RESEARCH ARTICLE

Whole Brain Radiotherapy Plus Chemotherapy in the Treatment of Brain Metastases from Lung Cancer: A Meta-analysis of 19 Randomized Controlled Trails

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Abstract

Objective: To evaluate the efficacy and safety of whole brain radiotherapy (WBRT) plus chemotherapy versus WBRT alone for treating brain metastases (BM) from lung cancer by performing a meta-analysis based on randomized controlled trials (RCTs). Methods: The PubMed, Embase, CENTRAL, ASCO, ESMO, CBM, CNKI, and VIP databases were searched for relevant RCTs performed between January 2000 and March 2012. After quality assessment and data extraction, the meta-analysis was performed using the RevMan 5.1 software, with funnel plot evaluation of publication bias. Results: 19 RCTs involving 1,343 patients were included. The meta-analyses demonstrated that compared to WBRT alone, WBRT plus chemotherapy was more effective with regard to the objective response rate (OR = 2.30, 95% CI = 1.79 – 2.98; P < 0.001); however, the incidences of gastrointestinal reactions (RR = 3.82, 95% CI = 2.33 - 6.28, P <0.001), bone marrow suppression (RR = 5.49, 95% CI = 3.65 - 8.25, P < 0.001), thrombocytopenia (RR = 5.83, 95% CI = 0.39 - 86.59; P = 0.20), leukopenia (RR = 3.13, 95% CI = 1.77 – 5.51; P < 0.001), and neutropenia (RR = 2.75, 95% CI = 1.61 - 4.68; P < 0.001) in patients treated with WBRT plus chemotherapy were higher than with WBRT alone. There was no obvious publication bias detected. Conclusion: WBRT plus chemotherapy can obviously improve total efficacy rate, butalso increases the incidence of adverse reactions compared to WBRT alone. From the limitations of this study, more large-scale, high-quality RCTs are suggested for further verification.

Keywords: Lung cancer - brain metastases - whole brain radiotherapy - chemotherapy - meta-analysis

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Introduction

Metastasis of advanced lung cancer may occur in various organs, brain is one of the most common sites, which has an incidence of 25% -65% and accounting for 40% -60% of all brain metastases (BM) (Kienast et al., 2010). BM is one of the main factors impacting on the quality of life and length of survival, thus, there is an urgently need to explore how to improve quality of life through better local control for patients with BM, as well as overall survival.

Surgery is the standard treatment for stabilized single-site brain metastasis or for the control of systematic tumors (Bovi et al., 2012). However, a diagnosis of BM from lung cancer means at a stage IV, that surgery is rather limited because most patients at this stage cannot tolerate surgery well. WBRT (whole brain radiotherapy) has long been a standard treatment for patients with BM and can improve survival time, however, WBRT can rarely eradicate the tumor due to poor tolerance of normal brain tissue to radiation, and approximately one-third patients have remaining uncontrollable localized tumors after WBRT treatment, and 50% patients die of progressive intracranial tumor (Gijtenbeek et al., 2011). The emergence of various new chemotherapy drugs has greatly enhanced the efficacy of the treatment in lung cancer patients, but most drugs cannot pass the blood-brain barrier (BBB), or have difficulty achieving effective concentrations in the brain tissue. Recent studies demonstrated that BBB is damaged in patients with BM, that means many drugs may penetrate the brain tissue (Grimm, 2012). However, chemotherapy alone did not significantly improve the survival rate of lung cancer patients with BM (Kyritsis et al., 2012).

A certain dose of radiation can weaken the BBB, so that drugs can reach the brain tissue, thus, radiotherapy plus chemotherapy is considered as a best therapeutic approach for the treatment of advanced lung cancer patients with BM (Siu et al., 2011). Several studies demonstrated that WBRT plus chemotherapy is more effective than WBRT alone (Postmus et al., 2000; Xiao et al., 2001; He et al.,

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2003; Guerrieri et al., 2004; Li et al., 2004; Pan et al., 2004; Ge et al., 2005; Verger et al., 2005; Xie et al., 2007; Zhao et al., 2007; Fan et al., 2008; Peng et al., 2008; Wang et al., 2008; Gao et al., 2009; Neuhaus et al., 2009; Sun et al., 2009; Zeng et al., 2009; Zhu et al., 2009; Bai, 2010, 2010; Dong et al., 2010; Gao, 2011; Guo, 2011). However, not all the results show the differences have statistical significance, and the sample sizes of some studies are small. Whether WBRT plus chemotherapy can improve the efficacy and quality of life are better that WBRT alone for lung cancer patients with BM remains controversy. So we will perform a meta-analysis to evaluate the efficacy and safety of WBRT plus chemotherapy versus WBRT alone for the treatment of BM from lung cancer, according to the PRISMA (Preferred reporting items for systematic reviews and meta-analyses) statement (Moher et al., 2009), in order to provide some insight for clinical practice.

Materials and Methods

Eligibility criteria

The article was included when it met the following criteria: (1) the study design is RCT and the patients were enrolled voluntarily and signed informed consent, (2) confirmed diagnosis primary lung cancer by pathology or cytology, and brain metastasis by CT or MRI, (3) the included patients without chemotherapy contraindications, no serious heart, lung, liver, kidney dysfunction and hematological abnormalities before treatment, and the KPS (Karnofsky scale) scores ≥ 60 points and expected survival time > 3 months, (4) the intervention group was WBRT plus chemotherapy, and WBRT alone in the control group. Both groups of patients received ≥ 2 cycles of treatment, (5) therapeutic effect was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST) standards or WHO short-term effect evaluation criteria on solid tumors (Eisenhauer et al., 2009). Complete remission (CR): tumor disappeared completely for at least 4 weeks, no new lesions; Partial response (PR): more than 50% tumor regression for at least for 4 weeks, and no new lesions; Stabilized disease (SD) or no change (NC): less than 50% tumor regression, or increase less than 25%; Progressive disease (PD): increase of more than 25%, or appearance of new lesions. The total efficacy was calculated by CR + PR. Adverse reactions were graded as level 0-IV according to WHO standards, (6) all needed informations were reported or could to be obtained by contecting the authors.

Study selection

We searched PubMed, Embase, ClinicalTrials.gov, the Cochrane Central Register of Controlled Trials (CENTRAL), American society of clinical oncology (ASCO), European Society for Medical Oncology (ESMO), the Chinese Biological Medicine Database (CBM), China National Knowledge Infrastructure (CNKI), and the Chinese scientific periodical database of VIP INFORMATION (VIP) for the relevant randomized controlled trials (RCTs). The retrieval time between January, 2000 and March, 2012, with no language restrictions, using the search terms "lung", "cancer", "carcinoma", "brain metastases", "metastases", "metastasis", "radiotherapy", "whole brain radiotherapy", "brain radiation", and "chemotherapy". Manual research was performed by reviewing the reference lists of identified RCTs.

Two reviewers independently evaluated citations according to eligibility criteria for relevance. They then documented their decisions in standardized forms, excluded cases that fail to meet the criteria of inclusion, and cross-checked the studies each included. Discrepancies were resolved by discussion or by a third reviewer.

Data extraction

For the included studies, the data were extracted by one reviewer and examined by a second reviewer.The following data were collected from each study: first author's surname, year of publication, study design, number of patients, length of follow-up, interventions, measurement indicators, outcomes (such as response rate, survival rate, symptom improvement, and adverse effects), and methodological quality.

Methodological quality assessment

Two independent reviewers assessed the methodological quality according to the Cochrane Handbook for Systematic Reviews of Interventions (version 5.1.0) (Higgins et al., 2011), and cross-checked the results. The items as follows: (1) random sequence generation, (2) allocation concealment, (3) blinding of participants and personnel, (4) blinding of outcome assessment, (5) incomplete outcome data, (6) selective outcome reporting, and (7) other sources of bias. All the seven criteria above were annotated with "low risk", "high risk", or "unclear risk" (lacking related information, or bias undetermined) during evaluation. Discrepancies were resolved by discussion or by asking a third reviewer.

Statistical analysis

The data were analyzed by using the RevMan 5.1.0 software (cochrane collaboration). Chi-square and I-square tests were used to test heterogeneity amongst the RCTs (Higgins et al., 2011). The significance threshold of chi-square test was set at $\alpha = 0.1$, it is deemed heterogeneity existed when $P < 0.1$. I^2 was used to quantify the heterogeneity across trials and to assess the impact of heterogeneity on the meta-analysis, the value was 0% to 40% (might not be important), 30% to 60% (may represent moderate heterogeneity), 50 to 90% (may represent substantial heterogeneity), and 75% to 100% (considerable heterogeneity), respectively. The odd ratio (OR) or risk ratio (RR) and relevant 95% confidence interval (CI) was estimated using a fixed effects model if there was no heterogeneity existed, other wise, the random-effect model was used. When the heterogeneity existed amongst studies, the sensibility analyses were performed to explore the sources of heterogeneity and robustness of results. When enough studies ($n \geq 9$) were included, the publication bias was evaluated by using the funnel plot.

Table 1. Characteristics of Randomized Controlled Trials Included in the Meta-analysis

References	Sample (T/C)	Age (T/C, years)	Interventions		Outcomes	Standard
			T	C		
Verger 2005	41/41	57.8±12.2/58.3±11.6	WBRT + temozolomide	WBRT	response rate, adverse event	WHO
Neuhaus 2009	47/49	34-75/42-75	WBRT + topotecan	WBRT	response rate, quality of life	—
Postmus 2000	60/60	39-75/38-75	WBRT + teniposide	WBRT	response rate, toxicity	—
He 2003	38/44	34-76	WBRT+ VP16/DDP or mitomycin/vindesine/DDP	WBRT	response rate, toxicity	WHO
Sun 2009	25/25	35-68	WBRT + Nimustine	WBRT	response rate, adverse event	RECIST
Peng 2008	19/21	35-71/32-72	WBRT + temozolomide	WBRT	response rate, adverse event	WHO
Zeng 2009	41263	30-72	WBRT + temozolomide	WBRT	response rate, adverse event	WHO
Zhu 2008	43/25	28-75/30-74	WBRT + teniposide	WBRT	response rate, toxicity	WHO
Pan 2004	38/36	35-65/35-65	WBRT + CTX/CCNU/VP16 or VM26/DDP	WBRT	response rate, toxicity	WHO
Bai1 2010	56/56	34-72/35-71	WBRT + paclitaxel/DDP	WBRT	response rate, adverse event	WHO
Bai2 2010	43/43	35-72/36-71	WBRT + teniposide/DDP	WBRT	response rate, adverse event	WHO
Xiao 2001	70/70	30-76	WBRT + CTX/MTX/CNU/VCR	WBRT	response rate, toxicity	—
Ge 2005	30/30	32-70	WBRT + teniposide	WBRT	response rate, toxicity	WHO
Dong 2010	15980	18-81	WBRT + temozolomide/carmustine	WBRT	response rate	WHO
Xie 2007	25/25	30-70	WBRT + temozolomide	WBRT	response rate, adverse event	WHO
Zhao 2007	30/30	36-72/34-70	WBRT + DDP/teniposide	WBRT	response rate, toxicity	WHO
Gao 2011	24/24	31-67	WBRT + gemcitabine/DDP	WBRT	response rate, toxicity	WHO
Gao 2009	23/25	35-75/38-72	WBRT + docetaxel	WBRT	response rate, adverse event	WHO
Guerrieri 2004	21/21	39-78/42-77	WBRT + carboplatin	WBRT	Survival, response rate, symptom control, symptomatic neurological progression, toxicity	WHO

Note: T, test group; C, control group

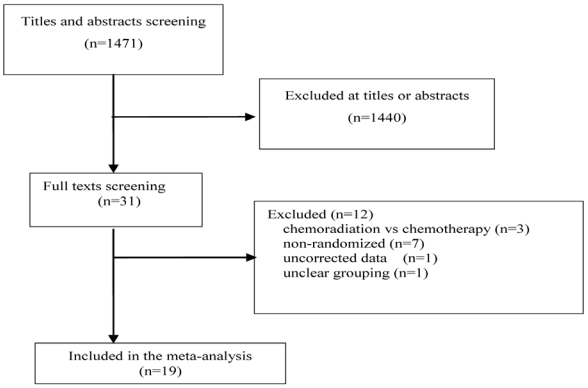

Figure 1. Flowchart of Studies Selection

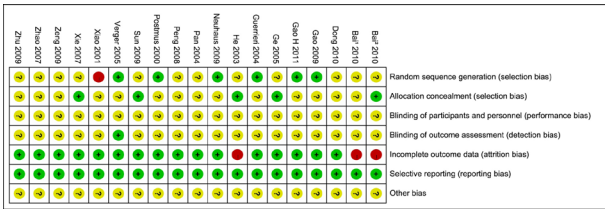

Figure 2. Summary Risk of Bias Assessment. Green pie chart, low risk of bias; Red pie chart, high risk of bias; Yellow pie chart, unclear risk of bias

Results

Selection of Studies

Figure 1 showed flowchart of studies selection. There were 1471 citations yielded, of which 1440 were removed during abstract review stage as being duplications or irrelevant to the specific question. The remaining 31 studies were to full text screening, and 19 RCTs were included (He et al., 2003; Guerrieri et al., 2004; Ge et al., 2005; Gao et al., 2009; Neuhaus et al., 2009; Bai, 2010, 2010; Dong et al., 2010; Gao, 2011; Pan et al., 2004; Peng et al., 2008; Postmus et al., 2000; Sun et al., 2009; Verger et al., 2005; Xiao et al., 2001; Xie et al., 2007; Zeng et al., 2009; Zhao et al., 2007; Zhu et al., 2009).

Characteristics of included studies

Finally 19 RCTs involving 1343 lung cancer patients with BM were included, of which 696 cases were in the group of WBRT plus chemotherapy and 647 cases in the group of WBRT alone. The specifics of the chemotherapy regimens were listed in Table 1. The efficacy of the 19 RCTs was evaluated as following: 15 studies according to WHO criteria (Xiao et al., 2001; He et al., 2003; Guerrieri et al., 2004; Ge et al., 2005; Verger et al., 2005; Xie et al., 2007; Zhao et al., 2007; Peng et al., 2008; Gao et al., 2009; Zeng et al., 2009; Zhu et al., 2009; Bai, 2010, 2010; Dong et al., 2010; Gao, 2011), one study according to RECIST (Sun et al., 2009), and 3 studies with unspecified the evaluation criteria (Postmus et al., 2000; He et al., 2003; Neuhaus et al., 2009). The assessments of the 19 studies by two independent reviewers were consistent.

Methodological quality

Figure 2 showed the results of authors' judgement of risk of biases. According to the bias risk assessment tool in the Cochrane systematic reviews handbook (Higgins et al., 2011), 6 RCTs (Postmus et al., 2000; Guerrieri et al., 2004; Verger et al., 2005; Zhao et al., 2007; Gao et al., 2009; Neuhaus et al., 2009) were randomized correctly using the method of random sequence Generation, one study (Xiao et al., 2001) was randomized incorrectly by grouping the patients in the order of admission, and the remain 12 RCTs were just mentioned "randomized" but unclear how to performed. Five RCTs used correct allocation concealment strategies (He et al., 2003; Ge et al., 2005; Sun et al., 2009; Xie et al., 2007; Bai, 2010), but the other 14 failed to describe the methods of allocation concealment. Blind rater was used in one RCT (Verger et al., 2005), while the blinding methods were not mentioned in the remaining 18 RCTs. Four RCTs (Postmus et al., 2000; He et al., 2003; Bai, 2010, 2010) reported the withdrawal or decease of patients but only 1 RCT (Postmus et al., 2000) used intent-

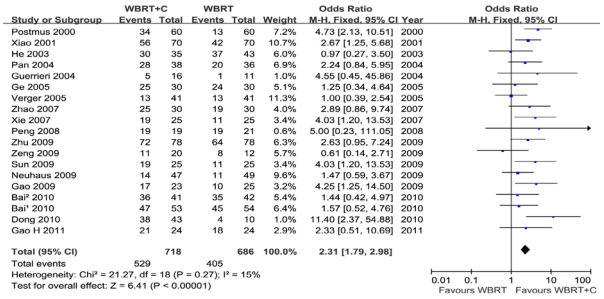

Figure 3. Total Efficacy Rate of WBRT Plus Chemotherapy vs. WBRT Alone

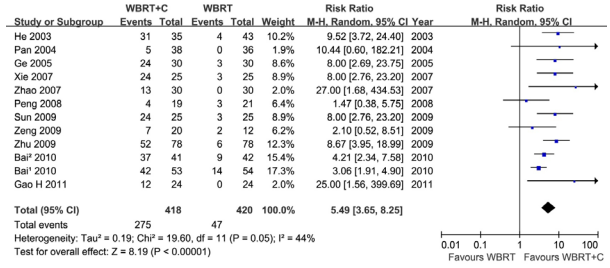

Figure 4. Incidence of Bone Marrow Suppression of WBRT Plus Chemotherapy vs. WBRT Alone

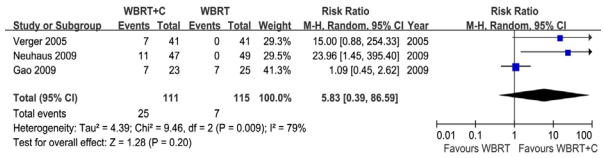

Figure 5. Incidence of Thrombocytopenia of WBRT Plus Chemotherapy vs. WBRT Alone

to-treat analysis, the other 15 RCTs did not report any loss of patients and provided complete outcome data. Other bias risk factors cannot be determined due to the limited information provided in the 19RCTs.

Total efficacy rate

All the 19 included RCTs clearly evaluated the response of radiochemotherapy for BM lesions and other metastases. There was no heterogeneity existed (P = 0.27, I^2 = 15%), therefore the fixed effect model was used for the meta-analysis. The results showed that in comparison to WBRT alone, WBRT plus chemotherapy obviously improved the total efficacy rate 2.31 times (OR = 2.30, 95% CI = 1.79 – 2.98; P < 0.001) (Figure 3).

Bone marrow suppression

Twelve RCTs (He et al., 2003; Pan et al., 2004; Ge et al., 2005; Xie et al., 2007; Peng et al., 2008; Sun et al., 2009; Zeng et al., 2009; Zhao et al., 2007; Zhu et al., 2009; Bai, 2010, 2010; Gao, 2011) reported the occurrence of bone marrow suppression, There was heterogeneity exsited (P = 0.05, I^2 = 44%), so the random-effects model was used. The results demonstrated that the incidence of bone marrow suppression in the group of WBRT plus chemotherapy was 5.49 times than WBRT alone (RR = 5.49, 95% CI = 3.65 - 8.25, P < 0.001) (Figure 4).

Hematological adverse reaction

Three RCTs (erger et al., 2005; Gao et al., 2009; Neuhaus et al., 2009) reported the occurrence of

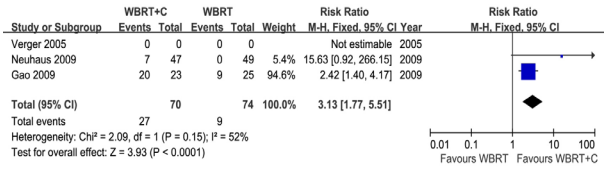

Figure 6. Incidence of Leukopenia of WBRT Plus Chemotherapy vs. WBRT Alone

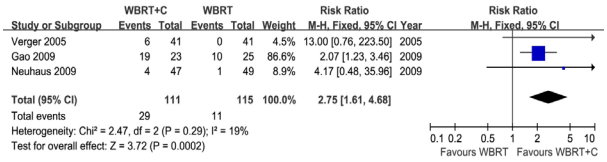

Figure 7. Incidence of Neutropenia of WBRT Plus Chemotherapy vs. WBRT Alone

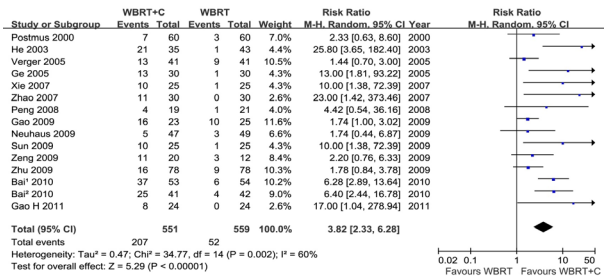

Figure 8. Incidence of Gastrointestinal Reaction of WBRT Plus Chemotherapy vs. WBRT Alone

thrombocytopenia. The results of meta-analysis by using random-effects model (p = 0.009, I^2 = 79%) showed that the incidence of thrombocytopenia in WBRT plus chemotherapy group was 5.83 times than WBRT alone group, but the difference was not statistically significant (RR = 5.83, 95% CI = 0.39 - 86.59; P = 0.20) (Figure 5). The sensitivity analysis by omiting one study each time showed that the result without substantial change, that mean the result was robust.

Three RCTs (Verger et al., 2005; Gao et al., 2009; Neuhaus et al., 2009) reported the occurrence of leukopenia. The results of meta-analysis by using fixed effect model (p = 0.15, I^2 = 52%) showed that the incidence of leukopenia in WBRT plus chemotherapy group was 3.13 times than WBRT alone group (RR = 3.13, 95% CI = 1.77 – 5.51; P < 0.001) (Figure 6).

Three RCTs (Verger et al., 2005; Gao et al., 2009; Neuhaus et al., 2009) reported the occurrence of neutropenia. For there were no evidence of homogeneity (p = 0.29, I^2 = 19%), the fixed effect model was used. The results demonstrated that the incidence of neutropenia in WBRT plus chemotherapy group was 2.75 times than the WBRT alone group (RR = 2.75, 95% CI = 1.61 - 4.68; P < 0.001) (Figure 7).

Gastrointestinal reaction

15 RCTs (Postmus et al., 2000; He et al., 2003; Ge et al., 2005; Verger et al., 2005; Xie et al., 2007; Zhao et al., 2007; Peng et al., 2008; Gao et al., 2009; Neuhaus et al., 2009; Sun et al., 2009; Zeng et al., 2009; Zhu et al., 2009; Bai, 2010, 2010; Gao, 2011) reported the occurrence of gastrointestinal reaction. There were evidence of heterogeneity among the studies (p = 0.002, I^2 = 60%), so the random-effects model was used. The results showed

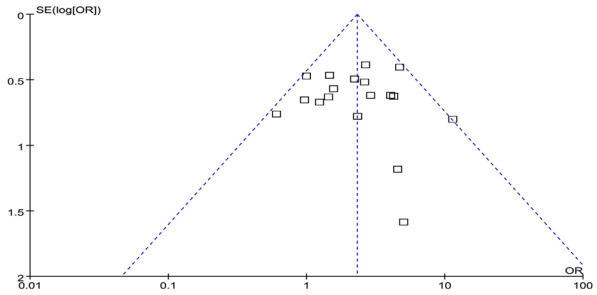

Figure 9. Funnel Plot of Publication Bias Based on the Total Rate of Efficacy

that the incidence of gastrointestinal reaction in the WBRT plus chemotherapy group was 3.82 times than the group of WBRT alone (RR = 3.82, 95% CI = 2.33 - 6.28, P <0.001) (Figure 8). The sensitivity analysis by omiting one study each time showed that the result without substantial change, that mean the result was robust.

Publication bias

A funnel plot was generated based on the total rate of efficacy, with OR values as the abscissa and logOR as the ordinate. Scatters of the 19CRTs were major concentrated on both sides of the straight line and close to the tip of the funnel, that suggested that there may be no obviously publication bias existed (Figure 9).

Discussion

Main findings: Tumor metastasis often occurs in patients with advanced lung cancer, which usually indicates that cancer cells have spread to distant organs through the blood stream. Brain is one of the most common sites of metastases, and it is often accompanied by extracranial metastasis to other organs. The incidence of BM is 20% -30% in patients with non-small cell lung cancer (Louie et al., 2009), while is greater than 50% in small cell lung cancer patients (Jo et al., 2011). BM often show symptoms of intracranial hypertension, which is often the direct cause of death.

WBRT is the most common and effective standard treatment for lung cancer patients with multiple brain metastases or lesions that are inoperable (Antonadou et al., 2002; Guerrieri et al., 2004; Verger et al., 2005). WBRT can rapidly relieve neurologic symptoms caused by BM, control the local progression of metastasis, improve the neurological function and quality of life, and prolong progression free survival time of these patients (Postmus et al., 2000). However, WBRT may cause radioactive nerve damage, even lead to brain atrophy and necrosis (Antonadou et al., 2002; Gijtenbeek et al., 2011), which is particularly a concern in large doses of radiation. The limitation on the dose of WBRT makes it difficult to completely eradicate the tumor. This means that the radiotherapy alone has very limited potential of improving survival time of lung cancer patients with BM.

Chemotherapy is necessary for patients with BM. However, it is difficult for chemical agents to reach the intracranial lesions due to the presence of blood-brain barrier, which limits the application of chemotherapy for patients with BM. Many recent studies showed that the BBB is damaged in patients with BM (Robinet et al., 2001; Grimm, 2012). Damaged BBB allows many chemotherapy drugs to penetrate into the intracranial lesion, thus improving the efficacy of chemotherapy. In addition, some research found that radiotherapy and chemotherapy work synergistically (Bai, 2010; Kienast et al., 2010; Kyritsis et al., 2012). On the one hand, radiation damages the BBB, and allows the chemotherapy drugs to penetrate the brain more readily. On the other hand, chemotherapy has a sensitizing effect for radiotherapy. Radiotherapy plus chemotherapy can eliminate subclinical lesions and micrometastases, and significantly improve the survival rate and the local control of lung cancer patients with BM.

The results of our meta-analysis based on 19 RCTs published from 2000 to 2012 with 1343 patients demonstrated that compared with WBRT alone, WBRT plus chemotherapy was more effective in objective response rate (total efficacy rate), and the incidence of adverse events was higher in WBRT plus chemotherapy group than in WBRT alone.

Limitations of Study: Because meta-analysis is a comprehensive analysis based on the results of previous studies, certain bias is inevitable due to the variable design, data collection, statistical analysis, data quality evaluation, information selection and processing in the original studies. For example, only 6 studies of the included were completely randomized, 5 RCTs mentioned allocation concealment, 1 RCT used blind evaluators, 3 RCTs reported withdrawal or decease of patients but no intention-to-treat analysis, so the quality of original studies were variable. In addition, the methods and doses of WBRT in these studies were different. The chemotherapy regimens and their application were also different. The sample sizes of these clinical studies were small, the weight of the data was usually not high, and only positive results of objective response rate were reported. Such factors may contribute to the existence of publication bias and an overestimation of the efficacy, which may unfavorably impact the authenticity and reliability of this meta-analysis.

Implications for further research: Our meta-analysis demonstrates that the objective total efficacy in WBRT plus chemotherapy group was obviously higher than that in WBRT alone, and adverse events incidence were also higher than that in WBRT alone. The potential benefit of long-term survival from radiochemotherapy remains controversial. New clinical trials of higher quality and larger sample-size are necessary to further verify the efficacy and safety of WBRT plus chemotherapy for patients with BM from lung cancer and to provide some insights for clinical practice.

Acknowledgements

The authors declare no conflict of interest with this research.

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