RESEARCH ARTICLE

# Whole Brain Radiotherapy Combined with Stereotactic Radiotherapy Versus Stereotactic Radiotherapy Alone for Brain Metastases: a Meta-analysis

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## Abstract

**Aim: This study was to evaluate the effect of whole brain radiation (WBRT) combined with stereotactic radiotherapy (SRS) versus stereotactic radiotherapy alone for patients with brain metastases using a meta-analysis. Materials and Methods: We searched PubMed, EMBASE, Cochrane Library from their inception up to October 2013. Randomized controlled trials involving whole brain radiation combined with stereotactic radiotherapy versus stereotactic radiotherapy alone for brain metastases were included. Statistical analyses were performed using RevMan5.2 software. Results: Four randomized controlled trials including 903 patients were included. The meta-analysis showed statistically significant lowering of the local recurrence rate (OR=0.29, 95%CI: 0.17~0.49), new brain metastasis rate (OR=0.45, 95%CI: 0.28~0.71) and symptomatic late neurologic radiation toxicity rate (OR=3.92, 95%CI: 1.37~11.20) in the combined group. No statistically significant difference existed in the 1-year survival rate (OR=0.78, 95%CI: 0.60~1.03). Conclusions: The results indicate that whole brain radiotherapy combined with stereotactic radiotherapy has advantages in local recurrence and new brain metastasis rates, but stereotactic radiotherapy alone is associated with better neurological function. However, as the samples included were not large, more high-quality, large-sample size studies are necessary for confirmation.**

**Keywords:** Brain metastases - whole brain radiation - stereotactic radiotherapy - meta-analysis

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## Introduction

Currently, an increasing number of patients with cancer develop brain metastases, over 100,000 patients were diagnosed brain metastases each year in the United States (Stelzer et al., 2013). Brain metastases leave patients with a very poor prognosis, and the average survival was 1–2 months without treatment (Patil et al., 2012). The most common primary cancers metastasis to brain were lung cancer, renal carcinoma, breast cancer and esophagus cancer (Schouten et al., 2002). Patients with one metastatic lesion and well-controlled systemic disease can get good prognosis after surgery, however, the use of surgery in the treatment of brain metastases still remains controversial (Yaeger et al., 2013).

In 1970s, the first option for brain metastases was the whole brain radiotherapy (WBRT), in recent years, the use of WBRT has decreased mainly because of the late toxicities are not self-limited and may have severe consequences that produce irreversible neurocognitive degeneration such as leukoencephalopathy, memory loss, emotional dysfunction, dementia, stupor, and coma (Abe et al., 2012; Mctyre et al., 2013).

As the long-term adverse effect of WBRT is severe and irreversible, the new treatment option of stereotactic radiotherapy (SRS) has been popular. Firstly, the invasion is less than surgical resection; Secondly, compared with the WBRT, more healthy tissue can be exposed (Lassman et al., 2003; Linskey et al., 2010). Unfortunately, a higher rate of local tumor recurrence was shown by SRS monotherapy (Aoyama et al., 2006).

Investigators tried to combine the WBRT and SRS together as a new option for brain metastases, however, the adverse effect is more severe in the decline of learning and memory functioning compared with SRS monotherapy (Chang et al., 2009). As the efficiency of WBTR plus SRS and SRS alone still remains unclear, this meta-analysis is to compare the outcomes of the two therapies for brain metastases in order to find a profit treatment option.

## Materials and Methods

*Literature Search*

We did a systematic review in accordance with the PRISMA guidelines (Moher et al., 2009). We searched

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**Table 1. Characteristics of the Included RCTs**

| Study(year) | Country | Patients | | Brain metastases | Radiation dose(Gy) | |
|---|---|---|---|---|---|---|
| | | WBRT+SRS | SRS | | WBRT+SRS | SRS |
| Chang et al. 2009 | USA | 28 | 30 | 1~3 | 30 | 19~20 |
| Rades et al. 2008 | Germany | 51 | 93 | 1~3 | 20~40 | 20~25 |
| Aoyama et al. 2006 | Japan | 65 | 67 | 1~4 | 30 | 22~25 |
| Sneed et al. 2002 | USA | 301 | 268 | 1~4 | 30~50.4 | unclear |

**Table 2. Methodological Quality Assessment of the Included Studies**

| Study(year) | Randomized | Allocated concealment | Blinding | Lost of follow up | Data integrity | Bias |
|---|---|---|---|---|---|---|
| Chang et al. 2009 | low | low | low | low | low | unclear |
| Rades et al. 2008 | unclear | unclear | unclear | low | low | unclear |
| Aoyama et al.2006 | low | unclear | unclear | low | low | unclear |
| Sneed et al. 2002 | unclear | unclear | unclear | low | low | unclear |

PubMed, Embase, the Cochrane Central Register of Controlled Trials from their inception up to October 2013. We used search terms including "whole brain radiation" or "whole brain radiotherapy", "metastases tumor of brain" or "brain metastases" or "brain metastasis", "stereotactic radiotherapy" or "stereotactic radiosurgery". Controlled vocabularies (eg, Medical Subject Heading terms) were used to identify synonyms. In addition, we manually reviewed the references of included studies and of review articles to identify additional articles not found by the initial search. All studies in human beings that were published in full text, abstract, or poster form were eligible for inclusion, with no restrictions on publication date, language, or status. Ongoing clinical trials were identified from the clinicaltrials.gov website, and additional studies of interest were found through internet searches and hand searches of bibliographies. We attempted contact with authors to clarify published data if needed.

The inclusion criteria were as follows: (1) any study on the treatment of brain metastases using WBRT combined SRS and SRS alone that has been or will be published; (2) randomized controlled trials; (3) included participants 18 years of age or older; (4) patients definitely diagnosed as having brain metastases as study subjects.

*Outcome*

The outcomes were 1-year survival rate, local recurrence rate, symptomatic late neurologic radiation toxicity rate and new brain metastases rate.

*Data extraction*

We selected studies and extracted the data according to a standard Cochrane protocol (Furlan et al., 2009). Two investigators independently reviewed eligible studies for study characteristics and clinical relevance and, if appropriate, extracted study data. We used consensus and a third reviewer, if necessary, to resolve disagreements. The following information was extracted onto standardized data collection forms: author, trial title and year of publication, study design, length of follow-up, number of participants and their characteristics.

*Risk of bias assessment*

We used the Cochrane risk of bias method to appraise study quality (Higgins et al., 2008); two reviewers independently rated each study on the six domains (low, unclear, or high bias for sequence generation; allocation concealment; blinding of participants, personnel and outcome assessors; incomplete outcome data; selective outcome reporting; and other sources of bias) and then compared assessments. Any disagreements were solved by consensus and a third reviewer.

*Statistical analysis*

We anticipated heterogeneity between studies due to different methods of analysis, different lag exposures, and population differences. Meta-analyses was done by software RevMan5.2 provided by Cochrane Collaboration. Enumeration data and measurement data were analyzed using odds ratio (OR), mean and standard deviation (SMD) respectively, for statistical efficacy analysis. Statistical heterogeneity between studies was evaluated using the $\chi 2$ test and the $I^2$ statistic, judging values of $I^2$less than 25% to be minimal, less than 50% to be moderate, and 50% or greater to be substantial. If there was no statistically significant heterogeneity in a given set of data, the fixed effects model was used for meta-analysis. If the results of trials showed heterogeneity, the random effects model was used. If heterogeneity among the groups is too large, then the descriptive analysis was used. We did subgroup analyses to establish whether karnofsky performances score (RPA) class affected our conclusions.

## Results

*Study Characteristics*

378 articles were initially reviewed under the search strategy and data collection methods. Duplicated studies were removed using Endnote software. Non-clinical randomized studies and irrelevance studies were excluded by reading the title and abstract. Finally 4 randomized controlled studies, a total of 903 patients were included. They are from American, Japan and Germany. All the included studies were followed up more than 12 months (Table 1).

*Quality Assessment of Included Studies*

Two of the studies (Aoyama et al., 2006; Chang et al., 2009) mentioned randomization, permuted-blocks randomization algorithm was used with a block. Other

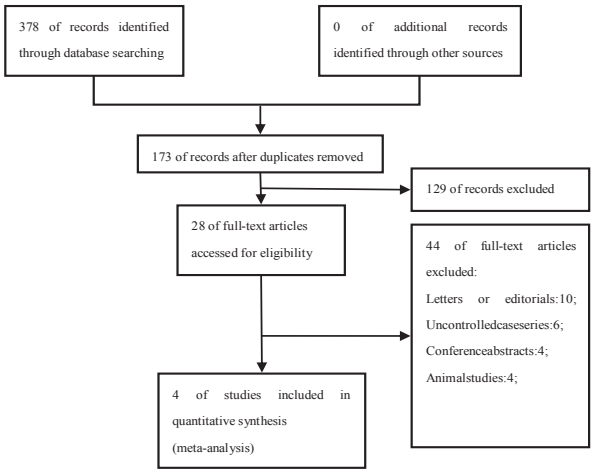


**Figure 1. Progress of Systematic Review of Literature**

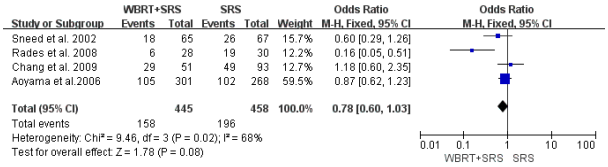


**Figure 2. Meta-analysis of 1-Year Survival Rate**

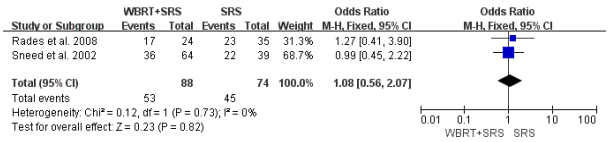


**Figure 3. Meta-analysis of 1-year Survival Rate of RPA Class I**

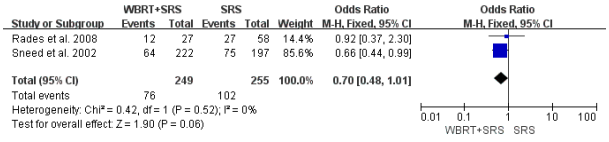


**Figure 4. Meta-analysis of 1-year Survival Rate of RPA Class II**

studies did not mentioned specific random method. None of the studies described the implementation of allocation concealment. One study (Chang et al., 2009) used blinding in patients' data, the others never used blinding. None of the studies had incomplete outcome data. There was no selective outcome reporting in the included studies and other potential threats to validity were unclear (Table 2).

*Outcome of Meta-Analysis*

*1-Year survival rate*

All the studies (Aoyama et al., 2006; Chang et al., 2009; Rades et al., 2008; Sneed et al., 2002) that including 903 patients reported the 1-year survival rate, heterogeneity was existed among them ($p$=0.02, $I^2$=68%), the random effects model was used, the result showed that there was no significant statistics difference between the two groups (OR=0.78, 95%CI: 0.60~1.03; $p$=0.08) (Figure 2).

*Subgroup analyzes*

Two prognostic classes were defined (RPA class I: Karnofsky performance score (KPS) ≥70%, age < 65 years, controlled primary, no extra cranial metastases; RPA class II: KPS ≥70%, age≥65 years and/or uncontrolled primary and/or extra cranial metastases) in order to elaborate the association with the RPA class on the survival rate.

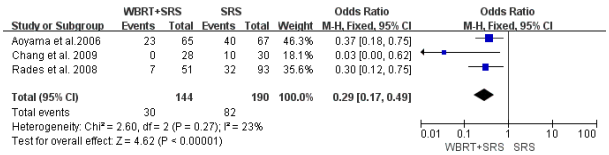


**Figure 5. Meta-analysis of Local Recurrence Rate**

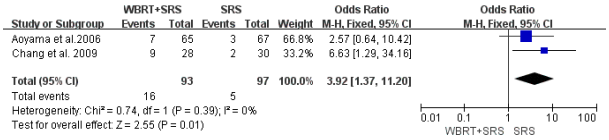


**Figure 6. Meta-analysis of Symptomatic Late Neurologic Radiation Toxicity Rate**

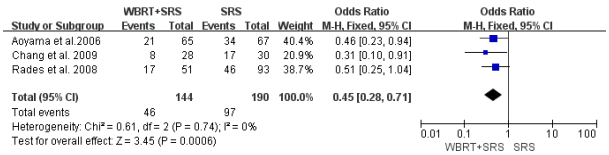


**Figure 7. Meta-analysis of New Brain Metastases Rate**

*RPA class I: 1-Year survival rate*

Two studies (Sneed et al., 2002; Rades et al., 2008) that contains 162 patients evaluated the 1-year survival rate of RPA class I, there is no heterogeneity between them ($p$=0.73, $I^2$=0%), the fixed effects model was used, the result showed that there was no significant statistics difference between the two groups (OR=1.08, 95%CI: 0.56~2.07; $p$=0.82) (Figure 3).

*RPA class II: 1-Year survival rate*

Two trials (Rades et al., 2008; Sneed et al., 2002) that including 504 patients reported the 1-year survival rate of RPA class II, there is no heterogeneity between them ($p$=0.52, $I^2$=0%), the fixed effects model was used, the result showed that there was no significant statistics difference between the two groups (OR=0.70, 95%CI: 0.48~1.01; $p$=0.06) (Figure 4).

*Local recurrence rate*

Three trials (Aoyama et al., 2006; Chang et al., 2009; Rades et al., 2008) contains 334 patients evaluated the local recurrence rate, there is no heterogeneity among them ($p$=0.27, $I^2$=23%), the fixed effects model was used, the result showed that there was a significant statistics difference between the two groups (OR=0.29, 95%CI: 0.17~0.49; $p$<0.00001) (Figure 5).

*Symptomatic late neurologic radiation toxicity*

Two studies (Aoyama et al., 2006; Chang et al., 2009) that including 190 patients reported the symptomatic late neurologic radiation toxicity rate, there is no heterogeneity between them ($p$=0.39, $I^2$=0%), the fixed effects model was used, the result showed that there was a significant

statistics difference between the two groups (OR=3.92, 95%CI: 1.37~11.20; $p$=0.01) (Figure 6).

*New brain metastases*

Three studies (Aoyama et al., 2006; Chang et al., 2009; Rades et al., 2008) that including 334 patients reported the new brain metastases rate, there is no heterogeneity among them ($p$=0.74, $I^2$=0%), the fixed effects model was used, the result showed that there was a significant statistics difference between the two groups (OR=0.45, 95%CI: 0.28~0.71; $p$=0.0006) (Figure 7).

## Discussion

There are several options, such as surgery, WBRT, SRS and chemotherapy for patients with brain metastases in progression (Ammirati et al., 2010). Our research is to elaborate the effect of WBRT combined SRS and SRS alone for brain metastases; as a result, four randomized controlled trails including 903 patients were analyzed. Finally, our research indicates that compared with SRS alone, WBRT combined SRS shows a better effect on the local recurrence rate, new brain metastases rate. However, the symptomatic late neurologic radiation toxicity rate in the WBRT combined SRS group is higher than the SRS alone group. And no difference of 1-year survival rate in the two groups.

The outcome of better local recurrence rate and new brain metastases rate may correlate to WBRT because which is also used to treat cancer patients with a high risk of developing brain metastases (termed prophylactic cranial irradiation (PCI)) and showed a good result. A meta-analysis published by Linden YM et al. indicates that PCI reduces the incidence of brain metastases and prolongs brain metastases-free period (Vander et al., 2001). Studies including NSCLC patients produced similar results (Gore et al., 2005).

Neurological function damage is obviously in the WBRT combined SRS group, such as learning decline and memory loss which is correlated to the quality of life. A randomized control trial that tested the neurological function by use the strategy of mini-mental status examination (MMSE) indicates that WBRT was effective at preventing the deterioration of neurological function in an early phase after treatment. However, to long-term survivors, WBRT could be a cause of continuous deterioration of neurological function (Aoyama et al., 2007). In another trail about NSCLC, Kundu S et al. also shows that stereotactic body radiotherapy has minimal toxicity but good efficacy (Kundu et al., 2013).

No difference of 1-year survival rate was found between the two kinds of therapies, which suggest length of survival was not influenced by SRS. Though the prognosis of brain metastases is associated with multiple factors such as age, performance status, and lack of extra cerebral metastases (Gaspar et al., 1997), the result still remains the same in the RPA class I and RPA class II group. However, Rades et al. showed that the 1-year survival rate was higher in the WBRT plus SRS group than in the SRS group, which may associated with age≤61 years, RPA classI, less brain metastases, longer interval from tumor diagnosis to irradiation and lack of extra cerebral metastases (Rades et al., 2008).

Four randomized controlled trails were included in our research. After the risk of bias and quality assessment, all the included studies showed high qualities and better conclusions. In a retrospective study published in 1999 by Sneed et al. (1999) which contains 62 patients with one to four brain metastases indicated similar conclusions with our research. 43 of them received WBRT+SRS and 19 of them received SRS alone, the results shouwed that no diffreence of 1-year survival rate was observed between the two groups (71% vs. 79%), the new brain metastases was higher in the SRS group (28% vs. 69%, $p$=0.03). A similar meta-analysis published by May Tsao also sopport our conclusion (Tsao et al., 2012).

Patients in our research were from different countries, as a result, there might be some differences exist among them. Additionally, the radiation does they received, their age, primary tumor, number of brain metastases and RPA class were totally different, these factors produced potential threatens to our results.

Our review has several limitations. First, blinding was not used in all the studies we included, this led to possible performance bias and measurement bias. Moreover, two of the four included studies did not describe the method of allocation. None of the study mentioned the allocation concealment, which led to selection bias. In addition, the primary tumors of brain metastases were not homogeneity and the out come measures were inconsistent. All these may distort the result. In future, more well-designed large scale randomized controlled clinical trials about whole brain radiotherapy combined with stereotactic radiotherapy compare with stereotactic radiotherapy alone for brain metastases should be taken for further study.

In conclusion, whole brain radiotherapy combined with stereotactic radiotherapy has an advantage on the local recurrence rate and new brain metastases rate, but stereotactic radiotherapy alone has an advantage on better neurological function and quality of life. In future, more well-designed large scale randomized controlled clinical trials about whole brain radiotherapy combined with stereotactic radiotherapy compare with stereotactic radiotherapy alone for brain metastases should be taken for further study in order to prove this result.

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