2-5. The median survival times for patients with RPA grades I,

Table III. Multivariable Cox regression analysis of overall survival in the subgroup of patients receiving first- or second-generation EGFR-TKIs as first-line therapy (n=136).

Characteristic	Univariate analysis			Multifactorial Cox analysis		
	HR	95% CI	P-value	HR	95% CI	P-value
Age, years	-	-	-	-	-	-
<60	1.000	-	-	1	-	-
≥60	1.502	1.022-2.207	0.038 ^a	1.101	0.873-1.938	0.598
KPS	-	-	-	-	-	-
≥80	1	-	-	1	-	-
<80	7.298	2.195-14.455	<0.001 ^a	5.415	1.269-9.640	<0.001 ^a
Extracranial metastasis	-	-	-	-	-	-
No	1	-	-	1	-	-
Yes	6.351	2.229-13.539	<0.001 ^a	3.484	0.813-5.747	<0.001 ^a
Number of brain metastases	-	-	-	-	-	-
1-3	1	-	-	1	-	-
>3	1.521	1.021-2.266	0.039 ^a	1.132	0.869-2.042	0.485
Primary tumor control	-	-	-	-	-	-
Yes	1.000	-	-	1.000	-	-
No	1.802	0.542-2.886	0.006 ^a	1.324	0.427-2.368	0.157

^aP<0.05. HR, hazard ratio; TKI, tyrosine kinase inhibitor; KPS, Karnofsky Performance Status; EGFR, epidermal growth factor receptor. For all categorical variables, the group with the more favorable prognosis was set as the reference category (HR=1.0).

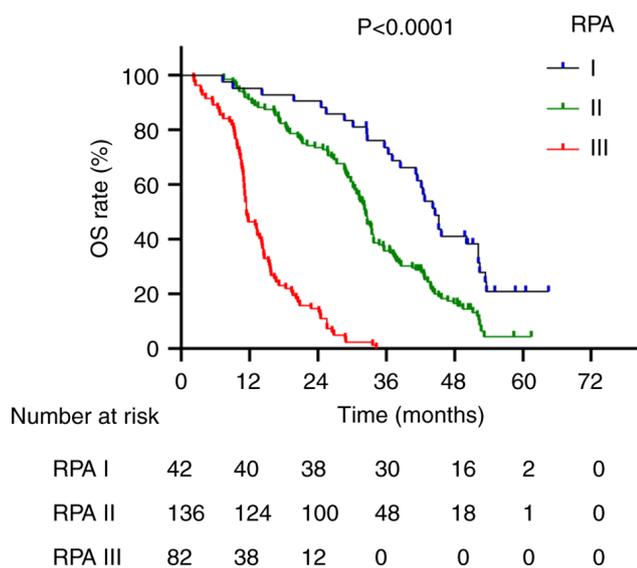


Figure 2. Survival curves for patients stratified by RPA scores (grade I, II and III). RPA, recursive partitioning analysis; OS, overall survival.

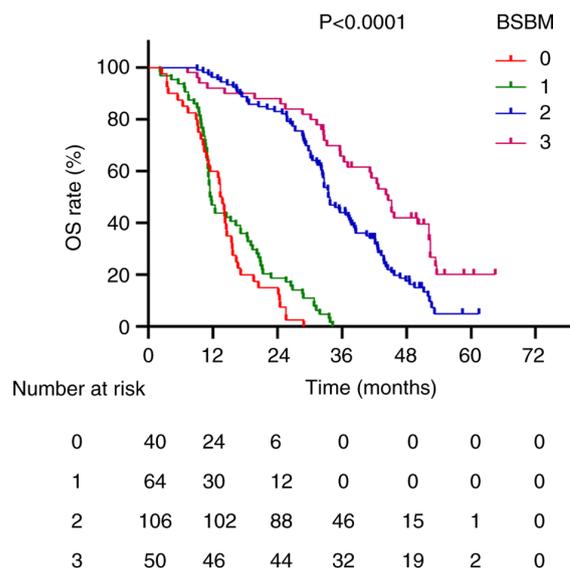


Figure 3. Survival curves for patients stratified by BSBM scores (0-3). BSBM, basic score for brain metastases; OS, overall survival.

II and III were 44.6, 32.4 and 11.5 months, respectively (P<0.0001; Fig. 2). For the BSBM scoring system, median survival times for scores of 0, 1, 2 and 3 were 13.6, 11.6, 33.5 and 44.6 months, respectively (P<0.0001; Fig. 3). Patients with DS-GPA scores of 0-1.0, 1.5-2.0, 2.5-3.0 and 3.5-4.0 had median survival times of 13.4, 20.5, 33.8 and 48.6 months, respectively (P<0.0001; Fig. 4). For the Lung-mol GPA system, median survival times for scores of 1.0-2.0, 2.5-3.0

and 3.5-4.0 were 11.5, 26.4 and 42.5 months, respectively (P<0.0001; Fig. 5).

Comparison of the predictive power of brain metastasis scoring systems. The ROC curves for the four scoring systems predicting 1-, 2- and 3-year survival demonstrated statistical significance (all P<0.001; Figs. 6-8). The area under the ROC curve (AUC) comparison revealed that the Lung-mol GPA

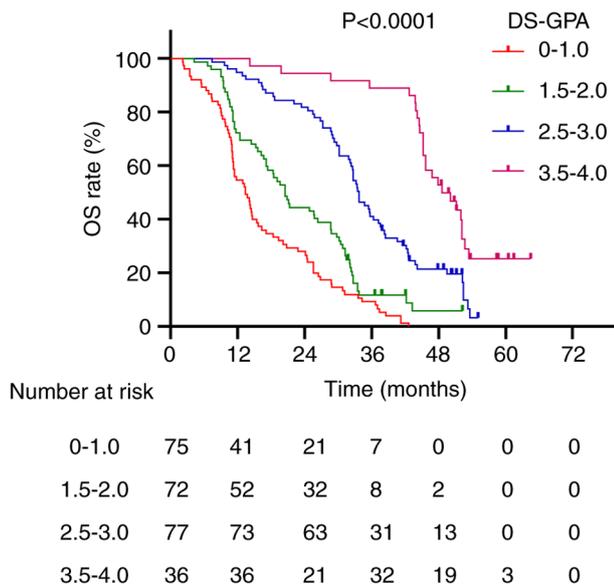


Figure 4. Survival curves for patients stratified by DS-GPA scores (0-4). DS-GPA, diagnosis-specific graded prognostic assessment; OS, overall survival.

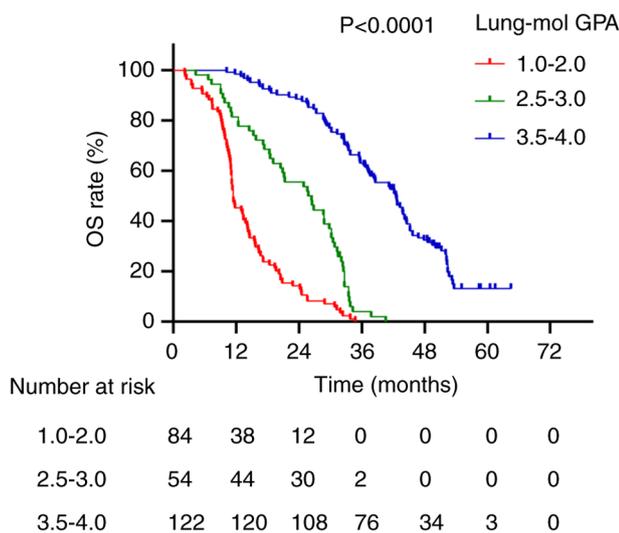


Figure 5. Survival curves for patients stratified by Lung-mol GPA scores (1.0-4.0). Lung-mol GPA, lung cancer-associated molecular graded prognostic assessment; OS, overall survival.

system exhibited the highest AUC values: 0.875 (95% CI, 0.828-0.913; $P < 0.001$), 0.876 (95% CI, 0.832-0.920; $P < 0.001$) and 0.891 (95% CI, 0.853-0.929; $P < 0.001$). These values were significantly higher compared with those of the other three scoring systems, with a statistically significant difference ($P < 0.05$; Table IV).

Comprehensive comparison of prognostic models. The comparison of AUC values for predicting 1-, 2- and 3-year survival, along with the results of the DeLong test, is shown in Table V. The Lung-mol GPA model consistently demonstrated significantly increased discriminatory ability compared with the other three models across all time points (all $P < 0.05$). The calibration plot for the Lung-mol GPA model at 2 years is

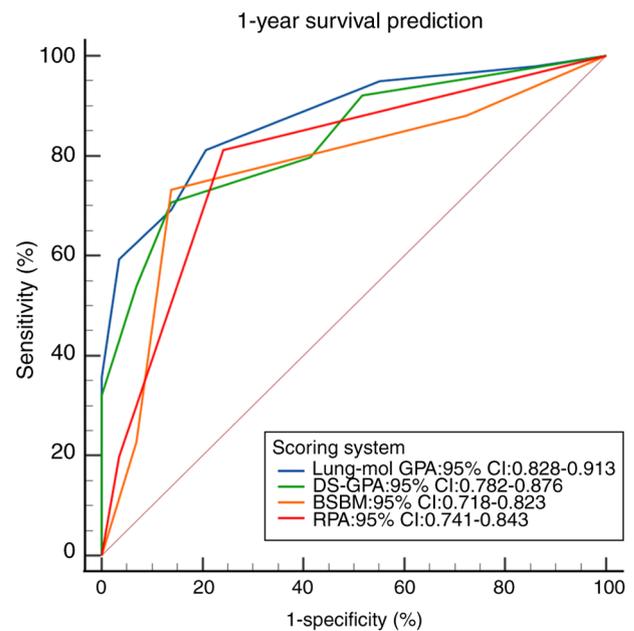


Figure 6. Receiver operating characteristic curves for predicting 1-year survival for the four prognostic scoring systems. Lung-mol GPA, lung cancer-associated molecular graded prognostic assessment; DS-GPA, diagnosis-specific graded prognostic assessment; BSBM, basic score for brain metastases; RPA, recursive partitioning analysis.

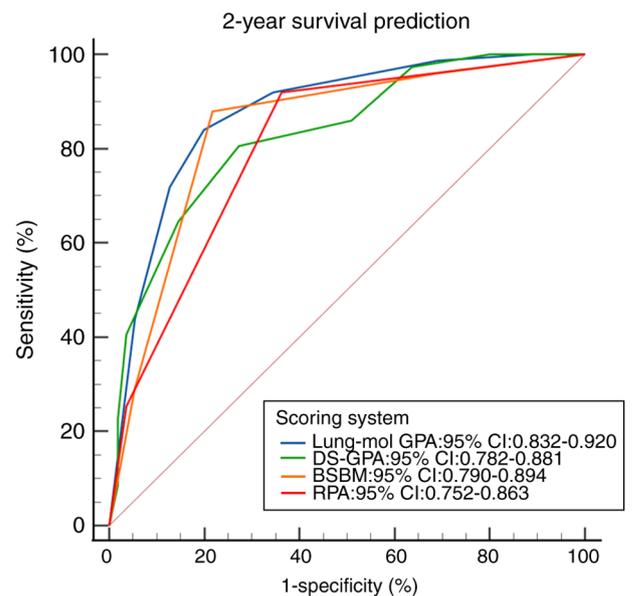


Figure 7. Receiver operating characteristic curves for predicting 2-year survival for the four prognostic scoring systems. Lung-mol GPA, lung cancer-associated molecular graded prognostic assessment; DS-GPA, diagnosis-specific graded prognostic assessment; BSBM, basic score for brain metastases; RPA, recursive partitioning analysis.

presented in Fig. 9. Visual inspection revealed strong agreement between predicted and observed outcomes, which was quantitatively supported by a non-significant Hosmer-Lemeshow test ($\chi^2 = 6.952$; $P = 0.443$; Table SIII), indicating no statistically significant deviation from perfect calibration. NRI analysis was performed to assess the improvement provided by the Lung-mol GPA. For 2-year survival prediction, the NRI for

Table IV. Prognostic performance of the scoring systems for 1-, 2- and 3-year OS.

Model	1-year OS			2-year OS			3-year OS		
	AUC	95% CI	P-value	AUC	95% CI	P-value	AUC	95% CI	P-value
Lung-mol GPA	0.875	0.828-0.913	<0.001 ^a	0.876	0.832-0.920	<0.001	0.891	0.853-0.929	<0.001 ^a
DS-GPA	0.833	0.782-0.876	<0.001 ^a	0.832	0.782-0.881	<0.001	0.841	0.788-0.893	<0.001 ^a
BSBM	0.773	0.718-0.823	<0.001 ^a	0.842	0.790-0.894	<0.001	0.824	0.776-0.873	<0.001 ^a
RPA	0.795	0.741-0.843	<0.001 ^a	0.808	0.752-0.863	<0.001	0.798	0.745-0.851	<0.001 ^a

^aP<0.05. AUC, area under the curve; OS, overall survival; Lung-mol GPA, lung cancer-associated molecular graded prognostic assessment; DS-GPA, diagnosis-specific GPA; BSBM, basic score for brain metastases; RPA, recursive partitioning analysis.

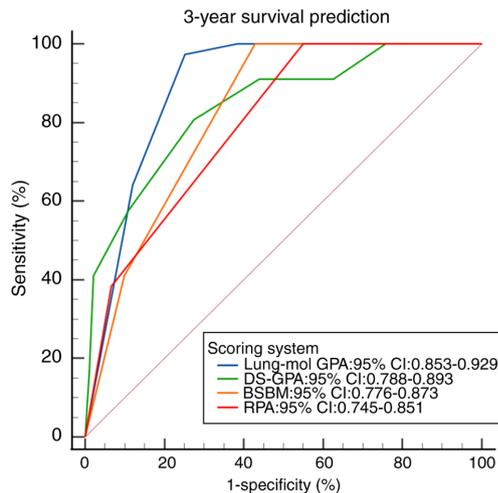


Figure 8. Receiver operating characteristic curves for predicting 3-year survival for the four prognostic scoring systems. Lung-mol GPA, lung cancer-associated molecular graded prognostic assessment; DS-GPA, diagnosis-specific graded prognostic assessment; BSBM, basic score for brain metastases; RPA, recursive partitioning analysis.

upgrading to the Lung-mol GPA model from the DS-GPA model was 0.325 (95% CI, 0.152-0.498; P<0.001; Table SIII), indicating a significant and clinically relevant improvement in the accurate reclassification of patient risk.

Discussion

The prognosis for patients with BM from lung cancer remains poor, despite advances in diagnostic and therapeutic techniques that have improved the detection of BM and extended survival (28,29). Previous studies investigating prognostic factors and validating scoring systems for NSCLC BM included a heterogeneous patient population (30-32), encompassing those who received multiple treatments, such as surgery, radiotherapy and chemotherapy, before the development of BM, as well as those diagnosed with BM at initial presentation who did not undergo treatment. The varied prognoses at different treatment stages and the inclusion of these diverse patient groups may have introduced notable biases into the study outcomes. To address this, the present study specifically focused on patients with inoperable, locally advanced lung adenocarcinoma secondary to BM following

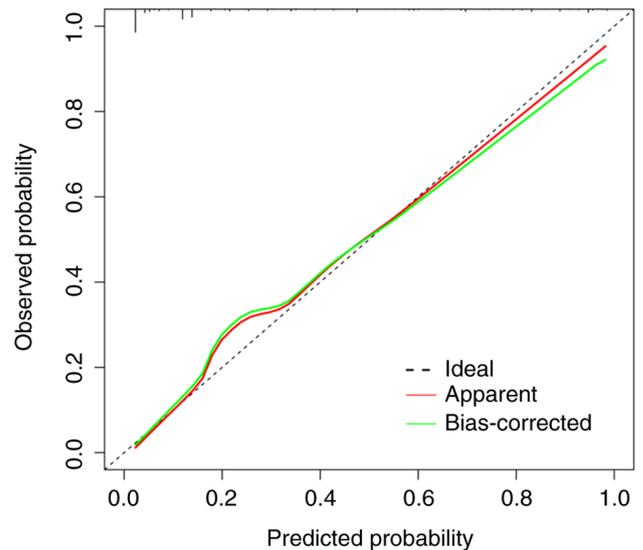


Figure 9. Calibration plot for the Lung-mol GPA model at 2 years. Lung-mol GPA, lung cancer-associated molecular graded prognostic assessment.

radical radiotherapy at initial diagnosis and EGFR mutation, thereby eliminating potential confounding factors.

The present study retrospectively analyzed the prognostic factors of patients with BM secondary to radical radiotherapy for EGFR-mutant lung adenocarcinoma and evaluated the effectiveness of the RPA, DS-GPA, BSBM and Lung-mol GPA scoring systems. The median OS for the 260 patients in the present study was 28.7 months. This contrasts with the findings of Li *et al* (33), who applied the same scoring systems to Chinese patients with BM from EGFR-mutated lung cancer, reporting a median survival time of 24.0 months. It is key to note that the associations identified in the present retrospective analysis, while robust within the present study cohort, should be interpreted as observational and do not imply causality. The findings require validation in prospective, multi-institutional settings to establish their generalizability. In the present study, prognostic factors influencing patient outcomes were analyzed and demonstrated that the KPS score, the presence of extracranial metastases and the type of EGFR-TKIs used were independently significant in the multivariable Cox analysis. The KPS score and the presence of extracranial metastases,

Table V. Pairwise comparison of the Lung-mol GPA model with other prognostic systems using the DeLong test.

Comparison	Time point, year	AUC (Lung-mol GPA)	AUC (other model)	AUC difference	95% CI for difference	Z statistic	P-value
Lung-mol GPA vs. DS-GPA	1	0.875	0.833	0.042	0.007-0.076	2.373	0.018 ^a
	2	0.876	0.832	0.044	0.009-0.079	2.461	0.014 ^a
	3	0.891	0.841	0.050	0.002-0.097	2.062	0.039 ^a
Lung-mol GPA vs. BSBM	1	0.875	0.773	0.102	0.059-0.143	4.766	<0.001 ^a
	2	0.876	0.842	0.034	0.000-0.068	1.970	0.049 ^a
	3	0.891	0.824	0.067	0.022-0.111	2.944	0.003 ^a
Lung-mol GPA vs. RPA	1	0.875	0.795	0.080	0.030-0.129	3.194	0.001 ^a
	2	0.876	0.808	0.068	0.027-0.109	3.281	0.001 ^a
	3	0.891	0.798	0.093	0.046-0.139	3.951	<0.001 ^a

^aP<0.05. AUC, area under the curve; Lung-mol GPA, lung cancer-associated molecular graded prognostic assessment; DS-GPA, diagnosis-specific GPA; BSBM, basic score for brain metastases; RPA, recursive partitioning analysis.

key indices in prior prognostic models (19,21-23), were also independently significant in the present study. Lower KPS scores were associated with worse patient outcomes. Zhang *et al* (34) indicated that patients with KPS scores of 80-100 had improved OS compared with those patients with KPS <80. To the best of our knowledge, all BM prediction models have associated KPS with survival duration (35,36). The present study findings aligned with the established role of KPS and further supported that a KPS <80 is an independent prognostic risk factor for patients with BM from EGFR-mutated lung adenocarcinoma.

Patients with concurrent extracranial metastases often have a larger tumor burden, higher malignancy and worse therapeutic outcomes, typically indicating a worse prognosis (37,38). Higaki *et al* (39) identified concurrent extracranial metastases as an independent risk factor affecting prognosis in a study of 294 patients with BM from EGFR-mutated NSCLC. This finding supported the inclusion of extracranial metastasis as a criterion in multiple prediction models (40). Furthermore, in the present study cohort, the use of third-generation EGFR-TKIs was associated with significantly improved patient survival and emerged as an independent prognostic factor in the present study model. In the FLAURA study, first-line treatment with osimertinib in patients with EGFR gene-sensitive mutation-positive NSCLC BM demonstrated a median PFS markedly increased to that of first-generation EGFR-TKIs. The domestic AENEAS and FURLONG studies also reported that third-generation EGFR-TKIs provided a notable PFS advantage over first/second-generation treatments (41-43).

Beyond its prognostic accuracy, the Lung-mol GPA model holds considerable potential in guiding clinical decision-making in the future. The present study findings suggested that risk stratification using this model could potentially inform the tailoring of therapeutic strategies. For example, patients classified into the most favorable prognostic group (Lung-mol GPA 3.5-4.0) have a median survival >40 months. In the Lung-mol GPA 3.5-4.0 group, there is strong justification to implement aggressive local control strategies, such as SRS, aimed at achieving long-term intracranial disease control while

minimizing neurocognitive toxicity. By contrast, for patients in the poorest prognostic group (Lung-mol GPA 1.0-2.0), with a median survival of <12 months, clinical focus may justifiably shift towards optimizing systemic therapy, ensuring optimal symptom control and discussing goals of care, as the potential benefits of intensive local interventions may be limited, to the best of our knowledge. Thus, the Lung-mol GPA scoring system can potentially serve as a valuable tool in adjusting treatment intensity according to individual patient prognosis in the future.

The validation of the RPA, DS-GPA, BSBM and Lung-mol GPA brain metastasis scoring systems was conducted in the present study. Survival curve analysis of these systems indicated that all four models effectively differentiate patient prognostic outcomes. However, no significant difference in prognosis was observed between patients scoring 0 and 1 in the BSBM system. This may be attributed to the relatively small number of cases with scores of 0 and 1, which were insufficient to demonstrate a significant difference. By contrast, significant prognostic differences were observed in the remaining scoring systems when compared within their respective groups. Further comparison of the prognostic predictive ability of the four scoring systems was performed using ROC curves, which revealed that the AUC of the Lung-mol GPA model was the highest, significantly surpassing the other three models. This suggested that the Lung-mol GPA model may be the most accurate prognostic prediction tool for this specific patient population in the present study. Li *et al* (33) also compared prognostic scoring systems in patients with EGFR-mutant lung cancer with BM and concluded that the Lung-mol GPA model was notably enhanced compared with the other three systems.

The present study had several limitations inherent to its retrospective and single-center design. First, the lack of systematically collected data on patient-reported outcomes, neurocognitive function and treatment-related adverse events (for example, as graded by the Common Terminology Criteria for Adverse Events) precludes a comprehensive risk-benefit analysis of the treatment strategies. Similarly, the absence

of a centralized neuroradiological review to determine intracranial objective response rates prevented an analysis of how the depth of intracranial response associates with survival. Second, although efforts were made to control for confounding factors using sensitivity and subgroup analyses, residual bias due to unmeasured or imperfectly adjusted factors cannot be excluded. Notably, while the present study accounted for the receipt of subsequent therapy, data on the precise timing, sequence and efficacy of subsequent treatment lines were not fully available. Furthermore, although corticosteroid use was similar between groups at baseline, unmeasured variations in the total duration and tapering schedules of corticosteroids may potentially influence both performance status and survival. Third, the generalizability of the present study findings may be limited by the exclusive focus on patients with lung adenocarcinoma with a specific disease trajectory (brain as the first site of metastasis after radical radiotherapy). Thus, the results may not be directly applicable to other NSCLC histological subtypes or patients with different patterns of disease recurrence. Lastly, the present study was designed to validate composite prognostic models rather than to assess the individual prognostic weight of each potential variable. Therefore, the present analysis was not powered to explore the specific roles of factors such as the number of BM or the EGFR mutation subtype (19DEL vs. L858R), which warrant investigation in future, larger-scale studies.

In summary, within a well-defined cohort of patients with EGFR-mutant lung adenocarcinoma and BM, the present retrospective analysis identified that a lower KPS score, the presence of extracranial metastases and the use of earlier-generation EGFR-TKIs were independently associated with worse OS. Among the prognostic models assessed, the Lung-mol GPA scoring system exhibited notably increased predictive accuracy for survival in this patient population. These findings suggested that the Lung-mol GPA model may potentially enhance prognostic stratification in this clinical context. However, due to the inherent limitations of the retrospective design, the present study results should be interpreted as hypothesis-generating regarding prognostic associations rather than as evidence of causality. The external validity of the present study conclusions requires validation in larger, prospective, multi-institutional studies incorporating patient-centered endpoints, such as quality of life and neurocognitive function, alongside survival in the future.

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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

JM completed the data analysis and paper writing. XY was responsible for the research design and guided the revision of the paper. JH contributed to the present study design and provided essential data analysis support. YZ and LG recruited the enrolled cases and contributed to the acquisition and interpretation of the data. JM and XY confirm the authenticity of all the raw data. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was performed in accordance with the Declaration of Helsinki and was approved by the local Ethics Committee of the Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine-Hebei Province (approval no. CZX2024180; Cangzhou, China). Each patient provided written informed consent for participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

References

1. Siegel RL, Miller KD, Fuchs HE and Jemal A: Cancer statistics, 2022. *CA Cancer J Clin* 72: 7-33, 2022.
2. Wang B, Guo H, Xu H, Yu H, Chen Y and Zhao G: Research progress and challenges in the treatment of central nervous system metastasis of non-small cell lung cancer. *Cells* 10: 2620, 2021.
3. Mulshine JL, Pyenson B, Heaton C, Aldige C, Avila RS, Blum T, Cham M, de Koning HJ, Fain SB, Field JK, *et al*: Paradigm shift in early detection: Lung cancer screening to comprehensive CT screening. *Eur J Cancer* 218: 115264, 2025.
4. Li Y, Yan B and He S: Advances and challenges in the treatment of lung cancer. *Biomed Pharmacother* 169: 115891, 2023.
5. Lahiri A, Maji A, Potdar PD, Singh N, Parikh P, Bisht B, Mukherjee A and Paul MK: Lung cancer immunotherapy: Progress, pitfalls, and promises. *Mol Cancer* 22: 40, 2023.
6. McLouth LE, Gabbard J, Levine BJ, Golden SL, Lycan TW, Petty WJ and Weaver KE: Prognostic awareness, palliative care use, and barriers to palliative care in patients undergoing immunotherapy or chemo-immunotherapy for metastatic lung cancer. *J Palliat Med* 26: 831-836, 2023.
7. Seute T, Leffers P, ten Velde GP and Twijnstra A: Neurologic disorders in 432 consecutive patients with small cell lung carcinoma. *Cancer* 100: 801-806, 2004.
8. Maldonado F, Gonzalez-Ling A, Oñate-Ocaña LF, Cabrera-Miranda LA, Zatarain-Barrón ZL, Turcott JG, Flores-Estrada D, Lozano-Ruiz F, Cacho-Díaz B and Arrieta O: Prophylactic cranial irradiation in patients with high-risk metastatic non-small cell lung cancer: Quality of life and neurocognitive analysis of a randomized phase II study. *Int J Radiat Oncol Biol Phys* 111: 81-92, 2021.
9. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, Uhlmann EJ, Wong ET, Dahlberg SE, Huberman MS and Costa DB: Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small-cell lung cancers. *Lung Cancer* 88: 108-111, 2015.
10. Wu F, Fan J, He Y, Xiong A, Yu J, Li Y, Zhang Y, Zhao W, Zhou F, Li W, *et al*: Single-cell profiling of tumor heterogeneity and the microenvironment in advanced non-small cell lung cancer. *Nat Commun* 12: 2540, 2021.

11. Lim ZF and Ma PC. Emerging insights of tumor heterogeneity and drug resistance mechanisms in lung cancer targeted therapy. *J Hematol Oncol* 12: 134, 2019.
12. Pan K, Concannon K, Li J, Zhang J, Heymach JV and Le X: Emerging therapeutics and evolving assessment criteria for intracranial metastases in patients with oncogene-driven non-small-cell lung cancer. *Nat Rev Clin Oncol* 20: 716-732, 2023.
13. Pike LRG, Miao E, Boe LA, Patil T, Imber BS, Myall NJ, Pollom EL, Hui C, Qu V, Langston J, *et al*: Tyrosine kinase inhibitors with and without up-front stereotactic radiosurgery for brain metastases from EGFR and ALK oncogene-driven non-small cell lung cancer (TURBO-NSCLC). *J Clin Oncol* 42: 3606-3617, 2024.
14. Jünger ST, Schödel P, Ruess D, Ruge M, Brand JS, Wittersheim M, Eich ML, Schmidt NO, Goldbrunner R, Grau S and Proescholdt M: Timing of development of symptomatic brain metastases from non-small cell lung cancer: Impact on symptoms, treatment, and survival in the era of molecular treatments. *Cancers (Basel)* 12: 3618, 2020.
15. Lancia A, Merizzoli E and Filippi AR: The 8th UICC/AJCC TNM edition for non-small cell lung cancer staging: Getting off to a flying start? *Ann Transl Med* 7 (Suppl 6): S205, 2019.
16. Moon SW, Choi SY and Moon MH: Effect of invasive mucinous adenocarcinoma on lung cancer-specific survival after surgical resection: A population-based study. *J Thorac Dis* 10: 3595-3608, 2018.
17. Li J, Zhang X, Wang Y, Jin Y, Song Y and Wang T: Clinicopathological characteristics and prognosis of synchronous brain metastases from non-small cell lung cancer compared with metachronous brain metastases. *Front Oncol* 14: 1400792, 2024.
18. Williams TM, Miller E, Welliver M, Brownstein J, Otterson G, Owen D, Haglund K, Shields P, Bertino E, Presley C, *et al*: A phase 2 trial of primary tumor stereotactic body radiation therapy boost before concurrent chemoradiation for locally advanced non-small cell lung cancer. *Int J Radiat Oncol Biol Phys* 120: 681-694, 2024.
19. Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG and Byhardt R: Recursive partitioning analysis (RPA) of prognostic factors in three radiation therapy oncology group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 37: 745-751, 1997.
20. Frappaz D, Bonneville-Levard A, Ricard D, Carrie S, Schiffler C, Xuan KH and Weller M: Assessment of Karnofsky (KPS) and WHO (WHO-PS) performance scores in brain tumour patients: The role of clinician bias. *Support Care Cancer* 29: 1883-1891, 2021.
21. Lorenzoni J, Devriendt D, Massager N, David P, Ruíz S, Vanderlinden B, Van Houtte P, Brotchi J and Levivier M: Radiosurgery for treatment of brain metastases: Estimation of patient eligibility using three stratification systems. *Int J Radiat Oncol Biol Phys* 60: 218-224, 2004.
22. Sperduto PW, Kased N, Roberge D, Xu Z, Shanley R, Luo X, Sneed PK, Chao ST, Weil RJ, Suh J, *et al*: Summary report on the graded prognostic assessment: An accurate and facile diagnosis-specific tool to estimate survival for patients with brain metastases. *J Clin Oncol* 30: 419-425, 2012.
23. Sperduto PW, Yang TJ, Beal K, Pan H, Brown PD, Bangdiwala A, Shanley R, Yeh N, Gaspar LE, Braunstein S, *et al*: Estimating survival in patients with lung cancer and brain metastases: An update of the graded prognostic assessment for lung cancer using molecular markers (lung-molGPA). *JAMA Oncol* 3: 827-831, 2017.
24. Cho A, Gatterbauer B, Chen Y, Jankowski T, Haider L, Tögl S, Kapfhammer I, Schreder M, Kirchbacher K, Zöchbauer-Müller S, *et al*: Effect of cumulative dexamethasone dose on the outcome of patients with radiosurgically treated brain metastases in the era of modern oncological therapy. *J Neurosurg* 143: 384-395, 2025.
25. Gillespie BW, Chen Q, Reichert H, Franzblau A, Hedgeman E, Lepkowski J, Adriaens P, Demond A, Luksemburg W and Garabrant DH: Estimating population distributions when some data are below a limit of detection by using a reverse Kaplan-Meier estimator. *Epidemiology* 21 (Suppl 4): S64-S70, 2010.
26. Surjanovic N, Lockhart RA and Loughin TM: A generalized Hosmer-Lemeshow goodness-of-fit test for a family of generalized linear models. *Test (Madr)* 33: 589-608, 2024.
27. Jewell ES, Maile MD, Engoren M and Elliott M: Net reclassification improvement. *Anesth Analg* 122: 818-824, 2016.
28. Schröder C, Windisch P, Lütscher J, Zwahlen DR and Förster R: Validation and discussion of clinical practicability of the 2022 graded prognostic assessment for NSCLC adenocarcinoma patients with brain metastases in a routine clinical cohort. *Front Oncol* 13: 1042548, 2023.
29. Chinese Association for Clinical Oncologists; Medical Oncology Branch of Chinese International Exchange and Promotion Association for Medical and Healthcare: Clinical practice guideline for brain metastases of lung cancer in China (2021 version). *Zhonghua Zhong Liu Za Zhi* 43: 269-281, 2021 (In Chinese).
30. Rades D, Hansen HC, Schild SE and Janssen S: A new diagnosis-specific survival score for patients to be irradiated for brain metastases from non-small cell lung cancer. *Lung* 197: 321-326, 2019.
31. Sperduto PW, De B, Li J, Carpenter D, Kirkpatrick J, Milligan M, Shih HA, Kutuk T, Kotecha R, Higaki H, *et al*: Graded prognostic assessment (GPA) for patients with lung cancer and brain metastases: Initial report of the small cell lung cancer GPA and update of the non-small cell lung cancer GPA including the effect of programmed death ligand 1 and other prognostic factors. *Int J Radiat Oncol* 114: 60-74, 2022.
32. Sperduto PW, Mesko S, Li J, Cagney D, Aizer A, Lin NU, Nesbit E, Kruser TJ, Chan J, Braunstein S, *et al*: Survival in patients with brain metastases: Summary report on the updated diagnosis-specific graded prognostic assessment and definition of the eligibility quotient. *J Clin Oncol* 38: 3773-3784, 2020.
33. Li R, Zhang SR, Liu XF, Zhang JW, Zhao JY, Bai P and Zhang XC: Prognostic factors for non-small cell lung cancer patients with central nervous system metastasis with positive driver genes. *Zhonghua Yi Xue Za Zhi* 103: 1202-1209, 2023.
34. Zhang M, Tong J, Ma W, Luo C, Liu H, Jiang Y, Qin L, Wang X, Yuan L, Zhang J, *et al*: Predictors of lung adenocarcinoma with leptomeningeal metastases: A 2022 targeted-therapy-assisted molGPA model. *Front Oncol* 12: 903851, 2022.
35. Mulvenna PM, Holt T and Stephens R: Response to 'Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: A multi-institutional analysis of 4,259 patients'. (*Int J Radiat Oncol Biol Phys* 2010:77:655-661). *Int J Radiat Oncol Biol Phys* 81: 1194, 2011.
36. Yamamoto M, Kawabe T, Higuchi Y, Sato Y, Barfod BE, Kasuya H and Urakawa Y: Validity of three recently proposed prognostic grading indexes for breast cancer patients with radiosurgically treated brain metastases. *Int J Radiat Oncol Biol Phys* 84: 1110-1115, 2012.
37. Winslow N, Boyle J, Miller W, Wang Y, Geoffroy F and Tsung AJ: Development of brain metastases in non-small-cell lung cancer: High-risk features. *CNS Oncol* 13: 2395804, 2024.
38. Schmid S, Garcia M, Zhan L, Cheng S, Khan K, Chowdhury M, Sabouhanian A, Herman J, Walia P, Strom E, *et al*: Outcomes with non-small cell lung cancer and brain-only metastasis. *Heliyon* 10: e37082, 2024.
39. Higaki H, Nishioka K, Otsuka M, Nishikawa N, Shido M, Minatogawa H, Nishikawa Y, Takashina R, Hashimoto T, Katoh N, *et al*: Brain metastases in Japanese NSCLC patients: Prognostic assessment and the use of osimertinib and immune checkpoint inhibitors-retrospective study. *Radiat Oncol* 18: 25, 2023.
40. Liang L, Wang Z, Duan H, He Z, Lu J, Jiang X, Hu H, Li C, Yu C, Zhong S, *et al*: Survival benefits of radiotherapy and surgery in lung cancer brain metastases with poor prognosis factors. *Curr Oncol* 30: 2227-2236, 2023.
41. Ohe Y, Imamura F, Nogami N, Okamoto I, Kurata T, Kato T, Sugawara S, Ramalingam SS, Uchida H, Hodge R, *et al*: Osimertinib versus standard-of-care EGFR-TKI as first-line treatment for EGFRm advanced NSCLC: FLAURA Japanese subset. *Jpn J Clin Oncol* 49: 29-36, 2019.
42. Lu S, Dong X, Jian H, Chen J, Chen G, Sun Y, Ji Y, Wang Z, Shi J, Lu J, *et al*: AENEAS: A randomized phase III trial of aumolertinib versus gefitinib as first-line therapy for locally advanced or metastatic non-small-cell lung cancer with EGFR exon 19 deletion or L858R mutations. *J Clin Oncol* 40: 3162-3171, 2022.
43. Shi Y, Chen G, Wang X, Liu Y, Wu L, Hao Y, Liu C, Zhu S, Zhang X, Li Y, *et al*: Central nervous system efficacy of furmonertinib (AST2818) versus gefitinib as first-line treatment for EGFR-mutated NSCLC: Results from the FURLONG study. *J Thorac Oncol* 17: 1297-1305, 2022.

