

A Simple Implement for Assessing the Survival of Elderly Patients With Melanoma Irradiated for Cerebral Metastases

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Abstract. *Background/Aim:* Secondary brain lesions occur commonly in patients with advanced melanoma. Despite increasing use of local therapies, many elderly patients qualify for whole-brain radiotherapy (WBRT). For these patients, a survival score was created. *Patients and Methods:* Seven characteristics were retrospectively investigated in 35 elderly (≥ 65 years) patients with melanoma, namely WBRT regimen, age, gender, Karnofsky performance score (KPS), number of brain lesions, non-cerebral metastases and interval from melanoma diagnosis to WBRT. *Results:* Age ≤ 71 years ($p=0.044$) and KPS $\geq 80\%$ ($p=0.005$) were significantly associated with more favorable survival. Based on these characteristics, patients received 0 ($n=13$), 1 ($n=12$) or 2 points ($n=10$). Two prognostic groups were designed, 0 or 1 point vs. 2 points, with actuarial 6-month survival rates of 12% and 48%, respectively ($p=0.002$). *Conclusion:* This simple implement allows quick estimation of the survival of elderly patients receiving WBRT for cerebral metastases from melanoma.

Melanomas account for 5-10% of malignant tumors spreading to the brain (1). For many patients with few secondary brain lesions, local therapies, namely surgery and different types of stereotactic radiotherapy, are used, either alone or combined with systemic therapies (2-6). In patients with more than a few lesions, whole-brain radiotherapy (WBRT) is quite often delivered. Many patients with melanoma developing cerebral metastases belong to the age group of 65 years and older.

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This group requires particular attention, since these patients more often have other diseases and reduced function of organs such as liver, kidney and bone marrow compared to younger patients. Elderly patients may be unable to withstand intensive local and systemic therapies and, therefore, receive WBRT alone. For the treatment of cerebral metastases, different WBRT regimens are available including 5 \times 4 Gy (overall treatment time of 1 week), 10 \times 3 Gy (2 weeks) and regimens with doses beyond 30 Gy (35-40 Gy with fractions of 2.0-3.0 Gy each, lasting 2.5 to 4 weeks). When selecting a WBRT regimen for an elderly patient with melanoma, physicians should consider the remaining lifespan. For patients with a reduced lifespan, short-term WBRT (*i.e.* 5 \times 4 Gy) appears to be appropriate, since this regimen was shown to have similar outcomes compared to longer programs in patients with poor survival prognoses (7). On the contrary, for patients expected to have longer remaining lifetime, longer-term WBRT regimens may be beneficial in terms of increased cerebral control and survival (8). Therefore, physicians would like to be able to estimate a patient's prognosis before the start of WBRT. This study was performed to support physicians during the decision-making process. It aimed to create a simple tool that allows estimating the survival prognosis following WBRT of elderly patients with melanoma presenting with cerebral metastases.

Patients and Methods

Thirty-five melanoma patients aged ≥ 65 years, who received WBRT for cerebral metastases, were analyzed in a retrospective way within this study, which received approval from the Ethics Committee (AZ19-011A). The data of several patients had been obtained from an existing database and had been used for other retrospective studies (9-13). In the current study, WBRT regimen (5 \times 4 Gy vs. 10 \times 3 Gy vs. 12-20 \times 2-3 Gy) and six pre-WBRT characteristics were analyzed for associations with survival. Distributions of the seven characteristics are shown in Table I. Pre-WBRT characteristics were age (≤ 71 vs. ≥ 72 years, median=72 years), gender (female vs. male), Karnofsky performance score ($\leq 70\%$ vs. $\geq 80\%$, median=70%), number of cerebral tumors [1-3 (limited) vs. ≥ 4 (multiple)], non-

Table I. Distribution of the evaluated characteristics.

Characteristic	Number of patients (%)
WBRT regimen	5x4 Gy 8 (22.9)
	10x3 Gy 18 (51.4)
	12-20x2-3 Gy 9 (25.7)
Age	≤71 Years 17 (48.6)
	≥72 Years 18 (51.4)
Gender	Female 8 (22.9)
	Male 27 (77.1)
Karnofsky performance score	≤70% 20 (57.1)
	≥80% 15 (42.9)
Number of brain metastases	1-3 (Limited) 12 (34.3)
	≥4 (Multiple) 23 (65.7)
Extracranial metastases	No 5 (14.3)
	Yes 30 (85.7)
Interval from melanoma diagnosis until WBRT	≤34 Months 18 (51.4)
	≥35 Months 17 (48.6)

WBRT: Whole-brain radiotherapy.

cerebral metastases (no vs. yes), and period from melanoma diagnosis until WBRT (≤34 vs. ≥35 months, median=34 months).

The survival analyses were performed with Kaplan-Meier method plus log-rank test. Characteristics that were significantly ($p < 0.05$) associated with survival after WBRT were used to create the prognostic tool. For each significant characteristic, points were assigned, namely 0 points in the case of less favorable survival and 1 point in the case of more favorable survival. The total points for patients were calculated by adding their individual points related to significant characteristics.

Results

Age ≤71 years ($p = 0.044$) and KPS of ≥80% ($p = 0.005$) were significantly associated with more favorable outcomes (Table II). Therefore, these characteristics were used to create the prognostic tool. The following points were assigned: 0 points for age ≥72 years and KPS of ≤70%, respectively, and 1 point for age ≤71 years and KPS of ≥80%. Thus, the patients received total scores of 0 ($n = 13$), 1 ($n = 12$) or 2 points ($n = 10$). Survival rates were 8%, 25% and 60% at 3 months, and 8%, 17% and 48% at 6 months ($p = 0.007$). Two prognostic groups were designed, with 0 or 1 point, and 2 points. Corresponding 3-month survival rates were 16% and 60%; 6-month survival rates were 12% and 48%, respectively ($p = 0.002$, Figure 1).

Discussion

Considerable research is carried out to improve the survival prognoses of patients with metastatic melanoma (2-6, 9-13). The prognoses of many elderly patients developing cerebral metastases from melanoma are very limited. Besides newer systemic treatment approaches, personalization of the

Table II. Six-month survival rates after whole-brain irradiation (univariate analyses).

	At 3 months (%)	At 6 months (%)	<i>p</i> -Value
WBRT regimen			
5x4 Gy	13	13	0.14
10x3 Gy	44	32	
12-20x2-3 Gy	11	11	
Age			
≤71 Years	41	34	0.044
≥72 Years	17	11	
Gender			
Female	25	25	0.46
Male	29	22	
Karnofsky performance score			
≤70%	10	10	0.005
≥80%	53	38	
Number of brain metastases			
1-3 (Limited)	42	25	0.76
≥4 (Multiple)	22	22	
Extracranial metastases			
No	40	40	0.14
Yes	27	19	
Interval from melanoma diagnosis until WBRT			
≤34 Months	22	17	0.16
≥35 Months	35	28	

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

treatment can lead to improved outcomes. To facilitate the selection of an optimally personalized treatment, survival scores are important. This also applies to the choice of the most appropriate WBRT regimen. Survival scores are already available for different types of radiotherapy and primary tumor types (4, 9, 10, 14). In our study, a specific implement for estimating the survival prognoses of elderly patients receiving WBRT for cerebral metastases from melanoma has been added. Patients belonging to the 0-to-1-point group achieved a median survival of only 1 month, and 3- and 6-month survival rates were only 16% and 12%, respectively. Thus, these patients should receive short-term WBRT with 5x4 Gy (7). Moreover, since a randomized study performed in patients with cerebral metastases from lung cancer and quite limited prognoses demonstrated that best supportive care was not significantly inferior to the same regimen plus WBRT with 5x4 Gy, one may also consider omitting WBRT for the patients of the 0-to-1-point group in the present study (15).

On the contrary, patients of the 2-point group in the current study achieved a median survival of 6 months, with the 3- and 6-month survival of 60% and 48%, respectively. Thus, these patients would appear to be more adequately treated with a longer-term WBRT program, since previous studies have suggested increased cerebral control and

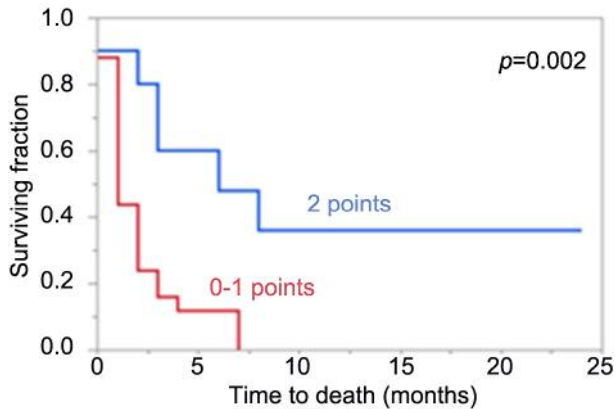


Figure 1. Kaplan-Meier curves of the groups with 0-1 points (n=25) and 2 points (n=10) with respect to survival after whole-brain radiotherapy.

survival using WBRT with higher doses (8). In general, the outcomes of patients developing cerebral metastases from melanoma may be improved by combining radiotherapy and immunotherapy (16). This applies particularly to those who have intermediate or favorable prognoses. However, one should be aware of the increased risk of side-effects including necrosis of normal brain tissue when immunotherapy is added. When using this new tool to estimate a patient’s survival time and to select a WBRT regimen, the limitations of our study, namely its small sample size and its retrospective design, need to be regarded.

In summary, a simple tool was developed that allows judging the remaining lifespans of elderly patients treated with WBRT for cerebral metastases from melanoma. This tool can be useful when aiming to pick the most suitable individual WBRT regimen.

Conflicts of Interest

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

Authors’ Contributions

T.N., S.J., S.E.S. and D.R. participated in the study design. T.N., S.J. and D.R. provided the data that were analyzed and interpreted by S.E.S. and D.R. S.E.S. and D.R. wrote the article that was reviewed and approved by all Authors.

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