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Brain Metastasis and Renal Cell Carcinoma: Prognostic Scores Assessment in the Era of Targeted Therapies

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Abstract. *Aim: This study aimed at exploring several brain metastatic prognostic scores in patients with renal cell carcinoma. Patients and Methods: We retrospectively analyzed data of 93 metastatic renal cell carcinoma patients who were diagnosed with brain metastases between October 2005 and July 2016 who received targeted therapy. Potential prognostic factors (RTOG RPA, BS-BM, and a newly developed score CERENAL) were analyzed. Results: A total of 75 patients received targeted therapy. All scores showed prognostic value in progression-free survival after first-line treatment with CERENAL being the sole independent prognostic factor associated with improved duration of first-line treatment. Both RTOG RPA and CERENAL were potential prognosticators for overall survival, whereas only the CERENAL score was associated with prolonged disease-specific survival. Conclusion: Several prognostic scores can be useful to predict survival of patients with brain metastases from renal cancer, especially the newly developed CERENAL score.*

Renal cell carcinoma (RCC) accounts for 2.4% of all malignancies diagnosed worldwide with 337,800 estimated new cases globally and 115,200 new patients in Europe in 2012 (1-3). At primary diagnosis, approximately 25% of patients are diagnosed with advanced RCC (4).

In case of metastatic disease, median overall survival (OS) is 18.8 months, with 5-year disease-specific survival rates of 32%, 19.5% and 0% found for patients with low-, intermediate- and high-risk respectively (1, 5). However, recent data from trials with immunotherapy in metastatic RCC showed 2-year OS rates up to 70% (5).

Brain metastases occur in 10% of metastatic RCC patients (6). Local treatment options such as surgery or radiotherapy are considered the standard of care to treat brain metastases. However, as brain metastases tend to be relatively resistant to whole-brain radiation therapy, use of stereotactic radiosurgery seems to result in a satisfactory control of brain metastases with only a limited survival benefit (7, 8). Nevertheless, overall prognosis remains poor with nearly all patients succumbing to the disease within 2 years of brain metastasis diagnosis (8, 9).

Several prognostic scores for brain metastases have been reported to determine the prognostic outcome of patients following brain surgery or radiotherapy, such as the Radiation Therapy Oncology Group Recursive Partitioning Analysis (RTOG RPA), the Score Index for Radiosurgery and the Basic Score for Brain Metastases (BS-BM) (10-12). However, these scores were developed and validated in studies with various tumor types, usually with none or only one small RCC subgroup.

Therefore, the goal of this retrospective study was to validate the brain metastasis prognostic scores RTOG-RPA and BS-BM in patients with renal cell cancer treated with targeted therapies. Next, we aimed at developing a potential new tool named CERENAL score for this population and evaluate the prognostic potential for PFS and OS.

Patients and Methods

Patient selection. We retrospectively identified metastatic RCC patients who were diagnosed with or developed brain metastases during the course of their disease in four international cancer centers

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Key Words: Brain metastasis, renal cell carcinoma, survival, prognostic factors.

between October 2005 and July 2016. Patient data were retrieved from the electronic patient files. All patients with brain metastases treated with targeted therapies, including tyrosine kinase inhibitors and mTOR inhibitors, were included. This study was approved by the Ethics Committee of all participating centers. Informed consent was given by all participants. The study was conducted according to the principles of the Helsinki declaration.

Prognostic factors. Brain metastasis prognostic scores were determined as described in literature. Patients were distributed among RTOG RPA classes I, II or III using age, Karnofsky performance status (KPS) and presence of extracranial metastases at brain metastasis diagnosis (10). Next, the BS-BM was determined using KPS, management of systemic disease and presence of extracranial metastases at brain metastasis diagnosis. Up to one point was attributed per prognostic factor with a final BS-BM ranging between 0 and 3 (11). Due to limited data in the patient data files on the volume of the brain lesions, the Score Index for Radiosurgery (12) could not be calculated.

As the majority of these scores were developed and validated in populations with mainly lung cancer, breast cancer, or malignant melanoma, a novel brain metastasis prognostic score was devised, namely CERENAL, based on the prognostic parameters used for the RTOG RPA and the BS-BM and findings in literature showing that a low number of intracranial metastases and SRS may predict a substantial survival benefit for metastatic RCC patients (8, 13). In this score, 1 point was attributed for each negative prognostic factor for a total score ranging between 0 and 6 points. All three brain metastasis prognostic scores are described in Table I. All prognostic scores were then dichotomized for survival analysis based on median numbers for each prognostic variable. Patients were subdivided as RTOG RPA class I-II *versus* RTOG RPA class III. For BS-BM and CERENAL, cut-off was taken at ≤2 and ≤4, respectively. Insufficient retrospective data was available to determine MSKCC or Heng criteria.

Table I. *Calculation of brain metastatic prognostic scores.*

RTOG RPA[#]			
CLASS	I	II	III
KPS	≥70	≥70	<70
	and	and	and
Age	<65	all	all
	and	and	and
Extracranial metastases	No	No/Yes	No/Yes
BS-BM*			
POINTS	0		1
KPS	≤70		≥80
Systemic disease	PD		SD – PR – CR – NED
Extracranial metastases	Yes		No
CERENAL*			
POINTS	0		1
KPS at diagnosis of first brain metastasis	>70		≤70
Age at diagnosis of first brain metastasis	≤50 years		>50 years
Progressive disease at diagnosis of first brain metastasis (primary tumor included)	No		Yes
Other extracranial metastasis	No		Yes
Number of brain metastatic lesions	1		≥2
Received stereotactic radiosurgery	Yes		No

[#]Patients are subdivided in class according to the combination of all three criteria. *Final score is obtained by sum of all individual points. KPS, Karnofsky performance status.

Statistical analysis. Spearman's rank correlation coefficient ϱ was assessed between prognostic scores. The overall percentage agreement was calculated pairwise for comparison between all dichotomized prognostic scores. Each prognostic score was calibrated for progression-free survival (PFS, time from treatment initiation until radiographic progression or discontinuation due to adverse events) and OS (time from brain metastasis diagnosis until day of death or last follow-up) by means of a logistic regression model (Hosmer-Lemeshow test). Small χ^2/larger *p*-values indicate a good model fit.

The hazard ratio (HR) of each prognostic score on first-line PFS, second-line PFS, OS and disease-specific survival (DSS) was determined by a 2-sided log-rank (Mantel–Cox) test. Patients that were lost to follow-up were censored in the survival analysis. Survival curves were plotted using the Kaplan–Meier method. Comparison of survival rates between all dichotomized prognostic scores for six-months first-line PFS, six-months second-line PFS, six-months OS, one-year OS, six-months DSS, and one-year DSS was performed using decision curve analysis (14). The covariate effect of the survival risk factors (reaching *p*-value <0.05 on univariate test), was determined *via* Cox proportional hazard model (backward method). Missing values were not included in the analyses. *p*-Values<0.05 were considered statistically significant. Analyses were performed with MedCalc Statistical Software v17.4 (MedCalc Software, Ostend, Belgium); SPSS v23.0 (IBM corporation, Armonk, NY, USA), GraphPad Prism v4.7 (GraphPad Software Inc., La Jolla, CA, USA) and RStudio v3.5.1 (RStudio, Boston, MA, USA).

Results

Patient characteristics and prognostic scores. Out of 93 RCC patients who were diagnosed with brain metastasis, eighteen patients did not receive targeted therapy and were excluded from all analyses. An overview of the clinical characteristics as well as a descriptive analysis concerning the diagnosis and specific treatment of brain metastases in the intention-to-treat cohort (75 cases) is given in Tables II and III, respectively.

Patient distribution among brain metastasis prognostic scores is shown in Table IV. Prognostic scores were comparable to each other. A moderate rank correlation was found between RTOG RPA and BS-BM (ϱ=–0.700, $p<0.0001$) and between CERENAL and BS-BM (ϱ=–0.702, $p<0.0001$) whereas a fair rank correlation was found between RTOG RPA and CERENAL (ϱ=0.533, $p<0.0001$). Dichotomization of the

Table II. *Clinical characteristics in the intention-to-treat cohort (n=75).*

Gender	
Male	57 (76)
Female	18 (24)
Median age, years	55 (28-82)
Histology	
Clear-cell	66 (88)
Papillary	2 (3)
Chromophobe	2 (3)
Not determined	5 (7)
Sarcomatoid component	
Yes	8 (11)
No	28 (37)
Not determined	39 (52)
Fuhrmann grade	
I-II	8 (11)
III	27 (36)
IV	9 (12)
Unknown	31 (41)
Nephrectomy	
Yes	57 (76)
No	18 (24)
IMDC risk group	
Good	12 (16)
Intermediate	28 (37)
Poor	16 (21)
Unknown	19 (25)
Site of metastasis	
Lungs	38 (51)
Liver	14 (19)
Bones	15 (20)
Adrenal glands	16 (21)
Lymph nodes	28 (37)
Other	13 (17)

Data given are number (percentage) except for age at RCC diagnosis: median (range).

Table III. *Brain metastases characteristics at brain metastasis diagnosis in the intention-to-treat cohort (n=75).*

Time between diagnosis of primary tumor and diagnosis of brain metastasis (months)	15 (0-381)
Brain metastasis at diagnosis	
Yes	15 (20)
No	60 (80)
Other metastatic sites involved at brain metastasis diagnosis	
No sites	2 (3)
Lungs	62 (83)
Lymph nodes	41 (55)
Liver	17 (23)
Bones	29 (39)
Adrenal gland	14 (19)
Other	20 (27)
Localization of brain metastasis	
Supratentorial	36 (48)
Infratentorial	2 (3)
Both	12 (16)
Unknown	25 (33)
Number of brain metastases	
1	38 (51)
2	13 (17)
3+	23 (31)
Not determined	1 (1)
Neurological symptoms	
Yes	47 (63)
No	28 (37)
Received first-line targeted therapy before brain metastasis diagnosis	
Yes	39 (52)
No	36 (48)
Additional therapy for brain metastases	
No additional therapy	8 (11)
WBRT alone	27 (36)
SRS alone	12 (16)
Surgery + WBRT	17 (23)
Surgery + SRS	3 (4)
WBRT + SRS	3 (4)
Surgery + WBRT + SRS	5 (7)

Data given are number (percentage) except for time between primary tumor and brain metastasis: median (range). SRS, Stereotactic radiosurgery; WBRT, whole-brain radiotherapy.

prognostic scores showed moderate overall percentage agreement (68%, 79%, 68%) for RTOG RPA *versus* BS-BM, CERENAL *versus* BS-BM, and RTOG RPA *versus* CERENAL, respectively. RTOG RPA, BS-BM and CERENAL showed excellent model fit for first-line PFS (χ^2=9.18E-9, p=0.9999; χ^2=6.40E-9, p=1.0000; and χ^2=4.57E-9, p=1.0000, respectively) and OS (χ^2=5.74E-9, p=1.0000; χ^2=5.74E-9, p=1.0000; and χ^2=7.86E-9, p=1.0000, respectively).

PFS after first- and second-line targeted therapy. A total of 36/75 patients (48%) were diagnosed with brain metastases at first-line treatment initiation. Median follow-up time since first-line therapy until death or last follow-up was 54.7 months (42.8-66.5). An overview of administered therapies with median duration of first-line therapy and PFS per therapy are given in Table V.

All prognostic scores showed significance in PFS after first-line targeted therapy. Patients classified as RTOG RPA class I/II showed a prolonged PFS in comparison with RTOG RPA class III [median PFS=10.3 *versus* 3.6 months; HR=0.28 (0.02-0.3), p=0.0013]. A similar outcome was found for the BS-BM score. Having a BS-BM score of 2 or 3 resulted in a 56% reduction in risk of progression [HR=0.44 (0.17-0.82), p=0.0140] with median PFS of 11.9 months compared with 5.6 months for BS-BM score lower than 2. Patients having a CERENAL score lower than 4 also had a longer median PFS (11.9 *versus* 4.1 months) resulting in a 64% reduction in risk of progression [HR=0.36 (0.09-0.57), p=0.0015; Figure 1A-C]. Decision curve analysis for six-months PFS showed that the CERENAL score achieved highest net benefit between the 0.2 and 0.4 risk threshold,

Table IV. *Brain metastasis prognostic scores at brain metastasis diagnosis in the intention-to-treat cohort (n=75).*

Prognostic scores	n	(%)	mOS (95%CI)	*p*-Value	mDSS (95%CI)	*p*-Value
RTOG RPA						
I	1	(1)	35.6 (–)	0.0001	35.6 (–)	0.0007
II	49	(65)	19.3 (10.2-30.5)		16.8 (10.2-32.5)	
III	25	(33)	6.0 (3.4-9.1)		6.0 (2.6-11.5)	
BS-BM						
0	13	(17)	5.6 (2.2-10.5)	0.0001	5.6 (1.0-12.2)	0.0015
1	36	(48)	9.1 (5.0-14.9)		10.2 (5.0-15.2)	
2	25	(33)	30.5 (19.3-40.6)		22.6 (14.2-67.6)	
3	1	(1)	35.6 (–)		35.6 (–)	
CERENAL						
1	2	(3)	58.9 (–)	<0.0001	35.6 (–)	<0.0001
2	11	(15)	39.3 (30.5-70.5)		67.6 (32.5-70.6)	
3	16	(21)	19.3 (9.2-22.6)		19.3 (9.2-23.8)	
4	21	(28)	6.3 (5.0-13.2)		6.3 (3.1-13.2)	
5	21	(28)	10.9 (4.4-15.2)		11.5 (4.7-15.2)	
6	4	(5)	1.0 (1.0-10.5)		1.0 (1.0-2.3)	

Data given are number (percentage). mOS and mDSS are given in months. 95%CI, 95% Confidence interval; BS-BM, basic score for brain metastases; mDSS, median disease-specific survival; mOS, median overall survival; RTOG RPA, radiation therapy oncology group recursive partitioning analysis.

Table V. *Targeted therapies administered in patients diagnosed with brain metastasis and survival outcome.*

Therapy	n	(%)	mPFS (95%CI)	mOS (95%CI)	mDSS (95%CI)
Intention-to-treat cohort*	75	(100)	10.1 (7.1-11.4)	11.5 (8.8-16.8)	12.2 (8.5-16.8)
First-line therapy§	36	(100)	10.1 (4.1-11.9)	16.8 (12.2-32.9)	15.2 (11.5-39.3)
Sunitinib	21	(58)	10.3 (7.8-14.2)	20.4 (4.2-67.6)	16.8 (12.2-70.5)
Pazopanib	3	(8)	2.6 (2.6-3.6)	10.5 (3.9-13.9)	13.9 (–)
Sorafenib	5	(14)	11.2 (10.1-11.9)	39.3 (19.3-58.9)	22.3 (19.3-40.6)
Everolimus	2	(6)	2.6 (2.6-5.6)	10.9 (10.9-11.5)	10.9 (10.9-11.5)
Temsirolimus	5	(14)	2.2 (1.0-23.4)	6.0 (2.3-23.8)	6.0 (2.3-23.8)
Duration first-line therapy (months)	9.6	(1.0-55.8)			
Number of patients stopped for AE	5	(14)			
Second-line therapy+	29	(100)	5.0 (3.1-6.5)	32.5 (15.2-52.7)	23.8 (14.9-40.6)
Sunitinib	4	(14)	5.1 (0.4-19.7)	39.3 (23.8-58.9)	39.3 (23.8-40.6)
Pazopanib	1	(3)	2.6 (–)	13.9 (–)	13.9 (–)
Sorafenib	5	(17)	2.8 (1.4-5.0)	11.5 (10.9-70.6)	11.5 (10.9-70.6)
Everolimus	12	(41)	4.1 (2.1-37.5)	32.5 (16.8-54.0)	22.4 (14.9-54.0)
Axitinib	4	(14)	3.5 (3.1-6.5)	10.5 (8.5-15.2)	15.2 (8.5-NR)
Temsirolimus	2	(7)	7.0 (–)	70.5 (70.5-70.6)	70.5 (70.5-70.6)
Interferon-γ	1	(3)	5.1 (–)	8.8 (–)	8.8 (–)
Duration second-line therapy (months)	3.5	(0.0-37.5)			
Number of patients stopped for AE	6	(21)			

Data given are number (percentage) except for duration of therapy: median (range). mPFS, mOS and mDSS are given in months. *mPFS in intention-to-treat cohort is independent of prior targeted therapy before brain metastasis diagnosis. §A total of 36 patients were diagnosed with brain metastases before first-line therapy was initiated. +Out of the 36 patients with brain metastases who were treated in first-line, 21 started second-line therapy together with eight patients diagnosed with brain metastases during first-line therapy. 95%CI, 95% Confidence interval; mDSS, median disease-specific survival; mOS, median overall survival; mPFS, median progression-free survival.

whereas RTOG RPA indicated the highest net benefit above the 0.4 risk threshold. BS-BM showed the lowest net benefit for every risk threshold (Figure 2A). A multivariate analysis proved that the CERENAL score was the sole independent prognostic factor associated with an improved PFS from first-line therapy (p=0.0029, Table VI, First-line PFS).

Twenty-one out of 36 patients diagnosed with brain metastases at start of first-line therapy together with 8 patients newly diagnosed with brain metastases during their first-line therapy received second-line targeted therapy. An overview of administered therapies and median duration of second-line therapy are given in Table V.

In comparison to first-line therapy, no prognostic value was found for RTOG RPA [$HR_{RTOG\ RPA\ class\ I/II}$=0.62 (0.18-1.66)], BS-BM [$HR_{BS\text{-}BM\ 2\text{-}3}$=0.65 (0.26-1.46)] or CERENAL [$HR_{CERENAL\ 1\text{-}3}$=0.76 (0.33-1.75)]. This is also shown on the decision curves for six-months PFS with only marginal net benefit found for CERENAL between the 0.55 and 0.75 risk threshold (Figure 2B).

OS and DSS. Of all patients, 63/75 (84%) were deceased and 9/75 (12%) were lost-to-follow-up at time of OS analysis. Median follow-up time since diagnosis of brain metastases until death or last follow-up was 62.1 months (52.6-71.5). Median OS per first- and second-line therapy are given in Table V.

Univariate analysis confirmed the prognostic value of the different prognostic scores. Patients classified as RTOG RPA class I/II showed a median OS of 20.4 *versus* 6.0 months for patients classified as RTOG RPA class III [HR=0.36 (0.11-0.44), $p<0.0001$]. Moreover, patients with BS-BM 2-3 had an improved outcome compared with patients with BS-BM 0-1 [median OS=30.5 *versus* 6.6 months; HR=0.38 (0.17-0.55), $p<0.0001$]. Median OS was significantly longer in patients with CERENAL 1-3 *versus* CERENAL 4-6 (30.5 *versus* 6.3 months) with a 59% reduction in risk of death [HR=0.37 (0.17-0.51), $p<0.0001$] (Figure 3A-C). Patients receiving local therapy for brain metastases had an improved median OS *versus* those who did not [13.9 *versus* 5.3 months; HR=0.44 (0.09-0.90), $p=0.0324$]. Highest net benefit for six-months OS was found for CERENAL for risk thresholds up to 0.4 whereas RTOG RPA proved more beneficial between the 0.4 and 0.5 risk threshold (Figure 2C). At one-year OS, BS-BM and CERENAL proved to be comparable on decision curve analysis with highest net benefit between the 0.3 and 0.55 risk threshold, although RTOG RPA is more beneficial between the 0.55 and 0.8 risk threshold (Figure 2D). This was deflected in the multivariate analysis which suggested that RTOG RPA ($p=0.0428$) and CERENAL score ($p=0.0063$) are independent prognostic factors (Table VI, OS).

Of all deceased patients, 49/63 (78%) died from their disease. Comparable to OS, all prognostic scores were significant for DSS. Median DSS for first- and second-line therapy are given in Table V. Having a prognostic favorable score resulted in a significant reduction in risk of death of 63%, 61% and 62% for RTOG RPA, BS-BM and CERENAL, respectively ($p=0.0002$, $p=0.0007$ and $p=0.0003$; Figure 4A-C). Likewise, patients who had additional brain metastatic therapy lived longer in comparison to patients who did not undergo local therapy [13.9 *vs*. 5.0 months; HR=0.42(0.08-0.94), $p=0.0390$]. Decision curves for six-months DSS and one-year DSS were similar with those observed for six-months OS and one-year OS (Figure 2E and F). However, in contrast to OS, only CERENAL ($p=0.0005$) was an independent prognostic factor associated with DSS in the multivariate analysis (Table VI, DSS).

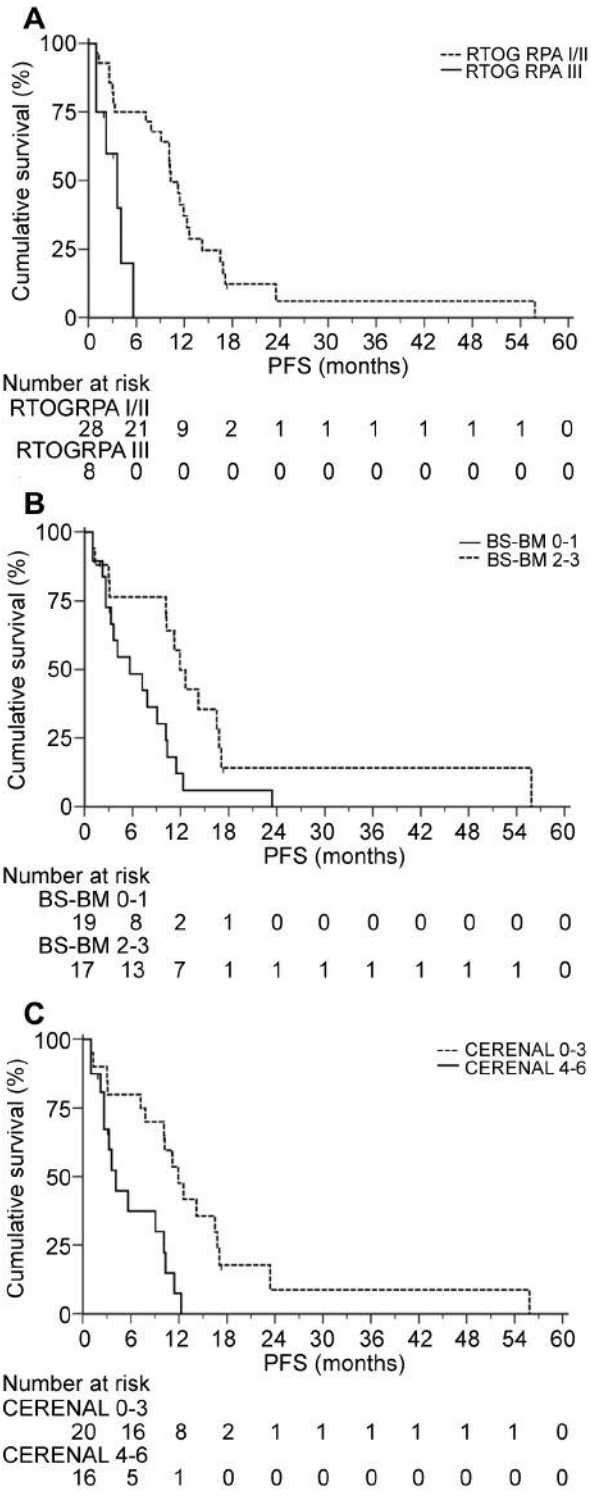

Figure 1. *Kaplan-Meier first-line progression-free survival curves for brain metastasis prognostic scores. Y-axis depicts cumulative survival (%), X-axis depicts survival time in months. Survival curves are demonstrated for (A) RTOG RPA (p=0.0013), (B) BS-BM (p=0.0140), (C) CERENAL (p=0.0015). BS-BM, Basic score for brain metastases; PFS, progression-free survival; RTOG RPA, radiation therapy oncology group recursive partitioning analysis.*

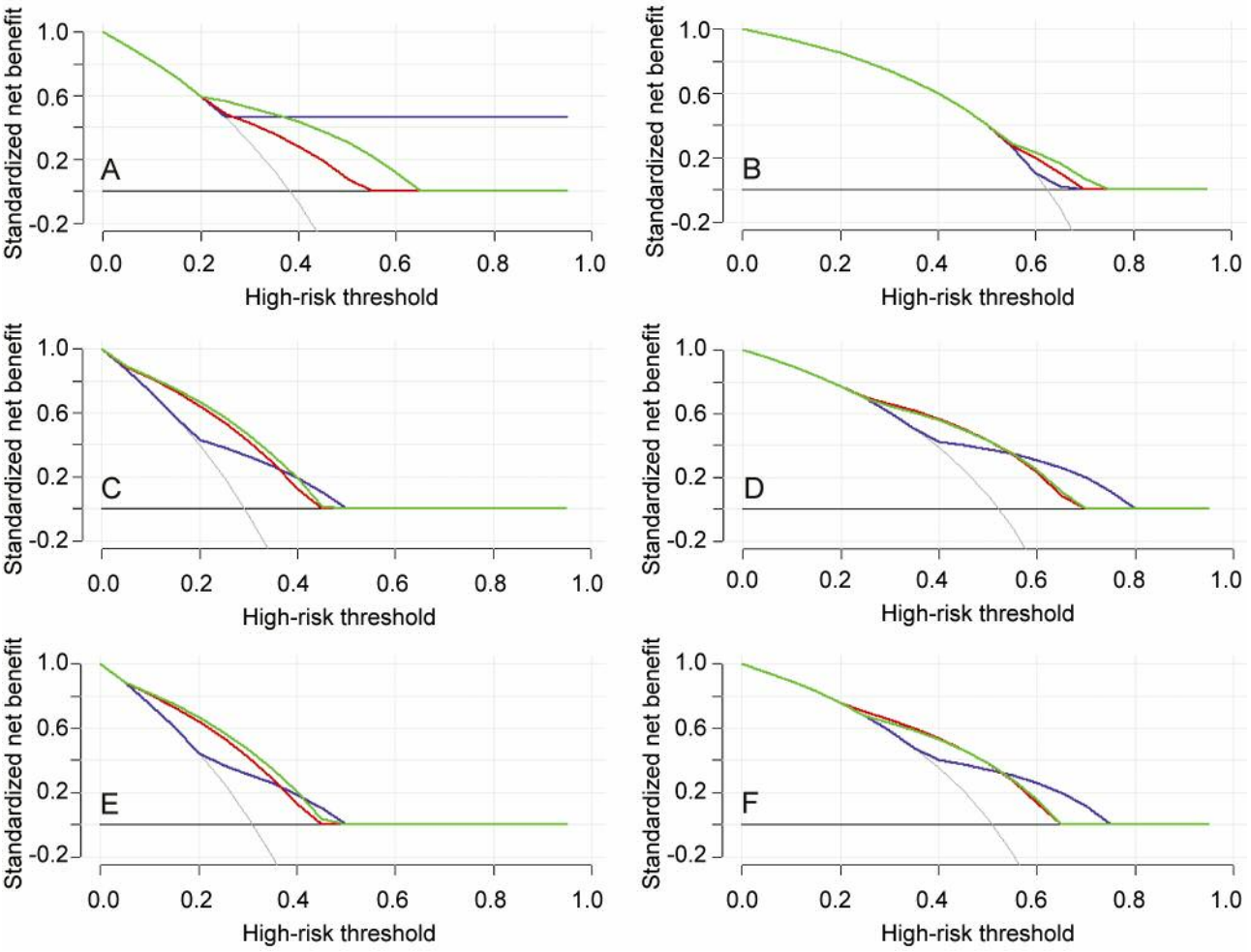

Figure 2. *Decision curve analysis for brain metastasis prognostic scores. Y-axis depicts the standardized net benefit, X-axis depicts the risk thresholds. Decision curves (RTOG RPA=blue line, BS-BM=red line, CERENAL=green line) are demonstrated for (A) six-months first-line PFS, (B) six-months second-line PFS, (C) six-months OS, (D) one-year OS, (E) six-months DSS, (F) one-year DSS. BS-BM, Basic score for brain metastases; PFS, progression-free survival; RTOG RPA, radiation therapy oncology group recursive partitioning analysis.*

Discussion

Patients with RCC diagnosed with brain metastases have a poor survival. Several brain metastatic prognostic scores have been reported in the literature over the last decade. Data in a metastatic RCC setting are, however, scanty. We, therefore, retrospectively determined the prognostic value of several prognostic scores, developed for brain metastases in solid tumors, in a cohort of 75 patients with brain metastatic RCC receiving targeted agents (tyrosine kinase inhibitors or mTOR inhibitors). Here, we evaluated two already described prognostic scores, RTOG RPA and BS-BM (10, 11), as well as a *de novo* composed score CERENAL.

In our study population, 75% of patients were diagnosed with metastatic disease at primary RCC diagnosis which is considerable higher compared to other reported data (4). This could be explained by the fact that the brain is rarely the only metastatic site in RCC. Nearly 20% of our patients presented with brain metastases at primary tumor diagnosis. This is comparable to the extent registered in other RCC studies (7-26.8%). It is notable that the time from primary RCC diagnosis to diagnosis of brain metastases is clearly shorter in our study (15 months) (15, 16).

In addition to the previously described prognostic scores RTOG RPA and BS-BM, we assessed the novel score named CERENAL in which points were attributed according to risk factors described in RTOG RPA and BS-BM. Furthermore, the number of brain metastatic lesions was also included in the CERENAL score since Ferrel *et al.* (13) reported an improved OS in RCC patients with a low number of intracranial metastases. Since SRS therapy has been shown to have a positive effect on the survival outcome of brain

Table VI. *Multivariate survival analysis*.

Parameter	HR (95%CI)	*p*-Value
First-line PFS		
RTOG RPA		
I/II	1	
III	2.76 (0.83-9.22)	0.0989
BS-BM		
0-1	1	
2-3	0.86 (0.23-3.15)	0.8186
CERENAL		
1-3	1	
4-6	3.59 (1.55-8.34)	0.0029
OS		
RTOG RPA		
I/II	1	
III	1.95 (1.02-3.72)	0.0428
BS-BM		
0-1	1	
2-3	0.65 (0.21-1.98)	0.4479
CERENAL		
1-3	1	
4-6	2.56 (1.30-5.03)	0.0063
Local therapy for brain metastases		
No	1	
Yes	0.78 (0.34-1.79)	0.5575
DSS		
RTOG RPA		
I/II	1	
III	1.90 (0.93-3.87)	0.0785
BS-BM		
0-1	1	
2-3	0.66 (0.19-2.32)	0.5174
CERENAL		
1-3	1	
4-6	3.34 (1.70-6.56)	0.0005
Local therapy for brain metastases		
No	1	
Yes	0.67 (0.27-1.66)	0.6698

Multivariate HRs were calculated *via* a Cox proportional-hazards regression model. 95%CI, 95% Confidence interval; BS-BM, basic score for brain metastases; DSS, disease-specific survival; OS, overall survival; PFS, progression-free survival; RTOG RPA, radiation therapy oncology group recursive partitioning analysis.

metastatic RCC patients (8), it was decided to include SRS in the CERENAL score. However, several trials have reported no difference in outcome between SRS and local therapies for brain metastases (17-20). Due to the fact that several mutual risk factors were used, all prognostic scores were comparable to each other with the highest level of agreement noticed between CERENAL and BS-BM. In addition, we confirmed the robustness of all prognostic scores used in our study.

In the present study, median OS was between 11.5 months (intention-to-treat group) and 16.8 months (brain metastases before first-line targeted therapy) which is similar to the survival data from other studies in RCC patients with brain metastases (9, 15, 16, 21). Compared to the OS data from large phase III trials, in which patients with brain metastatic disease were excluded, OS is significantly shorter (22-30). This difference, however, was not the result of a possible decrease in first-line PFS. Median first-line PFS was 10.1 months with the majority of patients receiving sunitinib as first-line therapy. This is only marginally shorter than the survival data from previously reported phase III trials COMPARZ and RECORD-3 (25, 29), suggesting that having brain metastases seems to have only little to no impact on first-line PFS. This has already been hypothesized by Kusuda *et al*. (31) who reported that sunitinib might harbor some effect on brain metastases. Next, second-line PFS was only 5.0 months which is in accordance with second-line PFS in large phase III trials (AXIS, RECORD-1) with tyrosine kinase inhibitors (23, 25, 28, 30) and the mTOR inhibitor everolimus (27).

Based on these data it is clear that RCC patients with brain metastases have a poor prognosis. Use of brain metastatic prognostic scores in these patients can, therefore, be useful to determine which patients would benefit from prolonged therapy. It has been previously described for melanoma, lung and breast cancer that the RTOG RPA and the BS-BM result in significantly different survival curves (19, 32-34). To our knowledge, such an extensive survival comparison has not yet been made for brain metastatic RCC.

RTOG RPA and BS-BM developed in other malignancies were significantly associated in our study with both OS and DSS. Moreover, our newly constructed CERENAL score was also able to distinguish patients with good prognosis from those with poor prognosis at the predefined cut-off value. Thus, any type of local therapy for brain metastases significantly prolonged OS and DSS. Consequent multivariate analysis revealed RTOG RPA and CERENAL as independent prognostic factors for OS but only CERENAL was associated with survival benefit for DSS with a 70% reduction in risk of death for CERENAL scores lower than 4. Besides, all prognostic scores were also useful during first-line therapy. Multivariate analysis, however, showed that only having a CERENAL score lower than 4 was associated with a 72% risk of progression compared to patients with a CERENAL score equal to or higher than 4. This was also clearly depicted in the decision curve analyses for first-line PFS, OS and DSS. It was clearly noted that CERENAL achieved higher net benefits at lower risk thresholds, whereas RTOG RPA was more beneficial at higher risk thresholds. This could indicate that CERENAL could be helpful as a prognostic tool and that the combination with RTOG RPA could lead to the highest net benefit for this patient population. None of the prognostic scores showed significance for second-line therapy.

Our study however has some limitations, especially due to its retrospective nature. Firstly, the presence of brain metastases in RCC is rare. Therefore, the study population is rather heterogeneous and does not allow us to draw hard conclusions. Secondly, due to its retrospective character, it is difficult to

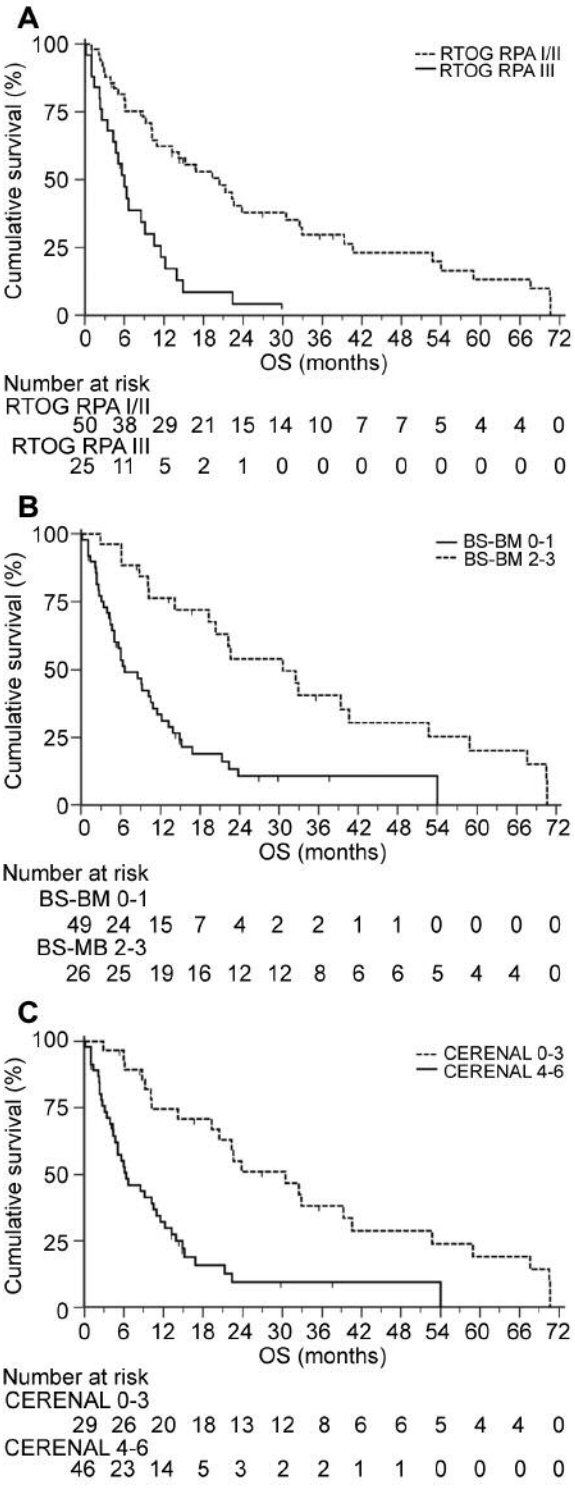

Figure 3. *Kaplan–Meier overall survival curves for brain metastasis prognostic scores. Y-axis depicts cumulative survival (%), X-axis depicts survival time in months. Survival curves are demonstrated for (A) RTOG RPA (p<0.0001), (B) BS-BM (p<0.0001), (C) CERENAL (p<0.0001). BS-BM, Basic score for brain metastases; OS, overall survival; RTOG RPA, radiation therapy oncology group recursive partitioning analysis.*

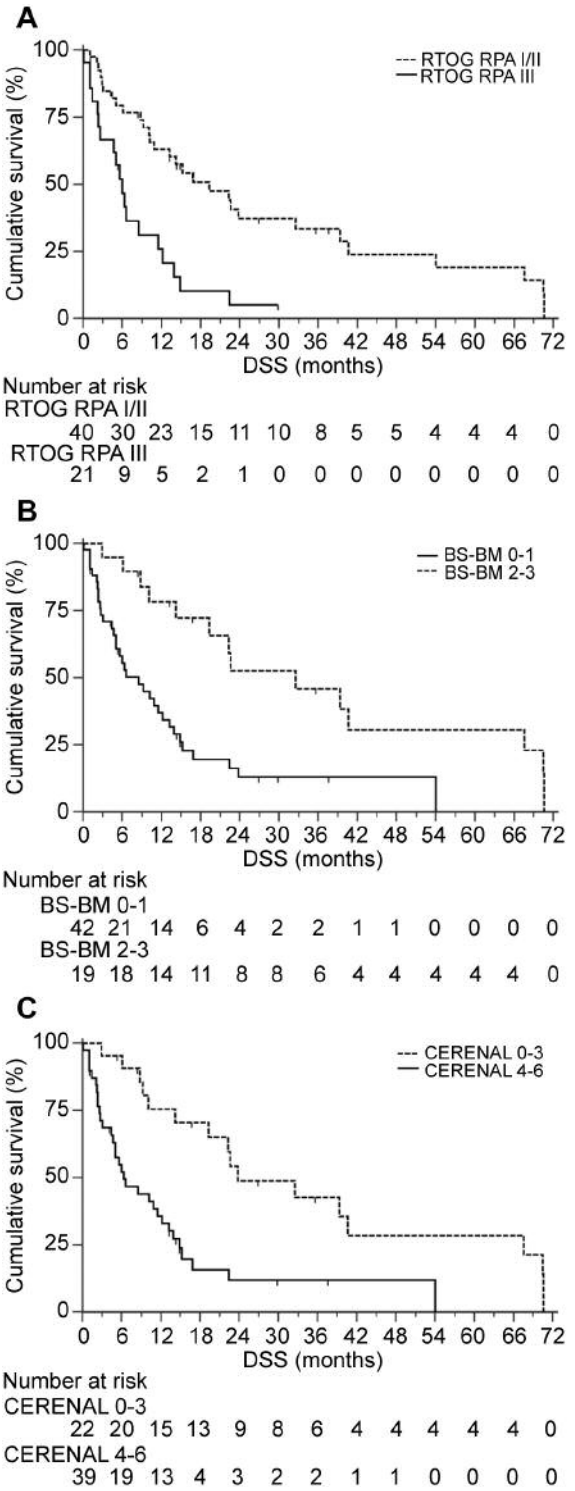

Figure 4. *Kaplan–Meier disease-specific survival curves for brain metastasis prognostic scores. Y-axis depicts cumulative survival (%), X-axis depicts survival time in months. Survival curves are demonstrated for (A) RTOG RPA (p=0.0002), (B) BS-BM (p=0.0007), (C) CERENAL (p=0.003). BS-BM, Basic score for brain metastases; DSS, disease-specific survival; RTOG RPA, radiation therapy oncology group recursive partitioning analysis.*

implement decision curve analysis for PFS and OS due to the high number of patients already progressed and deceased, respectively. Thirdly, insufficient data were present in the patient files to determine the prognostic effect of the MSKCC or Heng criteria in our study population. It would be of great interest to determine the added value of the proposed brain metastatic prognostic marker CERENAL value over the already validated prognostic criteria known in RCC. Nevertheless, our retrospective study has shown some interesting findings which can guide future prognostic research in RCC patients diagnosed with brain metastases. Further validation in prospectively enrolled RCC cohorts is, therefore, needed to fully evaluate the prognostic value of the CERENAL score.

Authors' Contributions

Guarantor of entire study integrity: ZEA; Study concepts and design: ZEA, SR, PB, NK, AA, NP and JBC; Clinical studies/data acquisition: ZEA, SR, PB, NK, RVP, DD, AA, TG, DP, TR, WW, NP and JBC; Experimental studies/data analysis: ZEA, SR, PB, AA, NP and TV; Statistical analysis: ZEA, PB, NP and TV; Literature research: ZEA, PB, NP and TV; Manuscript preparation: ZEA and TV; Manuscript editing: All authors; Final approval of manuscript: All authors.

Conflicts of Interest

The Authors declare no conflicts of interest with regard to this study.

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