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Prognostic Factors After Whole-brain Radiotherapy Alone for Brain Metastases from Malignant Melanoma

DIRK RADES[1], LENA SEHMISCH[1], STEFAN JANSSEN[1,2] and STEVEN E. SCHILD[4]

[1]*Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[2]*Private Practice of Radiation Oncology, Hannover, Germany;*
[3]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.*

Abstract. *Background/Aim: Many patients with brain metastases from melanoma receive whole-brain radiotherapy (WBRT). WBRT-regimens must consider the patient's prognosis in order to deliver the best therapy. Patients and Methods: Seven factors were correlated to intracerebral control and survival after WBRT alone in 92 patients with melanoma: WBRT regimen, age at WBRT, gender, Karnofsky performance score (KPS), number of brain lesions, number of extracranial metastatic sites, and time from melanoma diagnosis to WBRT. Results: On univariate analyses, KPS ≥80 (p=0.075) showed a trend towards improved intracerebral control. Greater WBRT dose (p=0.029), age ≤60 years (p=0.002), KPS ≥80 (p<0.001) and no extracranial site (p=0.008) were positively correlated with survival. On multivariate analyses, KPS (hazard ratio=2.11, 95% confidence interval=1.28-3.47; p=0.003) and number of extracranial metastatic sites (hazard ratio=1.27, 95% confidence interval=1.02-1.56; p=0.030) maintained significance regarding survival. Conclusion: The study identified predictors of survival for patients with melanoma receiving WBRT for brain metastases that can contribute to selection of individualized therapies.*

Almost 50% of patients with malignant melanoma may develop brain metastases over time (1, 2). Many of those patients presenting with a very limited number of intracerebral lesions measuring less than 4 cm who have controlled extracranial disease and a relatively favorable performance score are treated with radiotherapy in the form of stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT), with or without whole-brain radiotherapy (WBRT) (3-6). However, these criteria do not apply to many patients with intracerebral metastases from malignant melanoma. Such patients generally receive WBRT alone. In the case of an unfavorable prognosis, patients appear to be best treated with a short course of WBRT, *e.g.* 20 Gy in five fractions over 1 week (7, 8). Selected patients with a very poor survival prognosis of only a few weeks may also be candidates for best supportive care alone, which has been suggested for patients with brain metastasis from lung cancer (9). On the other hand, some patients with brain metastases from melanoma may have a much more favorable survival prognosis and would benefit from a longer course of WBRT with total doses greater than 30 Gy (7, 8, 10). Since the optimal treatment for an individual patient depends essentially on their expected survival prognosis, it would be desirable to be able to predict individual survival times. This could be facilitated if prognostic factors of survival for patients with brain metastases from melanoma were identified. Since patients selected for WBRT are quite different from those considered candidates for SRS or FSRT, prognostic factors should be separately identified for both patient groups (3-8). The present study focused on patients with brain metastases from melanoma who were treated with WBRT alone. In addition to survival, intracerebral control was investigated, since this is another very important endpoint after radiotherapy of brain metastases.

Correspondence to: Professor Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Ratzeburger Allee 160, 23562 Lübeck, Germany. Tel: +49 45150045401, Fax: +49 45150045404, e-mail: rades.dirk@gmx.net

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Patients and Methods

Ninety-two patients treated with WBRT alone for brain metastases from melanoma were retrospectively evaluated for intracerebral control and survival. A total of seven factors were analyzed for a potential association with these two endpoints: WBRT regimen (20 Gy in five fractions *vs.* 30 Gy in 10 fractions *vs.* >30 Gy in 12-20 fractions), age at WBRT (≤60 *vs.* ≥61 years; median age=60 years), gender, Karnofsky performance score (KPS ≤70 *vs.* KPS ≥80; median KPS=70), number of brain metastases (1-3 *vs.* ≥4),

number of extracranial metastatic sites (0 *vs.* 1-2 *vs.* ≥3), and the time from melanoma diagnosis to WBRT (≤35 *vs.* ≥36 months; median=35 months). The distributions of these factors are shown in Table I.

For univariate analyses of intracerebral control and survival, the Kaplan–Meier method and the log-rank test were applied (11). Those factors that were significantly associated with survival ($p<0.05$) or showed a trend for association ($p<0.08$) were subsequently included in a Cox proportional hazards model. The median follow-up time was 4 months (range=0-18 months) for the entire series and 7 months (range=6-13 months) in patients still alive at the last follow-up.

Table I. *Distributions of the factors investigated in this study.*

	No. of patients	(%)
WBRT regimen		
20 Gy in 5 fractions	22	24
30 Gy in 10 fractions	42	47
>30 Gy in 12-20 fractions	27	29
Age at WBRT		
≤60 Years	47	51
≥61 Years	45	49
Gender		
Female	27	29
Male	65	71
Karnofsky performance status		
≤70	48	52
≥80	44	48
Number of brain metastases		
1-3	30	33
≥4	62	67
Number of extracranial metastatic sites		
0	18	20
1-2	48	52
≥3	26	28
Time from melanoma diagnosis to WBRT		
≤35 Months	48	52
≥36 Months	44	48

WBRT: Whole-brain radiotherapy.

Results

Considering the entire cohort, the intracerebral control rates at 3 and 6 months were 64% and 34%, respectively. On univariate analyses, a KPS ≥80 ($p=0.075$) showed a trend towards improved intracerebral control. The results of the univariate analyses of intracerebral control are summarized in Table II. On the subsequent multivariate analyses, the KPS [hazard ratio (HR)=1.57, 95% confidence interval (CI)=0.92-2.67; $p=0.10$) did not achieve significance.

For the entire series, the survival rates at 3 and 6 months were 55% and 35%, respectively. On univariate analyses, a greater WBRT dose ($p=0.029$), age ≤60 years ($p=0.002$), a KPS ≥80 ($p<0.001$), and absence of extracranial metastases ($p=0.008$) were significantly positively associated with survival. The results of the univariate analyses of survival are given in Table III. On multivariate analyses, KPS (HR=2.11,95% CI=1.28-3.47; $p=0.003$) and number of extracranial metastatic sites (HR=1.27, 95% CI=1.02-1.56; $p=0.030$) maintained significance. In contrast, WBRT dose (HR=1.21, 95% CI=0.86-1.72; $p=0.28$) and age (HR=1.46, 95% CI=0.90-2.38; $p=0.12$) were not significant factors in the Cox proportional hazards model.

Discussion

The majority of patients with brain metastases from malignant melanoma who are not suitable for local therapies such as neurosurgical resection or stereotactic radiotherapy (SRS or FSRT) are treated with WBRT (7, 8). Several WBRT regimens are available ranging from short-course WBRT with 20 Gy given in five fractions over 1 week to longer-course WBRT programs with higher total doses of 30-40 Gy and doses per fraction of 2-3 Gy. In patients with brain metastases and a relatively favorable prognosis, who were selected for WBRT alone, longer-course WBRT programs were reported to result in better intracerebral control and survival rates (12). In contrast, in patients with a very limited survival prognosis, short-course WBRT appeared not to be inferior to longer-course regimens (13). Therefore, short-course WBRT would be preferable for these patients to avoid their spending more time than necessary receiving oncological treatments. For selected patients with an extraordinarily poor prognosis, WBRT may even be omitted and replaced by supportive care including dexamethasone (9). These considerations demonstrate how the survival prognosis of patients with brain metastases, including those with malignant melanoma, influences the choice of treatment approach. It is important to be able to judge a patient's remaining survival time as precisely as possible. Accurate knowledge about significant and independent prognostic factors marks an important step in achieving this goal (14, 15).

The present study was initiated to identify predictors of survival in patients with brain metastases from malignant melanoma who are not candidates for local therapies. In addition, it aimed to identify prognostic factors of intracerebral control, another important endpoint after WBRT of brain metastases. However, an independent predictor of intracerebral control was not identified analogously to the results of a previous study investigating predictors of disease-free survival in 14 patients receiving SRS for brain metastases from melanoma (4). In that study, the presence of only a single intracerebral lesion and absence of extracranial metastases had a trend for association but did not achieve significance.

Table II. *Intracerebral control rates at 3 and 6 months for patients treated with whole-brain radiotherapy alone for brain metastases from malignant melanoma. The p-values were obtained from the univariate analysis (log-rank test).*

	At 3 months (%)	At 6 months (%)	*p*-Value
WBRT regimen			
20 Gy in 5 fractions	73	62	
30 Gy in 10 fractions	60	29	
>30 Gy in 12-20 fractions	65	29	0.34
Age at WBRT			
≤60 Years	63	33	
≥61 Years	65	34	0.58
Gender			
Female	64	32	
Male	64	35	0.80
Karnofsky performance status			
≤70	52	20	
≥80	74	43	0.075
Number of brain metastases			
1-3	66	34	
≥4	63	33	0.64
Number of extracranial metastatic sites			
0	54	30	
1-2	69	39	
≥3	61	21	0.67
Time from melanoma diagnosis to WBRT			
≤35 Months	63	37	
≥36 Months	66	31	0.75

WBRT: Whole-brain radiotherapy.

Table III. *Survival rates at 3 and 6 months for patients treated with whole-brain radiotherapy alone for brain metastases from malignant melanoma. The p-values were obtained from the univariate analysis (log-rank test).*

	At 3 months (%)	At 6 months (%)	*p*-Value
WBRT regimen			
20 Gy in 5 fractions	36	18	
30 Gy in 10 fractions	51	35	
>30 Gy in 12-20 fractions	78	48	**0.029**
Age at WBRT			
≤60 Years	68	43	
≥61 Years	42	27	**0.002**
Gender			
Female	59	41	
Male	54	32	0.15
Karnofsky performance status			
≤70	33	19	
≥80	80	52	**<0.001**
Number of brain metastases			
1-3	73	40	
≥4	47	32	0.41
Number of extracranial metastatic sites			
0	61	56	
1-2	60	35	
≥3	42	19	**0.008**
Time from melanoma diagnosis to WBRT			
≤35 Months	46	31	
≥36 Months	66	39	0.57

WBRT: Whole-brain radiotherapy; significant *p*-values are shown in bold.

In contrast to intracerebral control, in the present study, survival was significantly associated with KPS and the number of extracranial metastatic sites on multivariate analysis. In addition, higher WBRT doses and age ≤60 years were associated with improved survival on univariate analyses. In a previous retrospective study of 51 patients receiving WBRT for brain metastases from malignant melanoma, better survival was associated with presence of only 1-3 cerebral lesions (p=0.012) and absence of extracranial metastases (p=0.006) but not with KPS and age (10).

Taking into account the results of the present study, KPS and the number of extracranial metastatic sites and possibly age of a specific patient should be considered when selecting the individualized treatment regimen. Thus, patients aged ≤60 years with brain metastases with a KPS of ≥80 lacking extracranial metastases and unsuitable for local therapy appear good candidates for longer-course WBRT with higher total doses and lower doses per fraction. According to previous studies of patients with brain metastases from different primary tumors, these patients would likely benefit from such a WBRT regimen in terms of better intracerebral control and better survival (12). In contrast, patients aged ≥60 years with a KPS of ≤70 and more than two extracranial metastatic sites should be considered for a short course of WBRT to help spare as much of their remaining life time from receiving extended therapy that may not change their outcome. Very old patients and those with a very low KPS, who have more than two extracranial metastatic sites may even be considered for best supportive care alone (9). When considering these recommendations, the retrospective nature of this study should be kept in mind. Retrospective studies always bear the risk of hidden selection biases. Ideally, a survival score would be developed taking into account the prognostic factors identified in this study. However, taking into account the impact of the WBRT dose on survival, such a score should be developed in a cohort of patients with brain metastases from melanoma who had received a WBRT dose greater than 30 Gy.

In conclusion, this study identified predictors of survival for patients receiving WBRT for brain metastases from

malignant melanoma. These factors can help the treating physicians when selecting for appropriate treatment for a specific patient.

Conflicts of Interest

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

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