

# Comparison of 20×2 Gy and 12×3 Gy for Whole-brain Irradiation of Multiple Brain Metastases from Malignant Melanoma

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**Abstract.** *Background/Aim:* Most patients with multiple brain metastases from melanoma receive whole-brain irradiation. In a previous study, doses >30 Gy resulted in better outcomes than 10×3 Gy. However, the optimal dose-fractionation regimen has not yet been defined. This study compared 20×2 Gy over four weeks, which was used in the previous study, to 12×3 Gy over two-and-a-half weeks. *Patients and Methods:* Eleven patients treated with 20×2 Gy for multiple brain metastases were compared to 12 patients treated with 12×3 Gy. *Results:* Intracerebral control rates at 6 and 12 months were 17% and 0% after 20×2 Gy vs. 42% and 11% after 12×3 Gy ( $p=0.28$ ). Survival rates at 6 and 12 months were 36% and 9% after 20×2 Gy vs. 50% and 25% after 12×3 Gy ( $p=0.75$ ). *Conclusion:* The less time-consuming regimen 12×3 Gy appeared not inferior to 20×2 Gy and a reasonable treatment option, particularly for patients with a limited life expectancy.

The incidence of cutaneous malignant melanoma has been constantly increasing over years (1). More than 40% of the patients with a malignant melanoma develop brain metastases (2). Many patients with a single or very few brain metastases of less than 4 cm in size, controlled extracranial disease and a good performance status receive stereotactic radiosurgery (SRS) or fractionated stereotactic radiotherapy (FSRT) (3, 4). However, many patients with brain metastases

from melanoma do not fulfil these criteria and receive whole-brain irradiation (WBI) alone instead. When WBI is administered, the best suitable dose-fractionation regimen for patients with cerebral metastases from melanoma still needs to be defined.

According to a previous study, an escalation of the radiation dose beyond the most commonly used regimen 10×3 Gy resulted in improved intracerebral control and survival rates (5). However, in that study, 10×3 Gy was not compared to a specific higher dose regimen. The majority of patients in the higher dose group had received 20×2 Gy over four weeks.

An overall treatment time of four weeks appears relatively long for patients with a very limited remaining lifespan, which accounts for many patients with multiple brain metastases from malignant melanoma. Therefore, the present study compared 20×2 Gy over four weeks to a shorter regimen, namely 12×3 Gy over two-and-a-half weeks, with respect to intracerebral control and survival.

## Patients and Methods

Eleven patients who received WBI alone with 20×2 Gy over four weeks for multiple brain metastases (defined as more than one metastatic cerebral lesion) were compared to 12 patients receiving WBI alone with 12×3 Gy over two-and-a-half weeks. Investigated endpoints included intracerebral control (freedom from progressive and/or new brain metastases) and survival, which were both referenced from the last day of WBI. Patients included in this study must have been evaluable for both end-points. The characteristics of both patient groups are shown in Table I. The comparison of both groups with respect to the distribution of the characteristics was performed with the Chi-square test. The fractionation regimen of WBI did mainly depend on the preferred regimen at the contributing centers at certain periods of time. Patients included in this study were treated between 2000 and 2015.

The comparison of both groups with respect to intracerebral control and survival was performed with the Kaplan-Meier method

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Table I. Distribution of patients' characteristics in both treatment groups.

Patients' characteristics	20x2 Gy N patients (%)	12x3 Gy N patients (%)	p-Value
Age			
≤64 years	7 (64)	7 (58)	0.93
≥65 years	4 (36)	5 (42)	
Gender			
Female	4 (36)	5 (42)	0.93
Male	7 (64)	7 (58)	
Karnofsky performance score			
≤70	5 (45)	5 (42)	0.98
≥80	6 (55)	7 (58)	
Extracranial non-cutaneous metastases			
No	4 (36)	1 (8)	0.45
Yes	7 (64)	11 (92)	
Interval from melanoma diagnosis to WBI			
≤24 months	3 (27)	4 (33)	0.97
≥25 months	8 (73)	8 (67)	

WBI, Whole-brain irradiation.

and the difference between the corresponding curves was calculated with the log-rank test (6). All *p*-values of <0.05 were defined as being significant.

## Results

Both treatment groups were well-balanced for most patients' characteristics (Table I). However, more patients in the 12x3 Gy group had extracranial non-cutaneous metastases than in the 20x2 Gy group (92% vs. 64%), although the difference was not significant (*p*=0.45).

The intracerebral control rates at 3, 6, 9 and 12 months were 56%, 17%, 0% and 0%, respectively, after 20x2 Gy vs. 74%, 42%, 11% and 11%, respectively, after 12x3 Gy (*p*=0.28, Figure 1). The survival rates at 3, 6, 9 and 12 months were 73%, 36%, 18% and 9%, respectively, after 20x2 Gy vs. 75%, 50% and 25%, respectively, after 12x3 Gy (*p*=0.75, Figure 2).

## Discussion

Due to its increasing incidence, malignant melanoma has gained importance in the field of oncologic research (7-11). A considerable number of patients with melanoma develop metastasis to the brain during the course of their disease (1). Radiotherapy is the most frequently applied type of treatment for these patients. Most patients with multiple intracerebral lesions receive WBI alone. A previous retrospective study of

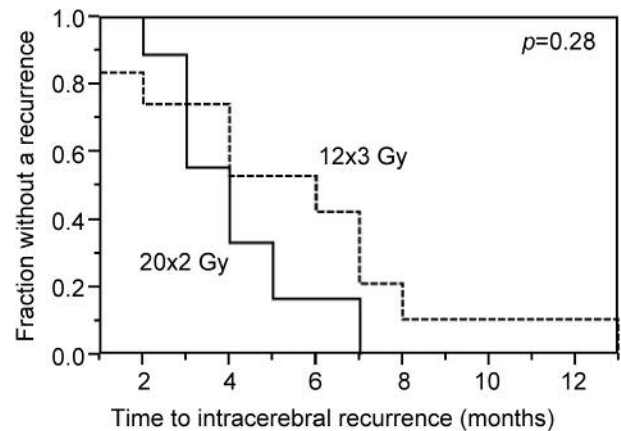


Figure 1. Kaplan-Meier curves for intracerebral control.

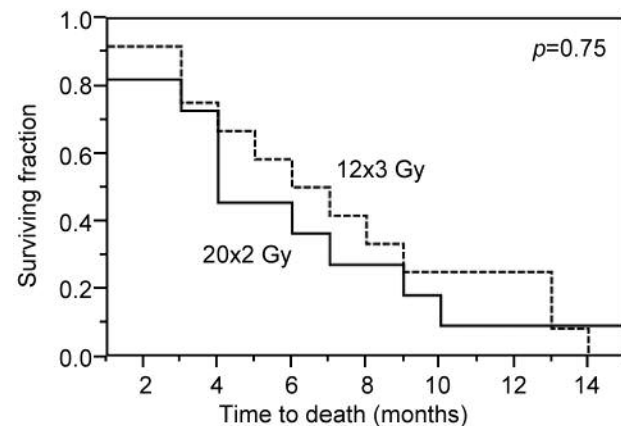


Figure 2. Kaplan-Meier curves for survival.

51 patients with brain metastases from melanoma suggested that the most common WBI regimen, 10x3 Gy, resulted in worse intracerebral control and survival when compared to higher doses (5). Six-month intracerebral control rates were 23% and 50%, respectively (*p*=0.021) and 6-month survival rates were 27% and 50%, respectively (*p*=0.009). In the higher dose group, different dose-fractionation regimens were combined. In that study, one of these regimens was 20x2 Gy given over four weeks. Taken into account the relatively poor survival prognosis of patients with multiple brain metastases from malignant melanoma, an overall treatment time of four weeks can be considered quite long. A shorter regimen would be preferable if it led to similar treatment outcomes as 20x2 Gy. The biological effective dose of a radiation regimen can be given as equivalent dose

in 2-Gy fractions (EQD2), which considers both total dose and dose per fraction (12). The EQD2 for 20×2 Gy with respect to tumor cell kill is 40 Gy. When using a dose per fraction of 3 Gy, the most similar EQD2 is achieved with 12 fractions (12×3 Gy), which corresponds to an EQD2 of 39 Gy. Therefore, it may be assumed that 20×2 Gy and 12×3 Gy will result in similar treatment outcomes. However, this has not yet been demonstrated. Therefore, the present study compared 20×2 Gy and 12×3 Gy with respect to intracerebral control and survival. According to the results obtained, 12×3 Gy was not inferior to 20×2 Gy. Intracerebral control and survival were even better with 12×3 Gy, although the results were not significant. Since this was a retrospective study with relatively small numbers of patients on both treatment groups, the results should ideally be confirmed in a larger prospective trial.

In conclusion, 12×3 Gy appeared similarly effective as 20×2 Gy with respect to intracerebral control and survival and can, therefore, be considered a reasonable option for patients with multiple brain metastases from melanoma, in particular for those patients with a limited life expectancy.

### 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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