Systematic Review and Meta-Analysis

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Stereotactic radiosurgery (SRS) alone versus whole brain radiotherapy plus SRS in patients with 1 to 4 brain metastases from non-small cell lung cancer stratified by the graded prognostic assessment

A meta-analysis (PRISMA) of randomized control trials

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Abstract

Background: The present study aims to assess the therapeutic effect of whole brain radiotherapy (WBRT) for brain metastases from non-small cell lung cancer stratified by graded prognostic assessment (GPA) through meta-analysis.

Methods: The Cochrane Library, PubMed, Ovid (Elsevier) were retrieved. The included randomized controlled trials (RCT) were evaluated, and the statistical analysis was performed using RevMan 5.3 software. Cochrane handbook was applied to evaluate the methodological quality. Statistical significance was considered as $P < .05$.

Results: There were 2 randomized control trials identified eligible for the meta-analysis. Stereotactic radiosurgery (SRS)+WBRT did not significantly improved overall survival (OS) in 2 subgroups. (GPA <2: HR, 0.93; 95% confidence interval [CI], 0.61–1.40; $P = .71$), (GPA ≥2: HR, 1.28; 95% CI, 0.58–2.80; $P = .54$). The use of SRS+WBRT significantly extended brain tumor recurrence (BTR) free time in both subgroups (GPA <2: HR, 5.46; 95% CI: 2.09–14.22; $P = .0005$), (GPA ≥2: HR, 4.24; 95% CI: 2.24–8.04; $P < .00001$). The meta-analysis showed salvage therapy was more frequent among the SRS-alone in 2 subgroups (GPA <2: RR, 5.83; 95% CI: 1.47–23.06; $P = .01$), (GPA ≥2: RR, 2.53; 95% CI: 1.30–4.93; $P = .006$). The rate of grade 3 or 4 late radiation toxic effects was similar in 2 subgroups between SRS and SRS+WBRT

Conclusions: Because there are few studies to meet inclusion criteria, we cannot include more researches. The results of this analysis must be carefully interpreted in view of the unclear risk of bias in inclusion in the study. This meta-analysis of 2 randomized trails indicated that the combined treatment group did not show a survival benefit over SRS alone. However, SRS+WBRT improved BTR free time in the subgroup both GPA <2 and GPA ≥2 with the similar grade 3 or 4 late radiation toxicities.

Abbreviations: BTR = brain tumor recurrence, GPA = graded prognostic assessment, NSCLC = non-small cell lung cancer, OS = overall survival, SRS = stereotactic radiosurgery, WBRT = whole brain radiotherapy.

Keywords: brain metastases, graded prognostic assessment, meta-analysis, stereotactic radiosurgery, whole brain radiotherapy

1. Introduction

Lung cancer is a malignant tumor originating from the bronchial mucosa or gland. According to statistics released in 2017, the number of newly diagnosed lung cancer in 2017 is 222,500 and the death toll from lung cancer is 155,870.[1] A large number of studies have shown that smoking is the leading cause of increased mortality in lung cancer. The WHO classification of anatomical sites can be divided into central and peripheral lung cancer. There are 2 main types based on biology and treatment: small cell lung cancer and non-small cell lung cancer.[2] One of the most common distant metastases in non-small cell lung cancer is the brain. The prognosis of patients with non-small cell lung cancer was poor, and the average survival time was only 1 month to 2 months.[3] Radiation therapy technology and the rapid development of new therapies, such as molecular target therapy for advanced lung cancer with brain metastasis more treatment and more expectations, surgery, radiotherapy, and chemotherapy treatment of comprehensive application to a certain extent, prolong the survival period of patients with brain metastases from lung cancer, significantly improved the quality of life. However, there is still a lot of room to improve the survival time of patients with brain metastases from non-small cell lung cancer. Since the 1950s, the palliative whole brain radiotherapy (WBRT) has been widely used in the treatment of multiple brain metastases. Recent studies have shown that the poor prognosis of non-small cell lung cancer (NSCLC) patients has not resulted

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SQ and YL have contributed equally to this work.

The present meta-analysis was approved by the Ethics Committee of Affiliated Hospital of Hebei University.

The authors of this work have no conflicts of interest to disclose.

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in survival benefit, and even the symptoms of WBRT core function have been questioned. QUARTZ study[4] suggested that WBRT could not improve survival in patients with poor prognosis, but WBRT was still the major palliative treatment for most brain metastases. Results from the EORTC 22952-26001 trail were that WBRT did not improve overall survival.[5] NCCTG N107C/CEC study[6] showed that overall survival was similar between stereotactic radiosurgery (SRS) and WBRT. Therefore, the purpose of this study is to assess the therapeutic effect of SRS+WBRT versus SRS alone in the treatment brain metastases from non-small cell lung cancer based on graded prognostic assessment (GPA), a new prognostic classification system.

There have been multiple prognostic classification systems of brain metastases, and the most widely used is GPA established after comprehensive analysis of a number of research results in Radiation Therapy Oncology Group (RTOG) by Sperduto in 2008. The scoring system takes into account age, KPS score, brain presence of extracranial metastases, and number of brain metastases. They considered the GPA system to be objective, easy to quantify, and easy to use predictors.[7,8] Based on the differences between the brain metastases from primary tumor, the scholars further put forward the diagnostic specificity GPA (diagnosis-specific GPA, DS-GPA). Prognostic indicators are the same as GPA, and score of 4 points is better prognosis, and 0 points is the worst prognosis.

The results of a secondary analysis of a randomized control trail published on Radiation Oncology in 2017[9] is controversial with the results of secondary analysis of the JROSG 99–1[10] study. Here, our study is to assess the therapeutic effect of WBRT stratified by the GPA, relevant indices such as overall survival (OS) and brain tumor recurrence (BTR) free time to provide guidelines for clinical decisions and further researches.

2. Methods

All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.1. Search strategy

We searched all published articles in the Embase and PubMed databases between January, 1996 and February, 2018, and also searched the Cochrane Library databases with keywords: (((((((radiotherapy[Title/Abstract]) OR radiation therapy[Title/Abstract]) OR irradiation[Title/Abstract]) OR WBRT[Title/Abstract])) AND (((stereotactic radiotherapy[Title/Abstract]) OR stereotactic surgery[Title/Abstract]) OR radiosurgery[Title/Abstract]))) AND ((brain metastases) AND ((((((((((Non-small Cell Lung Cancer[MeSH Terms]) OR Carcinoma, Non Small Cell Lung) OR Carcinomas, Non-Small-Cell Lung) OR Lung Carcinoma, Non-Small-Cell) OR Lung Carcinomas, Non-Small-Cell) OR Non-Small-Cell Lung Carcinomas) OR Nonsmall Cell Lung Cancer) OR Non-Small-Cell Lung Carcinoma) OR Non Small Cell Lung Carcinoma) OR Carcinoma, Non-Small Cell Lung) OR Non-Small Cell Lung Cancer)).

2.2. Study selection

Only English-language literatures were included. Firstly, the selection was conducted by screening abstracts and titles, followed by perusing the full articles. Selecting all trails was conducted independently by 2 reviewers using the exclusion and inclusion criteria. A third reviewer was invited to determine when there were disagreements on whether an article should be included.

2.3. Inclusion and exclusion criteria

About patients: Inclusion criteria: patients were diagnosed by contrast enhanced magnetic resonance imaging (MRI) scans as brain metastases from non-small cell lung cancer. Exclusion criteria: brain metastases from small cell lung cancer, lymphoma, digestive tumor, and breast cancer were excluded.

About study design and comparison: Inclusion criteria: randomized controlled trial (RCT) of SRS alone versus SRS +WBRT published as formal papers. Exclusion criteria: cohort study, case report, reviews, letters, and low quality clinical research were excluded. The study of unreported standard deviation, confidence interval (CI), HR, 95% CI, and *P*-value were excluded.

About outcome measurements: The included study reported overall survival, BTR free time, salvage brain treatment, grade 3 or 4 late radiation toxicities. Our analysis complied with the guidelines reported as the PRISMA statement.[16]

2.4. Quality assessment

The Cochrane handbook was used to evaluate the study quality. The literature quality evaluation includes: method of randomization, allocation concealment, blingding, result data integrity, results of selective reporting, and other sources of bias. Figs. 1 and 2.

2.5. Data extraction

Two authors extracted the data from 4 eligible trails. A third reviewer made a final determination when not uniform. The following data of all eligible trials were extracted: name of the first author, trial phase, publication year, type of study, number of enrolled patients, sex ratio, average ages, patients' performance status, outcomes, and interventions.

2.6. Outcome definition

The data for each study were recorded independently by 2 researchers. SRS without WBRT group was taken as SRS alone, SRS combined WBRT group was taken as SRS+WBRT. OS: death from all causes from time of randomization.

2.7. Statistical analysis

Heterogeneity was conducted using I^2 tests, and no heterogeneity was regard when $P > .1$ and $I^2 < 50\%$ with a fixed-effect statistical model, whereas a random-effect model was applied. The statistical significance was considered as $P < .05$. Our statistical analyses in this analysis were made by Revman 5.3.

3. Results

3.1. Selection of trails

Eight hundred sixty-six studies were identified in all. Of the results, only 3 randomized control trials were included in this analysis by filtering title, abstracts, and the full article (Fig. 3). All the patients in the group were divided into favorable prognosis group and unfavorable prognosis group, and the evaluation

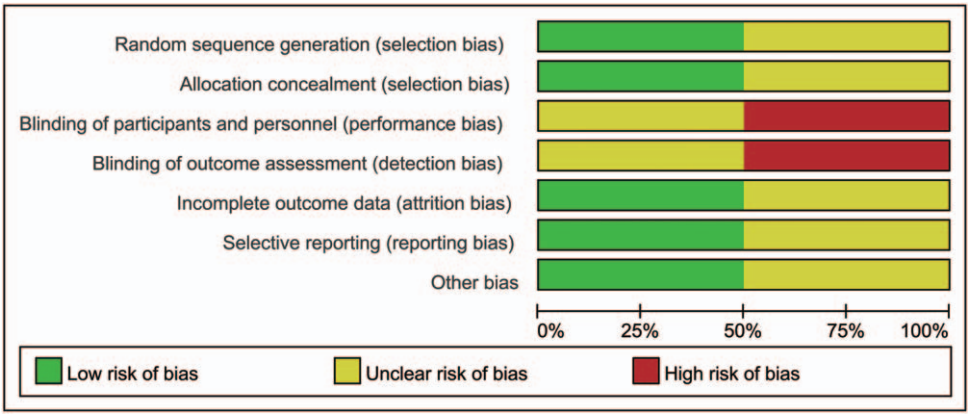

Figure 1. Risk of bias graph.

indexes were all OS, BTR, toxic effects, and salvage therapy. But there is a trial that includes not only lung cancer patients, but also breast cancer, digestive system tumors, renal cancer, melanoma, and the GPA grouping is different from the other 2. Therefore, we only included 2 trails in this study.

3.2. General characteristics

The identified trails are shown in Table 1. The 2 trails were all secondary analysis of phase II or III RCTs. These 2 studies are included in non-small cell lung cancer patients with 1 to 3[9] or 1 to 4[10] brain metastases stratified by GPA. In the N0574 trail, unfavorable prognosis group with GPA <2 and favorable prognosis group GPA ≥2 were randomly divided into SRS and WBRT+SRS. The results of the trail were OS, BTR, salvage therapy, 3 to 4 levels of toxic effects and neurocognitive impairment. In the JROSG 99–1 trail, the WBRT was delivered with 30 Gy in 10 fractions. SRS was delivered with 21.9 Gy in SRS alone group and the mean dose of SRS was 16.6 Gy in SRS +WBRT group. The primary endpoint was OS, and secondary endpoints included BTR free time, salvage therapy, and radiation toxicity. The characteristics of the 2 included trails are listed in Table 1.

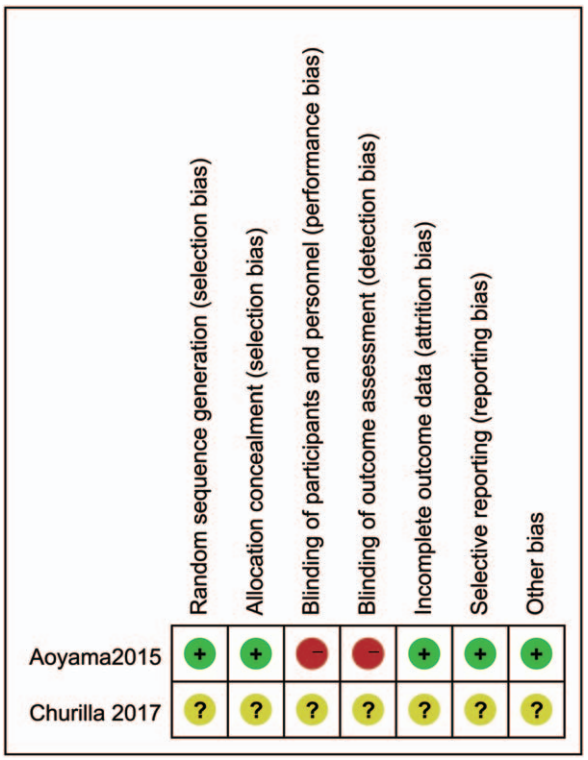

Figure 2. Risk of bias summary. +: low risk of bias; −: high risk of bias; ?: unclear risk of bias.

3.3. Results of meta-analysis

3.3.1. OS. Results of the OS are shown in Fig. 4. SRS+WBRT failed to improve OS in 2 subgroups. (GPA <2: HR, 0.93; 95% CI, 0.61–1.40; $P = .71$; heterogeneity $P = .24$, $I^2 = 0\%$). (GPA ≥2: HR, 1.28; 95% CI, 0.58–2.80; $P = .54$; heterogeneity $P = .07$, $I^2 = 69\%$) (Fig. 4).

3.3.2. BTR free time. Pooling data from included studies revealed that the use of WBRT+SRS contributed to a longer BTR free time in both GPA<2 group (HR, 5.46; 95% CI: 2.09–14.22; $P = .0005$; heterogeneity $P = .30$, $I^2 = 6\%$) and GPA ≥2 group (HR, 4.24; 95% CI: 2.24–8.04; $P < .00001$; heterogeneity $P = .09$, $I^2 = 66\%$) (Fig. 5).

3.3.3. Salvage brain treatment. Meta-analysis of salvage brain treatment revealed that salvage therapy is more frequent among the SRS-alone group, and the difference is significant. GPA <2 group (RR, 5.83; 95% CI: 1.47–23.06; $P = .01$; heterogeneity $P = .17$, $I^2 = 46\%$) and GPA ≥2 group (RR, 2.53; 95% CI: 1.30–4.93; $P = .006$; heterogeneity $P = .75$, $I^2 = 0\%$) (Fig. 6).

3.3.4. Grade 3 or 4 late radiation toxicities. The meta-analysis demonstrated that there was no difference in rates of grade 3 or 4 toxic effects in GPA ≥2 group between SRS and SRS+WBRT (HR, 0.33; 95% CI: 0.07–1.60; $P < .00001$; heterogeneity $P = .70$, $I^2 = 0\%$). Rates of grade 3 or 4 late radiation toxic effects did not differ in GPA <2 group between SRS and SRS +WBRT. (Fig. 7).

4. Discussion

There are many reports on the prognostic factors of brain metastasis of lung cancer, such as the number of brain metastases, brain metastasis location, pathological type, KPS score, control

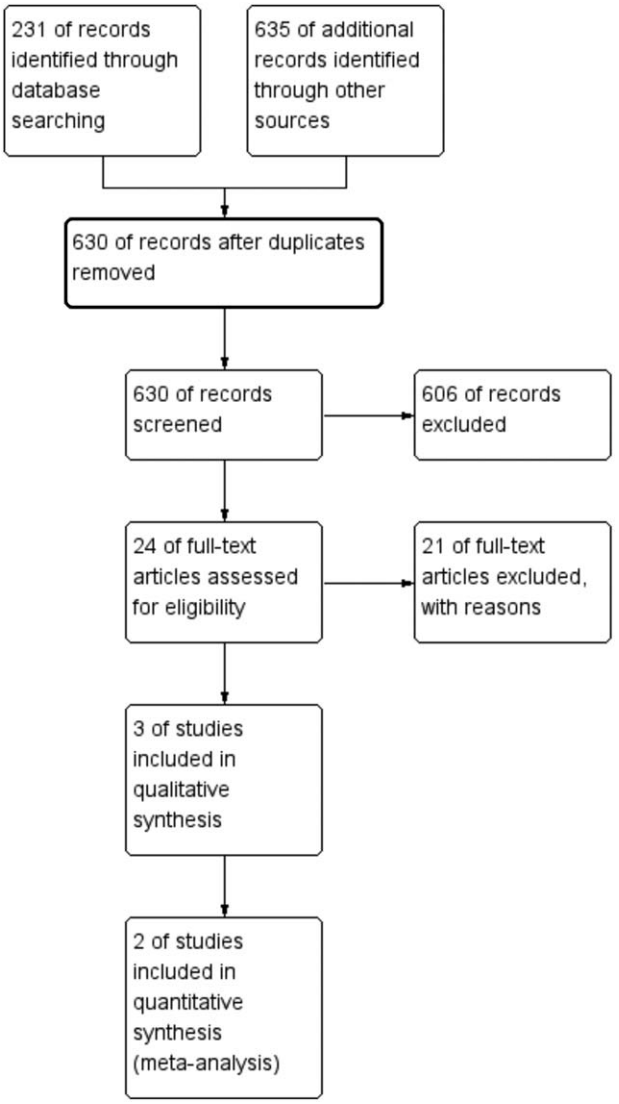

Figure 3. Flowchart of the study selection.

of the primary lesion, age of patient, and extracranial metastasis. These are the important factors influencing the prognosis. In the face of many possible prognostic factors, oncologists have tried to establish a system to evaluate the prognosis of brain metastasis from non-small cell lung cancer. RPA system founded in 1997 by Radiation Therapy Oncology Group (RTOG) is the first prognostic scoring system, which is to predict the survival of patients with brain metastases. The scoring system of survival includes 3 parameters, such as age, KPS, extracranial metastasis, and control of the primary lesion. While most of the clinical studies reported that the results of statistical analysis were different due to many different factors (including brain metastasis, liver metastasis, lung metastasis, and chemotherapy anemia) based on the same treatment. So a new accurate scoring system needs to be build.

In 2008, Sperduto[7] established a new scoring system of GPA by analyzing data from 5 randomized clinical trials. The scoring system takes into account age, KPS score, the number of brain metastases, and with or without extracranial metastasis. They considered GPA system objective and liable to quantitative analysis through comprehensive analysis.[8]

As early as 1999, Kondziolka concluded that WBRT combined with SRS significantly improved the control of brain disease in patients with 2 to 4 brain metastases. The OS for patients receiving SRS was 7.5 months, while the OS for WBRT+SRS was 11 months ($P=.22$). OS was not determined by histology or the number of brain metastases, but by extent of extracranial disease ($P<.02$).[11] Intriguingly, another randomized controlled trial by Chang et al[12] reported that the median survival and 1-year survival in the SRS group were higher than that in the SRS +WBRT group (15.2 vs 5.7 months, 63% vs 21%; $P=.003$). Two randomized controlled trials evaluating the efficacy of WBRT have been published. A Germany study of EORTC 22952–26001[5] reported that WBRT following SRS or surgical excision failed to improve OS for patients with 1 to 3 brain metastases in comparison with observation. A total of 194 patients with brain metastasis were enrolled in the NCCTG N107C/CEC 3 trail.[6] After surgical resection, the patients were randomly divided into SRS alone group and WBRT alone group. The outcome demonstrated that there was no significant survival benefit for WBRT over SRS in the treatment of resected brain metastasis.

None of the above randomized controlled trials incorporated patients according to prognostic scores, so clinical question of the survival of patients based on the prognostic score was unclear. Our meta-analysis in brain metastases of non-small cell lung cancer aimed to assess the key question: OS, BTR free time, and Grade 3 or 4 late radiation toxicities.

To the best of our knowledge, the present study is the most updated meta-analysis to assess the efficacy of WBRT on RCTs in patients with brain metastasis of non-small cell lung cancer stratified by GPA. The result of this meta-analysis demonstrated that SRS+WBRT had a significant advantage on BTR free time in both GPA<2 group ($P=.0005$) and GPA ≥2 group ($P=.00001$). As BTR free time in this meta-analysis, compared with SRS +WBRT, time to intracranial failure using SRS alone was significantly shortened ($P<.001$) in a meta-analysis conducted by Brown et al.[13] So we also had a reasonable outcome that the difference of salvage brain treatment was significant in both prognosis groups. Another meta-analysis of 763 patients published in 2017[14] compared SRS alone with SRS+WBRT. In addition of WBRT to SRS, it was not associated with improvement in OS (HR 1.03; 95% CI: 0.82–1.29, $P=.81$) in the

Table 1

Characteristics of the studies included in the meta-analysis.

Author, year	Country	Type	Patients enrolled	Brain metastases	Radiation dose, Gy
Churilla 2017	American	RCT	SRS 38	1–3	Unclear
			SRS+WBRT 25		Unclear
Aoyama 2015	Japan	RCT	SRS 45	1–4	21.9 Gy
			SRS+WBRT 43		16.6 Gy+30 Gy/10F

RCT = randomized controlled trials, SRS = stereotactic radiosurgery, WBRT = whole brain radiotherapy.

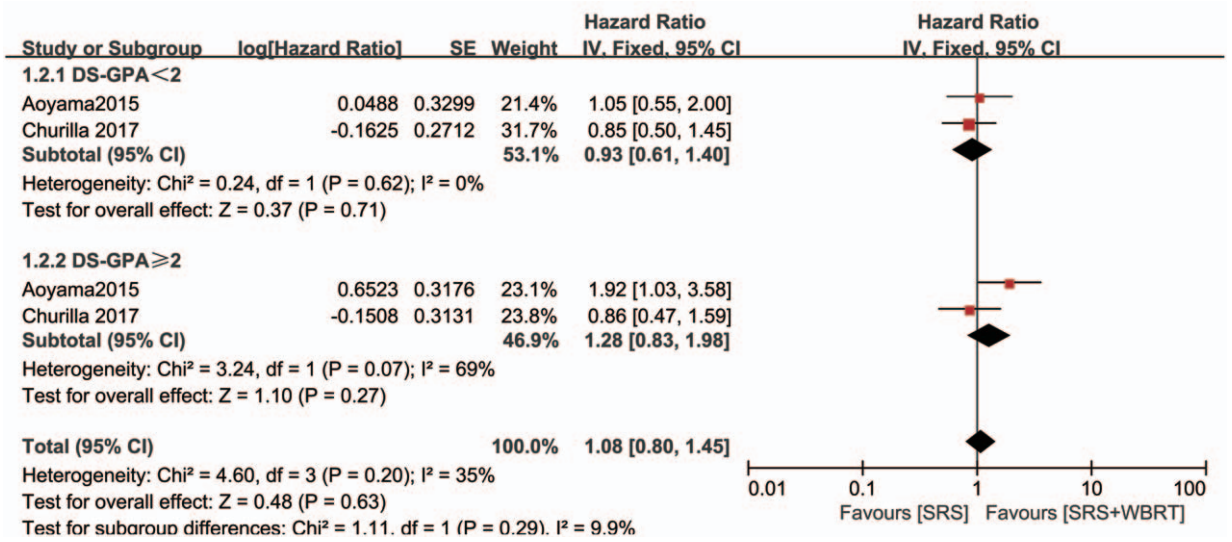

Figure 4. Forest plot of OS in the subgroup analysis. There was no significant difference between SRS and SRS+WBRT in 2 subgroups. OS = overall survival, SRS = stereotactic radiosurgery, WBRT = whole brain radiotherapy.

2 subgroups. Our outcome of OS was in agreement with the meta-analysis of Patil CG published in Cochrane Database in 2017.[15] Patil CG's meta-analysis only included 2 studies, with a total of 358 participants. Overall survival was no significantly improved by WBRT+SRS (HR = 0.82, 95% CI: 0.65–1.02). The result of OS of the subgroups was also consistent with a randomized clinical trial evaluating effect of SRS+WBRT for 1 to 3 brain metastases.[13] In this article, 213 patients were enrolled, and the patients were divided into SRS alone (n = 111, 20–24 Gy for SRS alone) group and SRS+WBRT group (n = 102, 18–22 Gy for SRS, 30 Gy in 12 fractions for WBRT). Median OS in SRS alone group and SRS+WBRT group was 10.4 months and 7.4 months, respectively ($P = .92$). We speculated that salvage therapy was more frequent in SRS alone group, which could explain why there was no difference in survival between the 2 groups. Besides, we also evaluated safety with grade 3 or 4 late radiation toxicities. In the present study, there was no significant difference in grade 3 or 4 late radiation toxicities between the 2 groups (OR 0.92; 95% CI: 0.59–1.42, $P = .71$). Similar results were found in another RCT Meta-analysis by Duan et al.[16] The results showed that WBRT combined with SRS had no advantages in 1-year OS (OR = 0.78, 95%CI: 0.60–1.03).

WBRT in different scaling concluded the similar results with ours. In the randomized control trial conducted by Kepka et al,[17] salvage therapy was more frequent in the SRT-TB arm (81%) than that was in WBRT arm (60%). The rate of grade 3 or 4 late radiation toxic effects was similar in 2 subgroups between SRT-TB arm and WBRT arm. There was no significant difference in OS between SRT-TB arm and WBRT arm. In the QUARTZ trial[4], 538 patients with brain metastasis from NSCLC were

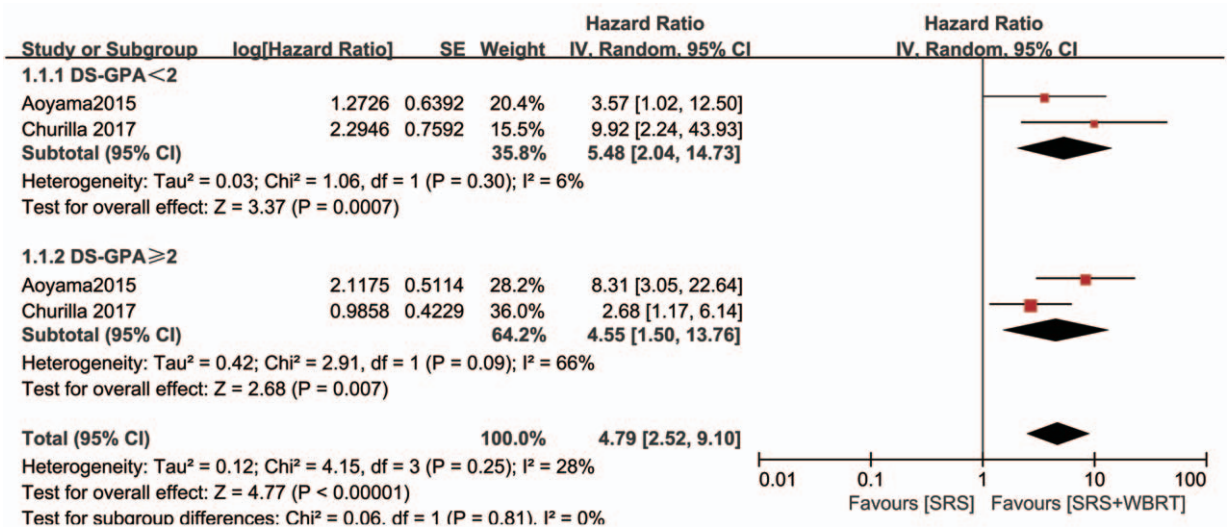

Figure 5. Forest plot of BTR free time in the subgroup analysis. There was a significant difference between SRS and SRS+WBRT in 2 subgroups. BTR = brain tumor recurrence; SRS = stereotactic radiosurgery, WBRT = whole brain radiotherapy.

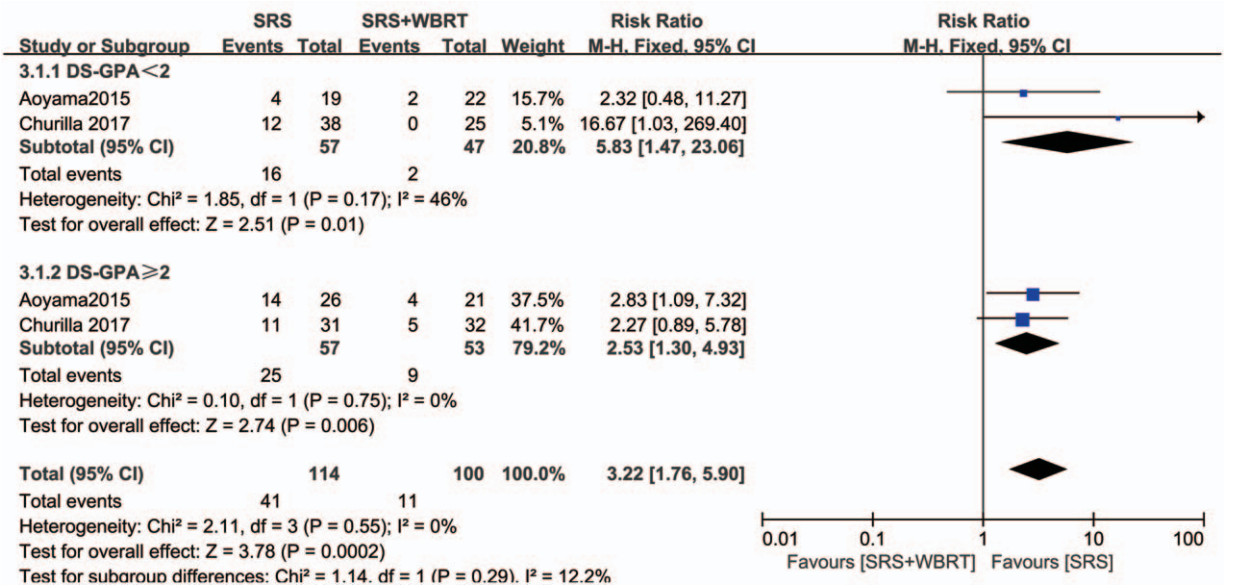

Figure 6. Salvage brain treatment in the subgroup analysis. Salvage therapy was more frequent among the SRS-alone group in 2 subgroups. SRS = stereotactic radiosurgery.

randomly divided into WBRT or best supportive therapy. Compared with the best supportive treatment, WBRT did not bring survival benefits and improved quality of life. Although it was a large sample phase III clinical study designed, there were limitations. Heterogeneity in the included patients is obvious, nearly 40% of the patients KPS is <70, and 63% of patients with primary tumor is not under control, 55% of patients have metastases of other locations. These unfavorable factors have also led to that 17% patients did not complete WBRT as planned in WBRT group. Prognosis is significantly lower than the previous study results.

Another point that cannot be ignored is the ethnic diversity of the patients included. Patients in the present meta-analysis were from Japan and America. The sensitizing EGFR mutation varies from ethnic group to ethnic group, and the mutation rate in the Caucasus is close to 10%, while in Asia it is as high as 50%. Due to lack of molecular information in the 2 included trails, we speculate that the number of patients receiving targeted therapy may influence the results of the trails.

However, some limitations in our meta-analysis should be mentioned. First, the main limitation is that the number of studies included is small with only 2 randomized controlled studies.

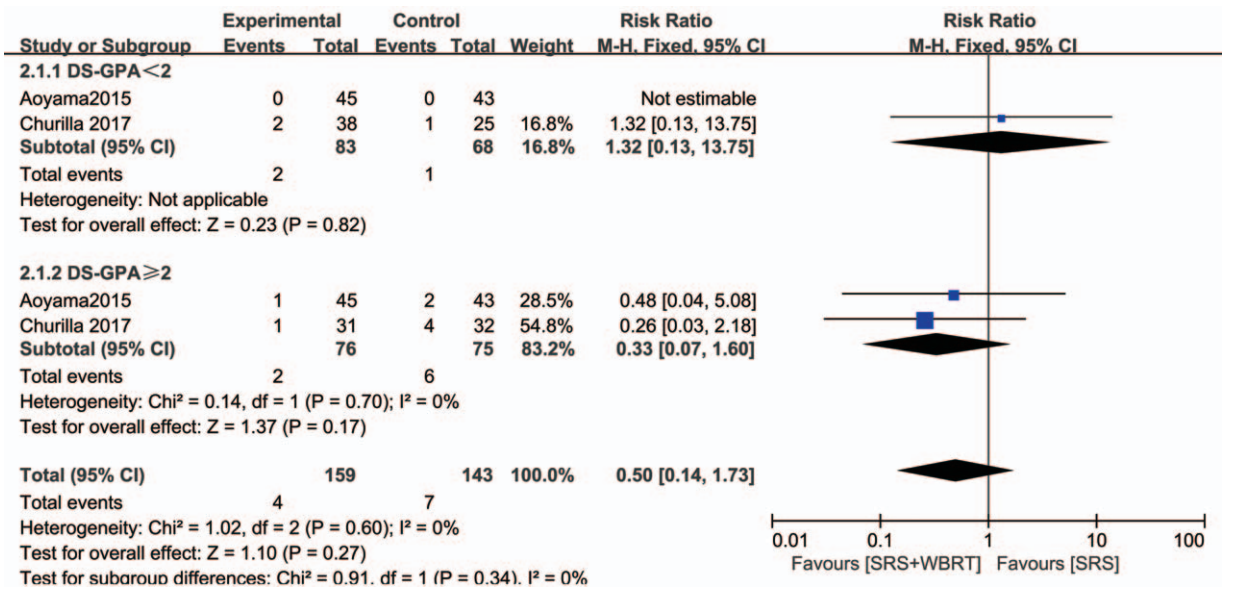

Figure 7. Forest plot of grade 3 or 4 late adverse events. There were no significant differences between SRS and SRS+WBRT in 2 subgroups. SRS = stereotactic radiosurgery, WBRT = whole brain radiotherapy.

There may be some bias due to the lack of inclusion in the literature. And the number of recruit in these 2 studies is significantly different, which resulted in a significant difference in weight between the 2 articles. Second, we cannot ignore the heterogeneity in the BTR results. The heterogeneity may be due to differences in baseline characteristics, treatment regiments, interventions, and observation indicators in the included trails. However, there is no way to further subgroup analysis because the 2 papers did not report the same subgroup. Third, literature retrieval is limited to English, which may lead to potential language bias.

The timing of this meta-analysis is quite appropriate. As far as we know, no similar meta-analysis has been published up to date. The 2 articles we included were both high quality randomized controlled studies, and our meta-analysis had reached level 1, so our results were reliable and available. In future, more well-designed large-scale randomized controlled trials about SRS +WBRT versus SRS alone for brain metastases stratified by the GPA should be taken for further study.

5. Conclusions

The risk of bias of 1 included study is unclear. Therefore, our conclusions must be explained based on unclear bias. No significant difference existed in survival between the two subgroups (GPA $\geq$2 and GPA $<$2) through 2 treatments (SRS +WBRT and SRS alone). WBRT+SRS improved BTR free time in both GPA $\geq$2 and GPA $<$2 groups. Salvage therapy was more frequent among the SRS-alone group. Rates of grade 3 or 4 toxic effects were similar in GPA $\geq$2 and GPA $<$2 groups between SRS and SRS+WBRT.

Author contributions

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Methodology: Hong-yun Shi, Lanhui Yuan.
Resources: Lei Su.
Software: Xi Zhang.
Writing – original draft: Shuai Qie.

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