AMERICAN UNIVERSITY OF BEIRUT

PROPHYLACTIC CRANIAL IRRADIATION IN PATIENTS
WITH NON-SMALL-CELL LUNG CANCER: A
SYSTEMATIC REVIEW AND META-ANALYSIS OF
RANDOMIZED CONTROLLED TRIALS

by
KARINE A. AL FEGHALI

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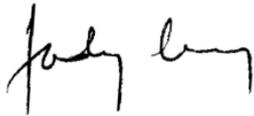at the American University of Beirut

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AN ABSTRACT OF THE THESIS OF

Karine Al Feghali for Master of Sciences
Major: Health Research (SHARP)

Title: Prophylactic Cranial Irradiation In Patients With Non-Small-Cell Lung Cancer: A Systematic Review And Meta-Analysis Of Randomized Controlled Trials

Background: Brain has been reported across multiple studies as first site of failure after curative treatment in 14-28% of patients with NSCLC. Although prophylactic cranial irradiation (PCI) is recommended in the management of small cell lung cancer (SCLC) patients and has been demonstrated to confer a survival advantage over observation in those who achieved a complete remission after curative treatment, it is still not routinely recommended in the management of NSCLC.

Objectives: To systematically review the benefits and harms of PCI in patients with NSCLC treated with a curative intent. We sought to examine the impact of prophylactic cranial irradiation on: (1) the incidence of brain metastases in patients with NSCLC, (2) overall survival and disease-free survival rates and (3) impact of PCI on patients' quality of life (QOL) and neurocognitive function (NCF), with emphasis on patients with the highest risk of developing brain metastases.

Materials and Methods: 1) Data sources: We selected all randomized controlled trials comparing PCI to no PCI in patients with NSCLC treated with a curative intent. We searched EMBASE, MEDLINE, PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) with search dates between 1946 and February 2016. We did not apply any limits for language. Search terms included "non-small-cell lung carcinoma", "cranial irradiation" and "randomized controlled trials". We reviewed the Cochrane Database for Systematic Reviews, and clinical trials registers and consulted experts in the field for information on potential unpublished data. ***2)*** Study selection: Two independent reviewers screened all papers identified by our search strategy for eligibility. ***3)*** Data collection: A data abstraction form was used independently by the two reviewers. All the data extraction was performed in duplicate and independent manner, and disagreements between the two reviewers were resolved by discussion. Trial authors were contacted, when needed, in order to gather missing information or to confirm accuracy of the information. Data was extracted on the following: study design, year of publication, inclusion/exclusion criteria, characteristics of trial participants, type of treatment received, details of the intervention, control, type of outcome measures, and statistical data. ***4)*** Risk of bias assessment: We assessed the risk of bias in each of the eligible randomized controlled trials using the Cochrane risk of bias tool. ***5)*** Data analysis: We meta-analyzed relative measures of treatment effect for brain metastasis, overall survival and disease-free survival. We used Parmar's methodology when pooling hazard ratios. We assessed the risk of publication bias using a funnel-plot. We also conducted sensitivity analysis by excluding studies published prior to 1995

Results: Out of 3,548 citations captured by the search strategy, we included eight papers and one abstract, reporting on six trials. Seven reports from six trials contributed data to the quantitative analysis. PCI was associated with a significant reduction in the

odds of brain metastases as compared with those who did not receive PCI (OR = 0.31; 95% CI: 0.20–0.46; p<0.001). The overall HR did not show survival benefit in patients with non-small-cell lung cancer patients who received PCI compared to patients who did not receive PCI (HR=1.08, 95 % CI: 0.90 – 1.31; p=0.41). Sensitivity analysis excluding older studies did not show substantively different findings. DFS was only reported in the 2 most recent trials that only included stage III NSCLC patients. There was significant improvement in DFS with PCI (HR, 0.67; 95% CI 0.46–0.98; p = 0.037). There were no statistically significant differences in any of the quality of life measures in two studies included in this qualitative analysis. One study measured neurocognitive function using the Hopkins Verbal Learning Test (HVLT), and found greater deterioration in immediate recall (p-value= 0.03) and delayed recall (p-value= 0.008) at 1 year in patients who received PCI. The quality of evidence was graded as "moderate" for the outcomes of incidence of brain metastases and OS, and "high" for the outcomes of DS, and QOL/NCF.

Conclusion: PCI in NSCLC does not confer an overall survival benefit. In the case of stage III NSCLC patients, this meta-analysis has shown that PCI improves DFS, but not OS. We believe that the benefit-risk ratio is still not clearly in favor of its use. However, it continues to be investigated extensively as evidenced by the significant number of ongoing clinical trials on the matter. Many questions remain unsettled and more research is needed on this topic. It would be important to incorporate prospective NCF testing in all future studies. Efforts to identify high-risk groups based on genetic profile and predictive biomarkers should be pursued, and research should focus on this high-risk patient population who might derive a survival benefit from PCI.

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LIST OF ABBREVIATIONS

PCI: Prophylactic Cranial Irradiation

RCT: Randomized Controlled Trial

CI: Confidence Interval

WHO: World Health Organization

SD: Standard Deviation

HR: Hazard Ratio

OR: Odds Ratio

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation

QOL: Quality of Life

NCF: Neurocognitive Function

RTOG: Radiation Therapy Oncology Group

ECOG: Eastern Cooperative Oncology Group

VALG: Veterans Administration Lung Cancer Group

SWOG: Southwest Oncology Group

SCLC: Small Cell Lung Cancer

NSCLC: Non-Small Cell Lung Cancer

HVLT: Hopkins Verbal Learning Test

OS: Overall Survival

DFS: Disease-Free Survival

RT: Radiation Therapy

CT: Chemotherapy

WBRT: Whole Brain Radiation Therapy

KPS: Karnofsky Performance Status

LS: Limited Stage

ES: Extensive Stage

Gy: Gray

F: Fraction

ALL: Acute Lymphoblastic Leukemia

CHAPTER 1

INTRODUCTION

1.1.   Epidemiology of lung cancer

Lung cancer is among the most common malignancies worldwide. It is predicted to be the second most commonly diagnosed cancer in 2016 in the United States, second to breast cancer in women and prostate cancer in men. It is also the most common cause of cancer deaths in men and women in the United States, accounting for more than one-quarter of cancer deaths [1]. Tobacco smoking was and continues to be the overwhelming risk factor for lung cancer, with 80-90% of lung cancer cases attributable to smoking [2]. Lung cancer incidence rates started declining in the mid-1980s in men and in the mid-2000s in women, paralleling the decreasing rates of tobacco use which occurred at different time points in men and in women [1].

Non-small-cell lung cancer (NSCLC) accounts for approximately 80 to 85% of lung cancer [3,4].

1.2.   Brain metastases in lung cancer

The brain is a frequent site of metastasis in both small cell lung cancer (SCLC) and NSCLC. The advances that have been made in the past two decades, in particular the use of multimodality therapy, effective systemic therapy and optimization of radiation therapy, have resulted in improved locoregional and systemic control, and have led to increasing

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proportion of patients with brain metastases [5–8]. The brain is indeed considered a sanctuary

site, with the presence of the blood-brain barrier preventing the passage of most systemic

treatments.

As a matter of fact, the brain has been reported across multiple studies as the first site

of failure after curative treatment in 14-28% of patients with NSCLC [5,7–13] with a higher

risk of brain metastases in the setting of adenocarcinoma and large cell carcinoma (non-

squamous histologies) [5–7,14] and stage IIIB (as compared to stage IIIA) [10]. Table 1

summarizes finding from these studies on brain metastases in NSCLC. Brain metastases

can be devastating to the patient, leading to impaired quality of life (QOL), impact on

neurocognitive function (NCF), potential life-threatening conditions, and decreased

survival. Therefore, attempts to decrease their incidence are crucial, based on the premise

that preventative treatment might have an impact on survival and QOL.

Multiple prognostic indices, such as the RTOG recursive partitioning analysis

(RPA) and Graded Prognostic Assessment (GPA) have been developed and validated in

patients with brain metastases to help guiding treatment. These indices incorporate

different factors such as age, Karnofsky Performance Status (KPS), extracranial

metastases, and number of metastases [15–17]. The response rate to whole brain radiation

therapy (WBRT) is only 50% [18,19], and survival for lung cancer patients who develop brain

metastases remain dismal, with a median of 3-18 months [5,9,18,20,21], despite advances in the

treatment of these brain metastases.

1.3. Prophylactic cranial irradiation: A historical perspective

The rationale behind prophylactic cranial irradiation is that the brain is a sanctuary site,

and most systemic therapies are not able to reach it due to the presence of the blood-brain barrier. Prophylactic cranial irradiation was first introduced in the 1960s in the treatment of acute lymphoblastic leukemia (ALL) to target the subclinical malignant cells in the central nervous system, and led to improvement in DFS and OS [22–24]. Intrathecal chemotherapy has now replaced PCI in ALL, after a meta-analysis demonstrated that PCI and intrathecal therapy led to similar outcomes [25], and PCI was associated with more potential late complications, such as neurotoxicity, endocrinopathies, and intellectual detriment, as well as secondary brain neoplasms [26–29], complications that are of particular concern in this curable population of pediatric patients.

Nowadays, current indications for PCI are few: selected cases of high-risk childhood ALL and acute myelogenous [30,31], highly aggressive Philadelphia-chromosome positive adult ALL with (in the GMALL PH-01 study, ClinicalTrials.gov Identifier: NCT01724879), limited-stage (LS) [32] and extensive stage (ES) SCLC [33].

1.4. Prophylactic cranial irradiation in LS- and ES-SCLC

Prophylactic cranial irradiation (PCI) is currently recommended in the management of small cell lung cancer based on a large body of evidence (Table 2).

The use of PCI in LS-SCLC was started in 1977 [34], and was shown to decrease the risk of brain metastasis substantially, and to improve OS of SCLC patients in complete remission based on randomized controlled trials [35–41] and an individual-patient-data-based meta-analysis by Auperin et al [32]. In this meta-analysis, PCI was shown to significantly reduce the rate of brain metastasis by 54% (59% versus 33% at 3 years, i.e. an absolute decrease of 25%, p –value < 0.001) In patients with SCLC, which translated into a

significant 5.4% benefit in 3-year OS with PCI (15.3% versus 20.7%) [32]. An RCT by the

European Organisation for Research and Treatment of Cancer (EORTC) Lung Cancer

Group also demonstrated that PCI is beneficial in patients with ES-SCLC with complete or

partial response to chemotherapy in terms of DFS (HR, 0.76 in favor of PCI; 95% CI 0.59-

0.96) and OS (HR, 0.68; 95% CI 0.52-0.88) [33]. It also reduces the incidence of

symptomatic brain metastases from 40.4% in the control group to 14.6% in the PCI group

at one year (HR, 0.27; 95% CI 0.16-0.44). The benefit-risk ratio of PCI in SCLC was also

addressed and, despite some neurotoxicity, PCI was shown to offer better quality-adjusted

life expectancy than no PCI [42].

1.5.   Prophylactic cranial irradiation: Timing, techniques and dose

The optimal timing for initiation of PCI has been investigated but not settled. In the

Auperin meta-analysis for SCLC, the time between initiation of induction therapy and PCI

(<4 months, 4-6 months, >6 months) had no effect on the risk of death, although there was

a significant trend (*p*-value=0.01) toward a greater effect of prophylactic cranial irradiation

on the incidence of brain metastasis in patients randomized sooner after induction therapy

than in those randomized later [32]. Similarly, in a more recent single-institution retrospective

study, early administration of PCI (<4 months) in SCLC led to a decrease in the rate of

brain metastases compared to later administration of PCI, but no OS benefit [43]. Also, a

pooled analysis from four phase II or III North Central Cancer Treatment Group trials

reached the same conclusion [44]. As far as timing of PCI in NSCLC is concerned, a

retrospective study indirectly addressed this question, as it randomized 134 patients with

stage IIIB NSCLC to induction chemotherapy followed by chemoradiation or definitive

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chemoradiation. 13.8% developed brain metastases in the induction therapy group, as compared to only 3.9% in the upfront chemoradiation group (*p*-value = 0.03), suggesting a benefit from earlier PCI use without delay caused by induction protocols [45].

Nowadays, and in the absence of level I evidence, PCI is typically started 4 to 6 weeks after completion of induction chemotherapy or chemoradiation.

Radiation to the intracranial content (planning target volume) is administered with the use of two opposed lateral fields with a linear accelerator (4 to 18 MV). Each field is treated 5 times per week, and doses are commonly prescribed to midline [33,46].

Different fractionations have been tried for PCI in SCLC, to a total dose ranging from 8 to 40 Gy. Examples of fractionations used include: 25 Gray (Gy) in 10 fractions [41], 30 Gy in 10 fractions [36], 40 Gy in 20 fractions [37], 8-36 Gy in 1-18 fractions [40]. The Auperin et al. meta-analysis indirectly compared different doses in limited-stage SCLC, and showed a dose-effect relationship with PCI. The incidence of brain metastases was indeed reduced by 24%, 48%, 66%, and 73% with a total dose of 8 Gy, 24–25 Gy, 30 Gy, and 36–40 Gy, respectively [32]. This finding led to a dose-escalation trial, RTOG 0212, randomizing standard-dose PCI (25 Gy) to high-dose PCI (36 Gy) in 720 SCLC patients in complete remission. Unexpectedly, the arm receiving higher dose PCI had worse survival than the standard-dose arm, with a 5% survival difference at 2 years (37% in the higher-dose group versus 42% in the standard-dose group), and no significant difference in the 2-year incidence of brain metastases [47]. A PCI dose of 25 Gy is now considered standard of care in SCLC.

1.6. Prophylactic cranial irradiation: Potential toxicities and strategies to prevent them

Prophylactic and therapeutic cranial irradiation is certainly not innocuous. Sheline's report in the 1980s was the first to subdivide radiation-induced brain injury into acute (early, during radiation), subacute (up to six months post-radiation therapy), and late effects (chronic, more than six months post-radiation therapy) [48,49].

Acute encephalopathy, consisting of headache, nausea, vomiting and fever with onset during treatment, occurs almost exclusively if high dose per fraction is used, and not with the conventionally used dose of 3 Gy or less per fraction [50,51]. This acute effect has been linked to edema formation secondary to blood-brain barrier disruption, due to apoptosis of endothelial cells [52–55]. Corticosteroids can help in treating these symptoms.

Subacute complications include somnolence syndrome, which symptoms are transient and include excessive sleepiness, drowsiness and anorexia, mainly documented in children receiving PCI for ALL [56,57], or in adults receiving definitive doses of radiation therapy (45 – 55 Gy) for primary brain tumors [58,59] Another subacute effect is impairement in verbal memory function 6-8 weeks after PCI completion as demonstrated by Welzel et al. [60].

Late or chronic effects are the most dreaded of all radiation-induced injuries, as they are usually irreversible. Molecular mechanisms underlying the development of these chronic effects are inflammation [61,62], hypoxia with vascular endothelial growth factor upregulation [63,64], and neurogenesis inhibition [65]. This cascade of events can lead to radiation-induced demyelination and leukoencephalopathy that can occur months to years after irradiation [49], as well as radiation necrosis [66]. In long-term SCLC survivors, PCI has been shown to result in progressive ventricular dilatation or cerebral atrophy up to 8 years after therapy completion, and slow decline in neurocognitive function [67,68].

The incidence and severity of radiation-induced toxicities do not only depend on radiation dose, but also on some patient-related factors, such as age, chemotherapy and existing comorbidities [49]. In RTOG 0212, age (> 60 years) was the most significant predictor for the development of chronic neurotoxicity (p-value = 0.005) [69]. Pre-existing medical conditions, such as hypertension, have also been shown to accelerate vascular radiation damage [70]. Also, all of the patients treated with PCI usually received preceding chemotherapy, which also plays a role in cognitive impairment [71,72].

Some strategies have been tested to potentially mitigate the neurocognitive complications of brain irradiation [73]. One of them is the use of neuroprotective drugs, such as angiotensin-converting enzyme inhibitors [74] angiotensin type-1 receptor blockers [75], erythropoietin [76], and lithium [77,78], all of which have been tested *in vivo*. Two of these potential neuroprotective drugs, memantine and donepezil, deserve special mention, as they have both been investigated in phase III clinical trials. The effectiveness of memantine, an N-Methyl-D-aspartate receptor antagonist, in reducing cognitive dysfunction has been tested in the phase III trial, RTOG 0614. There was a trend toward less decline in the primary endpoint of delayed recall at 24 weeks with memantine as compared to placebo. This result did not reach statistical significance though (p-value= 0.059), probably because of significant drop-out, resulting in a statistical power of 35% only. Also, the patients on the memantine arm had significantly longer time to cognitive decline, and better results in executive functioning and processing speed [79]. Also, donepezil, a reversible acetylcholine esterase inhibitor, has been tested in a phase III trial in 198 adult brain tumor survivors, and although it did not show significant improvement in the overall composite cognitive score (primary endpoint), it showed significant benefit over placebo in some specific cognitive

functions, such as memory, as well as motor speed and dexterity [80]. One of the limitations

of this study was the low dose of donepezil used (10 mg per day), given that studies on

patients with moderate-to-severe Alzheimer's disease showed significantly greater

cognitive benefits with higher doses of donepezil 23 mg/day than donepezil 10 mg/day [81].

Another strategy to avoid cognitive dysfunction, and more specifically short-term

memory loss, is hippocampal-avoidance PCI. It uses conformal radiation therapy to avoid

neural stem cells in the hippocampal dentate gyrus, which are mitotically active and

radiosensitive, and are responsible for formation of new memories [65,82,83]. This technique

was tested in the phase II cooperative trial RTOG 0933, which showed significant memory

preservation with hippocampal avoidance cranial irradiation, whereby relative decline in

Hopkins Verbal Learning Test–Revised Delayed Recall (HVLT-R DR) at 4 months was

7% in the experimental arm, which was significantly lower than pre-specified historical

control of patients with brain metastases treated without hippocampal avoidance [84]. An

ongoing trial, NRG-CC003 (ClinicalTrials.gov Identifier: NCT01780675), is currently

examining the role of hippocampal avoidance in the setting of PCI for SCLC specifically.

1.7.   Prophylactic cranial irradiation in NSCLC: Aim of the current systematic review

To date, prophylactic cranial irradiation has not been shown to be associated with

superior survival and is not routinely recommended in the management of NSCLC.

A Cochrane review was published in 2005, that included four randomized controlled trials

(RCTs) comparing prophylactic cranial irradiation (PCI) to observation in non-small-cell

lung cancer patients treated with a curative intent [85]. Authors included the Veterans

Administration Lung Cancer Group (VALG) trial [86], Umsawasdi et al [87], the Radiation Therapy Oncology Group 84-03 (RTOG 84-03) trial [46], and the Southwest Oncology Group (SWOG) trial [88] were included in this review. Search dates were from 1966 to December 2004. This review showed that PCI significantly reduced the incidence of brain metastases in three of the four RCTs, but no survival benefit was observed in any of the four studies. No meta-analysis of the data was performed in this systematic review, because of heterogeneity in the four randomized controlled trials that were included, as stated by the authors [46,85–88].

The current paper aimed at systematically reviewing the benefits and harms of PCI in patients with NSCLC treated with a curative intent and carrying out a meta-analysis taking into account the new RCTs published after December 2004 on the matter at hand. We attempted to address as well the effect of PCI on quality of life and neurocognitive function in patients with NSCLC, an issue that was not tackled in the above-mentioned Cochrane review. We were also planning to perform subgroup analyses to evaluate the effect of PCI on survival in highest risk patients, in an attempt to evaluate subsets of patients in whom PCI might be beneficial.

1.8.   Thesis Objectives

To systematically review the benefits and harms of PCI with a curative intent in patients with NSCLC.

(1) Examine whether PCI reduces incidence of brain metastasis as compared to no PCI in patients with non-small-cell lung cancer treated with a curative intent.

(2) Examine whether prophylactic cranial irradiation improves overall survival and

disease-free survival

(3) Examine the impact of PCI on quality of life

(4) Evaluate the effect of PCI on survival in highest risk NSCLC patients, in an attempt
    to evaluate subsets of patients in whom PCI might be beneficial.

1.9. Thesis Hypothesis

Our hypothesis is that PCI decreases the incidence of brain metastases in all patients with NSCLC, and might confer a survival advantage in highest risk NSCLC patients. The benefit-risk ratio, taking into account incidence of brain metastases, survival, neurocognitive toxicity and QOL, might be in favor of PCI only in stage III NSCLC.

CHAPTER 2

MATERIALS AND METHODS

This systematic review and meta-analysis was developed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A checklist of evidence-based set of items to be included in a systematic review and meta-analysis, adapted from the PRISMA statement, can be found in Appendix 1.

2.1. Protocol

Pre-specified objectives, eligibility criteria, outcomes of interest, search strategy and analysis plan were documented in a protocol, published in the PROSPERO International prospective register of systematic reviews (PROSPERO 2015: registration number CRD42015023982) [89].

2.2. Eligibility criteria

2.2.1. Type of studies:

- Inclusion criteria:

We included al prospective randomized controlled trials , with no restriction on language, publication date or publication status (published, unpublished material and abstracts).

- Exclusion criteria:

We excluded prospective studies that were not specifically randomizing the use of PCI.

2.2.2. Type of participants:

- Inclusion criteria:

We included trials recruiting participants with non-metastatic NSCLC of any age and stage who completed definitive locoregional therapy (a combination of surgery, and/or thoracic radiation therapy (dose >30 Gy)) with or without chemotherapy, with complete response, partial response, or stable disease after therapy were selected.

- Exclusion criteria:

We excluded studies including participants who had brain metastases upon diagnosis, who had progression or distant metastasis after locoregional therapy, or who were treated in a palliative intent..

2.2.3. Type of intervention:

Studies included compared PCI to no PCI. We did not segregate studies based on PCI dose or radiation therapy technique used.

2.2.4. Type of outcome measures:

The outcomes of interest were incidence of brain metastasis, time to brain metastasis, overall survival, disease-free survival and quality of life.

2.3. Information sources

A systematic search of the literature was conducted using the electronic databases EMBASE, MEDLINE, PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL) with search dates between 1946 and February 2014, then search was updated until July 2016. No limits for language were applied. Search terms included "non-small-cell lung carcinoma", "cranial irradiation" and "randomized controlled trials". The

Cochrane Database for Systematic Reviews was also reviewed. We searched for ongoing

trials in clinical trials registers: ClinicalTrials.gov, EU Clinical Trials Register (EU-CTR),

the International Clinical Trial registry Platform (ICTRP), and the International Standard

Randomised Controlled Trial Number (ISRCTN) registry, and contacted their principal

investigators. The search was also guided by reference lists of published studies (trials or

reviews) and pertinent books, as well as proceedings of meetings, such as abstracts from

the American Society of Clinical Oncology. Experts in the field (Benjamin Movsas, MD)

were consulted for information on potential unpublished data.

2.4. Search strategy

The detailed search strategy can be found in Appendix 2.

2.5. Study selection

We checked and excluded duplicate publications: duplicate of literatures retrieved

from different databases using EndNote library and duplicate reporting using manual check.

The title and abstracts of all papers identified were evaluated by two independent reviewers

in an unblinded standardized manner, for the presence or absence of all PICO (Population,

Intervention, Comparator, Outcomes) elements. The full text articles for the potentially

eligible studies were retrieved and were again independently screened for eligibility by two

reviewers. Studies were screened using a pre-specified screening template (Appendix 3).

Disagreement between reviewers was resolved by consensus in the title and abstract

screening step, and by seeking the opinion of an expert in the field in the full-text screening

step.

2.6. Data collection process

We devised a data abstraction form that the two reviewers (KA and RB) used independently (Table 1 in Appendix 4). This form was pilot-tested on 2 papers, randomly selected among the included studies to check for consistency between the reviewers, and was refined accordingly. All the data extraction was performed in duplicate. Disagreements between the two reviewers were resolved by discussion. If agreement was not reached, then the senior author (FG) made the final decision, after getting in contact with trial authors in order to confirm accuracy of the information or to gather missing information. Authors were contacted by emails explaining the purpose of our review, and a reminder email was sent to those who did not reply after one week of the initial one. In case of no reply to the second email, our plan was to exclude the study for lack of adequate information, or extract data from figures. We resorted to the latter method, i.e. using Kaplan-Meier curves when this was the best available information. We also tried to get in contact with the authors of RTOG 0214 [90] for information about the different subgroups (stage IIIA and stage IIIB, different histologies) and their outcomes. However, we did not get any response from the authors, and were therefore unable to perform meta-analyses based on histology, nor were we able to perform a meta-analysis comparing stage IIIA versus IIIB. We rather lumped all patients with stage III together (included in the three most recent trials).

2.7. Data items

Data was extracted from each one of the included trials on the following:
- Study design, year of publication

- Inclusion/exclusion criteria

- Trial participants: Age, gender, performance status, stage, type of non-small-cell lung cancer with histologic confirmation of the diagnosis (adenocarcinoma, large cell carcinoma, and/or squamous cell carcinoma), type of treatment received (surgery and/or chemotherapy and/or thoracic radiation therapy)

- Intervention: Dose and fractionation of the prophylactic cranial irradiation, versus observation

- Type of outcome measures: Incidence of brain metastasis, time to brain metastasis, overall survival, disease-free survival, effect on quality of life (using a validated score), and neurocognitive function.

2.8. Summary measures

The primary measures of treatment effect in this meta-analysis are the relative risks (RR) of incidence of brain metastasis and the hazard ratios (HR) for OS and DFS comparing prophylactic cranial irradiation to observation.

Hazard ratios were derived based on Parmar et al, Spruance et al. and Guyot et al. methods [91–93]. Parmar et al proposed three methods that allowed us to recalculate a HR and its standard error. First, the standard error (SE) was calculated indirectly in two studies (Li et al.[94] and Gore et al.[90,95]) that reported the HR and its 95% CI based on this equation:

$$\text{SE}\,[\ln(\text{HR})] = \frac{upper\ CI - lower\ CI}{2*1.96}$$

Second, we used the number of observed events in the intervention (Or) and control arm (Oc), the total number of observed events (O), the total randomized number of patients

in each arm (Rr, Rc), and the *p*-value of the log-rank test (if available) to recalculate the

HR and its SE in three studies (Russel et al., Cox et al. and Miller et al.) according to these

equations:

$$\ln(\text{HR}) = \frac{O-E}{Vr} \qquad \text{and} \qquad \text{var}[\ln(\text{HR})] = 1/Vr$$

$$\text{where: } O - E = \frac{\sqrt{O\,Rc\,Rr}}{Rc+Rr} X\, Z_{\left(1-\frac{p}{2}\right)} \qquad \text{and} \qquad Vr = \frac{Oc\,Or}{O}$$

Third, when hazard ratios could not be derived from the information given (no

number of events, total randomized number, or log-rank p-value was provided), and the

only information available was a Kaplan-Meier (KM) curve, we used pixel coordinates to

determine survival rates, working backwards and extracting data points from the KM curve.

Umswasadi et al. did not report the *p*-value of log-rank test [87], so the HR was estimated

through analyzing the KM curve using online software (WebPlotDigitizer, a web-based

tool to extract data from plots) and the equations mentioned in Parmar's study. Although

The Cochrane Handbook does not address methods for data extraction from figures [96], a

recently published paper has shown that extracting data from figures is more reliable than

manual extraction [97]. The second and third methods were tested on other studies (Li et al. [98]

and Gore et al.[90,95]) that reported HR in order to compare between reported and calculated

value of HR.

2.9. Synthesis of results and assessment of heterogeneity

Analyses were carried out on an intention-to-treat basis. The meta-analyses were

performed by computing RR or HR and 95% CI for each outcome using the random effect

model. Statistical heterogeneity among trials was assessed using the Chi-squared tests with

significance at p-value $\leq$ 0.1. We quantitatively assessed it using I^2, which measures the degree of inconsistency across studies in a meta-analysis. I^2 can be calculated, using the following formula, in which Q is the Cochran's heterogeneity statistic and df the degrees of freedom:

$$I^2 = \left(\frac{Q - df}{Q} \right) \times 100\%$$

I^2 ranges from 0-100%, with the adjectives "low", "moderate", and "high" arbitrarily assigned to I^2 values of 25%, 50%, and 75% respectively [99].

2.10. Additional analyses: Subgroup and sensitivity analyses

We were planning to perform a subgroup analysis to evaluate the effect of PCI on survival in highest risk patients (stage IIIA and IIIB), however it was not made possible by the available information. We were also not able to assess outcomes based on radiation therapy doses, and on NSCLC histology (squamous versus non-squamous), as not enough information was available.

Sensitivity analyses were performed, excluding older studies (before 1995), as we expected the potential benefit of PCI to be more evident in more recent studies after the introduction of cisplatin-based chemotherapy, and these latter studies to have a more rigorous methodology. Cisplatin was heralded in the 1980s as a radiosensitizing drug [100–102], and RCTs comparing radiation therapy to sequential or concurrent chemoradiation in inoperable stage III NSCLC were undertaken in the 1990's, showing superiority of combined treatment over RT alone in terms of local control and survival [103–107]. These trials established the role of chemotherapy, in addition to RT, as standard of care in these

patients. In the current era of lung cancer treatment, and with advances in systemic therapy and improved surgical and radiation techniques, loco-regional failure and incidence of non-brain metastasis have decreased, and more patients will live long enough to develop brain metastases.

Another sensitivity analysis was performed, including Umsawasdi et al., which was excluded from the primary analysis as its HR has been derived working backwards from the KM graph (using WebPlotDigitizer), a method that can lack precision and accuracy.

2.11. Risk of bias within studies

We used the Cochrane Collaboration's tool for assessing risk of bias in randomized trials, and check their internal validity (Table 2 in Appendix 4). This tool covers six domains of bias: (1) Selection bias, as assessed by random sequence generation and allocation concealment, (2) Performance bias, as assessed by blinding of participants and personnel, (3) Detection bias, as assessed by blinding of outcome assessment, (4) Attrition bias, i.e. incomplete outcome data, (5) Reporting bias due to selective outcome reporting, (6) Other biases due to problems not covered elsewhere [108]. We looked for selective reporting within studies by comparing the outcomes reported in the published report to the outcomes outlines in the protocol, if available, or in abstracts of presentations that preceded publication of the study.

Two independent reviewers assigned a judgment of high, low, or unclear risk of bias for each of these six domains, and then provided a summary assessment for the risk of bias for each study. We did not exclude studies based solely on the risk of bias.

2.12. Risk of bias across studies

We used the funnel-plot method to assess and correct for publication bias. We assessed symmetry of the funnel plot visually and formally using Egger's test. We acknowledge however that asymmetry in funnel plots could be due to various factors other than publication bias, such as selective outcome reporting, differences in trial quality or true heterogeneity in intervention effect.

2.13. Assessment of the quality of evidence

The quality of evidence was assessed for the outcomes of incidence of brain metastases, OS, DFS and QOL/NCF. Appraisal was carried using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. This instrument allows us to determine the extent to which one can be confident that an effect estimate truly represents reality. It depicts five factors that can lead to rating down the quality of evidence and three factors that can lead to rating up the quality of the evidence, from a starting point determined by study design. High likelihood of bias, inconsistency (heterogeneity, I^2), indirectness of evidence (indirect population, intervention, control, outcomes), imprecision (wide confidence intervals) and presence of publication bias can all lead to downgrading of evidence. If, to the contrary, a large magnitude of effect is demonstrated, or a dose response relationship is shown, or all plausible confounding would reduce a demonstrated effect or suggest a spurious effect when results show no effect, then the quality of the body of evidence will be upgraded. Based on this appraisal, the body of evidence can be classified into four levels of quality (high, moderate, low or very low) for each outcome of interest [109,110].

CHAPTER 3

RESULTS

3.1. Study selection

We identified a total of 3,550 records through systematic search of the electronic databases EMBASE, MEDLINE, PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL), as well as oncology meetings proceedings and references from previous reviews on the topic, with search dates between 1946 and July 2016. After removal of duplicate records, 2,741 records were retained. These articles' titles and abstracts were screened, and 19 records were retained at the end of this first screen. The remaining articles were excluded, as some were not targeting the study population of interest, for example patients with malignancies other than lung cancer (breast cancer, renal cancer, etc.), or patients with lung cancer with brain metastasis at diagnosis treated in a palliative intent; also, few studies were on SCLC and not NSCLC. Other abstracts were excluded because the intervention studied was whole brain radiation therapy for metastatic brain lesions and not as a prophylactic measure. Excluded also were abstracts of review articles on lung cancer and prophylactic cranial irradiation.

We retrieved the full text articles (some were only in the form of abstract) for 19 citations. Some of the articles were then excluded, as they were not RCTs. When multiple reports for the same RCT were found (or results were only reported in abstract form), we only retained the most recent report with the most updated results, unless different outcomes were reported in the different manuscripts or abstracts. Reasons for exclusion in

the final stages were: different fractionation for thoracic irradiation (and not brain irradiation) (n=1), pilot phase II study (n=1), preliminary reports/abstracts of RCT (n=4, only final and updated reports, even if in abstract form, were included in the meta-analysis), review article (n=1), use of PCI not randomized (n=3).

Of note, the trial by Pottgen et al. [111] was excluded (it was erroneously included in the systematic review by Xie et al. [112] as an RCT), as the administration of PCI was not based on a random allocation. In this trial, randomization was performed on two curative treatment options, and patients in one of the two arms all received PCI.

Eight reports (of six studies) were included in the qualitative analysis, and only seven of them in the quantitative analysis (one of these reports is an updated report, in abstract form, of an earlier study). Among these eight reports, two reported QOL measures, and the other seven reported on outcomes relating to incidence of brain metastasis as well as survival outcomes.

3.2. Study characteristics

The six studies (eight reports) included in this systematic review and meta-analysis are all prospective randomized controlled trials.

Table 1 details for each of these studies the design, characteristics of participants, with inclusion and exclusion criteria, the treatment modality used as a curative treatment for these NSCLC patients, specifics about the intervention and control arm, the outcomes assessed, as well as potential funding and conflicts of interest.

A total of 1,373 patients with NSCLC were included in this meta-analysis. Most of these patients were males (62-77%), and most had a Karnofsky Performance Status of more

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than 70% or an Eastern Cooperative Oncology Group Performance Status (ECOG PS) of 0 or 1, indicating that most patients were ambulatory and able to care for self.

All of the included studies mandated histological or pathological confirmation of the diagnosis of NSCLC. Most patients had stage III disease: exclusively stage III in Li et al. [98], Gore et al. [90], and Miller et al.[88]; 87% stage III in Umsawasdi et al. [87], and more than 70% in Russel et al [46].

There were some important differences across trials. First, distribution of NSCLC histologies (adenocarcinoma, squamous cell carcinoma and other histologies) differed markedly from one study to the other, some such as Li et al. included predominantly adenocarcinoma [98], while others such as Miller et al. had more squamous cell carcinomas [88].

Curative treatment preceding PCI administration also differed between trials, some of which could be considered suboptimal, based on today's standards of care, including old radiation therapy (RT) techniques, inadequate dose of thoracic RT, and suboptimal or no chemotherapy in a setting where it would have been indicated nowadays. The details of the curative therapy used in Umsawasdi et al. were discussed in another publication [113]; it consisted of chemoradiation as a definitive treatment for 63 patients (thoracic RT to a dose of 50 Gy in 25 fractions), and a combination of surgical resection, chemotherapy, and thoracic RT for the remaining 34 patients. The patients in Cox et al. either received primary "short-course" lung RT (42 Gy in 15 fractions), or "intermediate-course" lung RT (50 Gy in 25 fractions), with no chemotherapy [86]. Russel et al. allowed primary thoracic RT alone (without chemotherapy) to 60 Gy in 30 fractions, or resection of all gross intrathoracic disease followed by post-operative RT (50 Gy in 25 fractions) [46]. None of the patients in Miller et al. underwent surgery [88]. They were either treated with thoracic RT alone (58 Gy

in 29 fractions) or with neoadjuvant chemotherapy, followed by thoracic RT and adjuvant chemotherapy. RTOG 0214 [90] allowed all potentially curative therapy, defined as high-dose thoracic RT (>30 Gy) or surgery. Neoadjuvant, adjuvant or concurrent chemotherapy was permitted, as well as pre- or post-operative RT. Finally, all patients in the study by Li et al. had complete resection (pneumonectomy in 15%, lobectomy in 84%, and bilobectomy in 1% of patients) followed by adjuvant chemotherapy [98].

Most studies mandated a radionuclide/radioisotopic brain scan, a CT scan of the brain [46,86,87], or an MRI of the brain [90,98] after completion of curative treatment and prior to study entry. Miller et al. though did not mention the need for a pre-treatment brain imaging in the study.

Most studies used 30 Gy (in 10 or 15 fractions) as total dose for PCI, except the first 34 patients in Miller et al. who received 37.5 Gy in 15 fractions [88], and the patients in Cox et al. who were treated with 20 Gy in 10 fractions [86]. The comparative arm in the 6 studies included consisted of observation after potentially curative treatment.

Outcomes studied are incidence of brain metastases in all 6 studies, overall survival in 4 studies [46,86,88,90,98], disease-free survival in 2 studies [90,98], time to development of brain metastasis in 3 studies [46,86,87], QOL in 2 studies [98,114], and NCF in one study [114]. Heterogeneity between studies was also seen in the different follow-up protocols. Some protocols required brain imaging [46,86,87] only if symptoms developed, whereas others ordered them routinely every 6 months even without symptoms [90,98]. Miller et al. did not detail the investigations to be performed as part of the monthly follow-up visits after treatment completion [88].

3.3. Risk of bias assessment

Risk of bias assessment across all studies is shown in Figure 2 and detailed in Table 2. Only two studies had adequate random sequence generation: In Russel et al., the "randomization scheme described by Zelen" was used, and in Li et al, a minimization method with stratification was used. In the 4 other studies, the randomization method was unclear, making selection bias a possibility. As for allocation concealment, it was properly performed and detailed in 4 out of studies: Russel et al. (by RTOG headquarters), Cox et al. (centrally by telephone to the Statistical center at Statistical center at Frontier Science and Technology Research Foundation), and Li et al. (by an independent provider by telephone). It was not properly documented in the other two studies.

Blinding of participants and personnel was not feasible when testing such an invasive procedure, and all of the studies were "open-label". Blinding of outcome assessment was also not performed across all studies, but detection bias is not a concern as the outcomes of brain metastases and death are objective. Incomplete patient data was improperly addressed in two trials [86,87]; three patients were excluded from the intervention group in the trial by Umsawasdi et al., and one of these three patients developed brain metastasis. In the trial by Cox et al, a significant number of patients refused PCI and loss of these patients might have been related to the trial's outcome measures, thus possibly introducing attrition bias. Intention-to-treat analysis was performed in four out of six trials (Gore et al., Li et al., Russel et al., and Miller et al.), and incomplete outcome data was adequately assessed in these trials. Only one study (RTOG 0214) had predefined outcomes specified in a published protocol on www.rtog.com and clinicaltrials.gov, thus obviating

the risk of reporting bias. All other studies were at high risk of reporting bias as no protocols were found despite extensive search.

3.4. Results of individual studies and synthesis of results

3.4.1. Incidence of brain metastasis

All six individual studies included in the quantitative analysis demonstrated a reduction in the incidence of brain metastases with PCI as compared to observation, some were significant and others were not: 4% with PCI versus 14% with observation in Umsawasdi et al. (p=0.02), 9% vs. 19% in Russel et al. (p=0.1), 1% vs. 11% in Miller et al. (p=0.003), 6% vs.13% in Cox et al. (p=0.038), 17.3% vs. 26.8% (at 5 years) in Gore et al. (p=0.02), 20.3% vs. 49.9% (at 5 years) in Li et al (p<0.001) (Table 5). The results of these six studies were combined in a meta-analysis (Figure 3), including 657 patients in the PCI arm and 630 patients in the observation arm. PCI was associated with a significant reduction in the rate of brain metastases as compared with those who did not receive PCI (OR = 0.31; 95% CI: 0.20–0.46; p<0.001). There was minimal heterogeneity among included studies (Chi^2= 5.43, df = 5, p = 0.37, I^2 = 8). Figure 4 shows the inverted funnel plot regarding the outcome of incidence of brain metastases. Its symmetry was checked visually, and no publication bias was detected.

3.4.2. Overall survival

Figure 5 and Table 5 show six RCTs that were included in the meta-analysis for OS. The overall HR showed no survival benefit for PCI in the non-small-cell lung cancer patients compared to patients who did not have PCI (HR=1.08, 95 % CI: 0.90 – 1.31;

p=0.41). There was moderate heterogeneity among included studies (Chi^2= 9.31, df= 5, p =0.10, I^2= 46%). Figure 6 shows the funnel plot where no publication bias is detected regarding the included studies for the OS outcome.

We performed a sensitivity analysis including Umsawasdi et al., which was excluded from the primary analysis as its HR has been derived working backwards form the KM graph, a method that can lack precision and accuracy (Figure 7). However, the conclusion did not differ, and the point estimate and CI were very close to the ones from the primary analysis (HR=1.08, 95 % CI: 0.91 – 1.27; p=0.39).

Another sensitivity analysis including studies published after 1995 [88,90,98], when platinum-based chemotherapy, added to RT, became the standard of care for locoregionally advanced NSCLC [103–107] (Figure 8). The three studies in this sensitivity analysis included patients with stage III NSCLC exclusively. There was also no difference in overall survival between PCI and no PCI (HR=1.05, 95 % CI: 0.74 – 1.49; p=0.79).

3.4.3. Disease-free survival

Two studies (3 reports) reported on DFS [90,94,115], and were combined in a meta-analysis including 244 patients with stage III NSCLC in the PCI arm versus 252 in the no PCI arm (Figure 9).

In RTOG 0214 initial report, the 1-year DFS rates were 56.4% and 51.2% for PCI and observation arms, respectively (p-value = 0.11). In the study's updated report (in abstract form only), the 5-year DFS was 18.5% for PCI versus 14.9% for observation (p-value = 0.13), and HR for observation versus PCI was 1.20 (95% CI, 0.95-1.52) (according to KM curve included in Gore's presentation related to the abstract).

In Li et al. study, DFS was the primary endpoint. The 3-year and 5-year DFS were, respectively, 42.0% and 26.1% with PCI, and 29.8% and 18.5% with observation. The median DFS was significantly longer in the PCI group (28.5 months, 95% CI 21.9–35.1) compared with the control group (21.2 months, 95% CI 15.0–27.4).

The meta-analysis demonstrated significantly improved DFS with PCI (HR, 0.67; 95% CI 0.46–0.98; $p = 0.037$). There was no heterogeneity among included studies (Chi^2= 0.92, df= 1, p =0.34, I^2= 0%).

3.4.4. Time to brain metastasis

Three studies reported on the time to brain metastases. In Umsawasdi et al. trial, the median time to brain metastasis was delayed in the PCI group (50.5 weeks in the PCI group versus 23 weeks in the control group, p-value = 0.002) [87]. In Cox et al., the median time for development of brain metastases was prolonged from 29 weeks in the observation group to 34 weeks in the PCI group (statistical significance not reported) [86]. In Russel et al., PCI use also appeared to delay the onset of brain metastasis (no specific information provided) [46].

3.4.5. Brain metastasis as first site of recurrence – Relapse pattern

Three of the included studies report on the patterns of failure. In Umsawasdi et al., the brain was the first site of relapse in 12 out of 14 patients in the control arm who developed brain metastasis, and in none of the 2 patients who developed brain metastases in the PCI arm [87]. In Gore et al., brain metastasis as a component of first failure occurred in 23% of patients not receiving PCI versus 10% of patients receiving PCI, and brain metastasis as the only failure was reported in 21.5% (no PCI arm) versus 9.1% (PCI arm)

[90,95]. In the trial by Li et al., the crude 5-year brain relapse as first site of recurrence was 33.3% in the no PCI arm and 9.9% in the PCI arm (p-value<0.001) [98].

3.4.6. Toxicities, QOL and NCF analysis: a systematic review

Reported acute toxicities from PCI include epilation and acute skin reaction[46]. Other acute toxicities mentioned in the trial by Li et al. were grade 3 headache (1%) and fatigue (2%)[98].

Most trials report on the late toxicities, with more or less details. In the trial by Miller et al., it is reported that there were "no excess neurological toxicities" in patients treated with PCI as compared to those in the observation arm, however the definition of neurological toxicity was unclear [88]. In Umsawasdi et al., no late neurological complications were noted although there was no formal neurologic assessment [87]. In RTOG 0214, 4 patients in the PCI developed Grade 3 late toxicities (syncope, weakness, fatigue), but there was no late toxicity greater than Grade 3 [90]. Similarly, in Li et al., the main late toxicities were moderate headache or great lethargy (11.1%), severe headache (2.5%), Grade 3 skin atrophy (one patient), and grade 3 fatigue (one patient). Toxicities were not addressed in the trial by Cox et al. [86].

Late neurological complications from PCI and QOL have only been formally studied in 2 trials [98,114]. As these two studies used different QOL tools, it is impossible to combine them in a meta-analysis.

In the RCT by Li et al., QOL analysis can be found in the supplemental material. QoL was assessed by means of the Functional Assessment of Cancer Therapy-Lung (FACT-L) questionnaire for 129 out of 156 randomized patients (70 in the PCI arm, 59 in

the observation arm). No significant differences in QOL deterioration were found between the two groups.

QOL analysis for RTGO 0214 was performed using the European Organisation for Research and Treatment of Cancer (EORTC) core tool (QOL Questionnaire-QLQC30) and brain module (QLQBN20) [114]. There were no statistically significant differences at 6 or 12 months in any component of the EORTC-QLQC30 or QLQBN20 scale (p-value > 0.05) as compared to baseline, although there was a trend towards greater decline in patient-reported cognitive functioning in the PCI arm (unadjusted p-value = 0.02 at 6 months, adjusted p-value= 0.24). Similarly, there was no significant difference in NCF deterioration as determined by MMSE between the 2 arms, except at 3 months (p-value= 0.04). In the Activity of Daily Living Scale (ADLS), the percentage of patients who remained independent at 12 months is not different between the two arms (p-value= 0.88). The only significant difference in the NCF analysis was in the Hopkins Verbal Learning Test (HVLT), whereby patients who received PCI had greater deterioration in immediate recall (p-value= 0.03) and delayed recall (p-value= 0.008) at 1 year.

3.5. Quality of evidence evaluation using the GRADE framework

We applied the Grading of Evidence, Assessment, Development and Evaluation (GRADE) approach to the principal patient-important outcomes. Results are summarized in Table 3. The quality of evidence was rated down to "moderate" for the outcomes of incidence of brain metastases and overall survival because of the important risk of bias in three out of six studies included in the meta-analysis. As for the disease-free survival

outcome, the quality of the body of evidence was graded as "high", as the evidence was direct, precise, consistent, and free of biases.

CHAPTER 4

DISCUSSION

4.1 Review and discussion of findings

The present systematic review and meta-analysis showed that PCI significantly decreased the incidence of brain metastases in NSCLC (by 70%), improved disease-free survival in stage III patients, had no effect on overall survival, imparted some radiation-induced cognitive impairment, but had no impact on QOL.

4.1.1. Prophylactic cranial irradiation and incidence of brain metastases

As already shown in previous systematic review [85] and meta-analysis [112], our study showed that PCI decreases significantly the rates of brain metastases in patients with NSCLC as compared with no PCI (OR= 0.31, 95% CI 0.20-0.46). A previous meta-analysis by Xie et al., which did not include the RCT by Li et al., showed similar results, i.e. that PCI reduced the risk of brain metastases as compared with non-PCI in NSCLC patients (OR = 0.30, 95% CI, 0.21–0.43).

4.1.2. Prophylactic cranial irradiation and survival

Our meta-analysis showed no significant difference in overall survival between the PCI and control arms (HR = 1.08, 95%CI, 0.91-1.27), whereas Xie et al. meta-analysis showed a detrimental effect on OS of NSCLC patients with a HR of 1.19 (95% CI, 1.06–1.33, p=0.004). We argue in the next section (4.2) that Xie's methodology seems to be flawed and some HRs erroneously reported, leading to a wrong conclusion.

A non-randomized, population-based study using the Surveillance, Epidemiology,

and End Results (SEER) database also addressed the effect on PCI on survival in NSCLC

patients and is worth mentioning. It included a total of 17,852 patients with NSCLC,

among whom only 1.8% received PCI as part of their treatment. No statistically significant

difference in survival was shown between the patients who received PCI and those who did

not (HR, 1.04; 95% CI, 0.93-1.16), even in subgroups of patients at higher risk of brain

metastases (patients younger than 60 years, adenocarcinoma histology, or stage IIIB). In

this meta-analysis, we were unable to perform subgroup analysis because in most trials,

results were not stratified by histology, stage, and response to induction chemotherapy (if

applicable).

4.1.3. Prophylactic cranial irradiation and impact on QOL and NCF

A sequential association between neurocognitive effects and QOL decline was

demonstrated after whole brain radiotherapy in patients with brain metastases. It was

shown that neurocognitive deterioration preceded QOL decline by 9-153 days [116]. Such an

association has not been duplicated in the setting of PCI. Although RTOG 0214 showed a

decline in NCF based on HVLT-DR with PCI, there were no significant differences in

QOL between the patients who received PCI and those who did not [115].

Although not addressing the issue of prophylactic cranial irradiation exclusively, it

is interesting to discuss the results from the multicenter trial by Pottgen et al., which

compared two different locoregional treatment strategies in patients with operable stage III

NSCLC. In the first arm, patients underwent surgery followed by adjuvant thoracic RT. In

the second arm, therapy consisted of induction chemotherapy, followed by concurrent

chemoradiation and then surgery. All patients in the second arm received PCI (30 Gy in 10

fractions). One has to be careful in interpreting results pertaining to PCI use in this trial, as this was not the original aim of the trial, and patients randomized to arm 2 received a more aggressive locoregional treatment (trimodality approach) than patients in arm 1. PCI reduced the rate of brain metastasis as first site of failure, and the overall brain relapse rate. There was no significant difference in neurocognitive performance between the PCI and observation arms [111]. This is the only study, besides RTOG 0214 (included in our meta-analysis) [114] that reported on NCF in the setting of PCI for NSCLC.

Another study by Gondi et al. was not included in this systematic review as it pooled QOL and NCF results from two RTOG randomized studies: RTOG 0214 (already included in this review), and RTOG 0212 [47], which is discussed in the introduction of the current review, and randomized patients with limited-stage SCLC to standard-dose versus higher-dose PCI. PCI was associated with a higher risk of decline in self-reported cognitive functioning (SRCF) at 6 months (OR 3.60, 95% CI 2.34-6.37, P<0.0001) and 12 months (OR 3.44, 95% CI 1.84-6.44, P<0.0001). PCI was also associated with a significant decline on HVLT-Recall and HVLT-Delayed Recall at 6 and 12 months, but was not closely correlated with decline in SRCF at the same time points (P=0.05 and P=0.86, respectively). PCI was not associated with a decline in global health status/QOL or any other EORTC QLQ-C30 symptom or functional scales. Age >60 years was associated with higher rates of HVLT- DR decline at 12 months [115].

These results show that PCI-induced cognitive decline is not only captured on formal memory testing like HVLT but is also, and more importantly, self-reported, and thus experienced by the patient.

4.2. Critique of existing systematic reviews and meta-analysis on the use of PCI in NSCLC

The first systematic review on PCI in NSCLC was undertaken by the Cochrane Collaboration [85]. Two of the limitations of this Cochrane review were the absence of meta-analysis due to heterogeneity of the trials included at that time, and the fact that it was not updated since 2010. As a matter of fact, after the paper was published in 2005, new literature searches by the Cochrane group were performed, last one in May 2010, and therefore it does not include the two most recent RCTs: Gore et al. (RTOG 0214) [90,95] and Li et al [98]. When the review was last updated, RTOG 0214 was only published in the abstract form, and the studies on the impact of PCI on QOL and NCF [98,114] were not yet published.

Another systematic review and meta-analysis by Brown et al. was found in abstract form (two abstracts) [117,118]. The search performed by the authors and a librarian does not seem to be systematic. In the methods section of the abstract, it is mentioned that databases were searched using the search terms: "prophylactic cranial irradiation" AND "non-small cell lung carcinoma", and that 112 citations were retrieved. We argue that this search strategy does not seem to be exhaustive, and would not really capture all abstracts/manuscripts on the topic, as evidenced by the small number of retrieved studies. Also, they chose as one of their primary outcomes one-year survival, compromising the data to a single survival estimate at one point in time, instead of taking the entire survival curve into consideration by using HRs.

In another systematic review and meta-analysis by Xie et al.[112], the authors included a study by Pottgen et al.which is a randomized controlled trial, but is not randomizing the use

of prophylactic cranial irradiation specifically. Inclusion of this trial introduces a flaw in

the methodology of this meta-analysis. Another flaw is in 'Figure 4', a forest plot

evaluating the role of PCI on OS, by pooling HRs from six studies (including the non-

randomized trial of Pottgen et al.). In this forest plot, some of the hazard ratios included

were improperly reported. For example, they incorrectly reported a HR of 1.07 favoring

observation for Gore et al.[90,95], where they should have used the inverse of this ratio, as the

reference used in the statistical analyses by Gore et al. was the PCI group and not the

observation group (i.e. authors reported HR of observation versus PCI, and not PCI versus

observation). The title of this meta-analysis by Xie et al. "Prophylactic Cranial Irradiation

May Impose a *Detrimental Effect* on Overall Survival of Patients with Non-small Cell

Lung Cancer" is based on this forest plot where some of the HRs seem to be incorrect,

threatening the validity of the meta-analysis (low-quality evidence). The HRs we obtained

using a more rigorous methodology showed no survival detriment nor benefit from PCI

(HR, 1.08, 95% CI 0.91-1.27). Also, the RCT by Li et al.[98] was not included in Xie

systematic review because it was published in 2014.

4.3. Limitations and strengths of the current systematic review

Our systematic review and meta-analysis is unique, as the methodology used is

rigorous, the literature search thorough and exhaustive, and it includes the most recent

trials, one of which (Li et al.) was not included in any of the previously mentioned reviews.

Our study also fills a knowledge gap: it is the only meta-analysis done on stage III patients

specifically (although formal subgrouping – stage III versus I-II and stage IIIB versus IIIA,

pre-specified in the protocol, was not made possible by the available data), a group whom

we thought might benefit more from PCI. We believed that the therapeutic ratio of benefits versus risks might have been more advantageous in this group of patients than in patients with earlier stage NSCLC, as their propensity for brain metastases is much greater. Results of our meta-analysis showed otherwise, and even in this specific subset of patients, PCI seems to have no overall survival benefit, but had a significant disease-free survival benefit.

As part of the limitations, we were not able to perform subgroup analysis as most corresponding authors did not answer our e-mails. For instance, we asked for results stratified by stage (stage IIIA vs stage IIIB) in Gore et al., as well as NSCLC histology, but our request was left unanswered (two e-mails sent).

In Cox et al., 13% of the patients included had SCLC, and results were provided for NSCLC and SCLC separately for the endpoints of incidence of brain metastases and time-to-brain metastasis, but not for the endpoints of overall survival. This could have introduced a small error in the reporting for OS, which has probably been diluted when combining all the trials together in the meta-analysis shown in Figure 6.

Another limitation of our study is that in the current targeted therapy era, some of the drugs, such as erlotinib and gefitinib can effectively cross the blood-brain barrier and reduce the incidence of brain metastases in NSCLC [119–125], thus potentially lessening the reported effect of PCI on the incidence of brain metastases and maybe dampening the disease-free survival benefit.

4.4. Literature gaps, ongoing trials, and future directions

PCI was definitely shown to change the failure pattern of NSCLC, from failing in the brain first to failing outside of the brain. However, more information is needed from RCTs

to determine whether a specific subset of patients might derive a survival benefit from PCI. Patients at high risk of brain metastases include: (1) Patients with superior sulcus tumors, also known as Pancoast tumors, who have a 40% risk of failing in the brain [126,127], (2) Patients with operable stage IIIA-N2 NSCLC and with non-squamous histology [7,128,129] (We need another study like Li et al. [98] but adequately powered, or to be combined in a meta-analysis with the results from Li et al.), and (3) Patients with a complete pathological response to neoadjuvant therapy - in a study by Chen et al., 43% of patients developed brain metastases as first site of failure, and 55% of patients developed brain metastases at some point in their clinical course [130]. Other literature gaps include the impact of PCI on QOL and NCF, topics on which only insufficient evidence exists.

In order to determine whether our unanswered questions were being addressed, we searched four large clinical trial registries on August 10th, 2016 for any ongoing or completed trials relevant to our review for their potential inclusion in this manuscript or future versions of the manuscript. We searched the North American (http://clinicaltrials.gov/), European (https://www.clinicaltrialsregister.eu), World Health Organization (WHO) (http://apps.who.int/trialsearch/), and BMC (http://www.isrctn.com/) trial registries. Our search yielded seven trials relevant to our review.

Of the seven trials captured by this search, one was completed with its results posted in October 2015 (NCT00048997) and its results are already included in this meta-analysis [90,95,114]. A Chinese trial entitled "Prophylactic Cranial Irradiation (PCI) Versus no PCI in Non Small Cell Lung Cancer After a Response to Chemotherapy" (NCT00745797) was opened in 2008 and terminated back in January 2014 due to slow accrual and lack of funding.

Another trial from the Netherlands had a "completed" status in April 2015 (NCT01282437), with no published reports yet. This trial is interesting in that it randomized only stage III (III A and IIIB) patients to PCI or no PCI, and is examining development of symptomatic brain metastases as a primary endpoint, and time to development of neurological symptoms, side effects from PCI, and QOL/NCF (NCT01290809) as secondary endpoints. We marked this trial for tracking to follow up on its results as soon as they are available for it inclusion in future updates of our review.

Two other trials had an "ongoing but not recruiting" status, a Chinese study NCT02448992: "Hippocampal-Sparing Prophylactic Cranial Irradiation in Pathologically Nodal Positive Non-Small-Cell Lung Cancer" and a Mexican study NCT01603849: "Prophylactic Cranial Irradiation in Patients With Lung Adenocarcinoma With High Risk of Brain Metastasis", in January and February 2016 respectively. We also marked these two trials for tracking for future inclusion in updated versions of our review. It is interesting that one is trying to maximize the benefit-risk ratio by attempting to minimize the neurocognitive side effects of PCI, and the other is looking at a high-risk group, i.e. patients with a high-risk histology, adenocarcinoma.

Of the two remaining trials, one had a "recruiting" status back in July 2010 (Chinese trial NCT01158170: Prophylactic Cranial Irradiation in Erlotinib/Gefitinib-responders With Non-small Cell Lung Cancer (NSCLC)) while the other had a "not yet recruiting" status in January 2010 (Korean trial NCT00955695: "A Randomized, Phase III Trial of Prophylactic Cranial Irradiation (PCI) in Patients With Advanced Non-small Cell Lung Cancer (NSCLC) Who Are Nonprogressive on Gefitinib or Erlotinib". This trial is reserved for stage IIIB and IV NSCLC). Both trials have no reported results and their

statuses on clinicaltrials.gov have not been updated since 2010.

The Dutch (NCT01282437/ NCT01290809) and the Mexican (NCT01603849) ongoing studies reported above both address QOL and NCF, and might allow us in future versions of this review to perform a meta-analysis for QOL and NCF outcomes, by pooling their results with results from the trials by Li et al. [98], and Sun et al. [114], already included in the current review. The main issue with QOL/NCF outcomes is that different trials are using various instruments for QOL and NCF assessment, which might preclude pooling these results in a meta-analysis.

Tools should be developed to determine patients at the highest risk of brain metastasis based on a combination of factors. In the paper by Li et.al, a mathematical model was devised to predict the risk of brain metastasis, based on the number of metastatic lymph nodes, the surgical resection evaluation, histology, region of lymph node metastases, TNM stage, and adjuvant chemotherapy.

The following formula was reproduced from the supplementary material from Li et al. paper:

"Logit (p) = 8.215 − 0.903×(number of metastatic lymph node) − 0.872×(surgical resection evaluation) − 0.714×(histology) − 1.893×(region of lymph node metastases) − 0.948×(TNM stage) − 1.034×(adjuvant chemotherapy)

Scoring is as follows: number of metastatic lymph node (NML) is 1 if NML is less than 4, 2 if NML ranges from 4 to 6, and 3 if NML is more than 6; surgical resection evaluation (SRE) is 1 for complete resection, 2 for incomplete resection; histology is 1 for squamous, 2 for non-squamous; region of lymph node (LN) metastases is 1 for L1, 2 for L2 and L3; TNM stage is 1 for IIIA, 2 for IIIB; adjuvant chemotherapy is 0 for no

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chemotherapy, and 1 for chemotherapy. Finally, P=1-p, and $P \geq 0.44$ predicts for a high

risk of brain metastases."

Similar instruments could be devised to enroll patients in future clinical trials on the matter,

since only a highly selected subset of patients with NSCLC will most likely derive benefit

from the addition of PCI.

4.5. Conclusion and recommendations

In summary, PCI in NSCLC does not confer an overall survival benefit. In the case of

stage III NSCLC patients, this meta-analysis has shown that PCI improves DFS, but not OS.

Authors believe that the benefit-risk ratio is still not clearly in favor of its use. However, it

continues to be investigated extensively as evidenced by the significant number of ongoing

clinical trials on the matter. Many questions remain unsettled and more research is needed

on this topic. It would be important to incorporate prospective NCF testing in all future

studies. Research should focus on the high-risk patient population discussed above, and

efforts to identify other high-risk groups based on genetic profile and predictive biomarkers

should be pursued. Also, should novel and emerging targeted therapies improve the

survival of NSCLC patients, then PCI should be reconsidered seriously, especially if the

strategies being investigated to reduce the late neurotoxicity associated with its use (such as

hippocampal avoidance and/or neuroprotective drugs) prove to be beneficial.

If the number of RCTs increases enough (10 studies or more) to be able to perform

regression analysis, then a meta-regression could be valuable to examine the impact of

different study variables on the effect size. In a meta-regression, as in other regression

analyses, an outcome is predicted based on one or more explanatory variables. The

difference is that in a meta-regression the explanatory variable is a study characteristic, and the outcome is an effect estimate [131]. Finally, an individual patient data meta-analysis would be of great value. It should include only the most recent trials, and would need to be conducted after new data becomes available, as its importance would be to perform subgroup analysis based on histology, stage (IIIA versus IIIB), modality of curative treatment, and pathological response to induction chemotherapy if applicable.

Patients in the high-risk groups should be allowed to make an informed decision, based on the above body of evidence. Caution should be taken in discussing possible risks associated with PCI, especially in elderly people, and in patients with other comorbidities, who might be at higher risk of developing neurocognitive dysfunction. High-risk patients should be encouraged to enroll in clinical trials

TABLE 1: Failure patterns of NSCLC in the brain

Study *(author, year)*	Number of Participants	Curative treatment received	Brain as the first site of failure			Any brain failure		
Albain et al. (1995)	101	CT/RT: 12 CT /RT/Surgery: 89	Not reported			*Brain Metastases:*		
						Component of systemic failure	7 %	
						Isolated	19 %	
Kumar et al. (1996)	63	CT/RT: 17 CT/RT/surgery: 46	Not reported			*Brain Metastases:*	CT/RT	CT/RT/surgery
						Component of systemic failure	Not reported	11 %
						Isolated		13 %
Cox et al. (1999)	1765	RT only: 1415 CT/RT: 350	*Histology*	RT only	RT + CT	Not reported		
			Squamous Cell	11 %	8 %			
			Adenocarcinoma	20 %	16 %			
			Large Cell	18 %	16 %			
Keller et al. (2000)	470	RT only: 234 CT/RT: 236	Not reported			RT only		RT + CT
						14 %		14 %
Andre et al. (2001)	267	Primary Surgery: 186 Inductiion CT/surgery: 81 (Post-op CT in 10 patients and RT in 160 patients)	Not reported			*Brain Metastases:*	Surgery	Induction CT/surgery
						Component of systemic failure	18 %	32 %
						Isolated	11 %	22 %

Law et al. (2001)	42	CT/RT: 11 CT/RT/Surgery: 31	*Histology:*	Resection	Non- resection	*Stage of disease:*	CT/RT/Surgery	CT/RT/Surgery
			Squamous	17 %	0 %	Stage IIIA	33 %	43 %
			Non-squamous	32 %	40 %	Stage IIIB	19 %	25 %
Robnett et al. (2001)	142	Sequential CT +RT: 53 CCRT: 89	*Brain Metastases:*			Sequential CT +RT		CCRT:
			Component of systemic failure	8 %		39 % at 2 yrs		20 % at 2 yrs
			Isolated	11 %				
Carolan et al. (2005)	83	CT/RT: 67 CT/RT/Surgery: 16	24.6 % (95% CI, 14.7 % - 41.1 %) at 2 yrs			34.2 % (95% CI: 4.5 % - 47.7 %) at 2 yrs		

Abbreviations: NSCLC: Non-small-cell lung cancer; CT: Chemotherapy, RT: radiation theraoy, CI: Confidence interval

TABLE 2: Randomized controlled trials and a meta-analysis evaluating the role of PCI in patients with limited-stage and extensive-stage SCLC who responded to chemotherapy

Study (author, year)	Number of participants	PCI dosage (dose in Gy per fractions)	Brain Metastases Rates			Survival (median survival in months or overall survival rates)		
			Observation arm (No PCI)	Intervention arm (PCI)	p-value	Observation arm (No PCI)	Intervention arm (PCI)	*p*-value
Limited-stage SCLC								
Aroney et al. (1983)	29	30 Gy : 10 F	36 % (overall)	0 %	0.02	Not reported	Not reported	-
Ohonoshi et al. (1993)	46	40 Gy : 20 F	52 % (overall)	22 % (overall)	< 0.05	15 mths	21 mths	Not reported
Arriagada et al. (1995)	300	24 Gy : 8 F	67 % at 2 yrs	40 % at 2 yrs	$< 10^{-13}$	21.5 % at 2yrs	29 % at 2 yrs	0.14
Wagner et al. (1996)	31	25 Gy : 10 F	50 % (overall)	20 % (overall)	Not significant	8.8 mths	15.3 mths	Not reported
Gregor et al. (1997)	314	8-36 Gy : 1-18 F	54 % at 2 yrs	30 % at 2 yrs	0.00004	11 % at 3 yrs	21 % at 3 yrs	0.25
Laplanche et al. (1998)	211	24-30 Gy : 8-10 F	51 % at 4 yrs	44 % at 4 yrs	0.14	16 % at 4 yrs	22 % at 4 yrs	0.25
Auperin et al. (1999)	987	8-40 Gy : 1-20 F	58.6 % at 3 yrs	33.3 % at 3 yrs	< 0.001	15.3 % at 3 yrs	20.7 % at 3 yrs	< 0.001
Extensive-stage SCLC								
Slotman et al. (2007)	286	20-30 Gy : 5-10 f	40.4 % at 1 yr	14.6 % at 1 yr	< 0.001	13.3 % at 1 yr	27.1 % at 1 yr	0.003
Seto et al. (2014)	163	25 Gy : 10 f	58 % at 1 yr	32.4 % at 1 yr	< 0.001	15.1 mths	10.1 mths	0.091

Abbreviations: SCLC: Small cell lung cancer; PCI: prophylactic cranial irradiation; Gy: Gray; F: Fraction

FIGURE 1: PRISMA Flow Diagram

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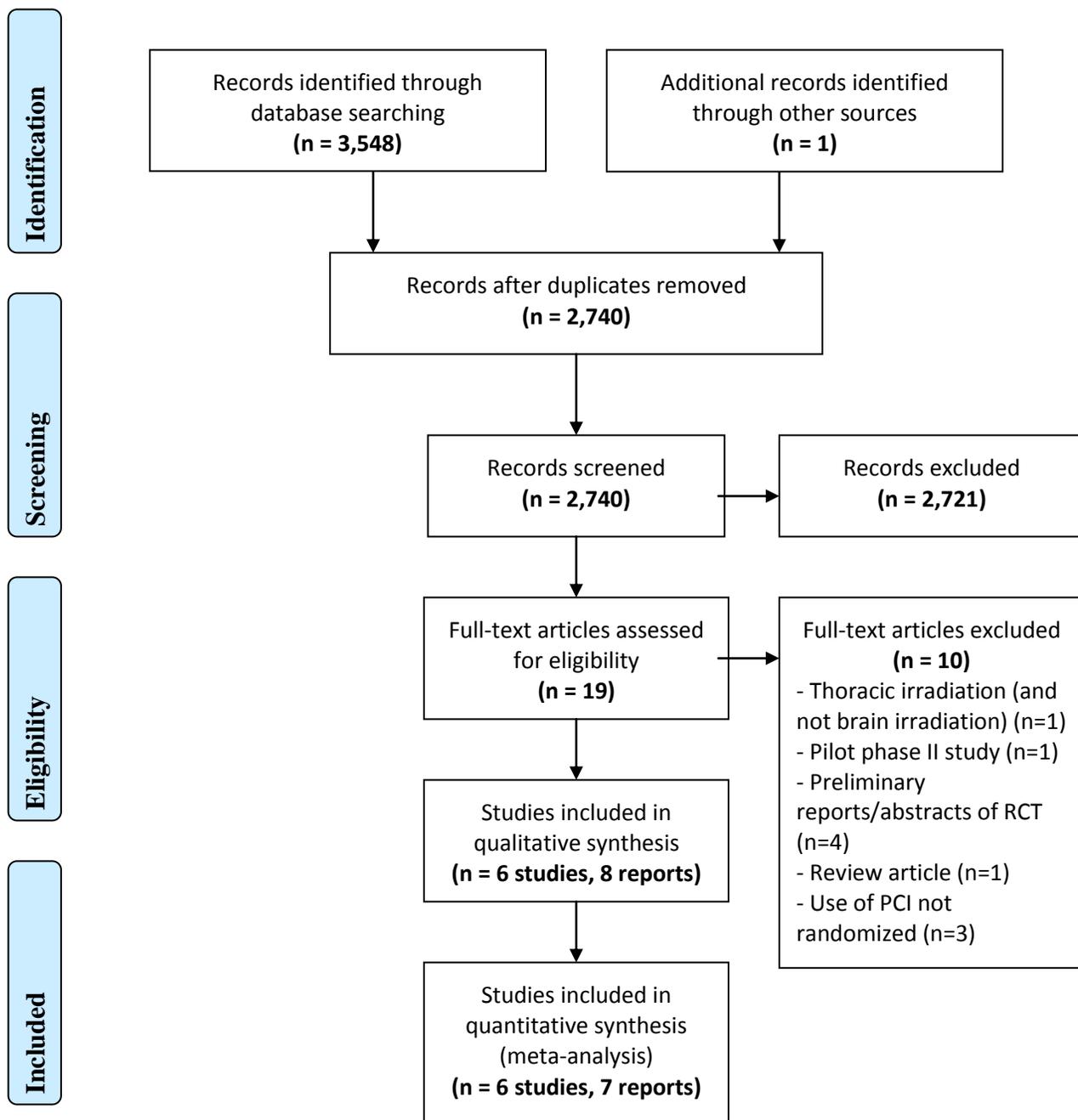
TABLE 3: Characteristics of included studies

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
Umsawasdi T, 1984	Randomized 2-arm trial. Radionuclide brain scan or CT scan of the brain if neurological symptoms developed Follow-up protocol not clear	100 patients with locally advanced non-small cell lung cancer (3 excluded) -Any age -Any performance status -13% stage I/II, 87% stage III -36% squamous cell carcinoma, 48% adenocarcinoma, 16% other histologies "Most patients were male, had good performance status, and minimal pretherapy	Combined chemoradiotherapy either as the sole treatment for active disease or as an adjuvant therapy Thoracic RT not described	*Inclusion criteria:* Patients with locally advanced NSCLC with normal bone marrow, liver, and renal functioning *Exclusion criteria:* Not clear	PCI (30Gy/10F/2 weeks)	Observation	Incidence of brain metastases, time to development of brain metastases, and survival reported Significant reduction in the incidence of brain metastases with PCI (4% versus 27%, p= 0.02) PCI significantly prolonged time to brain metastases (50.5 weeks versus 23 weeks, p=0. 02) No significant difference in survival	Supported in part by Grant CA 05831 Project 9A from the National Cancer Institute, NIH, USPHS, DHHS, Bethesda, Maryland and by Bristol Laboratories, Syracuse, New York COI: Not reported

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
		weight loss."					1 patient had transient memory loss, no late neurologic complications No formal assessment of QOL	
Russel AH, 1991	Randomized 2-arm trial. Clinical assessment every 3 months. CT head in all patients surviving 7.5 months from PCI completion, and in any patient developing new neurological symptoms	187 patients with adenocarcinoma or large cell carcinoma of the lung clinically confined to the chest:	-161 patients with inoperable or unresectable adenocarcinoma or large cell carcinoma of the lung confined to the chest who received primary thoracic RT (55-60Gy/30F/6 weeks) -26 patients with resected adenocarcinomas and large cell carcinomas of the lung who received post-operative RT (50Gy/25F/5 weeks) following resection of all gross intrathoracic	***Inclusion criteria:*** Patients with inoperable or unresectable adenocarcinoma or large cell carcinoma of the lung confined to the chest as well as patients with resected adenocarcinomas and large cell carcinomas of the lung ***Exclusion criteria:*** Prior malignancies, prior radiation or chemotherapy, or significant preexisting neurological deficits on the basis of cerebrovascular disease or primary	PCI (30Gy/10F/2 weeks) (PCI given concurrently with the sixth fraction of chest irradiation)	Observation	Incidence of brain metastases, median, 1- and 2-year OS reported PCI arm: 1-year OS: 40%; 2-year OS: 13% Observation arm: 1-year OS : 44%; 2-year OS : 21% --> No significant difference in survival between the 2 arms Eighteen of 94	Funding : Not reported COI: Not reported

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
			disease No chemotherapy was given concurrently with primary radiaton therapy for unresectable disease (so treatment was not optimal)	central nervous system disease			patients (19%) randomized to receive chest irradiation subsequently developed brain metastases, whereas 8 of 93 (9%) randomized to receive PCI developed brain metastases (p = 0.10). Although the time adjusted incidence of brain metastases did not significantly differ between the treatment arms, the administration of PCI did appear to delay the onset of late brain metastasis	
Miller TP, 1998	Randomized 2x2 factorial design (4-arm trial) Monthly follow-	254 patients with unresectable **stage III**	Arm 1: Chest RT alone (58Gy/29F/6 weeks) Arm 2: Chest RT	*Inclusion criteria :* Inoperable limited stage (stage III) NSCLC; limited stage = "unresectable	PCI 37.5Gy/15F/ 3 weeks (first 34 patients) or 30Gy/15F/3	Observatio n	Incidence of brain metastases and median survival	Supported in part by PHS Cooperative Agreement grants awarded by the National Cancer

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
	up for the first year. No details on investigations performed	NSCLC - Median age: 61 (29-78) - Females: 23% - ECOG PS 0-1: 89% - Stage III: 100% -52% squamous cell carcinoma, 31% adenocarcinoma, 17% large cell carcinoma	+ PCI Arm 3: Chest RT + CT (adjuvant and neoadjuvant CT) Arm 4: Chest RT + CT + PCI	disease confined to a single hemithorax, and/or ipsilateral hilar, mediastinal, or supraclavicular LNs, and encompassable in a single radiation port", KPS>60, ECOG PS<2, normal myocardial function, kidney function and bone marrow reserves *Exclusion criteria:* Cancer-related pleural effusions, prior history of all-cause acute respiratory failure, FEV1 <750cc, distant metastasis, inadequate documentation of stage or histology	weeks		reported. Significant reduction in the incidence of brain metastases with PCI (1% vs 11%, p=0.003) Significant reduction in median survival with PCI (8 months vs 11 months, p=0.004) No frank neurological toxicities No formal assessment of QOL	Institute, DHHS COI: Not reported
Cox JD, 1981	Randomized 4-arm trial. Clinical assessment and CXR every	410 patients with locally advanced **NSCLC and SCLC**	Arm 1: Intermediate-course irradiation (lung: 50Gy/25F/5 weeks)	*Inclusion criteria:* Lung carcinoma not candidates for curative resection, no distant metastasis,	PCI 20Gy/10F/2 weeks	Observatio n	Incidence of brain metastases, time to brain metastases and median survival	Supported in part by the Veterans Administration and grant CA 23415-02 awarded by the National

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
	month for the first 6 months after treatment, every 2 months for the next 18 months, and every three months thereafter. Radionuclide brain scan if neurological symptoms developed	- Any age - KPS>50 - No details on stage - 40% squamous cell carcinoma, 10% adenocarcinoma, 17% large cell carcinoma, 20% other NSCLC histologies and 13% SCLC 87 patients excluded out of 410 patients entered into the study (Analysis based on 323 patients) 42/323 patients had SCLC (excluded from this review)	Arm 2: Intermediate course + PCI (lung: 50Gy/25F/5 weeks; brain: 20 Gy/10F/2 weeks) Arm 3: Short-course irradiation (lung: 42Gy/15F/3 weeks) Arm 4: Short course + PCI (lung: 42Gy/15F/3 weeks; brain: 20 Gy/10F/2 weeks) The 2 thoracic RT schedules were combined for statistical analysis of PCI effect **Thoracic RT schedules and technique (2D) would not be considered optimal by modern standards.**	KPS>50, normal radionuclide brain scans *Exclusion criteria:* SCV or contralateral hilar LNs, bloody or malignant pleural effusion, previous RT or chemotherapy			reported Significant reduction in the **incidence of brain metastases** with PCI (6% versus 13%, p= 0.038) **Time to brain metastases**: 34 weeks versus 29 weeks. No significant improvement in **median survival** with PCI (35.4 weeks versus 41.4 weeks, p=0.5) No formal assessment of QOL or toxicity	cancer Institute, and by an Interagency Agreement between the Veterans Administration and the National cancer Institute. No. Y01-CM-70107 COI: Not reported

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
			No chemotherapy used.					
Gore EM, 2010 (updated analysis in an abstract form in 2012) Sun A, 2010 (NCF and QOL analysis)	Randomized 2-arm trial All patients had evaluation of NCF and QOL at baseline. NCF was reassessed at 3, 6, 12, 18, 24, 30, 36, and 48 months and then yearly. QOL was assessed, and brain imaging was performed at 6, 12, 24, 36, and 48 months and then yearly. Patients were observed in follow-up at 6 months from start of PCI, every 6 months for 2	356 patients with locally advanced NSCLC - Median age: 62 (39-84) - Females: 38% - ECOG PS 0-1: 96% - Stage III: 100% (Stage IIIA (54%) to IIIB (46%)) with stable disease or better (i.e., complete response or partial response) after potentially curative therapy -32% squamous cell carcinoma, 33% adenocarcinoma	Potentially curative therapy, defined as high-dose thoracic radiation therapy (RT; ie, >30 Gy) or surgery. Radiation could be given with or without neoadjuvant, adjuvant, or concurrent chemotherapy. Pre- or postoperative RT and/or chemotherapy were allowed	*Inclusion criteria:* Patients with locally advanced NSCLC of stages IIIA to IIIB who have 'a stable disease or better (ie, complete response or partial response) after potentially curative therapy, defined as high-dose thoracic radiation therapy (RT; >30 Gy) or surgery' and with 'no evidence of progressive intrathoracic disease, brain metastases, or extra-cranial metastases' *Exclusion criteria:* Acute or subacute grade >3 toxicities from previous therapy that did not	PCI (30Gy/15F/3 weeks)	Observation	1-year and 5-year survival, DFS, incidence of brain metastasis, NCF, and QOL No significant difference in 1-year overall survival (75.6% with PCI vs 76.9%, p=0.86), and 5-year overall survival (26.1% with PCI vs 24.6%, p=0.57, abstract only) No significant difference in 1-year DFS (56.4% with PCI vs 51.2%, p=0.11), and 5-year DFS (18.8% with PCI vs 14.9%, p=0.13, abstract	No funding COI: An author (James A. Bonner) indicated a financial or other interest relevant to the subject matter

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
	years, and then yearly.	, 6% large cell carcinoma, and 29% other NSCLC histologies		decrease to grade <2 at the time of enrollment			only) Significant decrease in 1-year (7.7% with PCI vs 18%, p=0.004), and 5-year incidence of brain metastases (17.3% with PCi vs 26.8%, abstract only) No significant difference in QOL as assessed by EORTC-QLQC30 or QLQBN20 (p>0.5) No significant differences in MMSE (p=0.60) or ADLS (p=0.88). Greater decline in immediate and delayed recall for the HVLT in the PCI arm at 1	

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
							year	
Li N, 2015	Randomized 2-arm trial MRI of the brain and baseline evaluation of QOL Patients were followed up every 3 months during the first 2 years after randomization, and every 6 months thereafter. Thoracic and upper abdomen CT and brain MRI scans were scheduled every 6 months after randomization for evaluation of tumor relapse/metastasis by investigators, and repeated if	156 patients with locally advanced NSCLC - Median age: 55 (31-73) in PCI arm, 57 (24-75) in control arm - Females: 29% - ECOG PS 0-1: 98% - Stage IIIA-N2: 100% -25% squamous cell carcinoma, 62% adenocarcinoma, and 13% other NSCLC histologies	Resection (lobectomy, bilobectomy or pneumonectomy) followed by adjuvant chemotherapy (platinum-based)	*Inclusion criteria:* Fully resected stage IIIA–N2 NSCLC with high cerebral metastases risk (after adjuvant chemotherapy, age18–75 years, ECOG PS 0–2, no evidence of tumor relapse. *Exclusion criteria:* Incomplete resection, previous RT or targeted therapy, other current or previous malignancies, any concurrent unstable disease, history of neurological or psychiatric disorders and pregnancy, N2 disease identified preoperatively The interval from day 1 of the last chemotherapy cycle	PCI (30Gy/15F/3 weeks)	Observation	DFS, incidence of brain metastases, OS, toxicity and QOL Significantly lengthened DFS in the PCI group compared with the control group (median DFS of 28.5 months versus 21.2 months [HR, 0.67; 95% CI 0.46–0.98; p = 0.037]. Decrease in risk of brain metastases (the actuarial 5-year brain metastases rate, 20.3% versus 49.9%; HR, 0.28; 95% CI 0.14–0.57; p < 0.001). The median OS	Supported by Guangdong Province Science and Technology project management (grant numbers 2005B3030 1002, 2010B031600064) No COI

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
	clinically indicated.			to randomization must be within 6 weeks.			was 31.2 months in the PCI group and 27.4 months in the control group (HR, 0.81; 95% CI 0.56–1.16; p = 0.310). Mild toxicities in PCI arm: headache, nausea/vomiting and fatigue No significant differences in deterioration rate for QOL and symptoms between the two groups, as assessed by total score (OR, 0.91; 95% CI, 0.43 to 1.95; P=0.81), the FACT-L TOI (OR, 0.87; 95% CI, 0.39 to 1.95; P=0.73) and the FACT-L LCS (OR, 1.03; 95%	

Study name (Author, year)	Study design and follow-up methods	Participants (N, age, gender, performance status, NSCLC stage and histology)	Treatment modality used as curative treatment	Inclusion/exclusion criteria	Intervention (PCI technique and dose)	Control arm	Outcomes assessed (with outcome measures)	Funding and conflicts of interest
							CI, 0.46 to 2.32; *P*=0.94)	

Abbreviations: NSCLC: Non-small cell lung cancer; PCI: prophylactic cranial irradiation; Gy: Gray; F: Fractions; CT: Computed tomography; RT: Radiation therapy; QOL: Quality of life; NCF: Neurocognitive function; COI: Conflict of interest; OS: Overall survival; ECOG: Eastern Cooperative Oncology Group; PS: Performance status; KPS : Karnofsky performance status ; LN : Lymph node ; DFS : Disease-free survival ; HR : Hazard ratio ; CI : Confidence interval; FACT-L: Functional Assessment of Cancer Therapy-Lung; OR: Odds ratio

TABLE 4: Risk of bias assessment across included studies

Study name (Author, year)	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias) Intention-to-treat analysis	Selective outcome reporting (Reporting bias)	Other sources of bias	Summary assessment
Umsawasdi T, 1984	Randomization method was not specified, although it is stated that this is a "prospective randomized study" *Unclear risk*	Not specified *Unclear risk*	Not specified *Unclear risk*	Not specified, yet outcomes are objective, so there is low risk for detection bias. *Low risk*	"Three of 49 patients who were randomized to receive EBI were excluded from the analysis because they did not receive EBI as planned due to scheduling error. One of these patients had CNS metastasis during their course of treatment". The fact that three patients were excluded from the intervention group, including one who developed brain metastases (one of the main endpoints of the study), could have introduced attrition bias. It also means that intention-to-treat	No published protocol *Unclear risk*	None *Low risk*	*Unclear*

Study name (Author, year)	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias) Intention-to-treat analysis	Selective outcome reporting (Reporting bias)	Other sources of bias	Summary assessment
					analysis was not performed. *High risk*			
Russel AH, 1991	"The randomization scheme described by Zelen was used to achieve institutional balance and incorporated three patient-related stratifications: prior surgery, pretreatment KPS, and histology." *Low risk*	"Following registration and confirmation of eligibility, patients were randomly assigned by RTOG headquarters" *Low risk*	Not specified *Unclear risk*	Not specified, yet outcomes are objective, so there is low risk for detection bias. *Low risk*	Complete outcome data on the 187 patients included : "One hundred sixty-nine patients have been followed until death." "18 patients remain alive." Intention-to-treat analysis: "All the analyses were based upon the intention-to-treat principle" *Low risk*	No published protocol *Unclear risk*	None *Low risk*	*Low*
Miller TP, 1998	Randomization method was not specified *Unclear risk*	"Patients were stratified on the basis of performance status […] and histology […]. After stratification, patients were randomized to receive one of	Not specified *Unclear risk*	Not specified, yet outcomes are objective, so there is low risk for detection bias. *Low risk*	"254 patients were entered on the study […]. 28 patients were declared ineligible." Reasons for exclusion are explained, are legitimate, and unlikely to affect	No published protocol *Unclear risk*	None *Low risk*	*Unclear*

Study name (Author, year)	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias) Intention-to-treat analysis	Selective outcome reporting (Reporting bias)	Other sources of bias	Summary assessment
		four treatments". Concern can be raised that selection bias might have been introduced by this stratification, if patients with poorer performance status were excluded from tougher treatment arms. *Unclear risk*			the outcome. *Low risk*			
Cox JD, 1981	"Patients were centrally randomized by telephone call" Randomization method was not specified, although "central" randomization points toward an adequate randomization, however more information is	"Patients were centrally randomized by telephone to the Statistical center at Frontier Science and Technology Research Foundation" *Low risk*	Not specified *Unclear risk*	Not specified, yet outcomes are objective, so there is low risk for detection bias. *Low risk*	"410 patients were entered into the study. The analysis of brain irradiation was based on 323 patients. 87 patients were excluded; 7 had no on-site report, 27 were not eligible according to protocol criteria, 12 refused brain	No published protocol *Unclear risk*	None *Low risk*	*Unclear*

Study name (Author, year)	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias) Intention-to-treat analysis	Selective outcome reporting (Reporting bias)	Other sources of bias	Summary assessment
	needed on the sequence generation. *Low to unclear risk*				irradiation, 10 never started treatment, 9 did not receive the assigned treatment, and 20 had unknown or inconclusive results of brain scans before treatment." Reasons for exclusion are detailed, however it is possible that imbalance might have resulted in the two arms in terms of baseline characteristics based on this high number of patients excluded. A significant number of patients refused PCI or never started treatment, and this attrition might have been related to the outcome of interest. Also, no			

Study name (Author, year)	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias) Intention-to-treat analysis	Selective outcome reporting (Reporting bias)	Other sources of bias	Summary assessment
					intention-to-treat analysis was performed. *High risk*			
Gore EM, 2010 (updated analysis in an abstract form in 2012) Sun A, 2010 (NCF and QOL analysis)	"Randomly assigned to either PCI or observation." No information on method of sequence generation in manuscript. *Unclear risk*	"Patients were stratified by stage (IIIA or IIIB), histology (nonsquamous or squamous), and therapy (surgery or none) and were randomly assigned to either PCI or observation." *Unclear risk*	Not specified *Unclear risk*	Not specified, yet outcomes are objective, so there is low risk for detection bias. *Low risk*	"Data from 340 eligible patients were analyzed as of November 2008. At the time of this analysis, there were 150 patients alive with 23.8 months of median follow-up […] and there were 17 patients alive with less than 12 months of follow-up; **three of these patients withdrew consent for follow-up**. […] At the time of this analysis, 190 deaths had occurred of 340 evaluable patients." Nearly complete outcome data	No selective outcome reporting. Predefined outcomes in a published protocol on www.rtog.com (RTOG 0214) and clinicaltrials.gov (NCT00048997) *Low risk*	None *Low risk*	*Low risk*

60

Study name (Author, year)	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias) Intention-to-treat analysis	Selective outcome reporting (Reporting bias)	Other sources of bias	Summary assessment
					Intention-to-treat analysis as seen in CONSORT diagram *Low risk*			
Li N, 2015	"Prospective, open-label, randomized, phase III trial. Eligible patients were randomly assigned in a **1:1 ratio** to receive either PCI or observation. Random assignment instructions were obtained through an independent provider by telephone. A **minimization procedure** was used with stratification according to ECOG PS (0 or 1 versus 2) and histology	"Random assignment instructions were obtained through an **independent provider by telephone**. A minimization procedure was used with **stratification** according to ECOG PS (0 or 1 versus 2) and histology (squamous versus nonsquamous) and center." *Low risk*	Blinding of participants and personnel not performed: "open-label" *High risk*	Not specified, yet outcomes are objective, so there is low risk for detection bias. *Low risk*	*No attrition bias:* The 156 patients who were randomized have been followed-up, and analyzed for safety and efficacy of PCI Intention-to-treat analysis as seen in CONSORT diagram *Low risk*	No published protocol *Unclear risk*	None *Low risk*	*Low risk*

Study name (Author, year)	Random sequence generation (Selection bias)	Allocation concealment (Selection bias)	Blinding of participants and personnel (Performance bias)	Blinding of outcome assessment (Detection bias)	Incomplete outcome data (Attrition bias) Intention-to-treat analysis	Selective outcome reporting (Reporting bias)	Other sources of bias	Summary assessment
	(squamous versus nonsquamous) and center." Minimization procedure was used as randomization method *Low risk*							

Abbreviations: EBI: Elective brain irradiation; PCI: prophylactic cranial irradiation; ECOG: Eastern Cooperative Oncology Group; PS: Performance status

FIGURE 2: Risk of bias assessment across included studies

TABLE 5: Summary of results - incidence of brain metastases and survival- extracted from the RCTs on NSCLC included in this systematic review and meta-analysis (PCI versus no PCI)

Study name (Author, year)	Primary therapy	Stage	PCI Dose	N	Brain metastases (%)			Median Survival (months) / Overall Survival (%)		
					PCI (+)	Observation	p	PCI (+)	Observation	p
Cox JD, 1981	RT only	Inoperable	20 (2 Gy x 10)	281	7/136 (6%)	16/145 (13%)	0.038	8.2 months	9.7 months	0.5
Umsawasdi T, 1984	Trimodality	I-II (13%) III (87%)	30 (3 Gy x 10)	97	2/46 (4%)	14/51 (27%)	0.002	22% (3 years)	23.5% (3 years)	NA
Russell AH, 1991	RT only	I/III	30 (3 Gy x 10)	187	8/93 (9%)	18/94 (19%)	0.1	8.4 months 40% (1 year) 13% (2 years)	8.1 months 44% (1 year) 21% (2 years)	0.36
Miller TP, 1998	CT/RT	III	30 (2 Gy x 15) 37.5 (2.5 Gy x 15)	226	1/111 (1%)	13/115 (11%)	0.003	8 months	11 months	0.004
Gore EM, 2012	Trimodality	III	30 (2Gy x 15)	340	19/163 (17.3%)	39/177 (26.8%)	0.009	75.6% (1 year) 26.1% (5 years)	76.9% (1 year) 24.6% (5 years)	0.57
Li N, 2015	Surgery and CT	IIIA-N2	30 (3 Gy x 10)	156	10/81 (12%)	29/75 (39%)	<0.001	31.2 months 44.5% (3 years) 27.4% (5 years)	27.4 months 38.7% (3 years) 22.8% (5 years)	0.310

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FIGURE 3: Effect of prophylactic cranial irradiation on the incidence of brain metastases in 1,287 patients with non-small-cell lung cancer enrolled in six randomized controlled trials

	PCI		No PCI			Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	M-H, Random, 95% CI
Miller 1998	1	111	13	115	3.9%	0.07 [0.01, 0.56]	
Umsawasdi 1984	2	46	14	51	6.7%	0.12 [0.03, 0.56]	
Li 2015	10	81	29	75	22.5%	0.22 [0.10, 0.50]	
Gore 2011	13	163	32	177	30.1%	0.39 [0.20, 0.78]	
Russell 1991	8	93	18	94	19.0%	0.40 [0.16, 0.97]	
Cox 1981	7	136	16	145	17.8%	0.44 [0.17, 1.10]	
Total (95% CI)		630		657	100.0%	0.31 [0.20, 0.46]	
Total events	41		122				

Heterogeneity: Tau^2 = 0.02; Chi^2 = 5.43, df = 5 (P = 0.37); I^2 = 8%
Test for overall effect: Z = 5.71 (P < 0.00001)

0.02 0.1 1 10 50
Favours [PCI]   Favours [No PCI]

FIGURE 4: Inverted funnel plot for trials addressing the incidence of brain metastases
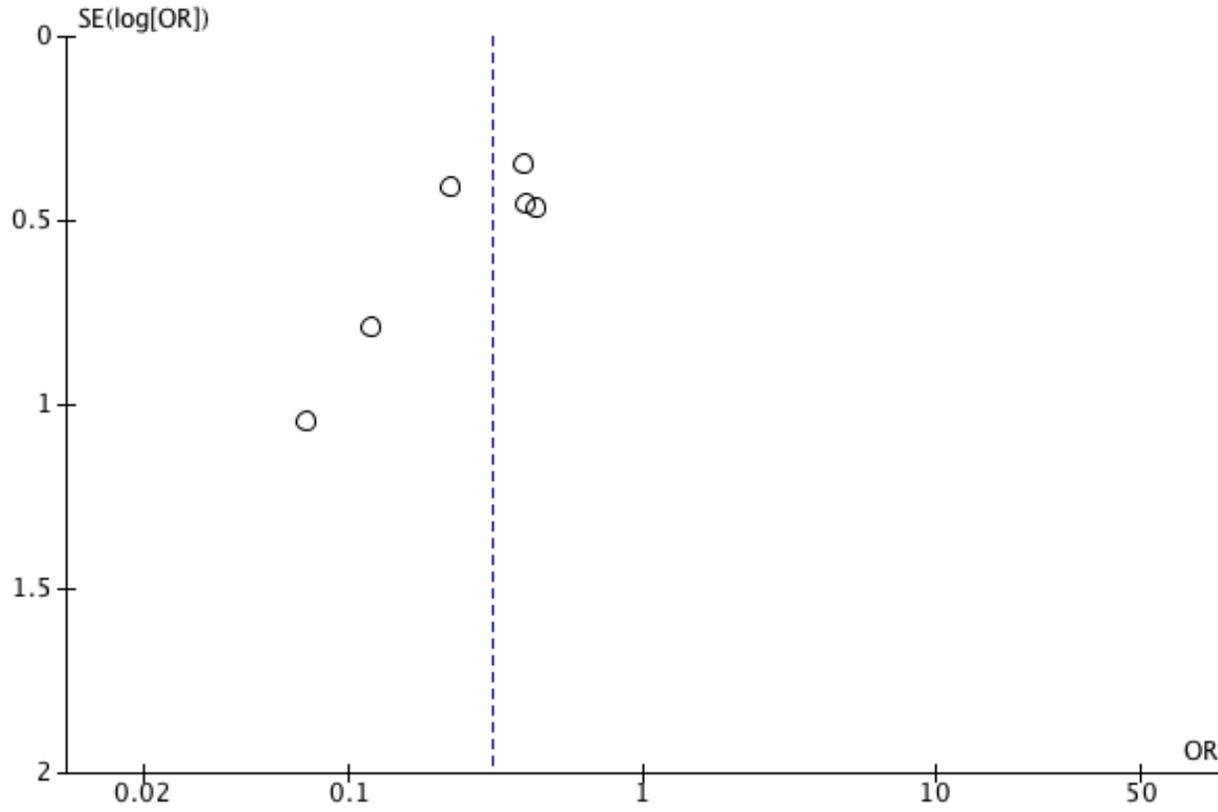
Abbreviations: OR, odds ration, SE, standard error

67

FIGURE 5: Effect of prophylactic cranial irradiation on overall survival in 1,190 patients with non-small-cell lung cancer enrolled in five randomized controlled trials

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Cox 1981	0.08531736	0.12649171	22.4%	1.09 [0.85, 1.40]
Gore 2011	-0.068	0.12664206	22.3%	0.93 [0.73, 1.20]
Li 2015	-0.211	0.18577513	15.6%	0.81 [0.56, 1.17]
Miller 1998	0.38553232	0.13395089	21.4%	1.47 [1.13, 1.91]
Russel 1991	0.14518842	0.15861258	18.4%	1.16 [0.85, 1.58]
Total (95% CI)			100.0%	1.08 [0.90, 1.31]

Heterogeneity: Tau² = 0.03; Chi² = 9.17, df = 4 (P = 0.06); I² = 56%
Test for overall effect: Z = 0.82 (P = 0.41)

Favours [PCI]   Favours [No PCI]

68

FIGURE 6: Inverted funnel plot for trials addressing overall survival
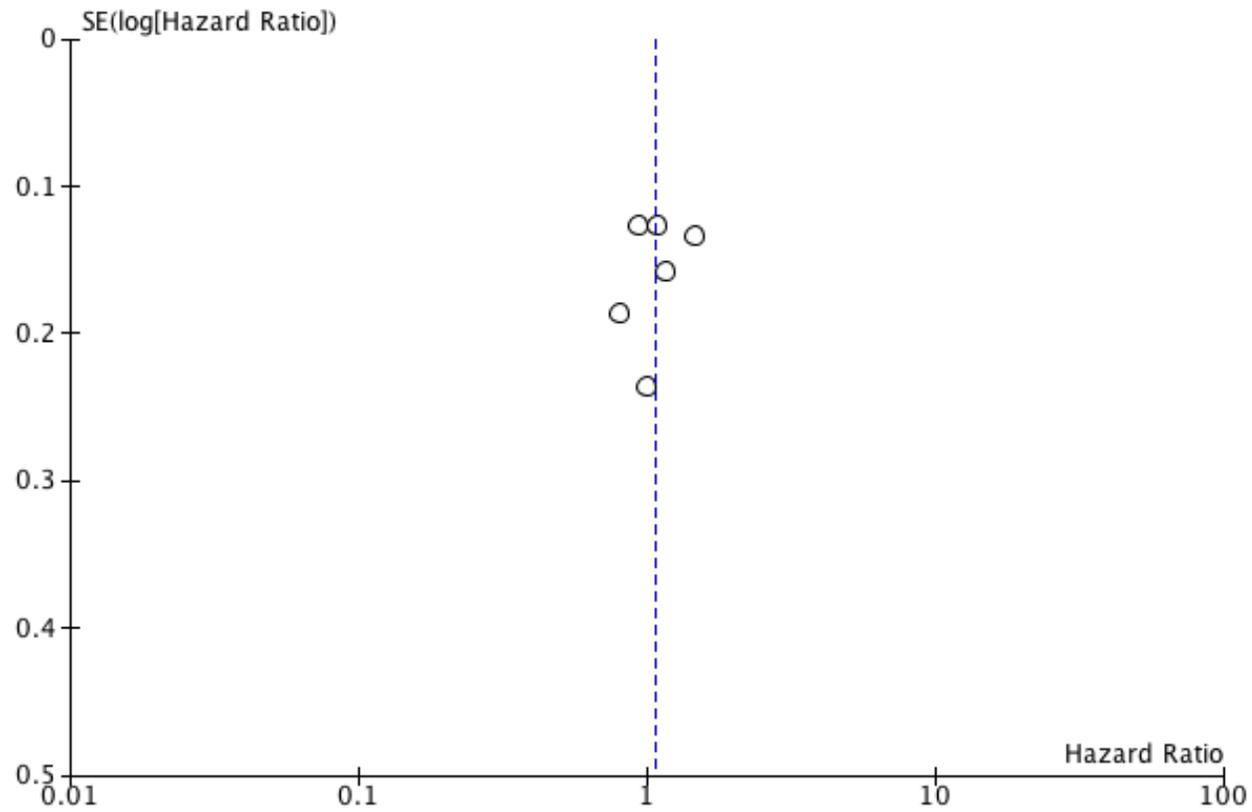
FIGURE 7: Sensitivity analysis: Effect of prophylactic cranial irradiation on overall survival in 1,287 patients with non-small-cell lung cancer enrolled in six randomized controlled trials (Umsawasdi et al. added)
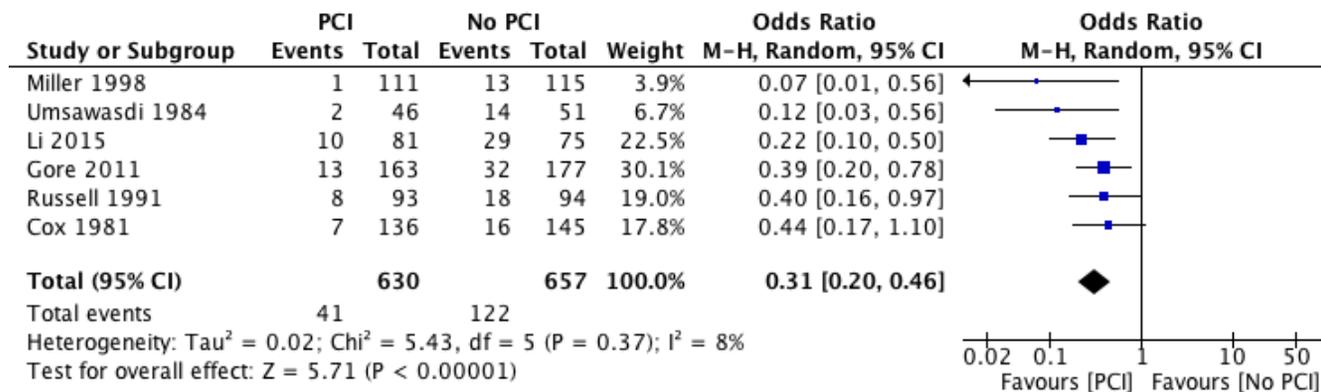
Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Cox 1981	0.08531736	0.12649171	20.5%	1.09 [0.85, 1.40]
Gore 2011	−0.068	0.12664206	20.5%	0.93 [0.73, 1.20]
Li 2015	−0.211	0.18577513	13.5%	0.81 [0.56, 1.17]
Miller 1998	0.38553232	0.13395089	19.4%	1.47 [1.13, 1.91]
Russel 1991	0.14518842	0.15861258	16.3%	1.16 [0.85, 1.58]
Umswasadi 1984	−0.00332238	0.23602592	9.7%	1.00 [0.63, 1.58]
Total (95% CI)			100.0%	1.08 [0.91, 1.27]

Heterogeneity: Tau^2 = 0.02; Chi^2 = 9.31, df = 5 (P = 0.10); I^2 = 46%
Test for overall effect: Z = 0.85 (P = 0.39)

Hazard Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Favours PCI   Favours no PCI

FIGURE 8: Sensitivity analysis: Effect of prophylactic cranial irradiation on overall survival in 722 patients with stage III non-small-cell lung cancer enrolled in three randomized controlled trials published after 1995

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Gore 2011	−0.068	0.12664206	35.6%	0.93 [0.73, 1.20]
Li 2015	−0.211	0.18577513	29.6%	0.81 [0.56, 1.17]
Miller 1998	0.38553232	0.13395089	34.9%	1.47 [1.13, 1.91]
Total (95% CI)			100.0%	1.05 [0.74, 1.49]

Heterogeneity: Tau^2 = 0.07; Chi^2 = 9.02, df = 2 (P = 0.01); I^2 = 78%
Test for overall effect: Z = 0.27 (P = 0.79)

Hazard Ratio IV, Random, 95% CI
0.01 0.1 1 10 100
Favours [PCI]   Favours [No PCI]

FIGURE 9: Effect of prophylactic cranial irradiation on disease-free survival in 496 patients with stage III non-small-cell enrolled in two recent randomized controlled trials

Study or Subgroup	log[Hazard Ratio]	SE	PCI Total	No PCI Total	Weight	Hazard Ratio IV, Random, 95% CI	Hazard Ratio IV, Random, 95% CI
Gore 2011	−0.1823	0.1206	163	177	71.8%	0.83 [0.66, 1.06]	
Li 2015	−0.40048	0.1922	81	75	28.2%	0.67 [0.46, 0.98]	
Total (95% CI)			244	252	100.0%	0.78 [0.64, 0.96]	

Heterogeneity: Tau² = 0.00; Chi² = 0.92, df = 1 (P = 0.34); I² = 0%
Test for overall effect: Z = 2.39 (P = 0.02)

0.01 0.1 1 10 100
Favours PCI Favours no PCI
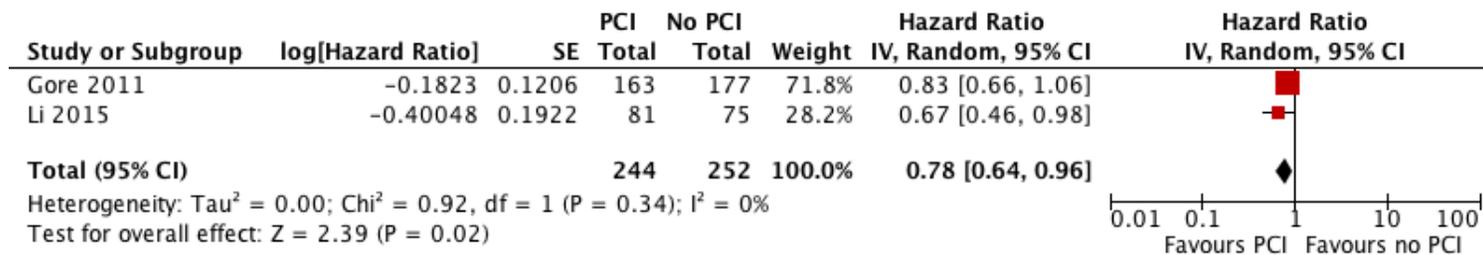
TABLE 6: Assessment of the quality of the evidence for each outcome using GRAD

№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	PCI	Control	Relative (95% CI)	Absolute (95% CI)	Quality	Importance
Quality assessment							**№ of patients**		**Effect**			
Incidence of brain metastases												
6	RCTs	Serious[1]	Not serious	Not serious	Not serious	-	630	657	RR 0.31 [0.20, 0.46]	128 fewer per 1000 (from 100 fewer to 148 fewer)	Moderate	Critical
OS												
5	RCTs	Serious[1]	Not serious[2]	Not serious	Serious[3]	-	630	657	HR 1.08 [0.90, 1.31]	70 more deaths per 1000 (87 fewer deaths to 270 more deaths)	Low	Critical
DFS												
2	RCTs	Not serious	Not serious	Not serious	Not serious	-	252	244	HR 0.78 [0.64, 0.96]	174 fewer per 1000 (from 32 fewer to 284 fewer)	High	Critical
QOL/NCF												
2	RCTs	Not serious	Not serious	Not serious	Not serious	Different QOL and NCF instruments were used in the two studies, thus results could not be combined in a meta-analysis	252	244	**QOL** -No differences in QOL deterioration between PCI and no PCI arms. **NCF-** Only difference in NCF analysis was in the HVLT with greater deterioration in immediate recall (p=0.03) and delayed recall (p= 0.008) at 1 year with PCI		High	Important

Abbreviations: GRADE, Grading of Evidence, Assessment, Development and Evaluation; CI, confidence interval; RCT, randomized controlled trial; RR, relative risk; HR, hazard ratio; RCT, randomized controlled trial; OS: Overall survival; DFS: Disease-free survival; QOL: Quality of life; NCF: Neurocognitive function; HVLT: Hopkins Verbal Learning Test

[1] Three out of the 6 studies included had low risk of bias; the other 3 studies had unclear risk of bias
[2] I^2 was 46% indicating moderate level of heterogeneity. This was taken into account along with the borderline risk of bias by downgrading the level of evidence by one level. This downgrading has been applied to the risk of bias criteria.
[3] The CI includes values that indicate benefit, and others that indicate harm.

APPENDIX 1: 2009 PRISMA Checklist on preferred reporting items for systematic reviews and meta-analysis

Section/topic	#	Checklist item
TITLE		
Title	1	Identify the report as a systematic review, meta-analysis, or both.
ABSTRACT		
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.
INTRODUCTION		
Rationale	3	Describe the rationale for the review in the context of what is already known.
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).
METHODS		
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).

Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.

Section/topic	#	Checklist item
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.
RESULTS		
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).

DISCUSSION		
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.
FUNDING		
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

www.prisma-statement.org.

APPENDIX 2: SEARCH STRATEGY

   a. **Database: Ovid MEDLINE(R) <1946 to February Week 3 2014>**
   (Then same search was run again until July 2016)

Search Strategy:

----
1   randomized controlled trial.pt. (363020)
2   controlled clinical trial.pt. (87529)
3   randomized.ab. (263363)
4   placebo.ab. (142471)
5   drug therapy.fs. (1664948)
6   randomly.ab. (187940)
7   trial.ab. (271136)
8   groups.ab. (1212670)
9   1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 (3117256)
10   humans.sh. (13184976)
11   9 and 10 (2549148)
12   exp Lung Neoplasms/ (168804)
13   exp Carcinoma, Bronchogenic/ (39136)
14   exp Bronchial Neoplasms/ (48792)
15   exp Pleural Neoplasms/ (10809)
16   ((lung* or pulmonary or bronch* or pleura*) adj2 (carcinoma* or cancer* or tumor* or tumour* or neoplas*)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier] (197526)
17   12 or 13 or 14 or 15 or 16 (200699)
18   exp Carcinoma, Large Cell/ (1838)
19   exp Adenocarcinoma/ (277518)
20   exp Carcinoma, Squamous Cell/ (101275)
21   (squamous adj cell adj4 (carcinoma* or cancer* or tumor* or tumour* or neoplasm*)).tw. (60223)
22   (large adj cell adj4 (carcinoma* or cancer* or tumor* or tumour* or neoplasm*)).tw. (3413)
23   adenocarcinoma*.tw. (89669)
24   (lung* or pulmonary or bronch* or pleura*).tw. (805435)
25   18 or 19 or 20 or 21 or 22 or 23 (394138)
26   24 and 25 (49473)
27   NSCLC.ti,ab. (16355)
28   exp Carcinoma, Non-Small-Cell Lung/ (30382)
29   (((non adj small) or nonsmall) adj3 ((lung* or pulmonary or bronch* or pleura*) adj3 (carcinoma* or cancer* or tumor* or tumour* or neoplas*))).mp. (35791)
30   29 or 26 or 27 or 28 (77115)
31   exp Carcinoma, Small Cell/ (16406)
32   SCLC.ti,ab. (4694)

33   ((lung* or pulmonary or bronch* or pleura*) adj3 (small adj2 (carcinoma* or cancer* or tumor* or tumour* or neoplas*))).mp. (33394)
34   31 or 32 or 33 (47045)
35   17 or 30 or 34 (213159)
36   35 not (34 not (34 and 30)) (201358)
37   exp Cranial Irradiation/ (4108)
38   pci.tw. (11374)
39   wbrt.tw. (698)
40   ((brain or crani* or head* or skull*) adj3 (radiotherap* or irradiat* or radiat*)).mp. (13019)
41   37 or 38 or 39 or 40 (25090)
42   11 and 36 and 41 (459)

b. Database: EMBASE

No.
Query
Results
722
#38
#1 AND #31 AND #37
69,210
#37
#32 OR #33 OR #34 OR #35 OR #36
1,435
#36
wbrt:ab,ti
26,763
#35
pci:ab,ti
42,700
#34
(brain OR crani* OR head* OR skull*) NEAR/3 (radiotherap* OR irradiat* OR radiat*)
3,975
#33
'brain radiation'/exp
2,616
#32
'skull irradiation'/exp
305,525
#31
#30 NOT (#29 NOT (#29 AND #22))
321,793
#30
#7 OR #22 OR #29
80,199
#29

#23 OR #26 OR #27 OR #28

79,443

#28
lung* OR pulmonary OR bronch* OR pleura* AND small NEAR/2 (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*)

6,769

#27
sclc:ab,ti

6,965

#26
#24 AND #25

1,816,340

#25
lung* OR pulmonary OR bronch* OR pleura*

9,490

#24
'small cell carcinoma'/exp

16,377

#23
'lung small cell cancer'/exp

117,949

#22
#16 OR #17 OR #18 OR #19 OR #20 OR #21

62,828

#21
non NEAR/1 small OR nonsmall AND (lung* OR pulmonary OR bronch* OR pleura*) NEAR/2 (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*)

55,722

#20
'lung non small cell cancer'/exp

29,842

#19
nsclc:ab,ti

4,896

#18
'lung squamous cell carcinoma'/exp

16,194

#17
'lung adenocarcinoma'/exp

67,893

#16
#14 AND #15

1,816,340

#15
lung* OR pulmonary OR bronch* OR pleura*

327,145

#14
#8 OR #9 OR #10 OR #11 OR #12 OR #13

70,343

#13
'adenocarcinoma'/exp

171,272

#12
adenocarcinoma*

54,179

#11
large NEAR/1 cell AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplasm*)

132,055

#10
squamous NEAR/1 cell AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplasm*)

97,802

#9
'squamous cell carcinoma'/exp

3,047

#8
'large cell carcinoma'/exp

305,960

#7
#3 OR #4 OR #5 OR #6

305,960

#6
(lung* OR pulmonary OR bronch* OR pleura*) NEAR/2 (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*)

2,368

#5
'pleura cancer'/exp

2,254

#4
'bronchus cancer'/exp

254,042

#3
'lung tumor'/exp

1,691,809

#1
'crossover procedure'/exp OR 'crossover procedure' OR 'double blind procedure'/exp OR 'double blind procedure' OR 'randomized controlled trial'/exp OR 'randomized controlled trial' OR 'single blind procedure'/exp OR 'single blind procedure' OR random* OR factorial* OR crossover* OR (cross AND over*) OR 'cross near/2 over' OR placebo* OR doubl* NEAR/1 blind* OR singl* NEAR/1 blind* OR assign* OR allocat* OR volunteer*

c. Database: PubMed

((((((((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]) AND ((((Lung Neoplasms) OR (Carcinoma, Bronchogenic) OR (Bronchial Neoplasms) OR (Pleural Neoplasms) OR (((lung* OR pulmonary OR bronch* OR pleura*) AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*)))) OR ((((lung* OR pulmonary OR bronch* OR pleura*)) AND ((Carcinoma, Large Cell) OR (Adenocarcinoma) OR (Carcinoma, Squamous Cell) OR ((squamous AND cell AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplasm*))) OR ((large AND cell AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplasm*))) OR (adenocarcinoma*))) OR (NSCLC[tiab]) OR (Carcinoma, Non-Small-Cell Lung) OR ((((non AND small) OR nonsmall) AND ((lung* OR pulmonary OR bronch* OR pleura*) AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*))))) OR ((Carcinoma, Small Cell) OR (SCLC[tiab]) OR (((lung* OR pulmonary OR bronch* OR pleura*) AND (small AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*)))))) NOT (((Carcinoma, Small Cell) OR (SCLC[tiab]) OR (((lung* OR pulmonary OR bronch* OR pleura*) AND (small AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*))))) NOT (((Carcinoma, Small Cell) OR (SCLC[tiab]) OR (((lung* OR pulmonary OR bronch* OR pleura*) AND (small AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*))))) AND ((((lung* OR pulmonary OR bronch* OR pleura*)) AND ((Carcinoma, Large Cell) OR (Adenocarcinoma) OR (Carcinoma, Squamous Cell) OR ((squamous AND cell AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplasm*))) OR ((large AND cell AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplasm*))) OR (adenocarcinoma*))) OR (NSCLC[tiab]) OR (Carcinoma, Non-Small-Cell Lung) OR ((((non AND small) OR nonsmall) AND ((lung* OR pulmonary OR bronch* OR pleura*) AND (carcinoma* OR cancer* OR tumor* OR tumour* OR neoplas*))))))))) AND ((Cranial Irradiation) OR (pci[tiab]) OR (wbrt[tiab]) OR (((brain OR crani* OR head* OR skull*) AND (radiotherap* OR irradiat* OR radiat*))))

APPENDIX 3: FULL-TEXT SCREENING FORM

TITLE: Prophylactic cranial irradiation in patients with non-small-cell lung cancer: a systematic review and meta-analysis of randomized controlled trials

Study ID:	First Author: Al Feghali	Year:	Screener Initials:

1. Is study design: prospective randomized controlled trial?
   - ☐ No → Exclude
   - ☐ Yes → go to the next question

2. Is study population: patients with non-small-cell lung cancer treated in a curative intent?
   - ☐ No → Exclude
   - ☐ Yes → go to the next question

3. Is intervention: prophylactic cranial irradiation (PCI)?
   - ☐ No → Exclude
   - ☐ Yes → go to the next question

4. Is comparison: no PCI?
   - ☐ No → Exclude
   - ☐ Yes → Include

Decision

- ☐ Include
- ☐ Exclude

Reason for exclusion (please check):
1. Study design is not "prospective randomized controlled trial"
2. Population is not "patients with non-small-cell lung cancer treated in a curative intent"
3. Intervention is not "PCI"
4. Comparison is not "no PCI"
5. Other:

APPENDIX 4: DATA EXTRACTION FORM

Table 1: Characteristics of included studies

Study Name (first author, year)	Study Design	Participants (N, age, gender, smoking status)	Median follow- up time	Type of NSCLC, stage, treatment modality used	Performa nce status	Inclusion/ex clusion criteria	Intervention (Radiation therapy technique and total dose)	Control	Outcomes assessed (with outcome measures RR and HR and mean differences*)	Funding and conflicts of interest

*Relative risks (RR) of mortality reduction and incidence of brain metastasis comparing prophylactic cranial irradiation to observation, hazard ratios (HR) of the time to death and the time to brain metastasis, and mean difference in quality of life scores

Table 2: Biases of included studies

Study Name (author, year)	Random sequence generation	Allocation concealment	Blinding	Completeness of data	Intention to treat analysis	Selective outcome reporting	Other biases

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