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Antineoplastic therapy combined with whole brain radiation compared with whole brain radiation alone for brain metastases: a systematic review and meta-analysis

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Abstract. – BACKGROUND: The standard treatment for brain metastases is whole brain radiation, but the medium survival is about 3-10 months and hadn't be improved for years.

AIM: This study was to evaluate the effect of antineoplastic therapy combined with whole brain radiation for brain metastases.

MATERIALS AND METHODS: We searched PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature Database, China Journal Full Text Database and references of the included studies up to May 2011. Randomized controlled trials involving antineoplastic combined with whole brain radiation compare with whole brain radiation alone for brain metastases were analysed. Study selection, data collection and quality assessment of studies were performed by two individual reviewers according to the Cochrane Handbook for systematic reviews of interventions 5.0.2. Statistic analyses were calculated using RevMan5.0.17 software. 9 randomized controlled trails, a total of 1582 patients were included.

RESULTS: There were no significant differences in overall survival, six to twenty-four months survival rate and death from central nervous system (CNS) cause, only the objective response rate was statistically higher in the combined group. (RR = 1.47, 95% CI: 1.10, 1.97; $p = 0.009$) Subgroup analysis of lung cancer got the same result, except that death from central nervous system (CNS) cause was higher in the combined therapy group, it was statistical significant (RR = 0.70, 95% CI: 0.53, 0.93; $p = 0.01$).

CONCLUSIONS: The benefit of antineoplastic combined with whole brain radiation for brain metastases was not concerned, either in the brain metastases from unselected primary tumors or lung cancer.

Key Words:
Antineoplastic, Whole brain radiation, Brain metastases, Meta analysis, Systematic review.

Introduction

Brain metastases are the most frequent neurological complication in patients suffering from cancer. It's estimated that nearly 25% of participants with cancer will develop metastatic cancer to the brain. Lung, breast and melanoma are the three types of cancer most prone to brain metastases[1]. Common symptoms of brain metastases are headache, weakness, cognitive and behavioral disturbances, seizures and ataxia, 7% of the patients have no symptoms[2]. The occurrence of brain metastases is a sign of progression disease. The prognosis of these patients is poor. In untreated patients, the median survival time is about one month[3]. Local control of a limited number (mostly 1-3, in some series > 3) of brain metastases can effectively be achieved by surgical resection or stereotactic radiosurgery[4,5]. Eventually, a considerable proportion of patients are treated with palliative approaches. Whole brain radiotherapy is recognized as the main palliative treatment, It has been shown to improve neurological symptoms. However, the median survival time improved to 4 months[6] after radiotherapy. The efficiency of chemotherapy in the treatment of brain metastases has been investigated, the median survival time in nonrandomized clinical trials were 3-10 months[7]. The role of it in the management of brain metastases is not determined[8]. Efforts have also been taken to combine whole brain radiation with chemotherapy. Some drugs for chemotherapy which have radiosensitising or have a high brain capillary permeability (e.g temozolomide, topotecan, paclitaxal, nimustine, tegatur, methyl-CCNU, ACNU, carboplatin) have been used in the combined therapy[9-13]. Some studies combined other

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anineoplastic with whole brain radiation. The most common drugs used are thalidomide and motexafin gadolinium. The two drugs do not belongs to chemotherapy, However they both have potential mechanisms of antitumor activity. Thalidomide inhibits the angiogenic activity[14] and inhibits stimulation to the tumor cell[15]. It can also improve tumor oxygenation so as to improve the therapeutic ratio of whole brain radiation[16]. Motexafin gadolinium is a kind of radiation sensitizer, different from other sensitizers, it disrupts redox-dependents pathways by targeting oxidative stress related proteins. In this way motexafin gadolinium induces the apoptosis of tumor cells[17]. The outcome of these therapeutic alliances did not meet each other. Some studies support the combined treatment[9,12,18-20], while other studies opposite[10,13,21,22]. In order to evaluate the efficiency and the safety of combined treatment strategies including whole brain radiation and antineoplastic, we reviewed the randomized controlled trials which compare antineoplastic combined with whole brain radiation and whole brain radiotherapy alone for brain metastases, use the method of the Cochrane systematic review to conduct a comprehensive evaluation to provide best clinical evidence.

Materials and Methods

Search Strategy and Selection Criteria

We searched PubMed, EMBASE, Cochrane Library, Chinese Biomedical Literature Database, China Journal Full Text Database and references of using the format, ("whole brain radiation" or "whole brain radiotherapy") and ("metastases tumor of brain" or "brain metastases" or "brain metastasis" or "CNS metastasis" or "CNS metastases") and ("drug therapy" or chemotherapy or "antineoplastic therapy") and ("metastases tumor of brain" or "brain metastases or brain metastasis" or "CNS metastasis" or "CNS metastases").

Searches were conducted independently by Dr. Ma and Dr. Meng. Reference lists from all relevant articles were reviewed to identify additional studies, and the final bibliography was distributed to experts in the field to identify missing or unpublished studies. All the randomized controlled trials which compare whole brain radiation alone and whole brain radiation combined with antineoplastic for brain metastases were included in our study, regardless of patients' nationality, race, gender and age.

Quality Assessment and Data Extraction

Two review authors (Dr. Ma and Dr. Meng) independently assessed the quality of the included studies according to the criteria described in Cochrane 5.0.2. Evaluation indicators include: randomization, allocation concealment, blinding, missing data, selective reporting of results, other possible bias. The included studies were devided into A (low risk of bias), B (moderate risk of bias), C (high risk of bias) 3 grade. Two reviewers (Dr. Tian and Dr. Meng) independently assessed these trials for eligibility and extracted data.

Statistical Analysis

Meta-analyses was done by software RevMan 5.0.17 provided by Cochrane Collaboration. Enumeration data and measurement data were analyzed using relative risk (RR), mean and standard deviation (SMD) respectively, for statistical efficacy analysis. Statistical heterogeneity between studies was evaluated using the χ^2 test and the I^2 statistic. 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 use of descriptive analysis.

Results

In accordance with the search strategy and data collection methods, 835 articles were initial reviewed. Duplicated studies were removed using Endnote software. Non-clinical randomized studies and irrelevance studies were excluded by reading the title and abstract. Finally 9 randomized controlled studies, a total of 1582 patients were included. They are from American, Spain, France, Belgium, Japan, Greece, China Hong Kong, Australia and Germany. All the included studies were followed up more than 12 months.

Quality Assessment of Included Studies

All the study[9-10,12-13,18-22] mentioned randomize, three of them[10,18,22] used stratified randomize, one study[19] used urn randomization scheme, one study[21] used randomized block. Other studies did not mentioned specific random method. None of the studies described the implementation of allocation concealment. One study[22] use blinding at start, then converted to open-label because of

poor enrollment. The others never use blinding. Five studies[9,10,13,20,21] had incomplete outcome data. There was no selective outcome reporting in the included studies and other potential threats to validity were unclear. Therefore all the studies were level C.

Outcome of Meta-Analysis

Six Months Survival Rate

Three studies[13,19,21] reported the six months survival rate, there was no heterogeneity among them ($p = 0.89$, $I^2 = 0\%$), the fixed effects model was used, the result showed that there was no significant difference between the antineoplastic combined with whole brain radiation group and the whole brain radiation group (RR = 0.91, 95% CI: 0.74, 1.12; $p = 0.37$) (Figure 1).

Twelve Months Survival Rate

Four studies[13,18,19,21] reported the twelve months survival rate, no heterogeneity was found among them ($p = 0.29$, $I^2 = 21\%$), the fixed effects model was used, the result showed that there was no significant difference between the antineoplastic combined with whole brain radiation group and the whole brain radiation group (RR = 0.97, 95% CI: 0.74, 1.27; $p = 0.82$) (Figure 1).

Eighteen Months Survival Rate

Four studies[13,18,19,21] reported the eighteen months survival rate, no heterogeneity was found among them ($p = 0.39$, $I^2 = 0\%$), the fixed effects model was used, the result showed that there was no significant difference between the antineoplastic combined with whole brain radiation group and the whole brain radiation group (RR = 0.83, 95% CI: 0.51, 1.36; $p = 0.47$) (Figure 1).

Twenty-four Months Survival Rate

Three studies[13,19,21] reported the twenty-four months survival rate, no heterogeneity was found among them ($p = 0.27$, I^2=24%), the fixed effects model was used, the result showed that there was no significant difference between the antineoplastic combined with whole brain radiation group and the whole brain radiation group (RR = 0.63, 95% CI: 0.23, 1.71; $p = 0.36$) (Figure 1).

Objective Response Rate

Five studies[9,10,12,13,20] reported the objective response rate of brain metastases after therapy, no heterogeneity was found among them ($p = 0.50$, $I^2 = 0\%$), the fixed effects model was used, the result showed that objective response rate was higher in the combined therapy group, there was statistic difference between two groups (RR = 1.47,95% CI: 1.10, 1.97; $p = 0.009$) (Figure 2).

Death from Central Nervous System (CNS) Cause

Five studies[9,12,13,19,20] reported the death from CNS cause, no heterogeneity was found among them ($p = 0.38$, $I^2 = 5\%$), the fixed effects model was used, the result showed that compared with the whole brain radiation group, patients in the combined group are prone to die from CNS cause. However, the difference had no statistical significance (RR = 0.85, 95% CI: 0.72, 1.01; $p = 0.06$) (Figure 3).

Median Survival Time

Eight studies[9,10,13,18,19,20-22] reported median survival time (Table II), however, none of them report the standard deviation, the meta-analysis can't be carried out. Among the eight studies, four[10,13,20,22] of them mentioned the p value between the antineoplastic combined with whole brain radiation group and the whole brain radiation group, they all had no statistical significance. p values in the other studies were not mentioned.

Time to Neurological Progression

Four studies[10,18,19,22] reported time to neurological progression due to Events Review committee (Table III), none of them report the standard deviation, the meta-analysis can't be carried out. Among the four studies, three[18,19,22] of them mentioned the p value between the antineoplastic combined with whole brain radiation group and the whole brain radiation group, they all had no statistical significance.

Outcomes in Lung Cancer

Six to twenty-four months survival rate, twelve months survival rate, eighteen months survival rate, twenty-four months survival rate and objective response are also analyzed in subgroup of lung cancer as following.

Six Months Survival Rate

Two studies[13,21] reported the six months survival rate of lung cancer, there was no heterogeneity among them ($p = 0.90$, $I^2 = 0\%$), the fixed effects model was used, the result showed that there was no significant difference between the antineoplas-

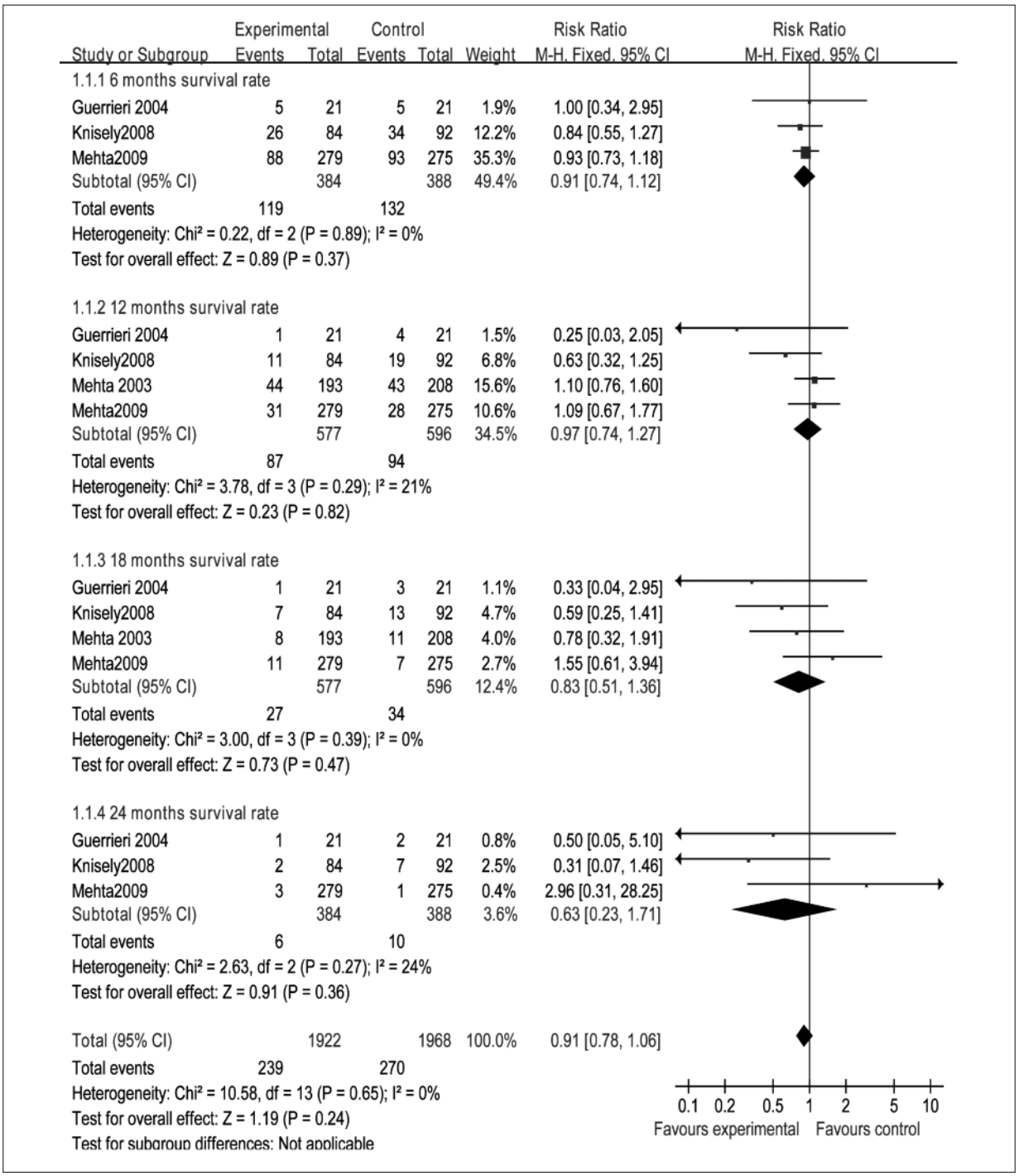

Figure 1. Overall survival rate.

tic combined with whole brain radiation group and the whole brain radiation group (RR = 0.94, 95% CI: 0.74, 1.18; $p = 0.58$) (Figure 4).

Twelve Months Survival Rate

Two studies[13,21] reported the twelve months survival rate of lung cancer, there was no heterogeneity among them ($p = 0.18$, $I^2 = 44\%$), the fixed effects model was used, the result showed that there was no significant difference between the antineoplastic combined with whole brain radiation group and the whole brain radiation group (RR = 0.99, 95% CI: 0.62, 1.57; $p = 0.96$) (Figure 4).

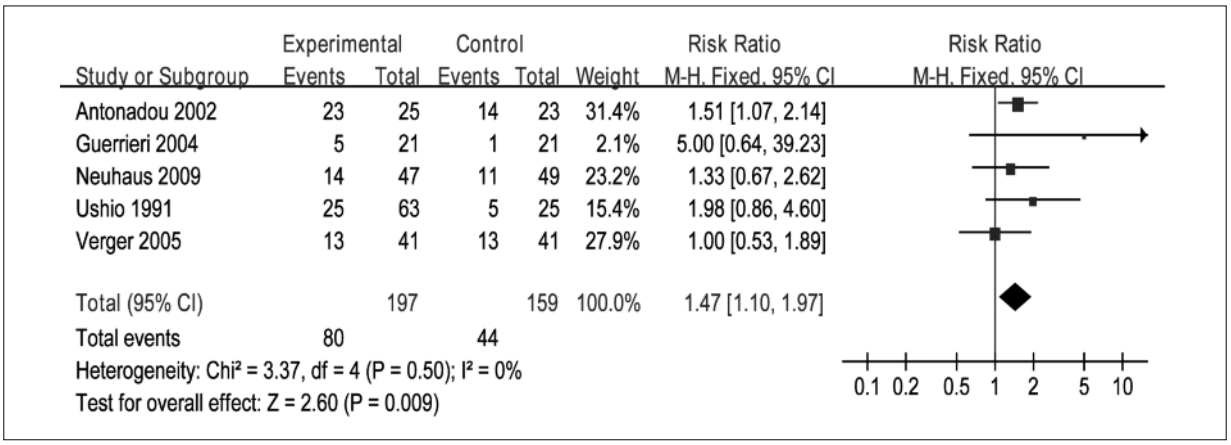

Figure 2. Objective response rat.

Eighteen Months Survival Rate

Two studies[13,21] reported the eighteen months survival rate of lung cancer, there was no heterogeneity among them (p = 0.20, I^2 = 39%), the fixed effects model was used, the result showed that there was no significant difference between the antineoplastic combined with whole brain radiation group and the whole brain radiotherapy group (RR = 1.19, 95% CI: 0.52, 2.70; p = 0.68) (Figure 4).

Twenty-four Months Survival Rate

Two studies[13,21] reported the twenty-four months survival rate of lung cancer, there was no heterogeneity among them (p = 0.28, I^2 = 14%), the fixed effects model was used, the result showed that there was no significant difference between the antineoplastic combined with whole brain radiation group and the whole brain radiotherapy group (RR = 1.32, 95% CI: 0.30, 5.79; p = 0.71) (Figure 4).

Objective Response Rate

Three studies[10,12,13] reported the objective response rate of brain metastases after therapy, no heterogeneity was found among them (p = 0.42, I^2 = 0%), the fixed effects model was used, the result showed that objective response rate was higher in the combined therapy group, there were statistic difference between two groups (RR = 1.77, 95% CI: 1.06, 2.94; p = 0.03) (Figure 5).

Death from CNS Cause

Two studies[12,18] reported the death from CNS cause, no heterogeneity was found among them (p = 0.69, I^2 = 0%), the fixed effects model was used, the result showed that compared with the whole brain radiation group, patients in the combined group were prone to die from CNS cause. The difference was statistical significance (RR = 0.70, 95% CI: 0.53, 0.93; p = 0.01) (Figure 6).

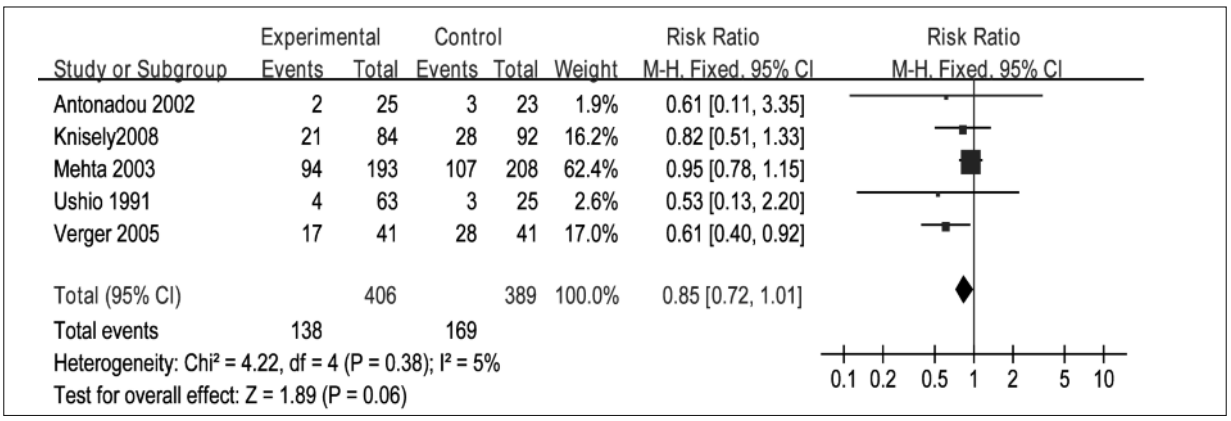

Figure 3. Death from CNS cause.

Table I. Basic information of the studies.

Study	Cases E C	Age, year E C	Gender (male/female) E C	Primary tumor	Systemic therapy	Outcome
Guerrieri et al 2004	21 21	39-78 42-77	15/6 15/6	Non-small cell lung cancer	Carboplatin 70 mg/d iv 20-30 min d1-5, Before every radiotherapy	Overall survival, objective response, symptom control toxicity, prognositic factors
Mehta et al 2003	193 208	50-66 51-66	92/101 90/118	Lung cancer Breast cancer other tumor	Motexafin Gadolininm 5 mg/kg/div 2-5 hours d1-10, before every radiotherapy	Overall survival, compliance and adverse events, time to Neurologic progression, time to neurocognitive progression, cause of death
Neuhaus et al 2009	47 49	34-75 42-75	32/15 30/19	Lung cancer	Toptecan 0.4 mg/m^2 Iv 30 min d1-5 Before every radiation	Overall survival, progression-free survival, adverse events
Ushio et al 1991	63 25	63 (mean) 57 (mean)	55/8 20/5	Lung cancer	Methyl-CCNU or ACNU or Methyl- CCNU+ ACNU or Tegafur	Response rate, Overall survival, cause of death
Mehta et al 2009	279 275	33-83 37-94	113/166 123/152	Non-small cell lung cancer	Motexafin Gadolinium 5 mg/kg/d, 2-5 hours d1-10 before every radiation	Overall survival, Interview to neurologic progression, adverse events
Antonadou et al 2002	25 23	61 (mean) 62 (mean)	19/6 16/7	Lung cancer Breast cancer Unknown tumor	Temozolomide 75 mg/m^2/d oral d1-28 before every radiotherapy	Overall survival, brain lesion response, neurologic symptom evaluation
Verger et al 2005	41 41	46-70 47-70	14/27 15/26	Lung cancer Breast cancer other tumor	Temozolomide 75 mg/m^2/d oral d1-10 before every radiotherapy 200 mg/m^2/d d11-15 28 day-cycle, 2 cycles	Overall survival, survival free of brain metastases progression, objective response, toxicity
Knisely et al 2008	84 92	31-38 33-78	35/49 45/47	Breast cancer Lung cancer Skin/melanoma Other tumor Unknown	Thalidomide 200 mg/d d1-15 during and after radiation	Overall survival, treatment compliance, toxicity,
Chua et al 2010	47 48	38-78 43-79	30/17 32/16	Non-small cell lung cancer	Temozolomide 75 mg/m^2 28-days cycle or 21-days cycle	Overall survival, time to Neurologic progression

Table II. Median survival time.

Study	Group E (month)	Group C (month)	*p* value
Guerrieri et al 2004	3.7	4.4	0.64
Metha et al 2003	5.2	4.9	0.48
Metha et al 2009	5.1	5.8	Not mentioned
Neuhaus et al 2009	2.9	3.2	Not mentioned
Antonadou et al 2002	8.6	7.0	0.447
Knisely et al 2008	3.9	3.9	Not mentioned
Verger et al 2005	4.5	3.1	Not mentioned
Chua et al 2010	4.4	5.7	0.59

Table III. Time to neurological progression.

Study	Group E (month)	Group C (month)	*p* value
Metha 2003	3.8	4.3	0.018
Metha 2009	15.4	10.0	0.122
Neuhaus 2009	2.4	2.2	Not mentioned
Chua 2010	3.1	3.8	0.95

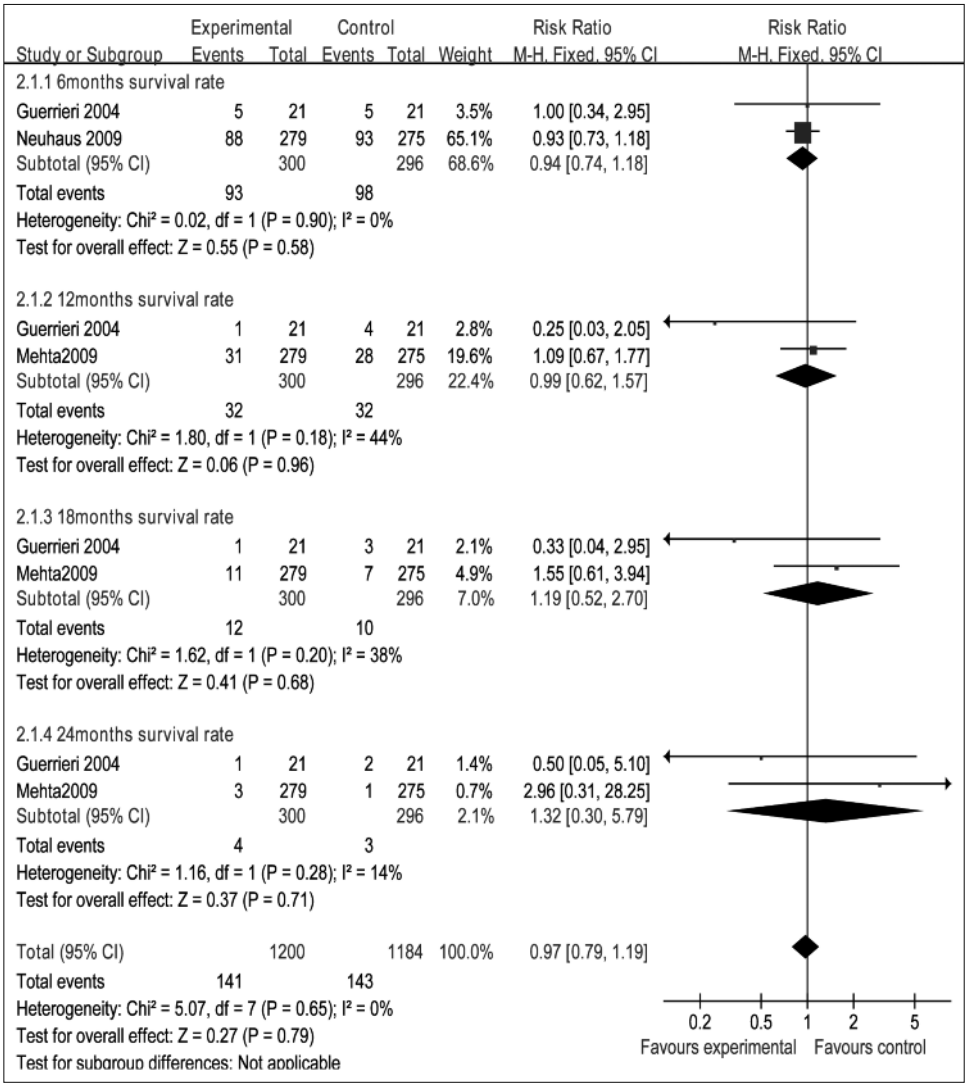

Figure 4. Overall survival rate of lung cancer.

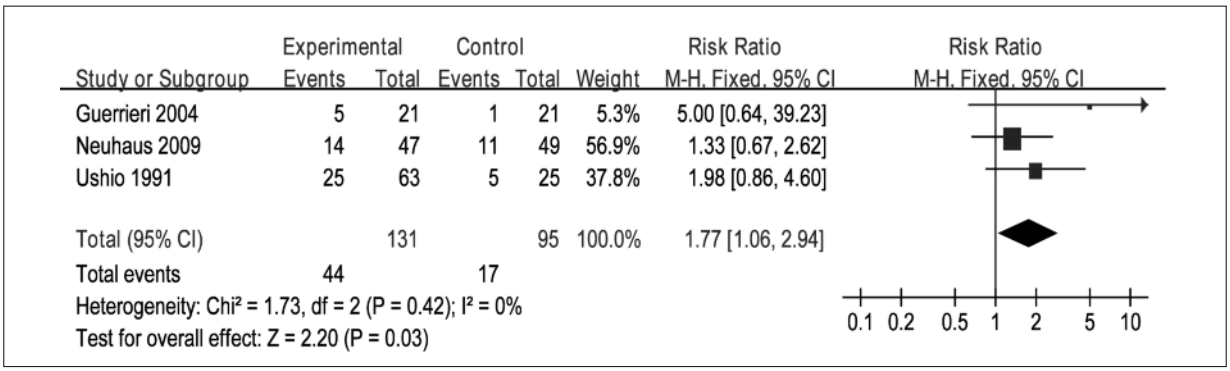

Figure 5. Objective response rate of lung cancer.

Discussion

Whole brain radiation has been a standard treatment for brain metastases for more than fifty years[23]. Yet the median survival time has not been prolonged significantly. Multimodal treatment strategies have been attempt, including whole brain radiotherapy plus radiosensitizers[24], Whole brain radiotherapy plus radiosurgery[25,26], whole brain radio therapy and systemic therapy[9,10,12,13,18-22], steroids and whole brain radiation[27]. Altered whole brain radiotherapy[28,29] is another kind of attempt. Only whole brain radiotherapy plus radiosurgery[25,26] was considered to improve local brain control in selected participants. Outcome of other therapies were disappointing, none of them proved to be effective in prolonging the overall survival. Some studies using whole brain radiation and systemic therapy[9,12,18-20] reporting a good response rate, especially in lung cancer[10,1-13]. Some of them reported a longer time to neurological progression[10,19], yet the outcome were contradictive with other studies. We analysis all the randomized controlled studies of antineoplastic combined with whole brain radiation compare with whole brain radiation alone for brain metastases. The result was negative. Only high objective response rate was found in the combined study group.

Patients involved in our study were adults those who had a diagnosis as brain metastases and hadn't received radiosurgery or radiotherapy before, within 2-3 weeks they received no chemotherapy. Most of the patients' primary tumors were lung cancer. Brain metastases from breast cancer, melanoma and other tumors were also included. In five studies, only lung cancer patients were recruited[10,12,13,19,22]. Still in three studies[13,19,22], research was focus on brain metastases from non-small-cell lung cancer. After randomization, patients in combined study group were given whole brain radiation together with systemic antineoplastic therapy. In our study systemic antineoplastic therapy included chemotherapy and other anticancer drugs. In chemotherapy subgroup, three studies[9,20,22] combined whole brain radiation with temozolomide. Temozolomide is considered to be an alkylating agent which can cross the blood-brain barrier and reaches the central nervous system in therapeutic concentrations[30]. Antonadou et al study[20] was a small scale, totally 48 patients attend the trial,

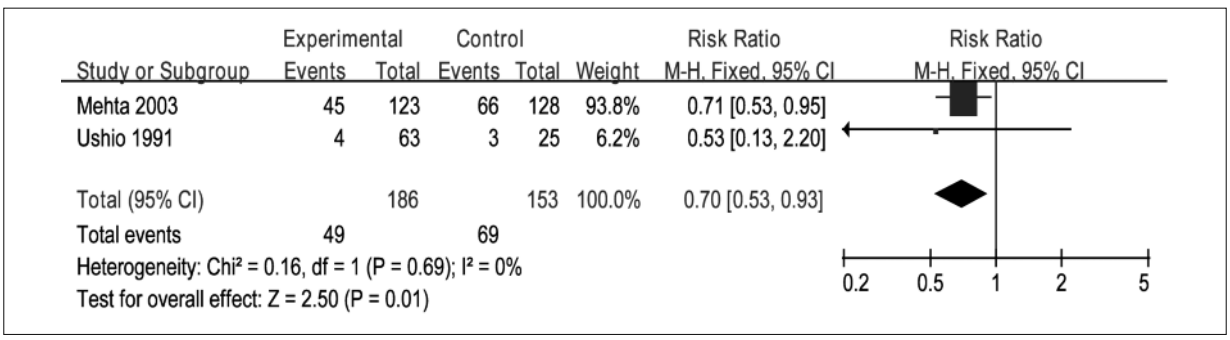

Figure 6. Death from CNS cause in lung cancer.

but the outcome was excited: the objective response rate in the combined study group was significantly superior to that achieved with whole brain radiation alone, and it was statistical significant. The overall survival was improved from 7.0 months in the whole brain radiation group to 8.6 months, but it has no statistic significance. Verger et al[9] recruited 82 patients, the objective response was equal in the two groups, but the portion of patients who were free of metastases progression were higher in the combined group which had statistical significant. Chua et al[9] outcome was completely on the contrary. No outcomes in favor of the combined therapy group. The study converted from phase III to a phase II study because of the poor enrollment, so it was unbalanced, and patients first received 21-days cycle, then received 28-days cycle after amending. Patients in the combined therapy group didn't oral temozolomide after radiation. All these contribute to the different outcomes. Side-effect of the combined strategies are not serious, common adverse events were nausea, vomiting, alopecia and fatigue. So the safety of the combined study was affirmed. All of the three studies about temozolomide were in small scale, and the observation values were not the same, so the further randomized controlled studies are needed to evaluate the effect of temozolomide of brain metastases.

Another three chemotherapeutics involved in our study were topotecan, carboplatin, chloroethylnitrosoureas, and tegafur. Topotecan has a high brain capillary permeability[31] and radiosensitising effect[32]. Carboplatin has been prove to have radiosensitising effect *in vitro*[33]. tegafur and chloroethylnitrosoureas are proved to cross blood-brain barrier effectively[34,35]. When these drugs combined with whole brain radiation, the outcome were not what we expected, and different from some non-controlled clinical trials. There were no significant advantages for concurrent therapy. The overall survival, median survival time, time to neurological progression, had no statistical difference between combined group and the whole brain radiation group. Only in Unish et al study[12] the objective response rate was higher in the combined group statistically. This may because combined therapy diminished the quality of life (QOL). Corn et al study[36] investigates the relationship between quality of life and median survival time among patients of brain metastases, and concluded that QOL is predictive of survival.

Thalidomide and motexafin gadolinium are all antineoplastic, can kill tumor cell systemically, but not belongs to chemotherapeutics. Besides anti-tumor effect, they are both radiation sensitizers[14-17]. In phase II trial they had beneficial results[37,38], good response rate and low death from central nervous system (CNS) cause rate were reported. In the studies we included, motexafin gadolinium was found[18,19] to prolong the interview of the interval to neurologic progression when the treatment was more prompt, and the objective was higher in the combined study group. The outcome of thalidomide in the study[21] was disappointing, 76% of the patients in the combined study group stopped taking thalidomide in two months because of the toxicity. Grade 3-4 adverse events were significantly higher in the combined study group. The most common side reaction was neurology, gastrointestinal and dermatology. In previous clinical trials thalidomide proved to increase the side-effect when combined to chemotherapy, especially the risk of thromboembolic disease[39]. It seems that thalidomide should be carefully used when combined with chemotherapy or radiotherapy.

When analysis all the randomized controlled clinical trials about antineoplastic combined with whole brain radiation compare with whole brain radiation alone for brain metastases, the combined treatments were not proved benefit in the overall survival and the time to neurological progression as we hoped. Six to twenty-four months survival rate had no statistical significance between the two groups. Very few people were still alive after six months. The outcome was the same in the subgroup of lung cancer. The objective response rate was higher in combined study group, yet death from central nervous system (CNS) cause had no statistical significance between the two groups. In the subgroup of lung cancer, patients in the combined groups were more likely to die from CNS cause. This may because lung cancer is heterogeneity, the effective systemic therapy is different, some drugs can cross the blood brain barrier, but can not control the primary tumor. Choosing optimal systemic antineoplastic therapy to respective cancer may benefit the patients of brain metastases more. Some authors believed that QOL was the more suile indicator to reflect the true status of patients suffering from brain metastases[40,41]. QOL should be added to the outcome measures in the future study.

Our review has several limitations. First, no blinding was used in the studies we included, therefore, all the studies are C-level. Moreover, four of the nine included studies did not describe the method of allocation, this led to possible performance bias and measurement bias. 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 outcome measures were inconsistent. All these may distort the result. In future, more well-designed large scale randomized controlled clinical trials about antineoplastic combined with whole brain radiation compare with whole brain radiation alone for brain metastases should be taken for further study.

Antineoplastic combined with whole brain radiation showed no significant advantage in treatment of brain metastases, though the objective response rate can be improved, the death from CNS cause, the overall survival had no statistical difference between the two groups. Therefore, antineoplastic combined with whole brain radiation shouldn't be recommended as standard treatment for brain metastasis before further study.

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