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Chemotherapy for brain metastases from small cell lung cancer (Review)

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[Intervention Review]

Chemotherapy for brain metastases from small cell lung cancer

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ABSTRACT

Background

Small cell lung cancer (SCLC) accounts for approximately 20% of all cases of lung cancer. It tends to disseminate early in the course of its natural history and to grow quickly. Approximately 10% to 18% of patients present with brain metastases (BM) at the time of initial diagnosis, and an additional 40% to 50% will develop BM some time during the course of their disease.

Objectives

The aim of this review was to evaluate the effectiveness and toxicity of systemic chemotherapy for the treatment of BM from SCLC.

Search methods

We searched the Cochrane Lung Cancer Review Group Specialised Register (July 2011), CENTRAL (2011, Issue 5), PubMed (1966 to July 2011), EMBASE (2005 to July 2011), LILACS (1982 to July 2011) and the International Clinical Trial Registry Platform (ICTRP).

Selection criteria

Randomized controlled trials (RCTs) comparing systemic chemotherapy (single agent or combination chemotherapy) with another chemotherapy regimen, palliative care, whole brain radiotherapy or any combination of these interventions for the treatment of BM as the only site of progression.

Data collection and analysis

Data extraction and 'Risk of bias' assessment were carried out independently by two review authors. As the included studies evaluated three different treatment modalities meta-analysis was not possible.

Main results

Three RCTs, involving 192 participants, met inclusion criteria for this review. No significant differences for overall survival (OS) were reported in any of the trials: in the first trial, 33 patients received whole brain radiation therapy and no significant difference was found between patients treated with topotecan and those not treated with topotecan. In a second trial, in which 120 patients were randomized to receive teniposide with or without brain radiation therapy, the authors reported that the median progression-free survival (brain-specific progression-free survival (PFS)) was 3.5 months in the combined modality arm and 3.2 in the teniposide alone arm. In a third trial, comparing sequential and concomitant chemoradiotherapy (teniposide plus cisplatin) in 39 participants, the survival difference between the two groups was not statistically significant. While the first trial reported no significant difference in PFS, the second RCT found a significant difference favoring combined therapy group. The second trial also found that patients receiving chemoradiotherapy (teniposide plus whole brain radiotherapy) had a higher complete response rate than those receiving only the topoisomerase inhibitor.

Authors' conclusions

Given the paucity of robust studies assessing the clinical effects of treatments, available evidence is insufficient to judge the effectiveness and safety of chemotherapy for the treatment of BM from SCLC. Published studies are insufficient to address the objectives of this review. According to the available evidence included in this review, chemotherapy does not improve specific brain PFS and OS in patients with SCLC. The combined treatment of teniposide and brain radiation therapy contributed to outcome in terms of increased complete remission and shorter time to progression (though not OS).

PLAIN LANGUAGE SUMMARY

Is chemotherapy beneficial to patients with brain metastases from small cell lung cancer?

Lung carcinoma is the single most common source of brain metastases (BM) in adults. Small cell lung cancer (SCLC) accounts for approximately 20% of all cases of lung cancer. It tends to disseminate early in the course of its natural history and to grow quickly. Approximately 10% to 18% of patients present with BM at the time of initial diagnosis, and an additional 40% to 50% will develop BM some time during the course of their disease.

After an extensive review of medical literature we identified three trials assessing different treatment strategies for patients with BM from SCLC. Only one of the studies compared chemotherapy (topotecan) versus no chemotherapy, but in patients treated with whole brain radiotherapy. Another study randomized patients to receive teniposide with or without brain radiation therapy, and the third one, compared sequential and concomitant chemoradiotherapy (teniposide plus cisplatin).

Studies show that people who received chemotherapy did not live longer or have a longer time before the BM grew again compared to those who were treated with brain radiation therapy alone. Hematological toxicities occurred more often in patients exposed to chemoradiotherapy in one study and in patients receiving sequential treatment in another study. A major limitation of this review was the low number of included studies and participants.

BACKGROUND

Description of the condition

Several studies have described the molecular pathophysiology of brain metastases (BM) and the basis for the differences in 'neurotropism' among various systemic tumors (Nathoo 2005; Palmieri 2007; Gril 2010; Lorger 2010). To form brain metastases successfully, tumor cells must attach to and penetrate the microvessel endothelium, degrade the extracellular matrix, and respond to autocrine and brain-derived survival and growth factors.

Approximately 150,000 patients in the US develop symptomatic BM each year, making them the most common intracranial malignancies. Any neoplasm is capable of metastasizing to the brain, although two thirds of all adult patients have lung cancer, breast cancer, or melanoma. Lung carcinoma is the single most common source of BM in adults, accounting for 30% to 50% of all cases (Nussbaum 1996; Nayak 2011). Lung carcinomas are also the tumors most likely to spread to the brain in the absence of other systemic metastases.

Small cell lung cancer (SCLC) accounts for approximately 15 to 20% of all cases of lung cancer. It tends to disseminate early in the course of its natural history and grow quickly. Around 10% to 18% of patients present with BM at the time of initial diagnosis, and an additional 40% to 50% will develop BM some time during the course of their disease (Quan 2004; Seute 2004).

The aims of treatment of symptomatic BM from SCLC are to improve survival, reduce symptoms, and to prevent complications, such as neurologic deficits and cognitive impairment. Traditionally, the standard treatment for symptomatic BM is whole brain radiotherapy (WBRT), with an overall response rate (ORR) ranging from 56% to 92% (Kristensen 1992; Seute 2005; Nieder 2006). Factors related to the prognosis of patients with SCLC who develop BM are the performance status, control of extracranial metastases, number of brain lesions, and age (Seute 2004).

Description of the intervention

For a long time systemic chemotherapy was not considered a potential therapy for BM, since it was assumed that the brain was a pharmacologic sanctuary where metastases were protected from cytotoxic drugs by the blood brain barrier (BBB). However, in recent decades it has become clear that the BBB is disrupted by tumor tissue (Stewart 1984; Siegers 1990; Stewart 1993; Stewart 1994). Since then, the effectiveness of first-line and second-line systemic chemotherapy for the treatment of BM from SCLC has been the topic of several studies (Kristensen 1992; Postmus 1999; Van den Bent 2003; Schuette 2004; Seute 2004; Seute 2006). In addition, several authors have claimed that synchronous BM from SCLC and other solid tumors have a response rate for systemic chemotherapy that is similar for the primary (Kristensen 1992; Postmus 1999; Van den Bent 2003). It has been suggested that BM from SCLC should initially be treated with systemic chemotherapy (Grossi 2001). The debate about whether WBRT should be part of the initial treatment is still ongoing (Schuette 2004; Soffietti 2005). The aim of this review is to investigate whether there is any evidence that can clarify the role of systemic chemotherapy in the treatment of BM from SCLC.

OBJECTIVES

The aim of this review was to evaluate the effectiveness and toxicity of systemic chemotherapy for the treatment of BM from SCLC.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials (RCTs) (phase II (B) or III) of parallel design, published in any language, were eligible for inclusion in the review. We excluded studies presented only in abstract form about which no further or sufficient information could be obtained from the authors.

Types of participants

We included patients with histologically confirmed SCLC in whom BM was found on either computer tomography (CT) scan or magnetic resonance imaging (MRI).

Types of interventions

Systemic chemotherapy (single agent or combination chemotherapy) compared with another chemotherapy regimen, palliative care, WBRT, or any combination of these interventions.

Types of outcome measures

Primary outcomes

- Overall survival (OS).
- Progression-free survival (PFS), defined as the time from the start of systemic treatment until progressive brain disease (enlarging BM, the onset of new BM based on CT or MRI, or both).
- Radiologic response of BM/local brain response. The radiologic response was determined as the percentage of patients achieving complete remission (CR) or partial remission (PR) on MRI. CR was defined as the complete disappearance of all tumors on MRI. PR was defined as at least a 50% decrease of total tumor size of the lesions measured, without the appearance of any new lesions or progression of any lesions. Stable disease was defined as a less than 50% decrease or less than 25% increase in size of lesions and no new lesions. Progressive disease was defined as a more than 25% increase in the size of lesions or the appearance of new lesions (Macdonald 1990). However, we accepted whatever definitions had been used in individual trials.

Secondary outcomes

- Control of the neurologic symptoms and signs.
- The response of the primary tumor and systemic metastases.
- Quality of life (QoL) measured using validated international scales.
- Toxicity (using the National Cancer Institute Common Toxicity Criteria).

Search methods for identification of studies

(1) Electronic databases

We identified relevant trials from:

(a) the Cochrane Lung Cancer Review Group Specialised Register, which contains the results of a comprehensive handsearching of

relevant lung cancer journals and conference proceedings (6 July 2011),

(b) the Cochrane Central Register of Controlled Clinical Trials (CENTRAL) (*The Cochrane Library*, 2011, issue 6), MEDLINE (accessed via Ovid; from 1966 to July 6, 2011), EMBASE (accessed via Ovid, from 1980 to July 6, 2011), LILACS (from 1982 to July 2011) (Manríquez 2008),

(c) ongoing trials in the International clinical trial registry platform (ICTRP) using the following key words: brain AND lung AND metastasis.

We searched MEDLINE (Appendix 1), EMBASE (Appendix 2), and CENTRAL (via Ovid; Appendix 3). We modified and adapted this search strategy for LILACS.

(2) References from published studies

We scanned bibliographies of relevant studies for possible references to additional trials.

(3) Unpublished literature

We searched for electronic addresses of leading researchers or researchers possibly involved in this field in electronic databases, to obtain additional published and unpublished trials.

(4) Adverse effects

We only included data from RCTs and clinical controlled trials. No further search for other types of studies was done (Golder 2005).

Data collection and analysis

Selection of studies

We assessed the eligibility of the retrieved articles from the title and abstracts. Where there was insufficient information for assessment, the authors reviewed the full articles. Two authors (LR and AFC) independently assessed all RCTs. There was no blinding of the author as to the origin or conclusions of the article for eligibility assessment, data extraction or 'Risk of bias' assessment.

Data extraction and management

Two review authors (LR and JRR) independently carried out data extraction using a pre-designed data extraction form. Data were extracted for all outcomes for all relevant drugs, paying particular attention to the dosage and periodicity of treatment. Data extraction was double-checked. Disagreements were solved by consensus.

Assessment of risk of bias in included studies

Two review authors (LR and JRR) independently assessed the risk of bias of included studies according to the areas and criteria proposed in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011) and results of those judgments are presented in the 'Risk of bias' tables. Disagreements were solved by consensus.

(1) Sequence generation (checking for possible selection bias)

For each included study we described the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the risk of bias as:

- low risk (any truly random process, e.g. random number table; computer random number generator),
- high risk (any non-random process, e.g. odd or even date of birth; hospital or clinic record number), or
- unclear risk.

(2) Allocation concealment (checking for possible selection bias)

For each included study we described the method used to conceal the allocation sequence and determined whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the risk of bias as:

- low risk (e.g. telephone or central randomization; consecutively numbered sealed opaque envelopes),
- high risk (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth),
- unclear risk.

(3) Blinding (checking for possible performance bias)

For each included study we described the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies are at low risk of bias if they were blinded, or if we judged that the lack of blinding could not have affected the results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the risk of bias as:

- low risk, high risk, or unclear risk for participants;
- low risk, high risk, or unclear risk for personnel;
- low risk, high risk, or unclear risk for outcome assessors.

(4) Incomplete outcome data (checking for possible attrition bias through withdrawals, dropouts, protocol deviations)

For each included study and for each outcome or class of outcomes, we described the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported, the numbers included in the analysis at each stage (compared with the total randomized participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. We categorized the risk of bias as:

- low risk,
- high risk,
- unclear risk.

(5) Selective reporting bias

For each included study we described how we investigated the possibility of selective outcome reporting bias and what we found.

We assessed the risk of bias as:

- low risk (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);

- high risk (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk.

(6) Other sources of bias

Where relevant for each included study any important concern about other possible sources of bias is reported.

We assessed the risk of bias as:

- low risk,
- high risk,
- unclear risk.

Assessment of heterogeneity

No meta-analysis was conducted in this review. For future updates of this review we will carry out tests for homogeneity using a standard Chi^2 test with significance being set at $P < 0.1$ when possible. The I^2 statistic will be used to estimate total variation across studies due to heterogeneity rather than chance. In percentages, less than 25% will be considered as low-level heterogeneity, 25% to 50% as moderate-level heterogeneity, and greater than 50% as high-level heterogeneity (Higgins 2011). We plan that if only significant methodologic heterogeneity is found, we should perform a sensitivity analysis.

Potential sources of heterogeneity

1. 'Risk of bias' assessment (low, intermediate, high).
2. Methods of symptom assessment.
3. Type of previous therapy for patients with progressive disease in the brain.
4. Stratification by Eastern Cooperative Oncology Group performance status.

Potential sources of heterogeneity could not be explored due to the scarcity of trials.

Data synthesis

We planned to estimate differences between treatments by pooling the results of RCTs that evaluated similar interventions and controls (with another chemotherapy regimen, palliative care, or WBRT), and to calculate a weighted treatment effect across RCTs using a random-effects model, but it was not possible since there was only one study for each comparison of treatments. However, for the individual studies, we expressed the results as risk ratio (RR) with 95% confidence intervals (CI) for dichotomous outcomes (i.e. radiologic response of BM/local brain response) and weighted mean difference (WMD) with 95% CI for continuous outcomes (i.e. survival time); or, when appropriate, we used the standardized mean difference (SMD) with 95% CI. For survival analysis, estimation of the hazard ratio and its variance (Parmar 1998) was used as the summary statistic where the data permit.

We summarized the available information and based our analysis on intention to treat whenever possible. We considered a level of $P < 0.05$ to be statistically significant. We provided a qualitative description for adverse effects when it was available. We planned to estimate publication bias by a visual inspection of a funnel plot; however there were fewer than nine studies involved in one subgroup (Higgins 2011).

Subgroup analysis and investigation of heterogeneity

Even though it was planned to make separate analysis for some subgroups of patients it was not possible because of the lack of necessary data. If information is available, future updates of this review will present separate analysis for:

- patients with synchronous BM (diagnosed within four weeks of the diagnosis of SCLC), and
- patients with SCLC previously treated with prophylactic cranial radiotherapy or systemic first-line chemotherapy, who subsequently developed BM as the only site of progression.

Sensitivity analysis

For further updates, we plan to perform sensitivity analysis by systematically excluding studies from the overall analysis based on the potential sources of heterogeneity hypothesized above, and if homogeneous subgroups have not already been identified and analyzed separately (Higgins 2011).

RESULTS

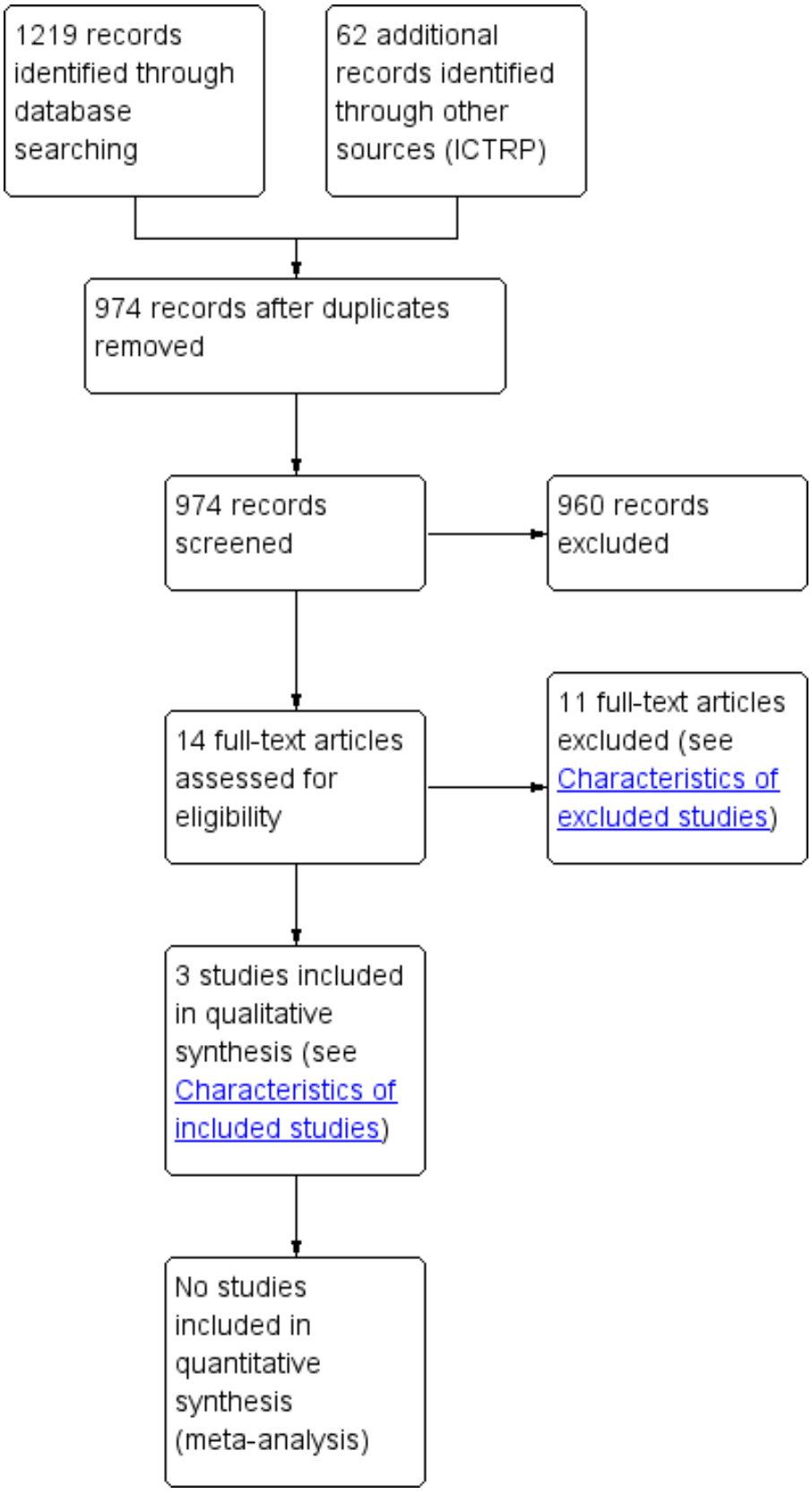
Description of studies

See: Characteristics of included studies.

Results of the search

The search identified 912 references. An initial trawl through this list, done by the three review authors, excluded 895 references that did not comply with the inclusion criteria (Figure 1). Fourteen studies were further excluded after first review because they were not RCTs, did not focus on chemotherapy for the treatment of BM from SCLC, or did not present disaggregated data on SCLC participants. The search identified no RCTs published in abstract form only. We actively contacted authors requesting information about additional trials but had no replies. In addition, no ongoing trials were identified after assessing 62 studies in the ICTRP database.

Figure 1. Study flow diagram.



Included studies

We included only three RCTs in the review (see Characteristics of included studies). One study was done in several European countries (Postmus 2000), another one in Germany (Neuhaus 2009) and the third in China (Liu 2010). Chemotherapy regimens were different in all three studies: topotecan, teniposide alone, and teniposide plus cisplatin. All the studies assessed survival time, two reported PFS time and two reported tumor response.

Only one of the RCTs compared chemotherapy with no chemotherapy (Neuhaus 2009) and included 33 patients with SCLC metastases (first line 5; recurrence 28); 17 patients received WBRT alone and 16 patients were treated with WBRT plus topotecan.

In another study that compared two schedules of administration of chemotherapy (teniposide plus cisplatin), a total of 39 patients were randomly allocated to receive either sequential chemoradiotherapy (20 patients) or concomitant chemoradiotherapy (19 patients) (Liu 2010).

In the third study both groups received chemotherapy, but one also received radiotherapy. They randomized 120 patients to receive teniposide (60 patients) or teniposide plus WBRT (60 patients) (Postmus 2000).

Excluded studies

Excluded studies and reasons for exclusion are listed in Characteristics of excluded studies.

Risk of bias in included studies

Allocation

The allocation strategy was considered adequate for one trial (Postmus 2000) and unclear for the other two (Neuhaus 2009; Liu 2010), while allocation concealment was judged as unclear in the three included RCTs (Neuhaus 2009; Postmus 2000; Liu 2010) (Figure 2; Figure 3). Although we actively contacted authors requesting information about their trials, we received no replies.

Figure 2. 'Risk of bias' graph: review authors' judgments about each 'Risk of bias' item presented as percentages across all included studies.

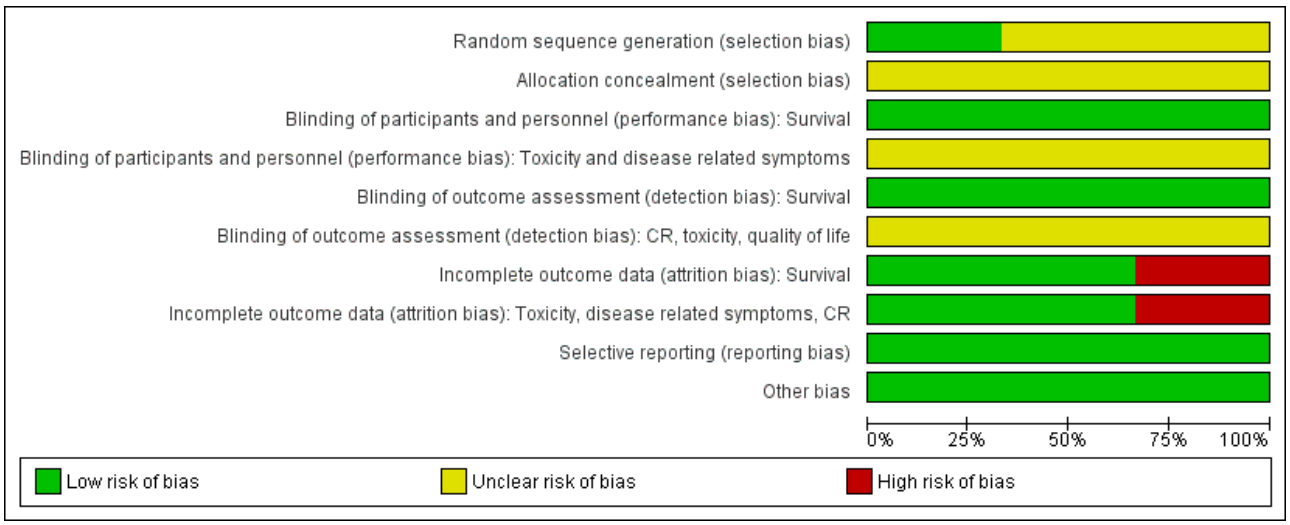
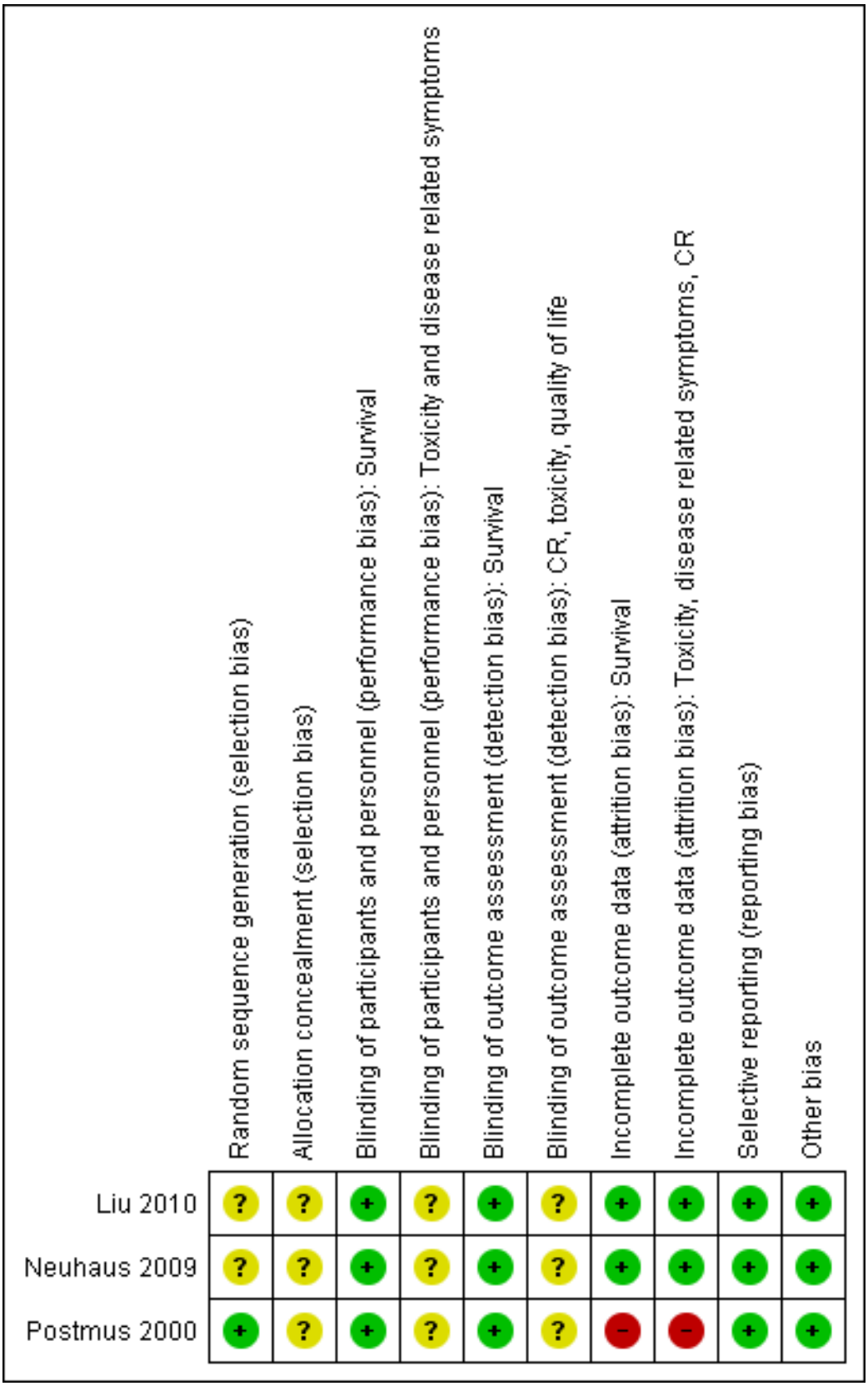


Figure 3. 'Risk of bias' summary: review authors' judgments about each 'Risk of bias' item for each included study.



Blinding

Blinding was not used in any of the three trials but main outcome measures, particularly survival, are not likely to be influenced by lack of blinding.

Incomplete outcome data

Losses to follow-up (Neuhaus 2009; Postmus 2000; Liu 2010) and reasons for stopping protocol therapy were reported (Postmus 2000). In one trial (Postmus 2000) 39 (65.0%) and 50 (83.3%) patients in the combined modality and teniposide-only arm, respectively, stopped treatment because of tumor progression. None of the patients completed all 12 courses of protocol therapy in the teniposide only arm while six (10%) patients did so in the combined modality arm.

Selective reporting

Relevant outcomes for this review were reported in all the studies.

Other potential sources of bias

The studies seemed to be free of other sources of bias.

Effects of interventions

Overall survival

Neuhaus 2009, in an RCT with 33 patients receiving WBRT, reported that the differences in survival time were not significant between patients treated with topotecan compared to those not receiving topotecan. Data on both SCLC and NSCLC were reported but numerical results for patients with SCLC were not presented in a disaggregated way.

In the RCT in which 120 patients were randomized to receive teniposide with or without WBRT (Postmus 2000), OS rated in the two groups were not statistically significant different, with a median survival of 3.5 months in the combined-modality arm and of 3.2 months in the teniposide-alone arm.

In the trial that compared sequential and concomitant chemoradiotherapy (Liu 2010), including 39 patients, the survival difference between the two groups was not statistically significant (Analysis 2.1).

Progression-free survival

Neuhaus 2009 reported that PFS differences in patients receiving WBRT were not significant between the patients treated with topotecan and those not receiving topotecan. However, no numerical data were reported in the article.

In the RCT in which participants were randomized to receive teniposide with or without WBRT (Postmus 2000), time to progression (TTP) in the brain, as assessed by contrast enhanced brain CT scan, was significantly better in the combined therapy group, but data were not provided to calculate the hazard ratio.

Liu 2010 did not publish an analysis of PFS.

Radiologic response of BM/local brain response

Neuhaus 2009 did analyze that outcome in their study but did not provide separate data for patients with SCLC.

Postmus 2000 found that patients receiving the combined treatment of teniposide and brain radiation therapy had higher complete BM response than those receiving only teniposide (RR 3.60 95% CI 1.43 to 9.07 Analysis 1.3).

Liu 2010 found that total response rates were similar among groups treated with sequential and concomitant chemoradiotherapy (Analysis 2.2; Analysis 2.3).

Secondary outcomes

Postmus 2000 did not find significant differences between groups receiving the combined treatment of teniposide and WBRT or teniposide alone for the following clinical outcomes: clinical response, toxicity, improvement on the ECOG performance status, and improvement in neurologic function score and status after two cycles.

Neuhaus 2009 found no differences in the occurrence of nonhematologic grade 3/4 toxicities between the treatment arms. Hematological toxicities occurred more often in patients exposed to chemoradiotherapy; 25 grade 3/4 hematological adverse events were reported, 24 in patients receiving combined treatment and one in a patient treated with WBRT alone.

Liu 2010 found that myelosuppression and grade 3/4 leukopenia were the most common adverse reactions, particularly in patients receiving sequential treatment compared with those receiving concomitant chemoradiotherapy (RR 8.42, 95% CI 1.16 to 61.10; Analysis 2.4). Other reported adverse events that had statistically significant differences between groups were grade 3/4 leukopenia (Analysis 2.7) and any grade of thrombocytopenia (Analysis 2.8). However, no significant differences were found for grade 3/4 anemia, thrombocytopenia, or nausea and vomiting between groups (Analysis 2.5; Analysis 2.6; Analysis 2.9). In addition, no events occurred in both arms of treatment for other grade 3/4 adverse events such as diarrhea, hepatic, and renal; no patient experienced grade 3/4 stomatitis in the sequential arm while one patient did in the concomitant arm (Analysis 2.10).

DISCUSSION

Summary of main results

We have found only one RCT that compared the effectiveness of chemotherapy with no chemotherapy for the treatment of BM due to SCLC, and it included only 96 participants. This study compared topotecan with no chemotherapy - all patients included received WBRT as co-intervention, without any significant advantage in OS, PFS, and intracranial disease control for concurrent chemoradiotherapy (WBRT + topotecan) when compared to WBRT alone (Neuhaus 2009).

One trial (Postmus 2000) assessed teniposide with or without WBRT. The effectiveness of teniposide with WBRT was comparable to that obtained with the teniposide alone for OS, TTP outside the brain and toxicity. However, TTP in the brain was significantly better in the combined group.

Another trial (Liu 2010) found that both sequential and concomitant chemoradiotherapy had a similar effect on survival and ORR, although patients in the concomitant group had a higher rate of myelosuppression.

Overall completeness and applicability of evidence

The evidence available on the effectiveness and toxicity of systemic chemotherapy for the treatment of patients with BM from SCLC comes from a single study that compared topotecan with no chemotherapy in patients treated with WBRT (Neuhaus 2009). In this study 28 of the 33 patients had recurrent disease, and most of them had also extracerebral progression. Under these circumstances life expectancy is usually less than 12 weeks without treatment, and in platinum-resistant patients less than 24 weeks. It remains unclear whether the results would be the same in patients not receiving cranial irradiation, in those with genetic abnormalities related to chromosomes 3p and 8q, and in those who were sensitive to platinum. We have found no RCTs comparing the effects of other chemotherapy regimens with no chemotherapy, in patients receiving or not receiving radiotherapy.

For settings in which regular treatment for BM from SCLC involves both chemotherapy and radiotherapy, evidence comes from a single RCT, which compared sequential chemoradiotherapy with concomitant chemoradiotherapy, and included only 39 patients, 22 of them with a single brain metastasis and 24 with also extracerebral metastases (Liu 2010). Although the response rate for the group receiving radiotherapy concomitant with chemotherapy was significantly higher than that for the sequential group, the incidence of III–IV hematologic toxicity, vomiting, and nausea was higher.

In the other RCT the objective was not to assess the effectiveness of chemotherapy but to address the contribution of radiotherapy in 120 patients all treated with chemotherapy (teniposide) (Postmus 2000). The intracranial RR was significantly higher in the combined-modality arm (57% vs. 22%, P < 0.001); although the TTP in the brain was also significantly longer in the combined-modality group, no improvement was obtained in OS (Postmus 2000). The median OS was 3.5 months in the combined-modality arm and 3.2 months in the teniposide-alone arm (P = 0.087). The majority of patients failed at extracranial sites, affecting any survival advantage that might have been the result of the improved intracranial control with combined WBRT and chemotherapy.

Quality of the evidence

The quality of the evidence available for all comparisons was moderate, mainly because there was only one study for each treatment comparison and main results were imprecise in some cases, as reflected in wide CIs. The Neuhaus 2009 study was closed early because of problems in recruiting patients and the author considered that the number of participants was too low to demonstrate any small advantage for the combined treatment (chemoradiotherapy).

Even though blinding of outcome assessment was not done in two of the RCTs, it is unlikely that this would have biased the outcome measures most relevant for patients, especially survival time. However, other outcomes, such as response rate, could be open to biased assessments. Similarly, the choice of patient made by the recruiter may have been influenced by the lack of allocation concealment.

Given the paucity of robust studies assessing clinical effects of treatments, available evidence is insufficient to judge the effectiveness and safety of chemotherapy for the treatment of BM from SCLC. Published studies are not adequate to address the objectives of this review.

Potential biases in the review process

It is quite unlikely that publication bias could have happened given that all included studies presented results not favorable for the more active interventions. Also the search strategy has been comprehensive, including search in most important clinical trial registers and contact with author of the studies, and data were analyzed and extracted independently by at least two review authors.

All relevant data for the objectives of this review were available from the publications of included studies.

Agreements and disagreements with other studies or reviews

Our review provides evidence derived from three trials using different interventions and duration of treatment. Our results for the main outcome, OS, are similar to the findings from other studies. Mehta 2010 assessed the role of chemotherapy in the management of newly diagnosed BM in a systematic review and evidence-based clinical practice guidelines. The authors (Mehta 2010) considered that routine use of chemotherapy following WBRT for BM has not been shown to increase survival. In one study, response rate of the group concomitant with chemotherapy was significantly higher than that of the sequential group, however further research is still needed (Liu 2010).

AUTHORS' CONCLUSIONS

Implications for practice

There are very few trials assessing the effectiveness and toxicity of systemic chemotherapy for the treatment of patients in whom BM is the only site of progression. The available evidence is insufficient to judge the effectiveness and safety of chemotherapy for the treatment of BM from SCLC. According to our findings, chemotherapy does not improve specific brain PFS and OS in patients with SCLC. The combined treatment of teniposide and WBRT contributed to outcome in terms of increased CR and better TTP (though not OS).

Implications for research

This systematic review has identified the need for well-designed, adequately powered RCTs to assess the benefits and harms of chemotherapy for the treatment of BM from SCLC (specifically in patients with only intracranial metastases, including the group treated with prophylactic cranial irradiation). Approximately 60% of SCLC patients will develop BM during the course of the disease (Quan 2004) and overall, the prognosis is poor, with a median OS in the range of 3 to 14 months (van Hazel 1983; Kochhar 1997). Studies frequently exclude SCLC-related BM, and therefore, advances in the treatment of the disease have been few over the last decades. One of the main reasons why patients with SCLC BM are rarely entered into research protocols is that approximately 60% to 90% of these patients have simultaneous progression at extracranial sites (Glantz 1997).

Many questions remain open. Some important considerations for future research are as follows:

1. The effects of different chemotherapy agents (including platinum-based regimens, differences between cisplatin and carboplatin, and combinations including irinotecan);
2. The effects of chemotherapy agents compared to supportive care;
3. The effectiveness of WBRT in patients with widespread metastatic disease;
4. Determining which patients with SCLC BM should be treated with chemotherapy alone.

ACKNOWLEDGEMENTS

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Liu 2010

Methods	RCT, parallel, open, single center, phase III trial Henan Provincial People's Hospital, Zhengzhou (China)
Participants	n = 39 Sex: 26 male, 13 female Mean age: 57 ± 18 years Inclusion criteria: • SCLC and BM lesions confirmed by histopathologic and MRI examinations, respectively • ECG, blood routine, hepatic and renal function findings normal
Interventions	Intervention Sequential radiotherapy and chemotherapy group: systemic chemotherapies 2 weeks after WBRT (n = 20) Control Concomitant radiotherapy and chemotherapy group: parallel systemic chemotherapies and WBRT (n = 19) WBRT: 1.8 to 2 Gy/time for 18 to 20 times, and the total dose in 4 weeks was 36 Gy Systemic chemotherapy: teniposide (Vm26) 60 mg/m^2, from day 1 to day 3; cisplatin (DDP) 20 mg/m^2, from day 1 to day 5. One cycle was defined as a 21-day therapy duration, with a total of 4 cycles
Outcomes	Main and secondary outcomes not differentiated:

Liu 2010 *(Continued)*

- clinical responses, based on the RECIST standards (4 grades, CR, PR, NC, and PD)
- median survival time
- cumulative survival rates
- acute and subacute toxicity (gastrointestinal, alopecia, renal dysfunction, and other adverse reactions)
- disease-related symptoms (including neurologic symptoms)
- KPS scale assessment
- body weight, height, physical exam, blood routine, ECG, chest and abdominal CT, brain MRI, bone marrow cells examination and ECT bone scan checks, with lesions measurement results recorded. Blood routine and hepatic and renal function had been re-examined before and after every treatment cycle

Notes	Publication presents preliminary results Competing interests and information on funding sources not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment. Mentioned as "randomized" but sequence generation process is not explained in a detailed way. Quote: "patients were randomly divided". Additional information requested to authors but no answer received
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment. Additional information requested to authors but no answer received
Blinding of participants and personnel (performance bias) Survival	Low risk	No information was provided. Probably unblinded. Outcomes measures are not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) Toxicity and disease related symptoms	Unclear risk	No information was provided. Probably unblinded
Blinding of outcome assessment (detection bias) Survival	Low risk	No information was provided. Probably unblinded. Outcomes measures are not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) CR, toxicity, quality of life	Unclear risk	No information was provided
Incomplete outcome data (attrition bias) Survival	Low risk	No losses in follow-up were reported
Incomplete outcome data (attrition bias) Toxicity, disease related symptoms, CR	Low risk	No losses in follow-up were reported
Selective reporting (reporting bias)	Low risk	Authors presented results on all outcome measures that were pre-specified as relevant

Liu 2010 *(Continued)*

		We searched for protocol information in the ICTRP
Other bias	Low risk	The study seems to be free of other sources of bias

Neuhaus 2009

Methods	RCT phase III
Participants	Patients with histologically confirmed lung cancer and intracerebral metastases. Initially only patients with recurrence of lung cancer after first-line therapy were included in the study. However, due to a slow recruitment, after 1 year an amendment allowing the inclusion of primary diagnosed patients was added. Randomization was performed by considering the parameters SCLC, NSCLC, extracerebral metastases, and a number of BM n = 96; 47 chemoradiotherapy, 49 radiotherapy Sex: 62 male, 34 female Median age: 58/59 years (range: 34 to 75 years) Clinical condition: • SCLC: 5 first-line, 28 recurrence • NSCLC: 15 first-line, 48 recurrence Inclusion criteria: • histologically confirmed lung cancer and intracerebral metastases • aged 18 to 75 years • at least 1 measurable lesion in the brain was confirmed by CT or MRI • sufficient bone marrow reserve (neutrophil counts 1500/µL, leukocyte counts ≥ 3500/µL, platelet counts ≥100,000/µL, and hemoglobin ≥ 9 g/dL). • adequate renal function (serum creatinine concentration ≤ 1.5 mg% or creatinine clearance > 60 mL/minute • performance status of 0 to 2 according to ECOG criteria Exclusion criteria: • prior to cerebral radiotherapy, surgery, or both of cerebral metastases (except stereotactic biopsy) • missing histologically confirmed nature of cancer • solitary intracerebral metastases suitable for neurosurgery • meningiosis carcinomatosa • active uncontrolled infection • concomitant or previous malignancies, except basal or squamous cell carcinoma or carcinoma in situ of the cervix • history of therapy with or without known allergy to topoisomerase I inhibitors • pregnant or breast-feeding women
Interventions	Arm A (chemoradiotherapy): topotecan was administered as a 30-minute infusion with 0.4 mg/m^2/day for 5 days over 4 weeks within 2 hours before radiotherapy. WBRT was applied with a fraction size of 2 Gy/day to a total of 40 Gy. Arm B (radiotherapy): WBRT was applied with a fraction size of 2 Gy/day to a total of 40 Gy. Continuation therapy: subsequently, patients with extracerebral cancer lesions from both arms had the option to receive 3 additional cycles of topotecan chemotherapy (1.25 mg/m^2/day, days 1 to 5, 4 cycles of 21 days), starting on day 15 after the end of WBRT. Where a patient had not received any kind of chemotherapy or chemoradiotherapy before entering the study, the institutionally preferred

Neuhaus 2009 *(Continued)*

	chemotherapeutic regimen was allowed to be used instead. Continuation therapy was stopped after 3 cycles or when tumor progression of the extracerebral metastases occurred
Outcomes	Primary end point: • OS (minimum clinically relevant therapeutic effect an increase in the survival time to 5.5 months) Secondary end points: • PFS • rates of complete responses of the cerebral lesions • duration of remission • status of the extracerebral tumors after continuation therapy and toxicity • QoL and safety A complete response was defined as a complete disappearance of all evidence of disease in the brain. A partial response was defined as radiologic response > 50% in all BM. Responses in tumor lesions < 50% or increase in size < 25% was defined as stable disease. A progressive disease was defined as either the occurrence of new lesions or an increase in size of > 25%
Notes	Numerical results for patients with SCLC were not presented in a disaggregated way, but authors reported in a narrative way that in relation with OS and PFS differences between compared groups were not significant either for SCLC and NSCLC Initially only patients with recurrence of lung cancer after first-line therapy could be included in the study. However, due to a slow recruitment, after 1 year an amendment allowing the inclusion of primary diagnosed patients was added An interim analysis was planned after the death of 150 patients. However, until 6 August 2004, that is, after a study duration of 34 months, only 95 patients in 11 centers had been recruited, and so the interim analysis was performed at that time point. This analysis did not show any benefit of chemoradiotherapy with regard to OS and thus, on the basis of the slow recruitment and the result of the interim analysis, a continuation of the study did no longer appear reasonable. The results described here represent the final analysis, in which 96 patients were included. Study supported by GlaxoSmithKline Competing interests not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficient information to permit judgment. Mentioned as "randomized" but sequence generation process is not explained in a detailed way. Probably centralized. Quote: "Randomisation was performed by considering the parameters SCLC, NSCLC, extracerebral metastases and a number of brain metastases". Additional information requested from authors but no answer received
Allocation concealment (selection bias)	Unclear risk	Insufficient information to permit judgment. Additional information requested from authors but no answer received
Blinding of participants and personnel (performance bias) Survival	Low risk	Stated as "open", but main outcome measure (OS) is it not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias)	Unclear risk	Stated as "open"

Neuhaus 2009 *(Continued)*

Toxicity and disease related symptoms		
Blinding of outcome assessment (detection bias) Survival	Low risk	Stated as "open", but main outcome measure (OS) is it not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) CR, toxicity, quality of life	Unclear risk	Stated as "open"
Incomplete outcome data (attrition bias) Survival	Low risk	Data was not presented for the SCLC subgroup No losses in follow-up reported. Causes for protocol deviations well reported. Quote: "The reasons for protocol deviations are mainly early deaths, haematological toxicities, dosage failure, worsening of general condition and tumour progression. In detail, in arm A the chemotherapy was delayed or reduced in nine patients because of neutropenia, and in six of them G-CSF was given at least once. Although no patient stopped topotecan because of neutropenia, one patient left the study because of prolonged thrombocytopenia." Quote: "The treatment was stopped as per the patients' wish, by the decision of the physician, tumour progression, severe side effects according to the NCIC CTCG guidelines or non-compliance of the patient."
Incomplete outcome data (attrition bias) Toxicity, disease related symptoms, CR	Low risk	Data were not presented for the SCLC subgroup No losses in follow-up reported. Causes for protocol deviations well reported Quote: "The reasons for protocol deviations are mainly early deaths, haematological toxicities, dosage failure, worsening of general condition and tumour progression. In detail, in arm A the chemotherapy was delayed or reduced in nine patients because of neutropenia, and in six of them G-CSF was given at least once. Although no patient stopped topotecan because of neutropenia, one patient left the study because of prolonged thrombocytopenia." Quote: "The treatment was stopped as per the patients' wish, by the decision of the physician, tumour progression, severe side effects according to the NCIC CTCG guidelines or non-compliance of the patient"]
Selective reporting (reporting bias)	Low risk	Authors presented results on all outcome measures that were pre-specified as relevant Search for protocol in clinical trials registers
Other bias	Low risk	Early termination of the study, but according to previously established criteria Quote: "The whole study was to be stopped in case new therapeutic regimens with superior benefit of either therapy arm were published, if the interim analyses showed that the criteria for stopping the study by using the methods of Pocock (Pocock 1978) and O'Brien and Fleming (O'Brien 1979) were reached and when the number of patients recruited was clearly below the expected value." Quote: "until August 6, 2004, that is, after a study duration of 34 months, only 95 patients in 11 centers had been recruited, and so the interim analysis was performed at that time point. This analysis did not show any benefit of chemoradiotherapy with regard to OS and thus, on the basis of the slow recruitment and the result of the interim analysis, a continuation of the study

Neuhaus 2009 *(Continued)*

	did no longer appear reasonable. The results described here represent the final analysis, in which 96 patients were included."

Postmus 2000

Methods	RCT, parallel, open, multicentric, phase III 11 centers in Europe (EORTC)
Participants	N = 120; 60 teniposide, 60 teniposide + WBRT Sex: 95 male, 25 female Median age: 60/61 years (range: 38 to 75 years) Inclusion criteria: • histologic or cytologic evidence of SCLC • BM confirmed by contrast-enhanced CT • evidence of extracranial tumor deposits • no previous treatment with either chemotherapy or radiotherapy (prophylactic or therapeutic) for BM • no prior treatment with teniposide • age less than 76 years • WBC count > 3000/mL • platelet count > 100,000/mL • creatinine concentration < 150 mmol/L • bilirubin concentration < 25 mmol/L Exclusion criteria: • uncontrolled infection • serious nonmalignant disease • expected difficulty with follow-up
Interventions	Intervention • teniposide alone Control • teniposide + WBRT Teniposide 120 mg/m^2 intravenous infusion on days 1, 3, and 5 every 3 weeks. Patients underwent treatment until they had received the maximum number of courses (n = 12) or until the disease had progressed inside or outside the brain. If the WBC count was ≤ 3000 /mL or the platelet count was ≤ 100.000/mL on the day of scheduled retreatment, treatment was delayed. Counts were measured weekly, and treatment was given at full doses when the WBC and platelet counts returned to ≥ 3000 / mL and ≥100.000/mL, respectively. If recovery was still incomplete after 2 weeks, the patient went off study. In the event of WHO grade 4 leukocytopenia, thrombocytopenia, or both during 2 subsequent courses, a 25% dose reduction for subsequent courses was advised WBRT consisted of 30 Gy (midplane dose) in 10 fractions in 2 weeks with parallel opposing fields. Both fields were treated each day. WBRT had to be started within 3 weeks after the start of teniposide and continued during administration of teniposide. All cranial meningeal surfaces, including the anterior, middle, and posterior cranial fossae, were included with a minimum 1-cm margin. Treatment was given with megavoltage equipment with a minimum source-to-skin distance or target-to-skin distance of 80 cm. Corticosteroids (dexamethasone 2 mg, 4 times) were given during irradiation and tapered off as soon as possible after WBRT

Postmus 2000 *(Continued)*

Outcomes	Primary end point: • duration of survival Secondary end points: • response rates • TTP • duration of response (complete and partial responders were considered together)
Notes	Analysis was performed on all eligible patients according to the intent-to-treat principle. The analysis of toxicity was based on the treatment patients actually received Competing interests and information on funding sources not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was done using minimization techniques with patients stratified according to their institution, number of BM (> 2), and prior chemotherapy (naive/pretreated)
Allocation concealment (selection bias)	Unclear risk	No further description in the manuscript. Probably central allocation. Additional information requested to authors but no answer received
Blinding of participants and personnel (performance bias) Survival	Low risk	No information was provided, but main outcome measure (duration of survival) is it not likely to be influenced by lack of blinding
Blinding of participants and personnel (performance bias) Toxicity and disease related symptoms	Unclear risk	No information was provided
Blinding of outcome assessment (detection bias) Survival	Low risk	No information provided, but main outcome measure (duration of survival) is it not likely to be influenced by lack of blinding
Blinding of outcome assessment (detection bias) CR, toxicity, quality of life	Unclear risk	No information was provided
Incomplete outcome data (attrition bias) Survival	High risk	Only 1 participant in the teniposide + WBRT was lost to follow-up. However, only 6 patients completed all 12 courses of protocol therapy in the combined group compared with 0 in the teniposide group. Reasons for stopping protocol therapy were reported in both groups. Tumor progression was the principal cause for stopping protocol therapy
Incomplete outcome data (attrition bias) Toxicity, disease related symptoms, CR	High risk	Only 1 participant in the teniposide + WBRT was lost to follow-up. However, only 6 patients completed all 12 courses of protocol therapy in the combined group compared with 0 in the teniposide group. Reasons for stopping protocol therapy were reported in both groups. Tumor progression was the principal cause for stopping protocol therapy
Selective reporting (reporting bias)	Low risk	Authors presented results on all outcome measures that were prespecified as relevant

Postmus 2000 *(Continued)*

Other bias	Low risk	The study seems to be free of other sources of bias

BM: brain metastases; CR: complete remission; CT: computer tomography; ECG: electrocardiogram; ECOG: Eastern Cooperative Oncology Group; ECT: emission computer tomography; G-CSF: granulocyte colony-stimulating factor; EORTC: European Organization for the Research and Treatment of Cancer Lung Cancer Cooperative Group; ICTRP: International Clinical Trials Registry Platform; MRI: magnetic resonance imaging; NC: no change; NSCLC: non-small cell lung cancer; OS: overall survival; PD: progressive disease; PFS: progression-free survival; PR: partial remission; QoL: quality of life; RCT: randomized controlled trial; RECIST: Response Evaluation Criteria In Solid Tumors; SCLC: small cell lung cancer; TTO: time to progression; WBRT: whole brain radiotherapy.

Characteristics of excluded studies *[ordered by study ID]*

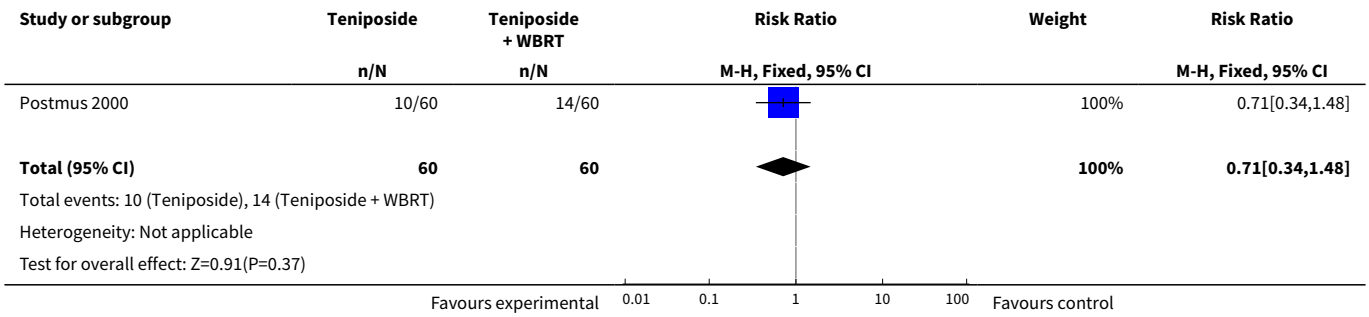
Study	Reason for exclusion
Antonadou 2002	The study did not include disaggregated data on results for small cells lung cancer patients
Fietkau 2001	Not a randomized study
Hanna 2002	The study did not include disaggregated data on results for small cells lung cancer patients
Loehrer 1995	The study did not include disaggregated data on results for small cells lung cancer patients
Malacarne 1996	Not a randomized study
Mehta 2003	Small cells lung cancer patients excluded
Meyers 2004	The study did not include disaggregated data on results for small cells lung cancer patients. Maybe included in "other cancers" category
Pandya 2009	The study did not include disaggregated data on results for patients with BM
Postmus 1992	Non-randomized study
Postmus 1995	Non-randomized trial
Schiller 2001	The study did not include disaggregated data on results for patients with BM
Suh 2006	The study did not include disaggregated data on results for small cells lung cancer patients. Maybe included in "other cancers" category
Thomas 1990	Not a randomized study
Yue 2004	Non-randomized trial

DATA AND ANALYSES

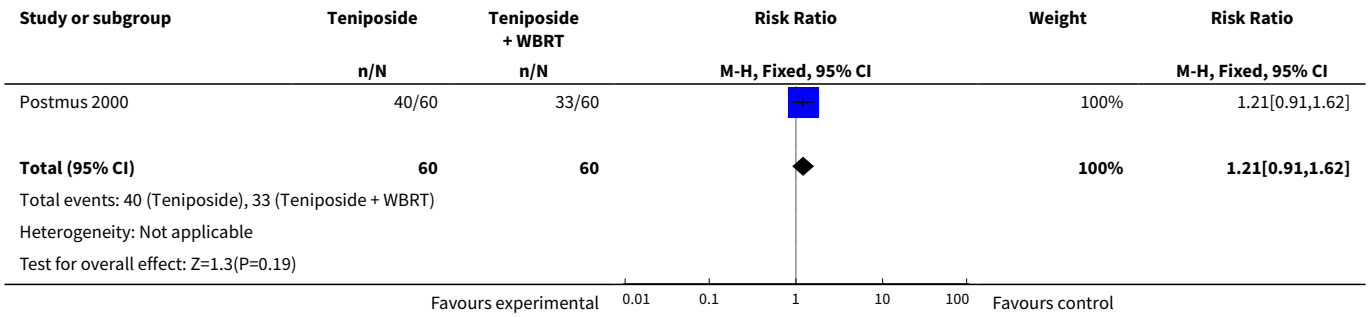
Comparison 1. Teniposide versus teniposide + whole brain radiotherapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Early death (overall response outside the brain)	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.34, 1.48]
2 Clinical response	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.91, 1.62]
3 Complete brain metastases response	1	120	Risk Ratio (M-H, Fixed, 95% CI)	3.6 [1.43, 9.07]
4 Partial brain metastases response	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.42 [0.17, 1.08]
5 Complete + partial brain metastases response	1	120	Odds Ratio (M-H, Fixed, 95% CI)	0.21 [0.10, 0.47]
6 Improvement on the ECOG performance status after 2 courses	1	120	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.74, 1.55]
7 Improved neurologic function score after cycle 2	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.29, 1.51]
8 Complete overall response outside the brain	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.13, 1.91]
9 Nausea and vomiting WHO grade 3-4 toxicity	1	120	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.12, 1.58]
10 Infection WHO grade 3-4 toxicity	1	120	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.38, 10.51]

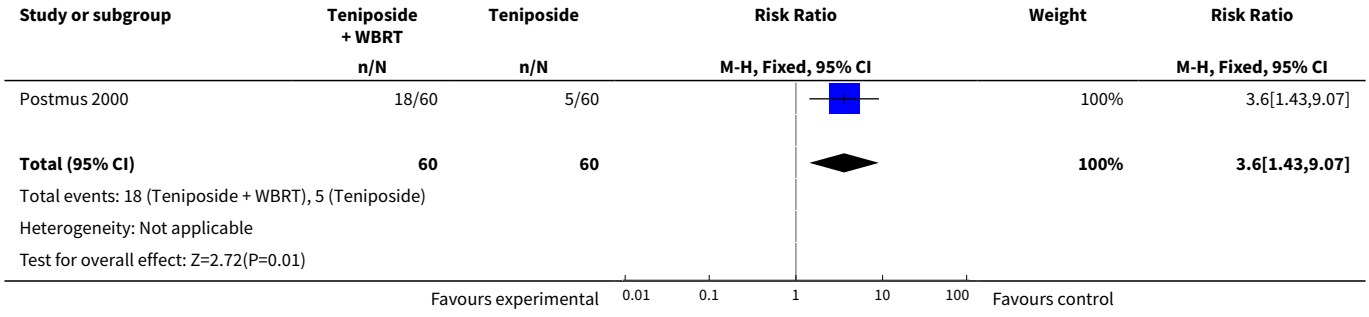
Analysis 1.1. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 1 Early death (overall response outside the brain).



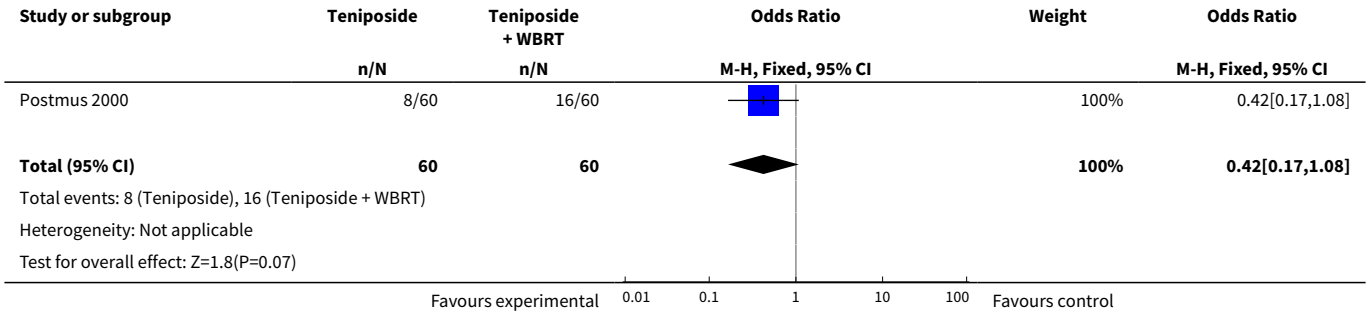
Analysis 1.2. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 2 Clinical response.



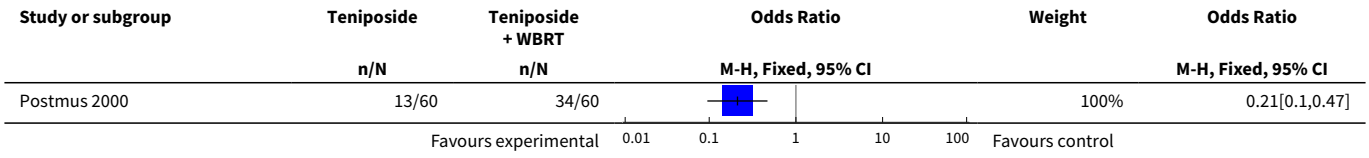
Analysis 1.3. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 3 Complete brain metastases response.

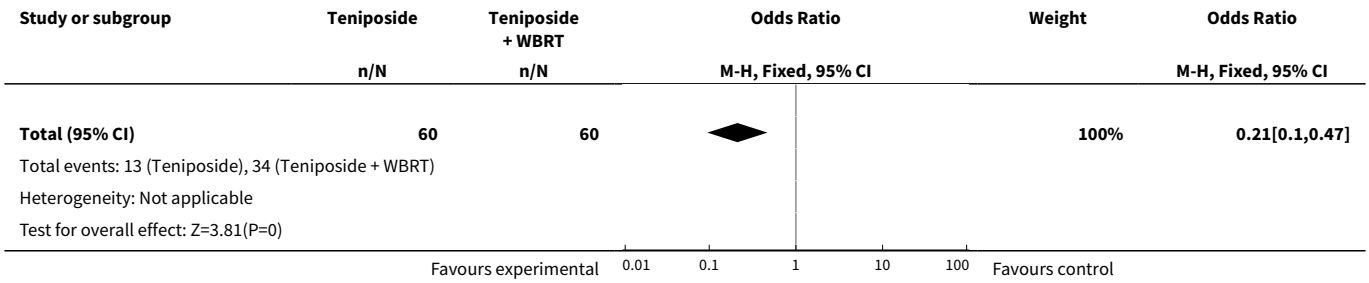


Analysis 1.4. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 4 Partial brain metastases response.

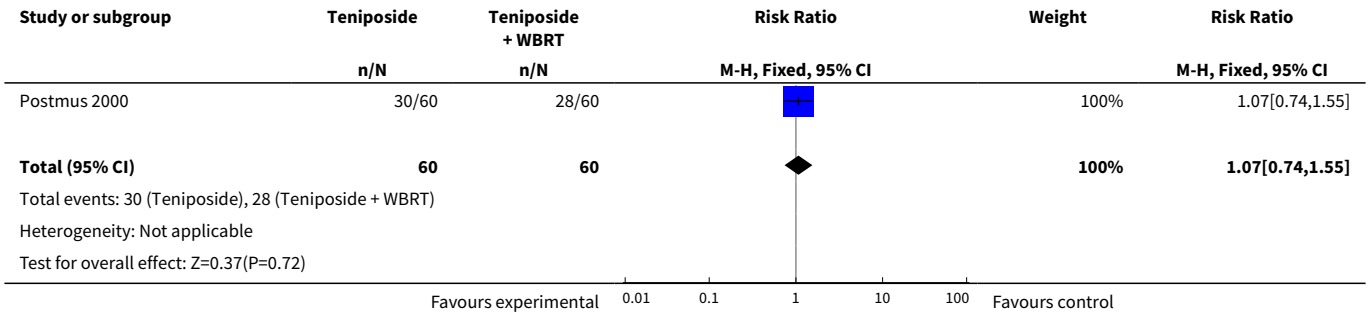


Analysis 1.5. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 5 Complete + partial brain metastases response.

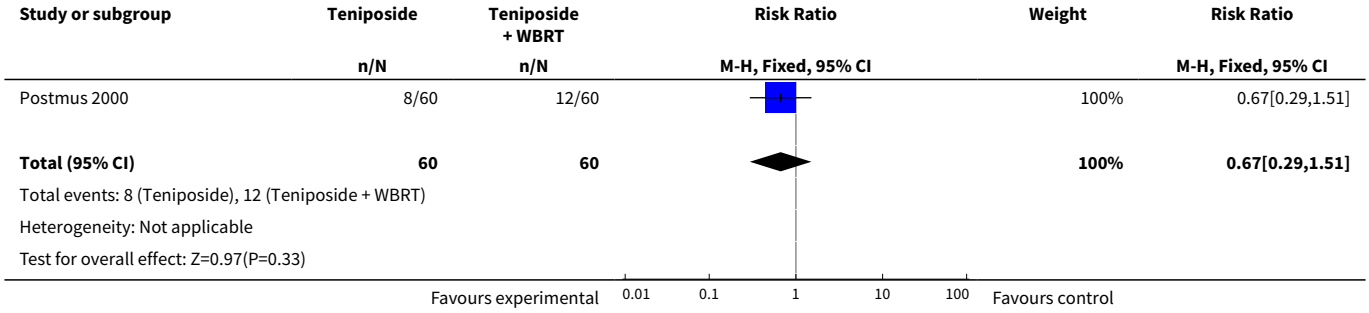




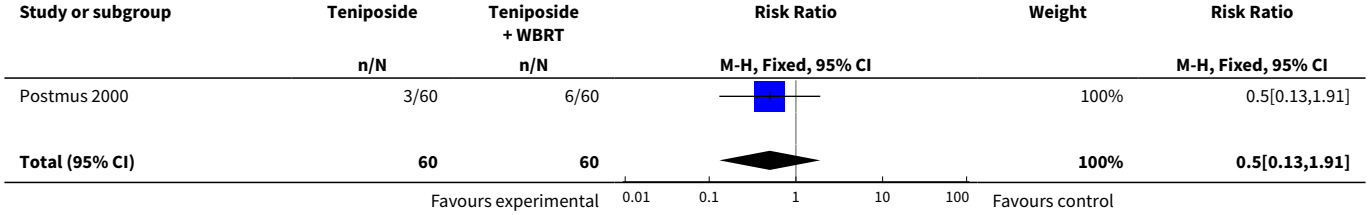
Analysis 1.6. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 6 Improvement on the ECOG performance status after 2 courses.

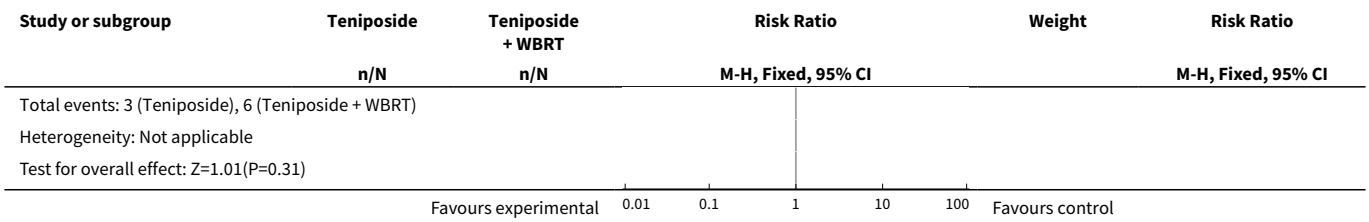


Analysis 1.7. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 7 Improved neurologic function score after cycle 2.

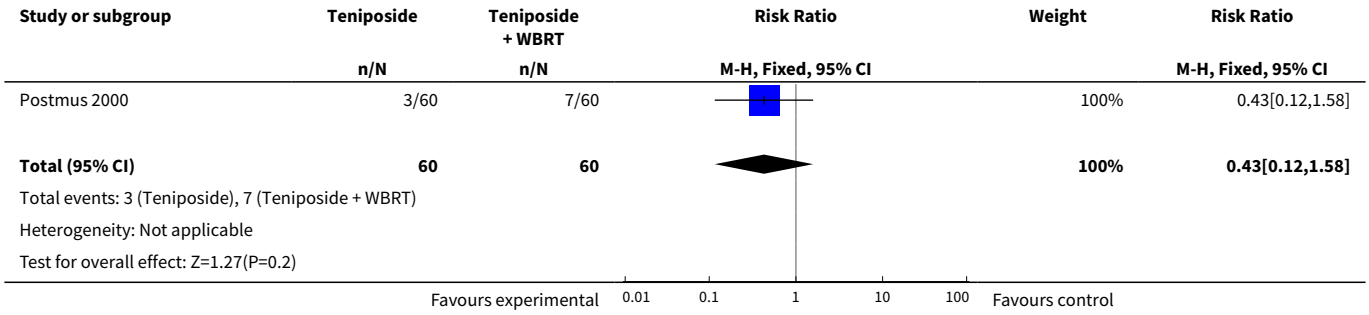


Analysis 1.8. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 8 Complete overall response outside the brain.

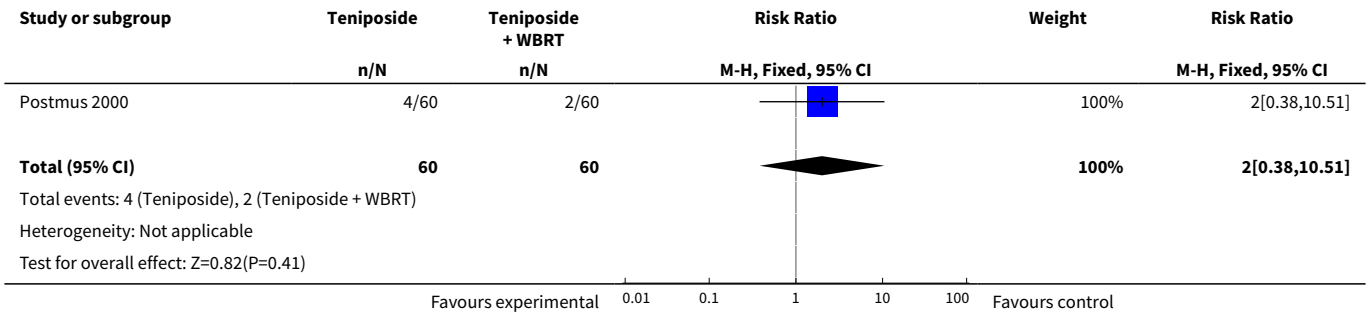




Analysis 1.9. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 9 Nausea and vomiting WHO grade 3-4 toxicity.



Analysis 1.10. Comparison 1 Teniposide versus teniposide + whole brain radiotherapy, Outcome 10 Infection WHO grade 3-4 toxicity.

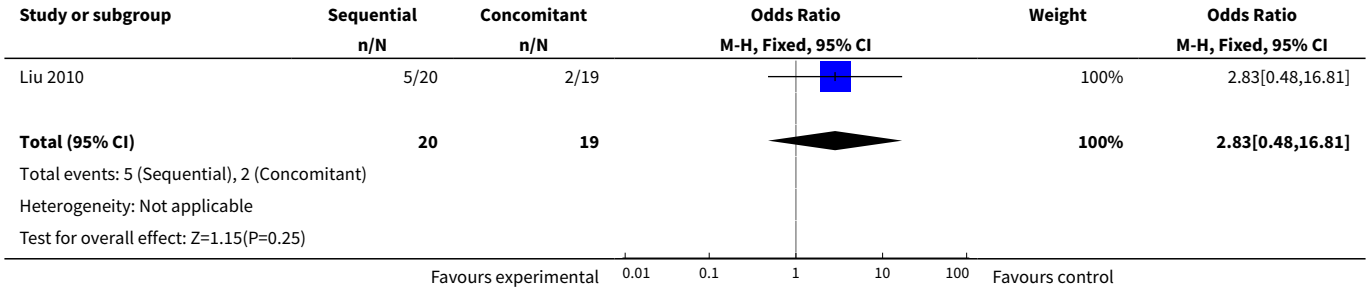


Comparison 2. Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant

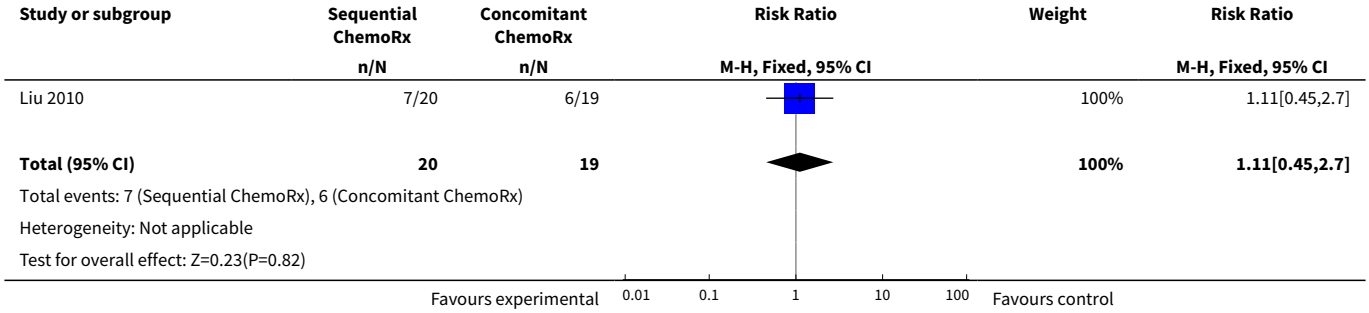
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Survival at 18 months	1	39	Odds Ratio (M-H, Fixed, 95% CI)	2.83 [0.48, 16.81]
2 Complete brain metastases response	1	39	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.45, 2.70]
3 Partial short-term response rates	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.38, 1.75]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Myelosuppression with III–IV leukopenia	1	39	Risk Ratio (M-H, Fixed, 95% CI)	8.42 [1.16, 61.10]
5 III-IV anemia level	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.16 [0.02, 1.20]
6 III-IV thrombocytopenia level	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.84]
7 III-IV leukopenia level	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.02, 0.86]
8 Thrombocytopenia	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.40 [0.17, 0.91]
9 III-IV nausea and vomiting level	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.84]
10 III-IV stomatitis level	1	39	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.35]

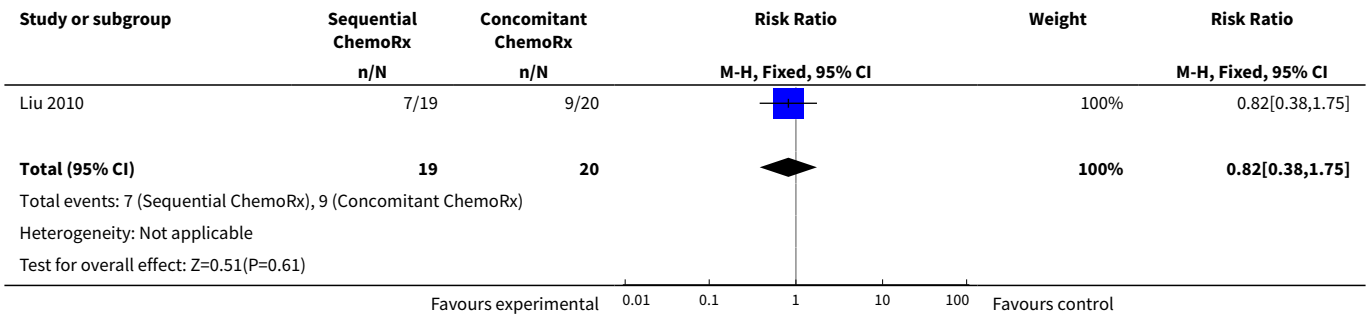
Analysis 2.1. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 1 Survival at 18 months.



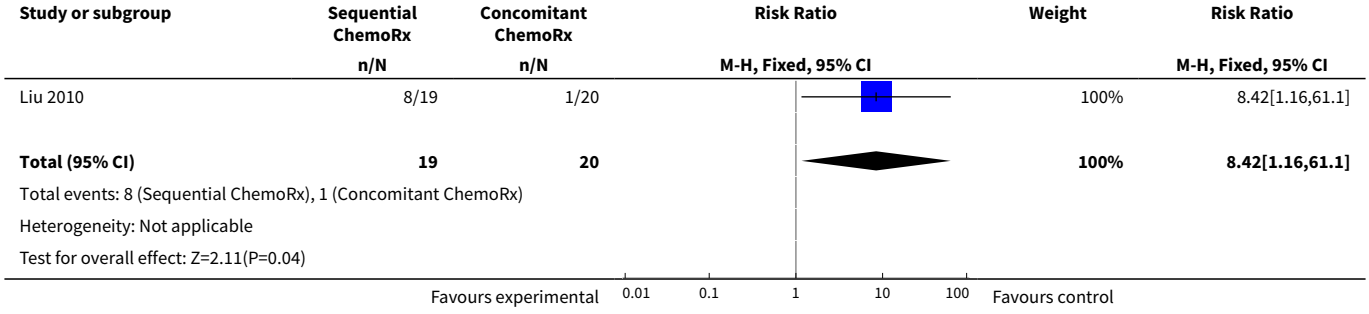
Analysis 2.2. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 2 Complete brain metastases response.



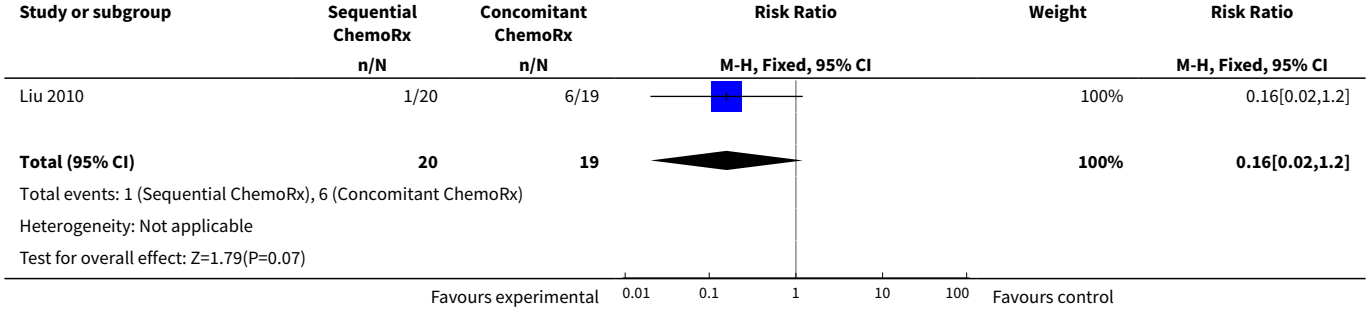
Analysis 2.3. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 3 Partial short-term response rates.



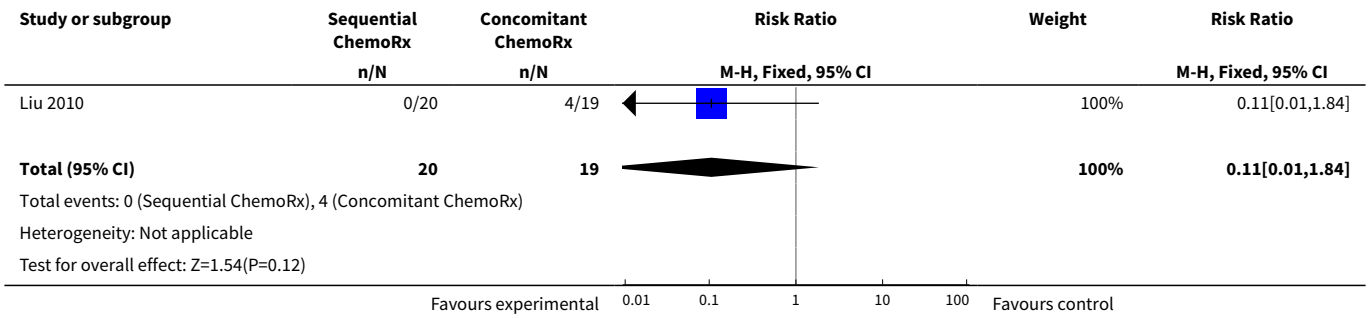
Analysis 2.4. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 4 Myelosuppression with III–IV leukopenia.



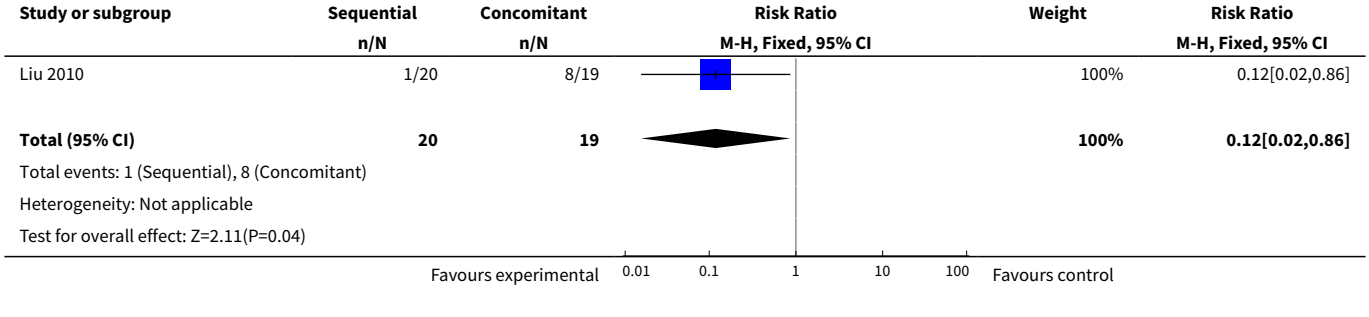
Analysis 2.5. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 5 III-IV anemia level.



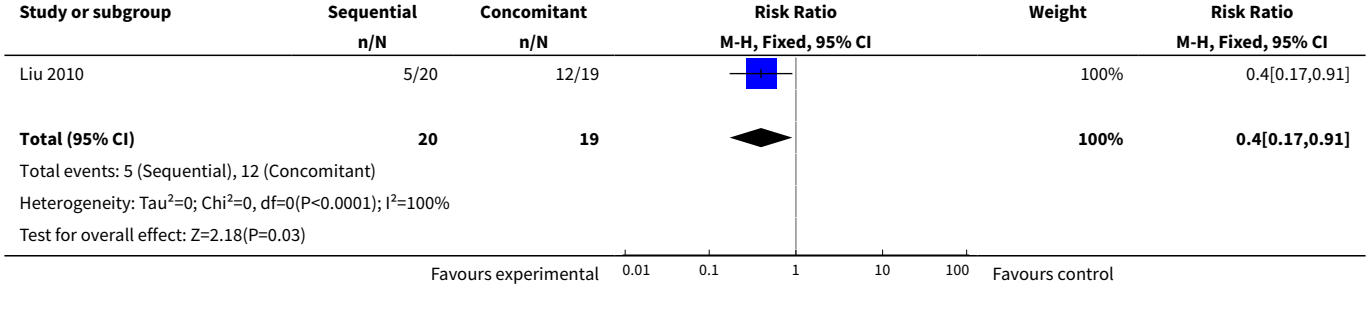
Analysis 2.6. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 6 III-IV thrombocytopenia level.



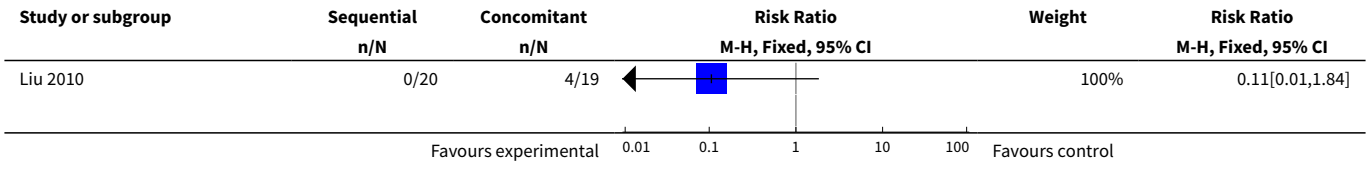
Analysis 2.7. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 7 III-IV leukopenia level.

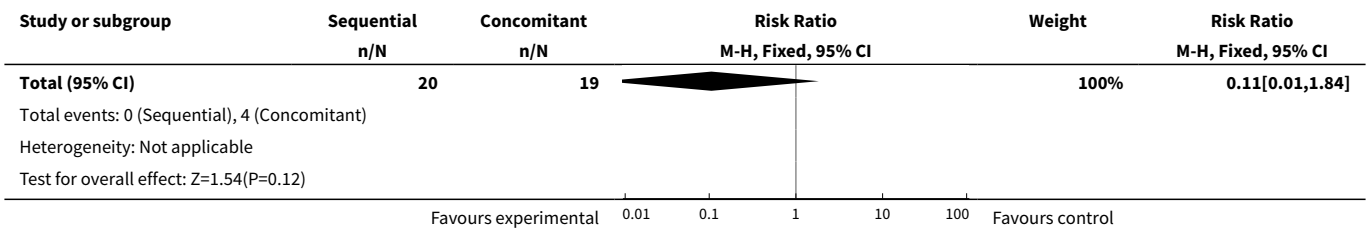


Analysis 2.8. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 8 Thrombocytopenia.

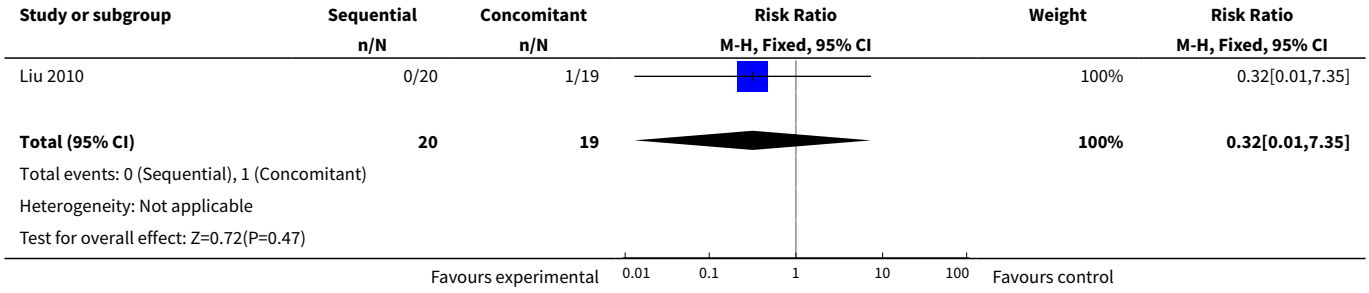


Analysis 2.9. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 9 III-IV nausea and vomiting level.





Analysis 2.10. Comparison 2 Whole brain radiotherapy + teniposide and cisplatin: sequential versus concomitant, Outcome 10 III-IV stomatitis level.



APPENDICES

Appendix 1. MEDLINE (PubMed, 6 July 2011)

#1 brain[tiab] OR cerebral[tiab] 728755

#2 neoplasm metastasis[mh] 134860

#3 metastas*[tiab] 185221

#4 #1 AND #2 3097

#5 #1 AND #3 10614

#6 #4 OR #5 11820

#7 "Carcinoma, Small Cell"[mh] 15901

#8 SCLC[tiab] 4382

#9 carcinoma*[tiab] OR cancer*[tiab] OR adenocarcinoma*[tiab] OR malignan*[tiab] OR tumor[tiab] OR tumors[tiab] OR tumour*[tiab] OR neoplasm*[tiab] 1859304

#10 small[tiab] AND cell[tiab] 171289

#11 reserve[tiab] AND cell[tiab] 2199

#12 oat[tiab] AND cell[tiab] 1575

#13 #10 OR #11 OR #12 174365

#14 #9 AND #13 75920

#15 lung*[tiab] OR pulmonary[tiab] OR bronchus[tiab] OR brochogenic[tiab] OR bronchial[tiab] OR bronchoalveolar[tiab] OR alveolar[tiab] 717310

#16 #14 AND #15 39524

#17 #7 OR #8 OR #16 46037

#18 #6 AND #17 1432

#19 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR drug therapy[sh] OR randomly[tiab] OR trial[tiab] OR groups[tiab]) NOT (animals[mh] NOT (humans[mh] AND animals[mh])) 2411998

#20 #18 AND #19 656

Appendix 2. CENTRAL (*The Cochrane Library* 2011, Issue 6; 6 July 2011)

#1 (brain OR cerebral):ti,ab 15468

#2 MeSH descriptor Neoplasm Metastasis explode all trees 3132

#3 metastas*:ti,ab 4188

#4 (#1 AND #2) 49

#5 (#1 AND #3) 373

#6 (#4 OR #5) 386

#7 MeSH descriptor Carcinoma, Small Cell explode all trees 753

#8 SCLC:ti,ab 551

#9 carcinoma*:ti,ab OR cancer*:ti,ab OR adenocarcinoma*:ti,ab OR malignan*:ti,ab OR tumor:ti,ab OR tumors:ti,ab OR tumour*:ti,ab OR neoplasm*:ti,ab 60011

#10 small:ti,ab AND cell:ti,ab 5891

#11 reserve:ti,ab AND cell:ti,ab 2863

#12 oat:ti,ab AND cell:ti,ab 78

#13 (#10 OR #11 OR #12) 8347

#14 (#9 AND #13) 5333

#15 lung*:ti,ab OR pulmonary:ti,ab OR bronchus:ti,ab OR brochogenic:ti,ab OR bronchial:ti,ab OR bronchoalveolar:ti,ab OR alveolar:ti,ab 33277

#16 (#14 AND #15) 4403

#17 (#7 OR #8 OR #16) 4564

#18 (#6 AND #17) 127 (120 in clinical Trials)

Appendix 3. EMBASE (Ovid, 1980 to 2011 Week 26; 6 July 2011)

1 (brain or cerebral).ti,ab. (796852)

2 exp metastasis/ (285646)

3 metastas*.ti,ab. (207675)

4 1 and 2 (13553)

5 1 and 3 (12516)

6 4 or 5 (15747)

7 exp lung small cell cancer/ (12193)

8 SCLC.ti,ab. (5195)

9 (carcinoma* or cancer* or adenocarcinoma* or malignan* or tumor or tumors or tumour* or neoplasm*).ti,ab. (2029015)

10 (small and cell).ti,ab. (185557)

11 (reserve and cell).ti,ab. (2470)

12 (oat and cell).ti,ab. (1529)

13 10 or 11 or 12 (188771)

14 9 and 13 (87734)

15 (lung* or pulmonary or bronchus or brochogenic or bronchial or bronchoalveolar or alveolar).ti,ab. (778801)

16 14 and 15 (46989)

17 7 or 8 or 16 (50506)

18 6 and 17 (1862)

19 Clinical trial/ (810309)

20 Randomized controlled trials/ (4595)

21 Random Allocation/ (53159)

22 Single-Blind Method/ (13675)

23 Double-Blind Method/ (99014)

24 Cross-Over Studies/ (29973)

25 Placebos/ (180293)

26 Randomi?ed controlled trial$.tw. (61040)

27 RCT.tw. (7053)

28 Random allocation.tw. (1025)

29 Randomly allocated.tw. (15048)

30 Allocated randomly.tw. (1674)

31 (allocated adj2 random).tw. (682)

32 Single blind$.tw. (10777)

33 Double blind$.tw. (115701)

34 ((treble or triple) adj blind$).tw. (237)

35 Placebo$.tw. (155788)

36 Prospective Studies/ (164952)

37 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 (1114331)

38 Case study/ (12385)

39 Case report.tw. (201855)

40 Abstract report/ or letter/ (782469)

41 38 or 39 or 40 (992855)

42 37 not 41 (1081476)

43 animal/ not human/ (1233322)

44 42 not 43 (1060563)

45 18 and 44 (443)

CONTRIBUTIONS OF AUTHORS

Ludovic Reveiz conceived the review question, developed and coordinated the protocol and the review, completed the first draft of the review, assessed the studies and extracted and analyzed data, approved the final version prior to submission, and is guarantor for the review. Ludovic Reveiz has contributed to this systematic review in a personal capacity and during his spare time. Most of the work was performed before joining the Pan American Health Organization. The Pan American Health Organization does not assume responsibility for the statements contained therein.

José-Ramón Rueda developed the review, completed the first draft of the review, assessed the studies and extracted and analyzed data, and approved the final version prior to submission. He performed part of the writing/editing of the review.

Andres Felipe Cardona conceived the review question, developed the protocol and the review, completed the first draft of the review, and approved the final version prior to submission.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- University of the Basque Country, Spain.
- Cochrane Lung Cancer Group, Spain.

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Cuello M, Viteri S, and Carrasco E were review authors in the protocol but did not participate in the review.

INDEX TERMS

Medical Subject Headings (MeSH)

*Lung Neoplasms; Antineoplastic Agents [*therapeutic use]; Brain Neoplasms [*drug therapy] [radiotherapy] [*secondary]; Cisplatin [therapeutic use]; Cranial Irradiation [methods]; Randomized Controlled Trials as Topic; Small Cell Lung Carcinoma [*drug therapy] [radiotherapy] [*secondary]; Teniposide [therapeutic use]; Topotecan [therapeutic use]

MeSH check words

Humans