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Recursive Partitioning Analysis (RPA) of Prognostic Factors for Overall Survival in Patients with Spinal Metastasis: A New System for Stratified Treatment

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■ BACKGROUND: Accurate survival estimate is necessary when determining the most appropriate treatment modality for metastatic spinal tumor. The main purpose of this study was to identify the prognostic factors of spinal metastasis and establish a decision tree model.

■ METHODS: A consecutive cohort of 507 patients from 3 institutional clinical centers who were treated for metastatic spinal tumor between 2005 and 2015 were retrospectively reviewed. In total, 70% of the participants were randomly selected as a "training sample." The prognostic effect of preoperative factors was evaluated using the "training sample," and a decision tree model was established. Then, the accuracy of the new model, as well as the Tokuhashi and Tomita score, was tested by the "test sample," which consisted of the remaining 30% of participants.

■ RESULTS: A decision tree model was generated based on the significant factors with an order of descending importance on predicting the prognosis. According to the new model, patients were classified into 3 groups, mean survival times of less than 6 months, 6—12 months, and more than 12 months, who were indicated for conservative therapy/palliative operation, palliative operation, and invasive excision, respectively. The newly established model was confirmed to be of high accuracy in predicting overall survival, whereas the Tokuhashi and Tomita scores were of modest accuracy and consistency.

■ CONCLUSIONS: A new decision tree model for prognosis prediction in spinal metastasis was established with a satisfactory accuracy and consistency. However, the Tokuhashi and Tomita systems were presented to be less correlated between the scores and actual survival.

INTRODUCTION

Recent treatment regimens have prolonged the average survival time in patients with cancer, especially after the application of modern systemic therapy such as targeted therapy, systematic chemotherapy, and immunological therapy, whereas metastasis to the spine has become a very common clinical outcome simultaneously. As many as 70% of patients with advanced cancer develop spinal metastases, among whom 20% usually suffer from neurologic deficits as a result of metastatic spinal cord compression.[1-5] In patients with metastatic spinal cord compression, nearly 10% were involved with a process of surgical decompression with/without stabilization, which can therefore restore neurologic function and improve quality of life.[1,2]

However, how to identify candidates for surgical procedures is not clear yet. It is generally accepted that life expectancy drives treatment regimens for spine metastasis. For instance, patients with life expectancy of less than 3 months are not indicated for surgery procedures, but they can obtain the maximal benefit from radiotherapy alone or supportive care.[6] Therefore, some surgeons and radiologists established several prognostic scoring systems to help selecting an appropriate therapeutic modality for individual patient, such as the scores of Tokuhashi, Tomita, Van der Linden, and Enkaoua.[7-11]

However, the predictive ability of these former established scores was demonstrated to be modest in many studies.[12-16] Ulmar et al.[12] found that the Tomita score showed no correlation between predicted and real survival for patients with renal cancer with

Key words
- Decision tree model
- Prognostic factor
- Recursive partitioning analysis
- Spinal metastasis
- Survival

Abbreviations and Acronyms
KPS: Karnofsky Performance Scale
RPA: Recursive partitioning analysis

Figure 1. The flow diagram of the study design. CHAID, Chi-Square Automatic Interaction Detection.

vertebral metastases. Hessler et al.[13] evaluated the accuracy of Tokuhashi score in predicting the survival of patients with vertebral metastases from lung cancer, and they found that the actual and predicted survival were similar in only 67.1% of the patients. Gakhar et al.[14] also presented that the modified Tokuhashi score was not a reliable tool to predict survival in patient with spinal metastases.

The statistical method traditionally used for these systems is the Cox proportional hazards model, whereas the decision tree model is established using a method of recursive partitioning analysis (RPA), which could create branches by splitting recursively using the most important predictors. Therefore, it could detect the most sensitive factor for predicting in each subdivided group of patients, which subsequently could improve the accuracy and consistence of model.

Hence, the current study was performed with the goal of detecting the significant prognostic factors of overall survival in patients with metastatic spinal tumor and establishing an easy-to-use decision tree model through a method of RPA. What's more, we'll validate the accuracy of the newly established model and compare it to the Tokuhashi and Tomita scores.

MATERIALS AND METHODS

Data Source and Inclusion Criteria

In this retrospective study, 3 clinical centers were systematically searched to identify all patients treated for metastatic spinal tumor between March 2005 and December 2015. Following thorough clinical examination, magnetic resonance imaging of the whole spine, a staging computed tomography scan, and other investigations (e.g., biopsy) as appropriate for the diagnosis were performed. Demographic data as well as medical conditions were collected from medical records, and survival data were obtained either from medical records or by telephone follow-up.

Patients were included when they met the following criteria: 1) a definitive diagnosis of spinal metastases; and 2) treated with various surgical interventions for medically intractable pain, rapidly progressive neurologic deterioration, and evidence of clinical or radiographic instability. Patients were excluded according to the following criteria: 1) treated with vertebroplasty or kyphoplasty procedures; and 2) lymphoma and multiple myeloma. This study was carried out in accordance with the Declaration of Helsinki and approved by the hospital ethics committee, and informed consent was obtained from the participants.

Recorded Data

A total of 507 patients were enrolled and 12 preoperative factors, including age, sex, primary tumor type, visceral metastasis, extraspinal bone metastasis, number of involved vertebrae, location of spinal metastasis, Frankel grade, Karnofsky Performance Scale (KPS) score, pathologic fracture, time to developing motor deficit, and urinary retention/ incontinence, were collected. The primary tumor type was divided into 3 groups by growth speed according to the Tomita score, including slow (breast, thyroid, prostate, etc.), moderate (kidney, uterus, ureter, etc.), and rapid (lung, stomach, esophagus, pancreas, etc.) growth speed.[9]

Table 1. Characteristics of the Study Population		
Variables	No. Patients, *n*	Percentage, %
Age, years		
≥65	172	34
<65	335	66
Sex		
Male	284	56
Female	223	44
Type of primary tumor by growth speed		
Group A (rapid)*	223	44
Group B (moderate)*	188	37
Group C (slow)*	96	19
Visceral metastasis		
Yes	112	22
No	395	78
Karnofsky Performance Scale		
10—40	57	11
50—70	282	56
80—100	168	33
Frankel grade		
A—C	171	34
D—E	336	66
Location of involved vertebrae		
Cervical	76	15
Non-cervical	431	85
Number of involved vertebrae		
Solitary	233	46
Multiple	274	54
Extraspinal bone metastasis		
Yes	225	44
No	282	56
Pathologic fracture		
Yes	91	18
No	416	82
Time developing motor deficit		
≤5 days	365	72
>5 days	142	28
Urinary retention/incontinence		
Yes	46	9
No	461	91

*Primary tumor was divided into 3 groups by growth speed according to the Tomita score, including rapid (lung, stomach, esophagus, pancreas, etc.), moderate (kidney, uterus, ureter, etc.), and slow (breast, thyroid, prostate, etc.) groups.

Treatment Modality

Three different surgical procedures were performed: palliative posterior decompression was conducted in 183 (36%) patients, subtotal tumorectomy in 248 (49%) patients, and total piecemeal spondylectomy in 76 (15%) patients. Reconstruction and stabilization procedures were conducted with titanium mesh, pedicle screws and hooks, bone cement and bone graft fusion alone, or with various combination in 345 (68%) patients. Adjuvant therapies were provided to 132 (26%) patients preoperatively, including radiotherapy, chemotherapy, targeted therapy, bisphosphonates, denosumab, and steroids. Radiotherapy, chemotherapy, and bisphosphonates were administered to 147 (29%) patients, 41 (8%) patients, and 51 (10%) patients, respectively, as postoperative adjuvant therapies.

Statistical Analysis

The flow diagram of the study design was presented in **Figure 1**. The "Chi-Square Automatic Interaction Detection" algorithm was applied for RPA and an analysis of variance was conducted to determine whether a node should be split. The nodes were always split by the most important predictors, and the maximum depth of the decision tree was restricted to no more than 3. During establishment of the decision tree, 70% of the patients were randomly selected as the "training sample" by computer program (using the "partition" button in IBM SPSS Modeler software, version 18.0; IBM Corp., Armonk, New York, USA). Then, the remaining 30% of patients were regarded as the "test sample" to verify accuracy of the newly established model, as well as the Tokuhashi and Tomita score.

The accuracy and consistence of the decision tree model was tested with the inter-group correlation coefficient and correlation coefficient (with simple linear regression) between predicted and actual survival time. In addition, a correlation analysis was carried out between Tokuhashi/Tomita score and patients' actual survival time with the correlation coefficient by linear regression. Developing of the decision tree and verification of the accuracy were conducted in SPSS Modeler version 18.0 and SPSS version 24.0 for Windows (ISM Corp.). All reported P values are based on 2-sided tests, with P values 0.05 considered significant.

RESULTS

Demographics and Clinical Characteristics

The characteristics of the patients were presented in **Table 1**. The mean age of the included patients was 59.6 ± 10.5 years (range: 18—84 years), and the percentage of male patients was 56%. The number of patients with primary tumors in the rapid growth speed group was added up to 223 (44%), whereas in moderate and slow groups were 188 (37%) and 96 (19%). The average survival time was 9.2 ± 0.8 months (range: 1—64 months).

Establishment of the New Predictive Model

A total of 355 (70%) patients were randomly selected as "training sample" by computer program. Based on this sample, the 12 characteristics shown in **Table 1** were analyzed for significance on predicting patients' survival. **Figure 2** shows the 7 significant factors with an order of descending importance on predicting of
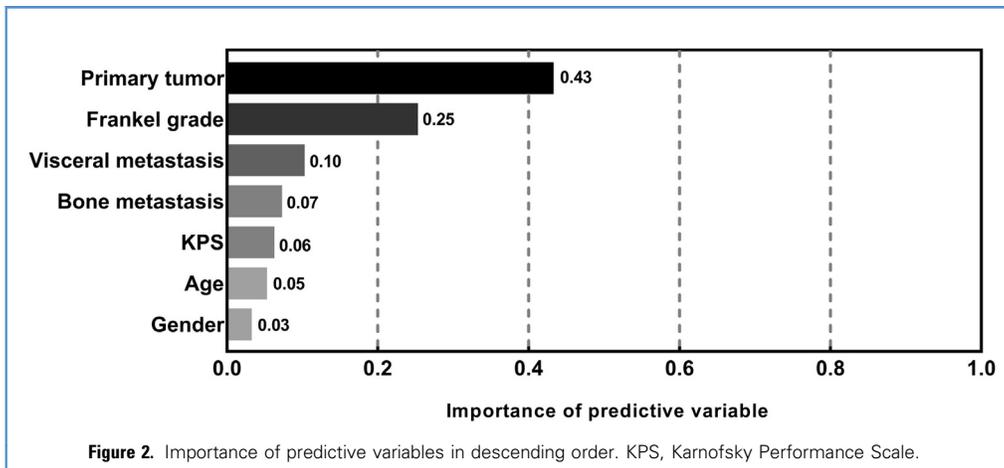
Figure 2. Importance of predictive variables in descending order. KPS, Karnofsky Performance Scale.

survival. As a result, primary tumor type was found to be the most important predictive variable, followed by Frankel grade, visceral metastasis, extra-spinal bone metastasis, KPS, age, and sex.

After recursively splitting the patients into subgroups, we established a decision tree model with a "tree depth" of 3 layers (Figure 3). In the first layer, patients were divided into 3 groups

by the primary tumor type. Then, the rapid subgroup was further split into 3 groups by KPS, whereas moderate and slow groups were split into 2 groups by Frankel grade in the second layer. After that, visceral metastasis, extra-spinal bone metastasis, age, and sex were used for further partitioning.
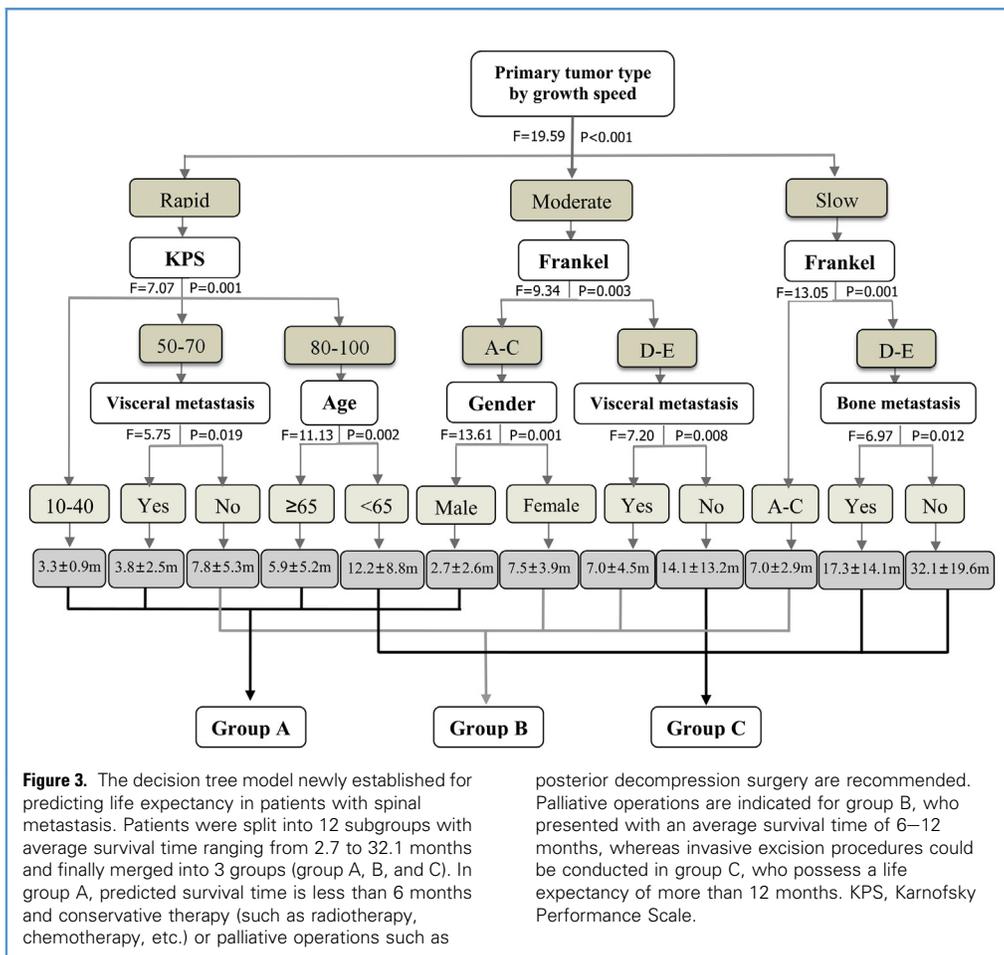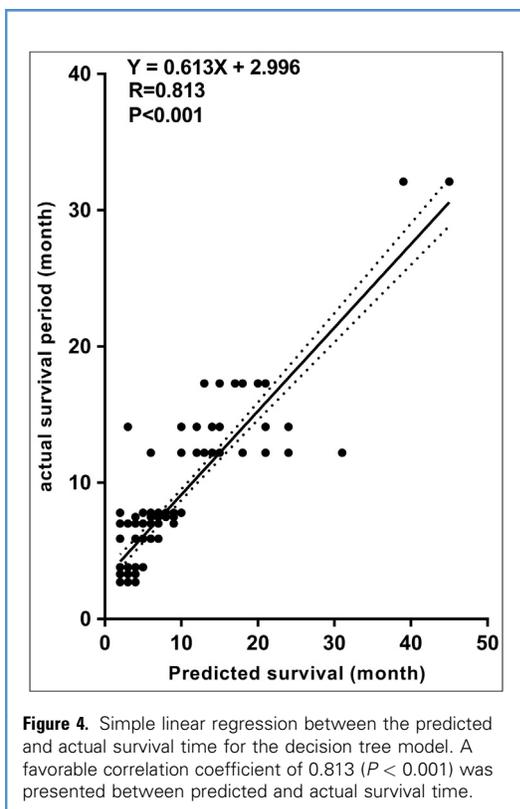

Figure 3. The decision tree model newly established for predicting life expectancy in patients with spinal metastasis. Patients were split into 12 subgroups with average survival time ranging from 2.7 to 32.1 months and finally merged into 3 groups (group A, B, and C). In group A, predicted survival time is less than 6 months and conservative therapy (such as radiotherapy, chemotherapy, etc.) or palliative operations such as posterior decompression surgery are recommended. Palliative operations are indicated for group B, who presented with an average survival time of 6–12 months, whereas invasive excision procedures could be conducted in group C, who possess a life expectancy of more than 12 months. KPS, Karnofsky Performance Scale.

Figure 4. Simple linear regression between the predicted and actual survival time for the decision tree model. A favorable correlation coefficient of 0.813 ($P < 0.001$) was presented between predicted and actual survival time.

Finally, patients were recursively partitioned into 12 "leaf nodes" in the third layer, with mean survival times of 3.3 ± 0.9, 3.8 ± 2.5, 7.8 ± 5.3, 5.9 ± 5.2, 12.2 ± 8.8, 2.7 ± 2.6, 7.5 ± 3.9, 7.0 ± 4.5, 14.1 ± 13.2, 7.0 ± 2.9, 17.3 ± 14.1, and 32.1 ± 19.6 months, respectively, and were merged into groups A, B, and C subsequently. In group A, a predicted survival time of less 6 months was presented and conservative therapy (such as radiotherapy, chemotherapy, etc.)/palliative operations (such as posterior decompression surgery) are recommended. Palliative operations are indicated for patients with an average survival time of 6–12 months in group B, whereas more invasive excision procedures could be conducted in patients from group C, who were presented to possess a life expectancy of more than 12 months.

Validation of the New Model
The remaining 152 (30%) patients were regarded as the "test sample" for accuracy verification. A favorable correlation coefficient ($R = 0.813$, $P < 0.001$) was presented between predicted and actual survival time for the decision tree model, through a method of simple linear regression, and an equation was built as "$Y = 0.613X + 2.996$" (**Figure 4**). The intergroup correlation coefficient between the predicted and actual survival was presented to be 0.801 ($P < 0.001$), which indicates excellent consistency and accuracy. Regarding the Tokuhashi and Tomita scores, simple linear regression was performed to detect the correlation between the scores and actual survival time, and the results are shown in **Figure 5**. The correlation coefficients were demonstrated to be 0.227 for Tokuhashi score and −0.282 for Tomita score, which

indicates weak correlation between the 2 scores and patients' survival time, and equations were established as "$Y = 1.043X + 1.676$" and "$Y = 20.090 − 1.940X$."
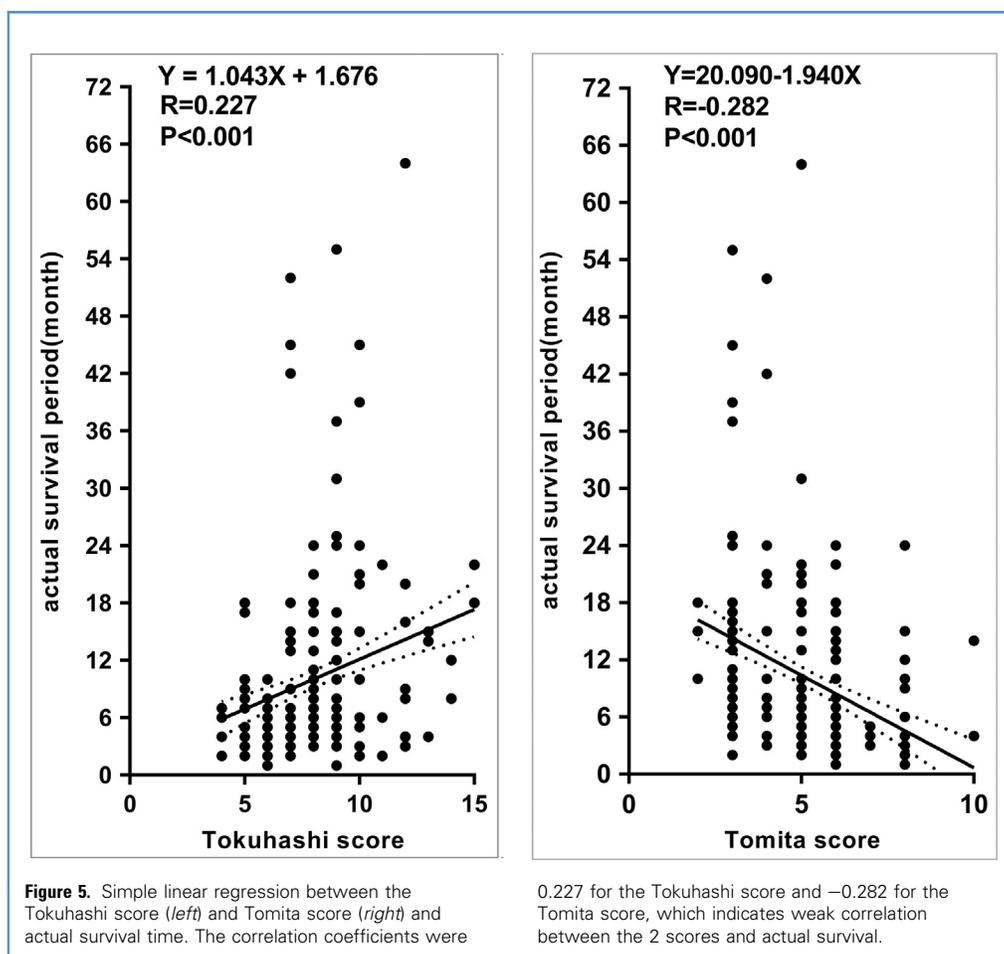
DISCUSSION
Accurate prediction of survival is necessary for metastatic spinal tumor when selecting the optimal therapeutic modality. Many spine surgeons and radiologists have been devoted to developing some valuable scores, including Tokuhashi,[7,8] Tomita,[9] van der Linden,[10] and Ekaoua,[11] to assist in predicting patients' life expectancy. However, these scores were established with a small number of patients and which involved various types of primary tumors. In addition, these scores used the same prognostic factors in survival predicting for every individual patient, but we speculate that patients with different preoperative characteristics (e.g., primary tumor type) may possess distinct significance on various prognostic factors.

In the study of Ulmar et al.,[12] it was reported that the Tomita score showed no correlation between the predicted and actual survival time for metastatic spinal tumor from renal cancer. Hessler et al.[13] also reported that the Tokuhashi score is a suboptimal tool when used for the prediction of an individual prognosis in the group of patients with lung cancer. The actual and predicted survival were similar in only 67.1% of the patients, whereas there was no correlation in the other 32.9%. In the study of Chen et al.,[16] the authors evaluated different prognostic scoring systems and factors in cases with spinal metastases from hepatocellular carcinoma. They found that only the revised Tokuhashi score is practicable and predictive, whereas some else factors, such as serum albumin and lactate dehydrogenase, also have prognostic value. However, Tomita score and Bauer score were demonstrated to be not predictive for patients with hepatocellular carcinoma, whereas the revised van der Linden score was only practicable for patients with good performance status and without visceral metastases. Thus, it is under general debate about the practicability and accuracy of these scores. In current study, we have carried out a process of RPA and established a decision tree model using a method of "machine learning." To our knowledge, this is the first established decision tree model for predicting the survival of patients with spinal metastases. A favorable correlation and an excellent consistence between predicted and actual survival also were presented, whereas Tokuhashi and Tomita scores were demonstrated to be less relevant to the actual survival.

Prognostic Factors Involved in the New Model
In the newly built model, a total of 7 prognostic factors were enrolled. Primary tumor type, as the most important prognostic factor in this study, has been widely discussed and adopted as prognostic factors in various scoring systems.[8-11,17-20] The biological behaviors of various types of primary tumor and their sensitivity to adjuvant therapies was different, which accounts for significant difference of prognosis among various primary tumor types. Frankel grade is a factor to reflect patients' preoperative neurologic status, as patients with Frankel D–E are ambulatory whereas patients with Frankel A–C were not. Frankel grade is prognostic factor that was full of controversy among various

Figure 5. Simple linear regression between the Tokuhashi score (*left*) and Tomita score (*right*) and actual survival time. The correlation coefficients were 0.227 for the Tokuhashi score and −0.282 for the Tomita score, which indicates weak correlation between the 2 scores and actual survival.

studies.[9,10,21-28] Rades et al.[21-24] found that preoperative neurologic status is a significant predictor, and they insisted that patients who are nonambulatory are more likely to suffer from some fetal complications such as pneumonia. Prasad and Schiff[25] also found that Frankel grade is the most robust prognostic factor apart from the primary tumor histology.

On the contrary, some studies believe that neurologic status is not a pure predictor but only a factor to reflect location and volume of the spinal lesion.[9,10,26-28] As stated by Tomita et al.,[9] patients with neural paralysis are not account for in the decreased life expectancy as neurologic status would be improved after individual therapy. In this study, Frankel grade is the most significant factor in patients with primary tumor of moderate and slow growth but not in group of rapid growth speed. Instead, KPS was presented to be the most significant factor for group of rapid growth speed. As reported in the studies of Ogihara et al.,[29] Chen et al.,[30] Park et al.,[31] and Lei et al.,[32] performance status is an important prognostic factor for spinal metastasis from lung cancer. In general, patients in the rapid group often are debilitated after spinal metastasis, and in patients with poor performance status, invasive operative procedures and adjuvant therapies such as radiotherapy, chemotherapy, and target therapy might not be tolerated. The presence of visceral and other bone metastasis generally has been accepted to be significant in former

studies, whereas age and sex are less accepted.[8-10,17,27,33] In this study, it was recursive partitioning that made the age and sex become significant in some special subgroups. As a result, it could make the model a more practicable and accurate tool for predicting survival of individual patients.

Clinical Relevance of the New Model

In fact, in some cases such as patients with disseminated cancer or patients with very poor performance status, the prognosis may be

Table 2. Harrington Classification of Metastases to the Spinal Column

Class	Criteria
Class I	No significant neurologic involvement
Class II	Involvement of bone without collapse or instability
Class III	Major neurologic impairment (sensory or motor) without significant involvement of bone
Class IV	Vertebral collapse with pain due to mechanical causes or instability but without significant neurologic compromise
Class V	Vertebral collapse with pain due to mechanical causes or instability combined with major neurologic impairment

Table 3. Revised Tokuhashi Score for Prognosis of Spinal Metastasis

Factors	Score
General condition (KPS)	
Poor (KPS 10—40)	0
Moderate (KPS 50—70)	1
Good (KPS 80—100)	2
Extraspinal bone metastases	
$\geq$3	0
1—2	1
0	2
No. of metastases in the vertebral body	
$\geq$3	0
2	1
1	2
Metastases to the major internal organs	
Unremovable	0
Removable	1
No metastases	2
Primary site of the cancer	
Lung, osteosarcoma, stomach, bladder, esophagus, pancreas	0
Liver, gallbladder, unidentified	1
Others	2
Kidney, uterus	3
Rectum	4
Thyroid, breast, prostate, carcinoid tumor	5
Neurologic status	
Complete (Frankel A, B)	0
Incomplete (Frankel C, D)	1
None (Frankel E)	2

In the revised Tokuhashi score, 6 prognostic factors were included, and the total score ranged from 0 to 15. Conservative treatment or palliative surgery was indicated in patients with a predicted prognosis of less than 6 months (score 0—8) or in those with multiple vertebral metastases, whereas excisional surgery was performed in patients with a predicated prognosis of 1 year or more (score 12—15), or with a predicted prognosis of 6 months or more (score 9—11), and with metastasis in a single vertebra. KPS, Karnofsky Performance Scale.

very limited, and primary goal of treatments should be directed toward optimal palliation and managing related complications.[34,35] However, in patients with sufficient life expectancy, it generally is accepted that the more extensive the surgical procedures, the more prolonged the palliative effect.[34] Therefore, how to choose the appropriate treatment for patients with spinal metastases depends mainly on an adequate prediction of survival.

Many scoring systems have been proposed to help indicate treatment options.[8-10,34] In 1986, Harrington et al.[34] developed a strategy for the treatment of metastatic spine tumors, which included 5 classes (class I-IV) based on the extent of bone destruction and neurologic compromise (Table 2). Harrington suggested patients with class I-III should be treated with primary radiotherapy, whereas primary surgical intervention was recommended for patients in class IV and V. The revised Tokuhashi score includes 6 prognostic factors, and the total score ranges from 0 to 15 (Table 3). Conservative treatment or palliative surgery is indicated in patients with a predicted prognosis of less than 6 months (score 0—8) or in those with multiple vertebral metastases, whereas excisional surgery is performed in patients with a predicated prognosis of 1 year or more (score 12—15), or with a predicted prognosis of 6 months or more (score 9—11), and with metastasis in a single vertebra.[8]

In our study, patients were recursively split into 12 subgroups with different average survival time ranging from 2.7 to 32.1 months, using 7 prognostic factors. For added convenience, the 12 subgroups were merged into 3 groups, including groups A, B, and C. The average survival time of patients is less than 6 months in group A. In consideration of the limited survival, conservative treatment (such as radiotherapy, chemotherapy, target therapy, etc.) or palliative surgery would be indicated for this group of patients. The mean survival time in group B ranges from 6 to 12 months and palliative surgery is recommended, whereas for patients with sufficient life expectancy of more than 12 months in group C, more benefits could be obtained from some invasive excision procedures.

Limitations
This study has some limitations. First, the current study was designed as a retrospective study, which would give rise to some inevitable bias in collected data. In addition, we have only analyzed the prognostic effect of preoperative characteristics. To our knowledge, some effective clinical interventions such as target or chemical therapies have altered cancer patients' life expectancy in specific tumor types in some extent. Therefore, we remind clinicians to be cautious when using this model for patients involved with these specific treatments. Finally, challenges also exist when using such model for decision making if not all data are available pretreatment (for example, pathology might not be available when the surgeon is deciding to operate on the patient). Therefore, a multidisciplinary and systematic consideration should be carried out with guiding of the decision model.

CONCLUSIONS
In conclusion, an easy-to-use decision tree model for predicting the prognosis of individual patients with spinal metastasis was established with a satisfactory accuracy and consistence. However, the Tokuhashi system and Tomita system were presented to be less correlated between scores and actual survival.

ACKNOWLEDGMENTS

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