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Outcomes After Whole-brain Radiotherapy for Brain Metastases with 5×4 Gy: Importance of Overall Treatment Time

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Abstract. *Background/Aim: To investigate the impact of overall treatment time (OTT) of whole-brain radiotherapy (WBRT) with 5×4 Gy on outcomes. Patients and Methods: Forty-four patients for whom WBRT was started on a Monday (OTT=5 days) were compared to 136 patients, for whom WBRT was started on another weekday (OTT=7 days; weekend break) regarding intracerebral control and survival. Seven other factors were also analyzed. Results: Intracerebral control at 6 and 12 months was 64% and 36% after OTT of 5 days vs. 57% and 38% after OTT of 7 days (p=0.68). On multivariate analysis, intracerebral control was positively associated with a better Eastern Cooperative Oncology Group performance score (ECOG-PS) (p<0.001). Survival at 6 and 12 months was 36% and 16% after OTT of 5 days vs. 35% and 19% after OTT of 7 days (p=0.81). On multivariate analysis, survival was positively associated with better ECOG-PS (p<0.001) and absence of extracerebral lesions (p=0.004). Conclusion: Prolongation of OTT to 7 days had no impact on outcomes after WBRT with 5×4 Gy.*

Depending on the type of primary tumour, up to 40% of adult patients with cancer develop brain metastases (1). About 60% of these patients present with four or more lesions, and in many the performance status is markedly reduced (2, 3). The majority of patients with brain metastases are candidates for whole-brain radiotherapy (WBRT) alone. For WBRT of brain metastases, different dose-fractionation regimens are available. Common regimens include 5×4 Gy in 1 week, 10×3 Gy in 2 weeks, 14-15×2.5 Gy in 3 weeks and 20×2 Gy in 4 weeks. A retrospective study of 416 patients showed that for patients with brain metastases, an escalation of the WBRT dose beyond 10×3 Gy did not improve intracerebral control or survival (2). An additional study suggested that patients with a favourable survival prognosis based on a validated score appeared to benefit from total doses greater than 30 Gy (4, 5). However, most patients requiring WBRT have an expected survival of only a few months (1). Taking into account their limited lifespan, most patients should receive a dose-fractionation regimen with a short overall treatment time (OTT) such as 5×4 Gy in 1 week. In a retrospective study of 442 patients treated with WBRT for multiple brain metastases, 5×4 Gy was not inferior to 10×3 Gy with respect to feasibility, intracerebral control and survival (6). Therefore, WBRT with 5×4 Gy is used at many centres for patients with brain metastases and poor expected survival. However, one question that has not yet been answered is the effect of a weekend break in treatment. Since 5×4 Gy consists of only five fractions, it may be important for an optimal treatment efficacy that WBRT is performed without a break (OTT=5 days). The presents study compared patients receiving 5×4 Gy, for whom WBRT was started on a Monday and administered on five consecutive days to patients for whom WBRT was started on another weekday (Tuesday to Friday) and interrupted for two days during the following weekend (OTT=7 days). If the weekend breaks lead to less favourable outcomes, one might consider continuing WBRT during the weekend or giving a sixth fraction to compensate for the 2-day break.

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Key Words: Brain metastases, whole-brain radiotherapy, overall treatment time, intracerebral control, survival.

Patients and Methods

This study compared 44 patients for whom WBRT alone with 5×4 Gy was started on a Monday (OTT=5 days) to 136 patients for whom WBRT was started on a Tuesday, Wednesday, Thursday or Friday (OTT=7 days: 5 days plus weekend break) for the endpoints

Table I. *Distribution of patient factors in the groups treated with whole-brain radiotherapy (WBRT) with an overall treatment time (OTT) of 5 days and WBRT with an OTT of 7 days.*

	OTT		
	5 Days (%)	7 Days (%)	*p*-Value
Age			
≤64 Years (n=96)	21 (48)	75 (55)	
≥65 Years (n=84)	23 (52)	61 (45)	0.63
Gender			
Female (n=95)	23 (52)	72 (53)	
Male (n=85)	21 (48)	64 (47)	0.98
ECOG performance score			
0-1 (n=23)	5 (11)	18 (13)	
2 (n=103)	25 (57)	78 (57)	
3 (n=54)	14 (32)	40 (29)	0.98
Primary tumor type			
Breast cancer (n=39)	9 (20)	30 (22)	
Lung cancer (n=80)	20 (45)	60 (44)	
Other cancer (n=61)	15 (34)	46 (34)	0.99
Number of cerebral lesions			
1-3 (n=29)	8 (18)	21 (15)	
≥4 (n=151)	36 (82)	115 (85)	0.91
Extracerebral metastases			
No (n=61)	14 (32)	47 (35)	
Yes (n=119)	30 (68)	89 (65)	0.91
Interval from cancer diagnosis to WBRT			
≤12 Months (n=105)	26 (59)	79 (58)	
>12 Months (n=75)	18 (41)	57 (42)	0.97

p-Values were obtained from the Chi-square test. ECOG: Eastern Cooperative Oncology Group.

Table II. *Univariate analysis of intracerebral control after whole-brain radiotherapy (WBRT).*

	At 6 months (%)	At 12 months (%)	*p*-Value
Overall treatment time			
5 Days (n=44)	64	36	
7 Days (n=136)	57	38	0.68
Age			
≤64 Years (n=96)	61	38	
≥65 Years (n=84)	55	36	0.79
Gender			
Female (n=95)	64	47	
Male (n=85)	51	16	0.07
ECOG performance score			
0-1 (n=23)	87	63	
2 (n=103)	61	41	
3 (n=54)	34	0	**<0.001**
Primary tumor type			
Breast cancer (n=39)	75	57	
Lung cancer (n=80)	53	31	
Other cancer (n=61)	52	21	0.08
Number of cerebral lesions			
1-3 (n=29)	76	54	
≥4 (n=151)	55	33	**0.021**
Extracerebral metastases			
No (n=61)	57	47	
Yes (n=119)	60	30	0.57
Interval from cancer diagnosis to WBRT			
≤12 Months (n=105)	49	33	
>12 Months (n=75)	72	45	**0.035**

ECOG: Eastern Cooperative Oncology Group. Significant *p*-values are shown in bold.

intracerebral control and survival. In addition to OTT, seven potential prognostic factors were investigated for associations with outcomes including age (≤64 *vs.* ≥65 years), gender, Eastern Cooperative Oncology Group performance score (ECOG-PS 0-1 *vs.* 2 *vs.* 3), primary tumour type (breast cancer *vs.* lung cancer *vs.* other), number of brain metastases (1-3 *vs.* ≥4), presence of extracerebral metastatic lesions (no *vs.* yes), and the interval from first diagnosis of cancer to WBRT (≤12 *vs.* >12 months) (Table I). The rates of intracerebral control and survival were referenced from the last day of WBRT. For univariate analyses, the Kaplan–Meier method and the log-rank test were used (7). Those prognostic factors that showed a significant association with treatment outcomes ($p<0.05$) were additionally analyzed in a multivariate manner with the Cox regression analysis.

Results

Patients were followed-up until death or for a median of 11.5 months (range=6-38 months). In the univariate analysis of intracerebral control, improved outcomes were significantly associated with an ECOG-PS of 0-1 ($p<0.001$), presence of only 1-3 cerebral lesions ($p=0.021$) and an interval from first diagnosis of cancer to WBRT of more than 12 months ($p=0.035$) (Table II). The OTT had no significant impact on intracerebral control ($p=0.68$, Figure 1). In the subsequent Cox regression analysis, the ECOG-PS remained significant [risk ratio (RR)=2.24; 95% confidence interval (95% CI)=1.50-3.39; $p<0.001$). The interval from first diagnosis of cancer to WBRT achieved borderline significance (RR=1.58; 95% CI=0.99-2.55; $p=0.054$). The number of cerebral lesions was not significant (RR=1.15; 95% CI=0.91-1.48; $p=0.25$).

In the univariate analysis of survival, age ≤64 years ($p=0.042$), female gender ($p=0.003$), ECOG-PS of 0-1 ($p<0.001$), breast cancer ($p=0.019$), presence of only 1-3 cerebral lesions ($p<0.001$), and absence of extracerebral metastases ($p<0.001$) were positively associated with better outcomes (Table III). In contrast, the OTT had no significant impact on survival ($p=0.81$, Figure 2). On Cox regression analysis, survival was significantly associated with ECOG-PS (RR=2.18; 95% CI=1.61-2.96; $p<0.001$) and extracerebral metastases (RR=1.77; 95% CI=1.20-2.68;

Table III. *Univariate analysis of survival after whole-brain radiotherapy (WBRT).*

	At 6 months (%)	At 12 months (%)	*p*-Value
Overall treatment time			
5 Days (n=44)	36	16	
7 Days (n=136)	35	19	0.81
Age			
≤64 Years (n=96)	44	25	
≥65 Years (n=84)	25	10	**0.042**
Gender			
Female (n=95)	43	29	
Male (n=85)	26	5	**0.003**
ECOG performance score			
0-1 (n=23)	74	43	
2 (n=103)	42	21	
3 (n=54)	6	2	**<0.001**
Primary tumor type			
Breast cancer (n=39)	51	43	
Lung cancer (n=80)	31	11	
Other cancer (n=61)	30	10	**0.019**
Number of cerebral lesions			
1-3 (n=29)	59	38	
≥4 (n=151)	30	14	**<0.001**
Extracerebral metastases			
No (n=61)	57	34	
Yes (n=119)	24	11	**<0.001**
Interval from cancer diagnosis to WBRT			
≤12 Months (n=105)	33	12	
>12 Months (n=75)	37	26	0.31

ECOG: Eastern Cooperative Oncology Group. Significant *p*-values are shown in bold.

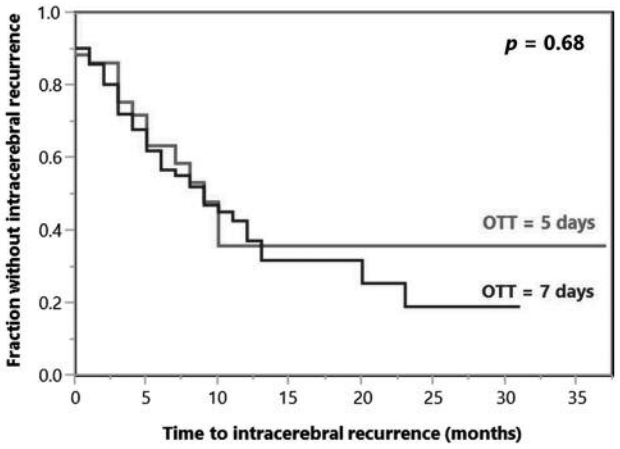

Figure 1. *Comparison of whole-brain radiotherapy (WBRT) with an overall treatment time (OTT) of 5 days and of 7 days with respect to intracerebral control.*

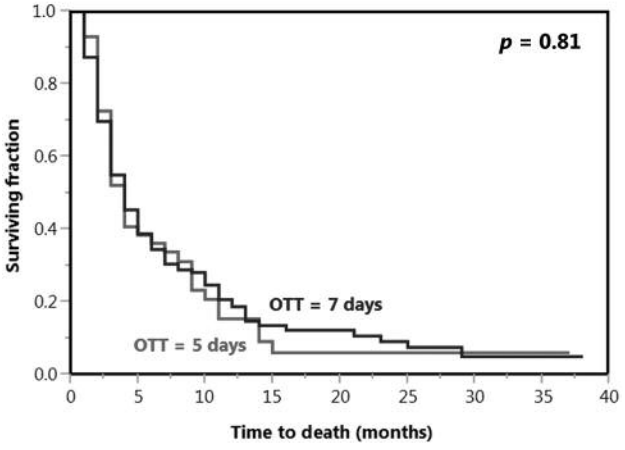

Figure 2. *Comparison of whole-brain radiotherapy (WBRT) with an overall treatment time (OTT) of 5 days and of 7 days with respect to survival.*

p=0.004). A trend was observed for age (RR=1.33; 95% CI=0.95-1.86; *p*=0.09) and gender (RR=1.41; 95% CI=0.98-2.04; *p*=0.06). Primary tumour type (RR=1.10; 95% CI 0.86-1.40; *p*=0.45) and number of cerebral lesions (RR=1.05; 95% CI=0.89-1.26; *p*=0.57) were not significant in the multivariate analysis.

Discussion

The treatment of patients with brain metastases has gained more attention in light of personalization of anticancer treatment (8-13). A recent randomized trial of 538 patients suggested best supportive care including dexamethasone alone for selected patients with brain metastases from non-small cell lung cancer achieved similar results as WBRT, with median survivals of only 57 and 65 days, respectively (8). In contrast, a retrospective study on 652 metastases in 95 patients (median=2 lesions, range=1-14 lesions) suggested that repeat radiosurgery is safe and effective. Median survival times were 18 months following the first radiosurgery treatment and 11 months following the second treatment, respectively (9). In a single-arm phase II study of 60 patients who received volumetric radiosurgery for 1-10 brain metastases, the median survival time was 10 months (14). The comparably long median survival times in the latter two studies suggest that these patients were not representative of the majority of patients with multiple cerebral lesions. The median survival times in most series of patients with multiple brain metastases are only a few months (1, 2, 5, 6). Thus, WBRT alone remains the standard approach for patients with multiple cerebral lesions. The WBRT program should be adjusted to the patient's survival prognosis. Patients with more favourable prognoses appear

to benefit from total doses greater than 30 Gy in terms of improved intracerebral control and survival (4). In contrast, for patients with less favourable prognoses who are considered candidates for WBRT, 5×4 Gy in 1 week appears the most appropriate regimen (6). The survival prognoses of patients with brain metastases can be estimated with several available scoring instruments (5, 10, 12, 15, 16).

If a patient is prescribed WBRT with 5×4 Gy, one aspect that has not yet been investigated regards the question of whether the weekday WBRT is started has an impact on treatment outcomes. In the present study, we compared the patients, who started their treatment on Monday and received five daily fractions of 4 Gy until Friday without a break to those patients who started WBRT on another weekday and had a 2-day break at the weekend. Both groups were compared with respect to intracerebral control and survival. According to the results of this study, the weekend break had no significant impact on either of the investigated endpoints. Therefore, continuation of the daily treatment during the weekend or an additional fraction of WBRT appears unnecessary. The retrospective design of this study should be taken into account when interpreting these results. However, a randomized trial to answer this question is unlikely: a planned delay of WBRT by 2 days due to trial design, which may lead to worsening of symptoms and a patient's prognosis, is unethical.

In contrast to the OTT, in the present study, the ECOG-PS was significantly associated with intracerebral control on multivariate analysis, and the interval from first diagnosis of cancer to WBRT achieved borderline significance. In addition, the number of cerebral lesions had an impact on intracerebral control on univariate analysis. These findings are consistent with the results of a previous study including patients with brain metastases who received different treatments including WBRT and radiosurgery (17). On Cox regression analysis of the present study, survival was significantly associated with PS and presence of extracerebral metastases. These two prognostic factors were also independent predictors of survival in all studies providing scoring systems for estimating the survival of patients irradiated for brain metastases (5, 15, 16).

In summary, based on the findings from this study of patients receiving WBRT with 5×4 Gy for brain metastases, prolongation of OTT from 5 to 7 days caused by a weekend break had no impact on intracerebral control or survival. Thus, continuation of the WBRT during the weekend or administrations of extra doses to compensate for this break are unnecessary.

Conflicts of Interest

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

References

1 Khuntia D, Brown P, Li J and Mehta MP: Whole-brain radiotherapy in the management of brain metastasis. J Clin Oncol *24*: 1295-1304, 2006.

2 Rades D, Haatanen T, Schild SE and Dunst J: Dose escalation beyond 30 Gray in 10 fractions for patients with multiple brain metastases. Cancer 2007, *110*: 1345-1350, 2007.

3 Tsao MN, Rades D, Wirth A, Lo SS, Danielson BL, Gaspar LE, Sperduto PW, Vogelbaum MA, Radawski JD, Wang JZ, Gillin MT, Mohideen N, Hahn CA and Chang EL: Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): An American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol *2*: 210-225, 2012.

4 Rades D, Panzner A, Dziggel L, Haatanen T, Lohynska R and Schild SE: Dose-escalation of whole-brain radiotherapy for brain metastasis in patients with a favorable survival prognosis. Cancer *118*: 3853-3859, 2012.

5 Dziggel L, Segedin B, Podvrsnik NH, Oblak I, Schild SE and Rades D: Validation of a survival score for patients treated with whole-brain radiotherapy for brain metastases. Strahlenther Onkol *189*: 364-366, 2013.

6 Rades D, Kieckebusch S, Lohynska R, Veninga T, Stalpers LJ, Dunst J and Schild SE: Reduction of overall treatment time in patients irradiated for more than three brain metastases. Int J Radiat Oncol Biol Phys *69*: 1509-1513, 2007.

7 Kaplan EL and Meier P: Non parametric estimation from incomplete observations. J Am Stat Assoc *53*: 457-481, 1958.

8 Mulvenna PM, Nankivell MG, Barton R, Faivre-Finn C, Wilson P, Moore B, McColl R, Brisbane I, Ardron D, Sydes B, Pugh C, Holt T, Bayman N, Morgan S, Lee C, Waite K, Stephens R, Parmar MMK and Langley RE: Whole brain radiotherapy for brain metastases from non-small lung cancer: Quality of life (QoL) and overall survival (OS) results from the UK Medical Research Council QUARTZ randomised clinical trial (ISRCTN 3826061). J Clin Oncol *33(suppl)*: abstr 8005, 2015.

9 Shultz DB, Modlin LA, Jayachandran P, Von Eyben R, Gibbs IC, Choi CY, Chang SD, Harsh GR, Li G, Adler JR, Hancock SL and Soltys SG: Repeat courses of stereotactic radiosurgery (SRS), deferring whole-brain irradiation, for new brain metastases after initial SRS. Int J Radiat Oncol Biol Phys *92*: 993-999, 2015.

10 Rades D, Dziggel L, Hakim SG, Rudat V, Janssen S, Trang NT, Khoa MT and Bartscht T: Predicting survival after irradiation for brain metastases from head and neck cancer. In Vivo *29*: 525-528, 2015.

11 Rades D, Huttenlocher S, Rudat V, Hornung D, Blanck O, Phuong PC, Khoa MT, Schild SE and Fischer D: Radiosurgery with 20 Gy provides better local contol of 1-3 brain metastases from breast cancer than with lower doses. Anticancer Res *35*: 333-336, 2015.

12 Janssen S, Dahlke M, Trang NT, Khoa MT and Rades D: Estimation of the six-month survival probability after radiosurgery for brain metastases from kidney cancer. Anticancer Res *35*: 4215-4217, 2015.

13 Dziggel L, Dahlke M, Janssen S, Hornung D, Blanck O, Khoa MT, Schild SE and Rades D: Predicting the risk of new cerebral lesions after stereotactic radiosurgery (SRS) for brain metastases from breast cancer. Anticancer Res *35*: 6793-6797, 2015.

14 Nichol A, Ma R, Hsu F, Gondara L, Carolan H, Olson R, Schellenberg D, Germain F, Cheung A, Peacock M, Bergman A, Vollans E, Vellani R and McKenzie M: Volumetric radiosurgery for 1 to 10 brain metastases: a multicenter, single-arm, phase 2 study. Int J Radiat Oncol Biol Phys *94*: 312-321, 2016.

15 Rades D, Dziggel L, Nagy V, Segedin B, Lohynska R, Veninga T, Khoa MT, Trang NT and Schild SE: A new survival score for patients with brain metastases who received whole-brain radiotherapy (WBRT) alone. Radiother Oncol *108*: 123-127, 2013.

16 Gaspar L, Scott C, Rotman M, Asbell S, Phillips T, Wasserman T, McKenna WG and Byhardt R: Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. Int J Radiat Oncol Biol Phys *37*: 745-751, 1997.

17 Rades D, Dziggel L, Haatanen T, Veninga T, Lohynska R, Dunst J and Schild SE: Scoring systems to estimate intracerebral control and survival rates of patients irradiated for brain metastases. Int J Radiat Oncol Biol Phys *80*: 1122-1127, 2011.

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