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CLINICAL STUDY

Development and validation of a prognostic nomogram for the overall survival of patients living with spinal metastases

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Abstract

Introduction The primary goal of treatment in spinal metastasis is typically to extend patients' lifespan as much as possible, and optimally to relieve the symptoms and so improve quality of life. It is crucial to avoid over- or under-treatment, according to each patient's individual situation. Thus, this study aimed to identify significant prognostic factors for patients living with metastatic spine disease, and create a new nomogram for the prediction of survival rates.

Methods Data from patients who had undergone operations for spinal metastasis between 2005 and 2016 were retrieved retrospectively, and randomized into training (70%) and validation groups (30%). A selection of pre-operative factors was analyzed using univariable and multivariable COX model for the training group. A nomogram was then developed using significant predictors in multivariable analysis. Accuracy was validated using a concordance index (C-index) and calibration curve for the training and validation groups, respectively.

Results A total of 244 participants were enrolled, including 171 in the training group and 73 in the validation group. Primary tumor, Frankel Grade, Karnofsky Performance Score (KPS) and adjuvant therapy were found to be significant for predicting survival rates. A nomogram was developed by utilizing these predictors. The C-indexes for the two groups were 0.711 and 0.703 respectively. Moreover, a favorable consistency between the predicted and actual survival probabilities was demonstrated using calibration curves.

Conclusions A user-friendly nomogram model for facilitating medical procedures during clinical encounters was established to aid clinical decision making for individual patients.

Keywords Spinal metastasis · Nomogram · Prognostic factor · Overall survival · Prognostic scoring system

Introduction

The overall survival (OS) of cancer patients has been extended, particularly when some advanced therapeutic modalities have been applied. As a result of this, the chance of metastasis occurring in bony tissue, which is the third most frequent metastatic site of advanced cancer (following lung and liver), has been increased [1, 2]. It is estimated that 350,000 people with bone metastasis die in the US every year [3]. The spine is the most common bony site to suffer from cancer metastasis for these people. Spinal metastasis may cause severe and intractable pain, pathologic fractures, spinal cord compression and spinal instability, and ultimately tends to be fatal [4].

The primary goal of treatment in spinal metastasis is typically to extend patients' lifespan as much as possible, and optimally to relieve the accompanied symptoms and so improve quality of life. It is crucial to avoid over- or under-treatment in spinal metastasis, according to each patients' unique situation [5]. This mean that patients who have a poor expectancy should receive less aggressive treatment, while those with a more favorable prognosis should be treated with more curative, radical modalities. It is therefore important to

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accurately predict the survival time of patients according to clinical characteristics before treatment commences.

Many predicting tools have been developed to assist clinicians in choosing the most appropriate therapeutic modality, including the revised Tokuhashi [6] the Tomita [7], the van der Linden [8] and the Oswestry Spinal Risk Index (OSRI) [9], to name a few. These scoring systems were predominantly established by rounding the effect estimates (such as hazard ratio, HR), to sum the sub-scores of all involved factors according to patients' situations, before correlating the total score to reach a survival estimate [6–9]. In contrast, the nomogram, which creates a simple, graphical representation of a statistical, predictive model for generating the numerical probability of a clinical event, has been demonstrated to be more reliable than many other systems and has thus been proposed as an alternative or even a new standard [10, 11]. The nomogram is a user-friendly model which is tailored to individual profile of patient, and has the potential to facilitate medical procedures during encounters related to clinical decision making.

Thus, in the current study, we set out to retrospectively collect the multicentric documents of patients living with metastatic spine disease, with the aim of identifying the significant prognostic factors of OS, using those factors to create a nomogram, and finally validating the accuracy of that newly established model.

Materials and methods

Patients

This research was conducted following the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis (TRIPOD) statement [12]. In accordance with the Declaration of Helsinki, and upon attaining the ethical approval from the hospital ethics committee, data of 448 patients from three clinical centers were retrospectively retrieved. Informed consent was obtained from all participants. Patients who had had surgery for metastatic spine disease between March 2005 and December 2016 will be included. Exhaustive clinical examinations, including magnetic resonance imaging (MRI) of the entire spine, computed tomography (CT) scans and biopsies were performed as appropriate for each specific diagnosis. The indications for surgical intervention include medically intractable pain and rapidly progressive neurological deterioration as well as evidence of clinical or radiographic spinal instability.

Recorded data

We collected demographic data as well as pre- and post-operative medical conditions from medical records or by telephone follow-up. Pre-operative factors which had been widely studied or identified as being associated with OS were included as explanatory variables in this study. These factors include:

- Gender (male or female);
- Age (<65 years vs. ≥ 65 years);
- Systematic co-morbidity, such as hypertension or diabetes (yes vs. no);
- Primary tumor histology, classified as hepatocellular carcinoma, lung cancer, gastrointestinal tract cancer, a tumor of unknown origin, breast cancer, prostate cancer, renal cellular cancer and other tumors;
- Visceral metastasis (yes vs. no);
- Extraspinal bone metastases (yes vs. no);
- Number of involved vertebrae (single vs. multiple);
- Pathological fracture (yes vs. no);
- Karnofsky Performance Score (KPS) (10–40 vs. 50–70 vs. 80–100);
- Frankel score (A–C vs. D vs. E);
- Sphincter dysfunction (yes vs. no);
- Serum albumin level (<35 g/L vs. ≥ 35 g/L);
- Time developing motor deficits before operation ($<$ 5 days vs. ≥ 5 days);
- Systemic adjuvant therapy; that is, non-surgical therapies, such as chemotherapy, radiotherapy, target therapy, hormonotherapy, immunotherapy and so on (yes vs. no).

Two researchers independently collected the data and entered it into a pre-built Microsoft Excel spreadsheet. The study's response variable was the OS, which is defined as the time period between operation and death or censoring. The time of developing motor deficit was defined as the time between the deterioration of motor function and surgery.

Statistical analysis

Participants were randomly divided into the training and validation samples with a ratio of 7:3, using a computer program. The distributions of baseline characteristics in the two samples were compared using Wilcoxon rank-sum test (for the Frankel Grade and KPS) or chi-square test (for other variables).

Following this, univariable and multivariable COX proportional hazard models were applied to the training group in order to detect any significant prognostic factors. Variables which presented with a P value of <0.15 in univariate analysis were included in the multivariate analysis with a method of backward stepwise selection process. Results of the univariate and multivariate analyses were shown with HR plus the 95% confidence interval (95% CI), and results were presented in a forest plot.

The spectrum of prognostic factors that may predict the OS according to multivariate analysis was used to develop a nomogram prognostic plot, which presented the numerical probability of surviving at 3, 6, 12 and 24 months as well as the median OS.

Predictors which had been found to be significant in the training group were then analyzed in the validation group using the Kaplan–Meier survival curve and a log-rank test in order to validate their significance. Following this, the internal and external validations of the prognostic accuracy of the nomogram were performed respectively for both the training and validation groups. The concordance index (C-index), which ranged from 0.5 to 1.0, was then used to test the discrimination, following which, the calibration curve was used to test the consistence for each time point. The building, validation and interpretations of the nomogram were carried out following Iasonos et al. [13].

We also compared the correlations between scores including the Tomita, Tokuhashi and our new nomogram and patients' survival time. The correlation coefficient (r) was calculated with the method of linear regression using the samples of whole cohort.

All statistical analyses were performed using the program R (version 3.5.1) for Windows (R Foundation for Statistical Computing, Vienna, Austria) and GraphPad Prism 7 (GraphPad Software, Inc., SanDiego, CA). Statistical tests with P value < 0.05 were considered significant.

Results

Demographics and clinical characteristics

244 patients met our inclusion criteria, who were divided into the training (171 cases) and validation samples (73 cases). Baseline characteristics of the population are shown in Table 1. All characteristics were found to be similar between the two samples. Figure 1a and b show the Kaplan–Meier survival curves for the training and validation groups. The mean OS was 10.5 ± 1.4 months (ranged 2–55) and 11.9 ± 1.0 (ranged 1–64) months in the two groups, respectively. Figure 2 shows the distribution of primary tumor types.

Therapeutic modalities and complications of the patients

All enrolled participants were surgically treated using four different surgical procedures, which were a palliative posterior decompression (71 cases, 29%), a sub-total tumorectomy (134 cases, 55%), a total piecemeal spondylectomy (27 cases, 11%), and a total en bloc spondylectomy (12 cases, 5%). Reconstruction and stabilization procedures were undertaken in 215 (88%) patients using either titanium mesh, pedicle screws or pedicle screws in conjunction with hooks, bone cement and bone graft fusion alone or with various combinations. Adjuvant therapies were provided for 180 (74%) patients post-operatively. These therapies including radiation, chemotherapy, radiosurgery, targeted therapy, hormonotherapy, bisphosphonates, denosumab and steroids.

A total of 38 major complications (22.2% of the patients) were recorded within 30 days after operation (see Table 2).

Prognostic factors associated with survival

Univariable and multivariable COX analyses were performed for the training group, results of which are graphically presented in a forest plot (Fig. 3). In the univariate analysis, 14 variables were analyzed, and four factors were found to be significant. These included primary tumor type (overall $P < 0.001$), Frankel Grade (overall $P < 0.001$), KPS (overall $P = 0.018$) and adjuvant therapy (HR = 2.09, CI 95% 1.45–3.00, $P < 0.001$). In addition, the number of involved vertebrae as well as visceral metastasis ($P < 0.150$) were shown to have marginal significance for predicting OS.

All of these variables were included in multivariable model. Primary tumor (overall $P = 0.023$), Frankel Grade (overall $P = 0.005$), KPS (overall $P = 0.011$) and adjuvant therapy (HR = 2.40, CI 95% 16.1–3.58, $P < 0.001$) were found to be significant predictors for survival, while the number of involved spine and visceral metastasis did not have statistical significance. The Kaplan–Meier survival curves for the four significant predictors are presented in Fig. 1c–f.

Establishment and validation of the nomogram

Based on the selected factors which were significantly associated with OS, a nomogram plot was developed using the training sample, as shown in Fig. 4. Patients' survival probabilities at 3, 6, 12 and 24 months, as well as their median survival time, are listed in a numerical form.

With the methods of Kaplan–Meier survival curve and the Log-Rank test, primary tumor ($\chi^2 = 14.6$, $P = 0.0415$), Frankel Grade ($\chi^2 = 18.7$, $P < 0.0001$) and KPS ($\chi^2 = 10.65$, $P = 0.0049$) were shown to maintain significance, while adjuvant therapy ($\chi^2 = 3.711$, $P = 0.054$) was found to be marginally significant for predicting OS, in the validation sample (see Figure S1).

The accuracy of the prediction model was further validated using the C-index (discrimination) and calibration curve (consistence). The C-indexes were 0.711 (CI 95% 0.621–0.801) for the training group, and 0.703 (CI 95% 0.614–0.792) for the validation group. Calibration curves for time points of 3, 6, 12 and 24 months both in training and validation groups are shown in Figure S2. A favorable

Table 1 Baseline characteristics of the study population

Characteristics	All patients	Training sample	Validation sample	*P* value[†]
Number	244	171	73	
Age-*N* (%)				0.491
< 65 years	155 (63.5)	111 (64.9)	44 (60.3)	
≥ 65 years	89 (36.5)	60 (35.1)	29 (39.7)	
Gender-*N* (%)				0.179
Male	155 (63.5)	104 (60.8)	51 (69.9)	
Female	89 (36.5)	67 (39.2)	22 (30.1)	
Systemic co-morbidity-*N* (%)				0.937
Yes	76 (31.1)	53 (31.0)	23 (31.5)	
No	168 (68.9)	118 (69.0)	50 (68.5)	
Primary tumor type-*N* (%)				0.929
HCC	15 (6.1)	10 (58.5)	5 (6.8)	
LC	120 (49.2)	83 (48.5)	37 (50.7)	
GITC	19 (7.8)	13 (7.6)	6 (8.2)	
Unknown origin	31 (12.7)	23 (13.5)	8 (11.0)	
BC	15 (6.1)	13 (7.6)	2 (2.7)	
PC	10 (4.1)	7 (4.1)	3 (4.1)	
RCC	17 (7.0)	12 (7.0)	5 (6.8)	
Other tumor	27 (11.1)	20 (11.7)	7 (9.6)	
Visceral metastasis-*N* (%)				0.626
Yes	55 (22.5)	40 (23.4)	15 (20.5)	
No	189 (77.5)	131 (76.6)	58 (79.5)	
Extraspinal bone metastasis-*N* (%)				0.433
Yes	111 (45.5)	75 (43.9)	36 (49.3)	
No	133 (54.5)	96 (56.1)	37 (50.7)	
Number of involved vertebrae-*N* (%)				0.592
Single	134 (54.9)	92 (53.8)	42 (57.5)	
Multiple	110 (45.1)	79 (46.2)	31 (42.5)	
Pathological fracture-*N* (%)				0.906
Yes	49 (20.1)	34 (19.9)	15 (20.5)	
No	195 (79.9)	137 (80.1)	58 (79.5)	
Preoperative Karnofsky Performance Score-*N* (%)				0.936
10–40	28 (11.5)	18 (10.5)	10 (13.7)	
50–70	132 (54.1)	95 (55.6)	37 (50.7)	
80–100	84 (34.4)	58 (33.9)	26 (35.6)	
Preoperative Frankel grade-*N* (%)				0.793
A–C	63 (25.8)	43 (25.1)	20 (27.4)	
D	109 (44.7)	80 (46.8)	29 (39.7)	
E	72 (29.5)	48 (28.1)	24 (32.9)	
Time developing motor deficit-*N* (%)				0.798
< 5 days	84 (34.4)	58 (33.9)	26 (35.6)	
≥ 5 days	160 (65.6)	113 (66.1)	47 (64.4)	
Urinary retention/incontinence-*N* (%)				0.837
Yes	18 (7.4)	13 (7.6)	5 (6.8)	
No	226 (92.6)	158 (92.4)	68 (93.2)	
Serum album level-*N* (%)[b]				0.952
< 35 g/L	33 (20.1)	23 (20.0)	10 (20.4)	
≥ 35 g/L	131 (79.9)	92 (80.0)	39 (79.6)	
Adjuvant therapy-*N* (%)				0.786
Yes	180 (73.8)	127 (74.3)	53 (72.6)	
No	64 (26.2)	44 (25.7)	20 (27.4)	

HCC hepatocellular carcinoma, *LC* lung cancer, *GITC* gastrointestinal tract cancer, *BC* breast cancer, *PC* prostate cancer, *RCC* renal cellular cancer

Table 1 (continued)

[a]Distribution of baseline characteristics between training and validation sample was compared using Wilcoxon rank-sum test (Frankel grade and KPS) or chi-square test (other variables). As a result, none of the variables was demonstrated to be significantly different between the two groups

[b]Information about the pre-operative serum album level was not available for 80 patients

consistency between predicted and actual survival probabilities can be seen for each time point in both the internal and external validations.

Figure 5 shows the relationship between the scores including Tokuhashi, Tomita and nomogram and the survival time. There was a favorable correlation ($r = -0.642$, $P < 0.0001$) between the total points in nomogram and the survival time according to linear regression analysis (Fig. 5c), while the correlation coefficients were -0.302 ($P < 0.0001$) between the Tokuhashi score and survival time (Fig. 5a), and 0.446

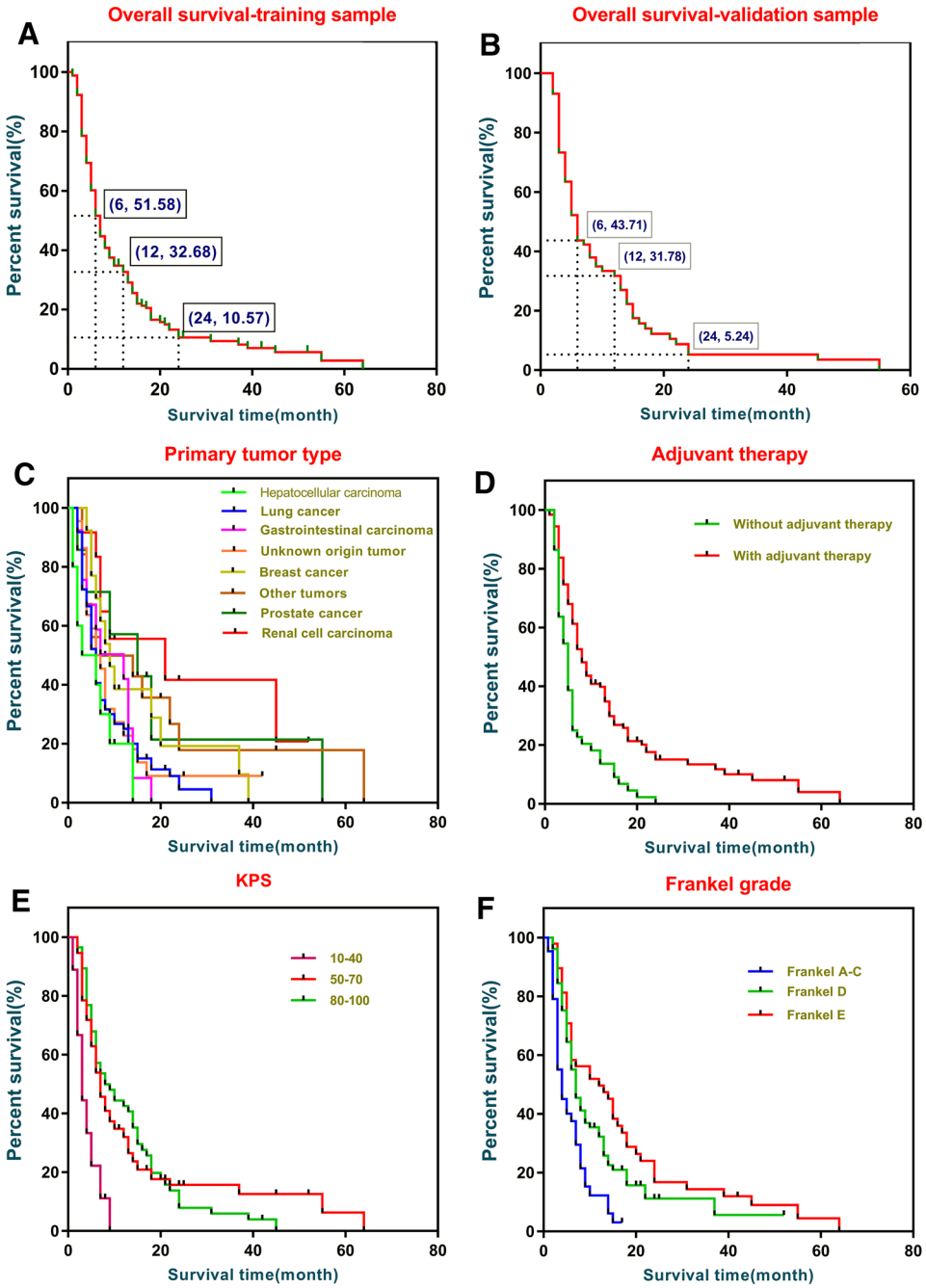

Fig. 1 The Kaplan–Meier survival curves for the training sample (**a**), validation sample (**b**) and factors significantly associated with overall survival in training sample, including the primary tumor type (**c**), adjuvant therapy (**d**), KPS (**e**) and Frankel grade (**f**). The survival rates at 6, 12 and 24 months were 51.58%, 32.68% and 10.57% in the training sample (**a**), and 43.71%, 31.78% and 5.24% in the validation sample (**b**)

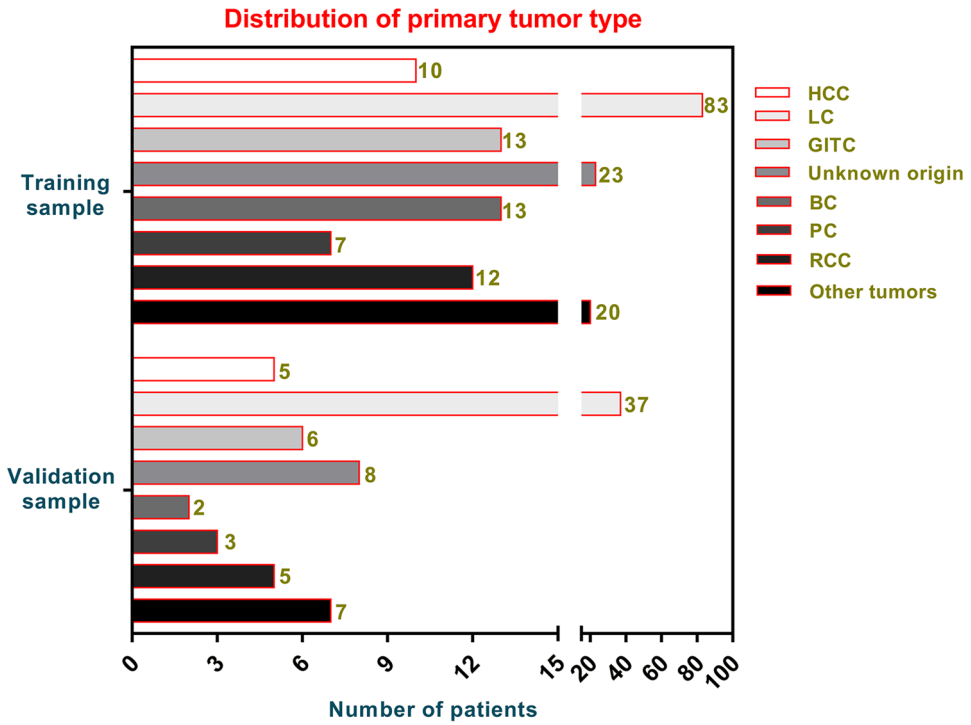

Fig. 2 Distributions of primary tumor types in the training and validation samples. *HCC* hepatocellular carcinoma, *LC* lung cancer, *GITC* gastrointestinal tract cancer, *BC* breast cancer, *PC* prostate cancer, *RCC* renal cellular cancer. Lung cancer was the most common type of primary tumor (83, 48.5%) followed by unidentified primary tumor (23, 13.5%), other tumors (20, 11.7%), gastrointestinal cancer (13, 7.6%)/breast cancer (13, 7.6%), renal cancer (12, 7.0%), hepatic cancer (10, 5.8%) and prostate cancer (7, 4.1%) in order of decreasing frequency, in the training sample. And Lung cancer was the most common type of primary tumor (37, 50.7%) followed by unidentified primary tumor (8, 11.0%), other tumors (7, 9.6%), gastrointestinal cancer (6, 8.2%), hepatic cancer (5, 6.8%)/ renal cancer (5, 6.8%), prostate cancer (3, 4.1%) and breast cancer (2, 2.7%) in order of decreasing frequency, in the validation sample

Table 2 Major post-operative complications

Complications	Number of patients (%)
Wound complications	15 (8.8)
Wound dehiscence/delayed healing	8 (4.7)
Wound infection	3 (1.8)
Wound dehiscence plus heart failure[a]	1 (0.6)
Hematoma formation	3 (1.8)
Systematic complications	13 (7.6)
Heart failure	4 (2.3)
Respiratory failure	5 (2.9)
MOF (multiple organ failure)	2 (1.2)
Cerebral infarction	2 (1.2)
Other complications	10 (5.8)
Pathological fracture	4 (2.3)
Internal fixation failure	3 (1.8)
30-day motality	3 (1.8)
Total	38 (22.2)

[a]There was one patient experienced with wound dehiscence and heart failure at the same period

($P < 0.0001$) between the Tomita score and survival time (Fig. 5b), which were demonstrated to be less acceptable when compared with the nomogram.

Discussion

The modern framework for the treatment of metastatic spine disease has mainly focused on extending survival expectancy and improving quality of life. Laufer et al. [14] proposed the neurologic, oncologic, mechanical, and systemic (NOMS) framework, which emphasized neurologic, oncologic, mechanical stability and systematic considerations, in order to guide the incorporation of multi-disciplinary therapeutic approaches such as conventional radiotherapy and radiosurgery as well as minimally invasive surgery, for spinal metastatic tumors (see Figure S3). With the innovation of various management means, such as effective pharmacology, radiation, target therapy, immunotherapy and hormonotherapy, it has become possible to achieve durable tumor control with minimal treatment-related morbidity. When choosing a therapeutic modality, it is crucial to consider patients' ability to tolerate proposed interventions based on their physiological

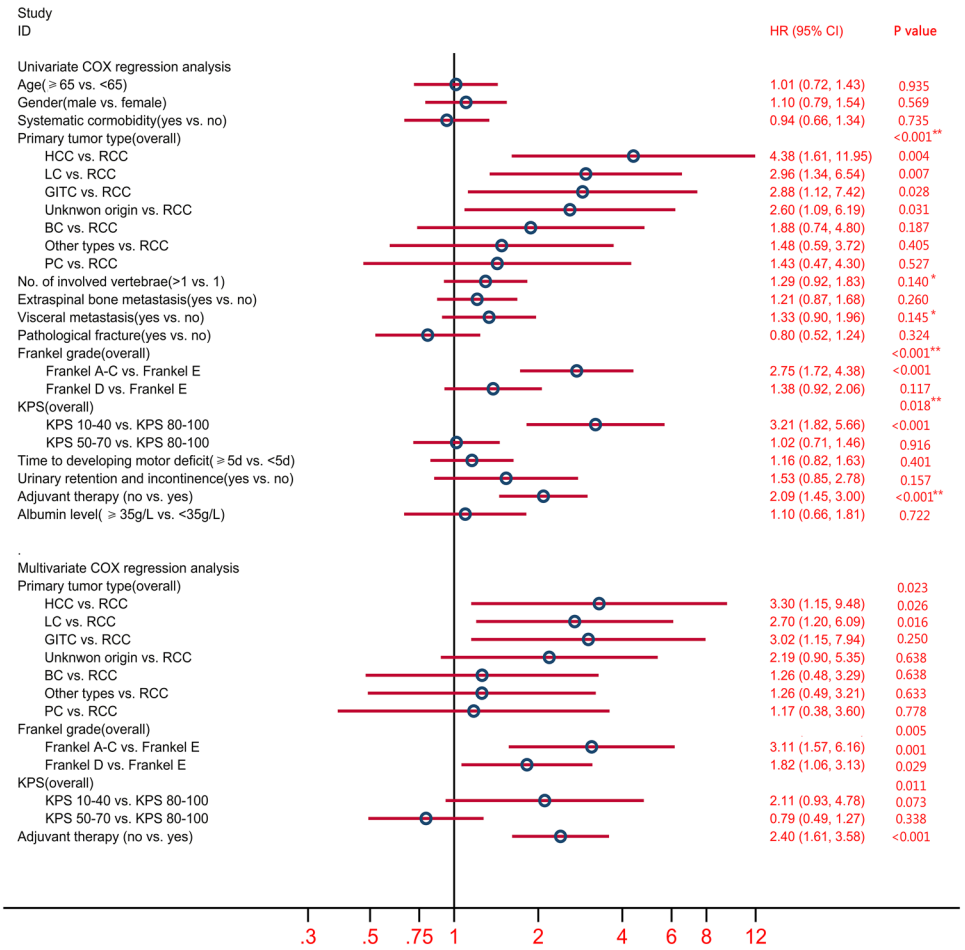

Fig. 3 Forest plot presenting the results of univariable and multivariable COX regression analyses. Primary tumor type ($P<0.001$), Frankel grade ($P<0.001$), KPS ($P=0.018$) and adjuvant therapy (HR = 2.09, CI 95% 1.45–3.00, $P<0.001$) were demonstrated to be significant in univariate analysis, and the number of involved vertebrae (HR = 1.29, CI 95% 0.92–1.83, $P=0.140$) and visceral metastasis (HR = 1.33, CI 95% 0.90–1.96, $P=0.145$) were shown to be marginally significant. While in multivariable analysis, primary tumor ($P=0.023$), Frankel grade ($P=0.005$), KPS ($P=0.011$) and adjuvant therapy (HR = 2.40, CI 95% 16.1–3.58, $P<0.001$) were identified as significant predictors for survival

status and life expectancy. Numerous prognostic scoring systems have been proposed which assist in the estimation of expected survival in patients with spinal metastases [6–9]. The accuracy and consistency of these various predicting systems have been continuously altered as a result of ever-evolving approaches to treating cancer. In our study, several pre-operative characteristics, including primary tumor type, Frankel Grade, KPS and adjuvant therapy, were shown to be significantly associated with OS. A new nomogram model was developed based on these four significant factors.

Our findings regarding the statistical significance of the four pre-operative characteristics are generally in accord with existing studies. Primary tumor type has been widely accepted to be one of the most robust OS predictors in multiple studies [6–9, 15–17]. Significant differences in survival among various tumor types are likely to be related to discrepancies in biological behaviors (such as growth speed, local invasion, and distant metastasis) in those different tumors [15, 16]. Therefore, metastatic spine invasion by various aggressive tumors, such as non-small cell lung cancer and tumors of unknown primary origin, may tend to benefit less from the extensive interventions which require a combination of prolonged hospital stays and intense physical therapy [14]. Unlike the groupings of primary tumor type in the Tomita [7] and Tokuhashi [6] scoring systems, we divided tumors into eight groups in order to retain as much primary tumor histology as possible.

Pre-operative adjuvant therapy has become a crucial prognostic factor, and so has received extensive attention among spinal surgeons. The continuing evolution of adjuvant therapeutic approaches has been altering choice of treatment over the past few decades. Previously, when radiation has not been available, laminectomy surgery to remove only the posterior elements of spine and so achieve indirect decompression was the only approach for managing spinal metastasis. However, when radiotherapy was introduced, many studies demonstrated that there was no benefit from laminectomy with or without radiotherapy when compared to radiotherapy, and so this surgery was largely abandoned [18–20]. Following this, a new surgical technique for removing tumor tissues directly and achieving immediate circumferential decompression was developed. Many studies reported that this direct decompression technique (with or without radiotherapy) provided superior survival and stabilization to radiotherapy alone [21–23]. In the randomized trial of Patchell et al. [24], patients were randomized

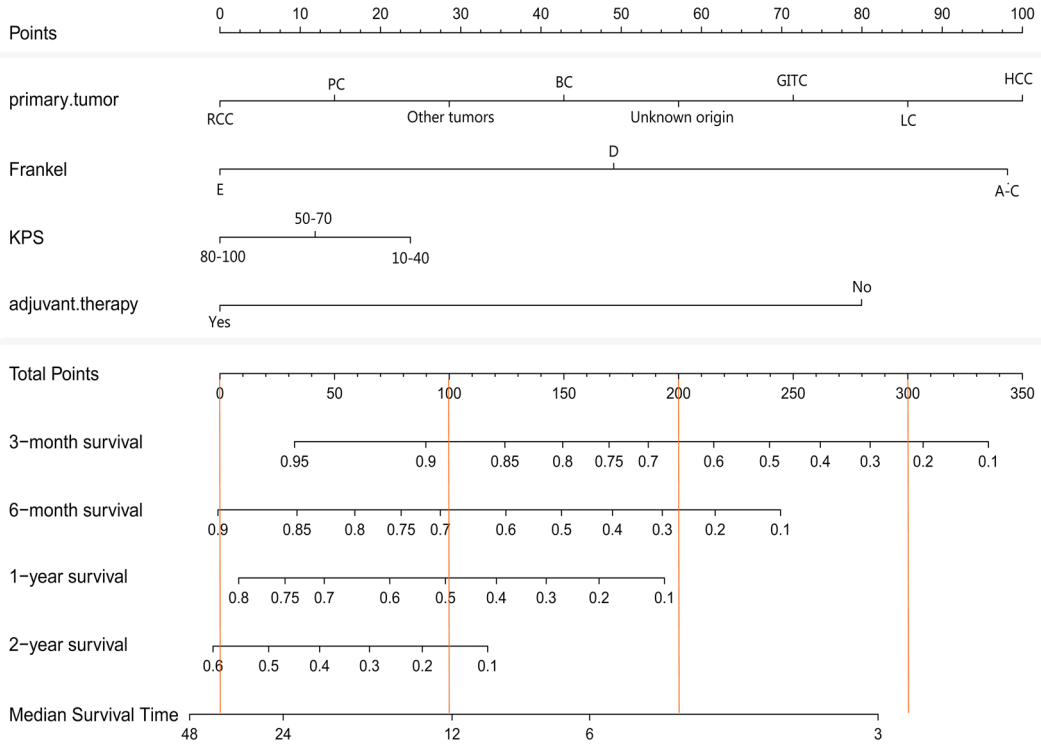

Fig. 4 The newly established nomogram based on the four significant predictors for survival. In this plot, patients' survival probabilities at 3, 6, 12 and 24 months, as well as the median survival time, were listed with numerical form. When using this nomogram for predicting survival of patients with spinal metastases, the point of each factor should be added up together to a total point, and then a vertical line should be drawn down the total point to get the survival probabilities of 3, 6, 12 and 24 months and the median survival time

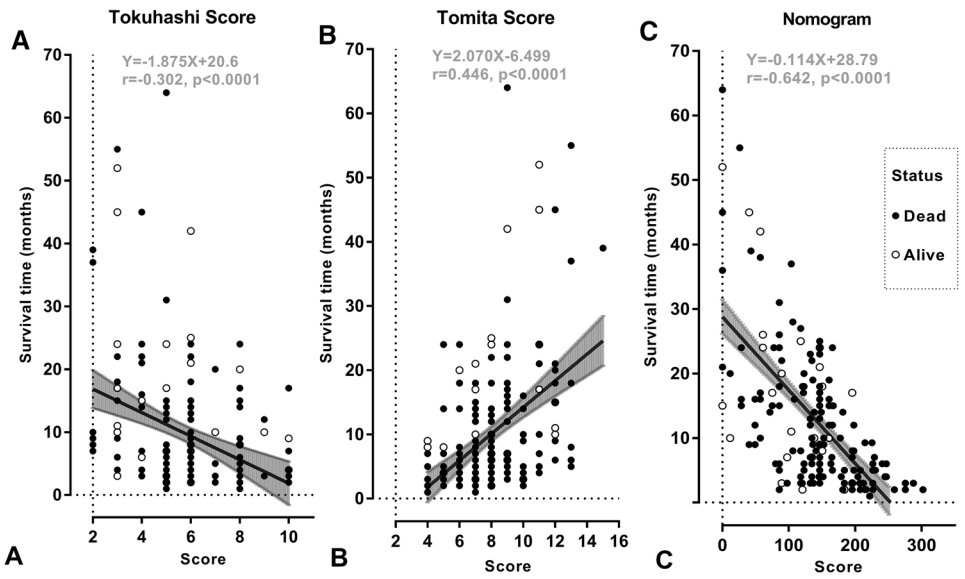

Fig. 5 Relations between three different scores (**a**, Tokuhashi score; **b**, Tomita score; **c**, nomogram) and survival time. There was a favorable correlation between the total point of nomogram and survival period, while a less acceptable relation between the other two prognostic scores and survival time

to either direct decompression plus radiotherapy or radiotherapy alone. These authors found that direct decompression surgery plus radiotherapy is superior to radiotherapy alone for this cohort of patients. Following the publication of this landmark article, the role of direct decompression surgery in managing metastatic spinal cord compression was established.

However, following the development of new treatment technologies including stereotactic radiosurgery, target therapy, effective chemotherapy and immunotherapy,

treatment decisions have accordingly moved on from simply selecting either surgery or conservative radiotherapy to becoming a complex, multi-disciplinary consideration. Previously, clinicians aimed to attain maximal tumor resection and so achieve durable tumor control. However, modern surgery aims to decrease the extent of surgery, which needs to only separate the tumor from the spinal cord and so maximize the radiation dose that can be safely applied to the tumor [14]. It is therefore not surprising that adjuvant therapy has been found to be a vital factor which is positively associated with OS.

The prognostic effect of pre-operative Frankel Grade on survival time has been reported as controversially differing in various studies [6, 25–27]. In the revised Tokuhashi [6] and Enkaoua [25] scoring systems, and studies of Rades et al. [17, 26, 27], the preoperative neurological status was included as one of the predicting factors. These authors hypothesized that patients living with walking dysfunction caused by spinal cord metastatic compression were more likely to experience various fatal complications such as pneumonia and deep venous thrombus, which would further adversely alter their prognosis. The results of our study is in accordance with these studies. KPS is another prognostic factor for spinal metastatic patients which has been commonly discussed in former studies [17, 26]. It is reasonable to assume that patients with a poor KPS may be too debilitated to tolerate the more curative and intensive therapeutic modalities.

Based on these widely discussed predictors for OS, our new nomogram model will provide numerical probabilities at different time points for an individual patient. We believe this must be a informative data for neurosurgeons when taking their patients to a systematic and multi-disciplinary treatment consideration.

This study has some limitations. Firstly, patient data were collected retrospectively, which may cause a latent risk of bias. Secondly, while we have carefully validated our newly established nomogram model both internally and externally, the validation group was randomly selected from the whole cohort, which originated from the same centers as the training group. Therefore, a study using participants from different centers or even different countries should be carried out to further test external validity as well as prognostic capacity on survival.

In summary, a nomogram plot, that is, a simple graphical representation that generates a numerical probability of survival, was developed for predicting OS of patients with spinal metastatic tumors. The new proposed nomogram plot is a user-friendly model tailored to the profile of each individual patient, which could facilitate medical procedures during encounters related to clinical decision making.

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Compliance with ethical standards

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

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

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