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Original Article

Whether applying whole brain radiotherapy in stereotactic radiotherapy benefits for patients with brain metastases in Chinese population: evidence from meta-analysis

Wenmei Su[1*], Zhennan Lai[1*], Fenping Wu[2], Hongsheng Guo[3], Zhixiong Yang[1]

[1]Department of Oncology in Affiliated Hospital of Guangdong Medical University, Zhanjiang 524023, Guangdong, China; [2]Department of Radiotherapy, The Tumor Hospital of Chengdu, The Seventh People's Hospital of Chengdu, Chengdu 610041, Sichuan, China; [3]Department of Histology and Embryology, Guangdong Medical University, Dongguan 523808, Guangdong, China. [*]Equal contributors.

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Abstract: This study aimed to perform a meta-analysis on patients with brain metastasis in Chinese population treated with stereotactic radiotherapy (SRT) plus whole-brain radiotherapy (WBRT) boost (hereafter denoted as SRT+WBRT) versus SRT alone. Methods: A comprehensive electronic search was conducted using an Internet retrieval system to identify eligible studies. The primary outcomes included one-year intracranial recurrent rate (ICR), one-year overall survival (OS), and radiation toxicity. Odds ratios and 95% confidence interval were calculated to compare the effects. Results: Twelve studies with 1046 patients were eligible for this meta-analysis. With regard to one-year ICR, SRT+WBRT showed a significant improvement compared with SRT alone (OR: 0.38, 95% CI: 0.24~0.59, $P < 0.0001$). When targeted on one-year OS, obvious differences favoring SRT+WBRT rather than SRT alone was found (OR: 0.71, 95% CI: 0.54~0.93, $P = 0.01$). However, no statistical difference radiation toxicity was observed in SRT+WBRT and SRT alone (OR: 0.95, 95% CI: 0.45~1.98, $P = 0.89$, respectively). Conclusions: For selected patients, the application of WBRT in SRT treatment performed an obviously better effect in controlling tumor recurrence and improving prognosis compared with SRT alone, and simultaneously shared the equivalent safety in radiation toxicity. For BM patients, SRT+WBTR exerted an obviously better effect in one-year ICR and one-year OS compared with WBRT alone. Thus, to improve the therapeutic effect, SRT+WBRT should be a routine treatment for patients with brain metastases in Chinese population.

Keywords: Stereotactic radiotherapy, whole-brain radiotherapy, brain metastases, Chinese population, meta-analysis

Introduction

Brain metastasis (BM) is one of the most common brain malignant neoplasms with an incidence of 25%-40% in cancer patients [1, 2]. Lung cancer approximately accounts for one-half of all BMs [3]. Without treatment, patients with BMs have a survival period of only 1-2 months. Therapeutic methods of BMs include whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), surgery and chemotherapy, but single treatment does not result in breakthrough. Previously, WBRT is the standard treatment for BMs, which can relieve clinical symptoms of most patients, but with a short median survival period of only 3-6 months and inevitable side-effects [4]. With advances in treatment, SRS, which provides a single irradiation with high dose for small intracranial lesions, offers an alternative of minimally invasive operation for surgical removal of BMs [5]. According to an evidence-based meta-analysis, SRS-boosted WBRT can improve local control compared with WBRT alone, but no gain in overall survival (OS) is observed [6]. To improve the effect of radiotherapy, only increasing radiation dose is feasible in theory; however, the range of increasing dose is limited and will lead to necrosis or edema of brain tissue with late response [7].

Since 1990s, stereotactic radiotherapy (SRT), which uses multiple fractions in BM treatment, is developed as a new technology based on

SRS and satisfies the requirements of clinical radiation biology more. With the advantages of accurate positioning and low radiation injury, SRT is widely used as a new option for BMs in Chinese population. However, whether it is necessary to combine SRT with WBRT in the management of BM patients is still not reach an agreement. Due to the increase of side-effect after WBRT, some experts have questioned the conventional usage of WBRT in patients with BM. The curative effects of SRT plus WBRT boost (hereafter denoted as SRT+WBRT) for patients with BM originating from multiple cancers have been reported in several studies compared with SRT alone, but the conclusions are controversial. Therefore, we conducted this meta-analysis to assess the efficacy of SRT+WBRT versus (vs.) treatment with SRT alone for patients with BM in Chinese population.

Materials and methods

Search strategy

We searched PubMed, Embase, Medline, Cochrane Central Register of Controlled Trials, and China National Knowledge Infrastructure for relevant studies via an Internet retrieval system. The retrieval period was until September 1, 2015, with no language restrictions. The search terms used are as follows: "stereotactic radiotherapy," "whole-brain radiotherapy", "brain metastases/metastasis", "random/randomized", and "Chinese". We also performed a manual research for the reference lists of the relevant trials and review articles to identify additional studies.

Inclusion and exclusion criteria

The inclusion criteria are as follows: (1) Trials designed by a randomized controlled study; (2) Patients diagnosed as BM of any malignancy; (3) subject investigated focused on Chinese population; (4) Treatment using combined irradiation of SRT plus WBRT as treatment group and single-radiation regimen of SRT alone as control group; and (5) Studies reporting at least one primary therapeutic outcome of the efficacy of SRT plus WBRT compared with that of SRT alone.

The exclusion criteria are as follow: Reviews, conference abstracts, editorials, or case reports; trials designed by a cohort study; research on other treatment methods; and studies with unavailable data. If more than one trial reported the same or overlapping patient groups from one institution, only those with the largest series were selected to avoid duplicated information.

Data extraction

Two authors (Su and Lai) independently reviewed the eligible studies and extracted the data according to the inclusion and exclusion criteria. Any disagreement was resolved by discussion. The following data were collected from each study: (1) publication details, such as first author's name, original country, year of publication, research period, sample size, and ratio of case and controls; (2) clinical characteristics, including number of brain metastases, number of extracranial metastases, score of Karnofsky performance scale, and radiation doses; and (3) therapeutic outcomes, contained one-year intracranial recurrent rate (ICR), one-year OS, and radiation toxicity. The ICR defined as occurrence of new metastasis before the end of follow-up. OS defined as the time from the beginning of radiotherapy to the date of death caused by any reason. The evaluation of radiation toxicity (≥ Grade 3) followed the central nervous system toxicity criteria of the Radiation Therapy Oncology Group [9].

Quality assessment

The quality of eligible studies was assessed by the Newcastle-Ottawa (NOS) for quality of case-control and cohort studies, which was commended by the Cochrane Non-Randomized Study Method Working Groups [10, 11]. The NOS allocated a score ranging within 0-9 points for four broad aspects: selection of the case and control groups (four criteria, one point for each), comparability of the case and control group (one criterion, one point), assessment of exposure (one criterion, two points), and outcome of the participants (two criteria, one point for each). Articles satisfying five points or more were regarded high-quality studies, and only these works were included in our meta-analysis.

Statistical analysis

In this meta-analysis, the results of each trial were treated as dichotomous frequency data, and event number were extracted from each

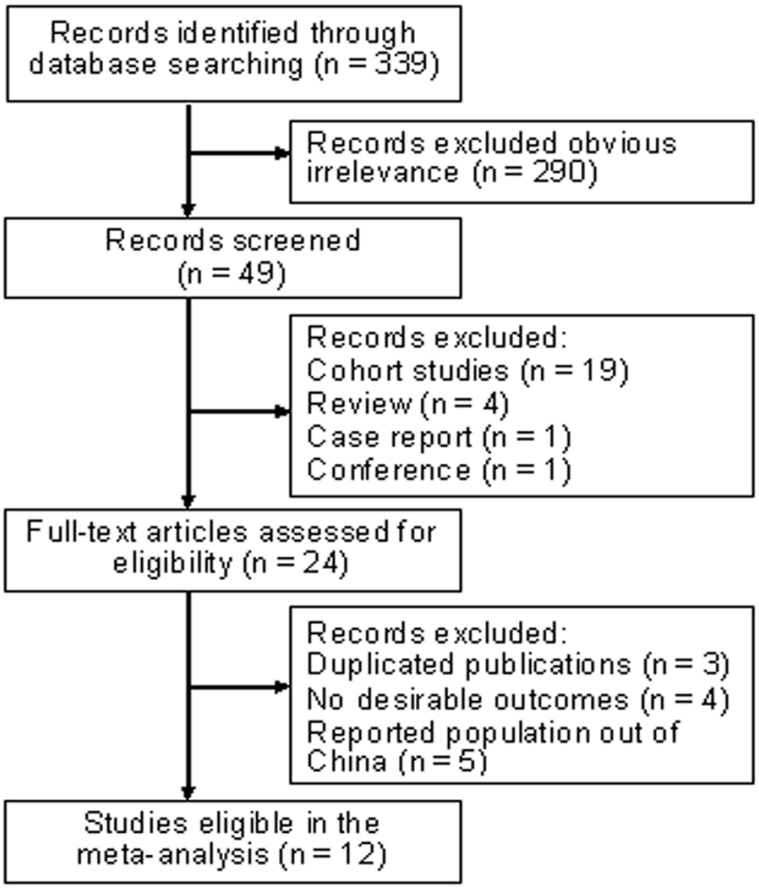

Figure 1. Flow diagram of the study selection process and specific reasons for exclusion in the meta-analysis.

included study. When the event number was not directly provided in the original data, then the method reported by Zhou et al was conducted to obtain required information from survival curves [12]. Combined odds ratios (ORs) and 95% confidence interval (CI) were used to evaluate the overall effects of SRT+WBRT on therapeutic outcome related to single radiotherapy regimen [13]. This meta-analysis was conducted using RevMan 5.2 software provided by Cochrane Collaboration.

Between-study heterogeneity was estimated using the chi-squared test based on *Q* statistic [14]. Results were considered with statistical significance when $P < 0.1$. I^2 was also used to quantify the heterogeneity by dividing the value into three classes ($I^2 < 25\%$, no heterogeneity; $I^2 = 25\%$-50%, moderate heterogeneity; and $I^2 > 50\%$, extreme heterogeneity). When no significant heterogeneity was observed, a fixed effect model (Mantel-Haenszel method) was performed on meta-analysis; otherwise, a random effect model (DerSimonian and Laird method) was applied.

Results

Literature search results

We identified a total of 339 potential relevant studies during the primary literature search, of which 12 articles [5, 15-25] with a total of 1046 patients were eligible for meta-analysis (**Figure 1**).

These 12 trials all originated from China; 10 were published in Chinese [15, 16, 18-25], whereas the two were in English [6, 17]. The publication dates ranged from 2003 to 2013, and the researching times were from 1995 to 2012. The numbers of brain metastases lesions were from 1 to 10 unequally, and patients with single lesion accounted for 40.1% of the total samples. Seven trials [5, 15, 16, 18, 19, 22, 25] researched patients with BM caused by lung cancer, whereas the other five studies [17, 20, 21, 23, 24] focused on patients with brain metastases originated from multiple cancers. According to the quality criteria, all of the trials were of high quality (five points or more). **Table 1** summarizes the main characteristics of the eligible trials.

Meta-analysis of one-year ICR

Six studies with 481 patients reported one-year ICR which ranged within 72.2%-88.4% and 57.7%-72.9% in SRT+WBRT, and SRT alone group, respectively. Pooled results explored that there was SRT+WBRT treatment had an effectively better for one-year LCR than SRT alone (Pooled OR: 0.38; 95% CI: 0.24-0.59; $P < 0.0001$; fixed model). No heterogeneity existed among the studies for this outcome ($I^2 = 8.0\%$, PH = 0.37). **Figure 2** shows a forest plot for this result.

Meta-analysis of one-year LCR

Eight studies with 633 patients estimated one-year LCR which ranged within 53.6%-97.7% and 66.7%-93.1% in SRT+WBRT, and SRT-alone

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

Study (year)	Language	Year of research	Sample size (T/C)	Primary tumor	No. of BM (% single)	No. of ECM	KPS score (≥ 70/< 70)	Radiation doses (Gy)	Outcomes	Quality score
Ye et al. (2013)	Chinese	2004-2012	66 (36/30)	NSCLC	1-4 (27.3%)	50	35/31	SRT alone: 42-45; SRT+WBRT: (12-15)+(42-45)	1-year OS, 1-year ICR	6
Cheng et al. (2013)	Chinese	2002-2009	60 (45/15)	NSCLC	1-4 (26.7%)	27	42/18	SRT alone: 15-30; SRT+WBRT: (10-15)+(30-40)	1-year LCR, 1-year OS	5
Ma et al. (2012)	English	2001-2011	171 (117/54)	NSCLC	≥ 1 (48.5%)	45	139/32	SRT alone: 16-54; SRT+WBRT: (18-42)+(30-40)	1-year LCR, 1-year OS, radian toxicity	7
Chen et al. (2012)	English	1995-2010	98 (54/44)	Multiple	≥ 2 (0.0%)	88	47/51	SRT alone: 24-50; SRT+WBRT: (20-45)+(30-40)	1-year OS, 1-year ICR	7
Li et al. (2012)	Chinese	1995-2006	99 (40/59)	Lung cacner	1-6 (50.5%)	54	52/47	SRT alone: 12-49; SRT+WBRT: (10-15)+(30-36)	1-year LCR 1-year OS, 1-year ICR	6
Lu et al. (2011)	Chinese	2003-2007	82 (54/28)	Lung cacner	1-10 (20.7%)	NR	NR	SRT alone: 12-30; SRT+WBRT: (12-30)+(28-32)	1-year LCR 1-year OS, radian toxicity	5
Wei et al. (2010)	Chinese	1999-2004	78 (39/39)	Multiple	1-6 (62.8%)	31	61/17	SRT alone: 11-40; SRT+WBRT: (12-30)+(30-40)	1-year OS	6
Ding et al. (2008)	Chinese	2000-2005	40 (20/20)	Multiple	1-4 (35.0%)	24	NR	SRT alone: 28-32; SRT+WBRT: (18-20)+(30-36)	1-year LCR 1-year OS, 1-year ICR	6
Cai et al. (2007)	Chinese	1996-2005	81 (40/41)	Lung cacner	1-5 (56.8%)	20	NR	SRT alone: 25-60; SRT+WBRT: (25-40)+(32-40)	1-year LCR 1-year OS, radian toxicity	6
Sun et al. (2006)	Chinese	2001-2005	86 (43/43)	Multiple	≥ 1 (79.1%)	22	73/13	SRT alone: 18-32; SRT+WBRT: (15-30)+(30-40)	1-year LCR, 1-year ICR 1-year OS, radian toxicity	6
Zhang et al. (2004)	Chinese	1995-2003	92 (66/26)	Multiple	≥ 1 (41.3%)	NR	NR	SRT alone: 16-22; SRT+WBRT: (16-22)+(36-40)	1-year LCR, 1-year ICR 1-year OS	5
Sheng et al. (2003)	Chinese	1996-2001	93 (52/41)	Lung cacner	1-5 (52.2%)	23	39/54	SRT alone: 25-60; SRT+WBRT: (25-60)+(30-45)	1-year LCR 1-year OS, radian toxicity	5

T: treatment group; C: control group; BM: brain metastases; ECM: extracranial metastases; NR: none reported; KPS: Karnofsky performance scale; SRT: stereotactic radiotherapy; WBRT: whole-brain radiotherapy; LCR: local control rate; OS: overall survival; ICR: intracranial recurrent rate; NSCLC: non small cell lung cancer.

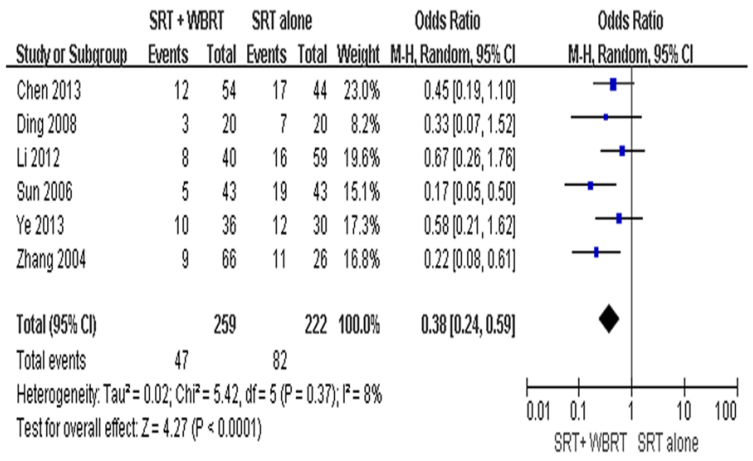

Figure 2. Meta-analysis results for one year intracranial recurrent rate comparing SRT+WBRT with SRT alone.

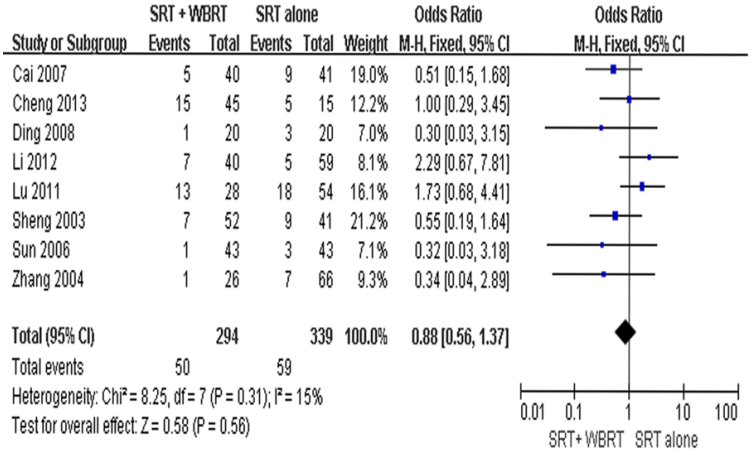

Figure 3. Meta-analysis results for one year local control rate.

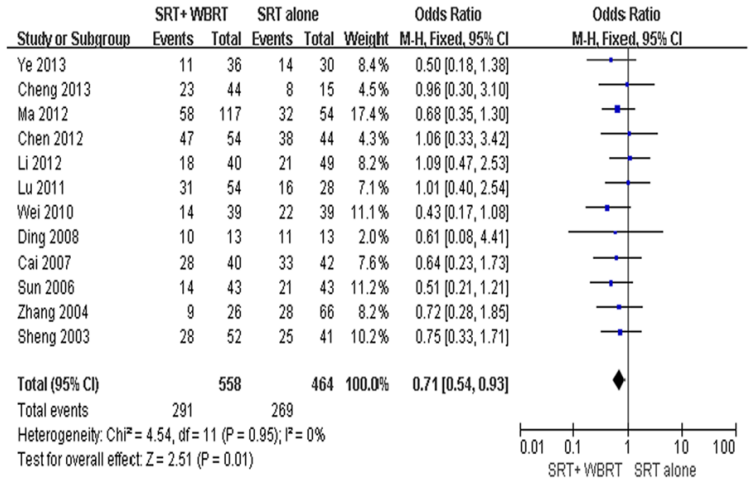

Figure 4. Meta-analysis results for one year overall survival rate.

group, respectively. Pooled ORs and 95% CI calculated from the individual studies indicated that there was no significantly difference for one-year LCR between SRT+WBRT treatment and SRT alone (Pooled OR: 0.88; 95% CI: 0.56-1.37; P = 0.56; fixed model). No heterogeneity existed among the studies for this outcome (I^2 = 15.0%, PH = 0.31). **Figure 3** shows a forest plot for this result.

Meta-analysis of one-year OS

All of the twelve studies with 1022 patients evaluated the one-year OS, which ranged within 13.0%-69.4% and 13.6%-57.6% in SRT+WBRT, and SRT-alone group, respectively. Pooled outcomes showed that SRT+WBRT treatment can significantly improve the one-year OS on patients with brain metastases rather than SRT alone (Pooled OR: 0.71; 95% CI: 0.54-0.93; *P* = 0.01; fixed model) and no heterogeneity existed (I^2 = 0.0%, PH = 0.95). **Figure 4** shows a forest plot for this result.

Meta-analysis of radiation toxicity

Five studies with 514 patients reported radiation toxicity which ranged within 5.0%-7.3% and 1.9%-14.0% in SRT+WBRT, and SRT-alone group, respectively. Pooled ORs and 95% CI indicated that there was no statistical difference between SRT+WBRT group and SRT alone group (Pooled OR: 0.95; 95% CI: 0.45-1.98; P = 0.89; fixed model). No heterogeneity existed among the studies for this outcome (I^2 = 0.0%, PH = 0.63). **Figure 5** shows a forest plot for this result.

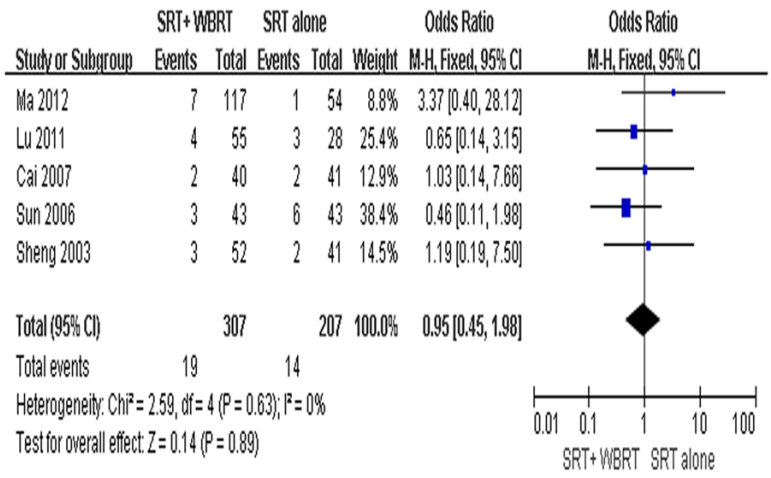

Figure 5. Meta-analysis results for radiation toxicity.

Discussion

Regardless whether single or multiple, BM prognosis is poor, and curative effect is not satisfactory. During the past decades, WBRT has been the standard treatment for BMs because it can palliates the neurological symptoms of BMs. However, its therapeutic effects are unsatisfactory, with a low local control rate and a short median survival time because of the limited radiotherapy doses and a high incidence of severe complications [26]. Therefore, the discovery of a more effective method is necessary.

With the development of new technology, SRS and SRT are widely used in clinic, but their mechanisms are not completely the same. SRS refers to a single dose of radiation delivered with high precision focally to a brain metastasis with the intent of maximizing local control while sparing normal brain tissue. SRS can form an extremely steep dose gradient in the edge of target region by non-coplanar area radiation of high energy X-ray. SRS can not only kill tumor cells effectively, but also protect the sensitive tissue surrounding local tumor; thus, this method can be applied to a single high-dose irradiation, without affecting the radiosensitivity of tumor cells [22]. Despite the advantages of high precision, and safe and reliable effects, SRS can also have limitations [27]. SRT, as a new technology developed on the basis of SRS since the early 1990s, conform more to the requirements of radiation clinical biology by using multiple integral treatments. The SRT mechanism can be summarized as follows: almost full recovery of sublethal cells in normal tissue caused by the irradiated injury in treatment interval, and reoxidation of anoxic tumor cells and transfer of cell in G0 phase into sensitive to radiation [28]. Thus, compared with SRS, SRT improves radiation technology by providing accurate localization and quantification of lesions and radiation dose, and by using multiple fractionated radiations, which can fix the flaws of SRS and achieve a better control of malignance without causing serious damage to normal tissues.

SRT shows a series of advantages over SRS and is thus widely used in clinical settings. However, the effects of SRT on WBRT are still unclear. WBRT can kill the tumor infiltrating cells around BMs and eliminate the tiny lesions, which cannot be found by iconography, thus the treatment may have a good effect on preventing BM recurrence [29]. However, according to some researchers, the prophylactic radiation of the whole brain cannot effectively prevent the second metastases of primary tumor in brain and has minimal benefit on patients with short expected survival [30]. Moreover, WBRT treatment is associated with side effects, such as alopecia, fatigue, and possible neurocognitive sequel, in those few patients with longer survival [31]. Thus, whether SRT+WBRT is an improved treatment warrants a comprehensive evaluation.

With respect to survival, we learned from the pooled outcomes of this meta-analysis that the therapeutic strategy of SRT+WBRT can yield survival benefits in patients with BMs when the alternative treatment is WBRT alone. The favorable survival rate of SRT+WBRT is probably attributed to their complementary effect. From the results in this paper, we can know that one-year ICR and one-year OS rate was found more longer in SRT+WBRT than SRT alone, which suggests that the length of survival is more influenced by WBRT. WBRT can only give a highest dose of 36-40 Gy, which is still far less than the lethal dose of tumor, because of the limiting

radiation tolerance dose of normal brain tissue; consequently, around 35%-60% of the patients still experience local control failure [32]. Therefore, the role of SRT as a boost to optimize local control when overall brain control is maximized by WBRT should be determined. When focused on one-year ICR, all of the results in our meta-analysis showed that SRT+WBRT therapy is better in controlling intracranial recurrence within a year than SRT alone. Because low radiological dose exists in SRT treatment alone, specifically for BMs with large volume, thereby SRT alone results in tumor relapse tendency. However, WBRT is effective in reducing the new lesions of BMs, specifically in patients with local BMs [33]. Therefore, the SRT+WBRT can significantly increase the ICR and OS in patients with multiple BMs.

The pooled outcomes of meta-analysis come from a comprehensively statistical analysis based on the results of a number of previous research, thus some biases are inevitable as follows: (1) most of the included studies did not clarify the method of randomization, blinding, and allocation concealment, which may lead to possible performance and measurement bias; (2) although the WBRT doses in these studies had slight differences, the SRT doses were within a wide range, and the radiation technologies were different, which may contribute to the existence of publication bias and an overestimation of efficacy; (3) the primary tumors of BM were not homogeneity, and the outcome measure were inconsistent, which may distort the results. In future, more well-designed and large-sample RCTs about this topic are needed to explore the exact value of WBRT combined with SRT treatment for BMs.

Conclusion

For selected patients, the application of WBRT in SRT treatment performed an obviously better effect in controlling tumor recurrence and improving prognosis compared with SRT alone, and simultaneously shared the equivalent safety in radiation toxicity. For BM patients, SRT+WBTR exerted an obviously better effect in one-year ICR and one-year OS compared with WBRT alone. Thus, to improve the therapeutic effect and prolong the survival time, we suggest that SRT+WBRT should be a routine treatment for patients with both single and multiple brain metastases in Chinese population.

Disclosure of conflict of interest

None.

Address correspondence to: Zhixiong Yang, Department of Oncology in Affiliated Hospital of Guangdong Medical University, Zhanjiang 524023, Guangdong, China. Tel: +86-0759-2387458; Fax: +86-0759-2388305; E-mail: yangzhixiong1963@hotmail.com

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