



Establishment and validation of a novel survival prediction scoring algorithm for patients with non-small-cell lung cancer spinal metastasis

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Abstract

Background This study was to develop an algorithm capable of predicting the survival of patients with NSCLC spinal metastasis for individualized therapy.

Methods We identified 176 consecutive patients with NSCLC spinal metastasis between 2006 and 2017. Twenty-four features, including age, gender, smoking, KPS, paralysis, histological subtype, tumor stage, surgery, *EGFR* status, CEA, CA125, CA19-9, NSE, SCC, CYFRA21-1, calcium, AKP, albumin, the number of spinal, extra-spinal bone and visceral metastasis, time to metastasis, pathological fracture, and primary or secondary metastasis, were retrospectively analyzed. Features associated with survival in the multivariate analyses were included in a scoring model, which was prospectively validated in another 63 patients (NCT03363685).

Results The median follow-up period was 12.00 months (interquartile range 6.00–23.40 months). One hundred forty-seven patients died during follow-up, with a median survival of 13.6 months being observed. Multivariate analysis revealed that the following features were associated with survival: age, smoking, CA125, SCC, KPS, and *EGFR* status. A scoring system based on these features was created to stratify patients into low-risk (0–3), intermediate-risk (4–6) and high-risk (7–10) groups, whose estimated median survival times 29.10, 10.40 and 3.90 months, respectively. The Harrell's c-index was 0.72. Model validation supported this model's validity and reproducibility.

Conclusions In patients with NSCLC spinal metastasis, survival was associated with age, smoking, CA125, SCC, KPS, and *EGFR* status. A validated scoring system based on these features was devised that can predict the survival times of those patients. This scoring system provides a basis for applying the NOMS framework and for facilitating individual treatment.

Keywords Non-small-cell lung cancer metastatic · Spinal metastasis · Survival prediction algorithm

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Introduction

Lung cancer remains the most common cancer and the leading cause of cancer-related death worldwide, with a 5-year overall survival (OS) rate of 18.1% being observed to date, whose estimated numbers of new cases and deaths in 2017 were 222500 and 155870, respectively [1]. Non-small-cell lung cancer (NSCLC) and small-cell lung cancer (SCLC) bear distinct clinical courses. NSCLC accounts for a large part of cases (~80%) and its prognosis is better than SCLC. Of these patients, 26–36% present with bone metastasis, which worsens the prognosis with a 2-year survival rate of 3% [2]. Spinal metastasis accounts for 40% of the bone metastases and elevates the risk of neurological and skeletal complications resulting in decreased quality of life (QOL) [3]. The at-risk patient's QOL drives doctors to

make decisions on whether the patients could benefit from proposed interventions. The treatment of spinal metastasis is palliative, with the goal of providing pain relief, maintenance or recovery of neurological function, local durable tumor control, spinal stability and improved QOL [4]. Since the benefits of any potential treatment should be balanced against the risks and disease burden for each individual patient, life expectancy would be one of the key factors to select a proper treatment.

Prognostic factors and predictive algorithms of OS in patients with spinal metastasis from unspecific origin have been reported by multiple investigators, including Tokuhashi [5], Tomita [6], Baur [7], Linden [8], Rades [9] and Katagiri [10] scores. The score proposed by Tokuhashi et al. in 1990 and modified in 2005 [11] represents the first attempt to predict the survival of patients with metastatic spine lesions and is the most widely used approach at this time. However, more than 10 years have passed since last revision of the Tokuhashi score. Several articles demonstrated its progressive loss in accuracy to predict survival, especially in patients with poor prognosis [12]. Medical developments may be one of the factors contributing to the decreased reliability of this previous score, and not all tumors have experienced the same therapeutic advances. Accumulating evidence in advanced NSCLC confirmed that the progress of chemotherapy and targeted therapy could alter the clinical course. In addition, the efficacies of previous scoring systems should be questioned when assessing patients with spinal metastases from certain types of cancer, since the patients with different types of tumors were enrolled in the database when those systems were established. Crnalic et al. reported in 2012 that the revised Tokuhashi score was difficult to apply to patients with prostate cancer with spinal metastasis due to the lack of consideration of hormone level, which was the most critical factor in their cohorts' survival [13]. Similarly, Hessler et al. considered that the Tokuhashi score did not prove to be a useful tool in the decision-making process for deciding on an adequate therapy for patients with lung cancer spinal metastases [4]. Taken together, there is a need for a practical NSCLC-spinal-metastasis-specific score system to support the choice of treatment strategy, and to the best of our knowledge, few previous studies have been conducted to construct such an algorithm. Rades et al. and Lei et al. established a survival score for patients with metastatic spinal cord compression (MSCC) from lung cancer to facilitate individualized treatment care [14, 15]. However, only 10% of patients with spinal metastases developed MSCC [16], and other patients with long life expectancy would be likely to benefit from individualized therapy according to the NOMS (Neurologic, Oncologic, Mechanical and Systemic) framework [17]. Therefore, the objective of the current study is to develop a scoring algorithm, based on readily available

clinical and pathological information that can predict the survival times for patients with NSCLC spinal metastasis.

Materials and methods

Patient selection

The patients for establishing the model were selected through a retrospective review of Shanghai Jiao Tong University Ruijin Hospital. Clinical data were extracted from the institution's electronic databases. Three hundred thirty-two consecutive patients diagnosed with lung cancer and receiving positive results in bone scans in the Department of Respiratory Medicine between June 2006 and January 2017 were potentially eligible for this study. To eliminate possible confounding factors, the cohort was limited to patients diagnosed with NSCLC through biopsy, and with spinal metastasis diagnosed through both radio nucleotide bone scans and magnetic resonance imaging (MRI). Patients with negative MRI (108), missing key data (9), no spinal metastasis (17) and SCLC were excluded. After exclusion, 176 patients with NSCLC spinal metastasis were available for study (Supplementary Fig. 1).

The model was prospectively validated. The patients recruited in the validation group consisted of 63 cases of NSCLC spinal metastasis in the Department of Respiratory Medicine, Oncology, and Orthopedics between January 2017 and January 2018 identified in the same way described above. The whole cohort was enrolled in clinical trial (NCT03363685). The follow-up was performed every 3 months after the diagnosis of NSCLC spinal metastasis in the first 2 years and every 6 months thereafter. This study was approved by the Ruijin Hospital Ethics Committee (RUIJIN2017NO170).

Features

Features of clinical status and primary and metastatic lesion were evaluated in this study.

Clinical features included age, gender, smoking history, performance status and paralysis. The performance status was assessed by the Karnofsky Performance Score. The evidence was sufficient to infer a relationship between tobacco use and poorer clinical outcomes [18]. Wide variation existed on the effects of paralysis on prognosis assessed by the Frankel grade [6–8, 11].

Primary lesion features consist of pathological features, treatment and serum markers. Pathological features included histological subtype and tumor stage. The histological subtypes were classified according to the WHO classification system, and were divided into non-squamous and squamous

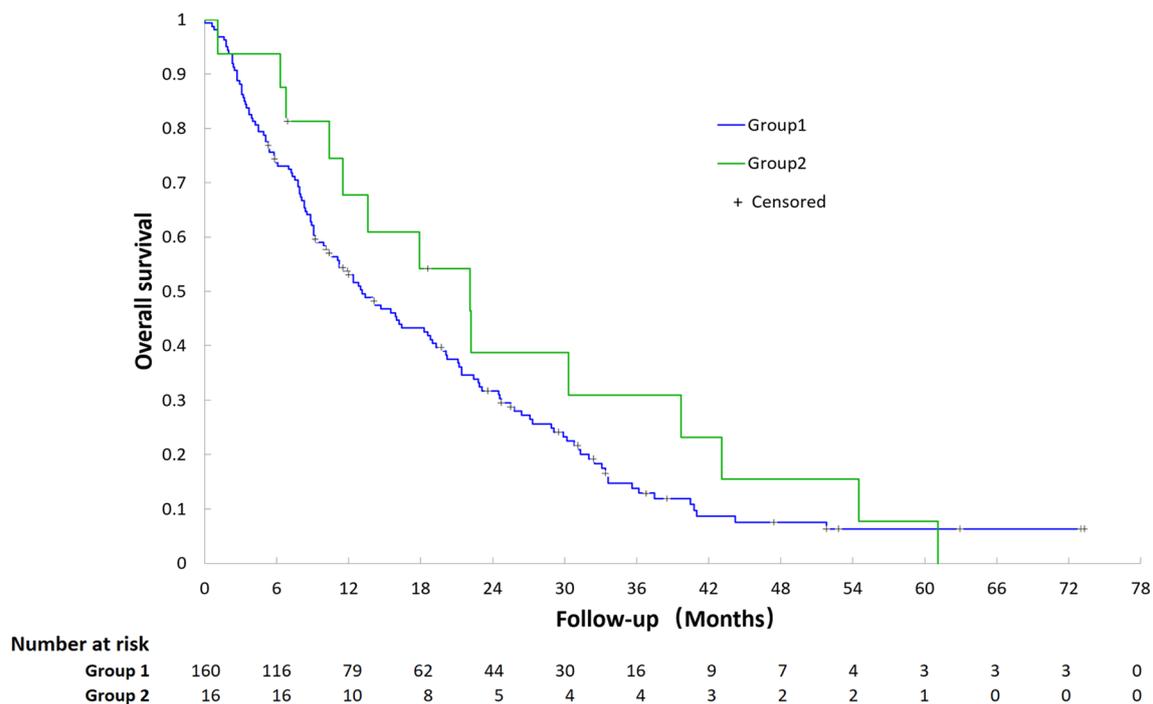


Fig. 1 Overall survival from the time of spine metastasis stratified by the revised Tokuhashi score (2005) in patients with NSCLC categorized into Groups 1 and 2 (scores of 0–8, 9–11, respectively)

cell carcinomas. Tumor stage was graded using the 2007 IASLC TNM primary tumor staging system.

Treatments included primary tumor surgery and epidermal growth factor receptor (*EGFR*). The identification of activating mutations in *EGFR*, together with an increased sensitivity to epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI), has been the first and most important step towards molecular-guided precision therapy of NSCLC. *EGFR* mutations have been observed among 48% of patients of East Asian origin and EGFR-TKI has been the first-line therapy for those patients [19].

Serum markers included CEA, CA125, CA19-9, NSE, SCC and CYFRA21-1, which were commonly used as predictive and prognostic factors in clinical settings [20]. Meanwhile, Ca, ALP, and ALB were also reported to have impact on survival [21]. The reference interval of those markers was as follows: CEA < 5 ng/ml; CA125 < 35U/ml; CA19-9 < 37U/ml; NSE < 17 ng/ml; SCC < 1.5 ng/ml; CYFRA21-1 < 3.3 ng/ml; Ca > 2.00 mmol/L; ALP < 126 IU/L; and ALB > 35 g/L.

Metastatic lesion features included the number of spinal metastasis, extra-spinal bone metastasis, visceral metastasis and pathologic fracture. All of these features were commonly observed in previous scoring algorithms. The times to metastasis and primary or secondary metastasis were also evaluated. Based on these features, we generated the revised Tokuhashi score (Supplementary Table 1) for each

patient to compare their predicted survival with actual survival time, and later performed survival analysis and model establishment.

Statistical methods

OS was estimated using the Kaplan–Meier method. The follow-up duration was calculated from the date diagnosed with spinal metastasis to death or to the last follow-up. Univariate and multivariate Cox proportional hazards models were fit to determine the features associated with survival. The correlation analysis and collinearity diagnosis were performed before the multivariate analysis performed. A multivariate model was built using a forward stepwise procedure with $P < 0.05$ as a deciding factor whether to include the feature in the model. A scoring system was developed using the β -regression coefficient values from the multivariate model. The coefficient of each variable was divided by the lowest β value and rounded into the nearest integer. Thereby, a prognostic score was calculated for each patient. Based on their score and the Kaplan–Meier survival curves, the resulting subgroups were stratified into low risk, intermediate risk, and high risk of death. The predictive ability of the final model was evaluated using the Harrell’s c-index [22].

The validation group was stratified into low-risk, intermediate-risk, and high-risk groups according to this scoring model. The Kaplan–Meier survival curves and the log-rank

test, the median survival times, and the Harrell's c-index were calculated and compared with the corresponding data from model group. The statistical analyses were performed using SPSS (version 21.0) and statistical software R (version 3.1.4). If the Harrell's c-index declines no greater than 5% compared to the model cohort, the validation result was considered positive [23–25].

We calculated the 95% CIs for the median values using the complementary log–log transformation, the 95% CIs for Hazard Ratios (HRs) from the Cox model, and for the survival rates using the formula: 95%CI = estimate \pm 1.96 (standard error). The standard error was calculated by following formula:

$$\text{Standard error} = S_t \sqrt{\sum \frac{D_t}{N_t(N_t - D_t)}}$$

N_t means the number of participants who are event free and considered at risk during interval t ; D_t means the number of participants who die during interval t ; S_t means the proportion surviving past interval t .

Results

The baseline characteristics of the model and validation cohorts are shown in Table 1. There is no difference in patient characteristics between the two cohorts.

Model group

The features of clinical status, primary and metastatic lesion of the 176 patients diagnosed with NSCLC spinal metastasis are summarized in Table 2. The median follow-up was 12.00 months (interquartile range 6.00–23.40 months). One hundred forty-seven patients died of NSCLC during follow-up. The median survival was 13.60 months (95% CI 10.15–17.04). The 3-month, 6-month, 1-year, 2-year and 3-year survival rates were 86.93% (95% CI 81.95–90.91), 74.96% (95% CI 68.55–81.37), 54.28% (95% CI, 46.83–61.54), 31.68% (95% CI 24.48–38.89), and 14.66% (95% CI 8.81–20.51), respectively.

According to revised Tokuhashi score, 160 patients were classified into Group 1 (score 0–8), and only 16 patients were classified into Group 2 (9–11). Since the highest score possible for NSCLC with spinal metastases is 10, there was no Group 3 (12–15). The predicted and actual survival times only matched in 50 cases (28.4%, Table 3). As a measure of the predictive ability of the revised Tokuhashi score in

our cohorts, Harrell's c-index was 0.52. The Kaplan–Meier survival analysis is shown in Fig. 1 (log-rank test, $P=0.303$).

In the univariate analysis, the following features were associated with survival: age at metastasis, gender, smoking history, CA125, CA19-9, NSE, SCC, ALB, KPS, Frankel grade and *EGFR* status. The correlation and collinearity analysis were performed in these variables (Supplementary Figs. 2, 3). The variance inflation factors (VIFs) of these variables are all less than 4, meaning no correction is required [26]. In addition, the correlations between these variables are mostly weak (Spearman correlation coefficient <0.3), except for that between gender and smoking (coefficient = -0.641), and between Frankel grade and KPS (coefficient = 0.839). According to the a priori knowledge from several recommendations [27, 28], we believe that smoking (vs gender) and performance status (vs Frankel grade) are more pertaining to the survival of NSCLC patients, thus being more suitable as the candidate variables for the multivariate model. Finally, multivariate analysis included age, smoking history, CA125, CA19-9, NSE, SCC, ALB, KPS and *EGFR* status, and revealed that age, smoking history, CA125, SCC, KPS and *EGFR* status were associated with the survival of NSCLC spinal metastasis. The results of the multivariate modeling are summarized in Table 4.

A scoring algorithm was developed to predict survival after spinal metastasis for NSCLC using the β -regression coefficient values from multivariate model. The coefficient for each feature was divided by the coefficient for smoking history (1–10/day), and rounded to the nearest integer (Supplementary Table 2). The features for the NSCLC spinal metastasis score were calculated as 1 (for *EGFR* negative), +2 (for KPS $<50\%$), +1 (for KPS 50–70%), +1 (age >60 years), 2 (SCC ≥ 1.5 ng/ml), +3 (CA125 ≥ 35 U/ml), +1 (smoking history 1–10/day), +2 (smoking history >10 /day), and 0 otherwise.

The mean score was 3.99 ± 2.30 (median, 4; range, 0–10). Kaplan–Meier-estimated OS based on this scoring system is shown in Fig. 2 and Table 5 (log-rank test, $P < 0.01$). Patients with scores ≥ 8 were combined because there were only 12 patients with scores of 8, 9 or 10. The results shown in Fig. 2 and Table 5 suggest that patients could be stratified into three groups based on their survival. Patients at low risk had scores of 0–3, at intermediate risk had scores of 4–6, and at high risk had scores of 7–10. The stratification of patients is illustrated in Fig. 3a, and the final prognostic algorithm is shown in Table 6. The median OS of the patients in the low-risk group ($n=73$) was 29.10 months (95% CI 22.59–35.61), in the intermediate-risk group ($n=76$) was 10.40 months (95% CI 7.56–13.24), and in the high-risk group ($n=27$) was 3.90 months (95% CI 2.12–5.68). The Harrell's c-index was 0.72.

Table 1 Baseline characteristics

Features	<i>N</i> patients in model group	<i>N</i> patients in validation group	<i>P</i> value
Event			0.846
Death	147	52	
Censor	29	11	
Age			0.503
≤ 60 years	94	38	
> 60 years	82	25	
Sex			0.382
Male	86	35	
Female	90	28	
<i>EGFR</i> status			0.304
Positive	93	28	
Negative	83	35	
KPS			0.641
≥ 80%	132	44	
50–70%	39	16	
< 50%	5	3	
SCC			0.760
< 1.5 ng/ml	148	54	
≥ 1.5 ng/ml	28	9	
CA125			0.997
< 35 U/ml	67	24	
≥ 35 U/ml	109	39	
CA19-9			0.871
< 37 U/ml	125	46	
≥ 37 U/ml	51	17	
NSE			0.558
< 17 ng/ml	90	29	
≥ 17 ng/ml	86	34	
ALB			0.300
≤ 35/L	70	30	
> 35/L	106	33	
Smoking history			0.439
0/day	119	39	
1–10/day	17	5	
> 10/day	40	19	
Frankel			0.763
3	10	4	
4	27	12	
5	139	47	
Histologic subtype			0.682
Non-squamous carcinoma	148	55	
Squamous cell carcinoma	28	8	
	Model group	Validation group	
Median survival (Months)	13.60	10.43	
95% Confidence interval	10.15–17.04	7.70–13.16	

P values were obtained from chi-square (X^2) test

Table 2 Characteristics of the model group in univariate analysis

Features	N Patients	HR	95% CI	P value
Age		1.204	0.869–1.669	0.047
≤ 60 years	94			
> 60 years	82			
Gender		1.924	1.382–2.678	< 0.001
Male	86			
Female	90			
Smoking history		1.562	1.289–1.893	< 0.001
0/day	119			
1–10/day	17			
> 10/day	40			
CEA		0.956	0.656–1.393	0.815
< 5 ng/ml	42			
≥ 5 ng/ml	134			
CA125		2.148	1.517–3.040	< 0.001
< 35 U/ml	67			
≥ 35 U/ml	109			
CA19-9		1.345	0.969–1.869	0.038
< 37 U/ml	125			
≥ 37 U/ml	51			
NSE		1.329	0.961–1.838	0.049
< 17 ng/ml	90			
≥ 17 ng/ml	86			
SCC		2.343	1.535–3.575	< 0.001
< 1.5 ng/ml	148			
≥ 1.5 ng/ml	28			
CYFRA 21-1		1.200	0.845–1.703	0.308
< 3.3 ng/ml	52			
≥ 3.3 ng/ml	124			
Ca		0.283	0.128–1.026	0.108
≤ 2.00 mmol/L	8			
> 2.00 mmol/L	168			
ALP		0.939	0.64–1.379	0.750
< 126 IU/L	134			
≥ 126 IU/L	43			
ALB		0.648	0.468–0.898	0.009
≤ 35/L	70			
> 35/L	106			
Number of spinal metastasis		1.106	0.753–1.625	0.608
1	42			
> 1	134			
Number of extra-spinal bone metastasis		1.109	0.691–1.779	0.668
0	23			
≥ 1	153			
Number of visceral metastasis		1.394	1.000–1.944	0.051
0	95			
≥ 1	81			
Time to metastasis		0.857	0.708–1.039	0.116
0 months	92			
1–3 months	41			
> 3 months	43			
Primary or secondary metastasis		0.857	0.597–1.415	0.359

Table 2 (continued)

Features	N Patients	HR	95% CI	P value
Primary metastasis	92			
Secondary metastasis	84			
KPS		0.650	0.486–0.870	0.004
< 50%	5			
50–70%	39			
≥ 80%	132			
Frankel		0.674	0.517–0.879	0.004
3	10			
4	27			
5	139			
Surgery		0.685	0.370–1.268	0.228
No	160			
Yes	16			
EGFR status		0.584	0.420–0.813	0.001
Negative	83			
Positive	93			
T classification		0.955	0.817–1.115	0.561
T1	11			
T2	44			
T3	26			
T4	95			
N classification		1.051	0.837–1.319	0.671
0	3			
1	12			
2	47			
3	114			
Histologic subtype		0.689	0.449–1.005	0.086
Non-squamous carcinoma	148			
Squamous cell carcinoma	28			

P values were obtained from univariate Cox analysis

Table 3 Comparison of expected and actual survival according to revised Tokuhashi score (2005)

Expected survival	No of patients	Actual survival		
		0–6 months	6–12 months	> 12 months
0–6 months	160	45	28	77
6–12 months	16	1	5	10
Total	176	46	43	87

Validation group

The validation group was stratified into low-, intermediate-, and high-risk groups. The characteristics of validation group are given in Table 7. The median follow-up was 9.77 months (interquartile range 5.12–16.43 months). 52 patients died during follow-up. The median survival was 10.43 months (95% CI 7.70–13.16). The median OS of the patients in the low-risk group ($n = 22$) was 21.63 months (95% CI 15.15–28.10), in the intermediate-risk group

($n = 33$) was 7.80 months (95% CI, 6.64–8.96), and in the high-risk group ($n = 8$) was 3.37 months (95% CI 0.00–10.43). The survival times of the different risk groups within the validation group were proven to be similar to those of the model group. Kaplan–Meier curves for the three risk groups from the validation group are shown in Fig. 3b (log-rank test, $P < 0.01$). The Harrell's c-index for the validation group was 0.674, achieved our pre-assumption of the positive outcome. Thus, this scoring algorithm appears valid and reproducible.

Table 4 Multivariate model for spinal metastases in patients with NSCLC

Features	β -regression coefficient	HR	95% CI	P value
<i>EGFR</i> status				
Negative vs positive	0.458 ± 0.186	1.581	1.098-2.276	0.014
KPS				
< 50 vs ≥ 80%	0.855 ± 0.480	2.353	0.918-6.026	0.075
50–70 vs ≥ 80%	0.585 ± 0.206	1.795	1.200-2.687	0.004
Age				
> 60 vs ≤ 60 years	0.475 ± 0.183	1.608	1.123-2.303	0.01
SCC				
≥ 1.5 vs < 1.5 ng/ml	0.885 ± 0.230	2.422	1.542-3.804	< 0.001
CA125				
≥ 35 vs < 35 U/ml	1.075 ± 0.201	2.929	1.976-4.341	< 0.001
Smoking history				
1–10 vs 0/day	0.412 ± 0.278	1.510	0.876-2.602	0.138
> 10 vs 0/day	0.728 ± 0.219	2.071	1.348-3.181	0.001

P values were obtained from multivariate Cox analysis

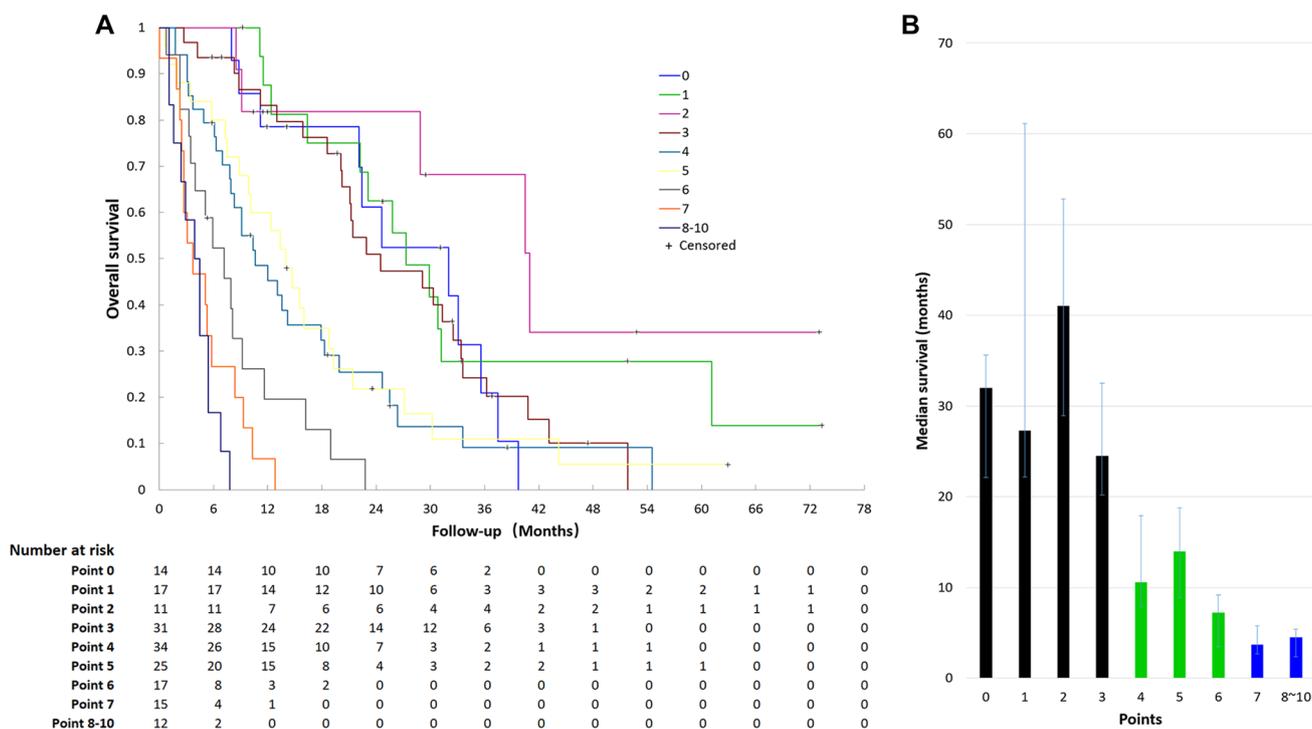


Fig. 2 Overall survival from the time of spine metastasis stratified by the current scoring system in patients with NSCLC. **a** Kaplan–Meier curve for the survival of each score from the model group. **b** His-

togram of the median survival times of each score from the model group (patients with scores ≥ 8 were combined)

Discussion

The treatment of NSCLC has undergone fundamental changes in the past decade. The introduction of second-generation and third-generation cytotoxic therapies, as well as anti-angiogenic therapies in combination with

chemotherapy was observed and altered the clinical outcome. Two of the most important therapeutic advances have been the identification of distinct molecular subsets amenable to targeted therapies, and the early success of immune point inhibitors [29]. The survival times and prognosis have marginally improved and the incidence of spinal metastasis also increased. For symptomatic patients

Table 5 Estimated overall survival after spinal metastasis for NSCLC by score

Score	N patients	Median	95% CI	1-Year survival	2-Year survival
0	14	32.00	22.10–35.60	78.6%	61.1%
1	17	27.30	22.20–61.10	87.5%	62.5%
2	11	41.00	28.90–52.80	81.8%	81.8%
3	31	24.50	20.20–32.50	83.2%	50.9%
4	34	10.60	7.90–17.90	45.3%	25.5%
5	25	14.00	8.90–18.80	60.0%	21.8%
6	17	7.20	3.50–9.20	19.6%	0%
7	15	3.70	2.70–5.80	6.7%	0%
8–10	12	4.50	2.40–5.40	0%	0%

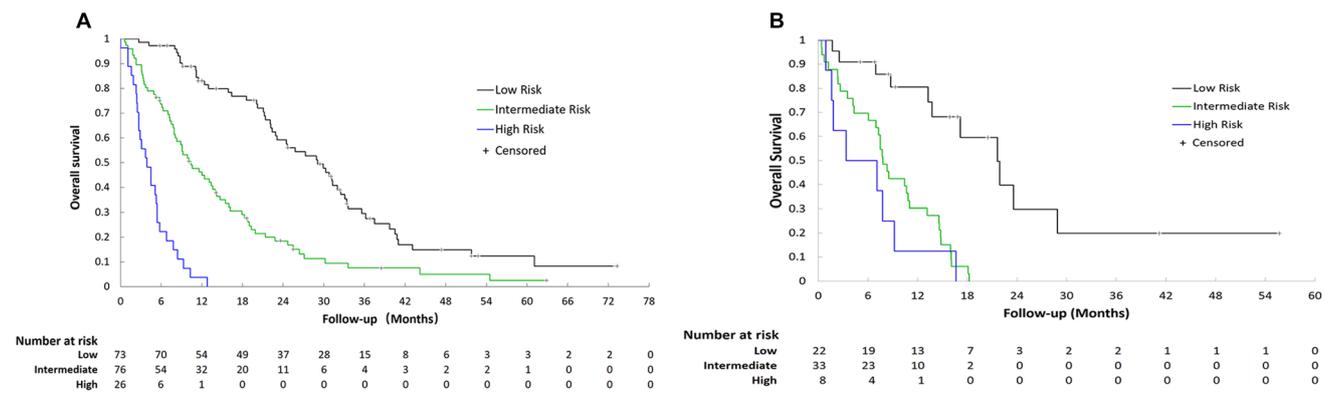


Fig. 3 a Overall survival from the time of spine metastasis stratified by the current scoring system in patients with NSCLC in the model group categorized into low-risk, intermediate-risk and high-risk groups (scores of 0–3, 4–6, 7–10, respectively), **b** Overall survival

from the time of spine metastasis stratified by the current scoring system in patients with NSCLC in the validation group categorized into low-risk, intermediate-risk and high-risk groups

with NSCLC spinal metastasis, there was a need to alleviate pain, reverse neurologic deficits, stabilize the spine and improve QOL. Since patients with very short survival times could not benefit from extensive interventions, survival prediction plays a vital role in treatment strategy decision-making [30].

Several algorithms have been previously reported, to predict survival following diagnosis with spinal metastasis from uncertain origin, such as the Tokuhashi, Tomita, Baur, Linden, Rades and Katagiri scores. Although the primary tumor type was included among all of the scoring systems, Tokuhashi [5] suggested in 1990 that the primary consideration should not be given to the nature of the original lesion but to its effects on the metastatic lesions. At that time, these systems were useful for predicting the survival and support decision-making process about operative indications and to avoid excessive medical treatment. However, as metastatic tumors have also been aggressively treated, the scoring systems have become unfit for the current situation with treatment diversification. Tokuhashi pointed out in 2014 that oncological viewpoints should be highlighted in algorithm making, including the stage and level of the disease, the

evaluation according to the nature of the primary cancer, the introduction of serum levels as a prognostic marker, and multidisciplinary treatments [31]. Rades et al. and Lei et al. established a survival score for patients with MSCC due to lung cancer, respectively [14, 15], but only 10% of the patients developed MSCC and others could also benefit from individualized therapy.

In our cohort, previous widely accepted algorithms like the revised Tokuhashi score failed to predict the OS, with the Harrell’s c-index being 0.52. Therefore, the goal of the current study was to identify the features associated with patient survival after diagnosis with NSCLC spinal metastasis, and to develop a novel NSCLC-spinal-metastasis-specific survival prediction algorithm capable of stratifying the patients for personalized therapy. The features of clinical status and primary and metastatic lesions were included in our analysis, and the results revealed correlations between *EGFR* status, KPS, age, CA125, SCC, smoking history and survival. The prognostic factors forming our scoring system had a Harrell’s c-index of 0.72. This algorithm stratifies the patients into low-risk (0–3), intermediate-risk (4–6) and high-risk (7–10) groups, whose estimated median survival time was

Table 6 The final prognostic algorithm for spinal metastatic NSCLC

Features	Score				
<i>EGFR</i> status					
Positive	0				
Negative	1				
KPS					
≥ 80%	0				
50–70%	1				
< 50%	2				
Age					
≤ 60 years	0				
> 60 years	1				
SCC					
< 1.5 ng/ml	0				
≥ 1.5 ng/ml	2				
CA125					
< 35 U/ml	0				
≥ 35 U/ml	3				
Smoking history					
0/day	0				
1–10/day	1				
> 10/day	2				
Risk groups	<i>N</i>	Total points	Median	95% CI	Interquartile range
Low	73	0–3	29.10	22.59–35.61	20.10–39.70
Intermediate	76	4–6	10.40	7.56–13.24	5.80–19.00
High	27	7–10	3.90	2.12–5.68	2.40–5.80
Risk groups	3-Month survival	6-Month survival	1-Year survival	2-Year survival	
Low	98.6%	95.9%	83.0%	59.2%	
Intermediate	89.5%	73.6%	44.8%	16.8%	
High	59.3%	22.2%	3.7%	0.0%	

Table 7 Characteristics of The Validation Group

Risk groups	<i>N</i>	Median	95% CI	
Low	22	21.63	15.15–28.10	
Intermediate	33	7.80	6.64–8.96	
High	8	3.37	0.00–10.43	
Risk groups	3-Month survival	6-Month survival	1-Year survival	2-Year survival
Low	90.9%	85.9%	74.3%	29.8%
Intermediate	78.8%	69.7%	30.3%	0.0%
High	62.5%	50.0%	12.5%	0.0%

29.10 months (95% CI 22.59–35.61), 10.4 months (95% CI 7.56–13.24), and 3.90 (2.12–5.68) months, respectively.

The survival of the validation cohort (10.43 months, 95% CI 7.70–13.16) tends to be different from that of the model cohort (13.60 months, 95% CI 10.15–17.04). We found five (17.86%) *EGFR*-positive patients in the validation cohort

failed to receive the according targeted therapy, while all of the *EGFR*-positive patients in the model cohort did. Such non-compliance to the known effective therapy might drastically dampen the outcome. However, because our validation cohort is within a prospective trial framework (NCT03363685) while non-compliance was not listed in

the pre-specified exclusion criteria, such patients could not be excluded from validation. Since the patient population is balanced between the two cohorts, and the validation result still achieved our pre-assumption of the positive outcome, the data monitoring committee agreed with the clinician researchers to the accepted prognostic value of the model based on these the real-world prospective data at present. Further long-term follow-up with a larger sample size is warranted to better address this question.

The current scoring system could provide a basis for applying the NOMS paradigm and for determining appropriate treatments [17]. The long-term benefits of an invasive, timely, or costly procedure might not manifest in patients with a short life expectancy who belong to the high-risk group. These patients should receive the best supportive care available and have the opportunity to discuss the goals of care with their family and physicians. The patients in low-risk group should be evaluated according to the NOMS algorithm. If the spine is deemed mechanically unstable by the Spine Instability Neoplastic Score (SINS) [32], surgical stabilization should be performed; if the neurologic risk is confirmed by a radiographic assessment of the degree of epidural spinal cord compression (ESCC) [33], appropriate radiotherapy or surgical decompression could be required. For the patients in the intermediate-risk group, they could benefit from some invasive treatment as well, and they should discuss their treatment with their oncologist.

EGFR-TKI improved progression-free survival (PFS) but not increase OS for patients with advanced NSCLC in most previous studies [34]. However, the current study found EGFR-TKI improved OS for patients with NSCLC spinal metastasis (median, 22.1 vs 9.1 months). This result is similar to those of Dohzono et al. who reported median OS was longer in patients with lung cancer spinal metastases treated with EGFR-TKIs than in those without (21.4 vs 6.1 months) [35]. Meanwhile, the National Cancer Institute of Canada Clinical Trials Group (NCIC CTG) [36] found Erlotinib was superior to placebo for the patients with IIIB or IV NSCLC in the analyses of OS (6.7 vs 4.7 months), PFS (2.2 vs. 1.8 months), and QOL.

Previous studies have reported the possibility that smoking history, CA125, SCC, KPS and age are NSCLC prognostic factors. The adverse clinical outcomes caused by tobacco use were revealed by the 2014 Surgeon General's Report, including adverse health outcomes, increased all-cause mortality and cancer-specific mortality, increased risk of second primary cancers, the risk of recurrence, poorer response to treatment, and increased treatment-related toxicity [37]. Because of their low sensitivity and specificity, the prognostic ability of CA-125 and SCC was controversial. CA-125 expresses in the epithelial lining of the respiratory tract, where it binds to mesothelin and galectin-1. Since the surface of the thoracic cavity is covered with mesothelial cells,

CA-125-mesothelin interactions might play a role in cancer progression. In addition, CA-125 binding to galectin-1 might induce T-cell apoptosis and suppress tumor immunity. SCC was speculated to suppress apoptosis by inhibiting serine and cysteine proteinases in the apoptosis pathway, resulting in the proliferation of cancer cells in carcinoma [38]. KPS and age reflect the patient's health condition. Patients with low KPS and the elderly usually have difficulties tolerating treatment-related toxicities, surgical approaches, high doses of radiation, and suffered higher rates of adverse events [39].

Although visceral metastasis was considered as a prognostic factor in every previous scoring system, it was not related to survival in this study. However, the *P*-value had border line *P* value ($P=0.051$), which meant that we could not completely exclude this feature from the potential prognostic factors. Targeted therapy might weaken the impact of visceral metastasis on prognosis. Certainly, selection bias was another possible explanation. Whether visceral metastasis is an independent risk factor for patients with NSCLC spinal metastasis warrants further investigation.

Conclusions

In patients with NSCLC spinal metastasis, survival was associated with age, smoking, CA125, SCC, KPS, and *EGFR* status. A validated scoring system based on these features was devised that can predict the survival times of those patients. This scoring system provides a basis for applying the NOMS framework and for facilitating individual treatment.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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