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Potential Impact of the Interval Between Imaging and Whole-brain Radiotherapy in Patients With Relatively Favorable Survival Prognoses

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Abstract. *Background/Aim: The interval between diagnostic imaging and whole-brain radiotherapy (WBRT) had no significant impact on survival in our previous study of WBRT for brain metastases. Since median survival time was only 2 months, a potentially negative impact by delaying treatment could have been missed. Therefore, we performed an additional analysis of patients surviving at least 4 months following irradiation. Patients and Methods: The interval between diagnosis of brain metastases and WBRT and ten other factors were retrospectively analyzed for survival in 191 patients surviving 4 months or longer following WBRT. Results: On univariate analyses, Eastern Cooperative Oncology Group (ECOG) performance score of 0-1, 1-3 brain metastases and absence of extra-cerebral metastases were significantly associated with longer survival, whereas the interval from diagnostic imaging to WBRT was not. On multivariate analysis, ECOG performance score remained significant, and extra-cerebral metastases showed a trend towards a longer survival. Conclusion: The interval between diagnostic imaging and WBRT didn't have a significant impact on patients surviving 4 months or longer. Depending on the need for symptom relief, WBRT may be postponed for very important reasons such as obtaining a multidisciplinary tumor board decision or definitive histology.*

Many cancer patients with brain metastases have multiple lesions and receive whole-brain radiotherapy (WBRT), either alone or in combination with local therapies including resection and radiosurgery (1). WBRT alone can also be a reasonable option for patients with very few cerebral lesions, if they have a poor performance score or a high comorbidity-index (2). When patients are assigned to WBRT, treatment is generally recommended to start as soon as reasonably possible, particularly in case of metastases-related debilitating symptoms (3). However, an early start of radiotherapy is not always reasonable. If discussion of the entire treatment concept in a multidisciplinary tumor board or a definitive histology are lacking but considered mandatory, a delay of up to a very few weeks may be justified. In a previous study, we have investigated whether such a delay would result in worse survival (4). According to the findings of that previous study, which compared three intervals between diagnostic imaging identifying the brain metastases and the start of WBRT (0-7 days, 8-14 days and 15-21 days), a delay of up to 21 days had no impact on survival. However, one unanswered question was whether a possible impact of the interval between diagnostic imaging and WBRT on survival may have been missed, because the median survival time was only 2 months and possibly too short to detect a significant impact (4). Therefore, we conducted this additional analysis limited to patients who survived at least 4 months following WBRT.

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Key Words: Whole-brain radiotherapy (WBRT), diagnostic imaging, treatment delay, survival prognosis.

Patients and Methods

The data of 191 patients who had been treated with WBRT alone for brain metastases between 2008 and 2017 and survived for at least 4 months following treatment, were retrospectively evaluated. The cerebral lesions were diagnosed with magnetic resonance imaging (MRI) in 135 patients or computed tomography (CT) in 56 patients.

The potential impact of the interval between the diagnostic imaging and WBRT (0-7 days *versus* 8-14 days *versus* 15-21 days), and of 10 additional characteristics on survival following WBRT was investigated. The distributions of these 10 characteristics related

Table I. *Patient characteristics related to the interval between imaging and WBRT.*

Factor	0-7 days N patients (%)	8-14 days N patients (%)	15-21 days N patients (%)
Gender			
Female (N=90)	40 (43)	37 (53)	13 (48)
Male (N=101)	54 (57)	33 (47)	14 (52)
Age			
≤65 years (N=101)	49 (52)	38 (54)	14 (52)
≥66 years (N=90)	45 (48)	32 (46)	13 (48)
ECOG performance score			
0-1 (N=133)	64 (68)	49 (70)	20 (74)
2 (N=51)	26 (28)	18 (26)	7 (26)
3-4 (N=7)	4 (4)	3 (4)	0 (0)
Primary tumor type			
Breast cancer (N=27)	16 (17)	8 (11)	3 (11)
Non-small cell lung cancer (N=92)	38 (40)	38 (54)	16 (59)
Small cell lung cancer (N=36)	18 (19)	13 (19)	5 (19)
Malignant melanoma (N=5)	2 (2)	2 (3)	1 (4)
Colorectal cancer (N=8)	6 (6)	2 (3)	0 (0)
Cancer of unknown primary (N=3)	1 (1)	1 (1)	1 (4)
Other tumors (N=20)	13 (14)	6 (9)	1 (4)
Controlled primary tumor			
No (N=103)	48 (51)	37 (53)	18 (67)
Yes (N=45)	24 (26)	17 (24)	4 (15)
Unknown (N=43)	22 (23)	16 (23)	5 (19)
Number of brain metastases			
1-3 (N=70)	25 (27)	31 (44)	14 (52)
≥4 (N=121)	69 (73)	39 (56)	13 (48)
Type of imaging			
Magnetic resonance imaging (N=135)	62 (66)	52 (74)	21 (78)
Computed tomography (N=56)	32 (34)	18 (26)	6 (22)
Metastases outside the brain			
No (N=33)	9 (10)	17 (24)	7 (26)
Yes (N=145)	80 (85)	45 (64)	20 (74)
Unknown (N=13)	5 (5)	8 (11)	0 (0)
WBRT regimen			
30 Gy in 10 fractions (N=55)	23 (24)	24 (34)	8 (30)
35-37.5 Gy in 14-15 fractions (N=128)	70 (74)	41 (59)	17 (63)
40 Gy in 20 fractions (N=8)	1 (1)	5 (7)	2 (7)
Completion of WBRT			
No (N=5)	2 (2)	2 (3)	1 (4)
Yes (N=186)	92 (98)	68 (97)	26 (96)

WBRT: Whole-brain radiotherapy; ECOG: Eastern Cooperative Oncology Group.

to the three intervals are summarized in Table I. For univariate analyses, the Kaplan–Meier method and the log-rank test were applied (5). Characteristics showing a significant association with survival ($p<0.05$) were further analyzed for independence in a multivariate manner with a Cox regression model.

Results

The median survival time of the 191 patients was 9 months; the 6-months and 12-month survival rates were 65% and 26%. On univariate analyses, an ECOG performance score of 0-1 ($p<0.001$), a limited number of 1-3 brain metastases ($p=0.010$) and absence of extra-cerebral metastases ($p=0.015$) showed significant associations with longer survival (Table II). In contrast, the interval between diagnostic imaging of brain metastases and WBRT was not significantly associated with survival ($p=0.50$, Figure 1).

In the additional Cox regression analysis, a better ECOG performance score remained significantly associated with improved survival (risk ratio [RR]=1.61; 95% confidence interval [CI]=1.18-2.16; $p=0.003$), absence of extra-cerebral metastases showed a trend towards a longer survival (RR=1.50; 95%CI=0.99-2.38; $p=0.058$), and for the number of brain metastases no significant association with survival was found (RR=1.11; 95%CI=0.98-1.26; $p=0.11$).

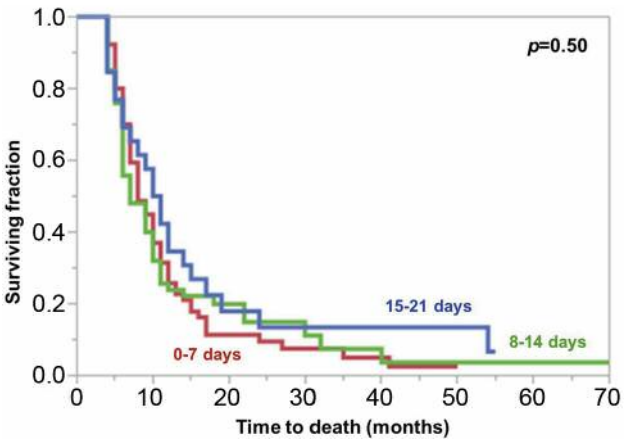

Figure 1. *Comparison of the three investigated intervals between imaging and WBRT for survival. The p-value was calculated using the log rank test.*

Discussion

Personalization of anti-cancer treatment requires adjustments to individual patient's personal situation and individual prognosis, particularly in the palliative care of brain metastases (6-15). A personalized treatment approach should be designed by physicians from different disciplines, ideally within a multidisciplinary tumor board. Moreover, to select the optimal treatment regimen, definitive histology should be available. The start of the treatment for brain metastases may be postponed for days to very few weeks while waiting for obtaining pathology or decision by a tumor board or patient. An important question is, whether such a delay would decrease patients' expected survival. To address this question, we performed a previously reported study of 573 patients treated with WBRT alone (4). Three intervals between imaging leading to the diagnosis of brain metastasis and the start of WBRT, *i.e.* 0-7 days, 8-14 days and 15-21 days, were compared with respect to survival. The 6-month survival rates were 22%, 20% and 22%, respectively, and the 12-month survival rates 8%, 9% and 11%, respectively (p=0.84). Thus, the interval between imaging and WBRT had no significant impact on survival. However, the median survival time in that study was quite short (2 months), and a potential negative impact of this delay may have been missed (4). Therefore, we also performed this study in patients who survived at least 4 months following WBRT. The median survival times of these patients were more favorable than in the previous study, *i.e.* 9 months *versus* 2 months (4). A median survival time of 9 months can be considered favorable, since it was even longer than that in the favorable-prognosis group (7.1 months) of the widely accepted recursive partitioning analysis classification (16). The worst prognostic group of the RPA classification had a median survival time of 2.3 months, which was similar to the 2 months of our previous study. The comparison with the RPA classification demonstrates that the present study was performed in a cohort of patients with brain metastases and a relatively favorable survival prognosis, as intended (16).

The results of the present study suggest that for patients with relatively favorable survival prognoses, the interval between

Table II. *Survival rates following whole-brain radiotherapy.*

Factor	At 6 months (%)	At 12 Months (%)	p-Value
Interval between diagnosis of brain metastases and WBRT			
0-7 days	70	26	
8-14 days	56	24	
15-21 days	69	35	0.50
Gender			
Female	63	29	
Male	66	24	0.95
Age			
≤65 years	68	28	
≥66 years	61	25	0.08
ECOG performance score			
0-1	71	31	
2	54	18	
3-4	29	0	**<0.001**
Primary tumor type			
Breast cancer	69	25	
Non-small cell lung cancer	68	36	
Small cell lung cancer	64	16	
Malignant melanoma	60	40	
Colorectal cancer	67	0	
Cancer of unknown primary	63	0	
Other tumors	47	14	0.07
Controlled primary tumor			
No	64	27	
Yes	68	25	0.48
Number of brain metastases			
1-3	69	33	
≥4	63	23	**0.010**
Type of imaging			
Magnetic resonance imaging	64	27	
Computed tomography	67	25	0.81
Metastases outside the brain			
No	75	50	
Yes	64	23	**0.015**
WBRT regimen			
30 Gy in 10 fractions	58	25	
35-37.5 Gy in 14-15 fractions	67	26	
40 Gy in 20 fractions	75	38	0.21
Completion of WBRT			
No	65	27	
Yes	65	26	0.33
Entire cohort	65	26	

WBRT: Whole-brain radiotherapy; ECOG: Eastern Cooperative Oncology Group; bold values=significant p-values.

diagnostic imaging and WBRT had no significant impact on survival at 6 and 12 months following WBRT. Therefore, for important reasons such as obtaining a decision from a multidisciplinary tumor board or definitive histology, a delay in the start of WBRT for some days appears possible without a significant decrement in survival. However, the necessity of controlling burdensome metastases-related symptoms such as headache, nausea, vomiting, seizures and disturbances of vision or hearing should be considered when postponing WBRT (1, 6). Corticosteroids, mainly dexamethasone, may help to control the symptoms and bridge the time until WBRT is started.

In summary, similar to the previous study, the interval between diagnosing of brain metastases by imaging and the start of WBRT for up to 21 days had no significant impact on survival also in patients with a relatively favorable survival prognosis. If clinical symptoms can be controlled with corticosteroids, WBRT may be postponed for up to three weeks for very important reasons.

Conflicts of Interest

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

Authors' Contributions

H.C.H., S.J., S.E.S. and D.R. participated in the design of the study. H.C.H., S.J., C.T., A.P.and D.R. provided data for the study. S.E.S. and D.R. performed the analyses. H.C.H., S.J., S.E.S. and D.R. performed the interpretation of the data and drafted the manuscript, which has been reviewed and approved in its final form by all other authors.

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