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Original Article

A Meta-analysis evaluating stereotactic radiotherapy combined with WBRT versus SRT alone for the NSCLC patients with brain metastases

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Abstract: Background: It is unclear whether patients with brain metastases benefit from stereotactic radiotherapy (SRT) combined with whole-brain radiotherapy (WBRT). Because the organization patterns of the primary tumors are different, the behaviors of brain metastases are also different. We performed a meta-analysis in patients with brain metastases from non-small cell lung cancer (NSCLC) treated with WBRT combined with SRT boost versus SRT alone. Methods: The meta-analysis outcomes of interest were overall survival (OS), and radiation toxicities. Using published Kaplan-Meier analyses, results were pooled according to hazard ratios (HR) and odds ratios (OR). Results: After searching the databases and evaluating the articles, 7 studies were included. Data from 6 studies for OS were pooled, which yielded an obvious difference between the SRT+WBRT group and SRT group in OS with an HR of 0.74 (95% CI 0.61-0.89; *P*=0.001). For the single metastasis group, there was no significant difference in OS between the two groupsin OS with a HR of 0.69 (95% CI 0.47-1.01; *P*=0.06). The incidence rate of radiation toxicities (≥ Grade 3) from 3 studies showed the OR of SRT+WBRT group compared with SRT group is 8.80 (95% CI 2.48-31.26; *P*=0.16), the SRT group have lower radiation toxicities (≥ Grade 3). Conclusion: NSCLC patients with brain metastases could obtain benefits from WBRT combined with SRT, which could prolong overall survival compared with SRT alone. The number of brain metastases was not prognostic for the two treatments. Patients can obtain benefit from SRT, which has a lower rate of radiation toxicities.

Keywords: Non-small cell lung cancer, brain metastases, stereotactic radiotherapy, whole brain radiotherapy, meta-analysis

Introduction

Lung cancer is one of the most common malignancies in the world. Non-small cell lung cancer (NSCLC) accounts for FF 85% of the newly diagnosed lung cancer cases. Brain metastases are often seen in these patients. However, with the short survival period and poor prognosis, the treatment for brain metastases is limited. Surgery, radiotherapy, chemotherapy or targeted therapy is administered to these patients [1].

For patients with multiple brain metastases, whole brain radiotherapy (WBRT) is the standard treatment. In addition, stereotactic radiotherapy (SRT) is generally limited to patients with a single lesion. With the large irradiation range, WBRT could control the clinical target volume better, but a small total radiotherapy dose could lead to local recurrence. With the advantage of accurate location, SRT could send high irradiation doses to the target volume. Because the toxic side effects are minimal, some researchers have suggested that the SRT could gradually replace WBRT gradually. However, given the defect of rapid radiotherapy dose decrease at the brain metastases' edge, the high rate of recurrence out of the target region could not be neglected [2]. WBRT combined with SRT could exert advantages and account for shortages. The results from a few retrospective clinical studies support the use of SRT with or without WBRT for NSCLC patients with brain metastases. The clinical behavior is

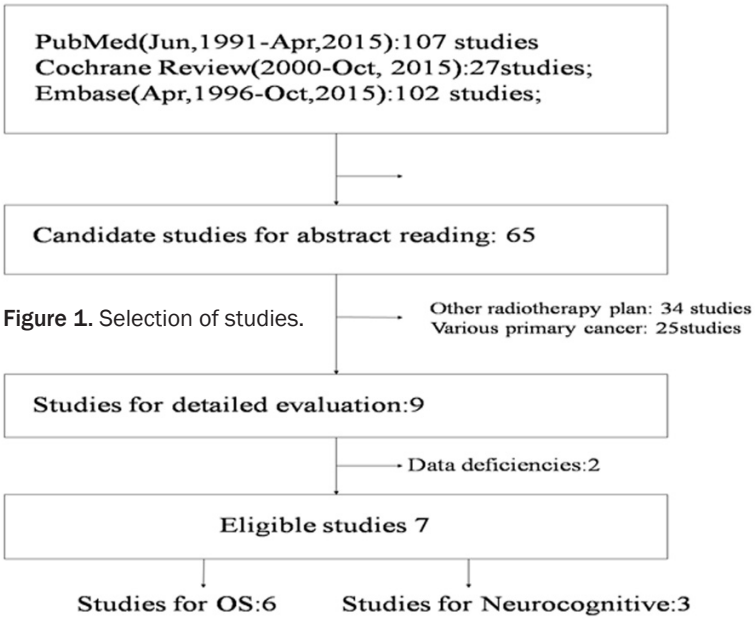

Figure 1. Selection of studies.

not same for the different types of cancer, and the progression of the tumor according to the primary tumor's pathological pattern [3], it is necessary to investigate the clinical outcome of metastatic brain tumors treated with SRT combined with (or without) WBRT for NSCLC patients.

Materials and methods

SRT refers to any single high fraction dose of focal radiotherapy using linear accelerator or gamma knife. WBRT refers to serial treatments of the entire brain with high energy rays using standard fractionation or accelerated hyperfractionation.

The inclusion criteria were diagnosis of NSCLC, newly diagnosed brain metastases and no prior radiotherapy, surgery, or other treatments. A literature search was carried out for randomized controlled trials (RCTs) comparing WBRT and SRT boost versus SRT alone. Prospective nonrandomized or retrospective cohort studies and studies reported only in abstract form were excluded. Patients who were under 18 years of age at the time of diagnosis and whose primary tumor had more than one histologic type were excluded, because the clinical information data collected from these patients would be inadequate.

The next step was to conduct the search to identify critical terms describing SRT, WBRT, and brain metastases (free text and truncated) along with their likely synonyms by examining the list of controlled vocabulary terms (e.g., medical subject heading (MeSH) terms), which was used to index known key references. Then, these terms were combined to form a structured search strategy reflecting important conceptual relationships. Specifically, terms and phrases describing the main intervention such as SRT and WBRT, were first combined with the Boolean operator "OR". Secondly, terms and phrases describing the NSCLC, and brain metastases, were combined using the Boolean operator "OR". Thirdly, terms and phrases identifying all randomized or controlled trials and comparative cohort studies were combined using the Boolean operator "OR". These three components were then linked with the Boolean operator "AND" to identify citations that fulfilled all three criteria.

The result of the search strategy was then applied to several electronic bibliographic databases, which cover biomedical, clinical, social science, and health services management topics. The unpublished or non-peer-reviewed information (i.e., grey literature) can also provide some valuable data. In addition, a series of reference databases designed to capture grey literature was employed. PubMed (1991 Jun to 2015), Cochrane Reviews (2003 to 2014), and Embase (1996 to 2015 October 06) were searched. The search strategies resulted in 107 publications, 27 publications, and 102 publications respectively. Seven studies [4-10] that meet this meta-analysis's requirements were identified (**Figure 1**). The primary outcome measures for this meta-analysis was OS, and the second outcome was the NSCLC patients' Neurocognitive function.

Quality assessment

The Newcastle-Ottawa quality assessment scale was performed to evaluate quality of the studies included on three aspects: "Selection",

Table 1. Summary of the eligible studies selected for this meta-analysis

Study	Design	Ethic	Clinical Characteristics (No. of patients)	Interventions	Follow-up Time	Outcomes	Radiation toxicities	Progress or Death	Notes
Todd W, 2003 [4]	Retrospective study	Americans	N=72	SRT+WBRT: n=45 SRT: n=27 (201-source 60 Co machine)	0.5-107 m	MST: SRT+WBRT: 12.0 m SRT: 7.7 m	NR	NR	NSCLC patients with solitary brain metastases were inclusion in this analysis.
Doo-Sik Kong, 2006 [5]	Retrospective study	Korean	N=35 No. of brain metastases 1-3 metastases n=23 ≥ 4 metastases n=12	SRT+WBRT: n=27 SRT: n=8 (hypofractionated stereotactic radiotherapy) Chemotherapy: n=20	0.75-43 m	All patients: MST: 12 m	NR	Progression of the brain lesions in 7 patients.	Brain lesions were diagnosed before or within 2 months from the diagnosis of the primary tumors.
Nicholas F, 2011 [6]	Retrospective study	Americans	N=207	SRT+WBRT: n=15 SRT: n=26	NR	MST: SRT+WBRT: 12.7 m SRT: 12.3 m	NR	Single metastasis group: 9 patients experienced some form of CNS progression.	NSCLC patients with one or more brain metastases, they had minimal or no neurologic symptoms, defined as a KPS ≥ 90.
Liang Hua, 2012 [7]	Retrospective study	Chinese	N=171 No. of brain metastases Single n=83 Multiple n=88	SRT+WBRT: n=117 SRT: n=54 (hypofractionated stereotactic radiotherapy)	1-75 m	MST: SRT+WBRT: 13 m SRT: 9 m	All patients (≥ Grade 3 toxicity): SRT+WBRT: n= 7 SRT: n=1	Neurologic Death -All patients: SRT+WBRT: n=35 SRT: n=26 -Single metastasis group: SRT+WBRT: n=15 SRT: n=16	Patients were treated with HSRT and had not previously received radiotherapy, surgery, or other treatments.
Edward A, 2013 [8]	Prospective study with Single-blind	Americans	N=68	SRT+WBRT: n=37 SRT: n=31 (Gamma Knife) chemotherapy SRT+WBRT: n=37 SRT: n=28		MST: SRT+WBRT: 25.1 m SRT: 28.2 m	All patients (Grade 3 toxicity): SRT+WBRT: n=17 SRT: n=0	NR	NSCLC brain metastases, had evaluable imaging obtained at around 1 or more years after WBRT or SRS.
Zhiyan Xu, 2013 [9]	Prospective study with randomized trial	Americans	N=64 No. of brain metastases Single n=32 Multiple n=32	SRT+WBRT: n=34 SRT: n=30 (gamma knife radiosurgery)	0.5-106 m	MST: SRT+WBRT: 9 m SRT: 9 m	1 patient developed radiation necrosis 1 year after GKS, 1 patient had radiological deterioration, which we were unable to differentiate between radiation necrosis and progression, 4 patients have asymptomatic white matter changes on the postradiosurgery MR images.	None of the patients experienced radiosurgery-related mortality.	NSCLC patients with 3 or fewer brain metastases, located 3 cm or less from the outer cortical surface of the cerebral hemispheres, no prior open craniotomy, and histologic confirmation.
Hidefumi Aoyama, 2015 [10]	Prospective study with randomized trial	Japanese	N=88 No. of brain metastases Single n=51 Multiple n=37	SRT+WBRT: n=43 SRT: n=45 (stereotactic radiosurgery)	0.5-163.8 m	MST: SRT+WBRT: 7.9 m SRT: 8.6m	All patients (Grade 3/4 toxicity): SRT+WBRT: n=2 SRT: n=1	NR	NSCLC and 1 to 4 brain metastases.

Note: NSCLC: non-small cell lung cancer; OS: overall survival; WBRT: whole-brain radiotherapy; HR: hazard ratios; OR: odds ratios; SRT: stereotactic radiotherapy.

Table 2. Quality assessment of the studies included

Papers	Selection				Comparability	Outcome			Total
	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis of the design or analysis	Assessment of outcome	Adequacy of follow up of cohorts	Was follow-up long enough for outcomes to occur	
Todd W, 2003 [4]	*	*	*	*	*	-	*	*	7
Kong, 2006 [5]	*	*	*	*	*	-	*	*	7
Nicholas F, 2011 [6]	*	*	*	*	*	-	*	*	7
Liang Hua, 2012 [7]	*	*	*	*	*		*	*	7
Edward A, 2013 [8]	*	*	*	*	*	*	*	*	8
Zhiyan Xu, 2013 [9]	*	*	*	*	*	*	*	*	8
Aoyama, 2015 [10]	*	*	*	*	*	-	*	*	7

Note: *: Met the requirementof the item; -: Didn't meet the requirement of the item.

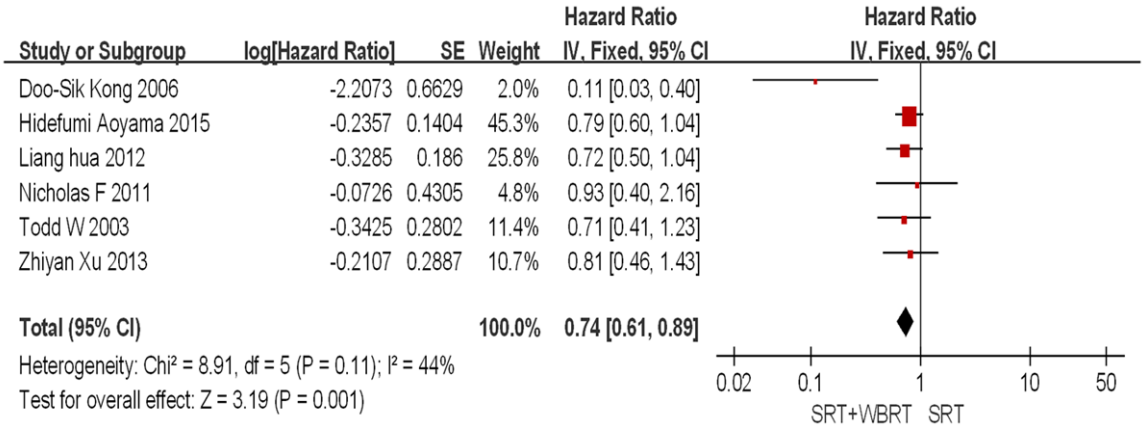

Figure 2. Overall Survival: SRT plus WBRT versus SRT alone boost for all patients.

"Comparability", "Outcome". The overall scores of Newcastle-Ottawascale were ranged from 0 to 8 (≥ 6 was generally considered to be of high quality) [11].

Data collection and analysis

All qualified research was searched and evaluated by 2 reviewers. The Generic inverse variance method and fixed effects model in Review Manager (RevMan 5) were used for this meta-analysis. The meta-analytic method makes fewer assumptions about the similarity of the studies in design and execution. The fixed effects analysis is a classical meta-analysis technique for pooled databases. It applies tests of heterogeneity to determine whether the participating studies are sufficiently similar to be combined in a meta-analysis. The log hazard ratio (lnHR) and its variance were the outcome measures for data pooling, which were estimated using Hazard Ratio Meta-analysis Tool Box. Forest plots were provided with pooled hazard ratios (HRs), and corresponding 95% confidence intervals (CIs). OS is the primary outcome of the meta-analysis.

Results

Study characteristics

A summary of pertinent information from the 7 analyzed RCTs [4-10] is provided in **Table 1**. Patient factors among the studies were similar while different groups were randomized at that time. Most patients had a Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) class of I or II [12], different levels of KPS and/or a WHO performance status (PS), stable systemic disease, and the maximum diameter of the individual brain target(s) did not exceed approximately 4 cm in size.

In quality assessment of the studies included in our review, all studies were considered to be of "high" methodological quality (**Table 2**).

RCTs comparing WBRT and SRT boost versus SRT alone

Seven RCTs [4-10] evaluated SRT and WBRT boost versus SRT alone. However, only the Zhiyan Xu [9] study researched the radiotherapeutic effect in the subgroup of single and multiple brain metastases of the two radiotherapy plans, and Todd W [4] only included the patients with solitary brain metastasis. Other studies did not divide groups by the number of brain metastases. Therefore, the pooled analysis for OS of patients with single metastasis could only be performed on data from the studies by Zhiyan Xu and Todd W [4, 9]. In Edward A's study [8], the main of the research was the disease incidence of leukoencephalopathy after radiotherapy, after communicated with the author, we couldn't obtain the survival analysis data ultimately. The data from this paper just applied to the incidence rate of radiation toxicities.

This pooled analysis of a total of 705 participants from 6 RCTs [4-7, 9, 10] yielded an obvious difference between the SRT+WBRT group and SRT group in OS with an HR of 0.74 (95% CI 0.61-0.89; *P*=0.001) (**Figure 2**).

For the single metastasis group, there was no significant difference between the SRT+WBRT

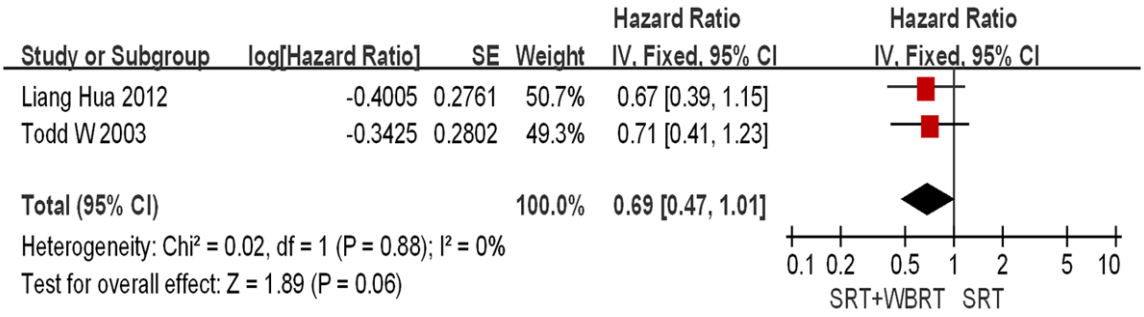

Figure 3. Overall Survival: SRT plus WBRT versus SRT alone boost for single metastasis group Radiation Therapy Oncology Group central.

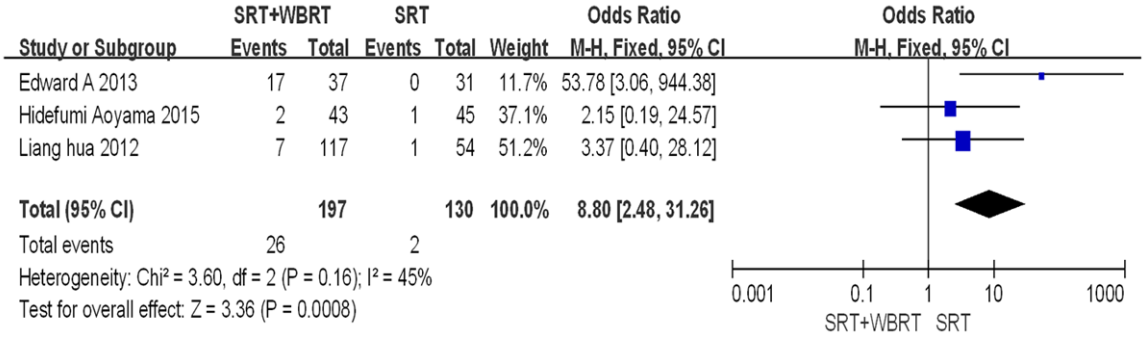

Figure 4. Radiation toxicities (≥ Grade 3): SRT plus WBRT versus SRT alone boost for all patients.

group and SRT group in OS with an HR of 0.69 (95% CI 0.47-1.01; P=0.06) (**Figure 3**).

The incidence rate of radiation toxicities (≥ Grade 3) from [13] 3 studies [7, 8, 10] showed the OR of SRT+WBRT group compared with SRT group is 8.80 (95% CI 2.48-31.26; P=0.16) (**Figure 4**), the SRT group have lower radiation toxicities (≥ Grade 3).

Selection bias

Although the seven studies [4-10] did not clearly describe approaches used to select patients for randomization beyond providing patient inclusion/exclusion criteria, no obvious discrepancies in any prognostic factors between treatment groups were noted.

Discussion

The role of WBRT

WBRT is the standard treatment of patients with multiple brain metastases with or without extensive extracranial disease. With its large irradiation range, WBRT could control the clinical target volume better. However, nausea and headache are adverse effects of WBRT. Leukoencephalopathy syndrome, which is a late adverse effect of WBRT, is more severe, progressive, and irreversible. Mild cases are typified by a chronic confusional state with inattention, memory loss, and emotional dysfunction. More severe cases produce major neurologic sequelae such as stupor, coma, dementia, and abulia. The degree of neurotoxicity resulting from WBRT correlates with the total dose received and with the time-dose-fractionation scheme [14].

The role of SRT

SRT is a non-invasive alternative to neurosurgical resection. For patients with surgically inaccessible metastases or those in poor medical condition, it is a valuable tool. It allows for precise focal delivery of a high single dose with a steep dose gradient to the surrounding normal tissue. With only one day of hospitalization or on an outpatient basis, SRT is an ideal palliative treatment. SRT for brain metastases is associated with few adverse effects. The risk of

necrosis was demonstrated to be a function of volume and prior or concurrent WBRT [15]. Complications include transient or symptomatic onset of peritumoral edema or delayed intratumoral hemorrhage or necrosis, which requires surgical intervention in approximately 4% of patients [16]. However, the omission of WBRT from the initial brain treatment has resulted in a significant increase in the recurrence of brain metastases [14, 17]. Regine et al. [18] reported that brain tumor recurrence could also be a cause of neurocognitive functional deterioration. High local control rates after SRT of 85-96% are reported in the literature [18-20]. Relapse rates of 26-39% outside the irradiated volume are reported after SRT for brain metastases of various primary tumors [21, 22].

The radiation toxicities

We considered the reason for death to be neurologically related if the patient died as a result of a direct complication from locally progressive lesions or from new brain metastases. If the patient died of a direct complication of the extracranial disease, the cause of death was considered systemically related [14].

Radiation toxicities according to the Radiation Therapy Oncology Group central nervous system toxicity criteria [3] were evaluated. Radiation toxicities shown in **Figure 3** demonstrated that the patients assigned to SRT and WBRT boost were significantly more likely to show a decline in neurocognitive abilities with those assigned to SRT alone.

Combination therapy of WBRT plus SRT

The question of whether the addition of WBRT to SRT is more beneficial than SRT alone has been addressed in various studies. However, the primary tumors site in these studies varied and included, such as breast cancer, renal carcinoma, melanoma and others, but brain metastases show different behavior. Whether or not SRT combined with WBRT is better for NSCLC patients remains controversial [14]. The meta-analysis for WBRT plus SRT compared with SRT alone, especially for NSCLC patients with brain metastasis, have not been previously conducted. Our study could provide guidance for oncologist as they develop treatment plan for some patients.

Chemotherapy

Two studies [5, 8] included patients treated with radiochemotherapy and the influence of treatment on disease development in these patients was assessed. In Doo-Sik Kong's study, [5] patients who received chemotherapy had a significantly longer survival time than those who did not.

Shortcoming

InTodd W's study [4], every patient had one brain metastasis, and the small sample size may have led to selection bias that influenced the outcome. Because the data were not sufficient in the other 4 studies [4-6, 9], the size was small, and therefore, the estimation of risk of radiation toxicities may have been biased.

Conclusions

The patient with only one metastasis could not obtain benefits from WBRT combined with SRT. NSCLC patients with multiple brain metastases may obtain benefits from the radiotherapy program, which could prolong overall survival compared with treatment with SRT alone, however the evidence is not sufficient, the conclusion from **Figure 2** was included all patients, which also included the patients with single brain metastasis. Although patients can obtain a benefit from SRT for its lower rate of radiation toxicities, the conclusion whether the WBRT and SRT or SRT alone is beneficial for patients is not to be made easily, patients with high KPS score may endure the toxic and side effects of WBRT combined with SRT, the detailed research need large sample to analysis. These results from the meta-analysis may aid the oncologist in the selection of a radiation regimen for NSCLC patients with brain metastases. A vast amount of factors may affect the treatment effect, such as age, gender, weight, race, chronic foundation disease and others. So we should still devote ourselves to the research of cancer treatment.

Disclosure of conflict of interest

None.

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