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Comparison of Diagnosis-specific Survival Scores for Patients With Cerebral Metastases from Malignant Melanoma Including the New WBRT-30-MM

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Abstract. *Background/Aim: Diagnosis-specific scoring systems developed for predicting survival of patients with cerebral metastases from malignant melanoma (MM) were evaluated. Patients and Methods: The new whole-brain radiotherapy (WBRT)-30-MM was created in homogeneously treated patients receiving 10×3 Gy of WBRT for cerebral metastases from MM. It consisted of three groups with significantly different 6-month survival rates of 0% (3-5 points), 30% (7 points) and 52% (9 points) (p=0.001). The WBRT-30-MM was compared to three other scores created for cerebral metastases from MM, including first updated DS-GPA classification, Dziggel-Score and Sehmisch-Score. Results: Positive predictive values (PPVs) for predicting death ≤6 months after WBRT were 100% (WBRT-30-MM), 77% (DS-GPA), 69% (Dziggel-Score) and 73% (Sehmisch-Score). PPVs for predicting survival ≥6 months were 52%, 38%, 63% and 75%, respectively. Conclusion: WBRT-30-MM was the most accurate instrument for predicting death ≤6 months. For predicting survival ≥6 months, Sehmisch-Score was most accurate, although all existing scorring systems appeared suboptimal for this purpose.*

The majority of patients with cerebral metastases are treated with whole-brain radiotherapy (WBRT), either in combination with a local therapy such as neurosurgical resection or stereotactic radiosurgery, or as the only treatment (1). WBRT alone is commonly used for patients with multiple cerebral metastases and patients in a poor general condition who may not benefit from resection or radiosurgery. WBRT is generally administered with five daily fractions per week. Common dose-fractionation regimens include 20 Gy in 5 fractions of 4 Gy, 30 Gy in 10 fractions of 3 Gy and 40 Gy in 20 fractions of 2 Gy delivered over one, two and four weeks, respectively (1). These regimens were reported to be similarly effective, particularly in patients with multiple cerebral metastases lesions (2, 3). When using higher dose per fraction of ≥3 Gy, one should be aware that theses regimens bear a higher risk of subsequent neuro-cognitive decline (4). However, the development of neuro-cognitive deficits may take several weeks or even a few months, and, therefore, many patients with poor survival prognoses will die before experiencing significant neuro-cognitive deficits. Thus, 20 Gy in 5 fractions should be administered to patients with very limited survival times. These patients can benefit by spending less time receiving radiotherapy. In contrast, patients with relatively favorable survival prognoses live long enough to suffer post-WBRT neuro-cognitive decline (1). Therefore, doses per fraction of <3 Gy should be used for these patients. Moreover, in patients with very favorable survival prognoses, total WBRT-doses of >30 Gy were reported to lead to better intracerebral control and survival than doses of 30 Gy (5). It is clear that the WBRT-regimen should be adapted to the patients' survival prognoses. Therefore, scoring tools were developed to help physicians estimate an individual patient's prognosis. Such tools are also available for single tumor entities spreading to the brain and for different radiation techniques, to achieve an optimal individualization of treatment. Very few tools were created from data of patients with cerebral metastases from malignant melanoma (MM) selected to receive WBRT alone including the first updated diagnosis-specific graded prognostic assessment (DS-GPA) classification for MM from 2012, the Dziggel-Score from 2013 (developed in patients with less radiosensitive tumors including MM) and the Sehmisch-Score

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from 2017 (6-8). These tools were developed in heterogeneously treated patient cohorts, which may have resulted in biases. Therefore, we developed an additional scoring tool, the WBRT-30-MM that was developed in patients homogeneously treated with WBRT alone using 30 Gy in 10 fractions of 3 Gy.

Patients and Methods

In a cohort of 51 patients uniformly treated with 10x3 Gy of WBRT alone for cerebral metastases from MM, eight characteristics (Table I) were investigated for potential influences on overall survival. These characteristics included the time from diagnosis of MM until WBRT (≤34 *versus* ≥35 months, median=34 months), pre-WBRT systemic treatment (no *versus* yes), controlled primary at the time of WBRT (no *versus* yes), extracerebral metastasis at the time of WBRT (no *versus* yes), age at the time of WBRT (≤62 *versus* ≥63 years, median=62 years), gender, Karnofsky performance score (KPS) (≤70 *versus* >70, median=70) and the number of cerebral metastases (≤3 (limited) *versus* >3 (multiple)). Characteristics that were significantly ($p<0.05$) associated with survival (calculated with the Kaplan–Meier method and the log-rank test) were used to design the WBRT-30-MM. The 6-months survival rates of the significant characteristics were divided by 10 to receive scoring points. Thereafter, the scoring points of each patient were summed up, and the patient scores were received. The patient scores formed the basis for the design of the prognostic groups.

The WBRT-30-MM was compared to three other scoring instruments designed for patients with cerebral metastases from MM, *i.e.* the first updated diagnosis-specific graded prognostic assessment (DS-GPA) classification for MM, the Dziggel-Score (developed in patients with less radiosensitive tumors including MM receiving different WBRT regimens) and the Sehmisch-Score (developed in MM patients receiving different WBRT regimens with total doses >30 Gy) (6-8). The four instruments were compared with respect to positive predictive values (PPVs) to identify patients who will die within 6 months following WBRT and patients who will survive for 6 months or longer.

Results

A significantly positive influence on survival was found for a controlled primary tumour at the time of WBRT ($p=0.002$) and absence of extracerebral metastasis ($p=0.012$) (Table II). The scoring points of the characteristics are summarized in Table III. Addition of the scoring points for each patient resulted in patient scores of 3, 5, 7 or 9 points with 6-month survival rates of 0%, 0%, 30% and 52%, respectively. According to the patient scores, three groups were formed, 3-5 points (n=7), 7 points (n=23) and 9 points (n=21), with 6-month survival rates of 0%, 30% and 52%, respectively ($p=0.001$, Figure 1).

The poor, intermediate and favorable prognoses groups of the WBRT-30-MM and the other instruments are given in Table IV. The PPVs of the poor prognoses groups to identify patients who will die within 6 months following WBRT were 100% (WBRT-30-MM), 77% (first updated DS-GPA classification), 69% (Dziggel-Score) and 73% (Sehmisch-Score), respectively (6-8). The PPVs of the favorable prognoses groups to identify patients who will survive for 6 months or longer were 52%, 38%, 63% and 75%, respectively (6-8).

Table I. *Distribution of the investigated characteristics in the entire cohort.*

Characteristic	Number of patients (%)
Time diagnosis of MM until WBRT	
≤34 Months	26 (51)
≥35 Months	25 (49)
Pre-WBRT systemic treatment	
No	22 (43)
Yes	29 (57)
Controlled primary	
No	7 (14)
Yes	44 (86)
Extracerebral metastasis	
No	10 (20)
Yes	41 (80)
Age	
≤62 Years	27 (53)
≥63 Years	24 (47)
Gender	
Female	15 (29)
Male	36 (71)
Karnofsky performance score	
≤70	28 (55)
>70	23 (45)
Number of cerebral metastases	
≤3	18 (35)
>3	33 (65)

MM: Malignant melanoma; WBRT: whole-brain radiotherapy.

Discussion

Cerebral metastases occur in up to 30-40% of patients with malignant tumors (1). Due to improved treatments for primary tumors and loco-regionally recurrent disease, patients live longer and the number of patients experiencing distant metastatic disease including cerebral metastases is growing. These patients often require an individualized treatment regimen that should account for the remaining survival time. Also, selection of the appropriate WBRT regimen should consider the survival prognosis (1).

In a previous study of 416 patients with multiple cerebral metastases, WBRT with 30 Gy in 10 fractions was compared to WBRT with higher doses including 40 Gy in 20 fractions and 45 Gy in 15 fractions (3). The 6-month survival rates were 33% after 30 Gy and 29% after higher doses, respectively ($p=0.86$), and the 6-month intracerebral control rates 39% and 41%, respectively ($p=0.61$). In a subsequent study of 442 patients that compared 30 Gy in 10 fractions to 20 Gy in 5 fractions, the 6-months survival rates were 27% and 24%, respectively ($p=0.29$) (2). Thus, patients with multiple lesions

Table II. *Survival rates after whole-brain radiotherapy.*

Characteristic	Survival rate (%)			*p*-Value
	At 3 months	At 6 months	At 12 months	
Time diagnosis of MM until WBRT				
≤34 Months	50	31	9	0.57
≥35 Months	64	40	6	
Pre-WBRT systemic treatment				
No	50	32	5	0.41
Yes	62	38	9	
Controlled primary				
No	29	0	0	**0.002**
Yes	61	41	9	
Extracerebral metastasis				
No	50	50	13	0.42
Yes	59	32	6	
Age				
≤62 Years	67	37	8	0.53
≥63 Years	46	33	7	
Gender				
Female	53	40	0	0.69
Male	58	33	9	
Karnofsky performance score				
≤70	36	25	4	**0.012**
>70	83	48	11	
Number of cerebral metastases				
≤3	72	33	6	0.73
>3	48	36	8	

MM: Malignant melanoma; WBRT: Whole-brain radiotherapy; Significant *p*-values are shown in bold.

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

Characteristic	6-month survival rate (%)	Scoring points
Controlled primary		
No	0	0
Yes	41	4
Karnofsky performance score		
≤70	25	3
>70	48	5

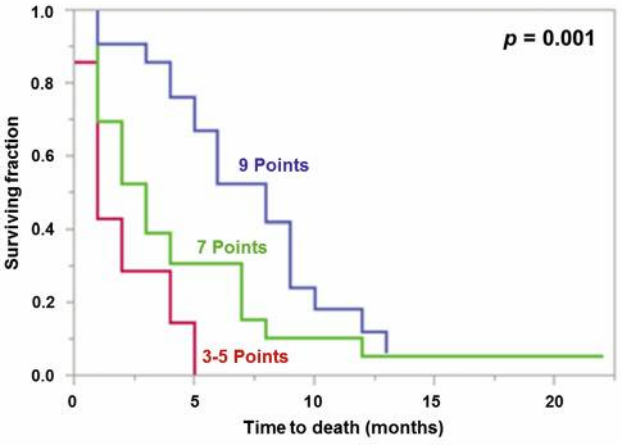

Figure 1. *Survival curves (Kaplan–Meier method) of the prognostic groups of the WBRT-30-MM.*

and limited survival prognoses appear candidates for WBRT with 20 Gy in 5 fractions. Due to findings from a randomized trial in 538 patients with cerebral metastases from non-small cell lung cancer, selected patients with very limited prognoses may even be considered for best supportive care (BSC) alone instead of BSC plus 20 Gy of WBRT (9).

For patients with cerebral metastases and very favorable survival prognoses, the situation is quite different. In these patients, WBRT with total doses >30 Gy resulted in significantly improved 1-year overall survival (61% *vs*. 50%) and 1-year intracerebral control (44% *vs*. 28%) compared to 30 Gy in 10 fractions (5). Moreover, due to the longer survival, the risk of experiencing WBRT-related late morbidity including neuro-cognitive deficits is higher in this group of patients. Thus, doses per fraction <3 Gy should be used, and other options to reduce the risk of neuro-cognitive decline such as hippocampal sparing and memantine should be strongly considered (4, 10, 11).

These data demonstrate that it is crucial to be able to judge a patient's survival time as accurately as possible to deliver the best possible treatment. Meanwhile, the treating radiation and medical oncologists can draw on several predictive tools helping them to estimate individual prognoses (12-20). In order to provide optimal individualization of the treatment regimen, separate tools were created for different primary tumors with a risk of intracerebral spread (12-18). One tumor type that requires particular attention is MM, since it is less radio-sensitive than many other primary tumor types. This issue was already recognized before, and predictive tools for patients with cerebral metastases from MM were developed including the DS-GPA classification, the Dziggel-Score and the Sehmisch-Score (6-8). All three previous scores were built from patients who received heterogeneous treatments. The treatments in the cohort used for creating DS-GPA were quite heterogeneous and included WBRT with different dose-fractionations including hyper-fractionation (two fractions per day), WBRT plus chemotherapy, WBRT plus a radio-sensitizer and WBRT plus a radiosurgery boost (6). Patients used for the Dziggel-Score received WBRT with different dose-fractionations and included also patients with cerebral metastases from colorectal cancer and renal cell carcinoma (7). The Sehmisch-Score was

Table IV. *Poor, intermediate and favorable prognoses groups of the WBRT-30-MM, first updated DS-GPA classification, Dziggel-Score and Sehmisch-Score (6-8).*

	WBRT-30-MM		DS-GPA		Dziggel-Score		Sehmisch-Score	
Survival prognosis	Scoring points	6-month survival	Scoring points	6-month survival	Scoring points	6-month survival	Scoring points	6-month survival
Poor	3-5	0%	0-1	23%	5-8	31%	0	27%
Intermediate	7	30%	2	53%	9-11	29%	1	29%
Favorable	9	52%	3-4	38%	12-14	63%	2	75%

developed in the least heterogeneously treated cohort of patients. All patients received WBRT alone with total doses >30 Gy, but still different dose-fractionation regimens (8). Thus, the creation of the previous tools may to lesser or greater extent had been impacted by hidden selection biases due to the different treatments the patients had received.

Therefore, we developed an additional tool, particularly for patients with cerebral metastases from MM, the WBRT-30-MM. All patients used for this tool received WBRT alone with 30 Gy in 10 fractions and, therefore, were more homogeneously treated than those patients used for the previous instruments. The WBRT-30-MM included three prognostic groups with 6-month survival rates of 0% (3-5 points), 30% (7 points) and 52% (9 points). The PPV to correctly predict death within 6 months after treatment was optimal with 100%. This PPV was higher than the PPVs for the other scores that were 77% for the first updated DS-GPA classification, 69% for the Dziggel-Score and 73% for the Sehmisch-Score, respectively (6-8). Thus, when aiming to identify patients who will likely die within 6 months after treatment, the WBRT-30-MM appears preferable. However, the PPV of the WBRT-30-MM to identify those patients who likely live for 6 months or longer was only 52%. The PPV for the first updated DS-GPA classification was even worse (only 38%), whereas the PPVs for the Dziggel-Score (63%) and particularly for the Sehmisch-Score (75%) were higher (6-8). Thus, when aiming to identify patients living for at least 6 months after treatment, the Sehmisch-Score appears to be the best option, although a PPV of 75% is not optimal. When using one of the predictive tools compared in this study, one should be aware that all scores were created from retrospective patient cohorts.

In summary, the new WBRT-30-MM was the most accurate instrument for predicting death ≤6 months after WBRT. For predicting survival ≥6 months, the Sehmisch-Score was most accurate, although the PPVs of all four instruments appeared suboptimal.

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

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

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