

Number of cerebral lesions predicts freedom from new brain metastases after radiosurgery alone in lung cancer patients

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Abstract. Numerous patients with few brain metastases receive radiosurgery, either alone or in combination with whole-brain irradiation. The addition of whole-brain irradiation to radiosurgery reduces the rate of intracerebral failures, particularly the development of new cerebral lesions distant from those treated with radiosurgery. Less intracerebral failures mean less neurocognitive deficits. However, whole-brain irradiation itself may lead to a decline in neurocognitive functions. Therefore, a number of physicians have reservations with regard to adding whole-brain irradiation to radiosurgery. Prognostic factors that allow an estimation of the risk of developing new cerebral metastases can facilitate the decision regarding additional whole-brain irradiation. Since primary tumors show a different biology and clinical course, prognostic factors should be identified separately for each primary tumor leading to brain metastasis. The present study investigated 10 characteristics in a series of 98 patients receiving radiosurgery alone for 1-2 cerebral metastases from lung cancer, the most common primary tumor associated with brain metastasis. These characteristics included radiosurgery dose, age, gender, performance status, histology, number of cerebral lesions, maximum total diameter of cerebral lesions, main location of cerebral lesions, extracranial spread and interval from first diagnosis of lung cancer to administration of radiosurgery. On univariate analysis, the number of cerebral lesions prior to radiosurgery (1 vs. 2 lesions) was the only characteristic significantly associated with freedom from new brain metastases ($P=0.002$). In cases of 2 lesions, 73% of patients developed new cerebral lesions within 1 year. On multivariate analysis, the number of brain metastases remained significant

(risk ratio, 2.46; 95% confidence interval, 1.34-4.58; $P=0.004$). Given the high rates of new cerebral lesions in patients with 2 brain metastases, these patients should be strongly considered for additional whole-brain irradiation.

Introduction

Numerous patients with few brain metastases receive neurosurgical resection or radiosurgery, either alone or in combination with whole-brain irradiation. As radiosurgery is similarly effective but less invasive than resection, the use of radiosurgery for the treatment of brain metastases has become more popular (1-3). Previous studies have shown that the addition of whole-brain irradiation can improve intracerebral control when compared with radiosurgery alone (4,5). As an intracerebral recurrence has been reported to be a major cause of neurocognitive deficits, the addition of whole-brain irradiation, which reduces the risk of intracerebral failure, also appears beneficial for the patients from this viewpoint (6,7). However, whole-brain irradiation itself can lead to a decline in neurocognitive function. This important treatment-related late morbidity was found to occur significantly more frequently after radiosurgery plus whole-brain irradiation than after radiosurgery alone at 4 months in a randomized trial of 58 patients with brain metastases from different primary tumors (8). Therefore, radiation oncologists often have reservations with regard to administering whole-brain radiotherapy in addition to radiosurgery (8). As new brain metastases distant from those treated with radiosurgery are the major cause of intracerebral failure, the decision for or against the addition of whole-brain irradiation would be facilitated if the risk of developing such new intra-cerebral lesions could be estimated (4). In order to achieve this goal, knowledge of significant predictors of the risk of developing new brain metastases is mandatory. As the primary tumors leading to brain metastases vary considerably with respect to their biology and course of disease, prognostic factors must be separately identified for each primary tumor associated with metastases to the brain. Of these primary tumors, lung cancer is the most common (~50%). Therefore, the present study focuses on patients receiving radiosurgery alone for a small number of cerebral metastases from lung cancer. The major goal of the study was the identification

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Table I. Univariate analysis of freedom from new brain metastases.

Parameter	Freedom from new brain metastases, %			P-value
	At 6 months	At 12 months	At 24 months	
Radiosurgery dose, Gy				
<20 (n=38)	59	52	46	0.98
≥20 (n=60)	75	45	28	
Age, years				
≤59 (n=49)	70	44	39	0.54
≥60 (n=49)	67	54	34	
Gender				
Female (n=47)	73	49	25	0.99
Male (n=51)	63	48	43	
ECOG performance score				
0-1 (n=64)	70	54	43	0.16
2 (n=34)	64	33	16	
Histology				
Adenocarcinoma (n=62)	67	42	23	0.23
Others (n=36)	70	63	53	
Number of cerebral lesions				
1 (n=61)	73	62	41	<0.01
2 (n=37)	60	27	15	
Max. diameter of cerebral lesions, mm				
≤18 (n=50)	75	53	44	0.11
>18 (n=48)	60	43	19	
Main location of cerebral lesions				
Supratentorial (n=84)	68	46	25	0.19
Infratentorial (n=14)	71	71	71	
Extracranial spread				
No (n=64)	74	50	40	0.19
Yes (n=34)	57	49	0	
Interval from lung cancer diagnosis to radiosurgery, months				
≤11 (n=51)	79	49	44	0.31
≥12 (n=47)	58	47	23	

ECOG, Eastern Cooperative Oncology Group.

of independent predictors regarding the development of new cerebral metastases in this particular group of cancer patients.

Patients and methods

Patients. A total of 98 patients receiving radiosurgery alone for 1-2 brain metastases of >4 cm in size from lung cancer at the University of Lübeck (Lübeck, Germany) or the University Medical Center Eppendorf (Hamburg, Germany) between January 2000 and 2014, were retrospectively analyzed with respect to freedom from new cerebral lesions. All patients were diagnosed with stage IV lung cancer, according to the American Joint Committee on Cancer staging system (9). The present study was approved by the ethics committee of the University of Lübeck

(Lübeck, Germany; reference no. 13-038A and 14-273A). Radiosurgery was performed with photon beams from a linear accelerator (Siemens Medical Systems, Concord, CA, USA; Varian Medical Systems, Palo Alto, CA, USA).

Characteristics. A total of 10 characteristics were evaluated for associations with freedom from new brain metastases. These characteristics consisted of the radiosurgery dose (<20 vs. ≥20 Gy; doses prescribed to the 80-90% isodose level) (10), age (≤59 vs. ≥60 years; median age, 59 years), gender, Eastern Cooperative Oncology Group performance score (0-1 vs. 2), histology (adenocarcinoma vs. others), number of cerebral lesions (1 vs. 2), maximum total diameter of all cerebral lesions (≤18 vs. >18 mm; median, 18 mm), main location of

the cerebral lesions (supratentorial vs. infratentorial), extracranial spread (no vs. yes), and the interval between the first diagnosis of lung cancer and the administration of radiosurgery (≤ 11 vs. ≥ 12 months; median interval, 11 months).

Statistical analysis. For the univariate analysis of freedom from new cerebral lesions, the Kaplan-Meier method and the log-rank test were used (11). Characteristics that achieved significance were additionally analyzed in a multivariate manner with the Cox proportional hazards regression analysis. The statistical analyses were performed with the JMP software, version 10 (SAS Institute Inc., Cary, NC, USA). $P < 0.05$ was used to indicate a statistically significant difference.

Results

The results of the univariate analysis of freedom from new cerebral lesions are shown in Table I. The only characteristic that was found to be significantly associated with freedom from new brain metastases was the number of cerebral lesions prior to radiosurgery ($P = 0.002$). If 2 brain metastases were present, only 27 and 15% of patients were free from new cerebral lesions at 12 and 24 months post-radiosurgery, respectively. According to the subsequent multivariate analysis, the number of brain metastases prior to radiosurgery was an independent prognostic factor (risk ratio, 2.46; 95% confidence interval, 1.34-4.58; $P = 0.004$).

Discussion

Brain metastases from lung cancer have become significant areas of focus in oncology research, including in genomic studies, and in the development of modern radiotherapy techniques and novel anticancer agents (12-14). A number of patients with few cerebral metastases receive radiosurgery, either alone or in combination with whole-brain irradiation. It is not yet clear whether the addition of whole-brain irradiation provides significant benefits for the patients. Additional whole-brain irradiation results in improved intracerebral control when compared with radiosurgery alone. The intracerebral control rates at 1 year were 66% after radiosurgery plus whole-brain irradiation and 51% after radiosurgery alone ($P = 0.015$), respectively, in a retrospective study of 144 patients from Germany and the Netherlands who presented with brain metastases from various primary tumor types (5). In a randomized trial of 132 patients from Japan, the intracerebral failure rates at 1 year were 47% after radiosurgery plus whole-brain irradiation and 76% after radiosurgery alone ($P < 0.001$) (4). Furthermore, in a prospective study from Japan re-evaluating 92 patients from the randomized trial, the rates of preservation of the neurocognitive function at 1 and 2 years were 79 and 79%, respectively, following radiosurgery plus whole-brain irradiation compared with 53 and 43%, respectively, following radiosurgery alone (7). In contrast to these results, a small randomized study ($n = 58$) found that a significant decline in neurocognitive functions was more frequent at 4 months after radiosurgery combined with whole-brain irradiation compared with after radiosurgery alone (8). However, this trial has been criticized, as

neurocognitive functions were not evaluated at 12 months, when intracerebral control was significantly worse in the radiosurgery alone group (27 vs. 73%; $P < 0.001$). Worse intracerebral control would likely have had a negative impact on the neurocognitive functions (6,7). Despite the aforementioned study results, a number of physicians have reservations regarding additional whole-brain irradiation. This hesitation is also supported the fact that a retrospective study and a randomized trial showed that improvement in intracerebral control did not translate into significantly better survival (4,5). The decision to add whole-brain irradiation to radiosurgery would be made easier in patients with a high risk of developing new cerebral metastases outside those treated with radiosurgery. This risk could be estimated if significant prognostic factors were identified.

In the current study, 10 factors were evaluated for significant associations with freedom from new brain metastases in lung cancer patients. The number of cerebral lesions was the only factor that had such an association. Patients with 2 lesions had a significantly greater risk than those patients with only a single lesion. Since the rates of freedom from new brain metastases at 1 and 2 years after radiosurgery alone were quite low in these patients, they are good candidates for the addition of whole-brain irradiation to radiosurgery. This will also likely apply to patients with > 2 cerebral lesions. In contrast to patients with 1 or 2 cerebral lesions from lung cancer, those patients with ≥ 3 lesions from lung cancer already receive radiosurgery plus whole-brain irradiation as the standard treatment procedure in the institutions that contributed to the present study. Therefore, patients with ≥ 3 lesions were not available for the study.

In conclusion, freedom from new brain metastases was significantly associated with the number of cerebral lesions (1 vs. 2) prior to radiosurgery. Given the high rates of new cerebral lesions in patients with 2 brain metastases, these patients should be strongly considered for the addition of whole-brain irradiation to radiosurgery.

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