Potential Impact of the Overall Treatment Time on Outcomes after Whole-brain Irradiation with 10×3 Gy for Brain Metastases

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Abstract. *Aim: To investigate the impact of the overall treatment time (OTT) of whole-brain irradiation (WBI) with 10×3 Gy on outcomes in patients with brain metastases. Patients and Methods: Seventy-three patients who started WBI on Monday (OTT=12 days, including one weekend without irradiation) were compared to 257 patients who began WBI on Tuesday to Friday (OTT=14 days, including two weekends) for intracerebral control and survival. Seven additional factors were analyzed, including age, gender, Karnofsky performance score (KPS), tumor type, number (N) of brain lesions, extracerebral metastases and interval between cancer diagnosis and WBI. Results: On univariate analysis, age (p=0.039), KPS (p<0.001) and N brain metastases (p=0.006) were associated with intracerebral control; OTT had no significant impact (p=0.20). Age (p<0.001), KPS (p<0.001), N brain metastases (p=0.037) and extracerebral metastases (p<0.001) were associated with survival; OTT had no significant impact (p=0.37). Conclusion: OTT (12 vs. 14 days) had no significant impact on outcomes after WBI with 10×3 Gy.*

Brain metastases are common in cancer patients occurring in up to 40% of patients during the course of disease (1, 2). Although radiosurgery alone has become more popular, most patients, who present with multiple cerebral metastases and/or in a reduced general condition, are not suitable for neurosurgery or radiosurgery and receive whole-brain irradiation (WBI) alone. The most common dose-fractionation schedule of WBI is 10×3 Gy. According to a large retrospective study, most patients treated with WBI for brain metastases do not benefit from total doses of WBI greater than 30 Gy in terms of improvement of intracerebral control and survival (3). When 10×3 Gy is used, one aspect that has not yet been investigated is the question: Are the outcomes after WBI affected by the overall treatment time (OTT)? More specifically, are patients who received WBI over 14 days, including two weekends without irradiation, doing worse than those patients who received the first WBI-fraction on a Monday resulting in an OTT of 12 days (only one weekend without irradiation)?

This study compared WBI with 10×3 Gy over 12 days to 10×3 Gy over 14 days with respect to intracerebral control and survival. If the longer OTT of 14 days did impair the outcome of WBI, the possible remedies were to continue WBI on Saturday and Sunday or to increase the dose of WBI for patients not starting with their WBI on a Monday.

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Patients and Methods

Three hundred and thirty patients who were treated with 10×3 Gy of WBI alone for brain metastases were included in this retrospective study. Seventy-three patients who started WBI on a Monday resulting in an OTT of 12 days (including one weekend without irradiation) were compared to 257 patients who began WBI started on another weekday (Tuesday to Friday) resulting in an OTT of 14 days (including two weekends without irradiation). Investigated end points included intracerebral control and survival. In addition to the OTT, seven factors were analyzed for both end points. These factors included age at WBI (≤62 *vs.* ≥63 years, median age=62.5 years), gender, Karnofsky performance score (KPS ≤60 *vs.* 70 *vs.* ≥80), primary tumor type (breast cancer *vs.* lung cancer *vs.* other), number of brain lesions (1-3 *vs.* ≥4), extracerebral metastases (no *vs.* yes) and interval between first diagnosis of cancer and WBI (≤12 *vs.* >12 months). The distributions of these factors in both OTT groups are summarized in Table I. Intracerebral control and survival rates were

Table I. *Comparison of potential prognostic factors of patients receiving whole-brain radiotherapy (WBRT) with an overall treatment time (OTT) of 12 days versus patients receiving WBRT with an OTT of 14 days (Chi-square test).*

	OTT 12 days (%)	OTT 14 days (%)	*p*-Value
Age			
≤62 years (n=165)	36 (49)	129 (50)	
≥63 years (n=165)	37 (51)	128 (50)	0.95
Gender			
Female (n=161)	41 (56)	120 (47)	
Male (n=169)	32 (44)	137 (53)	0.37
Karnofsky performance score			
≤60 (n=141)	28 (38)	113 (44)	
70 (n=90)	19 (26)	71 (28)	
≥80 (n=99)	26 (36)	73 (28)	0.85
Primary tumor type			
Breast cancer (n=69)	15 (21)	54 (21)	
Lung cancer (n=176)	42 (58)	134 (52)	
Other (n=85)	16 (22)	69 (27)	0.91
Number of cerebral lesions			
1-3 (n=79)	16 (22)	63 (25)	
≥4 (n=251)	57 (78)	194 (75)	0.86
Extracerebral metastases			
No (n=104)	21 (29)	83 (32)	
Yes (n=226)	52 (71)	174 (68)	0.81
Interval between cancer diagnosis and WBI			
≤12 months (n=206)	45 (62)	161 (63)	
>12 months (n=124)	28 (38)	96 (37)	0.94

Table II. *Univariate analysis of intracerebral control.*

	At 6 months (%)	At 1 year (%)	*p*-Value
Overall treatment time			
12 days (n=73)	45	28	
14 days (n=257)	36	19	0.20
Age			
≤62 years (n=165)	42	26	
≥63 years (n=165)	34	15	**0.039**
Gender			
Female (n=161)	42	25	
Male (n=169)	35	17	0.23
Karnofsky performance score			
≤60 (n=141)	18	5	
70 (n=90)	43	22	
≥80 (n=99)	56	34	**<0.001**
Primary tumor type			
Breast cancer (n=69)	47	36	
Lung cancer (n=176)	41	17	
Other (n=85)	26	17	0.21
Number of cerebral lesions			
1-3 (n=79)	56	26	
≥4 (n=251)	32	20	**0.006**
Extracerebral metastases			
No (n=104)	41	19	
Yes (n=226)	35	24	0.96
Interval between cancer diagnosis and WBI			
≤12 months (n=206)	39	21	
>12 months (n=124)	36	22	0.66
Entire cohort	38	21	

Values in bold show statistical significance.

referenced from the last day of WBI. Kaplan-Meier-method and log-rank test were used for the univariate analyses (4). Factors significantly associated with outcomes ($p<0.05$) on the univariate analyses were subsequently evaluated in a multivariate analysis with the Cox regression model.

Results

Median follow-up times were 4 months (range=0-40) for the entire cohort and 7 months (range=3-40) for patients alive at last follow-up. In the univariate analysis, age ≤62 years ($p=0.039$), KPS ≥80 ($p<0.001$) and presence of only 1-3 brain metastases ($p=0.006$) were significantly associated with improved intracerebral control (Table II), whereas the OTT had no significant impact ($p=0.20$, Figure 1). On multivariate analysis of intracerebral control, KPS maintained significance (risk ratio (RR)=1.59; 95% confidence interval (CI)=1.33-1.91; $p<0.001$), the number of brain metastases showed a trend (RR=1.10; CI=0.98-1.24; $p=0.095$) and age was not significant (RR=1.22; CI=0.92-1.62; $p=0.16$).

On univariate analyses, age ≤62 years ($p<0.001$), KPS ≥80 ($p<0.001$), only 1-3 brain metastases ($p=0.037$) and lack of extracerebral metastases ($p<0.001$) were associated with improved survival (Table III). Again, the OTT had no significant impact on outcomes ($p=0.37$, Figure 2). On multivariate analysis of survival, age (RR=1.33; CI=1.05-1.69; $p=0.019$), KPS (RR=1.63; CI=1.39-1.91; $p<0.001$) and extracerebral metastases (RR=1.44; CI=1.10-1.90; $p=0.008$) remained significant, whereas the number of brain metastases did not achieve significance (RR=1.02; CI=0.93-1.12; $p=0.73$).

Discussion

Brain metastases are common in cancer patients and will gain importance in the future due to improved treatment of primary tumors and metastases at non-central nervous system (CNS) sites (1, 2). Despite the fact that radiosurgery alone has been increasingly recommended for selected patients with a limited number of brain metastases, the majority of patients with metastases to the brain are still candidates for WBI (5-8). If WBI is the treatment of choice, the physicians may choose from different dose-fractionation schedules. The most appropriate regimen depends on the patients' survival

Table III. *Univariate analysis of survival.*

	At 6 months (%)	At 1 year (%)	*p*-Value
Overall treatment time			
12 days (n=73)	32	18	
14 days (n=257)	27	15	0.37
Age			
≤62 years (n=165)	35	20	
≥63 years (n=165)	21	10	**<0.001**
Gender			
Female (n=161)	31	18	
Male (n=169)	25	13	0.74
Karnofsky performance score			
≤60 (n=141)	8	2	
70 (n=90)	37	18	
≥80 (n=99)	49	31	**<0.001**
Primary tumor type			
Breast cancer (n=69)	29	21	
Lung cancer (n=176)	28	15	
Other (n=85)	28	12	0.90
Number of cerebral lesions			
1-3 (n=79)	39	18	
≥4 (n=251)	25	14	**0.037**
Extracerebral metastases			
No (n=104)	48	27	
Yes (n=226)	19	10	**<0.001**
Interval between cancer diagnosis and WBI			
≤12 months (n=206)	29	17	
>12 months (n=124)	26	13	0.27
Entire cohort	28	15	

Values in bold show statistical significance.

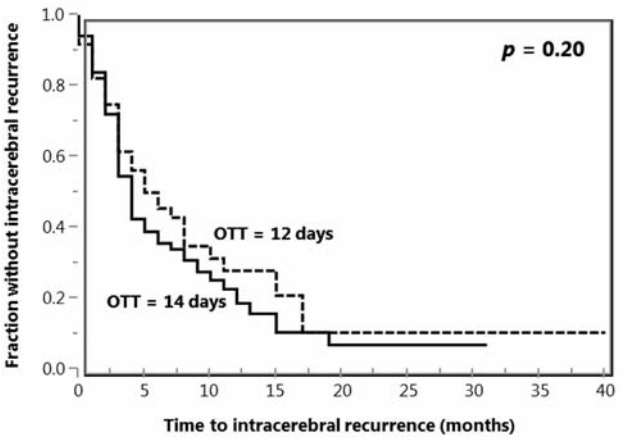

Figure 1. *Comparison of whole-brain radiotherapy (WBRT) with an overall treatment time (OTT) of 12 days and WBRT with an OTT of 14 days for intracerebral control.*

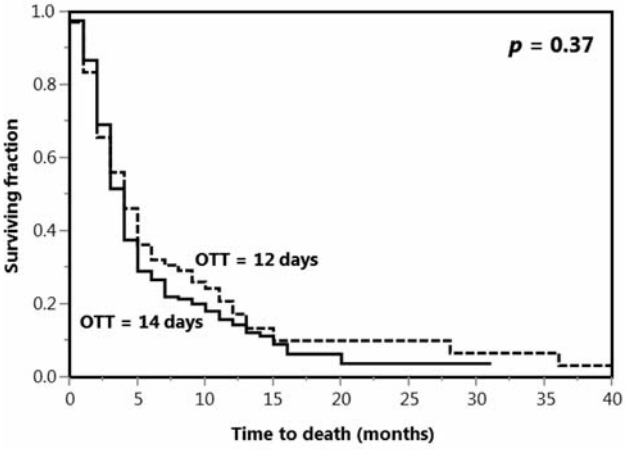

Figure 2. *Comparison of whole-brain radiotherapy (WBRT) with an overall treatment time (OTT) of 12 days and WBRT with an OTT of 14 days for survial.*

time. Selected patients with an extremely poor prognosis of only a few weeks may receive dexamethasone and supportive care without WBI since, in a randomized trial of selected patients with brain metastases from non-small cell lung cancer, the addition of WBI to best supportive care improved the median survival time by only 8 days (9). Patients with a poor survival prognosis of about three months may be good candidates for WBI with 5×4 Gy in one week, which was not inferior to 10×3 Gy in a large retrospective study of 442 patients receiving WBI alone (10). In that study, the WBI schedule was not significantly associated with either survival (p=0.29) or intracerebral control (p=0.07). In contrast, in another retrospective study of 186 patients, with a very favorable survival prognosis receiving WBI, the 1-year intracerebral control rates were 28% after 10×3 Gy and 44% after 20×2 Gy (p=0.047 on multivariate analysis) (11). One-year survival rates were 50% and 61%, respectively (p=0.008 on multivariate analysis). However, patients with such favorable survival prognoses represent a minority of patients presenting with brain metastases. Patients with an intermediate survival prognosis, namely with an expected survival time of 3 to 6 months, represent the largest group of patients with brain metastases (12). Thus, 10×3 Gy in two weeks is the most common dose-fractionation schedule for WBI of brain metastases worldwide. The survival groups of patients with brain metastases can be identified with specific survival scores (12-15).

If WBI with 10×3 Gy is performed, treatment usually starts on a weekday from Monday to Friday. Until now, one point has not been investigated, *i.e.* whether the start day and OTT are relevant for the outcomes of WBI. Treatment starting on a Monday includes one weekend break and results in an OTT of 12 days, whereas WBI started on a weekday between

Tuesday and Friday includes two weekend breaks and an OTT of 14 days. According to the results of the present study, the longer OTT due to an additional weekend had no significant impact on intracerebral control and survival. This means, that neither irradiation during at least one weekend nor addition of a compensatory fraction of WBI are required. When interpreting these findings, one should be aware of the retrospective nature of the study. However, the performance of prospective randomized studies to address this issue is quite difficult and, therefore, such studies cannot be expected soon.

In this study, the KPS was an independent predictor of intracerebral control, which agrees with the findings of a study that investigated prognostic factors and developed a prognostic score for predicting intracerebral control in patients receiving WBI and/or radiosurgery for brain metastases (16). In the multivariate analysis of survival in the present study, age, KPS and extracerebral metastases were independent predictors of survival. These findings are consistent with those of previous studies performed to develop the available survival scores for patients receiving WBI for brain metastases (12-15). These scores help select patients who are good candidates for WBI with 10×3 Gy.

In conclusion, for WBI with 10×3 Gy, the day of the first fraction (Monday *vs*. Tuesday to Friday) and the OTT (12 *vs*. 14 days) had no significant impact on intracerebral control or survival. Compensatory measures to adjust the biologic effect for the added weekend break appear unnecessary.

Conflicts of Interest

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

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