

## Pre-operative Seizures in Patients With Single Brain Metastasis Treated With Resection Plus Whole-Brain Irradiation and a Boost

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**Abstract.** *Background/Aim:* Seizures can be the initial symptom of brain metastases. This study investigated pre-treatment seizures in patients with a single lesion. *Patients and Methods:* Pre-operative seizures were analyzed in 104 patients with a single brain metastasis receiving resection plus whole-brain irradiation and a boost. Prevalence of seizures, risk factors and associations with survival (OS) were evaluated. *Results:* Thirty patients (34.6%) had seizures prior to neurosurgery. Significant associations between seizures and investigated characteristics were not found. However, age  $\leq 61$  years showed a trend ( $p=0.117$ ) for increased incidence of seizures. Time from diagnosis of malignancy until neurosurgery  $>12$  months was significantly associated with improved OS on univariate analysis ( $p=0.003$ ). Trends for a positive association with OS were found for no seizures ( $p=0.054$ ), female gender ( $p=0.066$ ) and breast cancer ( $p=0.098$ ). On multivariate analysis, time until neurosurgery  $>12$  months was independently associated ( $p=0.019$ ) with better OS, and seizures showed a trend ( $p=0.119$ ) for improved OS. *Conclusions:* Considering the high prevalence of seizures in this cohort, regular screening and monitoring of these patients appears reasonable. This applies particularly to patients aged  $\leq 61$  years.

Metastasis to the brain represents a relatively common situation in adult cancer patients and is often associated with serious symptoms impairing quality of life (1, 2). With respect to the number of lesions, patients can be classified as having single brain metastasis, oligo-metastatic disease (usually up to three lesions) or multiple brain metastases (usually more than three lesions) (2). A serious problem in patients with brain metastasis is the occurrence of seizures (3). Seizures can occur prior to the start of treatment and even be the initial symptom leading to the diagnosis of brain metastasis. Pre-treatment seizures appear much more common than seizures occurring during treatment or follow-up (3). Moreover, occurrence of seizures may be associated with the number of intracerebral lesions. However, the data reported appear conflicting. In the study of Wu *et al.*, pre-operative seizures were significantly associated with more than two intracerebral lesions, whereas in the study of Wolpert *et al.*, no significant association between pre-operative seizures and the number of brain metastases was observed (4, 5). Nevertheless, in the study of Wolpert *et al.*, single brain metastasis was the most important risk factor for seizures in non-operated patients (5). It appears reasonable to perform separate studies in patients with single, limited numbers or multiple intracerebral lesions, as well as in patients treated with or without neurosurgical resection to properly define the role of seizures in patients with brain metastasis. This study focused on patients with a single intracerebral lesion who received resection of their metastasis followed by whole-brain irradiation (WBI) and a boost to the resection cavity.

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**Key Words:** Brain metastasis, single lesion, seizures, neurosurgical resection, whole-brain irradiation, boost dose.

### Patients and Methods

*Patients.* This retrospective study investigated the role of seizures prior to neurosurgery in a series of 104 patients with a single brain metastasis from an anonymized database, who were treated with neurosurgical resection followed by WBI and a boost dose to the

Table I. Patient characteristics.

Characteristic		Number of patients (%)
Seizures prior to neurosurgery	No	68 (65)
	Yes	36 (35)
Age	≤61 Years	53 (51)
	≥62 Years	51 (49)
Gender	Female	46 (44)
	Male	58 (56)
Karnofsky performance score	≤70	24 (23)
	≥80	80 (77)
Primary tumor type	Breast cancer	16 (15)
	Lung cancer	51 (49)
	Colorectal cancer	10 (10)
	Other tumors	27 (26)
Extracranial metastatic spread	No	85 (82)
	Yes	19 (18)
Time from diagnosis of malignancy until neurosurgery	≤12 Months	52 (50)
	>12 Months	52 (50)

resection cavity between 1999 and 2017. WBI was performed either with 20 Gy in 5 fractions ( $n=66$ ) or 30 Gy in 10 fractions ( $n=38$ ). The boost included the additional delivery of one of the following: 15 Gy in 5 fractions ( $n=53$ ), 10 Gy in 5 fractions ( $n=36$ ), 20 Gy in 10 fractions ( $n=7$ ), 9 Gy in 3 fractions ( $n=5$ ) or 6 Gy in 2 fractions ( $n=3$ ). The study was approved by the corresponding Ethics Committee at the University of Lübeck, Lübeck, Germany on the 3<sup>rd</sup> of April 2020 (reference number 20-120A). Three issues were evaluated in this study: the prevalence of seizures prior to neurosurgery, potential risk factors for seizures, and a potential association between seizures and overall survival (OS).

**Variables and statistical analyses.** Six pre-treatment characteristics (Table I), including age (≤61 vs. ≥62 years; median age=61 years), gender, Karnofsky performance score (≤70 vs. ≥80; median performance score=80), type of primary tumor (breast cancer, lung cancer, colorectal cancer and other types), extracranial metastatic spread (no vs. yes) and time from diagnosis of malignancy until neurosurgery (≤12 vs. >12 months; median time=12.5 months), were investigated for associations with seizures prior to neurosurgery using the Chi-square test. All  $p$ -values <0.05 were rated significant, and  $p$ -values <0.12 indicated a trend.

These six characteristics and seizures prior to neurosurgery (no vs. yes) were also evaluated with respect to OS. Time to death was referenced from the day of neurosurgical resection. For univariate analyses of OS, we used the Kaplan-Meier method and the log-rank test. Characteristics being significant ( $p<0.05$ ) or showing a trend ( $p<0.12$ ) were additionally included in Cox proportional hazard ratio to investigate those characteristics for independence. The software used for performing statistical analyses was JMP 14 (SAS institute inc., Cary, NC, U.S.A.).

## Results

In the cohort of 104 patients, 36 patients had seizures prior to neurosurgery corresponding to a prevalence of 34.6%. Twenty-six of these patients had seizures without other

Table II. Associations between the investigated characteristics and occurrence of seizures prior to neurosurgery.

Characteristic	Patients with seizures (%)	$p$ -Value
Age		
≤61 Years	23 (43.3)	0.117
≥62 Years	13 (25.5)	
Gender		
Female	17 (37.0)	0.297
Male	19 (32.8)	
Karnofsky performance score		
≤70	5 (20.8)	0.192
≥80	31 (38.8)	
Primary tumor type		
Breast cancer	5 (31.3)	0.703
Lung cancer	15 (29.4)	
Colorectal cancer	5 (50.0)	
Other tumors	11 (40.7)	
Extracranial metastatic spread		
No	26 (30.6)	0.143
Yes	10 (53.6)	
Time from diagnosis of malignancy until neurosurgery		
≤12 Months	15 (28.8)	0.317
>12 Months	21 (40.4)	

symptoms, and 10 patients had at least one other symptom including motor deficits, dysarthria, cognitive deficits and headache. A significant association between occurrence of pre-operative seizures and one of the six investigated characteristics was not found. A trend was shown for age ≤61 years ( $p=0.117$ ). The results of the investigation with respect to potential associations between patient characteristics and seizures prior to neurosurgery are summarized in Table II.

When investigating the potential associations of the seven characteristics including pre-operative seizures with OS, the time from diagnosis of malignancy until neurosurgery achieved significance ( $p=0.003$ ) on univariate analysis (Table III). A time period of >12 months was associated with improved OS. In addition, trends for better OS were found for lack of seizures prior to neurosurgery ( $p=0.054$ , Figure 1), female gender ( $p=0.066$ ) and breast cancer ( $p=0.098$ ). These four characteristics were subsequently evaluated for independence with a Cox proportional hazard model (Table IV). In this multivariate analysis, a time from diagnosis of malignancy until neurosurgery of >12 months was significant for improved OS ( $p=0.019$ ), and seizures prior to neurosurgery showed a trend for better OS ( $p=0.119$ ).

## Discussion

Of patients developing brain metastases, those with a single lesion generally have better prognoses than patients with

Table III. Survival rates up to 24 months following neurosurgical resection (univariate analysis).

Characteristic		At 6 months (%)	At 12 months (%)	At 18 months (%)	At 24 months (%)	p-Value*
Seizures prior to neurosurgery	No	75	57	44	34	0.054
	Yes	81	72	58	58	
Age	≤61 Years	77	65	50	43	0.415
	≥62 Years	76	58	47	41	
Gender	Female	83	69	60	53	0.066
	Male	72	56	40	34	
Karnofsky performance score	≤70	67	44	38	38	0.198
	≥80	80	67	53	44	
Primary tumor type	Breast cancer	88	81	66	57	0.098
	Lung cancer	75	52	49	39	
	Colorectal cancer	40	40	30	30	
	Other tumors	89	76	44	44	
Extracranial metastatic spread	No	81	65	50	42	0.689
	Yes	58	46	46	46	
Time from diagnosis of malignancy until neurosurgery	≤12 Months	69	46	33	23	<b>0.003</b>
	>12 Months	85	77	64	60	

\*The p-values were obtained from the the log-rank test and refer to the entire period of follow up. Bold value indicates statistical significance.

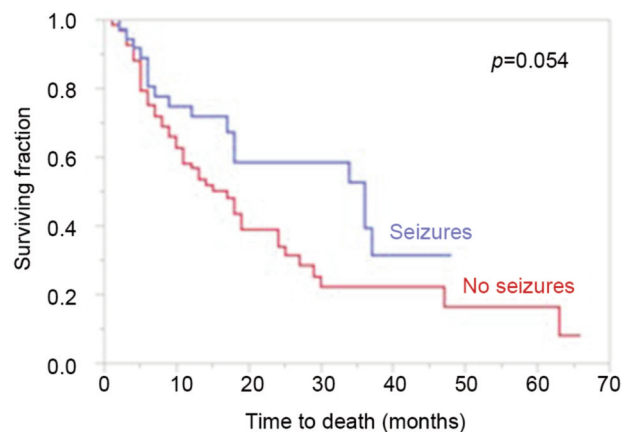


Figure 1. Kaplan-Meier curves related to seizures (n=36) or no seizures (n=68) prior to neurosurgery.

multiple lesions (2). Several options exist for the treatment of single brain metastasis including neurosurgery, radiosurgery, WBI and combinations of these modalities. In 1987, a retrospective study of 85 patients compared resection alone to resection plus WBI and found that the combined approach resulted in significantly better 1-year local control and median survival (6). In 1998, a randomized trial of 95 patients was published that found significantly better local control and intracerebral control at 1 year for resection plus WBI when compared to resection alone (7). These results did not lead to improved median OS, although patients receiving WBI were less likely to die of neurologic causes. However, the addition of WBI to

Table IV. Multivariate analysis of survival using the Cox proportional hazard model.

Characteristic	Hazard ratio	95% Confidence interval	p-Value
Seizures prior to neurosurgery	1.56	0.89-2.86	0.119
Gender	1.25	0.72-2.21	0.435
Primary tumor type	1.05	0.96-1.13	0.269
Time from diagnosis of malignancy until neurosurgery	1.95	1.11-3.47	<b>0.019</b>

Bold value indicates statistical significance.

resection can lead to a significant increase of post-treatment cognitive deficits, which was reported for patients treated with radiosurgery plus WBI for 1-3 brain metastases (8, 9). With modern approaches including hippocampus-sparing WBI and administration of memantine, the risk of cognitive decline can be significantly reduced (10, 11). Thus, resection plus WBI can be considered an appropriate treatment for patients with a single brain metastasis. The outcomes after resection plus WBI can be further improved with the addition of a radiation boost to the resection cavity. In a retrospective study of 195 patients with a single lesion, resection plus WBI and a boost was superior to resection plus WBI without a boost with respect to local control of the resected metastasis (12). OS rates, however, were not significantly different. Local control is an important

endpoint, since an intracerebral recurrence is often associated with neuro-cognitive deficits and impairment of the patients' quality of life (13-15). Therefore, resection plus WBI and a radiation boost appears preferable to resection plus WBI without a boost.

The present study focused on patients with a single lesion who received the treatment regimen including a radiation boost. It evaluated the prevalence of pre-operative seizures, risk factors for occurrence of seizures and associations with OS. The prevalence of preoperative seizures was 34.6%, which was within but on the top end of the range of 12-35% reported in the literature (3, 5, 16, 17). This comparably high prevalence may be explained to a certain extent by the fact that many patients (49%) in our study were lung cancer patients. It has been previously shown by Wolpert *et al.* that patients with lung cancer have increased incidence of seizures (5). Moreover, in the review article of Ruda *et al.*, lung cancer patients had the second highest prevalence of seizures of all primary tumor types (3).

In addition to the prevalence of seizures, the present study aimed to identify risk factors for pre-operative seizures. For none of the investigated characteristics, a significant association with the occurrence of seizures was observed. However, a trend was found for younger age. This finding agrees with the results of a previous study of 286 patients undergoing resection for brain metastases that also showed an inverse correlation between age and seizures prior to neurosurgery (18). The present study also investigated potential associations between pre-operative seizures and OS. In both univariate and multivariate analyses, trends for a positive correlation between seizures and OS were found. Such a correlation was not yet reported for patients with brain metastases but for patients with low-grade and high-grade gliomas (19, 20). In addition to pre-operative seizures, a significant correlation was found between OS and the time from the diagnosis of the malignancy until neurosurgical resection of the brain metastasis. The prognostic impact of the interval between tumor diagnosis and treatment for brain metastases was previously identified in a cohort of 1,085 patients receiving WBI alone (21). This characteristic was also included in a validated survival score for patients irradiated for brain metastases (21, 22). This demonstrates consistency between the present study and previous data. However, the present study was performed in a retrospective cohort of patients. Thus, a risk of a hidden selection bias exists, which needs to be considered when taking note of and interpreting our results.

In conclusion, considering the high prevalence of seizures in this cohort, regular screening and monitoring of these patients appears reasonable. This applies particularly to patients aged  $\leq 61$  years. Moreover, seizures showed a trend for a positive association with OS. These findings contribute to the understanding of the role of preoperative seizures in patients with a single brain metastasis.

## Conflicts of Interest

The Authors state that there are no conflicts of interest related to this study.

## Authors' Contributions

All Authors participated in the design of the study. D.R. and J.W. provided the data that were analyzed and interpreted by D.R. and S.E.S. D.R. and S.E.S. drafted the manuscript, which was reviewed and finally approved by the other Authors.

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