Identifying Melanoma Patients with 1-3 Brain Metastases Who May Benefit from Whole-brain Irradiation in Addition to Radiosurgery

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Abstract. *Background/Aim: To develop a tool for estimating the risk of developing new cerebral lesions in 69 melanoma patients receiving radiosurgery for 1-3 cerebral metastases. Patients and Methods: Ten factors were investigated: lactate dehydrogenase (LDH), radiosurgery dose, age, gender, performance status, maximum diameter, location and number of cerebral lesions, extra-cranial spread, time between melanoma diagnosis and radiosurgery. Two factors, number of lesions and extra-cranial spread, were included in the tool. Scoring points were achieved by dividing the 6-month rate of freedom from new cerebral lesions by 10. Results: Sum scores were 9, 11, 12 or 14 points. Six-month rates of freedom from new brain metastases were 28%, 63%, 59% and 92% (p=0.002). Three prognostic groups were designed: A (9 points), B (11-12 points) and C (14 points). Freedom from new cerebral lesion rates were 28%, 60% and 92% (p<0.001). Conclusion: Group A and B patients should be considered for additional whole-brain radiotherapy (WBRT).*

Many patients presenting with a limited number of brain metastases receive radiosurgery-alone. Currently the question whether or not these patients will benefit from whole-brain radiotherapy (WBRT) in addition to radiosurgery under debate. A small randomized trial of 58 patients with brain metastases from different primary tumors revealed that the additional WBRT resulted in increased deterioration of neurocognitive functions when compared to radiosurgery-alone at four months following treatment (1). According to another prospective study of 92 patients with a limited number of brain lesions from different tumor entities, neurocognitive function was better both one and two years after WBRT-plus-radiosurgery than after radiosurgery-alone, since the addition of WBRT has led to an improved cerebral control (freedom from brain metastasis) (2). These authors concluded that progression of the treated or new cerebral lesions was the major cause of neurocognitive deficits. The fact that the addition of WBRT to radiosurgery improves cerebral control rates has also been demonstrated in other studies (3, 4). This effect was particularly due to an increased rate of freedom from new brain lesions. Despite these findings, treating physicians are often hesitant to administer WBRT in addition to radiosurgery. This applies, in particular, to patients with brain metastases from melanoma, a less radiosensitive tumor when compared to others such as lung and breast cancer. Melanoma patients were shown to benefit from higher WBRT doses than those with brain metastases from other primaries (5).

Taking into account these findings and the physicians' concerns, it is desirable to be able to predict the risk of developing new brain metastases distant from the irradiated sites after radiosurgery-alone. Patients at high risk would be candidates for additional WBRT, whereas in patients with low risk, one might be more reserved regarding WBRT. This study was performed to develop a tool that allows one to estimate the risk of developing new brain metastases within six months following radiosurgery.

Patients and Methods

Patients and treatment approaches. Sixty-nine patients treated with radiosurgery-alone for 1-3 cerebral metastases from melanoma were retrospectively analyzed with respect to freedom from new cerebral lesions distant from the irradiated metastases. In 58 patients, radiosurgery was performed with a linear accelerator (Siemens, Medical Systems, Concord, CA, USA and Varian Medical Systems, Palo Alto, CA, USA) and in 11 patients with a Cyberknife (Accuray,

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Sunnyvale, CA, USA). Ten factors were evaluated for associations with freedom from new brain metastases including lactate dehydrogenase (LDH) levels prior to radiosurgery (normal *vs.* elevated), radiosurgery dose (equivalent to 17-18 Gy *vs.* 20 Gy *vs.* 21-22.5 Gy with respect to tumor cell kill, prescribed to the 73-90% isodose level), age (≤65 *vs.* ≥66 years; median, 66 years), gender, Karnofsky performance score (KPS) (70-80 *vs.* 90-100), maximum total diameter of all cerebral lesions (≤15 mm *vs.* >15 mm; median, 15 mm), main location of the cerebral lesions (frontal *vs.* temporal *vs.* others), number of cerebral lesions (1 *vs.* 2-3), extracranial spread (no *vs.* yes) as well as the time between first diagnosis of melanoma and radiosurgery (≤2 *vs.* >2 years).

Statistical analysis. For the univariate analysis of freedom from new cerebral lesions, the Kaplan-Meier method (6) and the log-rank test were used. Factors achieving significance ($p<0.05$) or showing a certain trend ($p\leq0.12$) in the univariate analysis were additionally analyzed with the Cox proportional hazards model. Those factors with a p-value of <0.15 in the multivariate analysis were included in a tool that was created to estimate the risk of developing new brain metastases distant from the irradiated cerebral lesions within 6 months following radiosurgery.

Results

The results of the univariate analysis of freedom from new cerebral lesions are shown in Table I. The number of brain metastases at the time of radiosurgery and extracranial spread were additionally included in the multivariate analysis. In this analysis, the number of brain metastases (1 *vs.* 2-3, risk ratio 1.82; 95% confidence interval (CI)=0.95-3.53; $p=0.07$) showed a strong trend, and extracranial spread (no *vs.* yes, risk ratio 1.77; 95% CI=0.84-4.17; $p=0.14$) a trend. Both factors were included in the predictive tool. Scoring points were achieved by dividing the rate of freedom from new brain metastases at six months (in %) by 10. These rates were 67% in case of one cerebral lesion (7 points), 41% in case of 2-3 lesions (4 points), 70% in case of no extracranial spread (7 points) and 50% in case of extracranial spread (5 points), respectively. The prognostic score represented the sum of the points obtained from the two factors, number of cerebral lesions and extracranial spread. Thus, prognostic scores were 9, 11, 12 or 14 points. The rates of freedom from new brain metastases at 6 months were 28%, 63%, 59% and 92%, respectively ($p=0.002$). Based on the prognostic scores, three prognostic groups were designed: A (9 points), B (11-12 points) and C (14 points). The corresponding rates of freedom from new brain metastases were 28% (group A), 60% (group B) and 92% (group C), respectively ($p<0.001$). Kaplan-Meier curves of the three prognostic groups are shown in Figure 1.

Discussion

Radiosurgery-alone is commonly used for patients with a very limited number of cerebral metastases due to melanoma. Uncertainty exists regarding the question whether the prognosis of these patients can be improved with the addition of WBRT. Some physicians are concerned that adding WBRT will increase the risk of developing neurocognitive deficits.

A randomized study comparing radiosurgery-alone to radiosurgery-plus-WBRT in patients with very few cerebral lesions from various primary tumors (mostly lung cancer and breast cancer) was stopped after an interim analysis of 58 patients, because patients receiving additional WBRT were significantly more likely to show a decline in neurocognitive function at 4 months than patients assigned to receive radiosurgery-alone (1). At one year, 73% of patients in the radiosurgery-plus-WBRT group and 27% of patients in the radiosurgery-alone group had no cerebral recurrence ($p<0.001$). One major criticism of this trial was that neurocognitive function was not evaluated at one year. It is possible that neurocognitive function at one year was better after radiosurgery-plus-WBRT than after radiosurgery-alone, since cerebral recurrence has been identified by other authors as the primary cause of neurocognitive deficits in patients irradiated for brain metastasis.

This concept was supported by the findings of Aoyama *et al*. who evaluated 92 of the 132 patients of their randomized trial comparing radiosurgery-alone to radiosurgery-plus-WBRT with respect to preservation of neurocognitive function (2). At one year, neurocognitive function was preserved in 79% of patients after radiosurgery-plus-WBRT and in 53% of patients after radiosurgery-alone, respectively. The preservation rates at two years were 79% and 43%, respectively. A beneficial effect of the addition of WBRT on cerebral control has also been observed in other studies. In a retrospective study of 144 patients with 1-3 cerebral metastases from different primaries, the cerebral control rates at one year were 66% with and 51% without WBRT ($p=0.015$) (3). In a randomized trial, 100 patients received radiosurgery-alone and 99 radiosurgery-plus-WBRT for 1-3 cerebral lesions (4). The WBRT reduced the 2-year recurrence rates both at treated sites (31% *vs.* 19%, $p=0.040$) and new sites (48% *vs.* 33%, $p=0.023$). In both studies, the improvement in cerebral control did not result in improved survival. Due to the latter finding and the fear of WBRT-related toxicities, the treating physicians are often hesitant to add WBRT to radiosurgery in spite of the fact that it significantly improves cerebral control. The concerns regarding WBRT exist in particular in cases of cerebral metastases from melanoma, since melanoma is less radiosensitive compared to other primary tumors leading to brain metastasis and may, therefore, need higher WBRT doses than the most commonly used regimen of 30 Gy in 10 fractions. In the multivariate analyses of a retrospective study of 51 patients who received WBRT-alone for brain metastases from melanoma, doses of 40 Gy in 20 fractions and 45 Gy in 15 fractions were associated with significantly better cerebral control ($p=0.020$) and survival ($p=0.010$)

Table I. *Analysis of freedom from new brain metastases distant from the irradiated lesions.*

	Freedom from new brain metastases rates at 6 months (%)	*p*-Value
Lactate Dehydrogenase (LDH)		
Normal (N=37)	61	
Elevated (N=19)	51	0.46
Radiosurgery dose		
17-18 Gy (N=16)	62	
20 Gy (N=36)	52	
21-22.5 Gy (N=17)	59	0.50
Age		
≤65 years (N=34)	62	
≥66 years (N=35)	50	0.52
Gender		
Female (N=39)	60	
Male (N=30)	51	0.27
Karnofsky performance score		
70-80 (N=28)	44	
90-100 (N=41)	63	0.14
Total max. diameter of all cerebral lesions		
≤15 mm (N=35)	61	
>15 mm (N=34)	51	0.29
Main location of cerebral lesions		
Frontal (N=23)	59	
Temporal (N=17)	64	
Other (N=29)	50	0.36
Number of cerebral lesions		
1 (N=40)	67	
≥2 (N=29)	41	0.047
Extracranial spread		
No (N=20)	70	
Yes (N=49)	50	0.12
Time melanoma diagnosis to radiosurgery		
≤2 years (N=28)	50	
>2 years (N=41)	60	0.36

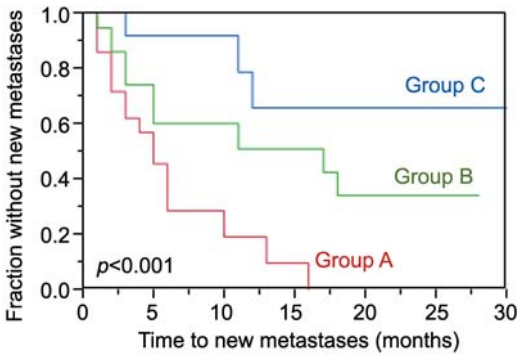

Figure 1. *Freedom from new cerebral lesions: Kaplan-Meier curves of the three prognostic groups A (9 points), B (11-12 points) and C (14 points). The p-value was obtained from the log-rank test.*

when compared to 30 Gy in 10 fractions (5). Similar results were observed for patients with brain metastases from renal cell carcinoma and colorectal cancer (7-9). Such higher WBRT doses are likely associated with a greater risk of neurocognitive deficits. Furthermore, if new cerebral lesions occur after radiosurgery-alone, a second course of radiosurgery or a neurosurgical intervention may be performed as salvage therapy.

Taking into account the pros and cons regarding the addition of WBRT to radiosurgery in patients with brain metastases from melanoma, it is still not clear whether or not WBRT should be added to radiosurgery. A randomized trial has been initiated to contribute to this unanswered question (10). However, another important question is whether a more personalized approach would be beneficial to patients. WBRT may be of benefit for certain patients, whereas other patients may not benefit from such a combined approach. The decision for or against the addition of WBRT should be based on the risk of new brain metastases distant from the treated lesions. In the current study, a tool has been developed that helps estimate the risk of developing new cerebral lesions within 6 months following radiosurgery- alone. Based on two prognostic factors, number of cerebral lesions and extracranial spread, three prognostic groups with significantly different 6-month rates of freedom from new cerebral metastases were designed. Patients of group A had a 6-month rate of only 28% and are, therefore, strong candidates for additional WBRT. The 6-month rate of freedom from new cerebral lesions in patients of group B was 60%. Also in these patients, freedom from new lesions needs to be improved and WBRT should be considered. Patients of group C had a 6-month rate of freedom from new lesions of 92% and, therefore, do not likely need WBRT in addition to radiosurgery. When using these recommendations in clinical routine, one should be aware of the retrospective nature of the data used to develop this new predictive tool.

In summary, this new predictive tool allows the estimation of the risk of new cerebral metastases distant from the irradiated sites after radiosurgery-alone in melanoma patients. Group A (and likely also group B) patients should receive WBRT in addition to radiosurgery in order to improve the rate of freedom from new cerebral lesions. This is of particular importance also because cerebral recurrence is associated with a decline in neurocognitive function.

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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