Oncology and Translational Medicine
DOI 10.1007/s10330-019-0344-4

June 2019, Vol. 5, No. 3, P114–P118

ORIGINAL ARTICLE

Whole-brain radiation therapy alone vs. combined therapy with stereotactic radiosurgery for the treatment of limited brain metastases: A systematic review

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Abstract

Objective The aim of the study was to compare the efficacy and safety of whole brain radiotherapy (WBRT) used alone and combined with stereotactic radiosurgery (SRS) in the treatment of limited (1–4) brain metastases.

Methods We searched for randomized controlled and matched-pair analysis trials comparing WBRT plus SRS versus WBRT alone for brain metastases. The primary outcomes were the overall survival (OS), intracranial control (IC), and localcontrol (LC). The secondary outcome was radiation toxicity. The log hazard ratios (lnHRs) and their variances were extracted from published Kaplan-Meier curves and pooled using the generic inverse variance method in the RevMan 5.3 software. The non-pooled outcome measures were evaluated using descriptive analysis.

Results Three randomized controlled trials and two matched-pair analysis studies were included. There was no difference in the OS for limited brain metastases between the two groups [lnHR 0.91 (95% CI 0.76–1.09, P = 0.32) *vs.* 0.72 (95% CI 0.44–1.19, P = 0.20)]. The LC and IC were significantly higher in the combined treatment group [lnHR 0.69 (95% CI 0.55–0.86, P = 0.001) *vs.* 0.41 (95% CI 0.29–0.58, P < 0.0001)]. For patients with a single lesion, one trial showed a higher survival in the combined treatment group (median OS: 6.5 months *vs.* 4.9 months, P = 0.04). The combined treatment was not associated with significantly higher incidence of radiation toxicity.

Conclusion Combined treatment with WBRT plus SRS should be recommended for patients with limited brain metastases based on the better LC and IC without increased toxicity. It should also be considered a routine treatment option for patients with solitary brain metastases based on the prolonged OS.

Received: 24 March 2019
Revised: 25 April 2019
Accepted: 17 May 2019

Key words: limited brain metastases; stereotactic radiosurgery (SRS); whole brain radiotherapy (WBRT); systematic review

It has been reported that 20%–40% of patients with cancer develop brain metastases. Patients with a limited number of metastatic lesions and well-controlled systemic disease may benefit from aggressive local therapeutic approaches in terms of a better prognosis. As a focal high-dose boost treatment, stereotactic radiosurgery (SRS) has been extensively employed in patients with brain metastases, either alone or combined with whole brain radiotherapy (WBRT). Clinical evidence has shown that adding SRS to WBRT was beneficial to patients with limited brain metastases [1–2]. This study investigated the effect of the addition of SRS to WBRT in the management of patients with 1 to 4 brain metastases.

Methods

Literature search

Studies comparing WBRT combined with SRS versus WBRT alone were searched in the following databases from inception up to January 2019: PubMed, Medline, Embase, the Cochrane Central Register of Controlled Trials, Wangfang Data, and Weipu.

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Selection criteria

The literature type was restricted to randomized controlled trials or matched-pair analysis studies comparing combined WBRT plus SRS versus WBRT alone for the treatment of adult patients (age > 18 years) with newly diagnosed brain metastases (single or up to 4) confirmed by MRI.

Data collection and analysis

Two investigators independently extracted study data following the inclusion criteria. Cases of conflicting opinion were resolved through discussion.

Outcome measurement

The primary outcome measures were the overall survival (OS), local control (LC), and intracranial control (IC). The secondary outcome measure was the treatment-related toxicity.

Statistical analysis

The generic inverse variance method in RevMan 5.3 software (The Cochrane Collaboration) was used for this meta-analysis. The outcome measures for data pooling were the log hazard ratios (lnHR) and their variances. A fixed-effect model was used when no heterogeneity was observed among the studies. Otherwise, a random effect model was adopted. The heterogeneity between the studies was assessed using the Q-test and I^2 statistic, and $P < 0.10$ and $I^2 > 50\%$ were considered to indicate heterogeneity between the studies.

Results

Studies' characteristics

The search strategy initially identified 126 articles. Irrelevant and duplicated studies were excluded after reading the abstracts. Finally, three randomized controlled trials and two matched-pair analysis studies with a total of 784 patients meeting our inclusion criteria were included. Table 1 shows the characteristics of each included study [3–7]. Patients had 1–4 brain metastases. The WBRT dosage schedules included 2.5 Gy × 15 F, 2.5 Gy × 12 F, 3 Gy × 10 F, and 2 Gy × 20 F, with a total of 30–40 Gy. The prescribed dose in SRS ranged from 14 Gy to 24 Gy depending on the tumor diameter and the number of brain lesions. Most dose prescriptions conformed to the Radiation Therapy Oncology Group guidelines.

Primary outcomes

Overall survival

Three studies [3, 6–7] evaluated the OS in patients with 1 to 3 brain metastases, as shown in Fig. 1. There was no significant difference between the two treatment groups (HR 0.91, 95% CI 0.76–1.09). Three studies [3–5] reported the OS data for patients with 2 to 4 brain metastases. Similarly, there was no significant difference between the two treatment groups (HR 0.72, 95% CI 0.44–1.19; Fig. 2). For patients with a single brain metastasis, Andrews *et al* [3] reported that the OS was 6.5 months in the WBRT plus SRS group and 4.9 months in the WBRT alone group (P = 0.0393). Rades *et al* [7] reported OS rates at 6, 12, 18, and 24 months of 83%, 64%, 34%, and 30%, respectively, in the WBRT plus SRS group, and 67%, 49%, 29%, and 18%, respectively, in the WBRT alone group (P = 0.12).

Local control

All five studies evaluated the LC. The pooled data analysis found that the patients who underwent WBRT plus SRS had less chance of local failure than those who underwent WBRT alone (HR 0.69, 95% CI 0.55–0.86, P = 0.001; Fig. 3).

Intracranial control

Three trials [3–5] evaluated the IC. The pooled data analysis revealed that the addition of SRS to WBRT significantly improved the IC of the treated lesions (HR 0.41, 95% CI 0.29–0.58, $P < 0.00001$; Fig. 4). Kondziolka *et al* [4] reported that the median time to any brain failure was 5 months in the WBRT alone group and 34 months in the combined treatment group (P = 0.002).

Secondary outcomes

Adverse events: Four trials [3–6] reported the treatment-related toxicities. The most common toxicities were nausea or vomiting and skin changes. Andrews *et al* [3]

Table 1 Characteristics of the included studies

Study type		Group A	Group B	*n*	Radiation dose (Gy) WBRT	Radiation dose (Gy) SRS	PTV of SRS
Andrews [3]	RCT	164	167	1–3	2.5 Gy × 15 F	$D_{max} \leq 2$ cm, 24 Gy; $2 < D_{max} \leq 3$ cm, 18 Gy; $3 < D_{max} \leq 4$ cm, 15 Gy	NR
Kondziolka [4]	RCT	14	13	2–4	2.5 Gy × 12 F	16 Gy	NR
Minniti [5]	MPA	66	66	2–3	3 Gy × 10 F	$D_{max} \leq 2$ cm, 20 Gy; $D_{max} > 2$ cm, 18 Gy	PTV: GTV + 2 mm
El Gantery [6]	RCT	21	21	1–3	3 Gy × 10 F	14 – 20 Gy (mean = 14.6 Gy, median = 14 Gy)	PTV: GTV + 1 mm
Rades [7]	MPA	168	84	1–3	3 Gy × 10 F or 2 Gy × 20 F	4–8 Gy × 2–5 F	NR

RCT: randomized controlled trial; MPA: matched-pair analysis; A: WBRT; B: WBRT + SRS; *n*: number of brain metastases; D_{max}: the broadest diameter of the metastases; PTV: planning target volume; GTV: contrast-enhanced gross tumor volume on MRI; NR: not reported

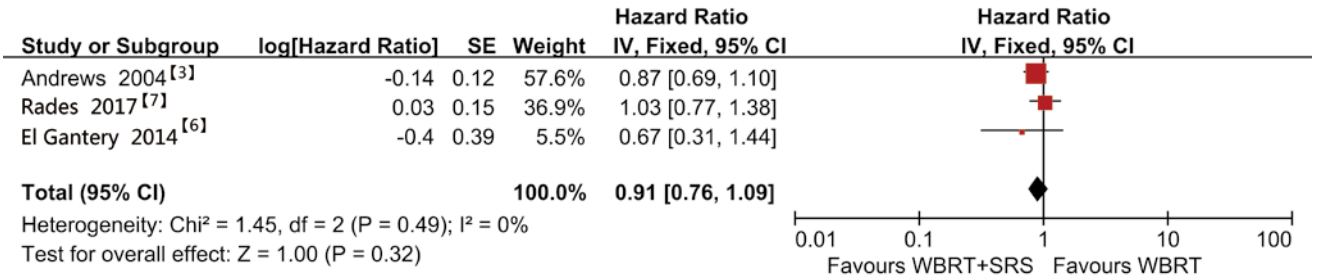

Fig. 1 Overall survival per group in patients with 1 to 3 brain metastases

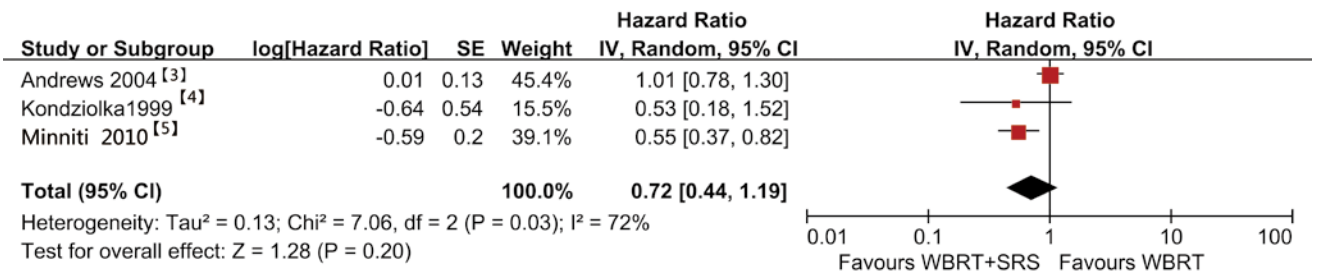

Fig. 2 Overall survival per group in patients with 2 to 4 brain metastases

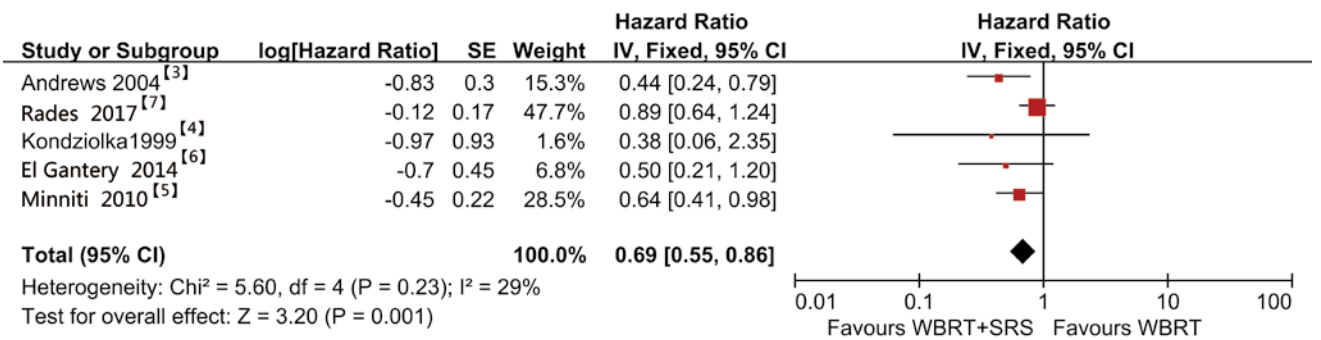

Fig. 3 Local control

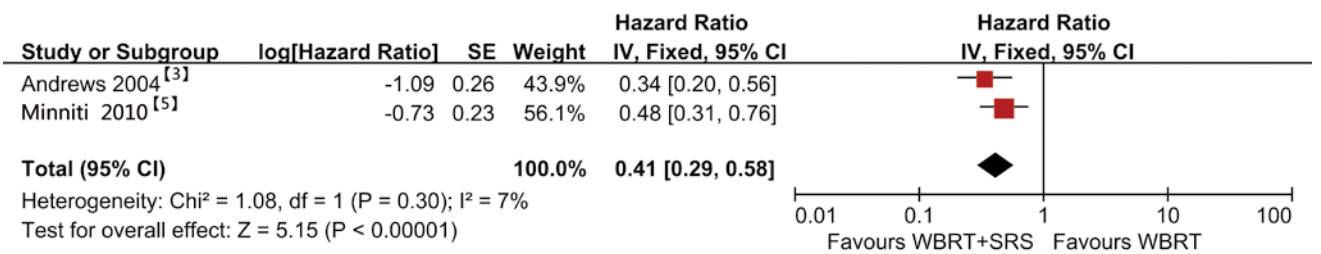

Fig. 4 Intracranial control

reported rates of 43% grade 1, 18% grade 2, 2% grade 3, and 1% grade 4 acute toxicities in the SRS boost group versus 36%, 26%, 0%, and 0%, respectively, in the WBRT alone group. There were 2% grade 3 and 1% grade 4 late toxicities in the WBRT arm, and 3% grade 3 and 3% grade 4 late toxicities in the combined curative arm. El Gantery *et al* [6] reported 14% acute and 14% late toxicity rates in the SRS boost arm versus 14% and 9%, respectively, in the WBRT alone arm. These data suggested that the rates of acute and late toxicities were similar between the two groups. Kondziolka *et al* [4] reported no neurologic morbidity related to SRS except for mild scalp erythema and hair loss associated with WBRT. Minniti *et al* [5] reported that six patients developed radio necrosis and six patients experienced neurocognitive deficits in the WBRT plus SRS group. The radio necrosis lesions were controlled by the use of steroids or surgery. Five patients experienced neurocognitive deficits in the form of grade 2 confusion or grade 2 memory loss in the WBRT alone group.

Discussion

Oligometastatic disease is defined as a maximum of five metastatic lesions for all disease sites, including no more than three active extracranial metastatic lesions. Small prospective and retrospective studies have suggested that aggressive consolidative therapy to the metastatic sites was associated with an improved OS in patients with oligometastatic non-small-cell lung carcinoma [8–9]. The current research findings are inconclusive as to whether patients who present with a limited burden of intracranial metastatic disease could benefit from a local consolidative therapy. The aim of this study was to systematically evaluate the benefit of adding SRS to WBRT in the treatment of limited brain metastases (1 to 4 brain metastases).

It has been determined that the combined treatment with WBRT and SRS significantly improved the LC compared to SRS alone in patients with intracranial oligometastatic disease. However, WBRT also leads to more pronounced neurocognitive impairment [10]. With the emerge of new methods to lower the risk of WBRT-induced neurocognitive decline [11–12], WBRT is still thought to bean essential part in the treatment of limited brain metastases. The present study also demonstrated that the addition of SRS to WBRT significantly improved the LC compared to WBRT alone for patients with limited lesions. However, the pooled data analysis showed no OS improvement with the use of combined treatment in patients with 1-4 brain metastases. For patients with solitary brain metastases, Andrews *et al* [3] concluded there was a survival advantage in the combined treatment group, whereas Rades *et al* [7] reported that the OS rates were not significantly different between the two groups. The study of Rades *et al* [7] was a small sample-size, matched-pair, retrospective study that may not be able to provide an adequate statistical power to detect a significant difference. In contrast, the study by Andrews *et al* [3] was a well-designed, large sample-size, randomized controlled trial; thus, the evidence rank was high. In view of this, we believe that the addition of SRS treatment to WBRT can improve the OS in patients with a single brain metastasis.

The analysis of the pooled data of the five trials revealed that the patients who underwent combined WBRT plus SRS treatment had a better control of the treated lesions, which indicated that the addition of SRS could improve the LC in patients with 1-4 brain metastases. There were three studies [3–5] that evaluated the IC. The data extracted from the study by Kondziolka *et al* [4] were not suitable for the pooling analysis. This study reported significant differences in the control of intracranial lesions favoring the combined treatment; the median time to intracranial failure was 5 months in the WBRT alone group and 34 months in the combined group (P = 0.002). The pooled data from the other two studies [3, 5] revealed that the addition of SRS to WBRT led to a significant improvement in the IC. However, considering the beneficial effect of the addition of SRS on the LC, the pooled outcome maybe largely resulting from this effect and may not indicate that distant brain control would also benefit from the additional SRS treatment. As the study did not provide data on new cerebral distant metastases, whether the addition of SRS improves the distant brain control needs to be confirmed by further clinical trials.

With respect to the side effects of radio therapy, there was no significant difference in the acute or late toxicity rates between the two groups, which suggested that the toxic effects may not be affected by SRS. It is well known that WBRT may induce cognitive impairment. SRS has emerged as a focused treatment modality characterized by delivering a high-dose fraction of ionizing radiation to a discrete target volume. It was assumed to be associated with a high risk of radionecrosis, particularly when combined with WBRT. In the current study, the SRS dose ranged from 14 to 24 Gy due to the differences in the size and number of the brain lesions. However, only the study of Minniti *et al* [5] reported radionecrosis and neurocognitive deficits. This indicates that the prescribed dose of SRS in each of the included trials was safe, and the addition of SRS to WBRT therapy was not associated with an increase in toxicity.

There are several limitations in our review. First, two of the included matched-pair studies were retrospective in nature, which always presents a potential risk of a hidden selection bias. Second, the prescribed dose/fractionation regimens of SRS, pathological type of primary tumors,

and the diameter of the metastatic foci in each study were not homogenous. Moreover, most of the studies did not assess the functional outcome or quality of life, which are extremely important outcomes in the treatment of advanced cancer. All the above may have distorted our results.

Taken together, our data suggest that the addition of SRS to WBRT has a beneficial effect on the LC and IC without increasing the risk of toxicity. Moreover, the addition of SRS has the potential of improving the OS in patients with a single brain metastasis. Therefore, SRS combined with WBRT should be recommended as a suitable treatment option for patients with 1–4 brain metastases, particularly for patients with a single brain metastasis.

Conflicts of interest

The authors indicate no potential conflicts of interest.

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DOI 10.1007/s10330-019-0344-4
Cite this article as: Wan C, Chen B, Liu YS, *et al*. Whole-brain radiation therapy alone vs. combined therapy with stereotactic radiosurgery for the treatment of limited brain metastases: A systematic review. Oncol Transl Med, 2019, 5: 114–118.