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Estimating Survival of Patients With Metastatic Renal Cell Carcinoma Receiving Whole-brain Radiotherapy With a New Tool

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Abstract. *Background/Aim: A new tool for estimating survival of patients receiving whole-brain radiotherapy (WBRT) for intracerebral metastases from renal cell carcinoma (RCC) was created. Patients and Methods: The new WBRT-30-RCC was developed in 34 patients homogeneously treated with 30 Gy in 10 fractions of WBRT and compared to updated diagnosis-specific graded prognostic assessment DS-GPA and Dziggel score for predicting death within 6 months and survival for at least 6 months following WBRT. Results: WBRT-30-RCC included three groups with 6-month survival rates of 6.7% for those with 8-10 points, 38.5% for those with 12-14 points and 66.7% for those with 16-18 points. Positive predictive values (PPV)s for predicting death within 6 months were 93.3% using WBRT-30-RCC, 77.3% using updated DS-GPA and 93.7% using the Dziggel score. PPVs for predicting survival for at least 6 months were 66.7%, 50.0% and 50.0%, respectively. Conclusion: WBRT-30-RCC was more precise than the other scores in predicting survival for at least 6 months, although all three scores were not optimal. For predicting death within 6 months, WBRT-30-RCC and Dziggel score were similarly accurate and superior to the updated DS-GPA.*

Patients with renal cell carcinoma (RCC) account for about 5% of patients with intracerebral metastases (1, 2). Since RCC is considered a less radiosensitive tumor, patients with a limited number of intracerebral lesions are preferably treated with local therapies including radiosurgery and fractionated stereotactic radiotherapy alone or combined with whole-brain irradiation (WBRT) (3-8). Patients with multiple lesions and those with significant co-morbidities and a markedly reduced performance status are often assigned to WBRT alone (1). Common WBRT programs are 5×4 Gy (1 week), 10×3 Gy (2 weeks), 14-15×2.5 Gy (3 weeks) and 20×2 Gy (4 weeks). Previous studies comparing 10×3 Gy to total doses of 40-45 Gy and 5×4 Gy to 10×3 Gy did not demonstrate improved outcomes with higher doses (9, 10). Thus, patients with a limited remaining lifespan can be treated with 5×4 Gy to save time without reducing intracerebral control and survival. Patients with very poor prognoses may also be considered for supportive care with corticosteroids, since in a randomized trial of patients with intracerebral metastases from non-small lung cancer and very limited survival prognoses, supportive care plus 5×4 Gy of WBRT was not superior to supportive care alone (11). On the other hand, patients considered for WBRT who have relatively favorable survival prognoses were reported to benefit from WBRT with 20×2 Gy when compared to 10×3 Gy in terms of improved intracerebral control and survival (12). Moreover, the risk of WBRT-induced neurocognitive decline can be reduced with the use of lower doses per fraction (<3 Gy), sparing the hippocampi and memantine (13-15). Since neuro-cognitive deficits become clinically relevant weeks to months following WBRT, these measures are less important for patients with a markedly reduced lifespan.

A patient's survival prognosis will have a significant impact on the WBRT-program that is optimal for each individual. Estimation of a patient's prognosis can be facilitated with the use of scoring instruments. Ideally, such instruments are available specifically for each primary tumor type known to spread to the brain, such as RCC. A specific instrument for patients with intracerebral metastases from RCC is already available, namely the diagnosis-specific graded prognostic assessment (DS-GPA) classification for RCC, which was first published in 2010 and updated in 2012 (16, 17). Another instrument, the Dziggel score, was created from data of patients with less radiosensitive solid tumors including RCC and presented in 2013 (18). However, these instruments were

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created in patient cohorts that received heterogeneous treatments including different WBRT programs or additional chemotherapy, misonodazole or radiosurgery (16-18). This heterogeneity may have led to selection bias during the development of the scoring instruments. To avoid such potential bias, we designed another instrument, WBRT-30-RCC, from a cohort where all patients had uniformly treated received 10×3 Gy of WBRT alone. The idea of developing a WBRT-30 score for RCC was supported by the very high accuracy of the previous non-diagnosis-specific WBRT-30 (19), which was superior to other non-diagnosis-specific instruments with respect to the identification of patients dying within 6 months or living for at least 6 months after WBRT (20-22).

Patients and Methods

Eight potential predictors of survival were retrospectively investigated in a series of 34 patients who were treated with 30 Gy in 10 fractions of WBRT alone between 1994 and 2014 (Table I). Investigated potential predictors included age at WBRT (≤63 *vs.* ≥64 years, median=63 years), gender, Karnofsky score (≤60 *vs.* >60%, median=60%), control of the primary tumor (no *vs.* yes), extra-cranial metastatic spread (no *vs.* yes), previous systemic treatment (no *vs.* yes), number of intracerebral metastatic lesions (1-3 *vs.* ≥4) and period between initial diagnosis of RCC and the beginning of WBRT (≤33 *vs.* ≥34 months, median=33.5 months).

Associations between these potential predictors and survival were investigated using the log-rank test and the Kaplan–Meier method. The 6-month survival rates (as percentages) were divided by 10 and rounded (no decimal place) resulting in single-figure numbers (points). Potential predictors with a difference of at least 2 points (*i.e.* equal to 20% difference in 6-month survival) between their subgroups were used for designing the WBRT-30-RCC score. The points of all potential predictors used were added for each patient to produce the patient scores. Depending on the 6-month survival rates associated with the patient scores, different survival groups were created.

Subsequently, the new WBRT-30-RCC and two other diagnosis-specific tools, the updated DS-GPA classification for RCC and the Dziggel score, which was made for patients with less radiosensitive tumor types (RCC, melanoma, and colorectal cancer) (17, 18). The comparison of the three tools was made with respect to accuracy (positive predictive value, PPV) in correctly predicting death within 6 months and survival for at least 6 months after WBRT.

Results

Four factors met the criteria for inclusion in the scoring instrument, *i.e.* Karnofsky score, extra-cranial metastatic spread, number of intracerebral metastatic lesions and the period between initial diagnosis of RCC and WBRT (Table II). The corresponding scoring points obtained from the 6-month survival rates of these factors are shown in Table III. The sums of these points led to patient scores of 8, 10, 12, 14, 16 and 18 points (Figure 1), and the creation of three groups, namely 8-10 points (n=15), 12-14 points (n=13) and 16-18 points (n=6). The corresponding 6-month survival rates of the three groups were 6.7%, 38.5% and 66.7%, respectively (trend: p=0.119, Table IV). Afterwards, the newly created WBRT-30-RCC was compared to the updated DS-GPA and the Dziggel score (17, 18). The PPVs for the least favorable groups of the three tools (Table V) in identifying patients dying within 6 months following WBRT were 93.3%, 77.3% and 93.7%, respectively (17, 18). The PPVs of the most favorable groups (Table V) in identifying patients surviving for at least 6 months following WBRT were 66.7%, 50% and 50%, respectively.

Table I. *Investigated potential predictors of survival.*

Potential predictor	Number of patients	Proportion (%)
Age at WBRT		
≤63 Years	19	56
≥64 Years	15	44
Gender		
Female	10	29
Male	24	71
Karnofsky score		
≤60%	18	53
>60%	16	47
Control of primary tumor		
No	5	15
Yes	29	85
Extra-cranial metastatic spread		
No	10	29
Yes	24	71
Previous systemic treatment		
No	19	56
Yes	15	44
Number of intracerebral lesions		
1-3	14	41
≥4	20	59
Period between initial diagnosis of RCC and WBRT		
≤33 Months	17	50
≥34 Months	17	50

WBRT: Whole-brain radiotherapy, RCC: renal cell carcinoma.

Discussion

A considerable number of patients with intracerebral metastases from RCC present with multiple lesions and a poor general condition. Many of these patients are considered for treatment with WBRT alone (1). Radiation oncologists can choose from a variety of dose-fractionation regimens mostly lasting between 1 and 4 weeks. The overall treatment time of a WBRT program should be adjusted to the patient's remaining lifespan. Patients with a short expected survival time appear appropriately treated with 5×4 Gy (1 week), since in a previous study of 442 patients treated with WBRT alone for intracerebral metastases, 5×4 Gy (1 week) was not inferior to 10×3 Gy (2 weeks). The corresponding survival rates at 6 months were 24% and 27% (p=0.29) (9).

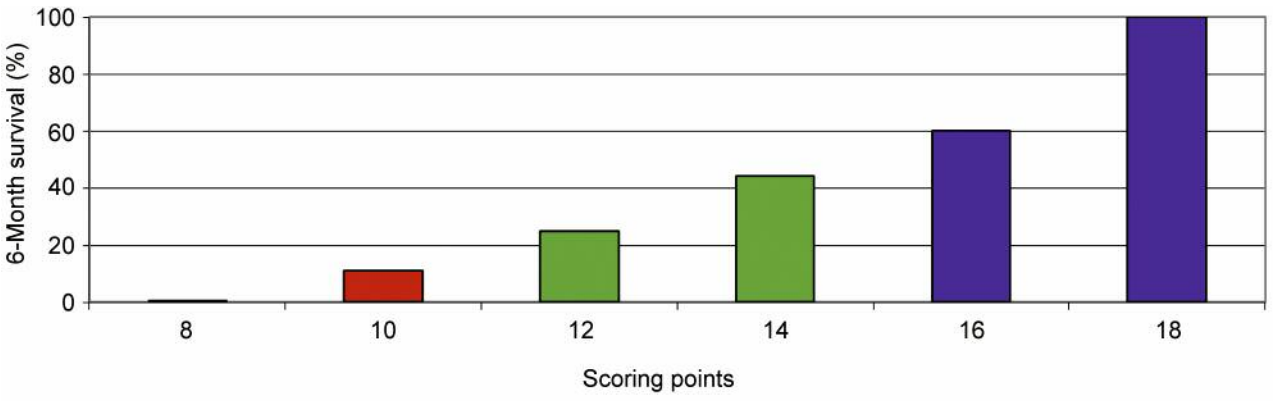

Figure 1. *The 6-month survival rates associated with scoring points.*

Table II. *Three- and 6-month survival rates following whole-brain radiotherapy (WBRT).*

Characteristic	Survival		*p*-Value
	3-Month (%)	6-Month (%)	
Age at WBRT			
≤63 Years	53	32	0.390
≥64 Years	47	27	
Gender			
Female	30	20	0.822
Male	58	33	
Karnofsky score			
≤60%	50	17	0.115
>60%	50	44	
Control of primary tumor			
No	40	40	0.426
Yes	52	28	
Extra-cranial metastatic spread			
No	55	55	0.100
Yes	48	17	
Previous systemic treatment			
No	42	32	0.730
Yes	60	27	
Number of intracerebral lesions			
1-3	57	43	0.470
≥4	45	20	
Period between initial diagnosis of RCC and WBRT			
≤33 Months	47	18	0.591
≥34 Months	53	41	

RCC: Renal cell carcinoma.

Table III. *Scoring points for the 6-month survival rates of the characteristics that were significantly associated with survival.*

Characteristic	6-Month survival rate (%)	Scoring points
Karnofsky score		
≤60%	17	2
>60%	44	4
Extra-cranial metastatic spread		
No	55	6
Yes	17	2
Number of intracerebral lesions		
1-3	43	4
≥4	20	2
Period between initial diagnosis of RCC and WBRT		
≤33 Months	18	2
≥34 Months	41	4

RCC: Renal cell carcinoma, WBRT: whole-brain radiotherapy.

Table IV. *Survival rates for the prognostic groups at 3 and 6 months after whole-brain radiotherapy. The p-value was calculated with the log-rank test.*

Prognostic group	Survival rate (%)		*p*-Value
	At 3 months	At 6 months	
8-10 points	46.7	6.7	<0.001
12-14 points	46.2	38.5	
16-18 points	66.7	66.7	

For highly selected patients with an extraordinarily short survival prognosis, supportive care plus dexamethasone without WBRT may be a reasonable option (11). In contrast to patients with a short remaining lifespan, those patients with a more favorable survival prognosis should not be treated with supportive care alone or 5×4 Gy of WBRT. In a study including only patients with favorable prognoses, 20×2 Gy (4 weeks) when compared to 10×3 Gy (2 weeks) resulted in significantly better cerebral control (44% *vs*. 28%) and survival (61% *vs*. 50%) at 1 year following WBRT (12).

Table V. *Prognoses according to whole-brain radiotherapy (WBRT)-30-renal cell carcinoma (RCC), updated diagnosis-specific graded prognostic assessment (DS-GPA) and Dziggel score (17, 18).*

	WBRT-30-RCC		Updated DS-GPA classification		Dziggel score	
Survival prognosis	Scoring points	6-Month survival (%)	Scoring points	6-Month survival (%)	Scoring points	6-Month survival (%)
Least favorable	8-10	6.7	0.0-1.0	22.7	5-8	6.3
Intermediate	12-14	38.5	1.5-2.0	33.3	9-11	50.0
Most favorable	16-18	66.7	≥3.0	50.0	12-14	50.0

Furthermore, the use of less than 3 Gy per fraction was reported to be associated with fewer declines in neurocognitive function than doses of 3 Gy and more (13). Therefore, patients with longer expected survival times should receive WBRT with 20×2 Gy or 14-15×2.5 Gy. In addition to using lower doses per fraction, preservation of cognitive function can be improved with hippocampal-sparing techniques and memantine (14, 15).

In order to adequately consider an individual patient's survival prognosis, scoring instruments were developed for patients irradiated for intracerebral metastases (19-22). Of these tools that were designed for patients with intracerebral metastases in general, *i.e.* without taking into account the differences between the primary tumor types associated with intracerebral metastases, the WBRT-30 was the most accurate instrument for correctly identifying patients likely to die within 6 months or to survive for a minimum of 6 months after WBRT (19). The corresponding PPVs of the WBRT-30 were 97% (compared to 85-96% for other tools) for identifying patients dying within 6 months and 96% (compared to 64-75% for other tools) for identifying those surviving for a minimum of 6 months (19-22).

Since primary tumor types vary with respect to their biology, metastatic patterns and prognoses, separate scoring instruments are required to provide an optimal personalization of treatment (16). This also applies to patients with intracerebral metastases from RCC. To address this issue, Sperduto *et al.* developed the DS-GPA classification for this group of patients in 2010, which was updated 2 years later (16, 17). Another previous scoring instrument that included patients with RCC is the Dziggel score, which was designed for patients with intracerebral metastases from less radiosensitive tumors (18).

However, the patients used to build the DS-GPA classification and the Dziggel score had received quite heterogeneous treatments, which likely would have led to selection biases. To overcome this problem and based on the positive experiences with the non-diagnosis–specific WBRT-30, we developed the new WBRT-30-RCC, which was specifically designed for patients with RCC from a cohort of patients treated uniformly with 10×3 Gy of WBRT. The PPV for identifying patients dying within 6 months was 93.3%, which was almost identical to that for the Dziggel score (93.7%) and superior to the updated DS-GPA classification (77.3%) (17, 18). The PPV of the WBRT-30-RCC to identify patients surviving for a minimum of 6 months was 66.7%, which was superior to the Dziggel score (50.0%) and the updated DS-GPA classification (50.0%) (17, 18). Thus, for identification of patients who will likely die within 6 months after WBRT, the WBRT-30-RCC and the Dziggel score provide high accuracy. For identification of patients who will likely live for a minimum of 6 months, the WBRT-30-RCC was superior to the other two instruments. However, the PPVs of all three tools were suboptimal. Moreover, the retrospective nature of the data that all three instruments were created from and the small sample size of the present study must be taken into account when using them.

In summary, given the limitations of the retrospective data, the WBRT-30-RCC appeared superior to previous tools for predicting survival of patients receiving WBRT alone for intracerebral metastases from RCC and can guide physicians to select the best treatment for an individual patient. Validation of the tool is required.

Conflicts of Interest

On behalf of all Authors, the corresponding Author states that there is no conflict of interest related to this study.

Authors' Contributions

H.C.H., S.J., S.E.S. and D.R. participated in the design of the study. H.C.H., S.J. and D.R. provided data. S.E.S. and D.R. performed the analyses and the interpretation of the data. H.C.H, S.E.S. and D.R. drafted the manuscript, which was reviewed and approved in its final form by all Authors.

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