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Original Research Article

Stereotactic radiosurgery results for brain metastasis patients with renal cancer: A validity study of Renal Graded Prognostic Assessment and proposal of a new grading index (JLGK2101 Study)

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ABSTRACT

Background and purpose: The Renal Graded Prognostic Assessment (GPA) is relatively new and has not been sufficiently validated using a different dataset. We thus developed a new grading index, the Renal Brain Metastasis Score (Renal-BMS).

Materials and methods: Using our dataset including 262 renal cancer patients with brain metastases (BMs) undergoing stereotactic radiosurgery (SRS) (test series), we validity tested the Renal-GPA. Next, we applied clinical factor-survival analysis to the test series and thereby developed the Renal-BMS. This system was then validated using another series of 352 patients independently undergoing SRS at nine gamma knife facilities in Japan (verification series).

Results: Using the test series, with the Renal-GPA, 95% confidence intervals (CIs) of the post-SRS median survival times (MSTs) overlapped between pairs of neighboring subgroups. Among various pre-SRS clinical factors of the test series, six were highly associated with overall survival. Therefore, we assigned scores for six factors, i.e., "KPS $\geq$ 80%/<80% (0/3)", "tumor numbers 1–4/$\geq$5 (score; 0/2)", "controlled primary cancer/not (0/2)", "existing extra-cerebral metastases/not (0/3)", "blood hemoglobin $\geq$ 11.0/<11.0 g/dl (0/1)" and "interval from primary cancer to SRS $\geq$ 5/<5 years (0/1)". Patients were categorized into three subgroups according to the sum of scores, i.e., 0–4, 5–8 and 9–12. In the test and verification series, post-SRS MSTs differed significantly ($p < 0.0001$) with no overlaps of 95% CIs among the three subgroups.

Conclusions: The Renal BMS has the potential to be very useful to physicians selecting among aggressive treatment modalities for renal cancer patients with BMs.

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Introduction

Brain metastases (BMs) reportedly develop in around 15% of patients with renal cell cancer [1,2]. The standard treatment for BMs is surgical removal and/or radiotherapy, i.e., stereotactic radiosurgery (SRS) or whole brain radiation therapy (WBRT) [3]. Recently, systemic anti-cancer agent treatments including immunotherapy have been shown to be effective for either the primary renal cancer or its metastases including those to the brain, and this has remarkably changed the treatment paradigm [4,5]. Also, since the 1990 s, SRS has been widely used for BMs from various primary cancers and has been shown to improve the outcomes of BM patients [6,7]. Considering the availability of multi-modality treatments, the development of a more suitable grading index is awaited because such an improvement is anticipated to help physicians select among treatment options.

Since Gaspar et al reported Recursive Partitioning Analysis (RPA) [8], several prognostic grading systems have been proposed, i.e., Score Index for Radiosurgery [9], Basic Score for Brain Metastases [10], Graded Prognostic Assessment (GPA) [11], Modified RPA [12], Graded Prognostic Model for Patients Surviving 3 Years or More After Stereotactic Radiosurgery [13], Initial Brain Metastasis Velocity [14] and so on. Furthermore, in the second decade of the 21st century, new grading systems specific to each original cancer were developed because it is widely known that there are considerable differences in oncological and clinical features as well as treatment responses among various primary tumor types [15,16]. Very recently, Sperduto et al modified their Diagnosis-Specific GPA to make it more suitable for renal cancer patients with BMs, and called their new system the Renal GPA [17]. With this system, patients are categorized into the four sub-groups, i.e., 0.0–1.0, 1.5–2.0, 2.5–3.0 and 3.5–4.0 by totaling the scores of Karnofsky performance status (KPS); 0/<80%, 1.0/80% or 2.0/90–100%, extra-cerebral metastases; 0/present or 0.5/absent, blood hemoglobin; 0/≥11 g/dl, 0.5/11.1–12.5 g/dl or 1.0/>12.5 g/dl, and BM number; 0/>4 or 0.5/1–4.

In the present study, we performed a validity test of the Renal GPA using our dataset including 266 renal cancer patients who underwent gamma knife SRS for BMs. Our results did not show this system to be sufficiently valid. Therefore, we developed a new grading index, the Renal Brain Metastasis Score (Renal-BMS). Using another dataset including 397 renal cancer patients who had been treated with gamma knife SRS, the Renal-BMS was validated.

Methods and Materials

Patient population

This was an institutional review board-approved study (Tokyo Women's Medical University (No. 1981) and Tsukiji Neurological Clinic (2020–07) for the test series and Keio University School of Medicine No. 20,210,085 for the verification series). Also, the academic committee of the Japanese Leksell Gamma Knife Society certified this study (JLGK2101). We employed our prospectively accumulated database including 7,355 consecutive patients who had undergone gamma knife SRS for BMs by either the second (MY) or the fourth (TS) author during the 20-year-period between 1998 and 2018. Among the 7355 patients, 266 with renal cancer were selected for validation of the Renal-GPA and for devising our new renal cancer-specific prognostic index (test series). Also, we used another dataset including 397 patients who were treated at nine gamma knife sites in Japan to validate our new grading system (verification series). Pre-SRS clinical characteristics are shown in Table 1.

Prior to referral to us for SRS, most of the patient selections had been made by the patients' primary physicians, followed by referral to our institutes because their facilities are not equipped with a gamma knife. It should be noted that patient selection criteria may have differed among the referring physicians. Therefore, the treating neurosurgeons in each

Table 1
Summary of clinical characteristics [Values are presented as the number of patients (%)].

Characteristics		Test series	Verification series	p value
No. of patients		266	397	
Gender	Female	71 (26.7)	100 (25.2)	0.67
	Male	195 (73.3)	297 (74.8)	
Age	<65 years	132 (49.6)	169 (42.6)	0.074
	≥65 years	134 (50.3)	228 (57.4)	
Karnofsky performance status	≥80	191 (71.8)	253 (63.7)	0.029
	≤70	75 (28.2)	144 (36.7)	
Modified-RPA class	1 + 2a	53 (19.9)	60 (15.1)	0.72
	2b	82 (30.8)	77 (19.3)	
	2c + 3	131 (49.2)	140 (35.2)	
	NA	0	120 (30.2)	
Neurological symptoms	No	89 (33.5)	122 (30.7)	0.46
	Yes	177 (66.5)	275 (69.3)	
Presentation	Metachronous	227 (85.3)	316 (79.6)	0.057
	Synchronous	39 (14.6)	81 (20.4)	
Primary cancer status	Controlled	139 (52.3)	174 (43.8)	0.033
	Not Controlled	127 (47.7)	223 (56.2)	
Extra-cerebral metastases	No	56 (21.1)	81 (20.4)	0.84
	Yes	210 (78.9)	316 (79.6)	
Prior surgery	No	222 (83.5)	326 (82.1)	0.65
	Yes	44 (16.5)	71 (17.9)	
Prior whole brain radiotherapy	No	259 (97.4)	388 (97.8)	0.77
	Yes	7 (2.6)	9 (2.3)	
Tumor number	<5	205 (77.1)	322 (81.1)	0.21
	≥5	61 (22.9)	75 (18.9)	
Cumulative tumor volume	<10 cc	209 (78.6)	307 (77.3)	0.71
	≥ 10 cc	57 (21.4)	90 (22.7)	
Largest tumor volume	<5 cc	167 (62.8)	203 (51.1)	0.79
	≥5 cc	99 (37.2(	126 (31.7)	
	NA	0	68 (17.1)	
Hemoglobin at SRS	<11 g/dl	71 (26.7)	90(22.6)	0.60
	≥11.0 g/dl	191 (71.8)	267 (67.2)	
	NA	4 (1.5)	40 (10.0)	
Interval from primary cancer diagnosis to SRS	≥60 months	73 (27.4)	115(28.9)	0.68
	< 60 months	192 (72.2)	281 (70.7)	
	NA	1 (0.4)	1 (0.2)	

Modified-RPA; Modified Recursive Partitioning Analysis, refers to the studies by Yamamoto et al. [12].
SRS; stereotactic radiosurgery, NA; not available.

institute decided whether or not the patient could be treated with SRS in each case. At most of the sites, the neurosurgeons did not perform SRS on patients with low KPS scores due to systemic diseases (<70%), a non-cooperative state due to poor neurocognitive function, diffuse meningeal dissemination, or an anticipated survival period of three months or less. Each patient, along with at least one adult relative, received a detailed explanation of the treatment strategies. Written informed consent was thereby obtained from each patient by each of the treating neurosurgeons prior to all SRS procedures.

Radiosurgical technique

Our radiosurgical techniques have already been reported in detail [18–20]. Briefly, we performed standard, single-session gamma knife SRS with frame placement for most patients in the test series and all of those in the verification series. With single-session SRS, the median dose to the tumor periphery was 20.00 (range; 8.00–25.00, inter-quartile range [IQR]; 18.00–21.00) Gy. However, in 16 patients (6.0 %) in the test series, a two-/three-stage treatment protocol was selected because there was only one or a few relatively large BMs [21,22]. Among these 16 patients, ten underwent two-stage treatment; peripheral doses of 14 Gy were delivered at a three-week interval, and the other six underwent 3-stage treatment; peripheral doses of 9–10 Gy were administered at a two-week interval. Although a few relatively large BMs were irradiated with 2-/3- stage SRS, the majority of smaller tumors were irradiated in a single SRS session usually at the first procedure. Therefore, these 16 patients were not excluded from the analysis set.

After SRS, all patients were routinely managed by their referring physicians, and patients were recommended to have clinical and neuroimaging examinations at an approximately 2- to 3-month interval.

Outcomes

Overall survival (OS) times were defined as the intervals between the first SRS and death, regardless of the cause (i.e., progression of systemic metastases and/or BM, another disease unrelated to the primary cancer, suicide, accident, etc.), or the day of the last follow-up.

Statistical analysis

For the baseline variables, we obtained summary statistics using frequencies and proportions for categorical data, as well as obtaining the median and IQR for continuous variables.

To identify baseline and clinical variables associated with OS, multivariable analysis was performed using the Cox proportional hazard model with a backward selection procedure. The variable selection procedure was set to a threshold of 0.05 for inclusion and 0.05 for exclusion. Additionally, the Akaike Information Criterion (AIC) was applied to determine the best model among those models. For each predictive factor, its distance from the base category in Cox regression coefficient units was divided by this constant and rounded to the nearest integer to obtain the point value. Dividing the coefficients by the absolute value of the smallest coefficient in the model and rounding up to the nearest integer, yielded the component score. We assessed the performance of the scoring system in an external validation cohort by examining calibration and discrimination.

All statistical analyses were performed by either the first author (RO) or the third author (YS), using SPSS software version 26 (IBM, Armonk, USA) and SAS software version 9.4 (SAS Institute, Cary, NC, USA). Prior to the statistical analyses, the 12th author (YH) performed data cleaning. These three authors were involved in neither the SRS treatments nor any aspects of clinical follow-up.

Results

The test series

The median post-SRS follow-up period for 34 censored observations (12.8%) was 16.7 (IQR; 3.9–70.2) months, with 232 patients (87.2%) having died as of the end of June 2020. The median survival time (MST) after SRS was 8.9 (95% CI; 7.4–10.5) months. The respective actuarial post-SRS survival proportions were 39.8%, 19.5%, 14.6%, 10.9% and 7.8% at the 12th, 24th, 36th, 48th and 60th post-SRS months. Among the total 266 patients, follow-up MR imaging was performed at least once in 228 (85.7%) and 93 (35.0%) underwent salvage SRS, generally for newly-appearing lesions (80 patients, 30.1%) and, less commonly, for recurrence of a treated lesion (13 patients, 4.9%), while salvage WBRT was administered to three (1.1%).

Validity test of the Renal GPA

Fig. 1 shows the Kaplan-Meier plots of the OS according to the Renal-GPA system. MSTs (months) per subgroup were 4.6/0.0–1.0, 5.5/1.5–2.0, 10.3/2.5–3.0 and 23.1/3.5–4.0, respectively, excluding four

Table 2
Post-stereotactic radiosurgery (SRS) median survival times (MSTs) and cumulative survival rates according to the Renal Graded Prognostic Assessment and the Renal Brain Metastases Score.

Grading System	Series	Sub-class	N	MST/95% CI (months)	Post-SRS cumulative survival rates/month						HR/95%CI*	p-value*
					6	12	24	36	48	60		
Renal Graded Prognostic Assessment	Test series	3.5–4.0	58	23.1/18.7–35.8	0.85	0.70	0.47	0.35	0.29	0.23		
		2.5–3.0	59	10.3/8.9–13.2	0.76	0.45	0.21	0.18	0.11	0.09	1.630/ 1.123–2.364	0.010
		1.5–2.0	90	5.5/3.8–9.5	0.48	0.31	0.08	0.04	0.04	0.02	1.803/ 1.260–2.579	0.0010
		0.0–1.0	55	4.6/2.8–6.7	0.40	0.11	0.04	0	0	0	1.544/ 1.055–2.258	0.025
Renal Brain Metestasis Score	Test series	0–4	100	19.2/17.0–23.1	0.84	0.71	0.40	0.34	0.26	0.21		
		5–8	112	8.2/6.5–9.6	0.61	0.27	0.10	0.05	0.03	0.01	2.696/ 1.977–3.688	<0.0001
		9–12	50	3.1/2.5–4.9	0.28	0.06	0.06	0.02	0	0	2.189/ 1.545–3.100	<0.0001
	Verifi-cation series	0–4	96	41.0/27.6-NA	0.95	0.89	0.65	0.59	0.47	0.39		
		5–8	185	17.0/14.2–20.4	0.85	0.64	0.35	0.20	0.18	0.14	2.646/ 1.749–4.005	<0.0001
		9–12	71	5.6/4.0–8.0	0.45	0.29	0.07	0.04	0	0	3.193/ 2.234–4.565	<0.0001

HR; hazard ratio, CI; confidence interval, NA; not available.
*In comparison with the upper subclass.

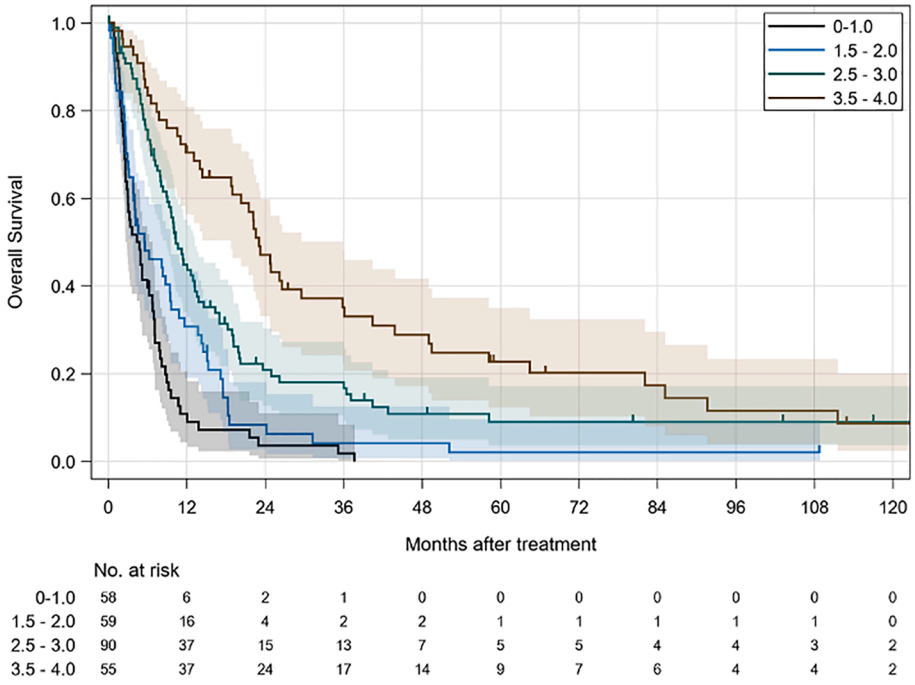

Fig. 1. Overall survivals according to the Renal Graded Prognostic Assessment system for the test series. Shadow showing 95% confidence interval.

patients in whom one or two of the pre-SRS clinical factors necessary for determining this system were not available. Although the log-rank p-value was 0.0001, two plotted lines, those for subclasses 0–1.0 and 1.5–2.0, crossed before the 6th post-SRS month. Furthermore, as shown in Table 2, 95% CIs of the MSTs overlapped between subgroups 2.5–3.0 and 1.5–2.0 and also between 1.5 and 2.0 and 0.1–1.0.

Proposed new grading system

A new grading system was created using variable selection by applying a Cox regression model taking the post-SRS OS rate as an objective variable and various clinical factors as explanatory variables (Table 3). Among various pre-SRS clinical factors, tumor number, KPS, primary cancer status, extra-cerebral metastases and the blood hemoglobin level were shown to be highly correlated with OS. Although the difference did not reach statistical significance ($p > 0.05$), the period between primary cancer diagnosis and SRS showed a clear tendency to be associated with OS. According to these results, our novel scoring system, i.e., the Renal-BMS shown in Table 4, was proposed. The total sum of these scores ranges from 0 to 12 and the smaller the total sum of scores is, the better an outcome can be expected. As this system was designed to be easily used by physicians, patients were categorized simply into three subgroups according to the sum of scores, i.e., 0–4, 5–8 and 9–12. There was no statistical basis for the two boundaries, i.e., between 4 and 5 or between 8 and 9. As shown in Fig. 2A, post-SRS MSTs differed significantly among the three Renal-BMS subgroups ($p < 0.0001$). Furthermore, as shown in Table 2, between each two pairs of neighboring subgroups, i.e., 0–4 vs 5–8 and 5–8 vs 9–12, there were no 95% CI overlaps and post-SRS MST differences reached the level of statistical significance (both $p < 0.0001$).

Table 3
Multi-variable analysis of clinical factors correlating with survival.

Variables		Adjusted HR	95% CI		p value
Tumor number	>5 vs 1-4	0.654	0.477	0.896	0.0083
Age	≥65 vs <65 years	1.005	0.767	1.317	0.97
Gender	Male vs Female	0.969	0.714	1.315	0.84
Karnofsky Performance Status	<80% vs ≥80%	2.138	1.553	2.945	<.0001
Neurological symptoms	Yes vs No	0.999	0.741	1.346	0.99
Volume of the largest tumor	≥10 cc vs <10 cc	0.884	0.572	1.365	0.58
Primary cancer status	Not vs Well controlled	1.673	1.271	2.202	0.0002
Extra-cerebral metastases	Yes vs No	2.205	1.533	3.170	<.0001
Blood hemoglobin	<11.0 vs ≥11.0 g/dl	1.392	1.023	1.894	0.036
Interval between primary cancer diagnosis and stereotactic radiosurgery	<5 vs ≥5 years	1.300	0.958	1.763	0.092

HR; hazard ratio, CI; confidence interval.

Verification series

The Renal-BMS was validated using the verification series of 352 renal cancer patients who had been treated with gamma knife SRS at 11 other gamma knife facilities in Japan excluding 45 patients in whom one

Table 4
Scoring system of the renal brain metastases score.

Variables		Score
Karnofsky Perfomance Status	≥80%	0
	<80%	3
Tumor number	1-4	0
	≥5	2
Primary cancer status	Controlled	0
	Not controlled	2
Extra-cerebral metastases	No	0
	Yes	3
Blood hemoglobin	≥11.0 g/dl	0
	<11.0 g/dl	1
Period between primary cancer diagnosis and SRS	≥5 years	0
	< 5 years	1

SRS; stereotactic radiosurgery.

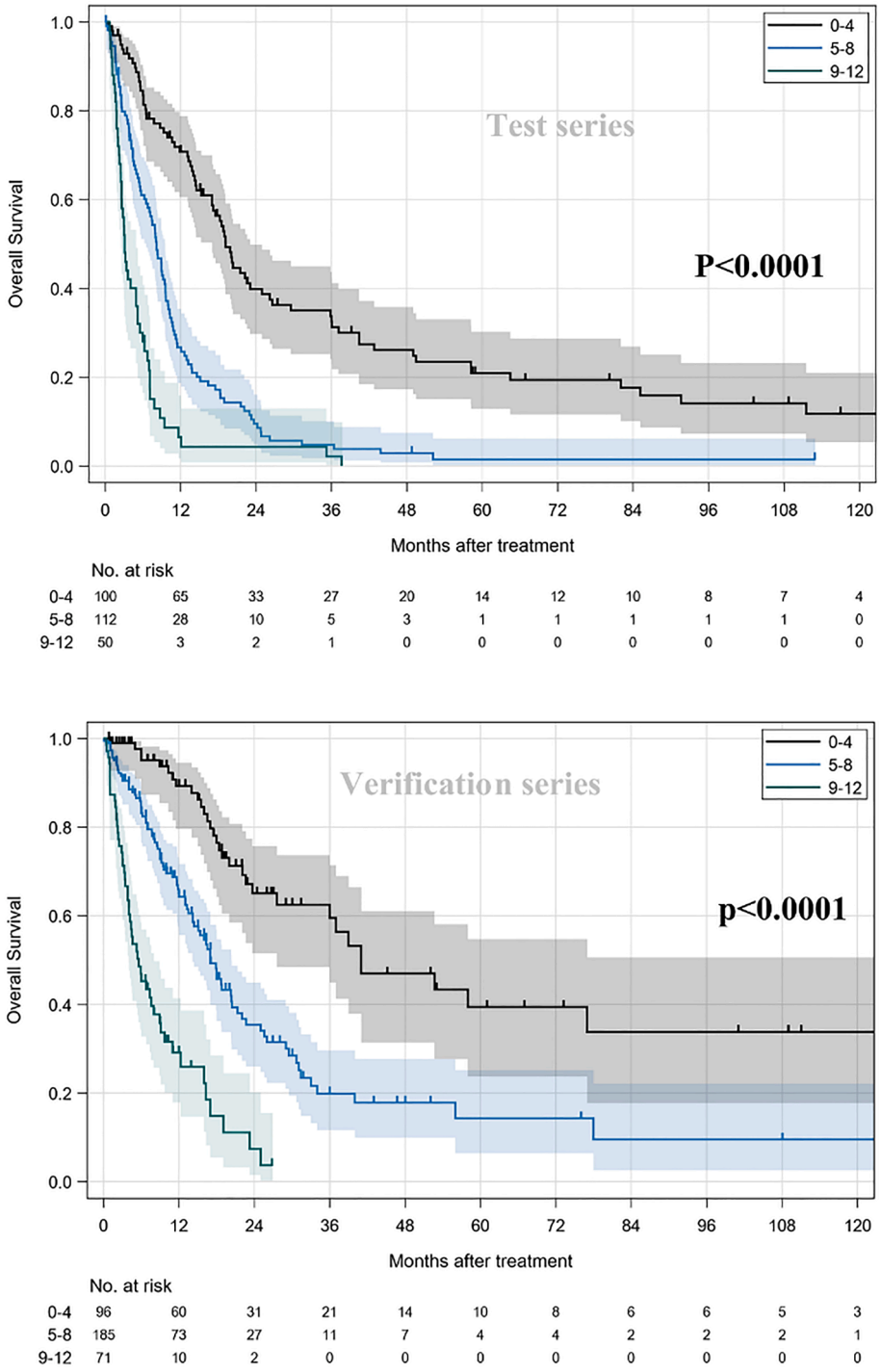

Fig. 2. Overall survivals according to the new grading index, the Renal Brain Metastasis Score system, for the test series (A) and the verification series (B) patients. Shadow showing 95% confidence interval.

or two pre-SRS clinical factors necessary for applying this system were not available. The MST after SRS was 18.0 (95% CI; 15.0–20.4) months. Pre-SRS clinical characteristics are shown in Table 1. The respective actuarial post-SRS survival proportions were 62.3%, 39.1%, 28.3%, 23.0% and 20.2% at the 12th, 24th, 36th, 48th and 60th post-SRS months. As shown in Fig. 2B, post-SRS MSTs differed significantly among the three Renal-BMS subgroups, with the Kaplan-Meier plot showing clear separation with statistical significance ($p < 0.0001$). Furthermore, as shown in Table 2, between each two pairs of neighboring subgroups, i.e., 0–4 vs 5–8 and 5–8 vs 9–12, there were no 95% CI overlaps and post-SRS MST differences reached the level of statistical significance ($p < 0.0001$).

Discussion

In the present study, we developed a new grading index for renal cancer patients with BMs, the Renal-BMS, because the recently-proposed Renal GPA system has a crucial inherent weakness, i.e., CIs of the MSTs between the 2.5–3.0 vs 1.5–2.0 subgroup or the 1.5–2.0 vs 0.0–1.0 subgroup showed overlapping [8]. It should be noted that, with our Renal-BMS system, there were no overlaps of 95% CIs for MSTs between any pair of neighboring subgroups and all inter-subgroup post-MST

differences reached the level of statistical significance in both the test series and the verification series (all $p < 0.0001$) (Table 2).

It is widely recognized that female gender, younger age, better KPS score, controlled primary cancer, absence of extra-cranial metastases, fewer tumors and smaller tumor volume correlate significantly with longer survival [8,17,23]. Therefore, certain combinations of these clinical factors were incorporated into the recently-reported, major prognostic grading indexes. In our test series, however, age, gender and tumor volume had no impact on patient survival. As Sperduto et al recently reported, the blood hemoglobin level was shown to correlate with survival in renal cancer patients with BMs [17]. Furthermore, as Soike et al recently reported and as Yamamoto et al validated employing their results, the interval between the day of primary cancer diagnosis and the day of appearance of BMs or SRS was shown to be an independent factor correlating with patient survival [14,24]. Therefore, we used KPS, tumor number, primary cancer status, extra-cerebral metastases, blood hemoglobin and the period between primary cancer diagnosis and SRS to devise our Renal BMS system. Regarding the threshold for the period from primary cancer diagnosis to SRS, the 5-year post-SRS period in our study is markedly longer than those of other reports in which intervals of 12–18 months have generally been applied in patients with lung, breast or gastro-intestinal cancers or melanoma [1,25]. Nevertheless, some renal cancer patients are known to experience recurrences long after the initial diagnosis and to develop BMs during relatively long follow-up periods. Therefore, the 5-year threshold after SRS in this study was considered to be appropriate.

Very recently, van Ruitenbeek et al reported the validity of the Renal GPA system based on a relatively small number of patients, 106 renal cancer patients whose BMs were treated with gamma knife SRS. They described significant post-SRS MST differences between two pairs of subgroups, 0.0–1.0 (3.0 months) vs 1.5–4.0 (11.0, $p = 0.01$) and 0.0–3.0 (6.0) vs 3.5–4.0 (20.0, $p = 0.01$) [26]. However, they did not report post-SRS MST differences between three pairs of neighboring subgroups. Furthermore, 95% CIs of the MSTs of each subgroup were not provided. Regarding pre-SRS clinical factors, they reported age, KPS, the blood hemoglobin level and time from primary cancer to BM detection to significantly impact to the survival of patients [26].

Due to the retrospective nature of this study, there were considerable biases in patient selection, treatments and observation protocols. One weakness of the present study is that, while the test series included a long-term cohort, patients for whom only limited follow-up data were available were included in the verification series. This means that patients with relatively early deterioration of their general condition after SRS or with relatively early post-SRS death were excluded. Also, as shown in Table 1, there were considerable biases in clinical characteristics among the two series, i.e., the KPS categories and the absence versus presence of extracerebral metastases. As a result, there were considerable differences in MSTs and cumulative survival rates between the two series. This might have influenced our results to some extent. However, despite these weaknesses, our validity test results remain robust.

As the referrals had been selected for SRS by each patient's primary physician at another hospital, the information on their prior systemic anti-cancer agent treatments was not provided to us in a considerable number of cases. Another crucial weakness of the present study is the lack of detailed information on systemic cancer treatments. The systemic treatment of metastatic renal cell cancer has progressed remarkably since the start of data collection, in 1998, for this study. The use of molecular-targeted therapy was approved in the early 2000 s (2005 in the USA, 2008 in Japan) [27,28] . The dataset that we used contained patients managed both before and after the approval of molecular targeted therapy. In 2018, an immune checkpoint inhibiting agent was approved for use in renal cancer patients [29–32]. Although there were profound changes in the treatment paradigm during the study period, our dataset did not include patients who had been treated after the approval of the immune checkpoint inhibiting agent. Confirmation of our results awaits further retrospective or, hopefully, prospective studies using other datasets, particularly patients who have received treatment with linac SRS systems.

Conclusions

We established the Renal-BMS consisting of six pre-SRS clinical factors using our retrospective cohort of 266 renal cancer patients with BMs treated with gamma knife SRS. By validating our system, we confirmed its greater ability to predict the outcomes of renal cancer patients with BMs.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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