Validation of Traditional Prognosis Scoring Systems and Skeletal Oncology Research Group Nomogram for Predicting Survival of Spinal Metastasis Patients Undergoing Surgery

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Background: Many scoring systems that predict overall patient survival are based on clinical parameters and primary tumor type. To date, no consensus exists regarding which scoring system has the greatest predictive survival accuracy, especially when applied to specific primary tumors. Additionally, such scores usually fail to include modern treatment modalities, which influence patient survival. This study aimed to evaluate both the overall predictive accuracy of such scoring systems and the predictive accuracy based on the primary tumor.

Methods: A retrospective review on spinal metastasis patients who were aged more than 18 years and underwent surgical treatment was conducted between October 2008 and August 2018. Patients were scored based on data before the time of surgery. A survival probability was calculated for each patient using the given scoring systems. The predictive ability of each scoring system was assessed using receiver operating characteristic analysis at postoperative time points; area under the curve was then calculated to quantify predictive accuracy.

Results: A total of 186 patients were included in this analysis: 101 (54.3%) were men and the mean age was 57.1 years. Primary tumors were lung in 37 (20%), breast in 26 (14%), prostate in 20 (10.8%), hematologic malignancy in 18 (9.7%), thyroid in 10 (5.4%), gastrointestinal tumor in 25 (13.4%), and others in 40 (21.5%). The primary tumor was unidentified in 10 patients (5.3%). The overall survival was 201 days. For survival prediction, the Skeletal Oncology Research Group (SORG) nomogram showed the highest performance when compared to other prognosis scores in all tumor metastasis but a lower performance to predict survival with lung cancer. The revised Katagiri score demonstrated acceptable performance to predict death for breast cancer metastasis. The Tomita and revised Tokuhashi scores revealed acceptable performance in lung cancer metastasis. The New England Spinal Metastasis Score showed acceptable performance for predicting death in prostate cancer metastasis. SORG nomogram demonstrated acceptable performance for predicting death in hematologic malignancy metastasis at all time points.

Conclusions: The results of this study demonstrated inconsistent predictive performance among the prediction models for the specific primary tumor types. The SORG nomogram revealed the highest predictive performance when compared to previous survival prediction models.

Keywords: Spinal metastasis, Survival prediction, Prognosis score, Skeletal Oncology Research Group nomogram, Prediction models
Disseminated metastasis is a major problem in the treatment of cancer patients. From cancer autopsies, the incidence of skeletal metastasis has been reported to range from 27% to 70%, and the spine is the most frequent location as the incidence ranges from 34% to 56%.1-4 With advances in modern chemotherapy, patients have longer survival, and therefore, the incidence of spinal metastasis has been increasing and becoming clinically apparent with significantly impaired quality of life for patients, which results in the need for surgery in the majority of patients.5,6 Nevertheless, the key factor that assists in surgical decision-making is the expected survival period.

There are many scoring systems that predict the patient overall survival based on the clinical parameters and type of primary tumor. The most common predictive models used in metastatic spine disease include the revised Tokuhashi,7 Tomita,8 and Katagiri9 scores and the more recent scoring algorithm and nomogram created by the Skeletal Oncology Research Group (SORG).10 To date, no consensus exists regarding which of these scoring systems has the greatest predictive survival accuracy, especially when applied to specific primary tumors.11-14 The scores have also been created using the variables input at the time of study, which may not include modern treatment modalities influencing patient survival, such as target therapies or advanced radiation techniques.15,16 Thus, the aim of the present study was to evaluate both the overall predictive accuracy of such scoring systems and the predictive accuracy based on the primary tumor using our patient database.

METHODS

Institutional Review Board approval was obtained at Ramathibodi Hospital, Mahidol University Medical Center (Protocol No. COA. MURA 2020/1653). A retrospective review was conducted on all patients aged more than 18 years, diagnosed with spinal metastasis, and had undergone surgical treatment at Ramathibodi Hospital, Mahidol University between October 2008 and August 2018. The hematologic malignancy included in this present study was lymphoma (4 cases) and multiple myeloma (14 cases). Informed consent was obtained from all patients or the first degree relative, if the patient was deceased, via telephone calls. The patient demographic data were retrieved from electronic medical records (EMR). Survival was calculated from the day of surgery to the date of confirmed death, which was collected either from EMR or through telephone calls. If the patient was still alive and had regular follow-ups, the latest EMR date were recorded. The exclusion criteria were as follows: (1) patients who underwent only spinal biopsy without additional procedures; (2) incomplete data (e.g., no definite pathological diagnosis); and (3) no confirmed death date recorded in EMR and patients who could not be contacted by phone.

All patients were scored based on retrospective data before the time of surgery. Scoring was performed by a study member (CB), who did not participate in the medical or surgical management of these patients and was blinded to postoperative survival. The scoring systems included the Tomita score,8 revised Tokuhashi score,7 revised Katagiri score,17 and SORG nomogram.10,14 A survival probability was calculated for each patient with respect to the given scoring systems. The predictive ability of each scoring system was assessed based on the time period of the original system description by using receiver operating characteristic (ROC) analysis at postoperative time points so that the area under the curve (AUC) could be calculated to quantify the predictive accuracy of each score.

Statistical Analysis

Statistical analysis was performed using STATA SE ver. 16.1 (StataCorp., College Station, TX, USA). The survival analysis of all patient cohorts and the specific tumor types were calculated using Kaplan-Meier plot and reported as the median survival time with a 95% confidence interval (CI). The predictive abilities of prognostic scoring algorithms were tested using ROC analysis at definite postoperative time points according to the description of the original model (i.e., 30, 90, and 365 days for SORG nomogram; 6 months, 12 months, and 24 months for the revised Katagiri score; and at all time points for revised Tokuhashi score and Tomita score). The AUC was calculated for each model to compare the accuracy between models. A ROC analysis with an AUC calculation for the represented pri-
mary tumor, according to each prognostic score, was then performed to test the predictive accuracy of each scoring system based on primary tumor etiology. Primary tumor types included in the analysis were breast, prostate, lung, and hematologic malignancy. An AUC cutoff was set at 0.70 for a scoring system to be considered to have sufficient predictive accuracy.\textsuperscript{18}

**RESULTS**

**Patient Demographic Data**
During the study period, there were 318 spinal metastasis patients who had undergone operations in our department. Eighty-three patients were excluded due to the operation being only a spinal biopsy, and 49 patients were excluded due to incomplete data or inability to confirm the death status. The remaining 186 patients were included in the analysis. Of these, there were 101 men (54.3%), and the mean age was 57.1 years (range, 17–87 years). The primary tumor was identified by tissue diagnosis at the metastasis site and confirmed with further investigation, including computed tomography scan of chest and abdomen. The identified primary tumors were as follows: lung in 37 (20%), breast in 26 (14%), prostate in 20 (10.8%), gastrointestinal tumor in 25 (13.4%), and others (including renal cell carcinoma [CA]) in 40 (21.5%). The primary tumor was unidentified in 10 (5.3%) patients (Table 1). Notably, a positron emission tomography scan was not used for diagnosing primary tumors or staging in this study. The clinical presenting symptom was pain in 59 (31.7%) and neurological deficit in 127 patients (68.3%).

The most common location of metastasis was thoracic spine in 114 (61.3%), lumbar spine in 40 (21.5%), and thoracolumbar spine in 15 patients (8.0%). The most common operation performed was spinal decompression and fixation. The \textit{en bloc} vertebral resection was performed in 9 patients. Spinal metastasis involving more than 3 spinal levels was confirmed in 113 patients (60.8%). Extraspinal metastasis was found in 135 patients (72.6%). Visceral metastasis was confirmed in 106 patients (57.0%), and pulmonary metastasis was observed in 80 patients (43.0%). Targeted therapy was prescribed in 26 patients (14%) and postoperative radiotherapy, mostly conventional external-beam radiation therapy (RT), was performed in 130 patients (69.9%) (Table 1). Laboratory findings and patient performance statuses are summarized in Table 2.

**Patient Survival and Predictive Abilities of Prognostic Scoring**
The median survival time and 95% CI according to primary tumor types are summarized in Table 3. The overall survival in our patient cohort was 201 days (Fig. 1). Patients with hematologic malignancy metastasis and thyroid cancer metastasis showed the highest median survival time at 942 and 547 days, respectively. Spinal metastasis patients with unknown primary tumor type showed the worst median survival time at 79 days. The AUC of each predictive survival score is shown in Table 4. The SORG showed the highest performance when compared to other prognosis scores in all tumor subtypes, but showed a lower performance when predicting 30-day and 90-day death events in lung cancer metastasis. The Tomita and revised Tokuhashi scores showed acceptable performance only in lung cancer metastasis when compared to other tumors. The revised Katagiri score demonstrated acceptable performance for predicting a death event for breast cancer metastasis at every time point, but revealed a variable performance for 6-month and 12-month death prediction in other spinal metastasis. For hematologic malignancy, only SORG demonstrated an acceptable performance at all time points. The overall performance of the New England Spinal Metastasis Score (NESMS) was 0.69 and it demonstrated highest performance for predicting a death event for prostate cancer metastasis but showed inadequate performance for predicting survival in CA breast and CA lung with spinal metastasis (Table 4).

**Patient Survival of Each Primary Tumor Based on Adjuvant Therapy**
The effects of new adjuvant treatment modalities, targeted therapy, and adjuvant radiotherapy were then analyzed using the log rank test. A Kaplan-Meier plot is illustrated in Fig. 2. For targeted therapy, longer survival was demonstrated in the patients who received targeted therapy compared to those without this treatment with the hazard ratio (HR) of 0.58 (95% CI, 0.39–0.84) ($p = 0.004$). However, there were no statistical differences of the effect of this treatment in the individual tumor (Table 5). For adjuvant radiation, the result showed longer survival time in the patients who received postoperative radiation compared to the patients who did not receive the radiation with the HR of 0.42 (95% CI, 0.29–0.62) ($p < 0.001$). The positive effect of postoperative RT was demonstrated in almost primary tumor except for prostate and thyroid cancer (Table 5).
DISCUSSION

General indications for surgery in spinal metastasis disease are spinal instability, progressive symptomatic deformities, neurologic deficits, and intractable pain resistant to other treatment. However, surgical risks must be weighed against life expectancy. The current research highlights the inconsistent results among the prediction models for specific primary tumor types. The machine learning-based prognosis system, SORG nomogram, revealed the highest predictive performance when compared to previous survival prediction models.

As mentioned above, the prognosis scores have been created using the variables input at the time of study, so data may not include modern treatment modalities, which influence patient survival. Therefore, such scores must be validated periodically to ensure that the predictive ac-
The Tokuhashi prognostic scoring system, for example, was established in 1990 based on 64 patients undergoing spinal surgery for spinal metastasis. The scoring system was then modified in 2005 based on an analysis of 164 patients who died after surgery and 82 who died after conservative treatment. External validation of the score is also required or adjusted. Similarly, evidence exists on several revised, validated, or adjusted versions of the Tomita and Katagiri prognostic scores.

In addition, the traditional prognostic score was developed based on the sum of HRs calculated by the small population being studied. The application of such a score may have limitations for some patients or specific tumor types identified in this study. The Tomita score and revised Tokuhashi score revealed acceptable performance for predicting the survival only in primary lung cancer metastasis when compared to another group of tumors. As these two prognosis scores did not include hematologic malignancy, the predictive ability for survival of hematologic malignancy revealed a poor result.

The ability to predict survival based on the revised Katagiri score has also been challenged. Our results showed a limited ability to determine the 6-month survival of patients other than primary breast CA; this survival prediction may misinform surgeons or other medical professionals regarding the surgical decision or the decision to provide more aggressive therapy based on the predicted prognosis. Therefore, some guidelines for the treatment of spinal metastasis patients rely on patient health status rather than survival expectancy.

The effect of the adjuvant therapy on the patient survival was explored in this study. The result showed longer survival in the patients who received the targeted therapy compared to those without treatment. However, the results of the present study failed to demonstrate the beneficial effect of such treatment in the individual tumor. This may be due to the relatively low numbers of targeted therapy prescribed in this patient cohort.

### Table 2. Laboratory Status before the Operation

| Factor                        | Value                           |
|-------------------------------|---------------------------------|
| Hb level (g/dL)               | 11.8 (6.9–15.6)                 |
| Hematocrit level (%)          | 36.0 (20.0–48.0)                |
| Platelet count (cell/cumm)    | 295,118 (86,000–774,000)        |
| WBC count (cell/cumm)         | 9,777 (2,500–125,000)           |
| Albumin level (g/dL)          | 33.92 (19.6–47.0)               |
| Albumin level > 35 g/dL       | 102 (54.84)                     |
| BUN (mg/dL)                   | 14.41 (3.0–42.0)                |
| Creatinine level (mg/dL)      | 0.79 (0.20–1.84)                |
| Sodium (mEq/L)                | 136.77 (126.0–144.0)            |
| Calcium (mg/dL)               | 9.19 (5.8–11.2)                 |
| Aspartate aminotransferase (U/L) | 42.48 ± 34.7                 |
| Total bilirubin level (mg/dL) | 0.88 (0.2–14.5)                 |
| CRP level (mg/L)              | 27.65 ± 40.81                   |
| ESR level (mm/Hr)             | 51.20 ± 29.05                   |

Values are presented as median (range), number (%), or mean ± standard deviation.

Hb: hemoglobin, WBC: white blood cell, BUN: blood urea nitrogen, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate.

### Table 3. Median Survival Time According to Primary Tumor Type

| Factor         | Median survival time (day) | 95% CI          |
|----------------|---------------------------|-----------------|
| Breast         | 344.0                     | 77.0–509.0      |
| Gastrointestinal* | 102.0                     | 50.0–145.0      |
| Hematologic    | 942.0                     | 299.0–1735.0    |
| Lung           | 168.0                     | 50.0–279.0      |
| Other†         | 218.0                     | 63.0–377.0      |
| Prostate       | 201.0                     | 68.0–637.0      |
| Thyroid        | 547.0                     | 60.0–1616.0     |
| Unknown        | 79.0                      | 22.0–139.0      |
| Overall        | 201.0                     | 131.0–279.0     |

CI: confidence interval.
*Including hepatocellular carcinoma. †Including renal cell carcinoma and sarcoma.
the targeted therapy, the positive effect on patient survival was demonstrated in the patients who received postoperative radiation treatment in all primary cancer except for prostate and thyroid cancer metastasis. We believed that with the RT, even with conventional external beam RT, the local recurrence was less or slower than the patients who did not receive the RT. As in this patient cohort, surgical intervention was mostly decompression or tumor debulking with spinal fixation, total en bloc spondylectomy was performed in only 9 cases (4.9%). The delay in local recurrence may prevent motor weakness, which should have a positive effect on the patient survival.29,30) Since the majority of the patients received the conventional external beam therapy, the beneficial effect of stereotactic body RT could not be demonstrated in this study. As tumor responses to advanced modern therapies are represented in overall prognosis, characterizing the prognosis using a traditional method without combination of the new treatment modalities may be misrepresenting the patient survival.

SORG nomogram is the recent algorithm used for predicting survival in spinal metastasis patients. The results from this study revealed that SORG nomogram has the highest performance when compared to the other prognosis scoring systems, similar to the results from previous studies.12,31) The SORG machine learning algorithms underwent a set of external validation with relevant patient cohorts including Asian populations. Moreover, recently, a systemic review revealed that SORG Nomogram and machine learning algorithms showed superior performance in survival prediction for surgery in spinal metastases.31-33) However, further improvement by comparative validation in large multicenter, prospective cohorts can still be obtained. Moreover, recently Karhade et al.34) developed machine learning algorithms for prediction of mortality after
surgery for spinal metastasis since 2019. These algorithms still require the latest datasets from reasonable patient cohorts that underwent advanced treatment modalities, such as targeted therapies or advanced radiation techniques, and should be updated regularly to ensure the most accurate results to be used in clinical practice.\(^{34,35}\)

The NESMS is the most recent scoring system to provide the predictive ability of patient survival.\(^{36,37}\) It was calculated and its prognostic ability was validated with our patient cohort by comparing with other scoring schemes. The overall performance score was 0.69, which implies that the performance of the scoring system was much superior to traditional prognostics scoring scheme. In addition, the performance was close to the revised Katagiri score and SORG nomogram. The NESMS scoring scheme demonstrated the highest performance when applied to prostate cancer with spinal metastasis and showed inadequate performance for predicting survival in CA breast and CA lung with spinal metastasis.

Certain limitations in the present study should be acknowledged. First, the predictive scores selected for validation in this study were mostly from Japan; only SORG and NESMS were from a western country. The study could therefore contain some bias. Second, since the purpose of the present study was to validate the prognosis scoring system, some significant factors related to patient survival might not be included. Additional research is therefore needed for clarification on these points. Third, The HR compared between tumor that received targeted therapy and postoperative radiation (Table 5) was calculated from the Log Rank test after Kaplan-Meier survival analysis comparing the exposure to the postoperative RT or targeted therapy of the individual tumor. We acknowledge that with this approach, the finding, i.e., HR, may be influenced by many factors such as the patient status or the aggressiveness of the surgical treatment, not implying that the HR in this present study is an independent factor for the patient survival. Further analysis with the multivariate analysis by Cox regression method is warranted to prove this hypothesis. Finally, not all primary tumor etiologies were equally represented for tumor-specific validation.

In conclusion, this study highlights the inconsistent predictive performance among the prediction models for the specific primary tumor types. SORG nomogram revealed the highest predictive performance when compared to previous survival prediction models. The predictive ability for survival of hematologic malignancy revealed a poor result in the traditional prognosis scoring system. Further research is therefore needed to clarify the additional factors that might impact patient survival.

**CONFLICT OF INTEREST**

No potential conflict of interest relevant to this article was reported.

**AKNOWLEDGEMENTS**

The authors would like to thank the Department of Rehabilitation, Faculty of Medicine Ramathibodi Hospital, Mahidol University for all the kindly assistance in carrying out this study.

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**Table 5.** Hazard Ratio Compared between Tumors that Received Targeted Therapy and Postoperative Radiation

| Factor     | Targeted therapy | Postoperative radiation |
|------------|------------------|-------------------------|
| Breast     | 0.67 (0.23–1.92) | 0.09 (0.02–0.40)*       |
| Gastrointestinal† | 0.41 (0.13–1.30) | 0.24 (0.08–0.71)*       |
| Hematologic | 1.11 (0.35–3.49) | 1.06 (0.31–3.61)        |
| Lung       | 0.55 (0.27–1.12) | 0.14 (0.06–0.37)*       |
| Other§     | 0.54 (0.19–1.52) | 0.24 (0.09–0.62)*       |
| Prostate   | NA§              | 1.08 (0.31–3.79)        |
| Thyroid    | NA§              | 0.26 (0.05–1.48)        |
| Unknown    | NA§              | 0.04 (0.002–0.71)*      |
| Overall    | 0.58 (0.39–0.84)*| 0.42 (0.29–0.62)*       |

Values are presented as hazard ratio (95% confidence interval). Hazard ratio was calculated by log-rank test.
*Statistically significant different between treatment groups. †Including hepatocellular carcinoma. §Including renal cell carcinoma and sarcoma. No targeted therapy prescribed.
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