

## Development of a Survival Score for Patients with Cerebral Metastases from Melanoma

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**Abstract.** *Background/Aim:* To develop a survival score for patients receiving whole-brain irradiation (WBI) alone for cerebral metastases from melanoma. *Patients and Methods:* Forty-five patients who met the required criteria were included. WBI doses had to be >30 Gy. Six variables were analyzed: age, gender, Karnofsky performance score (KPS), number of cerebral metastases, extracranial metastatic spread and interval from diagnosis of melanoma until WBI. In order to estimate patients' survival scores, variables showing at least a trend ( $p < 0.06$ ) on multivariate analysis were considered. One point was assigned to each variable correlating with better survival rates and zero points to those correlating with worse survival rates. *Results:* By multivariate analysis, age ( $p = 0.002$ ) achieved significance and KPS ( $p = 0.056$ ) showed a trend. Patients' survival scores were obtained by adding zero or one point from each variable and resulted in three groups of 0, 1 or 2 points. The median survival times of these groups were one, four and ten months ( $p < 0.0001$ ). *Conclusion:* A survival score was developed for patients assigned to WBI alone for cerebral metastases from melanoma. This new instrument may facilitate the decision for the appropriate WBI-program.

When cerebral metastases occur during the course of melanoma, the situation is associated with a poor outcome for the patient. Survival times of a few months were reported in the literature after the diagnosis of cerebral metastases from a melanoma. Sperduto *et al.* observed a survival time of 6.7 months in a study with 481 melanoma patients receiving different types of radiation therapy for cerebral metastases (1). Other studies found similar survival times (2-4).

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Although prognosis is generally unfavorable, survival times of patients with metastases to the brain from a melanoma vary quite a lot due to different patient characteristics and types of treatment. For example, in the study of Sperduto *et al.*, survival times ranged from 3.4 to 13.2 months (1).

For cerebral metastases therapy, different treatment options exist including surgical resection, radiosurgery, whole-brain irradiation (WBI), systemic agents or combinations of some of these modalities (5, 6). However, WBI alone is by far the most frequent treatment for cerebral metastases, particularly in cases of multiple lesions. Since melanoma is considered a less radiosensitive tumor type, many patients with one to three lesions are treated with radiosurgery alone (7, 8). However, for four or more lesions, WBI alone is the most common treatment also for patients with a melanoma. Previous studies suggested that patients with a very limited survival time should receive short-course WBI, for example with 20 Gy in 5 fractions over one week to keep the overall treatment time as short as possible (9). In contrast, patients who live considerably longer were reported to benefit from longer WBI-programs with higher total doses and lower doses per fraction in terms of more favorable outcomes and less pronounced late morbidities (10, 11). In order to provide the appropriate WBI-program for the affected patients, the treating physicians should incorporate the patient's survival time into their process of developing a personalized treatment strategy. Tumor-specific prognostic tools particularly designed for patients treated with WBI alone are required and already available for several tumor types. However, these tools would likely not be suitable for cerebral metastases from melanoma because of its relatively low radiosensitivity. Therefore, a specific survival score for patients receiving WBI alone for cerebral metastases from melanoma is needed. The development of such a tool was the aim of the present study. It included only patients who had received a WBI-dose beyond the worldwide most common regimen 30 Gy in 10 fractions because previous studies suggested that such a dose-escalation may improve outcomes of patients with cerebral metastases from melanoma (12, 13).

**Patients and Methods**

*Patients.* In this study, we retrospectively analyzed 45 patients with cerebral metastases from a melanoma that were treated with only WBI. The total WBI doses were greater than 30 Gy. Three patients had a single cerebral lesion, eight patients had two or three lesions and thirty-four patients four or more lesions. The following variables were analyzed regarding survival after completion of WBI: age ( $\leq 55$  vs.  $\geq 56$  years, median=55 years), gender, Karnofsky performance score (KPS  $\leq 70$  vs.  $\geq 80$ ), number of cerebral metastases (1-3 vs.  $\geq 4$ ), extracranial metastatic spread (yes vs. no) and interval from first diagnosis of melanoma until WBI ( $\leq 24$  vs.  $\geq 25$  months, median=25 months) (Table I).

*Statistical analysis.* The Kaplan-Meier method and the log-rank-test were used for the univariate analysis (14). Variables that showed statistical significance in the univariate analysis ( $p < 0.05$ ) were additionally analyzed with the Cox proportional hazard model in a multivariate manner.

*Survival score.* Variables correlating by statistically significance ( $p < 0.05$ ) or by a trend ( $p < 0.06$ ) in the multivariate analysis were included in the survival score. One point was assigned to each characteristic associated with more favorable survival rates and zero points to each characteristic associated with less favorable survival rates.

**Results**

In the entire series of this study, the median survival time was 4 months. Survival rates at three, six and twelve months were 60%, 33% and 15%, respectively. On univariate analysis, age at WBI  $\leq 55$  years ( $p < 0.0001$ ) and KPS  $\geq 80$  ( $p = 0.0008$ ) showed a significantly positive association with survival time (Table II). On multivariate analysis, age (Hazard Ratio 3.40, 95%-Confidence Interval 1.55-7.88,  $p = 0.002$ ) showed statistical significance and KPS (Hazard Ratio 2.09, 95%-Confidence Interval 0.98-4.46,  $p = 0.056$ ) showed a strong trend with survival. Hence, these variables were included in estimating the survival score for all patients. The score for an individual patient was obtained by adding the scoring points assigned to both variables, which resulted in patient groups of 0 (N=12), 1 (N=14) or 2 (N=19) points. These three groups showed statistically significant differences in their survival times (Figure 1,  $p < 0.0001$ ) and their median survival times were one, four and ten months, respectively. The survival rates at three, six and twelve months are shown in Table III.

**Discussion**

Melanoma research has gained scientific attention during the last decade including the introduction of new systemic agents and the identification of predictive clinical and preclinical markers (15-17). Due to an improvement in novel targeted therapies, melanoma patients live longer. Since the risk of

Table I. Investigated variables and their distribution.

	Number of patients	Proportion (%)
Age at WBI		
$\leq 55$ years	23	51
$\geq 56$ years	22	49
Gender		
Female	14	31
Male	31	69
Karnofsky performance status		
$\leq 70$	16	36
$\geq 80$	29	64
Number of brain metastases		
1-3	11	24
$\geq 4$	34	76
Extracranial metastatic spread		
No	6	13
Yes	39	87
Time melanoma diagnosis to WBI		
$\leq 24$ months	22	49
$\geq 25$ months	23	51

WBI, Whole-brain irradiation.

developing organ metastases increases with lifetime, more patients require treatment for metastatic disease. This applies also to cerebral metastases. Many of these patients are assigned to WBI alone. When WBI is indicated, different dose-fractionation programs are available. The most commonly delivered program is 30 Gy in 10 fractions over two weeks. Radiation oncologists generally agree that patients with a markedly limited lifespan should preferentially be treated with 20 Gy in 5 fractions over one week to prevent patients spend more than necessary of their remaining lifetime with WBI (9). On the other hand, WBI with higher total dose results in better outcomes in patients with more favorable survival prognoses (11). These data highlight that the expected survival time should have an impact on the WBI-program to be considered as optimal. In order to aid the treating physicians in their process of decision making, this study aimed to develop a survival score specifically for patients with cerebral metastases from melanoma identified as suitable candidates for WBI alone. Three prognostic groups were created with statistically significant different outcomes regarding survival. Patients of the 0-point group had a median survival time of only 1 month and should, therefore, be considered for 20 Gy in 5 fractions or even better only for supportive care (9, 18). Patients of the 1-point group had an intermediate median survival time of 4 months and appear adequately treated with a longer-course WBI program. Since many patients with cerebral metastases from a less radiosensitive tumor such as melanoma can benefit from total doses  $> 30$  Gy, 36 Gy in 12 fractions appears a reasonable option (19). Patients of the 2-point group had the

Table II. Survival rates of the investigated variables at 3, 6 and 12 months after WBI.

	At 3 months (%)	At 6 months (%)	At 12 months (%)	<i>p</i> -Value
Age at WBI				
≤55 years	78	57	31	<b>&lt;0.0001</b>
≥56 years	41	9	0	
Gender				
Female	71	43	21	0.18
Male	55	29	12	
Karnofsky performance status				
≤70	38	6	0	<b>0.0008</b>
≥80	72	48	24	
Number of brain metastases				
1-3	91	45	15	0.26
≥4	50	29	15	
Extracranial metastatic spread				
No	100	83	21	0.07
Yes	54	26	14	
Time melanoma diagnosis to WBI				
≤24 months	45	32	19	0.54
≥25 months	74	35	13	

WBI, Whole-brain irradiation; bold, significant *p*-values.

Table III. Survival rates of the three prognostic groups at 3, 6 and 12 months after WBI.

Prognostic group	At 3 months (%)	At 6 months (%)	At 12 months (%)	<i>p</i> -Value
0 points (n=12)	25	0	0	<b>&lt;0.0001</b>
1 point (n=14)	64	21	0	
2 points (n=19)	79	63	38	

Bold, significant *p*-value.

most favorable survival time (median 10 months) and should, therefore, receive a longer-course WBI-program. Since these patients likely live long enough to experience WBI-related late morbidities, 40 Gy in 20 fractions appears appropriate. WBI with doses per fraction of <3 Gy were reported to result in a less pronounced decline in neurocognitive function than doses per fraction of ≥3 Gy (10).

The median survival time of 4 months observed for the entire cohort of this study was within the range of those found in other studies of patients with WBI alone for cerebral metastases from melanoma (1, 4, 20). In these studies, median survival times ranged between 2.9 and 6.1

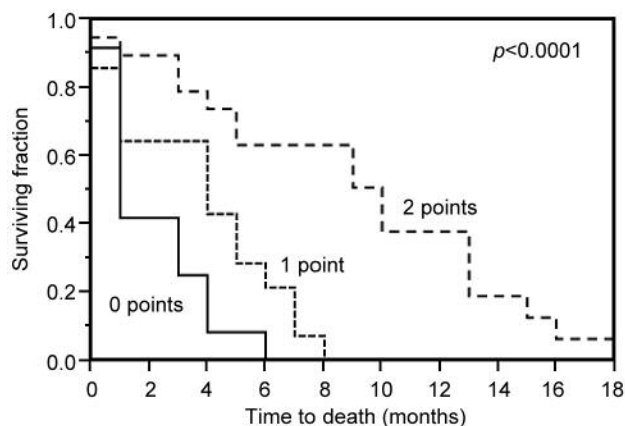


Figure 1. Kaplan-Meier curves of the three prognostic groups 0 points, 1 point and 2 points. The *p*-value was obtained using the log-rank test.

months. Nowadays, some prognostic factors for patients with cerebral metastases of melanoma are known. In the diagnosis-specific graded prognostic assessment (GPA), the variables KPS and number of brain metastases had a significant impact on survival (21). In other studies, the recursive partitioning analysis (RPA) classification was significantly correlated with survival in patients with cerebral metastases from a melanoma (22, 23). The RPA-classification originally introduced by Gaspar *et al.* in 1997 in patients with cerebral metastases from various tumor types was based mainly on KPS and age (24). Age was also identified as a significant predictor of survival in the studies of Fife *et al.* and Raizer *et al.* (4, 20). These data show some consistency with the results of the present study. However, one should bear in mind that this is a retrospective study, which may include a hidden bias, although only patients who had received WBI with doses >30 Gy, were included.

In summary, a survival score was developed specifically for patients with cerebral metastases from melanoma assigned to WBI alone. This new instrument may facilitate the decision for the appropriate WBI-program for an individual. Ideally, this score should be validated in a prospective cohort.

### Conflicts of interest

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

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