National Institute for Health and Care Excellence

Guideline version (Draft)

Lung Cancer Update

Evidence reviews for the clinical and cost-effectiveness of prophylactic cranial irradiation to prevent brain metastases in people with extensive SCLC

NICE guideline <number>

Evidence reviews

October 2018

Draft for Consultation

These evidence reviews were developed by the NICE Guideline Updates Team

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ISBN:

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Evidence reviews for the clinical and cost-effectiveness of prophylactic cranial irradiation to prevent brain metastases in people with extensive SCLC

Review questions

RQ4.2: What is the clinical and cost-effectiveness of prophylactic cranial irradiation (PCI) to prevent brain metastases in people with extensive SCLC?

Introduction

New evidence on PCI for people with extensive stage SCLC has become available since publication of the previous guideline that may affect previous recommendations. The aim of the review was to assess whether PCI is effective in preventing brain metastasis in people with extensive SCLC.

Table 1: PICO table

Population	People with extensive SCLC who are not known to have brain metastases.
Intervention	Prophylactic cranial irradiation (PCI)
Comparator	Standard care

Outcomes	• Mortality
	  ○ cancer-related
	  ○ treatment-related
	  ○ all-cause
	• Quality of life (as measured by QoL instrument, for example)
	  ○ ECOG score
	  ○ EORTC score
	  ○ EQ-5D
	• Length of stay
	  ○ hospital
	  ○ ICU
	• Adverse events
	  ○ Cognitive impairment (incidence of or mean change in cognitive scores)
	• Treatment-related dropout rates
	• Presence of brain metastasis – limited vs extensive stage (whatever grade/staging is available)

Methods and process

This evidence review was developed using the methods and process described in Developing NICE guidelines: the manual (2014). Methods specific to this review question are described in the review protocol in appendix A, and the methods section in appendix B. In particular, the minimally important differences (MIDs) used in this review are summarised in appendix B.

Declarations of interest were recorded according to NICE's 2018 conflicts of interest policy.

Clinical evidence

Included studies

This review was conducted as part of a larger update of the NICE Lung cancer: diagnosis and management guideline (CG121). A systematic literature search for randomised controlled trials (RCTs) and systematic reviews with a no date limit yielded 2,730 references.

Papers returned by the literature search were screened on title and abstract, with 32 full-text papers ordered as potentially relevant systematic reviews or RCTs.

Three papers representing 2 unique RCTs were included after full text screening. Both were interventional RCTs: Slotman 2007 (n=286, follow-up period 1 year), Takahashi (n=224, follow-up period 2 years). Multiple papers reporting results of the same study were identified and collated, so that each study rather than individual reports was the unit of interest in the review, therefore there were 2 unique studies.

For the search strategy, please see appendix C. For the clinical evidence study selection flowchart, see appendix D. For the full evidence tables and full GRADE profiles for included studies, please see appendix E and appendix F.

Excluded studies

Details of the studies excluded at full-text review are given in appendix H along with a reason for their exclusion.

Summary of clinical studies included in the evidence review

Two randomised controlled studies were included in this review.

Study locations

One randomised controlled study was from the Netherlands, UK, Egypt, Poland, Belgium, Cyprus, Turkey, Italy, Israel and Hungary (Slotman 2007) and 1 was from Japan (Takahashi 2017).

Outcomes and sample sizes

The reported outcomes with extractable data were mortality (hazard ratio), progression-free survival, adverse events (including change in Mini-Mental State Examination (MMSE) scores), the cumulative incidence of brain metastasis, the

cumulative incidence of symptomatic brain metastasis, the number of people who dropped out (either declining Prophylactic cranial irradiation (PCI) in the PCI group or insisting on undergoing PCI in the observation group) and change in quality of life at 9 months. The sample sizes of the 2 RCTs were 286 and 224 participants.

See full evidence tables and Grade profiles Appendix E and Appendix F.

Quality assessment of clinical studies included in the evidence review

See appendix F for full GRADE tables.

Economic evidence

Standard health economic filters were applied to the clinical search for this question, and a total of 312 citations were returned. Following review of titles and abstracts, no full text studies were retrieved for detailed consideration. Therefore, no relevant cost–utility analyses were identified for this question.

This area was not prioritised for full health economic modelling but an original QALYs-only analysis was produced for this review question. Full details are contained within Appendix I. The QALYs analysis used data from the Slotman 2007 trial on prophylactic cranial irradiation (PCI) versus best supportive care (BSC) to create a partitioned survival analysis with three health states, progression-free, post-progression and dead. Health related quality of life data from an indirect population of people with advanced non-small cell lung cancer was assigned to people in the two alive health states. The model included no sensitivity analysis and no health state or event related costs but enabled the committee to make a rough comparison between the costs of PCI and its associated incremental QALY gains of 0.133 at 5 years (the time horizon of the model). .

Evidence statement

Prophylactic cranial irradiation vs no routine MRI follow-up

High-quality evidence from 1 RCT reporting data on 186 people with extensive SCLC found that mortality (all-cause hazard ratio), and progression free survival (hazard ratio) favoured the PCI group compared to the observation only group. Moderate quality data from the same RCT found that the cumulative incidence of symptomatic brain metastases at 6 and 12 months favoured the PCI group compared to the observation only group. However, the moderate-quality data could not differentiate for the number of people who dropped out. Very low-quality evidence from the same RCT found that the data could not differentiate for quality of life at 9 months.

Prophylactic cranial irradiation vs observation. MRI brain follow-up at 3, 6, 9, 12, 18 and 24 months with treatment of asymptomatic brain metastases with chemotherapy and cranial irradiation

Moderate-quality evidence from 1 RCT reporting data on 217 people with extensive SCLC found that the data could not differentiate for mortality (all-cause hazard ratio). However, high-quality evidence from the same RCT found that the cumulative incidence of brain metastasis at 6, 12 and 18 months favoured the PCI group

compared to the observation only group. The risk ratio of people experiencing nausea, vomiting, anorexia, malaise or dermatitis at 3 months (adverse events, all grades) favoured the observation group compared to the PCI group. Moderate-quality evidence from the same RCT showed that the data could not differentiate alopecia, headache, dizziness, lethargy, muscle weakness or the number of people who dropped out (adverse events, all grades). The data could not differentiate for any adverse events of grade 3 or above at 3 months. Very low-quality evidence from the same RCT showed that the data could not differentiate for mini-mental state examination (MMSE) at 12 or 24 months.

Economic Evidence Statement

One directly applicable QALYs-only analysis with minor limitations conducted for this review question found PCI to be associated with an incremental QALY gain of 0.133 over usual care.

Recommendations

1.4.61 Consider prophylactic cranial irradiation for people with extensive-stage disease SCLC and WHO performance status 2 or less, if their disease has responded to first-line treatment. [2019]

Research recommendation

What is the effectiveness and cost-effectiveness of prophylactic cranial irradiation vs routine MRI follow up in patients with ES-SCLC without brain metastases?

Rationale and impact

Why the committee made the recommendations

The evidence showed that prophylactic cranial irradiation improves survival versus best supportive care.

Prophylactic cranial irradiation can adversely affect quality of life, and the survival benefits are limited. There is also some evidence from a study outside the UK that routine MRI follow-up may be more cost effective. The committee made a recommendation for further research, to provide evidence more relevant to the UK and to see if MRI could identify people who need whole-brain radiotherapy and so reduce the number of people having unnecessary treatment.

Impact of the recommendations on practice

The recommendation reflects current clinical practice.

Interpreting the evidence

The outcomes that matter most

The committee agreed that the outcome that matters most is mortality. This is because in the opinion of the committee, the life expectancy for someone with SCLC is generally so short that just a few months of extra life makes a difference. Secondary outcomes included adverse events, quality of life, number of people who dropped out, progression-free survival and time-to-brain metastasis. With regards to adverse events, the committee agreed that adverse events grade 3 or above were more important than counting all adverse events (the total of grades 1 to 5). This is because according to the Common Terminology Criteria for Adverse Events, adverse events grade 3 or above are generally considered to be 'medically significant'. For example, hospitalisation is indicated.

The quality of the evidence

The committee agreed that Takahashi 2017 was not applicable for the UK. This is because the investigators followed up participants at 3, 6, 9, 12, 18 and 24 months using MRI brain imaging. Participants with asymptomatic brain metastases detected by MRI received radiotherapy and subsequent chemotherapy. Such MRI follow-up is not UK practice. This is because in Japan they have approximately 52 MRI scanners per million population compared to approximately 6 per million in the UK. Therefore, such rigorous follow-up and treatment would not be possible in the UK.

Takahashi 2017 had considerably more men compared to women (86% men) compared to Slotman 2007 (55% men). The proportion of genders in Slotman 2007 more closely reflects the UK.

The committee acknowledged that Slotman 2007 was a multi-centre study and there was heterogeneity of methods between centres. However, the committee agreed that Slotman 2007 had greater applicability to people living in the UK compared to Takahashi 2017 as the vast majority of the study centres were in Europe, almost half being in the UK.

The committee agreed that they could not make more specific recommendations about when PCI should be considered based on the data available. This is because the exclusion criteria in Slotman 2007 discriminates on the basis of age, which is inappropriate.

Benefits and harms

Slotman 2007 is relevant to UK practice and Takaahashi 20017 is not. In Slotman 2007, the data favoured PCI for mortality, which is the most important outcome for people living with SCLC. In the Slotman 2007, the difference in survival duration was approximately 5.5 weeks between the PCI group and the observation group. The committee agreed that this is represents a meaningful benefit for a person living with SCLC, particularly as the person's life expectancy is months rather than years at diagnosis. In the PCI group, fewer people experienced cancer progression and symptomatic brain metastases compared to the observation only group.

It is not possible to assess the effects of PCI on adverse events from Slotman 2007 because the adverse event data was only collected from the PCI arm. The investigators wrote that some of the adverse events in the PCI arm were not from the

PCI intervention but were from brain metastases that developed. Takahashi 2017 may shed some light on the possible harms of PCI: Takahashi 2017 found an increased risk ratio for all grades of nausea, vomiting, anorexia, malaise or dermatitis at 3 months for PCI compared to observation. However, these were mostly grade 1 and grade 2 adverse events. Consequently, the committee agreed that these adverse events would require no or minimal medical intervention. The data could not differentiate for any adverse event grade 3 or above. However, the study was not powered with a view to doing this.

Takahashi 2017 could not differentiate for mortality. The committee agreed that interpreting this to mean that PCI is an unnecessary intervention in the UK would be misleading. This is because participants in both arms were followed up with brain MRIs at 3, 6, 9, 12, 18 and at 24 months: participants found to have asymptomatic metastases were treated with chemotherapy and radiotherapy. The committee considered this follow-up regimen for adoption in the UK. However, this study was not designed to investigate the clinical effectiveness of the follow up: both arms had it, and different follow up regimes was also outside of the scope of the review. In addition, it is very unlikely that the thoroughness of this follow up could be provided in the UK: there are approximately 9 times more MRI scanners in Japan compared to the UK.

The committee agreed that “consider” is the appropriate strength for the recommendation on PCI. This is because there is a mix of evidence in the two main trials. In addition, in the clinical experience of the committee, PCI is beneficial in a small and selected subgroup of people. The committee pointed out that both Slotman 2007 and Takahashi 2017 had exclusion criteria. These exclusion criteria included low performance status, life expectancy less than 3 months, age over 75 years, mental disorders, not being able to give informed consent and not being able to comply with the protocol and follow-up schedule. While not explicitly listed in the recommendation, these exclusion criteria reflect current UK practice when considering PCI. They felt that clinicians would be able to select which people were likely to benefit from PCI on a case-by-case basis.

The committee agreed that their recommendation should restrict consideration of PCI to people whose disease has responded to first-line treatment in order to reflect the inclusion criteria in Slotman 2007 and Takahashi 2017.

Cost effectiveness and resource use

No published cost-effectiveness evidence was identified and this question was not prioritised for original health economic modelling so a simple QALYs-only analysis (see Appendix I – QALY Analysis) was produced to help the committee with decision making.

The committee considered the original QALYs-only analysis produced for this guideline and noted that, if the levels of benefit in the Slotman 2007 trial, on which the analysis was based, were applicable to the current UK population then PCI would be associated with a mean benefit of 4 progression free life weeks, 14 total life weeks and 0.133 QALYs.

They noted several limitations of the analysis including that the utility data were drawn from a population with advanced SCLC, that side effects were assumed not to meaningfully affect QALYs and that no specific or general resource uses associated with the two strategies were included. Nevertheless, they considered the cost of delivering PCI and the level of benefit predicted by the model along with a simple threshold analysis that calculated the ICERs at various levels of general management cost for people with ES-SCLC and agreed that although some uncertainty exists around the cost effectiveness of PCI at £20,000/QALY, the ICER would be unlikely to be as high as £30,000/QALY. Furthermore, they noted that PCI and thoracic radiotherapy (TRT) are sometimes delivered together and that some, if not all, resource uses (appointments e.g.) can be shared between the two. Delivering both together is therefore likely to be cost effective because TRT is also associated with QALY gains (see RQ 3.5 of this update).

The committee noted that the PCI and TRT are both currently considered on a patient by patient basis on the balance of benefits and harms and they therefore thought that their recommendations would lead to a negligible difference in resource use.

Other factors the committee took into account

The committee gave special consideration to people living in deprived areas regarding access to this treatment. This is because socioeconomic status was identified as a potential equality issue in the equity impact assessment. However, the committee agreed that no additional recommendations were necessary. The committee did not have any reason to believe that the interventions work better or worse in different groups.

Appendix A – Review protocols

Review protocol for the clinical and cost-effectiveness of prophylactic cranial irradiation to prevent brain metastases in people with extensive SCLC?

Field (based on PRISMA-P)	Content
Review question	What is the clinical and cost-effectiveness of prophylactic cranial irradiation to prevent brain metastases in people with extensive SCLC?
Type of review question	Intervention
Objective of the review	This area was identified as requiring updating during the scoping phase of the update. The aim is to update the existing recommendation to offer prophylactic cranial irradiation to people with extensive SCLC in light of new evidence.
Eligibility criteria – population	People with extensive SCLC who are not known to have brain metastases.

Eligibility criteria – interventions	Prophylactic cranial irradiation
Eligibility criteria – comparator	Standard care

Outcomes and prioritisation	• Mortality
	  ○ cancer-related
	  ○ treatment-related
	  ○ all-cause
	• Quality of life (as measured by QoL instrument, for example)
	  ○ ECOG score
	  ○ EORTC score
	  ○ EQ-5D
	• Length of stay
	  ○ hospital
	  ○ ICU
	• Adverse events
	  ○ Cognitive impairment (incidence of or mean change in cognitive scores)
	• Treatment-related dropout rates
	• Presence of brain metastasis – limited vs extensive stage (whatever grade/staging is available)

Eligibility criteria – study design	• RCTs • Systematic reviews of RCTs • If no RCT data available, then quasi-randomised controlled trials or prospective observational data will be considered
Other inclusion exclusion criteria	• Non- English-language papers • Unpublished evidence/ conference proceedings
Proposed sensitivity/sub-group analysis, or meta-regression	Pre-existing performance status defined by ECOG and Karnofsky performance status scale
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See Methods Appendix B
Information sources – databases and dates	See Appendix C

	Main Searches: • Cochrane Database of Systematic Reviews – CDSR • Cochrane Central Register of Controlled Trials – CENTRAL • Database of Abstracts of Reviews of Effects – DARE • Health Technology Assessment Database – HTA • EMBASE (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) Citation searching will be carried out in addition on analyst/committee selected papers. The search will not be date limited because this is a new review question. Economics: • NHS Economic Evaluation Database – NHS EED • Health Economic Evaluations Database – HEED • EconLit (Ovid) • Embase (Ovid) • MEDLINE (Ovid) • MEDLINE In-Process (Ovid) The search will not be date limited because this is a new review question.

Identify if an update	This is to update the following recommendation: 1.4.54 Offer prophylactic cranial irradiation to patients with extensive-stage disease SCLC and WHO performance status 2 or less, if their disease has not progressed on first-line treatment. [new 2011]
Author contacts	Guideline update
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix C
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix F (clinical evidence tables) or I (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix F (clinical evidence tables) or I (economic evidence tables).
Methods for assessing bias at outcome/study level	See Appendix B
Criteria for quantitative synthesis	See Appendix B

Methods for quantitative analysis – combining studies and exploring (in)consistency	See Appendix B
Meta-bias assessment – publication bias, selective reporting bias	See Appendix B
Confidence in cumulative evidence	See Appendix B
Rationale/context – what is known	For details please see the introduction to the evidence review in the main file.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the evidence review. The committee was convened by the NICE Guideline Updates Team and chaired by Gary McVeigh in line with section 3 of Developing NICE guidelines: the manual. Staff from the NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the evidence review in collaboration with the committee. For details please see Developing NICE guidelines: the manual.
Sources of funding/support	The NICE Guideline Updates Team is an internal team within NICE.
Name of sponsor	The NICE Guideline Updates Team is an internal team within NICE.

Roles of sponsor	The NICE Guideline Updates Team is an internal team within NICE.
PROSPERO registration number	N/A

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Appendix B – Methods

Priority screening

The reviews undertaken for this guideline all made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. This uses a machine learning algorithm (specifically, an SGD classifier) to take information on features (1, 2 and 3 word blocks) in the titles and abstract of papers marked as being 'includes' or 'excludes' during the title and abstract screening process, and re-orders the remaining records from most likely to least likely to be an include, based on that algorithm. This re-ordering of the remaining records occurs every time 25 additional records have been screened.

Research is currently ongoing as to what are the appropriate thresholds where reviewing of abstract can be stopped, assuming a defined threshold for the proportion of relevant papers it is acceptable to miss on primary screening. As a conservative approach until that research has been completed, the following rules were adopted during the production of this guideline:

- In every review, at least 50% of the identified abstract (or 1,000 records, if that is a greater number) were always screened.
- After this point, screening was only terminated when the threshold was reached for a number of abstracts being screened without a single new include being identified. This threshold was set according to the expected proportion of includes in the review (with reviews with a lower proportion of includes needing a higher number of papers without an identified study to justify termination), and was always a minimum of 250.
- A random 10% sample of the studies remaining in the database when the threshold were additionally screened, to check if a substantial number of relevant studies were not being correctly classified by the algorithm, with the full database being screened if concerns were identified.

As an additional check to ensure this approach did not miss relevant studies, the included studies lists of included systematic reviews were searched to identify any papers not identified through the primary search.

Incorporating published systematic reviews

For all review questions where a literature search was undertaken looking for a particular study design, systematic reviews containing studies of that design were also included. All included studies from those systematic reviews were screened to identify any additional relevant primary studies not found as part of the initial search.

Quality assessment

Individual systematic reviews were quality assessed using the ROBIS tool, with each classified into one of the following three groups:

- High quality – It is unlikely that additional relevant and important data would be identified from primary studies compared to that reported in the review, and unlikely that any relevant and important studies have been missed by the review.

- Moderate quality – It is possible that additional relevant and important data would be identified from primary studies compared to that reported in the review, but unlikely that any relevant and important studies have been missed by the review.
- Low quality – It is possible that relevant and important studies have been missed by the review.

Each individual systematic review was also classified into one of three groups for its applicability as a source of data, based on how closely the review matches the specified review protocol in the guideline. Studies were rated as follows:

- Fully applicable – The identified review fully covers the review protocol in the guideline.
- Partially applicable – The identified review fully covers a discrete subsection of the review protocol in the guideline (for example, some of the factors in the protocol only).
- Not applicable – The identified review, despite including studies relevant to the review question, does not fully cover any discrete subsection of the review protocol in the guideline.

1.2.2 Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 2. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 2: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.
Moderate	Fully applicable	Details of included studies were used instead of undertaking a new literature search. Full-text papers of included studies were still retrieved for the purposes of data analysis. Searches were only done to cover the period of time since the search date of the review.

Quality	Applicability	Use of systematic review
Moderate	Partially applicable	Details of included studies were used instead of undertaking a new literature search for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date of the review. For other sections not covered by the systematic review, searches were undertaken as normal.

1.3 Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of quantitative studies for each outcome. For continuous outcomes analysed as mean differences, where change from baseline data were reported in the trials and were accompanied by a measure of spread (for example standard deviation), these were extracted and used in the meta-analysis. Where measures of spread for change from baseline values were not reported, the corresponding values at study end were used and were combined with change from baseline values to produce summary estimates of effect. These studies were assessed to ensure that baseline values were balanced across the treatment groups; if there were significant differences at baseline these studies were not included in any meta-analysis and were reported separately. For continuous outcomes analysed as standardised mean differences, where only baseline and final time point values were available, change from baseline standard deviations were estimated, assuming a correlation coefficient of 0.5.

1.4 Evidence of effectiveness of interventions

1.4.1 Quality assessment

Individual RCTs and quasi-randomised controlled trials were quality assessed using the Cochrane Risk of Bias Tool. Other study were quality assessed using the ROBINS-I tool. Each individual study was classified into one of the following three groups:

- Low risk of bias – The true effect size for the study is likely to be close to the estimated effect size.
- Moderate risk of bias – There is a possibility the true effect size for the study is substantially different to the estimated effect size.
- High risk of bias – It is likely the true effect size for the study is substantially different to the estimated effect size.

Each individual study was also classified into one of three groups for directness, based on if there were concerns about the population, intervention, comparator and/or outcomes in the study and how directly these variables could address the specified review question. Studies were rated as follows:

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.

- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

Meta-analyses of interventional data were conducted with reference to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2011).

Where different studies presented continuous data measuring the same outcome but using different numerical scales (e.g. a 0-10 and a 0-100 visual analogue scale), these outcomes were all converted to the same scale before meta-analysis was conducted on the mean differences. Where outcomes measured the same underlying construct but used different instruments/metrics, data were analysed using standardised mean differences (Hedges' g).

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method) reporting numbers of people having an event, and a pooled incidence rate ratio was calculated for dichotomous outcomes reporting total numbers of events. Both relative and absolute risks were presented, with absolute risks calculated by applying the relative risk to the pooled risk in the comparator arm of the meta-analysis (all pooled trials).

Fixed- and random-effects models (der Simonian and Laird) were fitted for all syntheses, with the presented analysis dependent on the degree of heterogeneity in the assembled evidence. Fixed-effects models were the preferred choice to report, but in situations where the assumption of a shared mean for fixed-effects model were clearly not met, even after appropriate pre-specified subgroup analyses were conducted, random-effects results are presented. Fixed-effects models were deemed to be inappropriate if one or both of the following conditions was met:

- Significant between study heterogeneity in methodology, population, intervention or comparator was identified by the reviewer in advance of data analysis. This decision was made and recorded before any data analysis was undertaken.
- The presence of significant statistical heterogeneity in the meta-analysis, defined as $I^2 \geq 50\%$.

In any meta-analyses where some (but not all) of the data came from studies at high risk of bias, a sensitivity analysis was conducted, excluding those studies from the analysis. Results from both the full and restricted meta-analyses are reported. Similarly, in any meta-analyses where some (but not all) of the data came from indirect studies, a sensitivity analysis was conducted, excluding those studies from the analysis.

Meta-analyses were performed in Cochrane Review Manager V5.3, with the exception of incidence rate ratio analyses which were carried out in R version 3.3.4.

Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. However, no relevant MIDs were found. In addition, the Guideline Committee were asked to specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one

intervention is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin. However, the committee agreed that in their experience, they could not define any MIDs. This is because the committee agreed that the protocol outcomes were objective rather than subjective measures and the committee were not aware of evidence supporting the use of MIDs for the protocol's outcomes. Therefore, the line of no effect was used as the MID for risk ratios, hazard ratios and mean differences.

GRADE for pairwise meta-analyses of interventional evidence

GRADE was used to assess the quality of evidence for the selected outcomes as specified in 'Developing NICE guidelines: the manual (2014)'. Data from all study designs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point, based on the criteria given in **Error! Reference source not found.**

Table 3: Rationale for downgrading quality of evidence for intervention studies

GRADE criteria	Reasons for downgrading quality
Risk of bias	Not serious: If less than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from studies at moderate or high risk of bias, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from studies at high risk of bias, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies at high and low risk of bias.
Indirectness	Not serious: If less than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the overall outcome was not downgraded. Serious: If greater than 33.3% of the weight in a meta-analysis came from partially indirect or indirect studies, the outcome was downgraded one level. Very serious: If greater than 33.3% of the weight in a meta-analysis came from indirect studies, the outcome was downgraded two levels. Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between direct and indirect studies.
Inconsistency	Concerns about inconsistency of effects across studies, occurring when there is unexplained variability in the treatment effect demonstrated across studies (heterogeneity), after appropriate pre-specified subgroup analyses have been conducted. This was assessed using the I^2 statistic. N/A: Inconsistency was marked as not applicable if data on the outcome was only available from one study. Not serious: If the I^2 was less than 33.3%, the outcome was not downgraded. Serious: If the I^2 was between 33.3% and 66.7%, the outcome was downgraded one level. Very serious: If the I^2 was greater than 66.7%, the outcome was downgraded two levels.

GRADE criteria	Reasons for downgrading quality
	Outcomes meeting the criteria for downgrading above were not downgraded if there was evidence the effect size was not meaningfully different between studies with the smallest and largest effect sizes.
Imprecision	If an MID other than the line of no effect was defined for the outcome, the outcome was downgraded once if the 95% confidence interval for the effect size crossed one line of the MID, and twice if it crosses both lines of the MID. If the line of no effect was defined as an MID for the outcome, it was downgraded once if the 95% confidence interval for the effect size crossed the line of no effect (i.e. the outcome was not statistically significant), and twice if the sample size of the study was sufficiently small that it is not plausible any realistic effect size could have been detected. Outcomes meeting the criteria for downgrading above were not downgraded if the confidence interval was sufficiently narrow that the upper and lower bounds would correspond to clinically equivalent scenarios.

The quality of evidence for each outcome was upgraded if any of the following three conditions were met:

- Data from non-randomised studies showing an effect size sufficiently large that it cannot be explained by confounding alone.
- Data showing a dose-response gradient.
- Data where all plausible residual confounding is likely to increase our confidence in the effect estimate.

Publication bias

Publication bias was assessed in two ways. First, if evidence of conducted but unpublished studies was identified during the review (e.g. conference abstracts, trial protocols or trial records without accompanying published data), available information on these unpublished studies was reported as part of the review. Secondly, where 10 or more studies were included as part of a single meta-analysis, a funnel plot was produced to graphically assess the potential for publication bias.

Evidence statements

Evidence statements for pairwise intervention data are classified in to one of four categories:

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.
- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is 'statistically significant'), but the magnitude of that effect is most likely to be less than the MID (i.e. the point estimate is in the zone of equivalence). In such cases, we state that the evidence could not demonstrate a meaningful difference.
- Situations where the confidence limits are smaller than the MIDs in both directions. In such cases, we state that the evidence demonstrates that there is no meaningful difference.

- In all other cases, we state that the evidence could not differentiate between the comparators.

For outcomes without a defined MID or where the MID is set as the line of no effect (for example, in the case of mortality), evidence statements are divided into 2 groups as follows:

- We state that the evidence showed that there is an effect if the 95% CI does not cross the line of no effect.
- The evidence could not differentiate between comparators if the 95% CI crosses the line of no effect.

1.5 Health economics

Literature reviews seeking to identify published cost–utility analyses of relevance to the issues under consideration were conducted for all questions. In each case, the search undertaken for the clinical review was modified, retaining population and intervention descriptors, but removing any study-design filter and adding a filter designed to identify relevant health economic analyses. In assessing studies for inclusion, population, intervention and comparator, criteria were always identical to those used in the parallel clinical search; only cost–utility analyses were included. Economic evidence profiles, including critical appraisal according to the Guidelines manual, were completed for included studies.

Economic studies identified through a systematic search of the literature are appraised using a methodology checklist designed for economic evaluations (NICE guidelines manual; 2014). This checklist is not intended to judge the quality of a study per se, but to determine whether an existing economic evaluation is useful to inform the decision-making of the committee for a specific topic within the guideline.

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 4.

Table 4 Applicability criteria

Level	Explanation
Directly applicable	The study meets all applicability criteria, or fails to meet one or more applicability criteria but this is unlikely to change the conclusions about cost effectiveness
Partially applicable	The study fails to meet one or more applicability criteria, and this could change the conclusions about cost effectiveness
Not applicable	The study fails to meet one or more applicability criteria, and this is likely to change the conclusions about cost effectiveness. These studies are excluded from further consideration

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 5.

Table 5 Methodological criteria

Level	Explanation
Minor limitations	Meets all quality criteria, or fails to meet one or more quality criteria but this is unlikely to change the conclusions about cost effectiveness
Potentially serious limitations	Fails to meet one or more quality criteria and this could change the conclusions about cost effectiveness
Very serious limitations	Fails to meet one or more quality criteria and this is highly likely to change the conclusions about cost effectiveness. Such studies should usually be excluded from further consideration

Where relevant, a summary of the main findings from the systematic search, review and appraisal of economic evidence is presented in an economic evidence profile alongside the clinical evidence.

Appendix C – Literature search strategies

Scoping search strategies

Scoping searches Scoping searches were undertaken on the following websites and databases (listed in alphabetical order) in April 2017 to provide information for scope development and project planning. Browsing or simple search strategies were employed.

Guidelines/website
American Cancer Society
American College of Chest Physicians
American Society for Radiation Oncology
American Thoracic Society
Association for Molecular Pathology
British Lung Foundation
British Thoracic Society
Canadian Medical Association Infobase
Canadian Task Force on Preventive Health Care
Cancer Australia
Cancer Care Ontario
Cancer Control Alberta
Cancer Research UK
Care Quality Commission
College of American Pathologists
Core Outcome Measures in Effectiveness Trials (COMET)
Department of Health & Social Care
European Respiratory Society
European Society for Medical Oncology
European Society of Gastrointestinal Endoscopy
European Society of Thoracic Surgery
General Medical Council
Guidelines & Audit Implementation Network (GAIN)
Guidelines International Network (GIN)
Healthtalk Online
International Association for the Study of Lung Cancer
MacMillan Cancer Support
Medicines and Products Regulatory Agency (MHRA)
National Audit Office
National Cancer Intelligence Network
National Clinical Audit and Patient Outcomes Programme
National Health and Medical Research Council - Australia
National Institute for Health and Care Excellence (NICE) - published & in development guidelines
National Institute for Health and Care Excellence (NICE) - Topic Selection
NHS Choices
NHS Digital

Guidelines/website
NHS England
NICE Clinical Knowledge Summaries (CKS)
NICE Evidence Search
Office for National Statistics
Patient UK
PatientVoices
Public Health England
Quality Health
Royal College of Anaesthetists
Royal College of General Practitioners
Royal College of Midwives
Royal College of Nursing
Royal College of Pathologists
Royal College of Physicians
Royal College of Radiologists
Royal College of Surgeons
Scottish Government
Scottish Intercollegiate Guidelines Network (SIGN)
UK Data Service
US National Guideline Clearinghouse
Walsall community Health NHS Trust
Welsh Government

Clinical search literature search strategy

Main searches

Bibliographic databases searched for the guideline

- Cochrane Database of Systematic Reviews – CDSR (Wiley)
- Cochrane Central Register of Controlled Trials – CENTRAL (Wiley)
- Database of Abstracts of Reviews of Effects – DARE (Wiley)
- Health Technology Assessment Database – HTA (Wiley)
- EMBASE (Ovid)
- MEDLINE (Ovid)
- MEDLINE Epub Ahead of Print (Ovid)
- MEDLINE In-Process (Ovid)

Identification of evidence for review questions

The searches were conducted between October 2017 and April 2018 for 9 review questions (RQ).

Searches were re-run in May 2018.

Where appropriate, in-house study design filters were used to limit the retrieval to, for example, randomised controlled trials. Details of the study design filters used can be found in section 3.

Search strategy

Medline Strategy, searched 16th October 2017 (with date limit) & 6th November 2017 (without date limit)
Database: Ovid MEDLINE(R) 1946 to October Week 4 2017
Search Strategy:
1 exp Lung Neoplasms/
2 ((lung* or pulmonary or bronch*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or lymphoma* or metast* or malignan* or blastoma* or carcinogen* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or microcytic*)).tw.
3 ((pancoast* or superior sulcus or pulmonary sulcus) adj4 (tumo?r* or syndrome*)).tw.
4 ((lung* or pulmonary or bronch*) adj4 (oat or small or non-small) adj4 cell*).tw.
5 (SCLC or NSCLC).tw.
6 or/1-5
7 exp Central Nervous System Neoplasms/
8 ((central nervous system* or CNS or cerebrospinal axi*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or lymphoma* or metast* or malignan* or blastoma* or carcinogen* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or microcytic* or disease*)).tw.
9 ((brain* or encephalon* or cerebr* or intracranial* or supratentorial* or cerebell*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or lymphoma* or metast* or malignan* or blastoma* or carcinogen* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or microcytic* or disease*)).tw.
10 ((gr?y or white) adj2 matter* adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or lymphoma* or metast* or malignan* or blastoma* or carcinogen* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or microcytic* or disease*)).tw.
11 ((mening* or leptomening*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or lymphoma* or metast* or malignan* or blastoma* or carcinogen* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or microcytic* or disease*)).tw.
12 (meningeoma* or meningothelioma*).tw.
13 Spinal Neoplasms/
14 ((spine or spinal* or intraspin* or dorsal* or vertebra* or myelon* or epidural* or dural*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or lymphoma* or metast* or malignan* or blastoma* or carcinogen* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or microcytic* or disease*)).tw.
15 or/7-14
16 exp Brain/
17 exp Meninges/
18 (brain* or encephalon* or cerebr* or intracranial* or supratentorial* or cerebell or mening* or leptomening*).tw.
19 ((gr?y or white) adj2 matter*).tw.
20 (single or solitary or singular).tw.
21 or/16-20

Medline Strategy, searched 16th October 2017 (with date limit) & 6th November 2017 (without date limit)
Database: Ovid MEDLINE(R) 1946 to October Week 4 2017
Search Strategy:
22 exp Neoplasm Metastasis/
23 exp Carcinoma/
24 (metast* or carcinoma* or carcinosis or carcinomatosis or epithelioma*).tw. (830586)
25 ((cancer* or neoplasm* or tumo?r* or lymphoma* or malignan* or blastoma* or carcinogen* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or microcytic*) adj3 (spread* or disseminat* or secondary* or migrat* or advanc* or termina* or involv*)).tw.
26 or/22-25
27 21 and 26
28 15 or 27
29 exp Cranial Irradiation/
30 ((cranial* or skull* or cranium* or calvari* or pituitar* or hypophys* or infundibl* or infracerebral*) adj4 (irradiat* or radiat* or radio*)).tw.
31 (PCI or PCRT).tw.
32 ((whole or full or total or complete or entire or thorough or comprehensive or extensive) adj4 (brain* or encephalon* or cerebr* or intracranial* or supratentorial* or cerebell or mening* or leptomening*) adj4 (irradiat* or radiat* or radio*)).tw.
33 WBRT.tw.
34 exp Brain Neoplasms/rt [Radiotherapy]
35 exp Meningeal Neoplasms/rt [Radiotherapy]
36 Radiosurgery/
37 radiosurg*.tw.
38 ((stereotac* or stereotax* or gamma* or linear or LINAC or cyberkni*) adj4 radiotherap*).tw.
39 or/29-38
40 6 and 28 and 39
41 Animals/ not Humans/
42 40 not 41
43 limit 42 to english language

Note: In-house RCT, observational studies and systematic review filters were appended. A date limit was originally applied (16th October 2017) and then removed following first review of the evidence.

244 Study Design Filters

The MEDLINE SR, RCT, and observational studies filters are presented below.
Systematic Review
1. Meta-Analysis.pt.
2. Meta-Analysis as Topic/
3. Review.pt.
4. exp Review Literature as Topic/
5. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
6. (review$ or overview$).ti.
7. (systematic$ adj5 (review$ or overview$)).tw.

The MEDLINE SR, RCT, and observational studies filters are presented below.
8. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw. 9. ((studies or trial$) adj2 (review$ or overview$)).tw. 10. (integrat$ adj3 (research or review$ or literature)).tw. 11. (pool$ adj2 (analy$ or data)).tw. 12. (handsearch$ or (hand adj3 search$)).tw. 13. (manual$ adj3 search$).tw. 14. or/1-13 15. animals/ not humans/ 16. 14 not 15
RCT 1 Randomized Controlled Trial.pt. 2 Controlled Clinical Trial.pt. 3 Clinical Trial.pt. 4 exp Clinical Trials as Topic/ 5 Placebos/ 6 Random Allocation/ 7 Double-Blind Method/ 8 Single-Blind Method/ 9 Cross-Over Studies/ 10 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw. 11 (random$ adj3 allocat$).tw. 12 placebo$.tw. 13 ((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw. 14 (crossover$ or (cross adj over$)).tw. 15 or/1-14 16 animals/ not humans/ 17 15 not 16
Observational 1 Observational Studies as Topic/ 2 Observational Study/ 3 Epidemiologic Studies/ 4 exp Case-Control Studies/ 5 exp Cohort Studies/ 6 Cross-Sectional Studies/ 7 Controlled Before-After Studies/ 8 Historically Controlled Study/ 9 Interrupted Time Series Analysis/ 10 Comparative Study.pt. 11 case control$.tw. 12 case series.tw. 13 (cohort adj (study or studies)).tw. 14 cohort analy$.tw. 15 (follow up adj (study or studies)).tw. 16 (observational adj (study or studies)).tw. 17 longitudinal.tw. 18 prospective.tw. 19 retrospective.tw.

The MEDLINE SR, RCT, and observational studies filters are presented below.
20 cross sectional.tw.
21 or/1-20

Health Economics literature search strategy

Sources searched to identify economic evaluations

- NHS Economic Evaluation Database – NHS EED (Wiley) last updated Apr 2015
- Health Technology Assessment Database – HTA (Wiley) last updated Oct 2016
- Embase (Ovid)
- MEDLINE (Ovid)
- MEDLINE In-Process (Ovid)

Search filters to retrieve economic evaluations and quality of life papers were appended to the review question search strategies. For some health economics strategies additional terms were added to the original review question search strategies (see sections 4.2, 4.3 and 4.4) The searches were conducted between October 2017 and April 2018 for 9 review questions (RQ).

Searches were re-run in May 2018.

Searches were limited to those in the English language. Animal studies were removed from results.

Economic evaluation and quality of life filters

Medline Strategy
Economic evaluations
1 Economics/
2 exp "Costs and Cost Analysis"/
3 Economics, Dental/
4 exp Economics, Hospital/
5 exp Economics, Medical/
6 Economics, Nursing/
7 Economics, Pharmaceutical/
8 Budgets/
9 exp Models, Economic/
10 Markov Chains/
11 Monte Carlo Method/
12 Decision Trees/
13 econom$.tw.
14 cba.tw.
15 cea.tw.
16 cua.tw.
17 markov$.tw.
18 (monte adj carlo).tw.

Medline Strategy
19 (decision adj3 (tree$ or analys$)).tw.
20 (cost or costs or costing$ or costly or costed).tw.
21 (price$ or pricing$).tw.
22 budget$.tw.
23 expenditure$.tw.
24 (value adj3 (money or monetary)).tw.
25 (pharmacoeconomic$ or (pharmaco adj economic$)).tw.
26 or/1-25
Quality of life
1 "Quality of Life"/
2 quality of life.tw.
3 "Value of Life"/
4 Quality-Adjusted Life Years/
5 quality adjusted life.tw.
6 (qaly$ or qald$ or qale$ or qtime$).tw.
7 disability adjusted life.tw.
8 daly$.tw.
9 Health Status Indicators/
10 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).tw.
11 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
12 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.

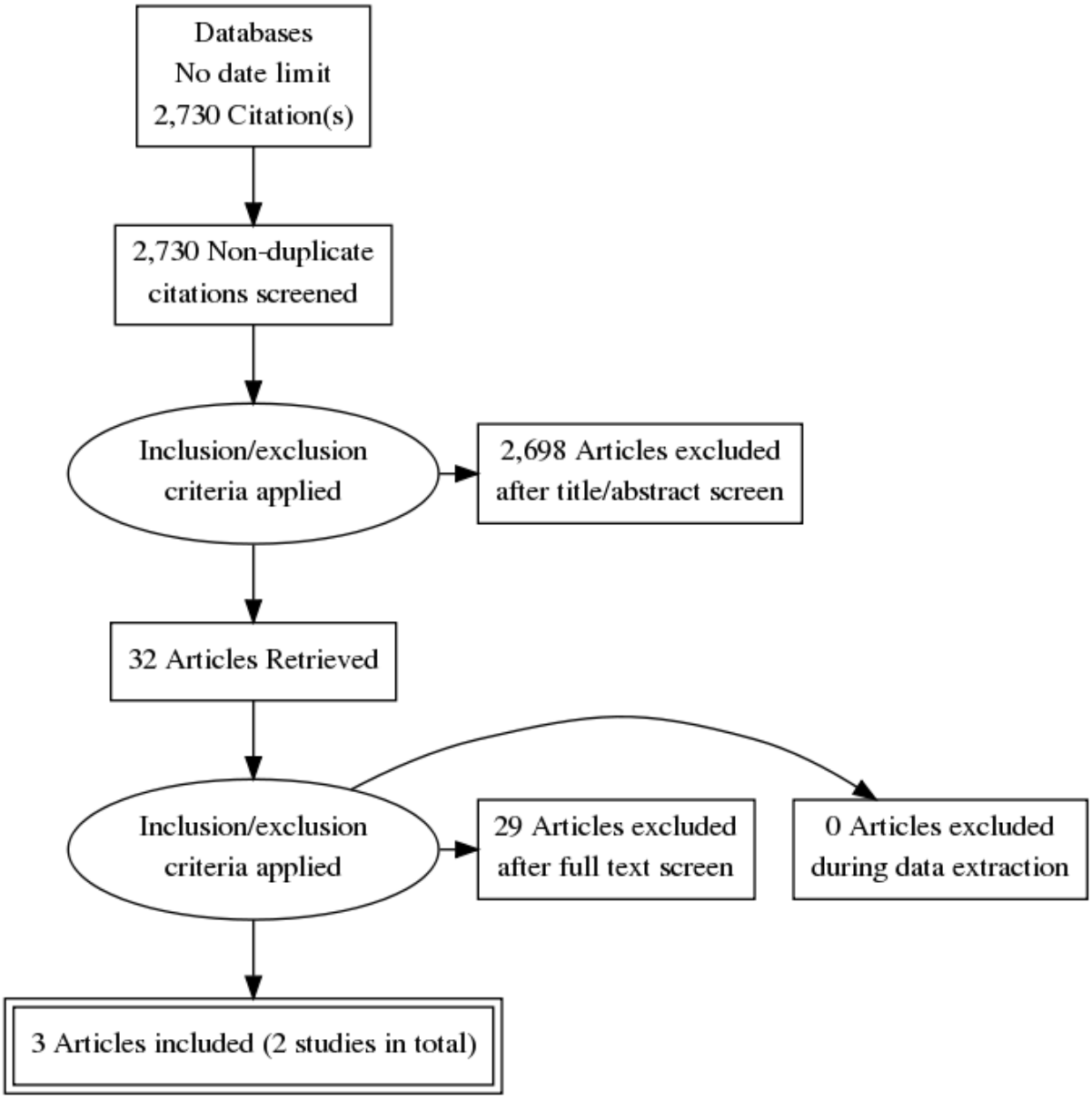
Medline Strategy	
31	or/1-30

261

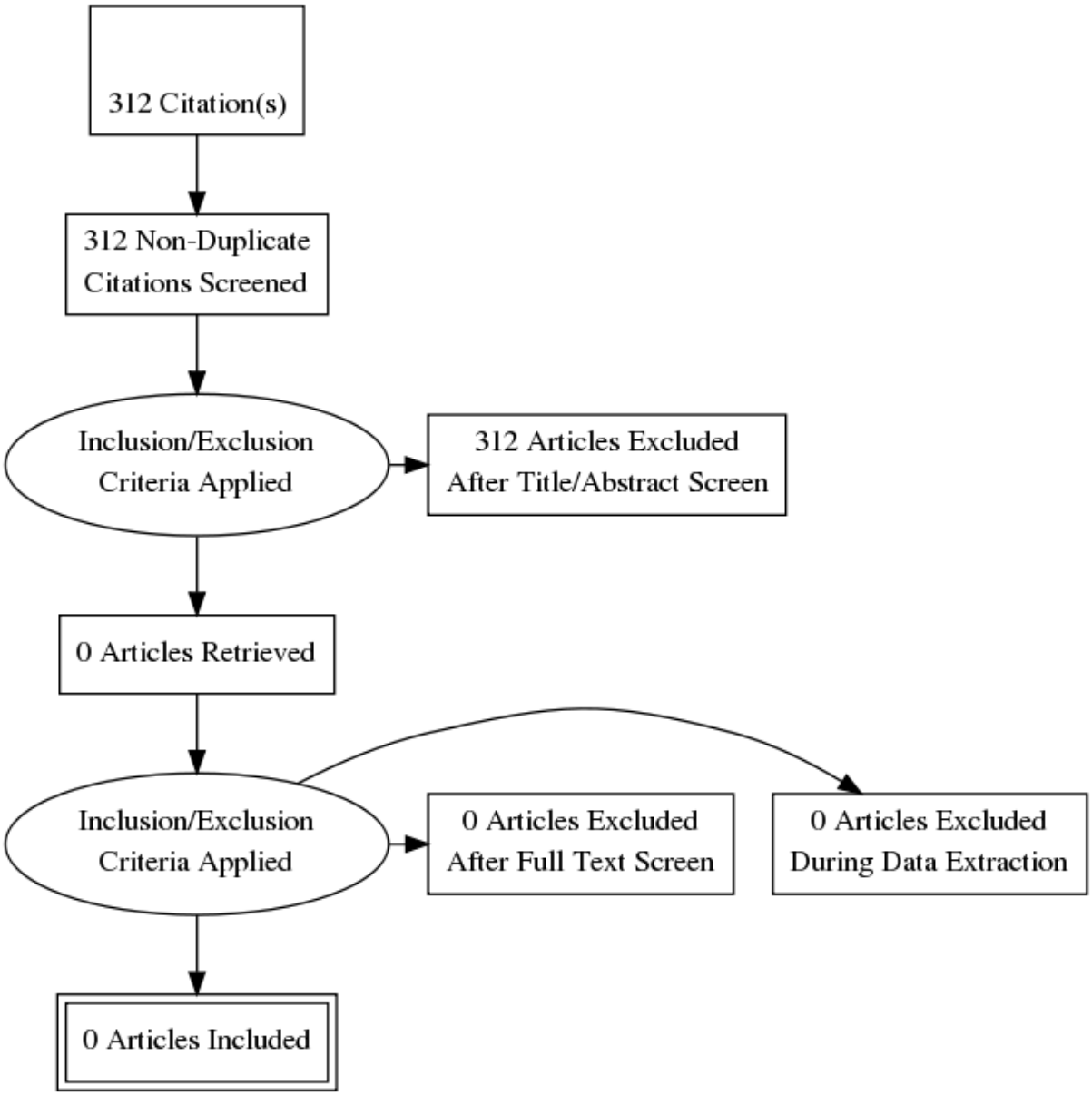
262
263

Appendix D – Evidence study selection

Clinical Evidence study selection



269 **Economic Evidence study selection**



270
271

Appendix E – Clinical evidence tables

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
Slotman 2007 (Including Slotman 2009)	Prophylactic cranial irradiation in extensive small-cell lung cancer (Including Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms: results of an international Phase III randomized controlled trial by the EORTC Radiation Oncology and Lung Cancer Groups)	**Study type** • Randomised controlled trial *This study also includes the paper Slotman 2009 ("Prophylactic cranial irradiation in extensive disease small-cell lung cancer: short-term health-related quality of life and patient reported symptoms - results of an international phase III randomized controlled trial by the EORTC radiation oncology and lung cancer groups")* **Study details** • Study location *The Netherlands, UK, Egypt, Poland, Belgium, Cyprus, Turkey, Italy, Israel, Hungary* • Study setting *Hospitals* • Study dates *Recruitment was between February 2001 to March 2006. The time of analysis was October 2006* • Duration of follow-up *12 months* • Sources of funding *Supported by grants from the National Cancer Institute and by funds from the Dutch Cancer Society for local data management. One of the ten investigators reported receiving consulting fees from Astra-Zeneca, GlaxoSmithKline, Transgene, and Transave; lecture fees from Roche, GlaxoSmithKline, Eli Lilly, and Abraxis; and grant support from Actelion, Roche, and GlaxoSmithKline.*	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias *Not mentioned* **Blinding of participants and personnel** • Unclear risk of bias *Not mentioned but this might not be possible* **Blinding of outcome assessment** • High risk of bias *There was no blinding. Some of the outcomes could be influenced by lack of blinding of outcome assessment: quality of life and symptoms of brain metastasis* **Incomplete outcome data** • High risk of bias *The rate of compliance with the quality-of-life assessment was 93.7% at baseline and decreased to 46.3% at 9 months (PCI: 45 returned forms expected, 21 received; observation: 37 returned forms expected, 17 received). This is a compliance rate of well under 80%, which is the generally accepted cut-off point for an acceptable compliance threshold or*

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
		Inclusion criteria • Cytologically/histologically confirmed extensive SCLC, defined as disease beyond the hemithorax and supraclavicular nodes or pleural effusion containing tumour cells • No evidence of brain or leptomeningeal metastases **Exclusion criteria** • History of radiotherapy to the irradiation field for prophylactic cranial irradiation • Any active concomitant malignancy • Under 18 years of age • Over 75 years of age • Performance status above 2, according to the WHO • No response to 4 to 6 cycles of initial chemotherapy *No specific criteria for a treatment response were defined; any response, as judged by the local investigator, was acceptable.* • An interval of more than 5 weeks between the last cycle of chemotherapy and randomisation • History of corticosteroid use • Previous cancer **Sample characteristics** • Sample size *286 people* • Split between study groups *PCI group: n= 143; no routine MRI follow-up group: n=143* • Loss to follow-up *None*	*dropping out threshold. The most common reason was administrative failure (40.1%).* **Selective reporting** • High risk of bias *Adverse events were only reported for the PCI group. Although we might expect more adverse events for the PCI group, not recording adverse events in the observation group means that a comparison cannot be made.* **Other sources of bias** • High risk of bias *The authors wrote in the methods section that the staging and follow-up procedures were not standardised for all the centres involved. Treatment for progression was not part of the protocol and was left to each centre's policy. Radiotherapy for symptomatic brain metastases was administered in 2 of 24 patients in the irradiation group (8.3%), as compared with 35 of 59 patients in the control group (59.3%). Treatment for extracranial progression (mostly consisting of chemotherapy, radiotherapy, or both) was given to 68.0% of patients in the irradiation group and 45.1% in the control group.* **Overall risk of bias** • High **Directness**

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
		• %female *PCI group: 32.2% women; no routine MRI follow-up group: 42.7% women* • Median age (range) *PCI group: 62 years (37-75); Observation only group: 63 years (39-75)* Pre-intervention procedures • Dependent on centre *Each centre specified whether contrast-enhanced CT, magnetic resonance imaging (MRI), or both of the brain would be performed before chemotherapy or after chemotherapy. Each centre had to adhere to this policy for all patients in both study groups.* **Interventions** • Prophylactic cranial irradiation (PCI) *Radiation to the intracranial content (planning target volume) was administered with the use of two opposed lateral fields with a linear accelerator (4 to 18 MV) or cobalt unit. Each field was treated daily on a schedule of four to five fractions per week. The dose was specified to the midline. The following schedules for cranial irradiation could be used: 20 Gy in 5 or 8 fractions, 24 Gy in 12 fractions, 25 Gy in 10 fractions, or 30 Gy in 10 or 12 fractions. The biologically equivalent doses for these schedules range from 25 to 39 Gy. Each center had to select one of these schedules and had to adhere to it for all study patients. Radiotherapy had to start 4 to 6 weeks after chemotherapy. The fractionation schedules that were most commonly used in the irradiation group were 20 Gy given in 5 fractions (89 patients), 30 Gy given in 10 fractions (23 patients), 30 Gy given in 12 fractions (9 patients), and 25 Gy given in 10 fractions (7 patients). Other schedules were used infrequently (six patients).*	• Partially directly applicable *Because the staging and follow-up procedures were not standardised for all the centres involved, it is difficult to judge how applicable the results are.*

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
		• No routine MRI follow-up **Follow-up** • Medical history and physical examination *Follow-up at 6 weeks and 3, 6, 9, and 12 months after randomisation and thereafter every 6 months. This included review of a checklist for key symptoms of brain metastases. Completion of surveys regarding quality of life.* • Contrast-enhanced CT or MRI brain if any suspicion of brain metastasis **Outcome measures** • Survival • Progression-free survival • Adverse events *Adverse events were only reported for the PCI group* • Development of symptomatic brain metastasis *The following key symptoms suggestive of a diagnosis of brain metastases were specified: signs of increased intracranial pressure, headache, nausea and vomiting, cognitive or affective disturbances, seizures, and focal neurologic symptoms. If any of these symptoms developed, CT or MRI of the brain was performed. Symptomatic brain metastasis was defined as the presence of at least one key symptom in combination with radiologic evidence (positive contrast-enhanced CT or MRI of the brain).* • Quality of life *The primary quality-of-life end points were global health status, hair loss, fatigue, role functioning, cognitive functioning, and emotional functioning as assessed with the EORTC's QLQ-C30.*	

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
		• Number of people who dropped out	
Takahashi 2017	Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial	**Study type** • Randomised controlled trial Study details • Study location *47 participating institutions in Japan* • Study setting *The 47 participating institutions are hospitals, cancer centres, medical centres and one faculty of medicine.* • Study dates *Recruitment was from April 2009 to July 2013* • Duration of follow-up *24 months. This was when the final MRI brain was planned for each patient. The median follow-up was 11.2 months for the PCI group (interquartile range 8.7 - 20.2) and 12.0 months for the observation only group (8.8 - 17.7)* • Sources of funding *The Ministry of Health, Labour and Welfare of Japan* **Inclusion criteria** • Cytologically/histologically confirmed extensive SCLC, defined as disease beyond one hemithorax including ipsilateral hilar, bilateral mediastinal, and bilateral supraclavicular lymph node metastases, and malignant pleural or pericardial effusion • Absence of brain metastases confirmed by gadolinium-enhanced MRI within 4 weeks before enrolment (non-gadolinium-enhanced MRI scans were acceptable if contraindicated)	**Random sequence generation** • Low risk of bias **Allocation concealment** • Unclear risk of bias *Patients and investigators were not masked to treatment allocation. However, masking probably is not possible.* **Blinding of participants and personnel** • Unclear risk of bias *Patients and investigators were not masked to treatment allocation. However, this might not be possible.* **Blinding of outcome assessment** • Unclear risk of bias *The investigators were not blinded. However, given the outcomes, it is uncertain as to whether this would make any difference.* **Incomplete outcome data** • Low risk of bias *This trial was stopped early. However, Bayesian predictive probability of prophylactic cranial irradiation being superior to observation was 0·011%,*

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
		Exclusion criteria • Under 20 years of age • Eastern Cooperative Oncology Group (ECOG) performance status of 3 or above • No response to 2 or more cycles of platinum-based doublet chemotherapy (either cisplatin or carboplatin combined with one non-platinum agent) *Responses to initial platinum-based doublet chemotherapy were categorised as complete response, partial response, and minor response. Complete response and partial response were defined according to the Response Evaluation Criteria in Solid Tumours (RECIST) version 1.1. In patients with measurable lesions, minor response was defined as between a 5% and 30% decrease in the sum of diameters of target lesions in accordance with RECIST 1.1, whereas in patients without measurable lesions before initial chemotherapy, minor response was defined as disappearance or shrinkage of some, but not all, lesions with no unequivocal progression. Responses were assessed by the local investigators and confirmation of response was not required.* • Tumour regrowth confirmed by thoracoabdominal CT within 4 weeks before enrolment (either contrast-enhanced or plain scan acceptable) • An interval of more than 6 weeks between the start of the last initial chemotherapy and enrolment • Estimated life expectancy of less than 3 months • History of radiotherapy to the irradiation field for prophylactic cranial irradiation • Any active concomitant malignancy • Any mental disorder or somatic comorbidities of clinical concern • Pregnancy or lactation	*resulting in early termination of the study because of futility.* **Selective reporting** • Low risk of bias **Other sources of bias** • Low risk of bias *It is a pity that quality of life was not measured. However, this is not a risk of bias as such.* **Overall risk of bias** • Low **Directness** • Indirectly applicable. The investigators followed up all participants at 3-month intervals up to 12 months and at 18 and 24 months after enrolment. Participants with asymptomatic brain metastases detected by MRI received radiotherapy and subsequent chemotherapy. Such MRI follow-up is not UK practice. This is because in Japan they have roughly 10 times the number of MRI scanners per head of population compared to the UK. Japan has the greatest number of MRI scanners per head of population compared to the rest of the world by quite a large margin. In addition, this study has considerably more men compared to women (86% men). This does not reflect the UK population of people living with SCLC.

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
		• Women with childbearing potential **Sample characteristics** • Sample size *224 people* • Split between study groups *PCI group: n= 113; Observation only group: n=111* • Loss to follow-up *1 person was lost to follow-up in the PCI group with regards to the safety analyses. This is because their case report form went missing.* • %female *PCI group: women = 16%; Observation only group: women = 12%* • Median age (range) *PCI group: 69 years (43-83); Observation only group: 69 years (37-86)* **Pre-intervention procedures** • Brain MRI and thoracoabdominal CT *All patients had them. Occurred within the 4 weeks before enrolment* **Interventions** • Prophylactic cranial irradiation (PCI) *Patients allocated to the prophylactic cranial irradiation group underwent cranial radiation at a total dose of 25 Gy delivered in ten daily fractions (2·5 Gy per fraction) using parallel opposing fields with a 4–10 MV linear accelerator with source-axis distance of at least 100 cm. Prophylactic cranial irradiation had to be started within 3–8 weeks after start of the previous cycle of chemotherapy. 106 patients in the prophylactic cranial irradiation group were irradiated with 25 Gy*	

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
		administered in ten fractions (median duration of prophylactic cranial irradiation 14 days [range 12–23]). Only five patients had 1–6 days of interruptions in their scheduled prophylactic cranial irradiation, all for personal reasons. • Observation only **Follow-up** • Brain MRI at intervals *All patients, irrespective of the presence or absence of neurological symptoms, were required to have brain MRI at 3-month intervals up to 12 months and at 18 and 24 months after enrolment, unless there were compelling reasons not to adhere to this protocol, such as patient refusal and physician judgment. Development of symptoms suggestive of brain metastases required brain MRI, or in some cases brain CT, to confirm or exclude the presence of brain metastases. If extracranial progression was suspected on the basis of symptoms or abnormal laboratory test values, the suspected sites of disease progression were to be examined by imaging tests as early as possible according to each institution's policy.* • Assessment for toxicities related to PCI *Toxicities related to prophylactic cranial irradiation, such as alopecia, dermatitis, headache, anorexia, nausea, vomiting, dizziness, malaise, lethargy, and muscle weakness (lower limb), were assessed at randomisation, just after prophylactic cranial irradiation (intervention group only) and at the same time as brain MRI (both groups) in accordance with the National Cancer Institute Common Terminology Criteria (CTC) version 3.0. Laboratory monitoring was done according to each institutional policy.* • Assessment of cognitive function	

Short Title	Title	Study Characteristics	Risk of Bias: quality assessment (RCT
		Cognitive function was assessed by mini mental state examination (MMSE) before and 12 and 24 months after randomisation. MMSE is an 11-question measure that tests five areas of cognitive function: orientation, registration, attention and calculation, recall, and language. Physicians administered the questionnaire in person. **Outcome measures** • Survival • Time to brain metastasis • Progression-free survival • Adverse events • MMSE scores • Number of people who dropped out	

Appendix F – GRADE tables

Prophylactic cranial irradiation vs no routine MRI follow-up

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	PCI	Observation	Summary of results (95% CI)	
Mortality: hazard ratio (values over 1 favour observation)									
1 (Slotman 2007)	RCT	Not serious	Not serious	N/A	Not serious	143	143	HR 0.68 (0.52, 0.88)	High
Progression-free survival (values over 1 favour PCI)									
1 (Slotman 2007)	RCT	Not serious	Not serious	N/A	Not serious	143	143	HR 1.31 (1.03, 1.67)	High
Time to brain metastasis: the cumulative incidence of symptomatic brain metastasis at 6 months (values over 0 favour observation)									
1 (Slotman 2007)	RCT	Serious[1]	Not serious	N/A	Not serious	143	143	MD -27.60 (-43.87, -11.33)	Moderate
Time to brain metastasis: the cumulative incidence of symptomatic brain metastasis at 12 months (values over 0 favour observation)									
1 (Slotman 2007)	RCT	Serious[1]	Not serious	N/A	Not serious	143	143	MD -25.80 (-41.01, -10.59)	Moderate
Number of people who dropped out (either declining PCI in the PCI group or insisting on undergoing PCI in the observation group) (values over 1 favour observation)									
1 (Slotman 2007)	RCT	Not serious	Not serious	N/A	Serious[2]	143	143	RR 3.00 (0.32, 28.50)	Moderate
Quality of life at 9 months (values over 0 favour PCI)									
1 (Slotman 2007, Slotman 2009)	RCT	Serious[4]	Not serious	N/A	Very serious[2,3]	21	17	MD -2.40 (-18.84, 14.04)	Very low

1. No blinding of the outcomes: symptoms of brain metastasis could have been affected by this. The staging and follow-up procedures were not standardised for all the centres involved
2. Non-significant result
3. Low numbers of participants (<40 in at least one arm)

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	PCI	Observation	Summary of results (95% CI)	
4. No blinding of the outcomes: quality of life measurements could have been affected by this. The staging and follow-up procedures were not standardised for all the centres involved									

Prophylactic cranial irradiation vs observation. MRI brain follow-up at 3, 6, 9, 12, 18 and 24 months with treatment of asymptomatic brain metastases with chemotherapy and cranial irradiation

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	PCI	Observation	Summary of results (95% CI)	
Mortality: hazard ratio (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	HR 1.27 (0.96, 1.68)	Moderate
Progression-free survival (values over 1 favour PCI)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	HR 0.98 (0.75, 1.29)	Moderate
Adverse events at 3 months: alopecia (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 1.18 (0.84, 1.64)	Moderate
Adverse events at 3 months: dermatitis (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Not serious	106	111	RR 7.68 (2.37, 24.90)	High
Adverse events at 3 months: dermatitis (grade 3 or above) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 5.23 (0.25, 107.76)	Moderate
Adverse events at 3 months: headache (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 2.44 (0.65, 9.20)	Moderate

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	PCI	Observation	Summary of results (95% CI)	
Adverse events at 3 months: anorexia (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Not serious	106	111	RR 2.44 (1.58, 3.78)	High
Adverse events at 3 months: anorexia (grade 3 or above) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 0.90 (0.31, 2.58)	Moderate
Adverse events at 3 months: nausea (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Not serious	106	111	RR 3.84 (1.93, 7.63)	High
Adverse events at 3 months: nausea (grade 3 or above) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 5.23 (0.25, 107.76)	Moderate
Adverse events at 3 months: vomiting (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Not serious	106	111	RR 8.38 (1.07, 65.84)	High
Adverse events at 3 months: dizziness (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 2.79 (0.76, 10.25)	Moderate
Adverse events at 3 months: dizziness (all grade 3 or above) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 3.14 (0.13, 76.24)	Moderate
Adverse events at 3 months: malaise (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Not serious	106	111	RR 1.66 (1.07, 2.56)	High
Adverse events at 3 months: malaise (grade 3 or above) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 3.14 (0.33, 29.73)	Moderate
Adverse events at 3 months: lethargy (all grades) (values over 1 favour observation)									

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	PCI	Observation	Summary of results (95% CI)	
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 2.79 (0.76, 10.25)	Moderate
Adverse events at 3 months: lethargy (grade 3 or above) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 3.14 (0.13, 76.24)	Moderate
Adverse events at 3 months: muscle weakness (all grades) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 1.05 (0.38, 2.88)	Moderate
Adverse events at 3 months: muscle weakness (grade 3 or above) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[1]	106	111	RR 0.17 (0.02, 1.43)	Moderate
Adverse events: cognitive impairment: MMSE assessment at 12 months									
1 (Takahashi 2017)	RCT	Serious[2]	Not serious	N/A	Very serious[1,3]	37	46	MMSE scores did not differ significantly between the two groups according to the Wilcoxon test	Very low
Adverse events: cognitive impairment: MMSE assessment at 24 months									
1 (Takahashi 2017)	RCT	Serious[2]	Not serious	N/A	Very serious[1,3]	5	8	MMSE scores did not differ significantly between the two groups according to the Wilcoxon test	Very low
Time to brain metastasis: the cumulative incidence of brain metastasis at 6 months (values over 0 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Not serious	113	111	MD -31.20 (-42.53, -19.87)	High
Time to brain metastasis: the cumulative incidence of brain metastasis at 12 months (values over 0 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Not serious	113	111	MD -26.10 (-38.80, -13.40)	High

Quality assessment						No of people		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**PCI**	**Observation**	**Summary of results (95% CI)**	
Time to brain metastasis: the cumulative incidence of brain metastasis at 18 months (values over 0 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Not serious	113	111	MD -23.70 (-36.50, -10.90)	High
Number of people who dropped out (either declining PCI in the PCI group or insisting on undergoing PCI in the observation group) (values over 1 favour observation)									
1 (Takahashi 2017)	RCT	Not serious	Not serious	N/A	Serious[2]	113	111	RR 2.95 (0.12, 71.58)	Moderate

1. Non-significant result
2. Incomplete outcome data: many participants did not want to have their MMSE assessed (At 12 months, 37 out of 54 had theirs assessed in the PCI group, and 46 out of 58 had theirs assessed in the observation only group. At 24 months, 5 out of 16 had theirs assessed in the PCI group, and 8 out of 20 had theirs assessed in the observation group. This represents over 20% of participants dropping out of this assessment during both time points, hence the serious risk of bias.
3. Low numbers of participants (<40 in at least one arm)

Appendix G – Excluded Studies

Short title	Title	Reason for exclusion
Aisner 1982	Combination chemotherapy for small cell carcinoma of the lung: continuous versus alternating non-cross-resistant combinations	The interventions of interest are chemotherapy regimens
Aroney 1983	Value of prophylactic cranial irradiation given at complete remission in small cell lung carcinoma	The population of interest is not people with extensive SCLC
Arriagada 1995	Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission	The population of interest is not people with extensive SCLC
Arriagada 2002	Patterns of failure after prophylactic cranial irradiation in small-cell lung cancer: analysis of 505 randomized patients	The population of interest is not people with extensive SCLC
Auperin 1999	Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. Prophylactic Cranial Irradiation Overview Collaborative Group	This systematic review could not be used because some of the studies are unpublished and others are in journals that are no longer obtainable. The reference list was checked to ensure that we had considered all studies. The population of interest is not people with extensive SCLC
Beiler 1979	Low dose elective brain irradiation in small cell carcinoma of the lung	The population of interest is not people with extensive SCLC
Cao 2000	Clinical study of prophylactic cranial irradiation for small-cell lung cancer	This study is written in Chinese. The population of interest is not people with extensive SCLC
Cao 2005	Long-term results of prophylactic cranial irradiation for limited-stage small-cell lung cancer in complete remission	The population of interest is not people with extensive SCLC
Cox 1981	Cranial irradiation in cancer of the lung of all cell types	The population of interest is not people with extensive SCLC
Eagan 1981	A case for pre-planned thoracic and prophylactic whole brain radiation therapy in limited small-cell lung cancer	The population of interest is not people with extensive SCLC
Gregor 1997	Prophylactic cranial irradiation is indicated following complete response to induction therapy in small cell lung cancer: results of a multicentre randomised trial. United Kingdom Coordinating Committee for Cancer Research (UKCCCR) and the European Organization for Research and Treatment of Cancer (EORTC)	The population of interest is not people with extensive SCLC

Hansen 1980	Prophylactic irradiation in bronchogenic small cell anaplastic carcinoma. A comparative trial of localized versus extensive radiotherapy including prophylactic brain irradiation in patients receiving combination chemotherapy	The population of interest is not people with extensive SCLC
Jackson 1977	Prophylactic cranial irradiation in small cell carcinoma of the lung. A randomized study	The population of interest is not people with extensive SCLC
Kristjansen 1994	Should current management of small cell lung cancer include prophylactic cranial irradiation?	The population of interest is not people with extensive SCLC
Laplanche 1998	Controlled clinical trial of prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission	The population of interest is not people with extensive SCLC
Le Pechoux 2009	Standard-dose versus higher-dose prophylactic cranial irradiation (PCI) in patients with limited-stage small-cell lung cancer in complete remission after chemotherapy and thoracic radiotherapy (PCI 99-01, EORTC 22003-08004, RTOG 0212, and IFCT 99-01): a randomised clinical trial	The population of interest is not people with extensive SCLC
Meert 2001	Prophylactic cranial irradiation in small cell lung cancer: a systematic review of the literature with meta-analysis	This systematic review could not be used because some of the studies are unpublished and others are in journals that are no longer obtainable. The reference list was checked to ensure that we had considered all studies. The population of interest is not people with extensive SCLC
Niiranen 1989	Treatment of small cell lung cancer. Two-drug versus four-drug chemotherapy and loco-regional irradiation with or without prophylactic cranial irradiation	The population of interest is not people with extensive SCLC
Ohonoshi 1993	Comparative study of prophylactic cranial irradiation in patients with small cell lung cancer achieving a complete response: a long-term follow-up result	The population of interest is not people with extensive SCLC
Pechoux 2016	Prophylactic cranial irradiation for patients with lung cancer	Narrative review. The population of interest is not people with extensive SCLC
Prophylactic 2000	Cranial irradiation for preventing brain metastases of small cell lung cancer in patients in complete remission	This systematic review could not be used because some of the studies are unpublished and others are in journals that are no longer obtainable. The reference list was checked to ensure that we had

		considered all studies. The population of interest is not people with extensive SCLC
Redmond 2017	Prospective Study of Hippocampal-Sparing Prophylactic Cranial Irradiation in Limited-Stage Small Cell Lung Cancer	Observational study
Seto 2014	Prophylactic cranial irradiation (PCI) has a detrimental effect on the overall survival (OS) of patients (pts) with extensive disease small cell lung cancer (ED-SCLC): Results of a Japanese randomized phase III trial	Conference abstract
Slotman 2008	Prophylactic cranial irradiation in patients with extensive disease caused by small-cell lung cancer responsive to chemotherapy: fewer symptomatic brain metastases and improved survival	This study is written in Dutch. This study is already reported in an included paper (Slotman 2007)
Slotman 2015	Use of thoracic radiotherapy for extensive stage small-cell lung cancer: A phase 3 randomised controlled trial	This study is about thoracic radiotherapy
Sorensen 2003	The role of prophylactic brain irradiation in small cell lung cancer treatment	The population of interest is not people with extensive SCLC
Wolfson 2011	Primary analysis of a phase II randomized trial Radiation Therapy Oncology Group (RTOG) 0212: impact of different total doses and schedules of prophylactic cranial irradiation on chronic neurotoxicity and quality of life for patients with limited-disease small-cell lung cancer	The population of interest is not people with extensive SCLC
Work 1996	Prophylactic cranial irradiation in limited stage small cell lung cancer: survival benefit in patients with favourable characteristics	The population of interest is not people with extensive SCLC
Zhang 2014	Prophylactic cranial irradiation for patients with small-cell lung cancer: a systematic review of the literature with meta-analysis	The population of interest is not people with extensive SCLC

Appendix H – References

Clinical Studies - Included

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Clinical studies – Excluded

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Zhang W, Jiang W, Luan L, Wang L, Zheng X, and Wang G (2014) Prophylactic cranial irradiation for patients with small-cell lung cancer: a systematic review of the literature with meta-analysis. BMC Cancer 14, 793

Health Economic studies – Included

No health economic studies were included in the review for question 4.2

Health Economic studies – Excluded

No relevant health economic studies were identified from title and abstract search for review question 4.2.

Appendix I – QALY Analysis

Background

The 2011 recommendation to offer prophylactic cranial irradiation (PCI) as standard care for people with extensive stage small cell lung cancer (ES-SCLC) and a good response to chemotherapy was based on the evidence generated by the 2007 Slotman Trial[a]. This trial found PCI was associated with improvements in both overall survival (OS) and progression-free survival (PFS) with hazard rations of 0.68 and 0.76 respectively. No published evidence was found that reported the cost-effectiveness of this intervention. This topic was not prioritised for original health economic modelling but we conducted a simple QALYs-only analysis based on the Slotman 2007 data to understand whether the evidence from this trial, along with the unit costs calculated in **Error! Reference source not found.**placed PCI in a space where it could plausibly be considered cost-effective. Of the two RCTs included in the review, we elected to use Slotman 2007 over Takahashi 2017[b] because the committee felt it was more reflective of UK practice and because it actually showed a survival benefit, which is the widely held clinical belief in this area. The two trials were not meta-analysed due to the considerable statistical heterogeneity between their results. The committee therefore considered the results of Takahashi in addition to these results.

While not explicitly part of this analysis, the committee have noted that PCI is often delivered alongside Thoracic Radiotherapy (TRT); we include consideration of the cost-effectiveness of PCI-TRT as a joint intervention in the 'Discussion' section below.

Methods

Population, interventions/comparators and outcomes

The population were people with ES-SCLC being considered for prophylactic cranial irradiation, meaning they had to have a good performance score and have had a good response to chemotherapy as well as the absence of various contra-indicating factors listed in the Slotman trial. The committee have advised us that the entry criteria to this trial were very similar to current UK practice. Outcomes for age and sex were not

[a] Slotman B et al (2007) Prophylactic cranial irradiation in extensive small-cell lung cancer. New England Journal of Medicine 357(7), 664-72
[b] Takahashi T et al (2017) Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. Lancet Oncology 18(5), 663-671

disaggregated in the Slotman trial so we have not included age and sex as specific treatment modifying factors in our analysis. Outcomes are reported in life weeks/years, progression free life weeks/years and QALYs.

Survival Curves

We digitised the survival data from the trial following the method in Guyot et al 2012[c]. This involves scanning the Kaplan-MEIER (KM) curves from the trial into a computer program that is able to generate survival functions from the graphical plots. We used the free software ENGUAGE[d] for this purpose. The digitally reconstructed KM data were compared to the plots in the Slotman trial via visual inspection and found to agree well. The Guyot algorithm uses the reconstructed KM data along with the numbers at risk data from the trial to generate a set of individual patient data (IPD) for use in survival analysis. Any differences between the proportion alive from the KM curves and the numbers at risk at defined time points are assumed to be the result of censoring. Censored individuals are assumed to be evenly distributed throughout preceding time intervals.

We then refitted the Cox proportional hazards models to check that our data had good agreement with that of the Slotman trial and found only small differences, which can probably be attributed to small errors in the digitisation process. The results of the Cox models are in Table 6**Error! Reference source not found.**.

Table 6: Results of Cox proportional hazards models

Cox Model	Hazard Ratio	p-value	LCL	UCL
Slotman 2007 (OS)	0.68	0.003	0.52	0.88
Digitised data (OS)	0.66	0.002	0.51	0.86
Slotman 2007 (PFS)	0.76	0.02	0.59	0.96
Digitised data (PFS)	0.76	0.03	0.6	0.97

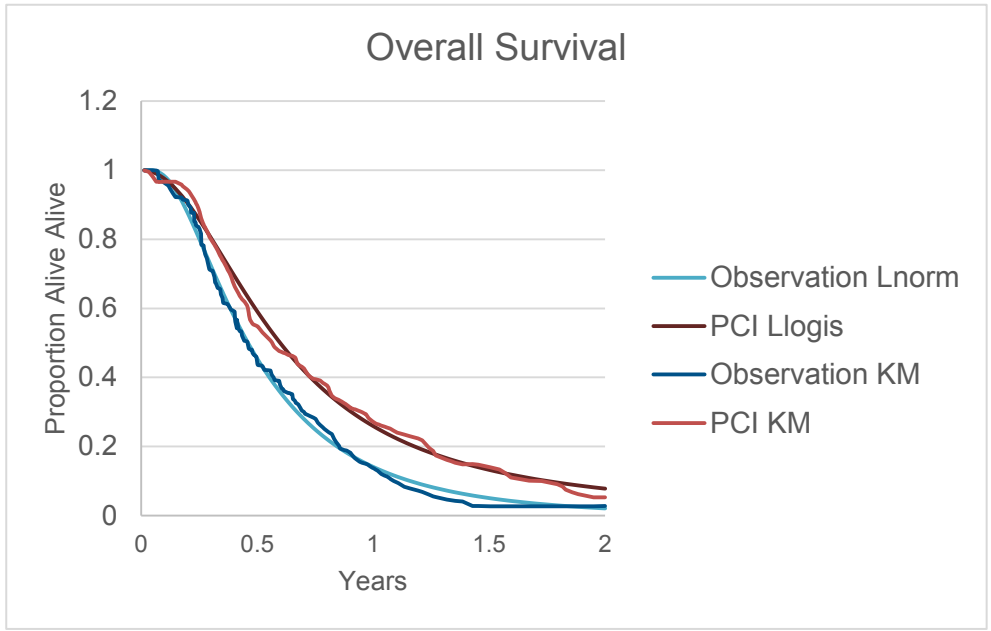
Once the IPD had been validated via visual inspection and the Cox models we fit a series of parametric curves to determine which should be used to simulate OS and PFS in the QALYs analysis. We chose parametric models over non-parametric or semi-parametric options as parametric models are more readily usable in economic models as setting of cycle lengths and investigation of uncertainty are much easier. We initially decided to try to fit a series of proportional hazards and accelerated failure time models where the curves for OS and PFS were related to one another i.e. had the same shape parameter but a different scale parameter, but due to the divergence of the OS KM curves and the crossing of the

[c] Guyot et al (2012) Enhanced secondary analysis of survival data: reconstructing the data from published Kaplan-Meier survival curves. BMC Medical Research Methodology
[d] http://markummitchell.github.io/engauge-digitizer/

PFS KM curves (possible violations of the proportional hazards assumption), we decided to fit independent models. In both the related and independent curve fitting, lognormal curves were found to fit the data best for OS and log-logistic curves were found to fit the data best for PFS. The results of the model selection are presented in Table 7 **Error! Reference source not found.** and graphical representation of the selected curves against the KM data appears in Figure 1.

Table 7: AIC statistic for survival model selection

Akaike Information Criterion (AIC) where lower values indicate better fit					
Curve	lognormal	loglogistic	weibull	exponential	gompertz
Obs OS	299.3	300.6	303.8	340.5	319.7
PCI OS	323	318	326.1	341.2	337.1
Obs PFS	350.1	347.6	355.6	372	369.2
PCI PFS	341.8	331.5	353.1	366.5	367.5



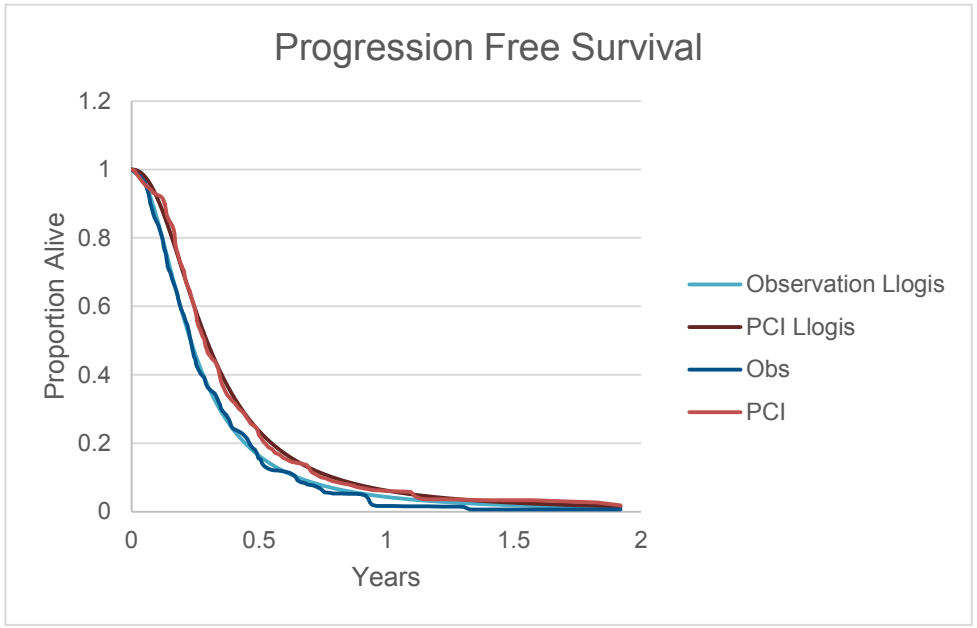


Figure 1: Overall and Progression Free Survival, KM data and fitted curves

Further validation of the survival data was undertaken by comparing the difference in the area under the curve (AUC) data for both the OS and PFS models and the relevant KM curves at 2 years (the final time point in the trial and therefore the final point where we had KM data available). The AUC is effectively the (truncated in this case) mean life expectancy and mean progression-free life expectancy and the difference in curves is the mean benefit of the intervention over observation. The parametric models were found to under-estimate mean survival benefit by 0.2 weeks (1.5 days) vs the KM data and under-estimate mean progression free life expectancy by 0.7 weeks (4.8 days). These were not seen as major limitations and could have been the subject of sensitivity analysis if the results of this model led to PCI being close to a decision-critical threshold.

Model structure

The model was a partitioned survival analysis[e]. This structure was chosen as it is the most frequently used in modelling advanced cancers. The partitioned survival model comprised 3 model states; Dead, Progression Free and Progressed. The proportion of people in the Dead state was 1-the OS function, the proportion of people in the Progression Free state was 1-the PFS function and the proportion of people in the Progressed state was therefore 1-Dead-Progression Free. The concept is illustrated in Figure 2, where the Y-axis value of the progressed state curve is equal to the difference between the overall and progression free survival curves.

[e] NICE DSU TSD 19: Partitioned survival analysis for decision modelling in health care: a critical review (2007)

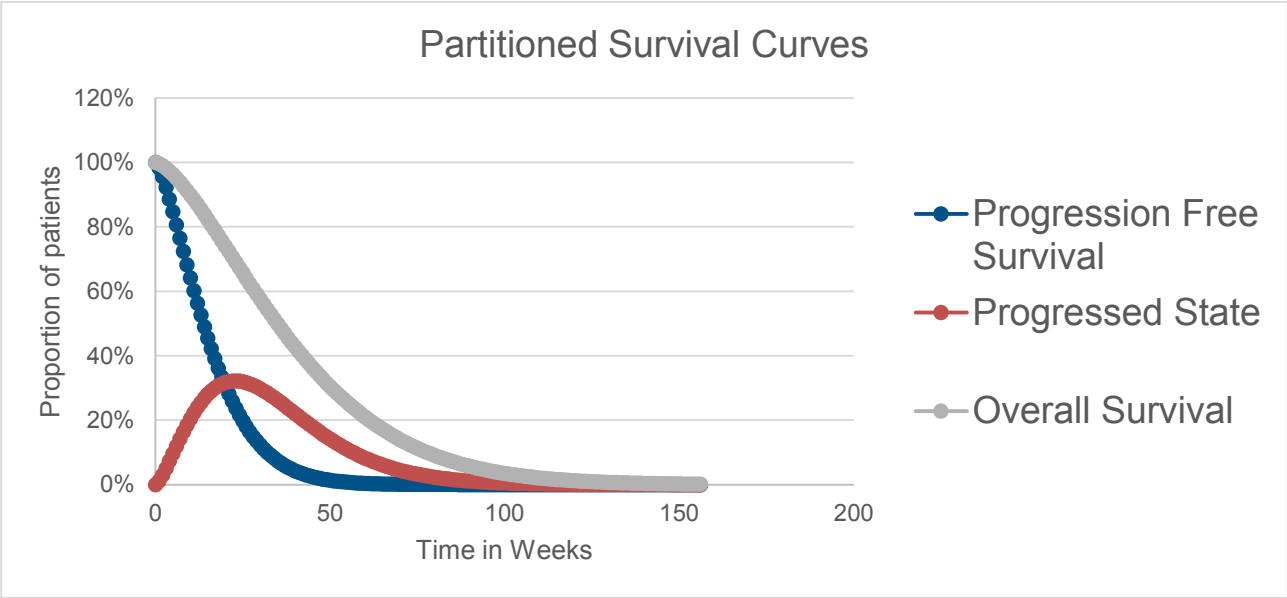


Figure 2: Illustration of partitioned survival analysis

Health Related Quality of Life

We were not able to find any specific HRQoL data for ES-SCLC so we took the data from the Patrice 2017[f] economic model for thoracic radiotherapy in this population. They were also unable to find relevant HRQoL data so extrapolated from progression free and progressed data from non-small cell lung cancer (NSCLC). The committee agreed that in light of the lack of evidence this was reasonable. Consistent with many

[f] Patrice et al (2017) Cost-Effectiveness of Thoracic Radiation Therapy for Extensive-Stage Small Cell Lung Cancer Using Evidence From the Chest Radiotherapy Extensive-Stage Small Cell Lung Cancer Trial (CREST). International Journal of Radiation Oncology

other partitioned survival models (including Patrice 2017), separate but uniform HRQoL was assumed for all patients in the Progressed state and all patients in the Progression Free State.

No HRQoL decrements were applied for treatment side-effects. This is because the committee noted that although there were statistically significant increases in side effects on treatment (from the evidence in Takahashi 2017), the vast majority of these side effects were at grades 1 and 2, which patients are able to tolerate reasonably well, and they would not expect them to persist for long. The Slotman trial also found no statistically significant difference in HRQoL between the intervention and observation arms. The resultant effect of treatment related side-effects on QALYs was therefore expected to be minimal.

Sensitivity Analysis

As the results of this analysis were primarily to be used to confirm the plausibility of the cost-effectiveness of the intervention no sensitivity analyses were undertaken.

Cycle length, time horizon and discounting

ES-SCLC is a rapidly progressing disease with a life expectancy of 6-9 months so the cycle length for the model was chosen as 1 week and results were reported at time horizons of 3, 4 and 5 years. Benefits were discounted at 3.5% per year.

Table of model parameters

Model Parameter	Mean Value	LCL	UCL	Source
Obs OS (meanlog)	-0.776	-0.899	-0.653	Calculated (Slotman 2007)
Obs OS (sdlog)	0.721	0.636	0.820	Calculated (Slotman 2007)
PCI OS (a)	2.046	1.748	2.396	Calculated (Slotman 2007)
PCI OS (b)	0.599	0.517	0.694	Calculated (Slotman 2007)
Obs PFS (a)	2.127	1.847	2.450	Calculated (Slotman 2007)
Obs PFS (b)	0.232	0.207	0.266	Calculated (Slotman 2007)
PCI PFS (a)	2.233	1.930	2.583	Calculated (Slotman 2007)
PCI PFS (b)	0.296	0.260	0.336	Calculated (Slotman 2007)

Model Parameter	Mean Value	LCL	UCL	Source
HRQoL Prog Free	0.653	-	-	Patrice et al 2017
HRQoL Progressed	0.473	-	-	Patrice et al 2017
Discount rate	0.035	-	-	NICE Reference Case

Results

Figure 3 shows the state membership of the model. Unfortunately, the PFS and OS parametric survival curves crossed over in the Observation model at approximately 3.1 years. In order to correct for this, Progressed state was set to 0 the cycle after it came close to 0 and the PFS state was set to be 1-OS. Since 99.5% of the total QALYs and 99.1% of progression free life years within the Observation model had been accrued by this time point, this limitation was assessed as minor. Setting the Progressed rather than PFS state to 0 was a decision taken semi-arbitrarily, although perhaps is slightly more reflective of the committee's experience that very occasionally patients with ES-SCLC are still alive 5 years after presentation.

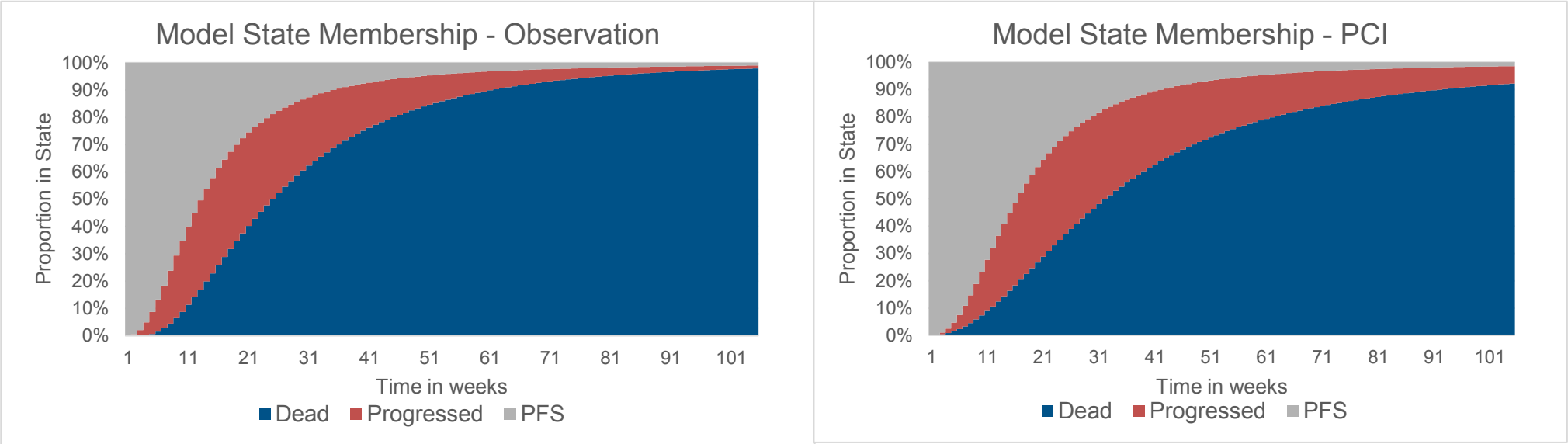


Figure 3: State membership in the model (graph truncated at 2 years)

3 The total life years, progression free life years and QALYs associated with observation and PCI at 3, 4 and 5 years/weeks are displayed in Table 8.

Time horizon	Obs (LYs)	PCI (LYs)	Diff (LYs)	Obs (PFLYs)	PCI (PFLYs)	Diff (PFLYs)	Obs (QALYs)	PCI (QALYs)	Diff (QALYs)
3 Years	0.603	0.824	0.222	0.343	0.417	0.075	0.345	0.461	0.115
4 Years	0.605	0.851	0.246	0.345	0.421	0.076	0.347	0.473	0.126
5 Years	0.606	0.867	0.261	0.346	0.424	0.077	0.347	0.480	0.133

Table 8: Model Results

Depending on the time horizon chosen, the few surviving patients at the uncertain tail end of the PCI survival curve appear to have quite a large contribution, raising the mean benefit from 11.5 to 13.6 life weeks (0.115 to 0.133 QALYs). Negligible differences were observed in progression free survival benefit because almost everyone had progressed in both model arms long before the earliest time horizon cut off of 3 years.

Discussion

The costs of the PCI intervention are in Table 9 .

Table 9: Costs of PCI

Resource	Cost	Source
PCI Planning + Fitting	£450	NHS Reference Costs 2016/17
Radiotherapy Fraction	£107	NHS Reference Costs 2016/17
Number of fractions	10	Standard of Care
Consent appointments (Consultant, First) x 1	168	NHS Reference Costs 2016/17
Appointments during treatment (monitor AEs) (Consultant) x 1	128	NHS Reference Costs 2016/17
Follow up appointment (Consultant) x 1	128	NHS Reference Costs 2016/17
Proportion accessing telephone service	33%	Committee assumption
Cost telephone apts per patient (non-Consultant) x 1	£39	NHS Reference Costs 2016/17
Total Costs per patient	£1,957	

If only the costs of the intervention are factored in then the ICER for PCI would be £14,768 per QALY (£1,957/0.133), which is within the range normally considered cost-effective by NICE. Obviously this does not account for the resources used in managing the side effects of treatment and the general cost associated with management of ES-SCLC including chemotherapy, radiotherapy, imaging and other contact with health professionals. The Slotman trial also reported a higher proportion of people being treated with radiotherapy for extracranial progression in the PCI than control arm (68% vs 45%). Although no reason is postulated for this in that paper it could be that patients with extracranial progression in the PCI arm are expected to be fitter due to a smaller proportion of them having brain metastases. If this is the case then the cost of additional

radiotherapy use would need to be considered as an intervention specific effect. Palliative care packages would be needed at some point for all patients in both arms so the net difference in these costs was expected to be negligible.

PCI is associated with a mean life expectancy gain of 0.26 life years. In the absence of a costs side of this model, the following equation is helpful in trying to estimate the total incremental costs associated with PCI:-

(Intervention cost + (general management cost * life year gain)) / QALY gain

Using this equation, a simple threshold analysis can be conducted varying the general yearly cost of ES-SCLC management. The resulting ICER associated with various arbitrary values for yearly general cost is shown in Table X. If the general costs are lower than £2500 per year and £7500 per year then PCI is cost effective when QALYs are worth £20,000 and £30,000 respectively. The committee noted that drug treatments for ES-SCLC are inexpensive compared to NSCLC and agreed that these values are plausible and therefore that the true ICER is unlikely to be above £30,000/QALY.

Yearly Management Cost of SCLC	**£1,000**	**£2,500**	**£5,000**	**£7,000**	**£7,500**
Indicative ICER	£16,740	£19,699	£24,629	£28,574	£29,560

Furthermore, the committee noted that Thoracic Radiotherapy (TRT) is often offered alongside PCI and the two can often be offered as part of a joint package that increases the cost effectiveness of both. It is unclear at present the extent to which the resource uses associated with PCI and TRT are combined in practice. Addenbrooke's Hospital (personal communication) do not code any additional charge for combined therapy but it may be that some hospitals charge for the radiotherapy sessions separately. Given that both types of radiotherapy may be given during the same session, using the same equipment, the former seems more likely. The potential costs of joint delivery of PCI and TRT and indicative ICERs are shown in Table 10

Table 10: Potential Joint PCI and TRT costs

	Cost
PCI + TRT Completely Separate	£3,827
Shared staff contact	£3,390
Separate planning and dosimetry only	£2,320
Separate radiotherapy sessions only	£3,027
Completely Shared cost	£1,957

Slotman 2007 considered Obs vs PCI and Slotman 2015[g] (the most important trial in the evidence review for TRT in this update and the basis for the Patrice 2017 cost utility analysis) considered PCI vs PCI + TRT. Following the principles of network meta-analysis, if the populations in the two trials are comparable then the effects can be considered additive. Participants had similar age and time from initial diagnosis and exclusion criteria for the two trials were similar. The proportion of people with persistent intrathoracic disease was notably higher in the TRT trial but the WHO performance score, an indication of overall level of disease burden, was similar between the two trials. The committee therefore agreed it reasonable, in an approximate analysis such as this, to assume the intervention effects were additive. As Patrice et al. found that TRT was associated with an increase of 0.09 QALYs and 0.167 life years, the total effectiveness of PCI + TRT vs observation may be close to 0.223 QALYs and 0.428 life years. That being the case, the equation above can again be used.

The resulting ICER associated with various arbitrary values and assuming entirely shared treatment costs for yearly general cost is shown in **Error! Reference source not found.**. If the general costs are lower than £10,000 per year and £18,000 per year then PCI + TRT is cost effective when QALYs are worth £20,000 and £30,000 respectively. The committee noted that drug treatments for ES-SCLC are inexpensive compared to NSCLC and agreed that these values are plausible and the true ICER is highly unlikely to be above £30,000/QALY.

Table 11: PCI + TRT Indicative ICERs

[g] Slotman et al (2015) Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 2015; 385: 36–42

Yearly Management Cost of SCLC	£1,000	£2,500	£5,000	£7,000	£7,500	£10,000	£15,000	£18,000
Indicative ICER (entirely shared treatment costs)	£9,969	£11,731	£14,668	£17,017	£17,604	£20,540	£26,413	£29,936

Strengths and Limitations

Our analysis was characterised by a number of strengths and limitations. We made use of the best available methods for digitising published survival curves and fitting parametric survival models to the resulting data while factoring in estimates of observation censoring. The data we generated were found to agree will with those published in the Slotman trial and the mean life expectancy, progression free life expectancy and QALY estimates we generated are therefore a high quality approximation of those data if extended to apply to a cohort of potentially infinite size.

This was not a cost-effectiveness analysis, however, and therefore could not produce definitive ICERs. While we had a good estimate of the cost of the PCI and PCI + TRT interventions, we made no attempt to estimate the general or specific costs of chemotherapy, radiotherapy, imaging, symptom management and contact with health professionals in patients with ES-SCLC. We also made no attempt to factor in either the cost or effect on HRQoL associated with the side effects of PCI +/-TRT. As discussed above, this may have only been a minor limitation. The utility data used in the model were also taken from a population with advanced NSCLC rather than ES-SCLC and therefore might not be accurate. Further evidence exists on the effectiveness of PCI and, while we chose not to use the Takahashi data, we could have considered breaking randomisation and combining the control arm of the Slotman 2015 study with the intervention arm of the 2007 study, for example. If the precise ICER of PCI were a target outcome we might have considered synthesising a wider evidence base. While there is some uncertainty about whether the true ICERs for PCI and PCI-TRT lie below the £20,000 threshold, the committee felt they had enough information to be confident that it that it would not lie above the £30,000 threshold. This helped them arrive at their 'consider' recommendations for these interventions.

Appendix J – Research recommendations

• Question	• What is the effectiveness and cost-effectiveness of prophylactic cranial irradiation vs routine MRI follow up in patients with ES-SCLC without brain metastases?
Population	Patients with ES-SCLC without brain metastases
Intervention	MRI Surveillance
Comparator	Prophylactic cranial irradiation with and/or without thoracic radiotherapy
Outcomes	Overall survival Progression free survival Health-related quality of life Adverse events grade 3 or above Safety
Study design	Randomised controlled trial

• Potential criterion	• Explanation
Importance to patients, service users or the population	Prophylactic cranial irradiation (PCI) is the standard care for patients with ES-SCLC without brain metastases, however this treatment can adversely affect quality of life and the survival benefits are known to be limited. Rather than all patients receiving PCI, which would only benefit a proportion of them, regular MRI could help to identify the patients that would benefit from whole brain radiotherapy.
Relevance to NICE guidance	Medium priority: The updated guideline currently recommends considering prophylactic cranial irradiation for people with extensive-stage disease SCLC and WHO performance status 2 or less, if their disease has responded to first-line treatment. Further research on the use of routine MRI could impact significantly on the treatment pathway and could help identify patients that would benefit from whole brain radiotherapy instead.
Current evidence base	The evidence review for this guideline included one study for PCI vs best supportive care, one study for MRI vs PCI conducted in a Japanese setting and one study comparing PCI and thoracic radiotherapy. Further research is therefore needed in a UK setting.
Equality	This study could improve equality of access to routine MRI and help identify patients who would benefit from whole brain radiotherapy rather than PCI.
Feasibility	There is a large enough population of people with this condition and the interventions are available in current clinical practice.