Comparison of Two Dose Levels of Stereotactic Radiosurgery for 1-3 Brain Metastases from Non-small Cell Lung Cancer

DIRK RADES[1], STEFAN HUTTENLOCHER[1], MARKUS DAHLKE[1], DAGMAR HORNUNG[2], OLIVER BLANCK[3], PHAM VAN THAI[4], NGO THUY TRANG[4], MAI TRONG KHOA[4] and STEVEN E. SCHILD[5]

[1]*Department of Radiation Oncology, University of Lübeck, Lübeck, Germany;*
[2]*Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany;*
[3]*CyberKnife Centre Northern Germany, Güstrow, Germany;*
[4]*Nuclear Medicine and Oncology Center, Bach Mai Hospital, Hanoi, Vietnam;*
[5]*Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.*

Abstract. *Aim: Two dose groups of patients treated with stereotactic radiosurgery (SRS) alone for 1-3 brain metastases from non-small cell lung cancer (NSCLC) were compared for outcomes. Patients and Methods: Based on the SRS dose administered to the margins of the brain lesions, 46 patients were assigned to groups treated with 15-18 Gy (n=13) or with 20 Gy (n=33). Seven additional factors were investigated: age (≤58 vs. ≥59 years), gender, Karnofsky performance score (KPS 70-80 vs. 90-100), number of brain metastases (1 vs. 2-3), histology (adenocarcinoma vs. other) extracerebral metastases and interval from NSCLC diagnosis to SRS (≤6 vs. >6 months). Results: Local control rates for 15-18-Gy and 20-Gy groups were 75% and 92% at one year (p=0.043). SRS dose was significant on multivariate analysis (p=0.030). SRS dose was not associated with freedom from new brain metastases (p=0.24) or survival (p=0.37). Conclusion: SRS with 20 Gy resulted in better control of the irradiated metastases than 15-18 Gy did.*

Non-small cell lung cancer (NSCLC) is the most common primary tumor leading to the development of brain metastases in adult patients with cancer (7). Most of these patients have multiple lesions and receive whole-brain radiotherapy (WBRT) alone (2-4). However, a considerable proportion of patients with brain metastases from NSCLC have a very limited number of lesions and may benefit from more intensive local treatment such as stereotactic radiosurgery (SRS) or neurosurgical resection (5, 6). Resection is usually reserved for patients with one or two cerebral lesions (7, 8). Radiosurgery, either alone or in combination with WBRT, is widely used for one to three lesions (5). Several studies have shown that the addition of WBRT to SRS results in better intra-cerebral control but has no significant impact on survival (9, 10). According to one randomized trial of 58 patients, the cost of the positive effect on intracerebral control is worse neurocognitive function (11). In that trial, the mean probability of decline in learning and memory function at four months was 52% in patients receiving SRS-plus-WBRT compared to 24% in patients receiving SRS-alone. In contrast, a prospective study of 92 patients from a randomized trial of 132 patients showed that neurocognitive function was better after WBRT-plus-SRS than after SRS alone at one year and at two years following treatment (12). This finding could be explained by the significantly lower rate of intra-cerebral recurrences after WBRT-plus-SRS (9). Because of these contradictory findings, it is unclear whether patients with a very limited number of brain metastases benefit from the addition of WBRT to SRS. Therefore, a considerable number of these patients are treated with SRS alone. However, when SRS alone is administered, the optimal SRS dose is currently undefined. The optimal dose may vary with respect to the type of primary tumor responsible for the brain metastases. The present study compared two dose levels of SRS alone, 15-18 Gy and 20 Gy, with respect to treatment outcomes in patients with newly-diagnosed brain metastases from NSCLC.

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

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Patients and Methods

Patients and treatment approaches. Forty-six patients treated with SRS alone for 1-3 newly-diagnosed brain metastases from NSCLC between 1999 and 2012 were included in this retrospective study. Forty-three patients received linear accelerator-based radiosurgery and two patients CyberKnife radiosurgery. Two groups were designated according to the dose given to the margin of the

metastases (representing the 78% to 90% isodose level): equivalent (alpha/beta=10 Gy) to 15-18 Gy (n=13) *versus* 20 Gy (n=33). The difference regarding the SRS doses was due to the variation of dose concepts at the contributing centers during the time the patients were treated and the treating physician's opinions.

Both dose groups were compared for local control of the irradiated metastases, freedom from new brain metastases and survival. In addition to the SRS dose, seven further potential prognostic factors were investigated including age (≤58 *vs.* ≥59 years, median age=58 years), gender, Karnofsky performance score (KPS 70-60 *vs.* KPS 90-100), number of brain metastases (1 *vs.* 2-3), histology (adenocarcinoma *vs.* other), extracranial metastases (no *vs.* yes) and the interval from first diagnosis of NSCLC to SRS (≤6 *vs.* >6 months). Patients' characteristics of the dose groups are shown in Table I.

Both dose groups were well balanced with respect to the other seven potential prognostic factors. The median maximum diameters of the lesions were 14 mm (range=2-28 mm) in the 15-18 Gy group and 13 mm (range=3-30 mm) in the 20 Gy group, respectively. All but three lesions, one in the 15-18 Gy group and two in the 20 Gy group, were supratentorial.

Statistical considerations. The univariate analyses of local control, freedom from new brain metastases and survival were performed with the Kaplan–Meier method and the log-rank test (13). The prognostic factors that were significant or showed a trend in the univariate analysis ($p<0.07$) were included in a multivariate analysis performed with the Cox hazards proportional model. Patients were followed-up until death or for a median time of 13 months (range=6-30 months) in patients alive at the last follow-up.

Table I. *Patient characteristics of the dose groups 15-18 Gy and 20 Gy.*

	15-18 Gy No. of patients (%)	20 Gy No. of patients (%)	*p*-Value
Age			
≤58 years	8 (62)	18 (55)	
≥59 years	5 (38)	15 (45)	0.93
Gender			
Female	7 (54)	15 (45)	
Male	6 (46)	18 (55)	0.92
Karnofsky performance score			
KPS 70-80	7 (54)	17 (52)	
KPS 90-100	6 (46)	16 (48)	0.98
Number of brain metastases			
1	8 (62)	18 (55)	
2-3	5 (38)	15 (45)	0.93
Histology			
Adenocarcinoma	9 (69)	24 (73)	
Other	4 (31)	9 (27)	0.97
Extracranial metastases			
No	11 (85)	24 (73)	
Yes	2 (15)	9 (27)	0.82
Interval from NSCLC diagnosis to SRS			
≤6 Months	7 (54)	20 (61)	
>6 Months	6 (46)	13 (39)	0.94

Results

The local control rates of the entire cohort at six months and at one year following SRS were 87% and 79%, respectively. In the univariate analysis, improved local control of the irradiated metastases was significantly associated with a SRS dose of 20 Gy ($p<0.001$) (Figure 1). An interval between NSCLC diagnosis and SRS greater than six months was associated with a trend towards better survival when compared to an interval of six months or less ($p=0.066$). The results of the univariate analysis of local control are summarized in Table II. In the multivariate analysis of local control, the SRS dose [risk ratio (RR)=4.50; 95% confidence interval (CI)=1.16-21.74; $p=0.030$] and the interval between NSCLC diagnosis and SRS (RR=4.34; 95% CI=1.02-22.41; $p=0.047$) were significant.

For the entire cohort, the rates of freedom from new metastases at six months and one year following SRS were 73% and 51%, respectively. In the univariate analysis of freedom from new metastases, none of the investigated potential prognostic factors, including SRS dose ($p=0.24$) (Figure 1), was associated with outcome (Table III). Therefore, a multivariate analysis was not performed for this endpoint.

For the entire cohort, the survival rates at six months and one year following SRS were 70% and 58%, respectively. In the univariate analysis, improved survival was associated with absence of extracranial metastases ($p=0.019$) (Table IV). The SRS dose was not significantly associated with survival ($p=0.37$) (Figure 1). In the multivariate analysis of survival, extracranial metastases (RR=2.55; 95% CI=1.09-5.72; $p=0.032$) maintained significance.

Discussion

Patients with NSCLC represent about 40% of all patients with cancer developing brain metastases (1). Many patients with 1-3 brain metastases receive SRS either alone or in combination with WBRT. Some physicians are hesitant to add WBRT, since a small randomized trial has suggested that this approach is associated with a higher rate of neurocognitive dysfunction than SRS alone (11). When SRS alone had been administered in prior studies, generally, the median SRS dose plus the range of SRS doses were stated and similar to those of the present study. However, the optimal SRS dose is undefined.

In the present study, we compared SRS doses of 15-18 Gy to a dose of 20 Gy given to the margins of the metastatic lesions. Both dose groups were well-balanced with respect to the other seven potential prognostic factors. The median maximum diameters and the corresponding ranges were also similar in both groups. These facts likely reduce the risk of a hidden selection bias. However, due to the retrospective

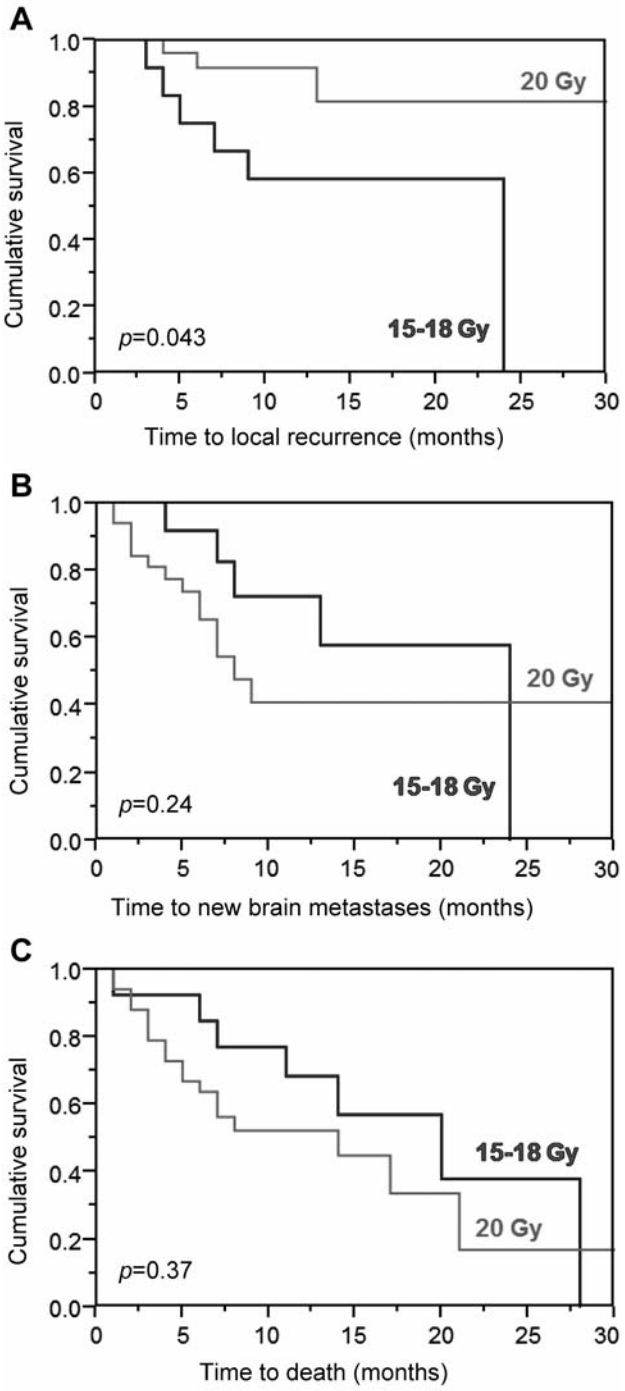

Figure 1. *Comparison of the two dose groups, 15-18 Gy and 20 Gy, with respect to local control of the irradiated metastases (A), freedom from new brain metastases (B) and survival (C).*

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

	Local control at six months (%)	Local control at one year (%)	*p*-Value
SRS dose			
15-18 Gy	75	58	
20 Gy	92	92	0.043
Age			
≤58 years	86	80	
≥59 years	87	76	0.70
Gender			
Female	90	77	
Male	83	83	0.44
Karnofsky Performance Score			
KPS 70-80	84	75	
KPS 90-100	89	81	0.35
Number of brain metastases			
1	86	78	
2-3	87	80	0.94
Histology			
Adenocarcinoma	93	83	
Others	68	68	0.14
Extracranial metastases			
No	90	81	
Yes	75	75	0.27
Interval from NSCLC diagnosis to SRS			
≤6 Months	92	86	
>6 Months	77	66	0.066

design of this study and the relatively small number of patients included, such a bias cannot be completely excluded.

According to the findings of this study, a SRS dose of 20 Gy results in significantly better local control of the irradiated metastases than doses of 15-18 Gy. The finding that a higher SRS dose is associated with better local control agrees with the results of a previous retrospective study of 86 patients (14). In 2002, a retrospective study compared <18 Gy/80%-isodose to ≥18 Gy/80%-isodose for local control of 1 to ≥4 brain metastases from NSCLC. The median follow-up in that study was six months. Local control at six months was 80% in the entire cohort. Local control rates were 57% after <18 Gy and 84% after ≥18 Gy ($p<0.01$). However, 20% of the patients in that study received WBRT in addition to SRS, which may have influenced the results.

In the present study, freedom from new brain metastases and survival were not significantly different in the dose groups. This can be explained by the fact that more patients of the 20 Gy group died from new brain metastases than did those in the 15-18 Gy group. The rates of freedom from new brain metastases at one year were 72% in the 15-18-Gy group and only 41% in the 20-Gy group. The finding that the local control rate in the 20 Gy group is more than two-fold greater than the rate of freedom from new lesions supports the concept that the addition of WBRT to SRS is of value.

Table III. *Univariate analysis of freedom from new brain metastases (distant control).*

	Distant control at six months (%)	Distant control at one year (%)	*p*-Value
SRS dose			
15-18 Gy	92	72	
20 Gy	65	41	0.24
Age			
≤58 years	76	55	
≥59 years	68	43	0.70
Gender			
Female	67	43	
Male	79	61	0.19
Karnofsky Performance Score			
KPS 70-80	77	53	
KPS 90-100	69	48	0.99
Number of brain metastases			
1	73	60	
2-3	73	39	0.29
Histology			
Adenocarcinoma	68	41	
Other	92	62	0.14
Extracranial metastases			
No	78	52	
Yes	64	64	0.33
Interval from NSCLC diagnosis to SRS			
≤6 Months	73	43	
>6 Months	75	64	0.36

Table IV. *Univariate analysis of survival.*

	Survival at six months (%)	Survival at one year (%)	*p*-Value
SRS dose			
15-18 Gy	85	68	
20 Gy	64	52	0.37
Age			
≤58 years	69	61	
≥59 years	70	49	0.25
Gender			
Female	77	62	
Male	63	52	0.91
Karnofsky Performance Score			
KPS 70-80	71	52	
KPS 90-100	68	63	0.33
Number of brain metastases			
1	73	59	
2-3	65	53	0.85
Histology			
Adenocarcinoma	76	65	
Other	54	34	0.074
Extracranial metastases			
No	77	67	
Yes	45	24	0.019
Interval from NSCLC diagnosis to SRS			
≤6 Months	78	64	
>6 Months	58	47	0.29

This conclusion is strengthened by the fact that the higher rate of new brain metastases in the 20-Gy group when compared to the 15-18-Gy group led to a non-significantly worse survival at one year in the 20-Gy group (52% *vs*. 68% in the 15-18 Gy group).

In addition to the SRS dose, improved local control was significantly associated with a longer interval (>6 months) from the first diagnosis of NSCLC and SRS. Improved survival was significantly associated with an absence of extracranial metastases. Patients with adenocarcinoma showed a trend towards improved survival when compared to patients with other histologies in univariate analysis.

A positive association between treatment outcomes and a longer interval from the diagnosis of NSCLC and SRS has been previously reported (15). Extracranial metastases and histology have also been recognized before as prognostic factors for treatment outcomes for both NSCLC and small-cell lung cancer (15-19). The results of the present study agree with the literature.

In summary, this study suggests that a SRS dose of 20 Gy is associated with improved local control when compared to doses of 15-18 Gy. Freedom from new brain metastases and survival were not significantly different in the two groups. The fact that many patients of the 20 Gy group died from new brain metastases despite very good local control of the irradiated metastases supports the addition of WBRT to SRS in terms of achieving optimal control within the brain in spite of controversy.

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 Khuntia D, Brown P, Li J and Mehta MP: Whole-brain radiotherapy in the management of brain metastases. J Clin Oncol *24*: 1295-1304, 2006.

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 Nieder C, Andratschke NH, Geinitz H and Grosu AL: Use of the Graded Prognostic Assessment (GPA) score in patients with brain metastases from primary tumours not represented in the diagnosis-specific GPA studies. Strahlenther Onkol *188*: 692-695, 2012.

4 Rades D, Dziggel L, Segedin B, Oblak I, Nagy V, Marita A, Schild SE, Trang NT and Khoa MT: A new survival score for patients with brain metastases from non-small cell lung cancer. Strahlenther Onkol *189*: 777-781, 2013.
5 Chiou SM: Survival of brain metastatic patients treated with Gamma Knife radiosurgery alone. Clin Neurol Neurosurg *115*: 276-284, 2013.
6 Mut M: Surgical treatment of brain metastasis: a review. Clin Neurol Neurosurg *114*: 1-8, 2012.
7 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.
8 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.
9 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.
10 Rades D, Kueter JD, Hornung D, Veninga T, Hanssens P, Schild SE and Dunst J: Comparison of stereotactic radiosurgery (SRS) alone and whole-brain radiotherapy (WBRT) plus a stereotactic boost (WBRT+SRS) for one to three brain metastases. Strahlenther Onkol *184*: 655-662, 2008.
11 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.
12 Aoyama H, Tago M, Kato N, Toyoda T, Kenjyo M, Hirota S, Shioura H, Inomata T, Kunieda E, Hayakawa K, nakagawa K, Kobashi G and Shirato H: Neurocognitive function of patients with brain metastasis who received either whole-brain radiotherapy plus stereotactic radiosurgery or radiosurgery alone. Int J Radiat Oncol Biol Phys *68*: 1388-1395, 2007.
13 Kaplan EL and Meier P: Non-parametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.
14 Zabel A, Milker-Zabel S, Thilmann C, Zuna I, Rhein B, Wannenmacher M and Debus J: Treatment of brain metastases in patients with non-small cell lung cancer (NSCLC) by stereotactic linac-based radiosurgery: prognostic factors. Lung Cancer *37*: 87-94, 2002.
15 Sheehan JP, Sun MH, Kondziolka D, Flickinger J and Lunsford LD: Radiosurgery for non-small cell lung carcinoma metastatic to the brain: long-term outcomes and prognostic factors influencing patient survival time and local tumor control. J Neurosurg *97*: 1276-1281, 2002.
16 Kress MA, Oermann E, Ewend MG, Hoffman RB, Chaudhry H and Collins B: Stereotactic radiosurgery for single brain metastases from non-small cell lung cancer: progression of extracranial disease correlates with distant intracranial failure. Radiat Oncol *8*: 64, 2013.
17 Kuremsky JG, Urbanic JJ, Petty WJ, Lovato JF, Bourland JD, Tatter SB, Elis TL, McMullen KP, Shaw EG and Chan MD: Tumor histology predicts patterns of failure and survival in patients with brain metastases from lung cancer treated with gamma knife radiosurgery. Neurosurgery *73*: 641-647, 2013.
18 Mariya Y, Sekizawa G, Matsuoka Y, Seki H and Sugawara T: Outcome of stereotactic radiosurgery for patients with non-small cell lung cancer metastatic to the brain. J Radiat Res *51*: 333-342, 2010.
19 Gerdan L, Segedin B, Veninga T, Schild SE and Rades D: Number of involved extracranial organs predicts survival in patients with brain metastasis from small-cell lung cancer. Anticancer Res *33*: 3887-3889, 2013.

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