Validation of Clinical Prediction Models and Study of the Role of Modern Therapies Using Real-World Data in Spine Oncology

Validation of Clinical Prediction Models and Study of the Role of Modern Therapies Using Real-World Data in Spine Oncology

by

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I have reviewed this thesis. It represents work done by the author under my guidance/ supervision.

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Background

With a rising incidence of cancer and improved life expectancy, more patients are being diagnosed and surviving longer with spinal metastases (1). Spinal metastases can significantly worsen patients' quality of life because they can cause pain, vertebral compression fractures (VCF), and malignant epidural spinal cord compression, leading to loss of motor and sensory functions, and fecal and/or urinary incontinence (2).

The NOMS framework (Neurologic, Oncologic, Mechanical, Systemic) guides the treatment of spinal metastases to maximize palliative goals such as pain relief, preservation or recovery of neurological functions, restoration of mechanical stability, and control of tumor progression (3). Spinal surgery is generally prioritized for spinal metastases presenting with symptomatic VCF, mechanical instability, and acute symptomatic malignant epidural spinal cord compression (4). The decision is shared among the spine surgeon, radiation oncologist, medical oncologist, palliative team, and most importantly the patient, to help identify risks and benefits of surgery and expectations of postoperative care, prognosis, and quality of life (5).

There has been increasing interest in prediction modeling to determine patients' prognosis with spine metastases (6). Most models were developed in single institutions and report results using only one data source (6). We hypothesize that a model representing data from one institution will not maintain the same

performance when assessed in other clinical settings (7). Without external validation, a prediction model's ability to accurately predict the outcome of new patients is questioned. As a result, implementation of a model without validation in the clinical workflow is not practical (8).

Although it is preferable to have one prediction model that is valid in all settings and individuals, researchers should validate models in clinically relevant subgroups. When validating a model predicting mortality in a research cohort that includes patients with different primary cancers and spinal metastases – for example, lung, prostate, liver, kidney, breast carcinoma- it will be easier to discriminate between patients who will die and will not die because the natural history of the cancers under investigation is different. Accordingly, the scientific work presented focuses on renal cell carcinoma (RCC). In the first part, we address the following question: How accurately can machine learning models predict the risk of mortality for adult patients when evaluated for spinal metastases in RCC?

Because the landscape of local and systemic therapy for RCC is rapidly changing, it is vital to understand how the risk captured by prediction models relates to treatment (9). However, patients with spinal metastases are under-represented in randomized clinical trials (RCT) for RCC (10–12). Historically, bone metastases are associated with a poor prognosis and a reduced benefit from targeted therapies in patients with RCC (12). In the second part of this scientific work, a target trial was designed using real-world data to determine the average treatment effect of receiving systemic therapy after spine surgery for RCC

metastasis. The two research studies address critical aspects of management of spine metastasis and highlight an integrated multidisciplinary approach that considers all aspects of care and available treatment options such as surgery, radiation, and systemic therapy.

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Predicting tumor-specific survival in patients with spinal metastatic renal cell carcinoma: which scoring system is most accurate?

Presented at the 2020 AANS/CNS Joint Section on Disorders of the Spine and Peripheral Nerves

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OBJECTIVE Although several prognostic scores for spinal metastatic disease have been developed in the past 2 decades, the applicability and validity of these models to specific cancer types are not yet clear. Most of the data used for model formation are from small population sets and have not been updated or externally validated to assess their performance. Developing predictive models is clinically relevant as prognostic assessment is crucial to optimal decision-making, particularly the decision for or against spine surgery. In this study, the authors investigated the performance of various spinal metastatic disease risk models in predicting prognosis for spine surgery to treat metastatic renal cell carcinoma (RCC).

METHODS Data of patients who underwent surgery for RCC metastatic to the spine at 2 tertiary centers between 2010 and 2019 were retrospectively retrieved. The authors determined the prognostic value associated with the following scoring systems: the Tomita score, original and revised Tokuhashi scores, original and modified Bauer scores, Katagiri score, the Skeletal Oncology Research Group (SORG) classic algorithm and nomogram, and the New England Spinal Metastasis Score (NESMS). Regression analysis of patient variables in association with 1-year survival after surgery was assessed using Cox proportional hazard models. Calibration and time-dependent discrimination analysis were tested to quantify the accuracy of each scoring system at 3 months, 6 months, and 1 year.

RESULTS A total of 86 metastatic RCC patients were included (median age 64 years [range 29–84 years]; 63 males [73.26%]). The 1-year survival rate was 72%. The 1-year survival group had a good performance status (Karnofsky Performance Scale [KPS] score 80%–100%) and an albumin level > 3.5 g/dL ($p < 0.05$). Multivariable-adjusted Cox regression analysis showed that poor performance status (KPS score < 70%), neurological deficit (Frankel grade A–D), and hypoalbuminemia (< 3.5 g/dL) were associated with a higher risk of death before 1 year ($p < 0.05$). The SORG nomogram, SORG classic, original Tokuhashi, and original Bauer demonstrated fair performance (0.7 < area under the curve < 0.8). The NESMS differentiates survival among the prognostic categories with the highest accuracy (area under the curve > 0.8).

CONCLUSIONS The present study shows that the most cited and commonly used scoring systems have a fair performance predicting survival for patients undergoing spine surgery for metastatic RCC. The NESMS had the best performance at predicting 1-year survival after surgery.

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KEYWORDS predictive analytics; spine surgery; ambulatory status; serum albumin; spine metastasis; cancer survival; renal cell carcinoma; oncology

ABBREVIATIONS AUC = area under the curve; ECOG = Eastern Cooperative Oncology Group; ESCC = epidural spinal cord compression; KPS = Karnofsky Performance Scale; mTOR = mammalian target of rapamycin; NESMS = New England Spinal Metastasis Score; RCC = renal cell carcinoma; ROC = receiver operating characteristic; SINS = Spine Instability Neoplastic Score; SORG = Skeletal Oncology Research Group; TKI = tyrosine kinase inhibitor.

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Renal cell carcinoma (RCC) is the most common malignancy of the kidney, with an estimated 74,000 newly diagnosed cases in 2019.[1] One-third of patients present with metastases, most commonly to the lungs,[2] followed by skeletal involvement (20%–35%), of which 40% occur along the spinal column.[3,4] Surgery for spinal metastases is considered for patients presenting with neurological deficits, radiculopathy, spinal instability, and mechanical pain. The incorporation of multiple classes of systemic therapies (tyrosine kinase inhibitors [TKIs], mammalian target of rapamycin [mTOR] inhibitors, and checkpoint blockade immunotherapy) into the management of patients with progressive RCC has significantly impacted overall survival.[5] Therefore, there is a need to reevaluate criteria to establish prognosis in patients for whom surgical management of progressive disease is considered.

Current surgical decision-making is guided by conceptual frameworks such as NOMS (neurological, oncological, mechanical, and systemic) that take into account the grade of spinal cord compression, spine instability, radiosensitivity of the tumor, and the systemic condition of the patient.[6] However, the benefits of a proposed treatment (often resection and/or stabilization followed by adjuvant radiation) in conditions of limited survival and the overall risk-benefit ratio of an invasive procedure can be difficult to assess.

Several scoring systems have been developed to estimate the prognosis of spinal metastatic disease, but their accuracy and reliability are less well established with RCC spinal metastasis, particularly in the context of contemporary multidisciplinary treatment plans for RCC involving newer systemic therapies, surgery, and radiosurgery.

Historically, the Tomita score,[7] original and revised Tokuhashi scores,[8,9] and original and modified Bauer scores[10,11] are among the most cited prognostic scores for spinal metastatic disease. The Katagiri prognostic score was developed to guide treatment of patients with skeletal metastasis.[12] The van der Linden prediction model was developed from the prospectively randomized Dutch Bone Metastasis Study.[13] More recently, the Skeletal Oncology Research Group (SORG) developed a classic algorithm[14] and a nomogram[15] to predict survival of metastatic patients selected for surgical treatment. In parallel, the New England Spinal Metastasis Score (NESMS)[16,17] was developed to predict 30- and 365-day survival. These prognostic tools were ultimately created to help spine surgeons navigate challenging management decisions, with more accurate estimates of life expectancy and related quality of life. The present study investigated the characteristics and performance of spine metastasis risk scores for their ability to predict the prognosis of contemporary RCC patients selected for surgical treatment.

Methods

Study Population

A retrospective review of electronic chart databases was conducted to retrieve data for all patients diagnosed with spinal metastases from RCC who underwent palliative surgery between 2010 and 2019. Spine surgeries were performed by neurosurgeons and orthopedic surgeons at the Massachusetts General Hospital and Brigham and Women's Hospital. The diagnosis of RCC spinal metastasis was confirmed by preoperative biopsies and/or postoperative pathology results. Patients were followed until death or October 1, 2019. A minimum follow-up period of 1 year from the time of surgery was required for inclusion in the study. All included patients were older than 18 years and had detailed medical records, known survival time, and recent follow-up. This study was approved by the IRB at the Massachusetts General Hospital.

Patient Characteristics

The following measures were calculated for all patients at presentation and at the 1-year follow-up according to definitions and cutoffs established by the scoring systems as follows: 1) sex (male and female); 2) age grouped into 2 categories (< 65 and > 65 years); 3) Karnofsky Performance Scale (KPS) grouped into 3 categories (KPS score 10%–40%, poor performance; KPS score 50%–70%, moderate performance; and KPS score 80%–100, good performance); 4) Eastern Cooperative Oncology Group (ECOG) performance grouped into 2 categories (ECOG grade 0–2 indicating good performance vs ECOG 3 or 4 indicating poor performance); 5) Frankel grade grouped into 2 categories (grade A–D vs grade E); 6) primary tumors classified as clear cell carcinoma and non–clear cell carcinoma; and 7) metastatic spine regions divided according to the 4 major regions of the spine (cervical, thoracic, lumbar, and sacral). We further classified spinal metastasis according to the number of spine levels involved (solitary spine metastasis and multiple spine metastases). Visceral metastasis, brain metastasis, and history of systemic treatment of all patients were reported. Preoperative laboratory test results were also included as follows: 1) low hemoglobin level (< 12 g/dL); 2) thrombocytosis defined as a platelet count > 400,000/μL; and 3) low albumin level (< 3.5 g/dL). The reference values of hemoglobin and platelet count were adopted from the International Metastatic RCC Database Consortium.

Predictive Scoring Systems

Preoperative prognostic scores were calculated for each of the scoring systems that are most commonly represented in the literature (Supplemental Table 1).[7–12,14,15,17–19] If the patient underwent multiple surgeries, the prognostic score was calculated before the first surgery. The van der Linden scoring system was excluded from this study because it was developed by excluding RCC patients.[13] All patients were assigned a prognostic category based on each prognostic score.

The scoring systems generally assigned a numeric value and defined a prognostic category that was associated with an estimated survival time (e.g., original Tokuhashi score 0–5 is associated with an estimated survival ≤ 3 months). For the SORG nomogram, a survival probability is provided for every patient. In this study, we classified the SORG nomogram probabilities into 2 categories according to the 1-year survival probability: if the assigned 1-year survival probability was ≥ 0.5, the patient was con-

sidered more likely to survive at 1 year; if the assigned 1-year survival probability was < 0.5, the patient was considered less likely to survive at 1 year.

Statistical Analysis

Patient demographics and baseline characteristics are summarized in Table 1. Patients were stratified into 2 groups: those with an observed survival of less than 1 year and those with an observed survival of more than 1 year. Survival groups were compared using the t-test or Wilcoxon rank-sum test for continuous variables and the chi-square test for categorical variables. The Kaplan-Meier survival curve was used to summarize the 1-year patient survival. Covariates demonstrating association with 1-year survival on univariate analysis ($p \leq 0.10$) were evaluated in a multivariable Cox proportional hazards regression model to determine the association of the covariates with 1-year survival ($p < 0.05$). Kaplan-Meier survival curves were generated to analyze the survival curves of the prognostic groups of each scoring system. A significant difference in survival between prognostic categories of each scoring system was determined using the log-rank test ($p < 0.05$). The C-statistic was used to test the predictive accuracy of prognostic scores that were significant in the log-rank test. Time-dependent receiver operating characteristic (ROC) curves for censored survival data at 3 months, 6 months, and 1 year were used to test the performance of the prognostic scores.

Discrimination was assessed by calculating the area under the ROC curve (AUC). A perfect model would have an AUC of 1, while an AUC of 0.5 would indicate that the model performs no better than the flip of a coin. We considered a prognostic score to have poor performance if AUC < 0.70, fair performance if 0.7 < AUC < 0.8, good performance if 0.8 < AUC < 0.9, and excellent performance if AUC ≥ 0.9. Survival analysis for the best prediction model was done using the Cox proportional hazard model. Calibration was examined using the Hosmer-Lemeshow goodness-of-fit test. Analyses were conducted using R (R Core Team, 2019, RStudio: Integrated Development for R. RStudio, Inc., http://www.rstudio.com/.).

Results

Demographic, Medical, and Tumor Characteristics

Patient characteristics are summarized in Table 1. Overall, there were 86 patients, with a median age of 62 years (range 29–84 years), who had surgery for metastatic spine disease from RCC. Most patients (63; 73.26%) were male. Performance was measured using the KPS and ECOG performance status, showing that 45 (72.6%) of patients who survived past 1 year had a good KPS score (80%–100%), while most patients who died before 1 year had a moderate KPS score (50%–70%) (n = 14, 58.3%) or poor KPS score (10%–40%) (n = 5, 20.8%) ($p < 0.001$). Similar results were noted with the ECOG grading scale with greater survival noted in patients with a better ECOG performance grade (grade 1 or 2, 87.1% vs 54.2%; $p = 0.001$). Also, 50% of those who were alive at 1 year had a baseline neurological deficit (Frankel Grade A–D) compared with 75% of those who did not survive past 1 year ($p = 0.063$). Only 2 patients had complete loss of motor function (Frankel grade A or B). Patients with Frankel grade E were offered surgery to treat pathologic fractures, spinal instability, and intractable pain. In 2 cases, a solitary metastasis was resected with concurrent nephrectomy. The presence of brain metastasis before spine surgery was similar between the groups (10.3% vs 13.0%; $p = 0.708$). Preoperative radiographic imaging revealed high-grade epidural spinal cord compression (ESCC grade 2 or 3) for 34 patients (54.84%) and low-grade epidural spinal cord compression (ESCC grade 0 or 1) for 28 patients (45.16%). More than half (47; 54.65%) had a pathologic fracture before surgery, and preoperative Spine Instability Neoplastic Score (SINS) scores identified 7 (8.75%) stable spines, 67 (83.75%) potentially unstable spines, and 6 (7.50%) unstable spines. Patients who died before 1 year did not have a higher ESCC grade ($p = 0.088$) or a difference in SINS categories ($p = 0.093$).

Clear cell carcinoma (n = 76; 88.37%) was the most commonly identified RCC histological subtype. Other diagnosed types (n = 10; 11.63%) were 6 unclassified tumors, 2 chromophobe tumors, and 2 clear cell carcinomas with sarcomatoid and rhabdoid differentiation. Fifty-one primary renal tumors (71.84%) had a Fuhrman grade of 3 or 4, and 20 tumors (28.16%) had a Fuhrman grade of 1 or 2. There was no significant difference in the Fuhrman grade between survival groups ($p = 0.089$). Patients who died before 1 year were more likely to have hypoalbuminemia (< 3.5 g/dL) before surgery (50% vs 16.2%; $p = 0.016$). There was no difference in anemia (hemoglobin < 12g/dL) or thrombocytosis (platelet count > 400,000/μL) before surgery between the two survival groups ($p > 0.05$).

Factors Independently Associated With Survival

Postoperatively, the 3-month survival rate was 91.86% (n = 79), the 6-month survival rate was 79.07% (n = 68), and the 1-year survival rate was 72.01% (n = 62) (Fig. 1). Cox regression analysis models were constructed to compare the prognostic significance of 16 different factors used in the 9 prediction scores. Prognostic factors are summarized in Table 2. Age, sex, tumor histology, tumor Fuhrman grade, visceral and brain metastases, location of spine metastasis, number of spine metastases, pathologic fracture, SINS score, ESCC grade, previous systemic therapy, hemoglobin level, and thrombocytosis were not associated with 1-year survival ($p > 0.05$). Univariate analysis revealed that performance status (KPS score [moderate] 50%–70% [HR 6.80, $p = 0.000245$]; KPS score [poor] 10%–40% [HR 6.78, $p = 0.00251$]; ECOG grade 3 or 4 [HR 3.52, $p = 0.0223$]), neurological deficit (Frankel grade A–D [HR 2.54, $p = 0.0492$]), and hypoalbuminemia (< 3.5g/dL [HR 4.049, $p = 0.00193$]) were significantly associated with death at 1-year after surgery. Only KPS score was included in the multivariable model because it was the most commonly used metric to assess performance status in prognostic scores. Multivariable analysis showed that moderate or poor KPS score (adjusted HR 5.31, $p = 0.0479$), Frankel grade A–D (adjusted HR 5.14, $p = 0.0356$), and hypoalbuminemia (adjusted HR 4.90, $p = 0.0236$) were associated with an increased risk of death at 1 year after surgery.

TABLE 1. Demographic, clinical, and tumor characteristics of 86 patients

	All Patients	Patient Survival >12 Mos	Patient Survival <12 Mos	p Value
Age, yrs	62 (29–84)*	60.8 ± 10.8†	61.2 ± 12.8†	0.789
<65	50 (58.14)	37 (59.7)	13 (54.2)	0.825
≥65	36 (41.86)	25 (40.3)	11 (45.8)	
Sex				0.258
Male	63 (73.26)	48 (77.4)	15 (62.5)	
Female	23 (26.74)	14 (22.6)	9 (37.5)	
KPS score				<0.001
Good	50 (58.14)	45 (72.6)	5 (20.8)	
Moderate	26 (30.23)	12 (19.4)	14 (58.3)	
Poor	10 (11.63)	5 (8.1)	5 (20.8)	
ECOG grade				0.001
1 or 2	67 (77.91)	54 (87.1)	13 (54.2)	
3 or 4	19 (22.09)	8 (12.9)	11 (45.8)	
Frankel grade				0.063
E	37 (43.02)	31 (50.0)	6 (25.0)	
A–D	49 (56.98)	31 (50.0)	18 (75.0)	
Tumor location				0.826
Thoracic	48 (55.81)	34 (56)	14 (58.3)	
Lumbar	27 (31.40)	19 (31)	8 (33.3)	
Cervical	10 (11.63)	8 (13)	2 (8.3)	
Sacral	1 (1.16)	1 (1.6)	0	
Tumor pathology				0.20
Clear cell	76 (88.37)	57 (91.9)	19 (79.2)	
Other types	10 (11.63)	5 (8.1)	5 (20.8)	
Fuhrman grade‡				0.089
1 or 2	20 (28.17)	18 (34.6)	2 (10.5)	
3 or 4	51 (71.83)	34 (65.4)	17 (89.5)	
Visceral metastasis‡				0.123
Present	51 (62.96)	33 (56.9)	18 (78.3)	
Absent	30 (37.04)	25 (43.1)	5 (21.7)	
Brain metastasis‡				0.708
Present	9 (11.11)	6 (10.3)	3 (13.0)	
Absent	72 (88.89)	52 (89.7)	20 (87.0)	
Systemic therapy‡				0.502
No	54 (65.85)	40 (69.0)	14 (58.3)	
Yes	28 (34.15)	18 (31.0)	10 (41.7)	
Spine metastasis				>0.99
Solitary	39 (45.35)	28 (45.2)	11 (45.8)	
Multiple	47 (54.65)	34 (54.8)	13 (54.2)	
Pathologic fracture				0.25
Absent	39 (45.35)	31 (50.0)	8 (33.3)	
Present	47 (54.65)	31 (50.0)	16 (66.7)	
SINS score‡				0.093
Stable	7 (8.75)	6 (10.7)	1 (4.2)	
Potentially unstable	67 (83.75)	48 (85.7)	19 (79.2)	
Unstable	6 (7.50)	2 (3.6)	4 (16.7)	

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TABLE 1. Demographic, clinical, and tumor characteristics of 86 patients

	All Patients	Patient Survival >12 Mos	Patient Survival <12 Mos	p Value
ESCC grade‡				0.088
Low grade	28 (45.16)	23 (53.5)	5 (26.3)	
High grade	34 (54.84)	20 (46.5)	14 (73.7)	
Hemoglobin, g/dL‡				0.268
≥12	42 (53.16)	32 (58.2)	10 (41.7)	
<12	37 (46.84)	23 (41.8)	14 (58.3)	
Thrombocytosis‡				0.555
Present	9 (11.39)	5 (9.1)	4 (16.7)	
Absent	70 (88.61)	50 (90.9)	20 (83.3)	
Albumin, g/dL‡				0.016
≥3.5	41 (71.93)	31 (83.8)	10 (50.0)	
<3.5	16 (28.07)	6 (16.2)	10 (50.0)	

Values represent the number of patients (%) unless stated otherwise.
* Median (range).
† Mean ± SD.
‡ These variables have missing values.

Kaplan-Meier Survival Analysis and Log-Rank Test of 9 Prognostic Scores

Kaplan-Meier curves and log-rank tests were evaluated to assess for significant differences between prognostic categories of each scoring system. The predicted 1-year survival risk between prognostic classes of each score is presented in Fig. 2. There was no statistically significant difference between the prognostic categories of the Katagiri, Tomita, and modified Bauer ($p > 0.05$) scores. A significant difference in survival was noted between prognostic categories of the original Bauer score, NESMS, SORG classic, SORG nomogram, revised Tokuhashi, and original Tokuhashi (log-rank test, $p < 0.05$) scores.

External Validation of Prognostic Scores

We calculated the AUC of the time-dependent ROC curves for the 6 prognostic scores with a significant log-rank test ($p < 0.05$) (Fig. 3). We used an AUC sequentially at 3 months, 6 months, and 1 year. We found that the revised Tokuhashi score had a poor performance at 3 and 6 months (AUC 0.67 and AUC 0.69, respectively), indicating that the model identifies the risk categories with poor accuracy. The SORG nomogram, SORG classic, original Tokuhashi, and original Bauer demonstrated a fair performance ($0.7 < AUC < 0.8$), indicating that these models can identify and separate patients into prognostic groups that have a significant difference in survival with fair accuracy. The NESMS had a good performance at 3 months (AUC 0.83), 6 months (AUC 0.84), and 1 year (AUC 0.88), indicating that the NESMS can differentiate survival between the prognostic categories with the highest accuracy. Furthermore, the Hosmer-Lemeshow goodness-of-fit test revealed that all models had poor calibration except NESMS ($p = 0.31$) and SORG classic ($p = 0.9$).

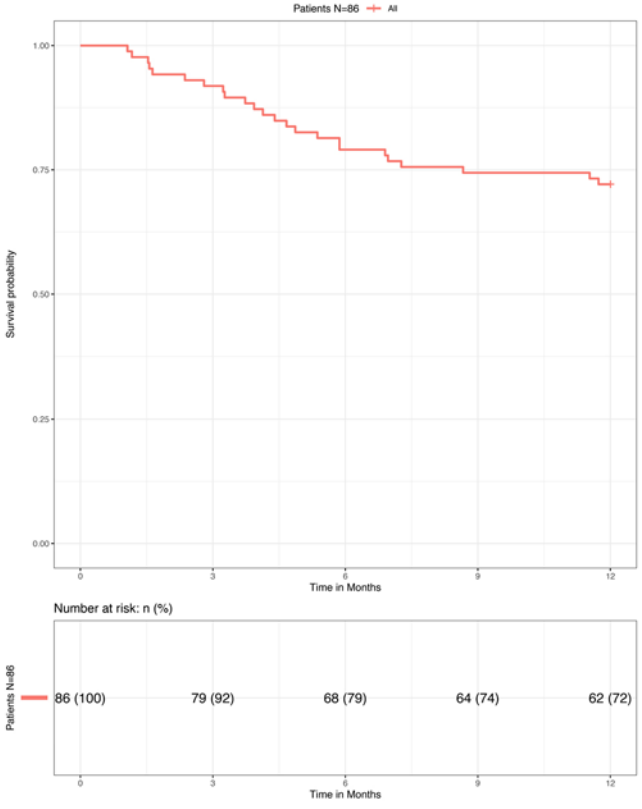

FIG. 1. Kaplan-Meier curve for patients (n = 86) with a 1-year survival probability after spine surgery. Risk table showing that the 3-month survival rate is 91.86% (n = 79), the 6-month survival rate is 79.07% (n = 68), and the 1-year survival rate is 72.01% (n = 62). Figure is available in color online only.

TABLE 2. Univariate and multivariable Cox proportional hazard ratio analysis: risk of 1-year mortality after spine surgery with associated variables

		Univariate			Multivariable		
Variable	Category	Regression Coefficient ± SE	HR (95% CI)	p Value	Regression Coefficient ± SE	HR (95% CI)	p Value
Age, yrs	<65	Reference					
	≥65	0.13 ± 0.41	1.14 (0.51–2.54)	0.753			
Sex	Male	Reference					
	Female	1.88 ± 0.42	1.88 (0.82–4.30)	0.134			
KPS score	Good	Reference					
	Moderate	1.92 ± 0.52	6.80 (2.44–18.93)	**0.000245**	1.67 ± 0.84	5.31 (1.02–27.76)	**0.0479**
	Poor	1.91 ± 0.63	6.78 (1.96–23.48)	**0.00251**	1.71 ± 1.23	5.54 (0.50–61.33)	0.1628
ECOG grade	1 or 2	Reference					
	3 or 4	3.52 ± 0.41	3.52 (1.57–7.92)	**0.00223**			
Frankel grade	E	Reference					
	A–D	0.93 ± 0.47	2.54 (1.01–6.47)	**0.0492**	1.63 ± 0.78	5.14 (1.12–23.63)	**0.0356**
Tumor location	Thoracic	Reference					
	Lumbar	−0.11 ± 0.44	0.99 (0.41–2.36)	0.98			
	Cervical	−0.44 ± 0.75	0.64 (0.15–2.84)	0.563			
	Sacral						
Tumor pathology	Clear cell	Reference					
	Non–clear cell	0.98 ± 0.50	2.67 (0.99–7.16)	0.0515	−0.35 ± 1.41	0.70 (0.04–11.09)	0.8015
Fuhrman grade	1 or 2	Reference					
	3 or 4	1.29 ± 0.75	3.65 (0.84–15.83)	0.0831	0.78 ± 0.94	2.18 (0.35–13.71)	0.4076
Visceral metastasis	Absent	Reference					
	Present	0.87 ± 0.51	2.38 (0.88–6.41)	0.0864	1.07 ± 0.68	2.91 (0.76–11.08)	0.1167
Brain metastasis	Absent	Reference					
	Present	0.27 ± 0.62	1.31 (0.39–4.40)	0.666			
Systemic therapy	No	Reference					
	Yes	0.44 ± 0.41	1.55 (0.69–3.51)	0.284			
Spine metastasis	Solitary	Reference					
	Multiple	−0.023 ± 0.05	0.97 (0.44–2.18)	0.954			
Pathologic fracture	Absent	Reference					
	Present	0.59 ± 0.43	1.79 (0.77–4.21)	0.175			
SINS score	Stable	Reference					
	Potentially unstable	0.76 ± 1.03	2.14 (0.29–16.00)	0.4578	1.59 ± 1.19	4.93 (0.48–50.58)	0.1793
	Unstable	1.86 ± 1.12	6.43 (0.71–57.62)	0.0962	0.27 ± 1.31	1.32 (0.10–17.09)	0.8038
ESCC grade	Low grade	Reference					
	High grade	0.97 ± 0.52	2.65 (0.95–7.36)	0.0615	0.03 ± 0.63	1.03 (0.29–3.58)	0.9675
Hemoglobin, g/dL	≥12	Reference					
	<12	0.56 ± 0.41	1.76 (0.78–3.97)	0.171			
Thrombocytosis	No	Reference					
	Yes	0.55 ± 0.54	1.74 (0.59–5.01)	0.313			
Albumin, g/dL	≥3.5	Reference					
	<3.5	1.40 ± 0.45	4.05 (1.67–9.80)	**0.00193**	1.59 ± 0.70	4.90 (1.24–19.42)	**0.0236**

Boldface type indicates statistical significance.

Cohort Survival Analysis Using the NESMS

We categorized our cohort into NESMS categories 0–3 (Table 3). In brief, a poor prognosis category (NESMS 0) includes patients with a modified Bauer score ≤ 2, impaired functional status, and hypoalbuminemia (< 3.5 g/dL). In contrast, a good prognosis category (NESMS 3) includes patients with a modified Bauer score ≥ 3, preserved functional status, and normal albumin level. In our cohort, the 1-year overall survival of patients in categories 0, 1, 2, and 3 were 22%, 30%, 78%, and 95%, respectively, with a

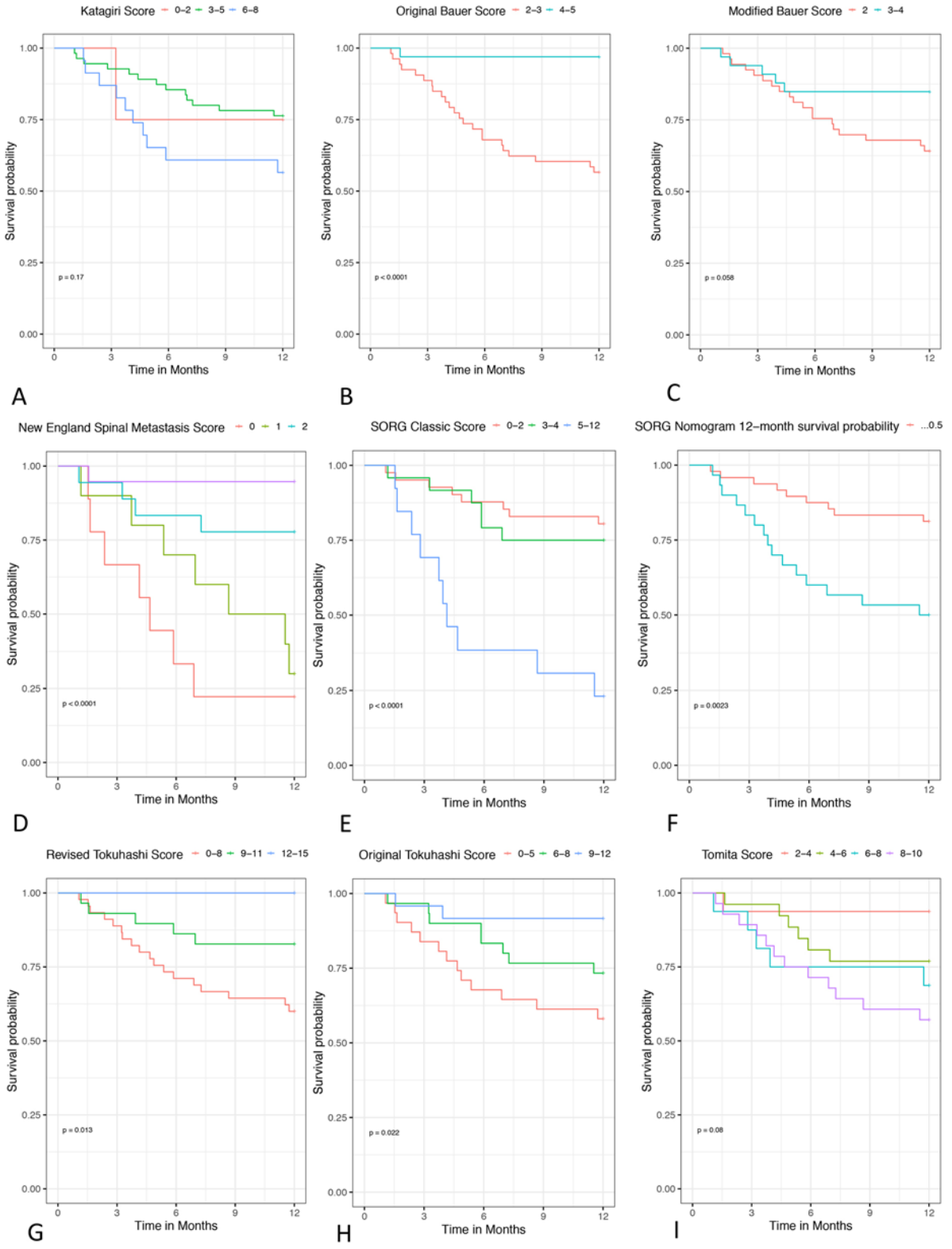

FIG. 2. Kaplan-Meier curves (log-rank test) for the prognostic groups of the 9 scoring systems. **A:** Katagiri ($p = 0.17$). **B:** Original Bauer ($p < 0.0001$). **C:** Modified Bauer ($p = 0.058$). **D:** NESMS ($p < 0.0001$). **E:** SORG classic ($p < 0.0001$). **F:** SORG nomogram ($p = 0.0023$). **G:** Revised Tokuhashi ($p = 0.013$). **H:** Original Tokuhashi ($p = 0.022$). **I:** Tomita ($p = 0.08$). Figure is available in color online only.

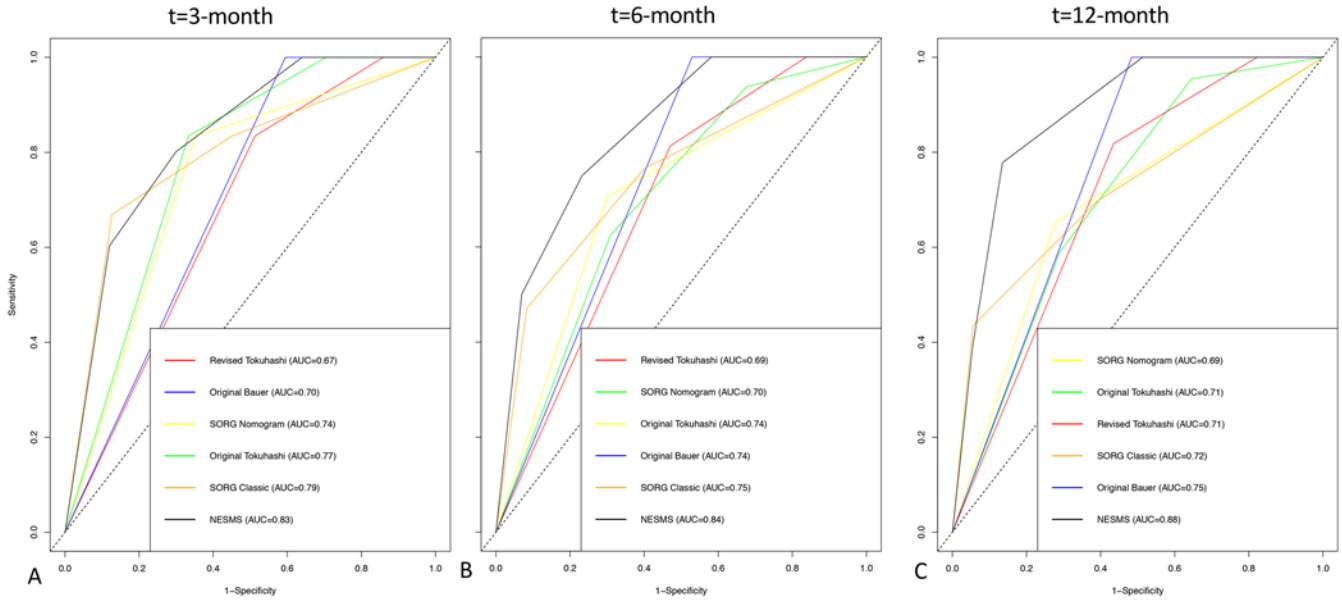

FIG. 3. A: Time-dependent ROC curves for 6 prognostic scores at 3 months. The AUC range was 0.67–0.83 and the NESMS had the best performance (AUC 0.83). **B:** Time-dependent ROC curves for 6 prognostic scores at 6 months. The AUC range was 0.69–0.84, and the NESMS had the best performance (AUC 0.84). **C:** Time-dependent ROC curves for 6 prognostic scores at 12 months. The AUC range was 0.69–0.88, and NESMS had the best performance (AUC 0.88). Figure is available in color online only.

log-rank test showing a statistically significant difference in survival between categories ($p < 0.0001$). The median survivals of patients with NESMS scores of 0 and 1 were 4.6 months and 10.1 months, respectively. The median survival of patients with an NESMS score of 2 or 3 was not reached within 1 year. The survival rates of each prognostic category at 3 months, 6 months, and 1 year are summarized in Table 3 ($p < 0.0001$).

Discussion

Metastatic RCC can be an aggressive disease that is radioresistant and progressive despite systemic therapies, often prompting surgical intervention.[20,21] Prediction of survival is relevant to decisions for or against spine surgery. Accurate estimation of survival time helps determine if the patient will benefit from the intended palliative goals of surgery to restore neurological function and mechanical stability of the spine while achieving pain relief without increasing morbidity and mortality. Over the past several decades, prognostic scores and prediction models have become abundant in the literature on metastatic spine disease. Surgeons have used prognostic scores in the clinical setting to stratify patients according to risk categories and use this stratification to weigh treatment options.[22] The most commonly used prognostic scores were developed by pooling patients diagnosed with spinal metastasis from different types of cancers. The heterogeneity of the studied populations is mirrored in the range of prognostic variables used across many models, as well as the variability of generated survival estimates.[6–13,15,17–19]

Patients diagnosed with spinal metastasis from RCC were included in all prognostic scores for spine metastasis, except the van der Linden score, but their proportion in the training and validation sets was relatively small compared with patients diagnosed with spinal metastasis from the prevalent cancers such as skin, lung, prostate, and breast carcinoma. Kidney cancer was grouped with uterine cancer but also with liver, prostate, and thyroid neoplasms, showing a heterogeneous grouping of the disease in these scores. However, the performance status and the progression of the disease to skeletal, visceral, or brain metastasis were frequently assessed.[23] More factors related to nutritional status and chronic inflammation (albumin, C-reactive protein, lactate dehydrogenase, white blood cell count, hemoglobin) were included in more recent models.[14,15,17] A meta-analysis identified 17 different prognostic factors associated with survival in spinal metastasis and highlighted that the revised Tokuhashi score was the most cited, with an overall predictive value of 66%.[24]

In this study, we found no difference in the proportion of prognostic factors commonly used in prognostic scores between the RCC survival groups. Our results demonstrate that there is no difference in sex, Frankel grade, tumor pathology, Fuhrman grade, visceral metastasis, number of spine metastasis, pathologic fracture, SINS score, ESCC grade, hemoglobin level, and thrombocytosis, in predicting survival among patients with metastatic RCC.

In this study, patients with RCC spinal metastasis had a postoperative 1-year survival rate of 72%. The prognostic variables that were associated with death before 1 year were poor performance, neurological deficit at presentation, and low albumin level (< 3.5 g/dL). Other studies have also highlighted the prognostic role of poor performance status and neurological deficit in spinal metastatic disease.[25] Patients with good functional status have significant positive changes in neurological function after surgery and are able to avoid infectious, vascular, and respi-

TABLE 3. Cox regression analysis for the NESMS

NESMS	No. of Patients	Survival Rate at 3 Mos	Survival Rate at 6 Mos	Survival Rate at 1 Yr*	Median Survival Reached w/in 1 Yr
3	19	95%	95%	95%	
2	18	94%	83%	78%	
1	10	90%	70%	30%	10.1 mos
0	9	67%	33%	22%	4.6 mos

* $p < 0.0001$, log-rank test.

ratory complications that are more likely to arise in less functional patients; these patients are also more likely to resume postoperative adjuvant therapy.[26]

In parallel, hypoalbuminemia (< 3.5 g/dL) has also emerged as an independent factor influencing survival as well as increasing the risk of perioperative mortality, transfusion, and prolonged hospitalization following surgery for spine metastasis.[27] Hypoalbuminemia indicates malnutrition and chronic inflammation. It follows the malignant progression of cancer as well as micrometastasis to the liver, eventually causing tumor cachexia.[28] Although the effect of optimizing the albumin level has not yet been investigated, a nutrition consult before surgery was associated with fewer complications and shorter hospitalization.[29]

In addition to clinical factors, primary tumor histology and biology play an important role in RCC prognosis. Our data suggest that patients diagnosed with non–clear cell carcinoma and clear cell carcinoma with sarcomatoid and rhabdoid differentiation may have a worse prognosis than those with clear cell RCC following spine metastasis surgery ($p = 0.0515$). These findings are consistent with the broader oncological literature in which metastatic non–clear cell RCC have worse progression-free survival and overall survival compared with clear cell RCC, due to a variety of factors that limit responses to systemic therapies.[30]

The current study is important because it seeks to externally validate and compare current spinal metastasis prognostic models using a cohort of metastatic RCC patients. Accurate prognostic tools help decide on the best treatment plan considering survival. Radiosurgery or less invasive approaches for decompression and stabilization that decrease surgical morbidity while at the same time maintain excellent functional outcomes and quality of life may be considered for limited estimated survival instead of a more aggressive surgical intervention and a longer rehabilitation plan.[31,32]

In fact, the Tomita and Tokuhashi scores continue to play an important role in clinical decision-making and guide treatment strategies based on expected survival. In current practice, these scores are used to guide decision-making toward conservative treatment for patients with short life expectancy, palliative surgery for intermediate life expectancy, and excisional surgery for long life expectancy (usually > 12 months). However, in this contemporary cohort, we showed that these prognostic scores have a poor performance in predicting survival. Also, the Katagiri, Tomita, and modified Bauer scores showed a poor performance in discriminating between the prognostic categories when scoring metastatic RCC patients. The poor performance of these scores can be explained by dissecting their underlying structure and knowing how they were originally developed, which population was included, and how variable the original cohort was in terms of tumor types, clinical characteristics, and provided management. Lung and breast cancer were the most common primary tumors in the original cohort from which these scores were developed, and metastatic RCC accounted for a small proportion of the total sample in the Tomita (n = 8; 13.11%); Katagiri (n = 16; 4.6%); and modified Bauer (23%) studies.[7,10,12] In addition, factors that are common among the 3 scores, including solitary skeletal metastasis and visceral metastasis, were not associated with prognosis in our RCC cohort ($p > 0.05$).

Interestingly, the original Bauer score had a better performance than the modified Bauer score, although the presence of a vertebral pathologic fracture at presentation was not determined to be a prognostic factor for 1-year survival in our study. However, pathologic fracture remains an important indicator of spine instability and a principal component of the SINS score, which was not associated with survival in this cohort ($p = 0.09$), but its prognostic value is under investigation and should be assessed in future studies given its importance in guiding treatment delivery.[33] Furthermore, the original Tokuhashi prognostic categories predict survival relative to 3-month and 12-month periods.[9] In parallel, the revised Tokuhashi prognosis classes predict survival relative to 6-month and 12-month periods.[8] Both scores had a fair performance at predicting survival in our study, but it should be noted that they were developed based on cohorts that included mostly lung and breast cancer patients, using the same prognostic variables but reaching different risk categories and predicted prognosis.[8,9]

In contrast to other scores, the NESMS, originally based on a heterogeneous cohort of spinal metastatic disease with 11% of cases being RCC metastasis,[16] had the best performance at predicting 1-year survival after surgery. Interestingly, a moderate or poor KPS score and hypoalbuminemia (< 3.5 g/dL), which were strongly associated with death before 1-year survival in our analysis, are the main composite variables of the NESMS in addition to the modified Bauer grade. A poor prognostic category (NESMS 0) includes patients with a modified Bauer score ≤ 2, impaired functional status, and hypoalbuminemia (< 3.5 g/dL), while a score of 3 indicates a good prognosis. Although the NESMS was originally developed to pre-

dict 1-year mortality, our results showed that the NESMS maintains a good performance to discriminate 3-month and 6-month survival between its prognostic categories (0–3), which are important time points to look at in order to optimize surgical intervention or provide patients with other treatment alternatives when life expectancy is short.

In this study, an NESMS of 0, referring to the group of patients with a poor prognosis, was associated with a median survival of 4.6 months. We expect the median survival of prognostic classes to change in the future as the armamentarium of systemic therapies (TKIs, mTOR inhibitors, checkpoint blockade immunotherapies, combinations, and novel strategies) for advanced cases of RCC expands.[34,35] Novel neoadjuvant and adjuvant therapies such as targeted therapy and radiosurgery are not part of any of the prognostic scores for spinal metastasis and therefore are not weighted when estimating survival despite their well-established effect on survival. In this regard, these scoring systems do not reflect the underlying molecular and genetic makeup of RCC; they particularly do not consider treatment responses to systemic therapies and radiosurgery. In the future, specific scoring systems that incorporate both operative risks and survival based on tumor biology may further improve their predictive value and facilitate optimal selection of operative candidates.

This study has several limitations inherently associated with retrospective studies. Some variables were missing and could not be reported, specifically the baseline albumin, prompting the analysis of a smaller proportion of patients scored by NESMS (n = 56; 65%). Although NESMS was validated using NSQIP (National Surgical Quality Improvement Program; 2007–2013) data and the SORG classic and nomogram were validated using retrospective data, we cannot rule out a minimal and very limited data overlap since these prognostic scores included a small percentage of metastatic RCC patients from the participating centers. In addition, this study represents patients treated at 2 tertiary care centers of one healthcare entity, which may result in clustered practice patterns that might yield different results in other settings. Furthermore, all patients included in this study were offered surgical intervention, which introduces a selection bias to the study because patients were considered to be adequate surgical candidates, hence the relatively long survival time for patients classified by the NESMS to have a poor prognosis (NESMS 0).

Conclusions

Currently, standard prediction models for spine metastatic disease have a poor to fair performance in predicting the survival of contemporary metastatic RCC patients after spine surgery. We found that hypoalbuminemia, which reflects the overall health of cancer patients, is associated with survival and therefore should be assessed before surgery. Additionally, tumor-specific factors such as the primary tumor histology (clear cell carcinoma and other types) and response to treatment should be further investigated to assess their importance in the decision framework for the treatment of spine metastasis. The NESMS demonstrated good performance for predicting 1-year survival after surgery because it incorporates factors that were highly associated with metastatic RCC survival such as performance status and albumin level. Future models that incorporate genetic factors, molecular markers, and response to treatments are expected to provide more accurate clinical decision tools to improve survival and patient outcomes.

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Disclosures

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions

Conception and design: Shin, Massaad, Shankar. Acquisition of data: Massaad, Shankar. Analysis and interpretation of data: Shin, Massaad, Hadzipasic, Alvarez-Breckenridge, Shankar. Drafting the article: Shin, Massaad, Hadzipasic. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Statistical analysis: Massaad. Administrative/technical/material support: Shin, Massaad, Kiapour, Shankar. Study supervision: Shin.

Supplemental Information

Online-Only Content

Supplemental material is available with the online version of the article.

Supplemental Table 1. https://thejns.org/doi/suppl/10.3171/2020.4.SPINE20173.

Previous Presentations

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The Effectiveness of Systemic Therapies after Surgery for Metastatic Renal Cell Carcinoma to the Spine: A Propensity Analysis Controlling for Sarcopenia, Frailty, and Nutrition

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STRUCTURED ABSTRACT

Objective: The effectiveness of starting systemic therapies after surgery for spinal metastases from renal cell carcinoma (RCC) has not been evaluated in randomized clinical trials. Agents that target tyrosine kinases, mammalian target of rapamycin signaling, and immune checkpoints are now commonly used. Variables like sarcopenia, nutritional status, and frailty may impact recovery from spine surgery and are considered when evaluating a patient's candidacy for such treatments. Better understanding the significance of these variables may help improve patient selection for available treatment options after surgery. We used comparative effectiveness methods to study the treatment effect of postoperative systemic therapies on survival.

Methods: Univariable and multivariable Cox regression analyses were performed to determine factors associated with overall survival (OS) in a retrospective cohort of adult patients who underwent spine surgery for metastatic RCC between 2010-2019. Propensity score matched (PSM) analysis and inversive probability weighting (IPW) were performed to determine the treatment effect of postoperative systemic therapy on OS. To address confounding and minimize bias in estimations, PSM and IPW were adjusted for covariates including age, gender, frailty, sarcopenia, nutrition, visceral metastases, IMDC (International Metastatic RCC Database Consortium) risk score, and performance status.

Results: 88 patients (73.9% male; median age, 62 [29-84] years) were identified. 49 of 88 (55.7%) had intermediate IMDC risk and 29 of 88 (33.0%) had poor IMDC risk. Median follow-up was 17 months (1-104 months) during which 57 (64.7%) died. Poor IMDC risk (HR, 3.2, [1.08-9.3]), baseline performance status (ECOG 3-4; HR, 2.7 [1.5-4.7]), and nutrition (Prognostic Nutritional Index 1st tertile; PNI <40.74; HR=2.69, [1.42-5.1]) were associated with worse OS. Sarcopenia and frailty were not significantly associated with poor survival. Postoperative systemic therapy was associated with prolonged OS, demonstrated by similar effects from multivariable Cox analysis (HR, 0.55 [0.30-1.00]), PSM (HR, 0.53 [0.29-0.93]), and IPW (HR, 0.47 [0.24-0.94]) and comparable confidence intervals. Median survival for those receiving postoperative systemic therapy was 28 (CI 95%, 19-43) months versus 12 (CI 95%, 4-37) months for those who only had surgery (log-rank P = .027).

Conclusion: This comparative analysis demonstrates that postoperative systemic therapy is associated with improved survival in specific cohorts with metastatic spinal RCC after adjusting for frailty, sarcopenia, and malnutrition. The marked differences in survival should be taken into consideration when planning for surgery.

MANUSCRIPT

Introduction

Renal cell carcinoma (RCC) is among the 10 most commonly diagnosed cancers in the United States, with an estimated 73,750 new cases in 2020.[1] Approximately 30 to 40% of patients treated for RCC will develop distant metastases at some point in their disease.[2,3] Bone is a common site of metastasis in advanced RCC, occurring in approximately 30% of patients, with up to 85% of those patients experiencing skeletal related events.[4,5,6] While systemic therapy is the cornerstone of treatment in advanced RCC, the treatment of spinal metastases from RCC often involves surgery and radiation to restore and preserve neurological function, spinal stability, and palliate pain.[7,8]

With advances in cancer therapies, targeted therapies and immunotherapies are now commonly utilized in advanced RCC.[9–11] Despite such advances, treatment effects in spinal metastatic disease are uncertain and patients may be selected for surgery without clear assessments of postoperative survival estimates and therapeutic options. To that end, considerable effort has gone into developing predictive models for survival among patients with spinal metastatic disease.[12,13] Surgical decision making tools for spinal metastases like the NOMS (Neurologic, Oncologic, Mechanical, Systemic) framework help guide surgeons with essential components of assessing neurology, radiosensitivity, and spinal stability, but do not weigh the significance of variables such as sarcopenia, frailty, nutrition, and systemic therapies on survival.[14] The complex interplay of these factors expectedly impacts survival, but has been understudied. To date, patients with spinal metastases are underrepresented in randomized controlled trials (RCT) for the treatment of advanced RCC and thereby represent a current knowledge gap.[15,16,17]

Frailty within patients with spinal metastases has been associated with postoperative mortality and morbidity but its quantitative assessment requires validation and further development.[18] Likewise, there is interest in evaluating sarcopenia and nutrition in these patients to better understand their impact on treatment outcomes.[19,20] The impact of sarcopenia on long-term outcomes in advanced RCC is particularly relevant as studies have shown that sarcopenia was associated with higher toxicity related to the administration of targeted therapeutic agents.[21–24] To better understand the effect of such variables on survival in patients with spinal metastases, a study using comparative effectiveness analytics was performed.

Methods

Study Population, Data Source, and Design

This retrospective cohort study included medical record data from all patients aged more than 18 years surgically treated for RCC spinal metastases between 2010 and 2019 at the Massachusetts General Hospital and Brigham and Women's Hospital. This study was approved by the Partners Institutional Review Board. Informed consent for retrospective analysis of de-identified data was waived. The study is compliant with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines.

Patients included in this study received open surgery for a number of indications including decompression and stabilization of the spine following a diagnosis of epidural spinal cord compression, vertebral compression fracture, spinal instability, and/or intractable pain. All treatment plans were discussed in multidisciplinary forum. Following surgery, patients received radiation therapy to the spine for locoregional control consisting of either postoperative stereotactic radiosurgery or fractionated external beam radiation therapy. Postoperative systemic therapy included tyrosine kinase inhibitors (TKIs), mammalian target of rapamycin (mTOR) inhibitors, and monoclonal antibodies to VEFG or to immune checkpoints. (**Figure 1**).

Study Variables

Demographic variables including gender, age, and Body Mass Index (BMI) were recorded. International Metastatic Renal-Cell Carcinoma Database Consortium's IMDC risk groups (favorable [0 risk factors], intermediate [1 to 2 risk factors], or poor [≥ 3 risk factors]) were assigned for each patient. IMDC unfavorable risk factors included duration from diagnosis to systemic therapy < 1 year, Karnofsky performance score (KPS) <80%, hemoglobin less than the lower limit of normal, corrected calcium level greater than the upper limit of normal (ULN), neutrophil count greater than the ULN, and platelet count greater than the ULN (**Supplementary Table 1**). The IMDC is widely used in oncology to help prognosticate and select therapies for metastatic RCC.

Frailty was assessed by the application of the modified frailty index (mFI) as a continuous score.[25] The mFI models 11 comorbidities by assigning 1 point for each frailty component for a total score of 11 (**Supplementary Table 2**). A frailty level was given for each patient based on

their score, with scores of 0, 1, 2 and ≥ 3 out of 11 indicating no frailty, mild frailty, moderate frailty, and severe frailty respectively.

The prognostic nutritional index (PNI) which is a combined nutritional-inflammatory score based on serum albumin levels and lymphocyte counts [10×serum albumin (g/dL) + 0.005×total lymphocyte count (per mm^3)] was calculated and recorded as it is commonly used to reflect the immunological nutritional condition of cancer patients.[26,27] Patients were divided into tertiles according to the preoperative PNI (<40.74, 40.74 and 47.24, >47.24). Adequate nutritional status was defined as a PNI >47.24 (upper tertile) as a validated cut-off for optimal PNI has not yet been established.

Sarcopenia was assessed by measuring the L3-skeletal muscle index (L3-SMI) on axial computed tomography (CT) images at the lumbar L3 level with the transverse processes fully visible. Sarcopenia was assessed on CT abdomen and pelvis captured within 6 months before spine surgery using image segmentation features in Osirix (v8.0.1; Pixmeo SARL, Bernex, Switzerland) **(Figure 2)**. Sex-specific diagnosis of sarcopenia was made for L3-SMI < 41 cm^2/m^2 in women, <43 cm^2/m^2 in men with BMI <25 kg/m^2, and <53 cm^2/m^2 in men with BMI > 25 kg/m^2.[28,29]

The primary outcome of this study was overall survival (OS), defined as the time from surgery to death or last follow-up; for patients who survived, follow-up was censored at the last evaluation of their condition.

Propensity Score Analysis

To control for confounding variables that may bias determinations for post-operative treatment, we used a propensity matching approach to balance the cohorts based on receipt of postoperative systemic therapy. Accordingly, individual propensity scores were calculated based on the following covariates: age, gender, IMDC risk group, frailty (mFI), visceral metastases, prognostic nutrition index (PNI) tertiles, and sarcopenia.

Missing data, which accounted for less than 5% for IMDC risk group, PNI, and sarcopenia, were imputed using multiple imputation by chained equation. Patients who received postoperative systemic therapy (PST) and those who did not receive PST were then paired 1:2 on these propensity scores, based on nearest neighbor method without any replacement, with a caliper distance of 0.1 of the standard deviation of the logit of the propensity score (**Supplementary**

Figures 1 and 2). In addition, we checked whether adding interaction terms would further improve balance of the propensity score model. Baseline characteristics and outcomes were compared between groups before and after PS matching using standardized differences, with differences less than 10% considered acceptable (**Supplementary Figure 3)**. To further account for selection bias given that more patients were assigned to treatment, we used logistic regression incorporating inverse probability weighting, another comparative effectiveness method. Unlike propensity score matching which estimates the Average Treatment Effect among the treated (ATT; conditional on the treated), the inverse probability weighting estimates the Average Treatment Effect (ATE; marginal effect in the population). Given that there is limited guidance on which specific methods may be preferable, we compared both estimates to avoid suboptimal analysis that preserves more bias and/or imprecision than necessary. Although we sought to address the clinical equipoise regarding the use of postoperative systemic therapy using propensity analysis adjusting for measured confounders, we cannot guarantee conditional exchangeability with this methodology. Unlike randomized studies, the reasons for selecting treatment may still be associated with some unmeasured confounders even after rigorous adjustment.

Statistical analysis

Descriptive statistics were performed on all variables and $\chi 2$ tests were used when appropriate. The distribution of covariates in the unmatched and the matched cohorts were compared using $\chi 2$ test with reported estimates and confidence intervals. The median survival time (in months) along with the corresponding 95% confidence interval were computed using Kaplan–Meier estimates for those who received PST vs. those who did not receive PST after matching on the propensity score. To determine factors associated with OS, we performed univariable and multivariable Cox proportional hazards models and reported the hazard ratio (HR) and 95% CI. Variables trending toward significance on univariable analysis ($P < .10$) were included in a Cox multivariable regression to identify factors significantly associated with improved OS. All analyses were performed using R software version 3.5.1 (R Project for Statistical Computing). All *P* values were 2-sided, and *P* values less than .05 were considered statistically significant.

Results

Patient Characteristics

In total, 88 patients met the inclusion criteria and were included in this study. Of the 88 patients, 65 (73.9%) were men and 23 (26.1%) were women with a mean (SD) age of 60.8 (11.4) years. Using the International Metastatic RCC Database Consortium risk score, patients were stratified into favorable risk (IMDC; 10 patients [11.3%]); intermediate risk (IMDC = 1-2; 49 patients [55.7%]), and poor risk groups (IMDC ≥ 3; 29 patients [33.0%]). The distribution of the components of the IMDC score, including time of diagnosis to systemic therapy, Karnofsky Performance Status (KPS), hemoglobin level, calcium level, neutrophil and platelets counts, are summarized in **(Supplementary Table 1).** Before surgery, 56 (63.6%) patients had visceral metastases and 64 (72.7%) had baseline good (ECOG 0-2) performance status. Preoperative frailty assessment found 22 (25.0%) patients were frail, and imaging evaluation revealed 45 (51.1%) patients had sarcopenia before surgery. Stratification of patients by the tertiles of the prognostic nutritional index (PNI) found 29 (33.0%) patients had PNI < 40.74; 29 (33.0%) patients had PNI between 40.74 and 47.24; and 30 (34.0%) had PNI > 47.24 **(Table 1).**

Systemic Therapy and Overall Survival

The median follow-up period of this study was 17 months (range, 1 to 104 months) during which 57 (64.7%) patients died. Delivery of systemic therapy after spine surgery was less common in patients who had a poor baseline performance status (ECOG 3-4; 45.5% vs. 16.4%; absolute difference, 29.1%; P =.007).

Of factors that were associated with OS on univariate Cox regression analysis (**Table 2),** men (adjusted HR, 0.5 [95% CI, 0.27 to 0.93]), and administration of postoperative systemic therapy (adjusted HR, 0.55 (0.30-1.00)]), were associated with prolonged OS. Intermediate IMDC risk group (adjusted HR, 1.65[95% CI, 0.61 to 4.51]), poor IMDC risk group (adjusted HR, 2.11[95% CI, 0.76 to 5.86]), the presence of visceral metastases (adjusted HR, 2.36[95% CI, 1.26 to 4.41]), inadequate nutritional status (PNI ≤ 40.74, adjusted HR, 1.52[95% CI, 0.75 to 3.08]), poor baseline performance status (ECOG 3-4; adjusted HR, 2.11[95% CI, 0.76 to 5.86]) were associated with worse OS. However, the association between IMDC risk group, baseline

performance status (ECOG), and nutritional status (PNI) with OS did not reach statistical significance (P >.05).

Propensity Score Matching Characteristics and Outcomes

In this cohort, 55 (62.5%) of 88 patients received postoperative systemic therapy after surgery. These patients were matched on the propensity score with 28 patients who did not receive postoperative systemic therapy (PST). The baseline characteristics of the those who received PST and did not receive PST in the matched cohort are described in the **Table 1**. In the unmatched patient population, men (81.8% vs. 60.6%; P=.05) and patients with good baseline performance status ECOG 0-2 (83.6% vs. 54.5%; P=.007) were more likely to receive postoperative systemic therapies.

The distribution of age categories, IMDC risk groups, prognostic nutritional index, frailty, presence of visceral metastases, and sarcopenia were comparable among the treatment groups. In the propensity matched cohort, the distribution of the covariates was adequately balanced the two groups. The median overall survival was 28 months (95% CI, 19-43 months) in the PST group and 12 months (95% CI, 4-37 months) in those who did not receive PST (log-rank P=.027) **(Figure 3).** Postoperative systemic therapy was associated with prolonged OS in the matched cohort (HR, 0.53; 95% CI 0.29-0.93). Additional analysis using inverse probability weighting (IPW) method showed similar results (**Table 3**).

Discussion

The treatment for spinal metastases has evolved over the last decade with the evolution of surgical techniques and adoption of tools such as stereotactic radiosurgery.[30] Local strategies to maximize decompression of the neural elements, address mechanical stability when needed, and provide local tumor control have shown benefit for spine specific measures of pain, function, and health related quality of life.[31,32] However, the benefit of administering systemic therapy after surgery has been less well studied.

In this study, our treated patient population had a median survival of 17 months compared to the historic median survival of 11 months.[6,33] In this analysis, patients who received systemic therapy after surgery had a prolonged survival (28 months vs. 12 months) after adjusting for demographic, clinical, and nutritional features.

Remarkable progress has been made in the clinical application of newer immunotherapies and combinational therapies for the benefit of patients with advanced RCC. In our study population, patients most commonly received TKIs and/or immune checkpoint blockade. Considering that our study included patients over the span of 10 years, a variety of systemic strategies were employed based on the strongest evidence available at the time of treatment. Standards of care continue to evolve rapidly. As a result, only 3 patients within this analysis were treated with combined anti-VEGFR TKI and immune checkpoint blockade, a commonly employed strategy at present on the strength of multiple recent phase III studies.[10,11]

Beyond clinical trials that included patients with bone metastases without stratifying specifically for spinal metastases, only a few studies explored the effect of systemic therapies after surgery or radiosurgery in patients with RCC metastatic to the spine.[23,34,35] Miller et al. reported improved OS in a series of 100 patients with advanced RCC who underwent stereotactic radiosurgery to the spine with concurrent TKIs compared to radiosurgery (SRS) alone.[34] The authors showed that patients receiving SRS with concurrent first line TKI therapy had a lower incidence of local failure compared to those receiving SRS alone, or those who failed first-line therapy (4% vs. 19-27%; $P<.01$).[34] Shankar et al.[35] reported improvement in overall survival for those receiving systemic therapies after palliative spine surgery for RCC and stratified outcomes by functional status. In this study, patients with KPS <80 who received postoperative systemic therapy had prolonged survival compared to those with similar KPS who did not receive postoperative systemic therapy, suggesting therapeutic benefits for patients considered frail.

There are limited data regarding the effectiveness of systemic therapy in spinal metastases for advanced RCC. These patients may be under-represented in randomized clinical trials investigating therapies for advanced RCC. Recognizing this, we sought to investigate this knowledge gap using comparative effectiveness analyses.

Along with the prognostic factors typically studied for spinal metastases, the intermediate and high-risk groups of the IMDC risk scores were associated with shorter OS after spine surgery. The IMDC, which combines disease and functional characteristics (KPS) with laboratory markers, is commonly used to risk-stratify patients into distinct prognostic classes in clinical trials and to provide risk-directed treatment selection in real-world clinical practice.[10,11] The distribution of predominantly intermediate and poor risk IMDC categories in our population is similar to clinical trials investigating systemic therapies that included participants with bone metastases.[15,16] Among

ongoing clinical trials of targeted therapies for RCC, patients with spinal cord compression from advanced RCC are eligible to participate only if they meet strict inclusion criteria; for example, completed surgical treatment at least 4 weeks before and did not receive steroid treatment at least one week before start of protocol therapy (NCT03136627). This emphasizes the need for careful patient selection for surgery and optimization of any modifiable risk factors which may impact recovery and eligibility for such trials.[14,30]

The results of the present study provide further insight into the prognostic role of sarcopenia, frailty, and nutrition. Sarcopenia in the context of metastatic spine cancer has been calculated by measuring the ratio of the average psoas area to the L4 vertebral body area.[36] Although the psoas size is a simple metric to assess sarcopenia, the European Working Group on Sarcopenia in Older People advocate that the psoas is a minor muscle to be solely representative of sarcopenia.[37] In this study, we measured the cross-sectional area of all muscles on axial CT at the L3 vertebral level, using total muscle mass measurements to confirm the diagnosis of sarcopenia. Although previous studies found sarcopenia to be associated with shorter survival, sarcopenia was not associated with poor outcomes in our study.[36,38] These findings highlight the need for consensus criteria and methods to investigate sarcopenia, perhaps also evaluating muscle strength and function, in addition to muscle size. Specifically, in advanced RCC, the prognostic role of sarcopenia is still not clear as some studies have shown no difference in time to treatment failure between sarcopenic and non-sarcopenic patients.[39]

Although sarcopenia contributes to physical frailty, the syndrome of frailty represents a broader concept incorporating various medical comorbidities that define a state of weakened physiologic reserve. Various models have been proposed to quantify frailty, but a validated tool specific to spinal metastases is lacking.[18,40] Therefore, a consistent metric to evaluate frailty in this setting has yet to be defined. In this study, 75% of patients had low frailty levels (mFI <3), which is similar to findings of De la Garza et al. showing 18% severe frailty in patients with spinal metastases.[18] Although there is an inherent selection bias to offer surgery for patients who are considered able to tolerate surgery and are less frail, our study shows that systemic therapy was offered similarly among frailty groups after surgery and that frailty was not associated with poorer survival. This is similar to findings from Bourassa-Moreau et al.[38] who found that frailty was not predictive of adverse events and mortality after surgery for spinal metastases. We speculate that there could be some degree of unmeasured frailty that is not currently assessed that may predispose

patients with advanced RCC to poorer outcomes.[17] The variability in frailty models in the literature highlight opportunities for further investigation.

Furthermore, our assessment of nutritional status based on PNI in patients with spinal metastases was associated with poor overall survival. PNI, which is based on albumin level and lymphocyte count, is reflective of both cancer cachexia and chronic inflammation. The PNI has been used extensively in other medical and surgical oncology fields and has been shown to be a predictor of survival and complications.[41–43] To our knowledge, this is the first study evaluating the PNI in this context of spinal metastases. To date, various laboratory markers such as albumin have been studied in prognostic models and associated with survival.[44,45] Future investigation of nutritional status in spinal metastases should explore whether PNI has more prognostic predictive power than its separate components.

The data provided here may help surgeons adjudicate the role of surgery when treating patients faced with limited survival and uncertain likelihood of starting or resuming systemic therapies. Surgeons may be less inclined to operate if there is only a plan for hospice or palliative care despite the potential palliative benefit of spine surgery. To our knowledge, this is the first study critically examining how variables such as sarcopenia, frailty, and nutrition associate with the impact of systemic therapies on survival using comparative effectiveness statistical methodology. If surgeons know that there is no plan for postoperative cancer therapy, or if it is contingent on the patient's outcome and recovery from surgery, then perhaps more weight should be given to these factors of sarcopenia, nutrition, and frailty in the surgical decision-making process. Surgeons using the NOMS algorithm may determine the patient is a surgical candidate based on the N, O, M categories but there is generally less clarity with the S part of this algorithm. As such, if surgeons know that patients may not recover well with little chance of systemic therapy, this may help guide the decision for surgery. Likewise, considering the dearth of patient-focused decision-making tools for spine surgery, this may help patients better understand and prepare for end of life planning when limited or no options for cancer treatment are likely after surgery.

Limitations

This study has a number of limitations that are inherent to retrospective data collection. Although patients were matched based on perioperative factors to minimize bias, unknown confounders not captured in the data set might produce residual bias. Although the effect estimates

of postoperative systemic therapy was consistent in the methods used, a perfect balance (Standardized differences=0 in PSM and IPW) could not be achieved. The results of this study should be cautiously interpreted within the limitations of the methods used, because an average on the observed and unobserved covariates can only be achieved in randomized controlled trials. Patients who developed postoperative complications or who did not survive a long-enough postoperative period were less likely to have received systemic therapy, leading to what is known as immortal time bias. The heterogeneity of spine surgery techniques and practices at these centers during this time period may factor into this as well.

Furthermore, the sample size was not sufficiently large to reach narrower confidence intervals for median OS and statistical significance for some of the covariates under investigation. This may compromise some of our estimates and there is a concern, given the limited event rate, that our model is not representative of the full spectrum of outcomes that exist for patients with RCC spinal metastases. Our study represents surgical and oncologic practices at two tertiary care centers in North America. Such clustering of data may lead to unintended practice bias and may not necessarily be representative of other health-care settings. Further study with prospective data collection across multiple centers will facilitate further analysis of these variables of sarcopenia, frailty, nutrition, and systemic therapies in this context, which to date have been understudied.

Conclusion

This study demonstrates that the use of postoperative systemic therapies following surgery for RCC spinal metastases was associated with an improvement in survival after adjusting for frailty, sarcopenia, and malnutrition. Poor IMDC risk, baseline performance status, and nutrition were associated with worse survival. Sarcopenia and frailty were not significantly associated with survival.

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Tables

		Unmatched Cohort			Matched Cohort			
Characteristic	**No. (%)**	**No PST**	**PST**	***P Value***	**No. (%)**	**No PST**	**PST**	***P Value***
Overall No.	**88**	**33**	**55**		**83**	**28**	**55**	
Age Categories				0.15				0.21
< 65	50 (56.8)	15 (45.5)	35 (63.6)		35 (42.2)	15 (53.6)	20 (36.4)	
≥ 65	38 (43.2)	18 (54.5)	20 (36.4)		48 (57.8)	13 (46.4)	35 (73.6)	
Sex				0.05				0.29
Men	65 (73.9)	20 (60.6)	45 (81.8)		62 (74.7)	17 (60.7)	45 (81.8)	
Women	23 (26.1)	13 (39.4)	10 (18.2)		21 (25.3)	11 (39.3)	10 (18.2)	
IMDC risk group				0.51				0.83
Favorable risk	10 (11.3)	3 (9.4)	7 (12.7)		11 (13.3)	3 (10.8)	8 (14.5)	
Intermediate risk	49 (55.7)	21 (63.6)	28 (51.0)		44 (53.0)	16 (57.1)	28 (50.9)	
Poor risk	29 (33.0)	9 (27.3)	20 (36.4)		28 (33.7)	9 (32.1)	19 (34.5)	
ECOG				0.007				0.05
Grade 0-2	64 (72.7)	18 (54.5)	46 (83.6)		63 (75.9)	17 (60.7)	46 (83.6)	
Grade 3-4	24 (27.3)	15 (45.5)	9 (16.4)		20 (24.1)	11 (39.3)	9 (16.4)	
Visceral/Pleural metastases				0.82				>0.99
Present	56 (63.6)	20 (60.6)	36 (65.5)		54 (65.1)	18 (64.3)	36 (65.5)	
Absent	32 (36.4)	13 (39.4)	19 (34.5)		29 (34.9)	10 (35.7)	19 (34.5)	
Modified frailty index				0.16				0.33
0	21 (23.9)	4 (12.1)	17 (30.9)		21 (25.3)	4 (14.3)	17 (30.9)	
1	23 (26.1)	8 (24.2)	15 (27.3)		22 (26.5)	7 (25.0)	15 (27.3)	
2	22 (25.0)	10 (30.3)	12 (21.8)		21 (25.3)	9 (32.1)	12 (21.8)	
≥ 3	22 (25.0)	11 (33.3)	11 (20.0)		19 (22.9)	8 (28.6)	11 (20.0)	
Prognostic nutritional index				0.23				0.34
1st tertile	29 (33.0)	14 (42.4)	15 (27.3)		27 (32.5)	12 (42.9)	15 (27.3)	
2nd tertile	29 (33.0)	11 (33.3)	18 (32.7)		26 (31.3)	8 (28.6)	18 (32.7)	
3rd tertile	30 (34.0)	8 (24.2)	22 (40.0)		30 (36.1)	8 (28.6)	22 (40.0)	
Sarcopenic				0.47				0.54
Yes	45 (51.1)	19 (57.6)	26 (47.3)		42 (50.6)	16 (57.1)	26 (47.3)	
No	43 (48.9)	14 (42.4)	29 (52.8)		41 (49.4)	12 (42.9)	29 (52.7)	

Table 1. Baseline demographics and clinical characteristics for patients who received postoperative systemic therapy (PST) and those who did not receive PST in the unmatched and matched cohorts.

	Overall Survival Analysis			
	Univariable		Multivariable	
Variable	HR (95%CI)	*P* Value	HR (95%CI)	*P* Value
Age Categories				
< 65	1 [Reference]	NA		
≥ 65	1.3 (0.76-2.2)	0.36		
Sex				
Women	1 [Reference]	NA	1 [Reference]	NA
Men	0.44 (0.26-0.76)	0.003	0.50 (0.27-0.93)	0.03
IMDC risk group				
Favorable risk	1 [Reference]	NA	1 [Reference]	NA
Intermediate risk	2.1 (0.73-5.9)	0.17	1.65 (0.61-4.51)	0.33
Poor risk	3.2 (1.08-9.3)	0.04	2.11 (0.76-5.86)	0.15
ECOG				
Grade 0-2	1 [Reference]	NA	1 [Reference]	NA
Grade 3-4	2.7 (1.5-4.7)	<0.001	1.57 (0.82-3.02)	0.17
Visceral metastases				
Absent	1 [Reference]	NA	1 [Reference]	NA
Present	2.1 (1.2-3.7)	0.02	2.36 (1.26-4.41)	0.007
Modified frailty index				
0	1 [Reference]	NA		
1	1.0 (0.48-2.2)	0.93		
2	1.5 (0.69-3.1)	0.33		
≥ 3	1.9 (0.92-4.0)	0.08		
Prognostic nutritional index				
3rd tertile	1 [Reference]	NA	1 [Reference]	NA
2nd tertile	0.76 (0.37-1.6)	0.47	0.59 (0.28-1.26)	0.17
1st tertile	2.69 (1.42-5.1)	0.003	1.52 (0.75-3.08)	0.24
Sarcopenic				
No	1 [Reference]	NA		
Yes	0.93 (0.54-1.6)	0.78		
Postoperative systemic therapy				
Not Administered	1 [Reference]	NA	1 [Reference]	NA
Administered	0.47 (0.28-0.8)	0.005	0.55 (0.30-1.00)	0.05

Table 2. Cox Proportional Hazards Regression Models for Overall Survival among 88 patients (All Cohort).

Analysis	Overall mortality
No. of events/no. of patients at risk (%)	
Surgery Alone	24/33 (72.7)
Surgery + PST	33/55 (60.0)
Crude analysis — hazard ratio (95% CI)	0.47 (0.28-0.8)
Multivariable analysis — hazard ratio (95% CI) *	0.55 (0.30-1.00)
Propensity-score analyses — hazard ratio (95% CI)	
With inverse probability weighting†	0.47 (0.24-0.94)
With matching‡	0.53 (0.29-0.93)

Table 3. Associations between postoperative systemic therapy and overall morality after surgical interventional for spinal metastases in the Crude Analysis, Multivariable Analysis, and Propensity-Score Analyses.
Shown is the hazard ratio from the multivariable Cox proportional-hazards model, with stratification according to for age, gender, performance status, IMDC, visceral metastasis, frailty, nutrition, and sarcopenia.
† Shown is the primary analysis with a hazard ratio from the multivariable Cox proportional-hazards model with the same strata and covariates with inverse probability weighting according to the propensity score. The analysis included all the patients (n=88).
‡ Shown is the hazard ratio from a multivariable Cox proportional-hazards model with the same strata and covariates with matching according to the propensity score. The analysis included 83 patients (55 who received postoperative systemic therapy; PST and 28 who did not receive PST).

Figures

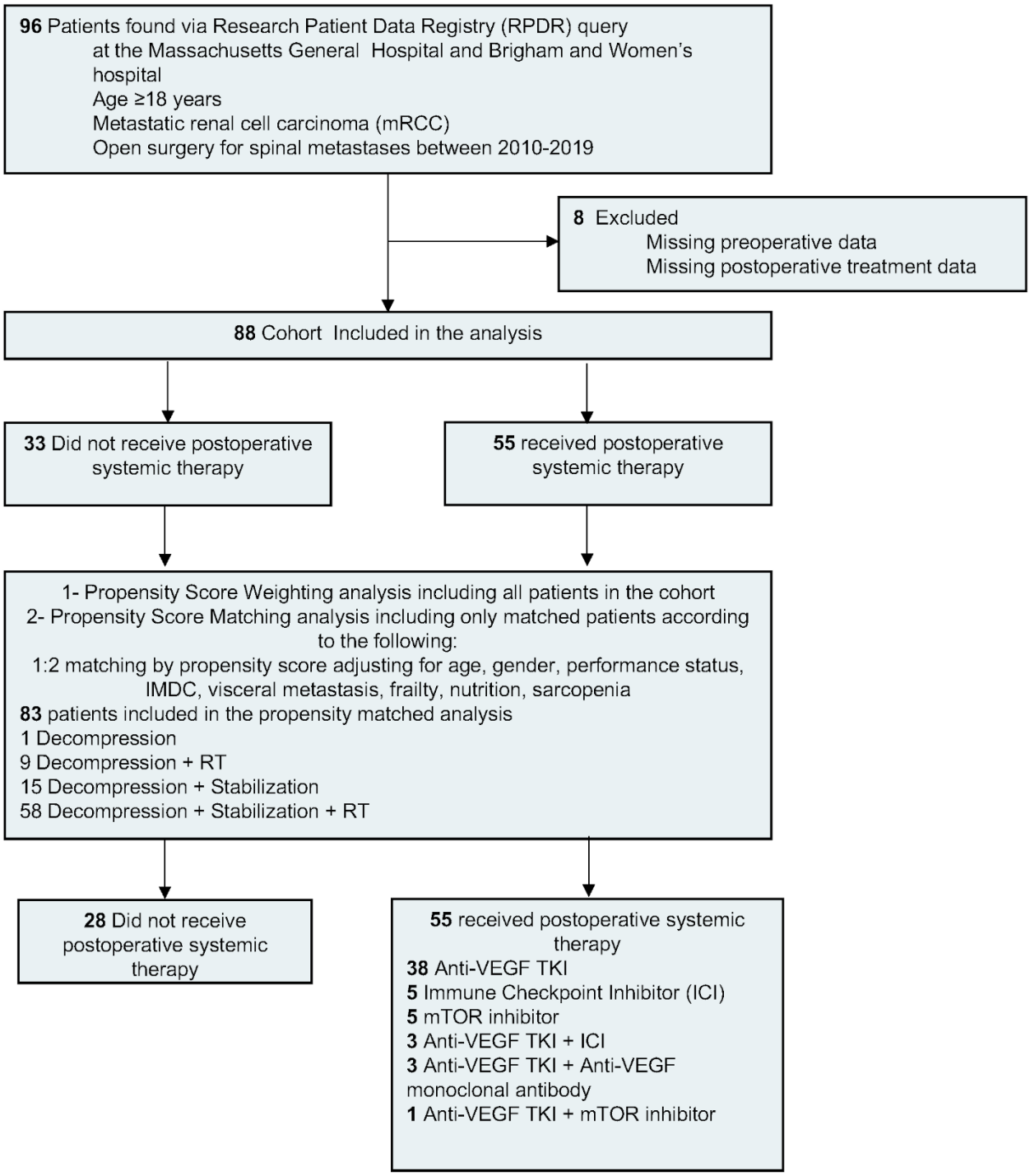


Figure 1. Flowchart showing the characteristics of the cohort. Abbreviations: Immune Checkpoint Inhibitor (ICI), International Metastatic RCC Database Consortium (IMDC), mammalian target of rapamycin (mTOR), Metastatic renal cell carcinoma (mRCC), Radiotherapy (RT), Tyrosine kinase inhibitors (TKIs), Vascular endothelial growth factor (VEGF)

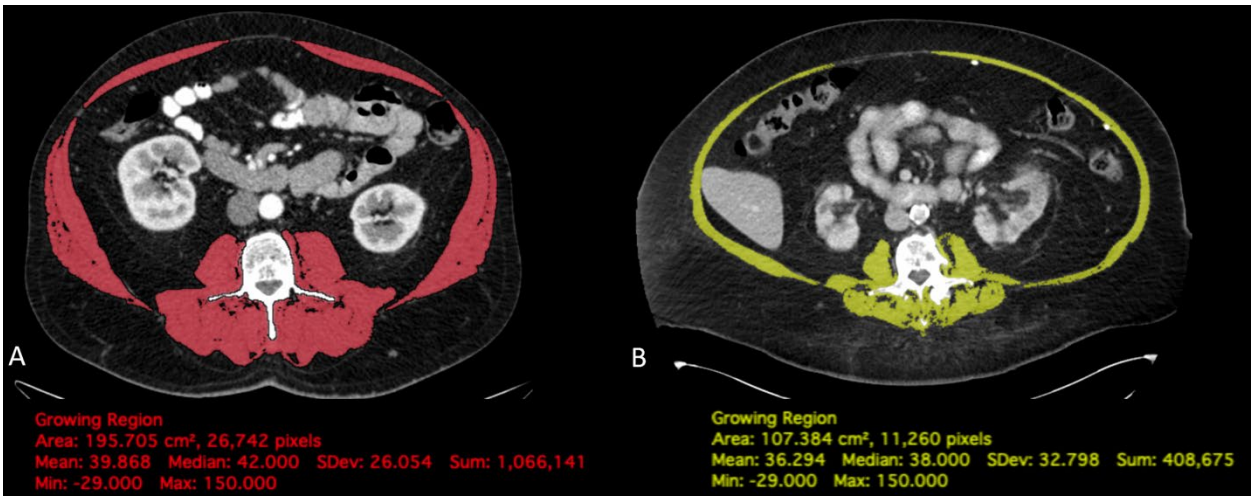


Figure 2. Image Segmentation at L3 vertebral level (unit threshold range of -29 to 150) of the psoas, erector spinae, quadratus lumborum, transversus abdominis, external and internal oblique, and rectus abdominis muscles. The L3- Skeletal Mass Index (L3-SMI) was calculated by measuring the cross-section area of skeletal muscles at this level divided by the patient height2 (m2). A. L3-SMI representative of a non-sarcopenic patients. B. L3-SMI representative of sarcopenia

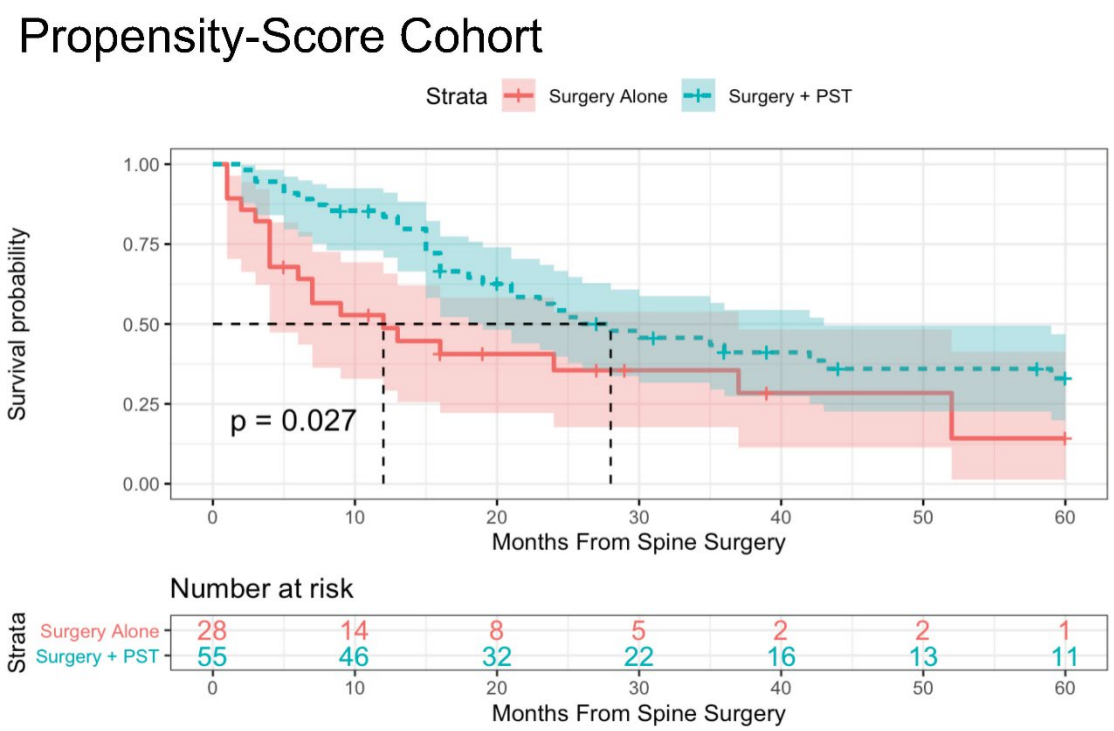


Figure 3 - Kaplan-Meier Survival Analysis in the matched cohort

Supplementary Table 1. Distribution of variable components of the IMDC (International Metastatic RCC Database Consortium) risk score for renal cell carcinoma.

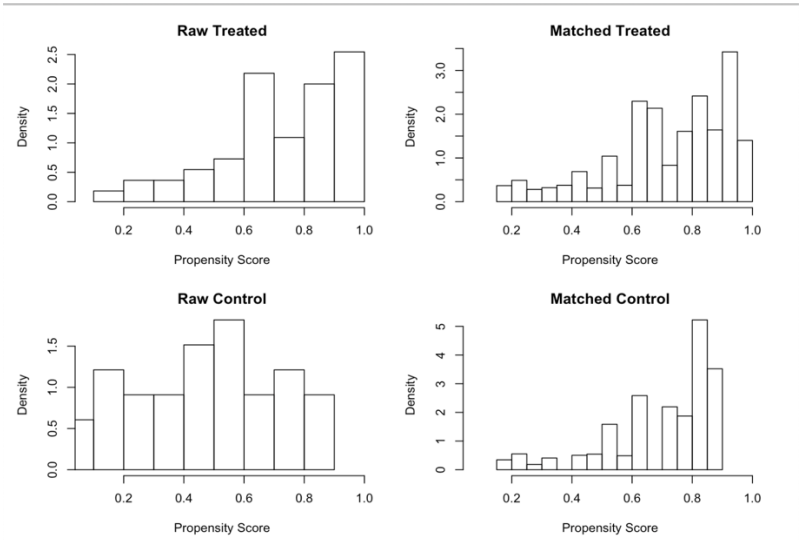
		IMDC risk group count (%)		
Variable	**Total =88**	**Favorable risk (n=10)**	**Intermediate risk (n=49)**	**Poor risk (n=29)**
Less than one year from time of diagnosis to systemic therapy	33 (37.5)	0 (0)	13 (26.5)	20 (68.9)
Karnofsky Performance status (KPS) <80%	48 (54.5)	0 (0)	25 (51.0)	23 (79.3)
Hemoglobin < lower limit of normal Normal: 120 g/L or 12 g/dL	43 (48.8)	0 (0)	23 (46.9)	20 (68.9)
Calcium > upper limit of normal Normal: 8.5-10.2 mg/dL	11 (12.5)	0 (0)	4 (8.2)	7 (24.1)
Neutrophil > upper limit of normal Normal: 2.0–7.0×10^9/L	29 (32.9)	0 (0)	11 (22.4)	18 (62.1)
Platelets > upper limit of normal Normal: 150,000 to 400,000	12 (13.6)	0 (0)	0 (0)	12 (41.4)

Supplementary Table 2. Eleven variables of the modified frailty index

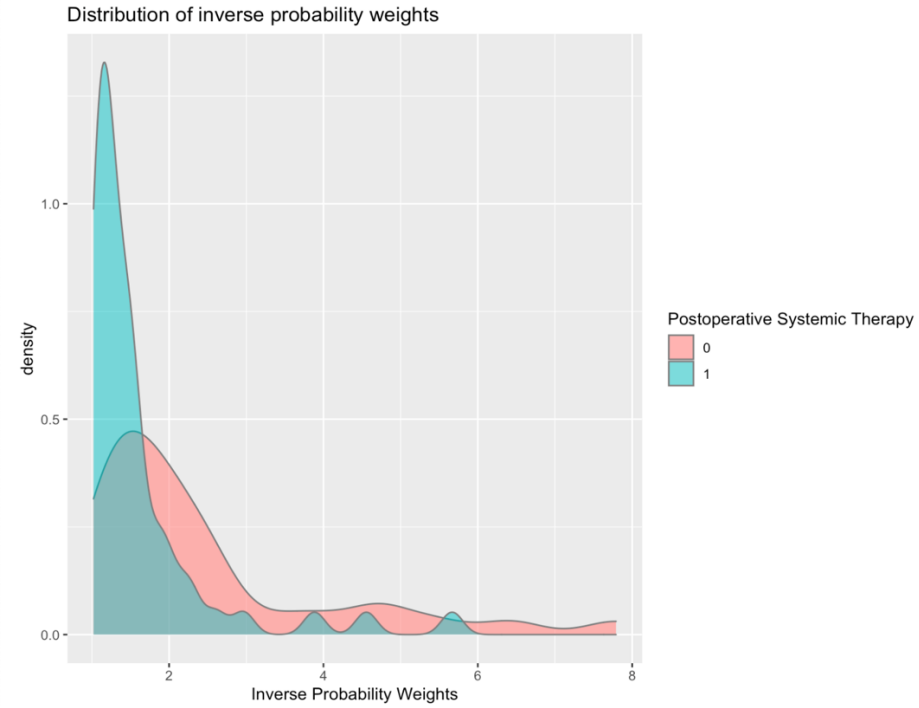
History of diabetes mellitus
History of congestive heart failure
History of hypertension requiring medication
History of either transient ischemic attack or cerebrovascular accident
Functional status 2 (not independent)
History of myocardial infarction
History of either peripheral vascular disease or rest pain
History of cerebrovascular accident with neurological deficit
History of COPD or pneumonia
History of either prior PCI, PCS, or angina
History of impaired sensorium

Notes: Functional status measured in the 30 days prior to surgery. The presence of each variable was scored as 1. Point, the score ranges 0-11, with a score of 0 representing absence of. Frailty, while a. score of 11 represents highest degree of frailty.

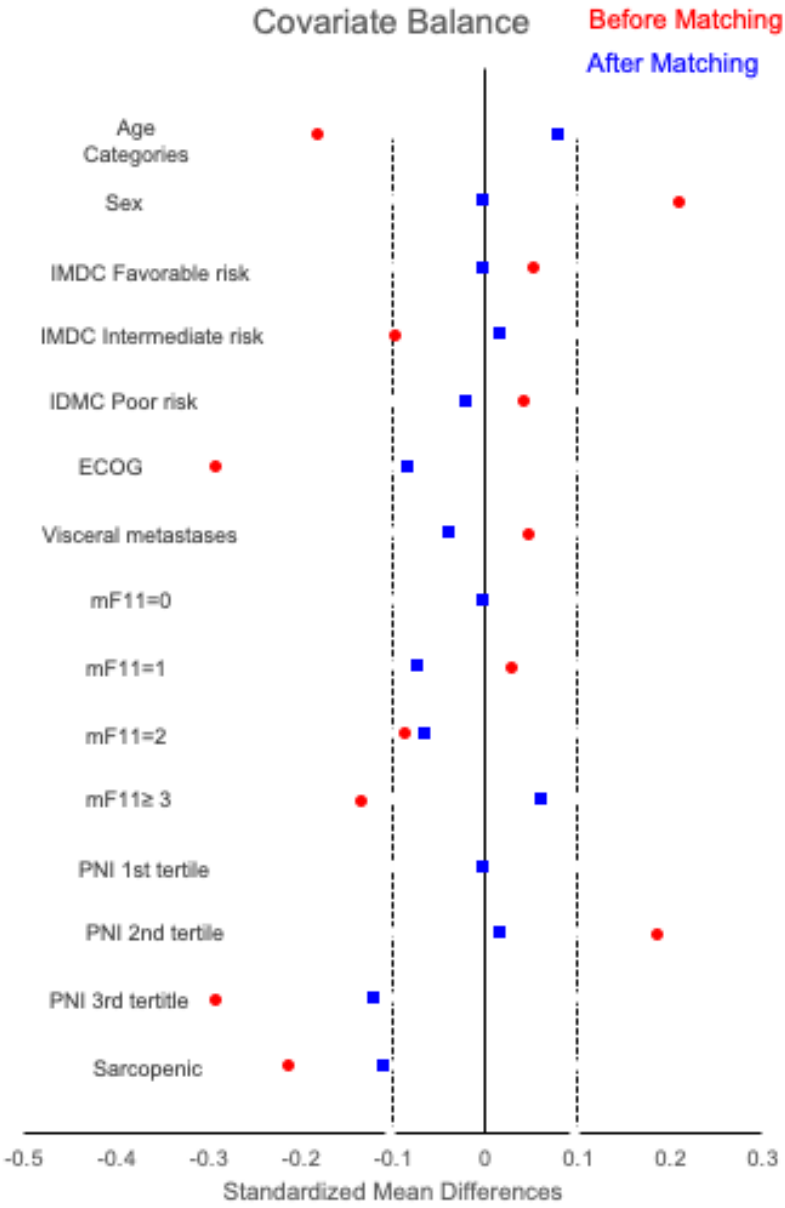
Abbreviations: COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; PCS, prior cardiac surgery.



Supplementary Figure 1. Histograms showing the distribution of propensity scores (distance) before and after matching. The Matched Treated (Surgery + Postoperative systemic. therapy) and Matched Control (Surgery Alone) distributions are roughly similar.



Supplementary Figure 2. Density plot showing the distribution of the inverse probability weights (IPW) in those who received postoperative systemic therapy (Surgery + PST; Blue) and those who did not receive postoperative systemic therapy (Surgery Alone; Red)



Supplementary Figure 3. Standardized mean differences in the unmatched and matched sample.

Summary of Conclusions

We have demonstrated that prediction models underperformed when tested with data of patients surgically treated for spinal metastases. Recent models, which include a larger group of patients treated with newer modalities, showed good calibration and discrimination to predict mortality after spine surgery. As practice changes over time, models need to be recalibrated and validated every few years to ensure validity in clinical settings. Our study estimates that patients who receive systemic therapy for RCC after surgery have longer survival than those who do not receive systemic therapy. Real-world evidence may support systemic therapy administration in patients with spinal metastases who are often not represented in RCT to treat advanced RCC. With few data guiding these treatment decisions, the need for communication among surgeons, radiation, and medical oncologists to reach a consensus on a treatment recommendation is paramount. Such decisions will have ramifications on surgical considerations to maximize the benefit of these surgeries on pain and quality of life.

Discussion and Perspectives

Strategies to treat spinal metastases are dramatically evolving (13). Because treatment strategies are determined by estimating the prognosis of the primary cancer, prediction models should be routinely updated to include the latest data available. Moreover, substantial efforts should be directed to create multicenter collaborative data initiatives that could improve (but still cannot guarantee) generalizability (14). Like the New England Spinal Metastases Score (NESMS), available models would likely continue to improve if more data were available, but it is noteworthy to mention that successful external validation of any prediction model should be followed by research to assess the clinical impact of the model (15). This can be done by randomizing the use of a prediction model between physicians and showing whether use improves patient outcomes such as morbidity or quality of life (16).

Management decisions are challenging for patients with spinal metastases, especially when life expectancy and quality of life are not easily predictable (17). RCT to treat advanced RCC includes patients with bone metastases that are not necessarily representative of surgical candidates with spinal cord compression or mechanical instability, often frailer, presenting with multisite metastases and limited functional status (18). Recent evidence from the METEOR and CheckMate 025 trials showed that newer therapeutic regimens might be more effective against bone metastases (19,20).

We have demonstrated from simulation of an RCT with observational data that systemic therapy after surgery may prolong survival, offering more time for patients who develop epidural spinal cord compression (ESCC) and suffer from debilitating mechanical pain to see the benefits of surgical intervention.

Since treatment after baseline has long been ignored by clinical prediction models, our analytical approach provides a new strategy to better quantify the systemic component of the NOMS framework (21). Treatment initiation after baseline should be considered when estimating mortality risk (22). We argue that if investigators evaluate the risk of death by ignoring initiation of systemic therapy after baseline (time of spine surgery), they are very likely to miss a modifiable factor that could potentially affect their estimated risk of mortality after surgery. When predicting in the presence of modifiable factors (treatment initiation), both prediction and causal inference methods could be used to estimate mortality risk. Causal inference methods would be needed to estimate the risk had the modifiable factor not been available (counterfactual prediction). Prediction methods would be necessary to estimate the risk in three scenarios, (1) given that the patient may receive the treatment, (2) will have enough time (survive) to receive the treatment, (3) survives the period of interest and does not receive the treatment (22).

In conclusion, future studies attempting to predict prognosis in spinal metastases should consider the treatment effect of systemic therapy. This strategy could help estimate the “S” (systemic) component of the NOMS framework when several treatment options are possibly available, like in advanced RCC. Finally, prospective validation of prediction models and reporting of results according to guidelines are important steps to demonstrate their utility and integration in the clinical workflow for treating spinal metastases (23).

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