Radiosurgery with 20 Gy Provides Better Local Contol of 1-3 Brain Metastases from Breast Cancer than with Lower Doses

DIRK RADES[1], STEFAN HUTTENLOCHER[1], VOLKER RUDAT[2], DAGMAR HORNUNG[3], OLIVER BLANCK[4], PHAM CAM PHUONG[5], MAI TRONG KHOA[5], STEVEN E. SCHILD[6] and DOROTHEA FISCHER[7]

Departments of [1]Radiation Oncology, and [7]Gynecology and Obstetrics, University of Lübeck, Lübeck, Germany;
[2]Department of Radiation Oncology, Saad Specialist Hospital, Al Khobar, Saudi Arabia;
[3]Department of Radiation Oncology, University Medical Center Eppendorf, Hamburg, Germany;
[4]CyberKnife Centre Northern Germany, Güstrow, Germany;
[5]Nuclear Medicine and Oncology Center, Bach Mai Hospital, Hanoi, Vietnam;
[6]Department of Radiation Oncology, Mayo Clinic, Scottsdale, AZ, U.S.A.

Abstract. *Aim: To determine the optimal dose of radiosurgery-alone for patients with 1-3 cerebral metastases from breast cancer. Patients and Methods: Patients receiving 20 Gy (n=20) were compared to those receiving 16-18.5 Gy (n=10) for local control, distant brain control and overall survival. Seven other variables were also evaluated. Results: Radiosurgery dose achieved significance on univariate (p=0.002; log-rank and Wilcoxon test) and multivariate analysis (p=0.004) of local control. Twelve-month local control rates were 94% after 20 Gy and 48% after 16-18.5 Gy. On univariate analysis of distant brain control, radiosurgery dose was not a significant factor, with 12-month rates of 73% and 60%, respectively. Regarding overall survival, radiosurgery dose was of borderline significance (p=0.059; Wilcoxon test). Twelve-month overall survival rates were 75% and 40%, respectively. On Cox regression analysis, radiosurgery dose exhibited a trend for improving survival (p=0.10). Conclusion: Radiosurgery with 20 Gy resulted in significantly better local control and led to a trend towards improved overall survival compared to treatment with 16-18.5 Gy.*

Patiens with breast cancer account for about 20% of all patients developing cerebral metastases (1, 2). When compared to other tumor entities associated with such spread, patients with breast cancer have a more favorable survival prognosis (3). Many of these patients have only a very small number of cerebral lesions which are often treated with neurosurgical resection or non-invasive modalities, such as radiosurgery and fractionated stereotactic radiotherapy (4-6). It is not yet clear whether radiosurgery should be supplemented by whole-brain irradiation. The latter has been reported to increase the risk of radiation-related neurocognitive deficits (7). This is particularly important for patients with a more favorable survival prognosis, such as those with breast cancer, because these patients will live long enough to experience such radiation-related late sequelae (3). Therefore, many patients with very few cerebral lesions from breast cancer receive radiosurgery without whole-brain irradiation. When radiosurgery alone is administered, one major goal is long-term control of the treated lesions, which ideally should also translate into longer survival times. However, the optimal dose of radiosurgery for cerebral metastasis from breast cancer is not known. In the present study, two radiosurgery dose levels, 20 Gy and 16-18.5 Gy, were compared for local control of the treated lesions, distant brain control and overall survival.

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

The study included 30 patients with breast cancer who received radiosurgery-alone for primary treatment of one to three cerebral metastases between 2001 and 2013. Radiosurgery was delivered with a CyberKnife (n=6) or a linear accelerator (n=24). The main goal of this study was to compare two dose levels, equivalent to 16-18.5 Gy and 20 Gy (alpha/beta ratio of 10 Gy for tumor cell kill). The doses were prescribed to the margin of the metastatic lesions (isodose level=75-90%). Doses varied according to the concepts preferred by the treating radiation oncologists. The two groups were retrospectively compared for local control of the treated lesions, distant brain control and overall survival. Seven other variables were also analyzed including age (<60 *vs.* ≥60 years, median=59 years), Eastern Cooperative Oncology Group performance score (ECOG 0-

Table I. *Characteristics of the groups 16-18.5 Gy and 20 Gy.*

	Entire cohort N patients (%)	16-18.5 Gy N patients (%)	20 Gy N patients (%)	*p*-Value
Age				
<60 years	17 (57)	5 (50)	12 (60)	
≥60 years	13 (43)	5 (50)	8 (40)	0.92
Performance status				
ECOG 0-1	20 (67)	6 (60)	14 (70)	
ECOG 2	10 (33)	4 (40)	6 (30)	0.93
Number of cerebral lesions				
1	25 (83)	9 (90)	16 (80)	
2-3	5 (17)	1 (10)	4 (20)	0.94
Maximum diameter of all cerebral lesions				
≤10 mm	15 (50)	6 (60)	9 (45)	
>10 mm	15 (50)	4 (40)	11 (55)	0.97
Main location of the cerebral lesions				
Supratentorial	20 (67)	6 (60)	14 (70)	
Infratentorial	10 (33)	4 (40)	6 (30)	0.93
Extra-cranial spread				
No	11 (37)	3 (30)	8 (40)	
Yes	19 (63)	7 (70)	12 (60)	0.93
Time from breast cancer diagnosis to radiosurgery				
≤48 months	15 (50)	5 (50)	10 (50)	
>48 months	15 (50)	5 (50)	10 (50)	1.00

p-Values were derived form the comparison of both groups, which was perfomed with the Chi-square test.

Table II. *Local control of the treated lesions (univariate analysis).*

	Local control		*p*-Value	
	At 6 months (%)	At 12 months (%)	Log-rank test	Wilcoxon test
Radiosurgery dose				
16-18.5 Gy	60	48		
20 Gy	100	94	0.002	0.002
Age				
<60 years	94	82		
≥60 years	75	75	0.55	0.46
Performance status				
ECOG 0-1	90	80		
ECOG 2	78	78	0.73	0.67
Number of cerebral lesions				
1	88	78		
2-3	80	80	0.97	0.97
Maximum diameter of all cerebral lesions				
≤10 mm	87	80		
>10 mm	86	77	0.92	0.97
Main location of the cerebral lesions				
Supratentorial	89	78		
Infratentorial	80	80	0.94	0.81
Extra-cranial spread				
No	82	73		
Yes	89	83	0.49	0.45
Time from breast cancer diagnosis to radiosurgery				
≤48 months	93	79		
>48 months	80	80	0.99	0.90

1 *vs*. ECOG 2), number of cerebral lesions (1 *vs*. 2-3), maximum diameter of all cerebral lesions (≤10 *vs*. >10 mm), extracranial spread (no *vs*. yes) and time from breast cancer diagnosis to radiosurgery (≤48 *vs*. >48 months).

Univariate analyses of three investigated end-points were performed with the Kaplan–Meier method. The variables achieving significance ($p<0.05$) or borderline significance ($p<0.06$) when compared with the log-rank test or the Wilcoxon test were subsequently evaluated in a multivariate manner with the Cox regression analysis.

Results

The comparison of the two dose groups with respect to the distribution of the other seven variables did not reveal any significant difference (Table I). The radiosurgery dose was the only variable that achieved significance ($p=0.002$ with both log-rank test and Wilcoxon test) in the univariate analysis of local control of the treated lesions (Table II). The local control rates at 12 months were 94% after 20 Gy and 48% after 16-18.5 Gy, respectively. In the subsequent Cox regression analysis, the radiosurgery dose was also significantly associated with local control [risk ratio (RR)=13.86; 95% confidence interval (CI)=2.18-270.27; $p=0.004$].

In the univariate analysis of distant brain control, performance status was the only variable that achieved significance ($p=0.041$ with the log-rank test). The radiosurgery dose was not a significant factor (Table III). In the Cox regression analysis, performance status showed a strong trend regarding an association with distant brain control [RR=3.26; 95% confidence interval (CI)=0.91-11.25; $p=0.068$].

With respect to overall survival, the performance status achieved significance with both the log-rank test ($p<0.001$) and the Wilcoxon test ($p<0.001$). The radiosurgery dose achieved borderline significance ($p=0.059$) when the Wilcoxon test was used (Table IV). In the Cox regression analysis of overall survival, the performance status remained significant (RR=7.52; 95% CI=2.49-24.82; $p<0.001$). The radiosurgery dose showed a trend (RR=2.58; 95% CI=0.89-7.94; $p=0.10$).

Table III. *Distant brain control (univariate analysis).*

	Distant control		*p*-Value	
	At 6 months (%)	At 12 months (%)	Log-rank test	Wilcoxon test
Radiosurgery dose				
16-18.5 Gy	60	60		
20 Gy	89	73	0.56	0.29
Age				
<60 years	88	82		
≥60 years	67	44	0.16	0.12
Performance status				
ECOG 0-1	85	75		
ECOG 2	67	50	0.041	0.08
Number of cerebral lesions				
1	79	65		
2-3	80	80	0.67	0.89
Maximum diameter of all cerebral lesions				
≤10 mm	80	73		
>10 mm	79	61	0.73	0.72
Main location of the cerebral lesions				
Supratentorial	84	67		
Infratentorial	70	70	0.71	0.84
Extracranial spread				
No	82	64		
Yes	78	71	0.95	0.96
Time from breast cancer diagnosis to radiosurgery				
≤48 months	86	79		
>48 months	73	56	0.20	0.24

Table IV. *Overall survival (univariate analysis).*

	Survival		*p*-Value	
	At 6 months (%)	At 12 months (%)	Log-rank test	Wilcoxon test
Radiosurgery dose				
16-18.5 Gy	60	40		
20 Gy	90	75	0.19	0.059
Age				
<60 years	88	71		
≥60 years	69	54	0.30	0.18
Performance status				
ECOG 0-1	95	85		
ECOG 2	50	20	<0.001	<0.001
Number of cerebral lesions				
1	76	60		
2-3	100	80	0.84	0.33
Maximum diameter of all cerebral lesions				
≤10 mm	87	80		
>10 mm	73	47	0.10	0.13
Main location of the cerebral lesions				
Supratentorial	80	65		
Infratentorial	80	60	0.85	0.75
Extracranial spread				
No	91	82		
Yes	74	53	0.14	0.13
Time from breast cancer diagnosis to radiosurgery				
≤48 months	87	80		
>48 months	73	47	0.35	0.19

Discussion

The results of anticancer treatment are constantly improving, also due to modern diagnostic procedures and identification of prognostic markers (8-10). Due to more effective treatment of the primary tumors and locoregional lymph nodes, more patients live long enough to experience metastatic disease including cerebral lesions. Breast cancer is the second most frequent tumor type in patients developing cerebral metastases (1). In patients with a limited number of cerebral lesions, radiosurgery, either alone or combined with whole-brain irradiation, is an effective treatment option (5). The benefit of adding whole-brain irradiation is controversial. The combined approach leads to improved control of the disease within the brain, mainly by preventing the development of new lesions (11-12). This is of particular important, as an intra-cerebral recurrence results in decreased neurocognitive function. However, whole-brain irradiation itself can also lead to neurocognitive dysfunction, which was demonstrated in a small randomized trial (7). Therefore, many oncologists are hesitant to give whole-brain irradiation in addition to radiosurgery. This applies particularly to patients with breast cancer, who are known to have a more favorable survival prognosis than patients with cerebral metastasis from other tumor entities (1). Thus, many patients with cerebral metastasis from breast cancer receive radiosurgery without whole-brain irradiation. For this group of patients, the optimal dose of radiosurgery alone is not known. The dose should be sufficiently high to provide long-term local control of the treated lesions but not higher than needed to avoid unnecessary damage to the healthy surrounding tissues.

In the present study, two dose levels, 20 Gy and 16-18.5 Gy, were compared for treatment outcomes. A dose of 20 Gy provided significantly better local control rates of the treated lesions than lower doses. This superiority almost translated into a significant survival benefit. At least a trend towards better overall survival was observed, when a dose of 20 Gy was delivered. In addition to the radiosurgery dose, the performance status was significantly associated with the outcomes of radiosurgery, particularly with overall survival. This finding agrees well with the existing literature reported for patients irradiated for cerebral metastasis from breast cancer. In two retrospective studies of patients with breast cancer receiving whole-brain irradiation alone for metastasis to the brain, the performance status given as Karnofsky performance score proved to be one of the most predominant predictors of overall survival (13-14). This demonstrates consistency of the results of the present study.

In summary, according to the results of this study, radiosurgery-alone with 20 Gy is significantly superior to 16-18.5 Gy with respect to local control of the treated lesions in patients with 1-3 cerebral metastases from breast cancer. Furthermore, 20 Gy showed a trend towards improvement of overall survival. Thus, if radiosurgery-alone is given to these patients, 20 Gy is preferable compared to lower doses.

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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