Radiosurgery Alone for 1-3 Newly-diagnosed Brain Metastases from Melanoma: Impact of Dose on Treatment Outcomes

DIRK RADES[1], LENA SEHMISCH[1], STEFAN HUTTENLOCHER[1], OLIVER BLANK[1,2], DAGMAR HORNUNG[3], PATRICK TERHEYDEN[4], JAN GLIEMROTH[5] and STEVEN E. SCHILD[6]

Departments of [1]Radiation Oncology, [4]Dermatology and [5]Neurosurgery, University of Lübeck, Lübeck, Germany; [2]CyberKnife Center Northern Germany, Güstrow, Germany; [3]Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany; [6]Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.

Abstract. *Background/Aim: To compare different doses of stereotactic radiosurgery (SRS) for 1-3 newly-diagnosed cerebral metastases from melanoma. Patients and Methods: Fifty-four patients were assigned to dose groups of 20 Gy (N=36) and 21-22.5 Gy (N=18). Variables additionally analyzed were age, gender, Karnofsky Performance Score (KPS), lactate dehydrogenase (LDH) before SRS, number of cerebral lesions, extracranial lesions, time from melanoma diagnosis to SRS. Results: The 12-month local control was 72% after 20 Gy and 100% after 21-22.5 Gy (p=0.020). Freedom from new cerebral metastases (p=0.13) and survival (p=0.13) showed no association with SRS dose. On multivariate analyses, improved local control showed significant associations with SRS doses of 21-22.5 Gy (p=0.007) and normal lactate dehydrogenase levels (p=0.018). Improved survival was associated with normal LDH levels (p=0.006) and KPS 90-100 (p=0.046). Conclusion: SRS doses of 21-22.5 Gy resulted in better local control than 20 Gy. Freedom from new brain metastases and survival were not significantly different.*

Brain metastases occur in up to 10% of melanoma patients during the course of their disease (1). Most patients with multiple lesions are treated with whole-brain radiotherapy (WBRT)-alone (2, 3). In patients with a very limited number of lesions, stereotactic radiosurgery (SRS) and neurosurgery also play important roles (4-7). Neurosurgical resection is usually limited to patients with a single lesion, whereas radiosurgery is widely used for patients with one to three lesions. It has been demonstrated in randomized trials including patients with brain metastases from different primary tumors that WBRT in addition to SRS improves intracerebral control of metastatic disease but not survival (8-9). On the other hand, a small randomized trial has suggested that the addition of WBRT to SRS is associated with a significant decline in neurocognitive function (10). Therefore, it is controversial whether or not WBRT should be added to SRS in patients with a very limited number of brain metastases. In patients with brain metastases from a less radiosensitive tumor such as melanoma, physicians are more reserved to add WBRT to SRS than in patients with other primary tumors. When SRS alone is administered to brain metastases from melanoma, the most appropriate SRS dose is still undefined. The present study has compared two different dose groups (20 Gy *versus* 21-22.5 Gy) in such patients with respect to local control of the treated metastases, freedom from new brain metastases and overall survival.

Correspondence to: Dirk Rades, MD, Department of Radiation Oncology, University of Lübeck, Lübeck, Ratzeburger Allee 160, D-23538 Lübeck, Germany. Tel: +49 4515006661, Fax: +49 4515003324, e-mail: Rades.Dirk@gmx.net

Key Words: Melanoma, brain metastases, radiosurgery.

Patients and Methods

Patients and treatment approaches. The data of 54 patients who received SRS-alone for 1-3 newly-diagnosed brain metastases from melanoma between 2000 and 2013 were retrospectively reviewed. Forty-four patients were treated with linear accelerator (LINAC)-based radiosurgery and ten patients with CyberKnife radiosurgery. Two groups were designed according to the dose administered to the margin of the metastatic lesions (representing the 73% to 90% isodose level): 20 Gy (N=36) and 21-22.5 Gy (N=18). In the 20 Gy group, six patients received 3×10 Gy (equivalent to 1×20 Gy with respect to tumor cell kill), while in the 21-22.5 Gy group, three patients received 3×11 Gy (equivalent to 1×22 Gy with respect to tumor cell kill). The difference regarding the SRS doses was due to the variety of physician opinions at the contributing centers when these patients were treated.

The two dose groups were compared with respect to treatment outcomes in terms of local control of the irradiated metastases, freedom from new brain metastases and overall survival. In addition to the SRS dose, seven other potential prognostic factors were evaluated for associations with treatment outcomes. These factors

Table I. *Patient characteristics of the two dose groups 20 Gy (N=36) and 21-22.5 Gy (N=18).*

	20 Gy N patients (%)	21-22.5 Gy N patients (%)	*p*-Value
Age			
≤65 years	18 (50)	11 (61)	
>65 years	18 (50)	7 (39)	0.75
Gender			
Female	18 (50)	11 (61)	
Male	18 (50)	7 (39)	0.75
Karnofsky Performance Score			
KPS 70-80	14 (39)	8 (44)	
KPS 90-100	22 (61)	10 (56)	0.93
Serum LDH levels			
Normal	18 (50)	10 (56)	
Elevated	8 (22)	4 (22)	
Unknown	10 (28)	4 (22)	0.96
Number of brain metastases			
1	23 (64)	10 (56)	
2-3	13 (36)	8 (44)	0.86
Extracranial metastases			
No	11 (31)	5 (28)	
Yes	25 (69)	13 (72)	0.97
Interval from melanoma diagnosis to SRS			
≤24 months	14 (39)	7 (39)	
>24 months	22 (61)	11 (61)	1.00

Table II. *Univariate analysis of local control of the irradiated metastases.*

	Local control at 6 months (%)	Local control at 12 months (%)	*p*-Value
SRS dose			
20 Gy	83	72	
21-22.5 Gy	100	100	0.020
Age			
≤65 years	88	73	
>65 years	90	90	0.40
Gender			
Female	78	78	
Male	100	85	0.72
Karnofsky Performance Score			
KPS 70-80	86	86	
KPS 90-100	90	80	0.75
Serum LDH levels			
Normal	96	91	
Elevated	76	38	0.024
Number of brain metastases			
1	82	77	
2-3	100	89	0.27
Extracranial metastases			
No	87	77	
Yes	90	83	0.90
Interval from melanoma diagnosis to SRS			
≤24 months	89	70	
>24 months	90	90	0.77

included age (≤65 *vs.* >65 years), gender, Karnofsky performance score (KPS; 70-80 *vs.* 90-100), serum lactate dehydrogenase (LDH) levels prior to SRS (normal *vs.* elevated), number of brain metastases (1 *vs.* 2-3), extracranial metastases (no *vs.* yes) and the interval from first diagnosis of melanoma to SRS (≤24 *vs.* >24 months). The patient characteristics of the two dose groups are summarized in Table I. Both groups were balanced with respect to the other seven investigated potential prognostic factors. Median maximum diameters of the irradiated lesions were 8 mm (range: 2-24 mm) in the 20 Gy group and 9 mm (2-25 mm) in the 21-22.5 Gy group, respectively. All but six lesions (four in the 20 Gy group and two in the 21-22.5 Gy group) were located in the supra-tentorial regions.

Statistical analysis. The comparison of the two dose groups with respect to the patients' characteristics was performed with the Chi-square test. The univariate analyses of treatment outcomes were performed with the Kaplan-Meier method and the log-rank test (11). The prognostic factors that were significant in the univariate analysis ($p<0.05$) were additionally evaluated in a multivariate analysis, performed with the Cox hazards proportional model. Patients were followed until death or for median 13 (6-28) months in survivors.

Results

The local control rates of the entire cohort at 6 months and at 12 months following SRS were 89% and 81%, respectively. In the univariate analysis, improved local control of the irradiated metastases was significantly associated with SRS doses of 21-22.5 Gy ($p=0.020$, Figure 1) and normal pre-radiotherapy LDH levels ($p=0.024$). The results of the univariate analysis of local control are summarized in Table II. Both SRS dose ($p=0.007$) and LDH levels ($p=0.018$) maintained significance with the Cox proportional hazards analysis.

Freedom from new metastases at 6 and 12 months following SRS was observed in 55% and 43% of patients, respectively. In the univariate analysis of freedom from new metastases, age ≤65 years ($p=0.049$) and the presence of only one brain metastasis ($p=0.027$) were associated with improved outcome (Table III). The SRS dose was not significantly associated with the development of new brain metastases ($p=0.13$). In the multivariate analyses, neither age ($p=0.17$) nor the number of brain metastases ($p=0.11$) were significantly associated with freedom from new brain metastases.

The overall survival rates of the entire cohort at 6 and 12 months following SRS were 67% and 49%, respectively. In the univariate analysis, improved overall survival was associated with KPS 90-100 ($p<0.001$) and normal pre-radiotherapy LDH levels ($p<0.001$) but not with SRS dose ($p=0.13$) (Table IV).

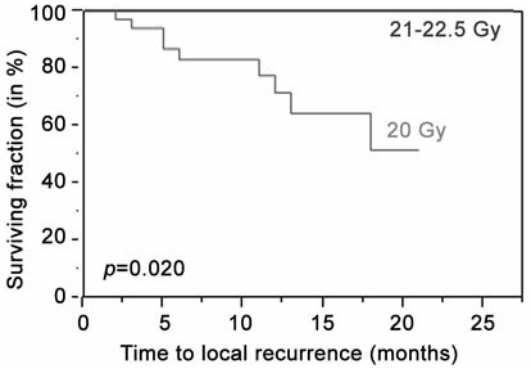

Figure 1. *Comparison of the two dose groups with respect to local control of the irradiated metastases.*

Table III. *Univariate analysis of freedom from new brain metastases.*

	Freedom from new brain metastases at 6 months (%)	Freedom from new brain metastases at 12 months (%)	*p*-Value
SRS dose			
20 Gy	52	31	
21-22.5 Gy	61	61	0.13
Age			
≤65 years	68	48	
>65 years	42	36	0.049
Gender			
Female	59	45	
Male	51	41	0.52
Karnofsky Performance Score			
KPS 70-80	45	40	
KPS 90-100	63	46	0.12
Serum LDH levels			
Normal	63	54	
Elevated	47	23	0.15
Number of brain metastases			
1	68	47	
2-3	34	36	0.027
Extracranial metastases			
No	69	49	
Yes	50	41	0.19
Interval from melanoma diagnosis to SRS			
≤24 months	46	33	
>24 months	61	50	0.16

On multivariate analysis, KPS (p=046) and LDH levels (p=0.006) maintained significance.

Acute or late side-effects grade ≥2 according to Common Terminology Criteria for Adverse Events (CTCAE) 3.0 were not observed in any dose group.

Table IV. *Univariate analysis of overall survival.*

	Overall survival at 6 months (%)	Overall survival at 12 months (%)	*p*-Value
SRS dose			
20 Gy	64	42	
21-22.5 Gy	72	65	0.13
Age			
≤65 years	66	57	
>65 years	68	41	0.33
Gender			
Female	59	41	
Male	76	57	0.87
Karnofsky Performance Score			
KPS 70-80	41	20	
KPS 90-100	84	68	<0.001
Serum LDH levels			
Normal	82	70	
Elevated	42	21	<0.001
Number of brain metastases			
1	67	47	
2-3	67	51	0.64
Extracranial metastases			
No	94	66	
Yes	55	42	0.055
Interval from melanoma diagnosis to SRS			
≤24 months	71	50	
>24 months	64	48	0.62

Discussion

Since survival prognosis of patients with a malignant disease has improved, more patients live long enough to develop brain metastases. Thus, the treatment of brain metastases has become more important. Despite the fact that two small retrospective analyses with 41 and 62 patients with brain metastases from renal cell carcinoma or melanoma have suggested an improved intracerebral control with the addition of WBRT to SRS, many patients with a very limited number of brain metastases from melanoma are treated with SRS-alone (12-13). However, the optimal SRS dose for melanoma patients with 1-3 brain lesions has not been defined. The present study compared two dose groups of 20 Gy and 21-22.5 Gy. According to our results, SRS doses of 21-22.5 Gy resulted in significantly better local control of the irradiated metastases. However, the development of new brain metastases and overall survival were not significantly altered by the SRS dose. In contrast to our findings, SRS doses >20 Gy did not result in better local control rates than 20 Gy in the retrospective study of Shehata *et al*. of 160 patients (14). However, this particular study included a heterogeneous cohort of patients, *i.e.* patients with brain metastases from different primary tumors including more

radiosensitive tumors than melanoma, with patients having newly-diagnosed and patients with recurrent brain metastases, as well as patients treated with SRS-alone or SRS-plus-WBRT. Therefore, a comparison of this study and our present study has substantial limitations.

There is a risk of a hidden selection bias in the current analysis due to the retrospective nature and the relatively small number of patients contained within this work. We have tried to limit biases by including a homogeneous cohort of patients with only one primary tumor type, newly diagnosed lesions and all patients treated with SRS alone. The two dose groups were balanced with respect to the other investigated potential prognostic factors (Table I). Additionally, multivariate analyses were performed to identify and adjust for the influence of the various prognostic factors.

In addition to the SRS dose, improved local control was significantly associated with normal LDH levels prior to SRS. Normal LDH levels and KPS 90-100 were significantly associated with improved overall survival in the corresponding multivariate analysis. A positive association between overall survival and KPS has been previously described for patients receiving Gamma Knife radiosurgery alone for brain metastases from melanoma in a retrospective series of 106 patients (15). The pre-treatment serum LDH level has been recently identified as a significant prognostic factor for overall survival of melanoma patients receiving radiosurgery for brain metastases (16, 17). The fact that our findings agree with those from the literature demonstrate consistency of our results.

In conclusion, our findings suggest that SRS doses of 21-22.5 Gy result in better local control than a dose of 20 Gy, whereas freedom from new brain metastases and overall survival were not significantly different. These results should ideally be confirmed in a prospective randomized trial.

Conflicts of Interest

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

References

1 Sampson JH, Carter JH Jr., Friedman AH and Seigler HF: Demographics, prognosis, and therapy in 702 patients with brain metastases from malignant melanoma. J Neurosurg *88*: 11-20, 1988.

2 Dziggel L, Segedin B, Podvrsnik NH, Oblak I, Schild SE and Rades D: Validation of a survival score for patients treated with whole-brain radiotherapy for brain metastases. Strahlenther Onkol *189*: 364-366, 2013.

3 Dziggel L, Segedin B, Podvrsnik NH, Oblak I, Schild SE and Rades D: A survival score for patients with brain metastases from less radiosensitive tumors treated with whole-brain radiotherapy alone. Strahlenther Onkol *190*: 54-58, 2014.

4 Chiou SM: Survival of brain metastatic patients treated with Gamma Knife radiosurgery alone. Clin Neurol Neurosurg *115*: 276-284, 2013.

5 Mut M: Surgical treatment of brain metastasis: a review. Clin Neurol Neurosurg *114*: 1-8, 2012.

6 Rades D, Küter JD, Gliemroth J, Veninga T, Pluemer A and Schild SE: Resection plus whole-brain irradiation *versus* resection plus whole-brain irradiation plus boost for the treatment of single brain metastasis. Strahlenther Onkol *188*: 143-147, 2012.

7 Rades D, Küter JD, Meyners T, Pluemer A, Veninga T, Gliemroth J and Schild SE: Single brain metastasis: Resection followed by whole-brain irradiation and a boost to the metastatic site compared to whole-brain irradiation plus radiosurgery. Clin Neurol Neurosurg *114*: 326-330, 2012.

8 Aoyama H, Shirato H, Tago M, Nakadawa K, Toyoda T, Hatano K, Kenjyo M, Oya N, Horota S, Snioura H, Kunieda E, Inomata T, Hayakawa K, Katoh N and Kobashi G: Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases. A randomized controlled trial. JAMA *295*: 2483-2491, 2006.

9 Kocher M, Soffietti R, Abacioglu U, Villà S, Fauchon F, Baumert BG, Fariselli L, Tzuk-Shina T, Kortmann RD, Carrie C, Ben Hassel M, Kouri M, Valeinis E, van den Berge D, Collette S, Collette L and Mueller RP: Adjuvant whole-brain radiotherapy *versus* observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. J Clin Oncol *29*: 134-141, 2011.

10 Chang EL, Wefel JS, Hess KR, Allen PK, Lang FF, Kornguth DG, Arbuckle RB, Swint JM, Shiu AS, Maor MH and Meyers CA: Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol *10*: 1037-1044, 2009.

11 Kaplan EL and Meier P: Non parametric estimation from incomplete observations. J Am Stat Assoc 53: 457-481, 1958.

12 Brown PD, Brown CA, Pollock BE, Gorman DA and Foote RL: Stereotactic radiosurgery for patients with "radioresistant" brain metastases. Neurosurgery *62(Suppl 2)*: 790-801, 2008.

13 Hara W, Tran P, Li G, Su Z, Puataweepong P, Adler JR Jr, Soltys SG, Chang SD and Gibbs IC: Cyberknife for brain metastases of malignant melanoma and renal cell carcinoma. Neurosurgery *64(Suppl 2)*: A26-32, 2009.

14 Shehata MK, Young B, Reid B, Patchell RA, St Clair W, Sims J, Sanders M, Meigooni A, Mohiuddin M and Regine WF: Stereotatic radiosurgery of 468 brain metastases < or =2 cm: implications for SRS dose and whole brain radiation therapy. Int J Radiat Oncol Biol Phys *59*: 87-93, 2004.

15 Gaudy-Marqueste C, Regis JM, Muracciole X, Laurans R, Richard MA, Bonerandi JJ and Grob JJ: Gamma-Knife radiosurgery in the management of melanoma patients with brain metastases: a series of 106 patients without whole-brain radiotherapy. Int J Radiat Oncol Biol Phys *65*: 809-816, 2006.

16 Eigentler TK, Figl A, Krex D, Mohr P, Mauch C, Rass K, Bostroem A, Heese O, Koelbl O, Garbe C and Schadendorf D: Number of metastases, serum lactate dehydrogenase level, and type of treatment are prognostic factors in patients with brain metastases of melanoma. Cancer *117*: 1697-1703, 2011.

17 Marcus DM, Lowe M, Khan MK, Lawson DH, Crocker IR, Shelton JW, Melton A, Maynard N, Delman KA, Carlson GW and Rizzo M: Prognostic factors for overall survival after radiosurgery for brain metastases from melanoma. Am J Clin Oncol, epub ahead of print, PMID: 23428955, 2013.

Received May 15, 2014
Revised June 23, 2014
Accepted June 24, 2014