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Whole brain radiotherapy plus stereotactic radiosurgery (WBRT + SRS) versus surgery plus whole brain radiotherapy (OP + WBRT) for 1–3 brain metastases: Results of a matched pair analysis

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ABSTRACT

This study is the first one to compare WBRT + SRS to OP + WBRT for 1–3 brain metastases. Survival (OS), intracerebral control (IC) and local control (LC) of the treated metastases were retrospectively evaluated in 52 patients undergoing WBRT + SRS and in 52 patients undergoing OP + WBRT. Both groups were matched for WBRT schedule, age, gender, performance status, tumour, number of brain metastases, extracerebral metastases, RPA class and interval from tumour diagnosis to WBRT. One-year OS was 56% after WBRT + SRS and 47% after OP + WBRT ($p = 0.034$). One-year IC was 66% and 50% ($p = 0.003$). One-year LC was 82% and 66% ($p = 0.006$). On multivariate analyses, it was found that improved OS was associated with younger age ($p = 0.044$), no extracerebral metastases ($p < 0.001$), RPA class 1 ($p < 0.001$) and longer interval from tumour diagnosis to WBRT ($p = 0.001$). IC was associated with younger age ($p = 0.002$) and longer interval ($p = 0.004$); WBRT + SRS achieved borderline significance ($p = 0.052$). Improved LC was associated with longer interval ($p = 0.017$); WBRT + SRS showed a trend ($p = 0.09$). WBRT + SRS appears at least as effective as OP + WBRT.

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1. Introduction

The optimal treatment for patients with a very limited number of brain metastases is controversial. Treatment often includes surgical resection (OP) or stereotactic radiosurgery (SRS). Concerns exist regarding the addition of whole brain radiotherapy (WBRT) to OP or SRS, as the addition of WBRT is suspected to have increased the rate of neurocognitive deficits. However, several authors believe that the major cause of neurocognitive dysfunction is the recurrent brain metastasis rather than WBRT.[1–3] No prospective data exist that support the omission of WBRT in patients with 1–3 brain metastases. However, the question remains, whether OP + WBRT or WBRT + SRS is superior with respect to treatment outcomes?

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Only two retrospective studies have been reported that compared the results of OP + WBRT and WBRT + SRS for single brain metastasis.[4,5] Both studies suggested of better local control (LC) of the treated metastases but not of significantly improved survival (OS) for WBRT + SRS. One of these studies suggested that cerebral control distant from the treated metastasis was similar with both therapies.[4] However, intracerebral control (IC, control within the entire brain) has not yet been reported. Thus, further studies are required to address these controversies.

The present matched pair analysis is the first study that compared OP + WBRT and WBRT + SRS in patients with 1–3 brain metastases. Furthermore, this study investigated IC in addition to OS and LC.

2. Patients and methods

The outcome of 104 patients treated for 1–3 brain metastases between 1998 and 2008 with WBRT + SRS or OP + WBRT was retrospectively analysed. Fifty-two of 134 patients undergoing OP + WBRT during that period of time were matched to 52 patients undergoing WBRT + SRS. Only RPA classes 1 and 2 patients were included, because patients with poor performance status (RPA class 3 patients) are not usually selected for SRS or OP. Further criteria for inclusion were 1–3 brain metastases (diameter $\leqslant$ 4 cm), no prior RT or OP to the brain, confirmation of metastases by magnetic resonance imaging and administration of dexamethasone (12–32 mg/day) during WBRT. WBRT was administered with a linear accelerator and 6–10 MV photon beams, either delivering 5×4 Gy in 1 week ($n = 16$), 10×3 Gy in 2 weeks ($n = 50$) or 20×2 Gy in 4 weeks ($n = 38$). SRS was performed as linac-based SRS ($n = 43$) or GammaKnife SRS ($n = 9$). The SRS dose was 15–25 Gy (median dose: 20 Gy), prescribed to 80% isodose line with linac-based SRS and 50% isodose line with GammaKnife SRS. Data regarding baseline characteristics and follow-up were obtained from patients, general practitioners, treating oncologists and patient files. Patient characteristics are summarised in Table 1.

The comparison of the two groups was performed as a matched pair analysis. The groups were matched for WBRT schedule (5×4 Gy versus 10×3 Gy versus 20×2 Gy), age ($\leqslant$60 versus >60 years), gender, Eastern Oncology Cooperative Group Performance Score (ECOG-PS 0–1 versus 2), tumour type (breast cancer versus lung cancer versus other tumours), number of brain metastases (1 versus 2–3), extracerebral metastases at the time of WBRT (no versus yes), recursive partitioning analysis class (RPA 1 versus 2[6]) and interval from tumour diagnosis to WBRT (<18 versus $\geqslant$18 months). The pairs were allowed to differ only with respect to one of these factors. The nine potential prognostic factors were also evaluated for OS, IC and LC.

Patients were followed until death, or those who were alive at their follow-up were followed from 3 to 57 months (median: 12 months) . Intracerebral and local failures were confirmed by magnetic resonance imaging. Time to any endpoint was measured from the completion of WBRT. OS, IC and LC rates were calculated using the Kaplan–Meier method.[7] The differences between the Kaplan–Meier curves were determined with the Wilcoxon test (univariate analysis).

Table 1 – Patient characteristics of the treatment groups.

	Entire cohort ($n = 104$) N (%)	WBRT + SRS ($n = 52$) N (%)	OP + WBRT ($n = 52$) N (%)
WBRT schedule			
5×4 Gy	16 (15)	8 (15)	8 (15)
10×3 Gy	50 (48)	25 (48)	25 (48)
20×2 Gy	38 (37)	19 (37)	19 (37)
Age			
$\leqslant$60 years	56 (54)	28 (54)	28 (54)
>60 years	48 (46)	24 (46)	24 (46)
Gender			
Female	62 (60)	31 (60)	31 (60)
Male	42 (40)	21 (40)	21 (40)
ECOG performance score			
0–1	60 (58)	30 (58)	30 (58)
2	44 (42)	22 (42)	22 (42)
Primary tumour			
Breast cancer	18 (17)	9 (17)	9 (17)
Lung cancer	56 (54)	28 (54)	28 (54)
Other tumours	30 (29)	15 (29)	15 (29)
Number of brain metastases			
1	60 (58)	30 (58)	30 (58)
2–3	44 (42)	22 (42)	22 (42)
Extracerebral metastases			
No	66 (63)	33 (63)	33 (63)
Yes	38 (37)	19 (37)	19 (37)
RPA class			
Class 1	52 (50)	26 (50)	26 (50)
Class 2	52 (50)	26 (50)	26 (50)
Interval FD of tumour to WBRT			
<18 months	54 (52)	27 (52)	27 (52)
$\geqslant$18 months	50 (48)	25 (48)	25 (48)

The prognostic factors found to be of significance ($p < 0.05$) were included in a multivariate analysis, which was performed with the Cox proportional hazards model.

3. Results

The median survival time was 13 months for the entire cohort. On univariate analysis, it was found that improved OS was significantly associated with WBRT + SRS (Fig. 1), age $\leqslant$ 60 years, ECOG-PS 0–1, breast cancer, lack of extracerebral metastases, RPA class 1 and an interval from tumour diagnosis to WBRT > 18 months. The results of the univariate analysis are summarised in Table 2. Because the RPA class includes age, performance status and extracerebral metastases, these are confounding variables. Therefore, two multivariate analyses were performed, one including age, ECOG-PS and extracerebral metastases, and the second including RPA class. On multivariate analyses, it was found that age (RR: 1.75; 95% confidence intervals (CI): 1.04–2.94; $p = 0.035$), extracerebral metastases (RR: 2.38; 95% CI: 1.41–4.03; $p = 0.001$), RPA class (RR: 2.63; 95% CI: 1.58–4.46; $p < 0.001$) and interval from tumour diagnosis to WBRT (RR: 2.47; 95% CI: 1.49–4.15; $p < 0.001$) remained significant. Treatment regimen (RR: 1.47; 95% CI: 0.91–2.39; $p = 0.12$), ECOG-PS (RR: 1.51; 95% CI: 0.91–

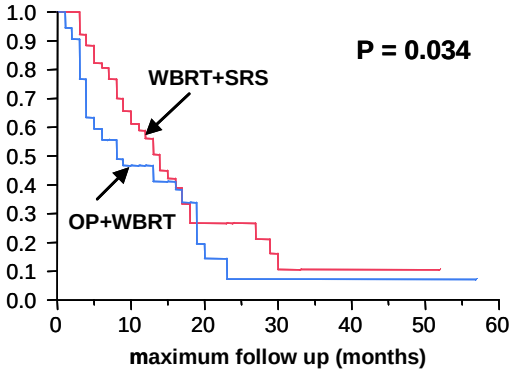

Fig. 1 – Comparison of WBRT + SRS and OP + WBRT with respect to survival (Kaplan–Meier curves).

Table 2 – Results of the univariate analysis regarding survival.

	At 6 months (%)	At 12 months (%)	P
Treatment			
WBRT + SRS ($n = 52$)	81	56	**0.034**
OP + WBRT ($n = 52$)	56	47	
WBRT schedule			
5×4 Gy ($n = 16$)	69	53	0.94
10×3 Gy ($n = 50$)	72	52	
20×2 Gy ($n = 38$)	63	50	
Age			
⩽60 years ($n = 56$)	79	66	**0.005**
>60 years ($n = 48$)	56	35	
Gender			
Female ($n = 62$)	71	55	0.30
Male ($n = 42$)	64	46	
ECOG performance score			
0–1 ($n = 60$)	72	60	**0.040**
2 ($n = 44$)	63	39	
Primary tumour			
Breast cancer ($n = 18$)	94	82	**0.011**
Lung cancer ($n = 56$)	60	43	
Other tumours ($n = 30$)	67	49	
Number of brain metastases			
1 ($n = 60$)	73	52	0.70
2–3 ($n = 44$)	61	51	
Extracerebral metastases			
No ($n = 66$)	77	62	**<0.001**
Yes ($n = 38$)	53	34	
RPA class			
Class 1 ($n = 52$)	81	67	**<0.001**
Class 2 ($n = 52$)	55	37	
Interval FD of tumour to WBRT			
<18 months ($n = 54$)	59	36	**0.005**
⩾18 months ($n = 50$)	78	66	
Entire cohort	68	52	

2.48; $p = 0.11$) and primary tumour type (RR: 1.13; 95% CI: 0.76–1.69; $p = 0.55$) were not significant.

A recurrence anywhere in the brain occurred in 48 patients (46%). On univariate analysis, it was found that WBRT + SRS (Fig. 2), age ⩽ 60 years and an interval from tumour diagnosis to WBRT > 18 months were significantly associated with improved IC (Table 3). On multivariate analysis, it was found that

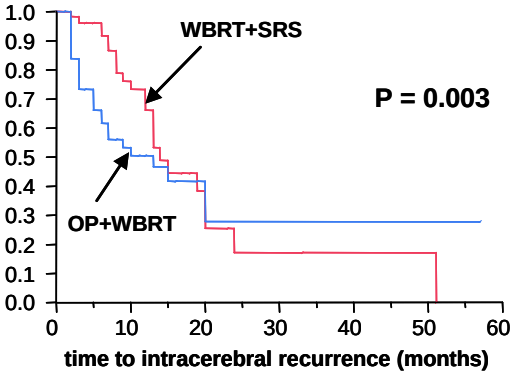

Fig. 2 – Comparison of WBRT + SRS and OP + WBRT with respect to intracerebral control (Kaplan–Meier curves).

Table 3 – Results of the univariate analysis regarding intracerebral control.

	At 6 months (%)	At 12 months (%)	P
Treatment			
WBRT + SRS ($n = 52$)	91	66	**0.003**
OP + WBRT ($n = 52$)	62	50	
WBRT schedule			
5×4 Gy ($n = 16$)	85	65	0.42
10×3 Gy ($n = 50$)	78	62	
20×2 Gy ($n = 38$)	72	51	
Age			
⩽60 years ($n = 56$)	81	76	**0.018**
>60 years ($n = 48$)	72	35	
Gender			
Female ($n = 62$)	76	56	0.81
Male ($n = 42$)	79	65	
ECOG performance score			
0-1 ($n = 60$)	79	58	0.70
2 ($n = 44$)	74	60	
Primary tumour			
Breast cancer ($n = 18$)	94	71	0.12
Lung cancer ($n = 56$)	71	50	
Other tumours ($n = 30$)	77	64	
Number of brain metastases			
1 ($n = 60$)	77	53	0.49
2–3 ($n = 44$)	78	67	
Extracerebral metastases			
No ($n = 66$)	81	63	0.21
Yes ($n = 38$)	69	48	
RPA class			
Class 1 ($n = 52$)	82	67	0.11
Class 2 ($n = 52$)	71	48	
Interval FD of tumour to WBRT			
<18 months ($n = 54$)	65	40	**0.002**
⩾18 months ($n = 50$)	89	74	
Entire cohort	77	59	

age (RR: 2.68; 95% CI: 1.45-5.01; $p = 0.002$) and interval from tumour diagnosis to WBRT (2.44; 95% CI: 1.32–4.61; $p = 0.004$) remained significant, while WBRT + SRS achieved borderline significance (RR: 1.79; 95% CI: 0.99–3.24; $p = 0.052$).

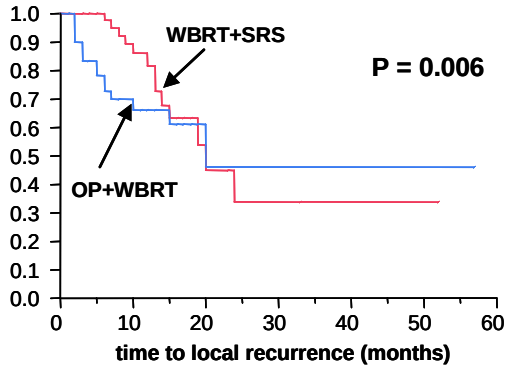

Fig. 3 – Comparison of WBRT + SRS and OP + WBRT with respect to local control of the treated metastases (Kaplan–Meier curves).

Table 4 – Results of the univariate analysis regarding local control of the treated metastases.

	At 6 months (%)	At 12 months (%)	P
Treatment			
WBRT + SRS ($n = 52$)	98	82	**0.006**
OP + WBRT ($n = 52$)	73	66	
WBRT schedule			
5×4 Gy ($n = 16$)	92	71	0.84
10×3 Gy ($n = 50$)	83	79	
20×2 Gy ($n = 38$)	86	70	
Age			
⩽60 years ($n = 56$)	88	83	0.14
>60 years ($n = 48$)	82	62	
Gender			
Female ($n = 62$)	86	73	0.94
Male ($n = 42$)	86	78	
ECOG performance score			
0–1 ($n = 60$)	87	74	0.61
2 ($n = 44$)	84	77	
Primary tumour			
Breast cancer ($n = 18$)	94	82	0.27
Lung cancer ($n = 56$)	82	68	
Other tumours ($n = 30$)	87	80	
Number of brain metastases			
1 ($n = 60$)	82	72	0.18
2–3 ($n = 44$)	91	79	
Extracerebral metastases			
No ($n = 66$)	89	78	0.26
Yes ($n = 38$)	80	68	
RPA class			
Class 1 ($n = 52$)	88	77	0.46
Class 2 ($n = 52$)	84	72	
Interval FD of tumour to WBRT			
<18 months ($n = 54$)	78	61	**0.018**
⩾18 months ($n = 50$)	93	85	
Entire cohort	86	75	

Local recurrence of the treated brain metastases was observed in 29 patients (28%). On univariate analysis, it was found that improved LC was significantly associated with WBRT + SRS (Fig. 3) and a longer interval from tumour diagnosis to WBRT. The latter maintained significance in the multivariate analysis (RR: 2.55; 95% CI: 1.18–5.68; $p = 0.017$), while WBRT + SRS showed at least a trend (RR: 1.91; 95% CI: 0.90–4.13; $p = 0.09$).

Grade ⩾ 3 acute toxicity (Common Toxicity Criteria 2.0[8]) occurred in 4% of the patients treated with WBRT + SRS and 4% of the patients treated with OP + WBRT. Grade ⩾ 3 late toxicity rates (Radiation Therapy Oncology Group (RTOG) criteria) occurred in 4% and 5% of patients, respectively (Table 4).

4. Discussion

Uncertainty exists regarding the best available regimen for patients with 1–3 brain metastases. It has been demonstrated that WBRT can improve the results of OP or SRS. Patchell et al. presented a randomised trial with 95 patients comparing OP alone and OP + WBRT in patients with single brain metastasis.[9] The 1-year LC rates were 54% without and 90% with additional WBRT ($p < 0.001$). The 1-year IC rates were 30% and 82%, respectively. However, the median survival time was not significantly different. In two retrospective series, Smalley et al. suggested of both improved LC and OS with WBRT in addition to OP.[10,11] Aoyama et al. reported of a randomised study comparing SRS alone and WBRT + SRS, and demonstrated improved 1-year LC (86% versus 70%, $p = 0.019$) and 1-year IC (53% versus 24%, $p < 0.001$) but not 1-year OS (39% versus 28%, $p = 0.42$) with additional WBRT in 132 patients with 1–4 lesions.[12] Similar results were found in retrospective studies.[13,14]

Although not improving OS in most studies, adding WBRT to OP or SRS is very reasonable. The addition of WBRT to OP or SRS significantly improves LC and IC. Both LC and IC are important end-points in addition to OS, because an intracerebral recurrence is the major cause of neurocognitive deficits.[1–3]

Due to a lack of data, it is unclear if OP + WBRT or WBRT + SRS results in a better outcome. Only two retrospective studies are available for patients with a single brain metastasis, and no published studies for patients with 1–3 brain metastases. The two retrospective studies for patients with a single lesion suggested that LC is better after WBRT + SRS than after OP + WBRT,[4,5] whereas OS was not significantly different. Schoggl et al. compared 67 patients undergoing WBRT + SRS (GammaKnife, median dose: 17 Gy) to 66 patients undergoing OP + WBRT.[4] The 1-year OS rates were 52% after WBRT + SRS and 44% after OP + WBRT ($p = 0.55$). The 1-year LC rates were 95% and 83%, respectively ($p < 0.05$). O'Neill et al. compared 23 patients treated with SRS to 74 patients treated with OP.[5] Of these patients, 96% and 82%, respectively, underwent additional WBRT. The 1-year OS rates were 56% after SRS and 62% after OP ($p = 0.15$). Local failure rates were 0% after SRS and 58% after OP ($p = 0.020$).

WBRT + SRS resulted in significantly better outcomes than OP + WBRT in the univariate analysis of the present study. For

IC, the results achieved borderline significance in the multivariate analysis, and for LC, there was at least a trend. For OS, the results were not significant in the multivariate analysis. The toxicity rates were relatively low in both the groups, which is in agreement with the results from the literature.[15]

A clear understanding of the impact of various prognostic factors can aid in appropriate treatment selection and trial design. Proper patient stratification based on significant prognostic factors prevents the introduction of uncontrolled biases into trials. Of the potential prognostic factors investigated in addition to the treatment regimen, performance status, extracerebral metastases, RPA class and interval between tumour diagnosis and WBRT were significantly associated with OS. These findings are in accordance with the data presented by Gaspar et al. that led to the RPA-classification.[6] A shorter interval between the tumour diagnosis and WBRT likely reflects the faster growth of a more aggressive tumour.

WBRT + SRS appeared at least as effective as OP + WBRT regarding treatment outcomes. Because WBRT + SRS is far less invasive and does not require anaesthesia, it appears preferable to OP + WBRT for 1–3 brain metastases. This study is part of the rationale for a planned randomised trial.

Conflict of interest statement

None declared.

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