National Institute for Health and Care Excellence

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Lung Cancer Update

Evidence reviews for the clinical and cost-effectiveness of first use of thoracic radiotherapy for people with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies

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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RQ 3.5: In people with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies, when is first use of thoracic radiotherapy clinically and cost effective?

Introduction

New evidence has become available since the previous guideline was published that may have an impact on existing recommendations. A randomised controlled trial (RCT) suggests that some people with extensive-stage SCLC with a partial response to first-line treatment have improved survival if they have thoracic radiotherapy and prophylactic cranial irradiation (PCI) compared to those who have PCI alone (Slotman 2015). Experts advise us that oncologists are already adopting the approach in their practice. Therefore, this review aims to compare thoracic radiotherapy to no thoracic radiotherapy for people with extensive-stage SCLC who have had had first-line treatment with systemic anti-cancer therapies who have had a partial response.

Table 1: PICO table

Population	People with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies who have had a partial response
Intervention	Thoracic radiotherapy
Comparator	No thoracic radiotherapy

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
	• Exercise tolerance

	• Adverse events (Grade 3 or above)
	  ○ dyspnoea
	  ○ hypoxia and need for home oxygen
	  ○ stroke
	  ○ cardiovascular disease
	  ○ pneumonitis
	  ○ oesophagitis
	• Treatment-related dropout rates

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 RCTs and systematic reviews of RCTs with no date limit yielded 1,131 references.

Papers returned by the literature search were screened on title and abstract, with 13 full-text papers ordered as potentially relevant RCTs, systematic reviews of RCTs or if no RCT data available, quasi-randomised controlled trials or prospective data. Studies were excluded if they did not meet the criteria of enrolling participants with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies who have had a partial response.

Three papers representing 3 unique RCTs, were included after full text screening: Gore 2017 (RCT, n=86, indefinite follow-up but with a median of 9 months), Slotman 2015 (RCT, n=495, indefinite follow-up but with a median of 24 months), Jeremic 1999 (RCT, n=109, indefinite follow-up but with a median of 9 months),

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

Three randomised controlled studies were included in this review.

Study locations

One RCT was from the Netherlands, UK, Norway and Belgium, 1 RCT was from the USA, and 1 RCT was from Yugoslavia.

Outcomes and sample sizes

The reported outcomes with extractable data were mortality (hazard ratio, survival rates at various intervals and median survival), response to treatment (median disease-free survival, hazard ratio for time to progression, risk ratio whose cancer had progressed at various intervals, median time to first relapse and duration of response) and the risk ratio of participants who experienced a grade 3 or higher adverse event. The sample sizes for the 3 RCTs were n=690 altogether.

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 498 citations was returned. Details of the literature search are provided in Appendix C. Following review of titles and abstracts, 1 full-text study was retrieved for detailed consideration. One relevant cost–utility analysis with a partitioned survival model was identified. Therefore 1 study was included in this review.

Thoracic Radiation Therapy in Extensive-Stage Small Cell Lung Cancer

Patrice et al. (2017) conducted a cost-utility study comparing standard therapy with thoracic radiation therapy versus stand therapy alone for extensive-stage small cell lung cancer (ES-SLCL). Treatment effects were from the Chest Radiotherapy Extensive-Stage Small Cell Lung Cancer Trial (CREST, RCT (Nederlands Trial Register, number NTR1527, n=498). This study is Slotman 2015, which is included in this review. People who participated in CREST had demonstrated a response to induction chemotherapy. Participants were randomised to receive PCI with Thoracic Radiation Therapy (TRT) (n=247) or PCI alone (n=248).

A partitioned survival model was created to estimate the direct medical costs and QALYs from a US health care payers' perspective. The base case time horizon was 24 months (consistent with the maximum progression free survival) whilst an additional analysis had a time horizon of the participants' lifetime. Parametric probability distributions were independently fitted to the estimated individual patient time-to-event for OS and PFS for each treatment group to address uncertainty associated with small patient numbers at the tails of the Kaplan-Meier survival curves. Curve fitting was performed in the R program (R Foundation for Statistical Computing, Vienna, Austria).

Participants entered the model in the progression free survival health state after completing the induction chemotherapy.

TRT costs were obtained from the 2016 Centers for Medicare & Medicaid Services Physician Fee Schedule (CMSPFS) national payment amount. Post-treatmentt surveillance costs associated with the PFS health state were obtained from the 2016 CMSPFS and included a level 3 established patient office visit, chest and/or abdominal computed tomography scans, and laboratory work every 3 months during years 1 and 2, every 6 months during years 3 through 5, and annually thereafter. At the time of progression, an additional 1-time cost was incurred for workup and restaging of disease that was derived from the relapse patterns reported in the CREST and calculated using the 2016 CMSPFS.

The model assumed that PPS costs were incurred through the second to last month of life, and the terminal cost was assigned in the last month of life. Costs were inflated to 2016 US dollars using the medical care component of the US Chained Consumer Price Index. A discount rate of 3% was used for costs and outcomes beyond one year.

Patient preferences for the PFS and PPS health states associated with metastatic lung cancer were obtained from the literature and were elicited from members of the general public using standard gamble techniques (Nafees, 2008). Utility values for metastatic non-SCLC were used as a proxy for the comparable ES-SCLC health states based on available data.

Results of the study are shown in Table 2 and Table 3.

Table 2. Results from Patrice (2017) for Thoracic Radiation Therapy with Standard Therapy compared to Standard Therapy Alone (24 month horizon)

	Absolute		Incremental		
Strategy	**Cost**	**Effect**	**Cost**	**Effect**	**ICER**
Standard Therapy Alone	$116,313	0.430 QALYs			
Thoracic Radiation Therapy with Standard Therapy	$115,775	0.479 QALYs	-$538	0.049 QALYs	**Dominant**

Table 3. Results from Patrice (2017) for Thoracic Radiation Therapy with Standard Therapy compared to Standard Therapy Alone (Patient lifetime horizon)

	Absolute		Incremental		
Strategy	**Cost**	**Effect**	**Cost**	**Effect**	**ICER**
Standard Therapy Alone	$121,723	0.447			

Strategy	Absolute		Incremental		
	Cost	Effect	Cost	Effect	ICER
Thoracic Radiation Therapy with Standard Therapy	$139,306	0.537	$17,583	0.090 QALYs	$194,726/QALY

In the base case 24 month scenario analysis, the TRT strategy produced 0.049 QALYs whilst resulting in a saving of $538, rending TRT as dominant as compared to Standard Therapy alone. In the patient life time horizon analysis, the TRT strategy resulted in an ICER of $194,726/QALY. The authors explained this relatively high ICER by highlighting that post-treatment participants who had survived experienced high costs of salvage therapy.

In the 24 months one-way deterministic sensitivity analysis, the TRT ICER was found to be most sensitive to changes in the parameters of the TRT and ST PFS and OS distributions. In the patient lifetime one-way deterministic sensitivity analysis, the use of alternative PFS distributions resulted in the TRT ICERs ranging from $79,291 to $381,264. For the 24-month time horizon probabilistic sensitivity analysis, TRT was expected to be cost-effective and preferred over the ST strategy in 68%, 81%, and 96% of the simulations at willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $200,000/QALY, respectively. In contrast, when a lifetime horizon was assumed, ST was expected to be cost-effective and preferred over the TRT strategy in 89%, 82%, and 55% of the simulations at willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and $200,000/QALY, respectively.

The authors concluded that by use of the actual follow-up interval reported in the CREST, adding TRT to chemotherapy and PCI strongly dominates a strategy of chemotherapy and PCI alone in participants with ES SCLC. Since the long-term incremental survival benefit of TRT is small relative to ongoing incremental costs to manage progressive metastatic disease, the ICER of TRT is less favourable and situated near the upper boundary of contemporary thresholds for cost-effectiveness when evaluating a lifetime scenario.

Evidence statements

For all participants who had at least a partial response to chemotherapy: thoracic radiotherapy + prophylactic cranial irradiation (PCI) vs PCI only

Very low to low-quality evidence from 2 RCTs reporting data on 581 people who had at least a partial response found that the data favoured those who had thoracic radiotherapy + PCI for the risk ratio of people still alive at 1.5 and 2 years, hazard ratio for progression and the risk ratio of cancer progression at 3 months compared to people who had PCI. However, the data could not differentiate mortality (all-cause hazard ratio), progression-free survival at 6 months, risk ratio for cancer progression at 1 year and adverse events.

For participants who had a complete extra-thoracic response (and who had either a complete or partial thoracic response to chemotherapy: Accelerated hyperfractionated radiation therapy + carboplatin/etoposide + PCI + 2x cisplatin/etoposide vs 2x cisplatin/etoposide + PCI + 2x cisplatin/etoposide

Very low to low-quality evidence from 1 RCT reporting data on 109 people who had a complete extra-thoracic response (and who had either a complete or partial thoracic response) found that the data favoured accelerated hyperfractionated radiation therapy for mortality (risk ratio of people alive at 1, 2, 3, 4 and 5 years), the risk ratio of people experiencing nausea and vomiting grade 3 and above, the risk ratio of people experiencing alopecia grade 3 or above and the risk ratio of people experiencing kidney toxicity grade 3 or above compared to people who had no radiation therapy. The data favoured people who had no radiation therapy for the risk ratio of people experiencing oesophageal toxicity grade 3 or above compared to accelerated hyperfractionated radiation therapy. However, the data could not differentiate thoracic recurrence-free survival at 5 years, extra-thoracic metastases-free survival at 5 years, the risk ratio of people experiencing leukopenia grade 3 or above, the risk ratio of people experiencing thrombocytopenia grade 3 or above, the risk ratio of people experiencing anaemia grade 3 or above, the risk ratio of people experiencing infection grade 3 or above, the risk ratio of people experiencing bronchopulmonary toxicity grade 3 or above or the risk ratio of people requiring hospital admission for an adverse event.

Health economics evidence statement

One partially applicable partitioned survival model with minor limitations compared thoracic radiation therapy and standard therapy with standard therapy alone for participants with extensive-small cell lung cancer in the US. In the base case 24 month analysis, the thoracic radiation therapy was found to be less expensive and more effective than standard therapy alone, and therefore a dominant treatment strategy. In the life time analysis, the ICER was found to be $194,726 per QALY. The lifetime analysis showed that the difference in the effectiveness of the treatments was 0.09 QALYs (0.16 life years).

Recommendations

First-line treatment for extensive-stage disease small-cell lung cancer

1.4.58 Consider thoracic radiotherapy with prophylactic cranial irradiation for people with extensive-stage disease SCLC who have had a partial or complete response to chemotherapy within the thorax and at distant sites. [2019]

Rationale and impact

Why the committee made the recommendations

There was some uncertainty in the evidence. However, the study most relevant to UK practice showed that thoracic radiotherapy improves long-term survival for people who have had a partial or complete response to chemotherapy, if they live longer than 1 year after the radiotherapy. The committee specified that thoracic

radiotherapy should be given alongside prophylactic cranial irradiation. This is to match recommendation 1.4.61. In addition, the reviewed clinical trials gave thoracic radiotherapy alongside prophylactic cranial irradiation.

Impact of the recommendations on practice

The 2011 recommendation only recommended thoracic radiotherapy for people with a complete response to chemotherapy at distant sites. Therefore, this recommendation could increase the number of people who could be given thoracic radiotherapy.

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 lot of difference.

The quality of the evidence

The committee agreed that the quality of the evidence was low or very low. The committee agreed that the methods used in Slotman 2015 reflect UK practice whereas the methods used in Jeremic 1999 and Gore 2017 do not. For example, Slotman 2015 had a total radiation dose of 30 Gy. By contrast, Jeremic 1999 used a total radiation dose of 54 Gy and Gore 2017 used a total radiation dose of 45 Gy. Slotman 2015 used both 2D and 3D radiotherapy planning techniques but Jeremic 1999 did not. The committee agreed that Slotman 2015 was better quality than Gore 2017. This is because in Gore 2017, those randomised to the thoracic radiotherapy plus PCI arm were on average 5 years older compared to the PCI only arm (comparing median ages of the two groups). A potential risk of bias in Slotman 2015 is that measuring mortality beyond 1 year was not included in the study protocol. However, measuring mortality beyond 1 year is usually normal for cancer studies that include mortality as an outcome.

Benefits and harms

The committee agreed that the recommendation should be a “consider” because there was inconsistency across studies and the benefits of thoracic radiotherapy, such as survival, are experienced by a minority of people who undergo the intervention. For example in Slotman 2015, there is no difference in mortality at 1 year for people who have thoracic radiotherapy and those who do not. However, the data favours thoracic radiotherapy compared to no radiotherapy at 1.5 years and 2 years. This might suggest there is a subgroup of participants who respond to treatment better than others do. However, there is insufficient data to investigate this possibility further.

The committee agreed that the disadvantage to people receiving thoracic radiotherapy would be the journeys that they would have to make to hospital in order to receive it. However, the committee agreed that this would be outweighed by the advantage of improved survival.

In Slotman 2015 and Gore 2017, the data could not differentiate for adverse events grade 3 or above. However, the investigators did not state that they powered these studies to detect adverse events. In the committee's experience, some people do experience adverse events but the potential benefit of increased survival is more important to patients.

In Jeremic 1999, more people receiving thoracic radiotherapy experienced oesophageal toxicity grade 3 or above compared to people who did not have thoracic radiotherapy. However, the total dose of radiation was relatively high at 54 Gy compared to 30 Gy in Slotman 2015, which is more representative of current practice.

The committee specified that thoracic radiotherapy should be given alongside prophylactic cranial irradiation. This is to match recommendation 1.4.92 and how thoracic radiotherapy was used in all 3 RCTs they reviewed. There was no evidence on the effectiveness of thoracic radiotherapy alone in the 3 RCTs. With regards to recommendation 1.4.92, people who have prophylactic cranial irradiation have improved survival. This was the finding of the study most relevant to UK practice (Slotman 2007).

Slotman 2015 was the RCT that most closely resembled current practice. This study involved administering thoracic radiotherapy and PCI to participants who had a partial response at distant sites and within the thorax. Therefore, the committee agreed that the recommendation should reflect this.

Cost effectiveness and resource use

The Patrice et al 2017 cost-effectiveness analysis that was included in this review was based on the clinical evidence from the Slotman 2015 trial. This is a US based analysis so the costs and ICERs are not relevant to the UK context, but, as the underpinning clinical data were based on the Slotman 2015 trial and the methods used to calculate QALYs were high quality and not health system specific, the committee considered the estimates of differential QALY gain to be relevant. The committee considered this evidence along with the QALYs only analysis of PCI (Evidence Review H) and noted that it was highly likely that offering both interventions together would be cost effective, particularly as much, if not all, of the costs of the intervention can be shared. This means that in many situations, the addition of thoracic radiotherapy to prophylactic cranial irradiation will gain QALYs with a negligible up front resource use. A full discussion of this evidence can be found in Appendix J of Evidence Review H.

According to advice from experts, oncologists in the UK are already adopting the thoracic radiotherapy approach in Slotman 2015. While this recommendation applies to people with a greater range of thoracic response than the previous guideline recommendation, it also specifies that thoracic radiotherapy should only be considered alongside prophylactic cranial irradiation. The committee changed the 'offer' recommendation for prophylactic cranial irradiation made in the previous guideline to a 'consider', which might lead to a small reduction in its use and therefore the number of situations in which thoracic radiotherapy is considered. Therefore, this recommendation is expected to lead to a negligible change in resource use.

Other factors the committee took into account

The committee noted that in the studies it was a requirement for the participants to have a good performance status before thoracic radiotherapy was undertaken.

Appendix A – Review protocols

Review protocol for when first use of thoracic radiotherapy is clinically and cost effective for people with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies

In people with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies, when is first use of thoracic radiotherapy clinically and cost effective?

Field (based on PRISMA-P)	Content
Review question	In people with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies, when is first use of thoracic radiotherapy clinically and cost effective?
Type of review question	Intervention
Objective of the review	This area was identified as requiring updating in the 2016 surveillance review. The aim of the evidence review is to establish at what point during systemic anti-

	cancer therapy thoracic radiotherapy should be offered.
Eligibility criteria – population	People with extensive-stage SCLC who have had first-line treatment with systemic anti-cancer therapies who have had a partial response
Eligibility criteria – interventions	Thoracic radiotherapy
Eligibility criteria – comparator	No thoracic radiotherapy

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
	• Exercise tolerance

	• Adverse events (Grade 3 or above)
	  ○ dyspnoea
	  ○ hypoxia and need for home oxygen
	  ○ stroke
	  ○ cardiovascular disease
	  ○ pneumonitis
	  ○ oesophagitis
	• Treatment-related dropout rates

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	Partial or complete vs stable response to thoracic radiotherapy
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 4. 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 4: 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

Quality	Applicability	Use of systematic review
		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.
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.

4.2 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.

4.3 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 Table 5

Table 5: 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. 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.

GRADE criteria	Reasons for downgrading quality
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.

4.5 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.

4.6 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 6.

Table 6 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 7.

211 **Table 7 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

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

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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
NHS England

Guidelines/website
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 12th February 2018 **Database: Ovid MEDLINE(R) 1946 to Present with Daily Update** **Search Strategy:**
1 Small Cell Lung Carcinoma/
2 Carcinoma, Small Cell/
3 SCLC.tw.
4 ((pancoast* or superior sulcus or pulmonary sulcus) adj4 (tumo?r* or syndrome*)).tw.
5 or/1-4
6 ((small or oat or reserve or round) adj1 cell adj1 (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.
7 (non adj1 small adj1 cell adj1 (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.
8 6 not 7
9 5 or 8
10 exp Radiography, Thoracic/
11 ((chest* or thorac* or thorax) adj4 (radiotherap* or radiotreat* or roentgentherap* or radiosurg* or radiograph*)).tw.
12 ((chest* or thorac* or thorax) adj4 (radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw.
13 ((chest* or thorac* or thorax) adj4 (RT or RTx or XRT)).tw.
14 (TRT or TCRT).tw.
15 or/10-14
16 exp Radiotherapy/
17 Radiation Oncology/
18 radiotherapy.fs.
19 or/16-18
20 exp Thorax/
21 (chest* or thorac* or thorax).tw.
22 20 or 21
23 19 and 22
24 15 or 23
25 9 and 24
26 limit 25 to english language
27 Animals/ not Humans/
28 26 not 27

Note: In-house RCT, observational studies and systematic review filters were appended. No date limit as this is a new question.

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$)).tw. 8. ((quantitative$ 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/

The MEDLINE SR, RCT, and observational studies filters are presented below.
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.
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/

Medline Strategy
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.
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.

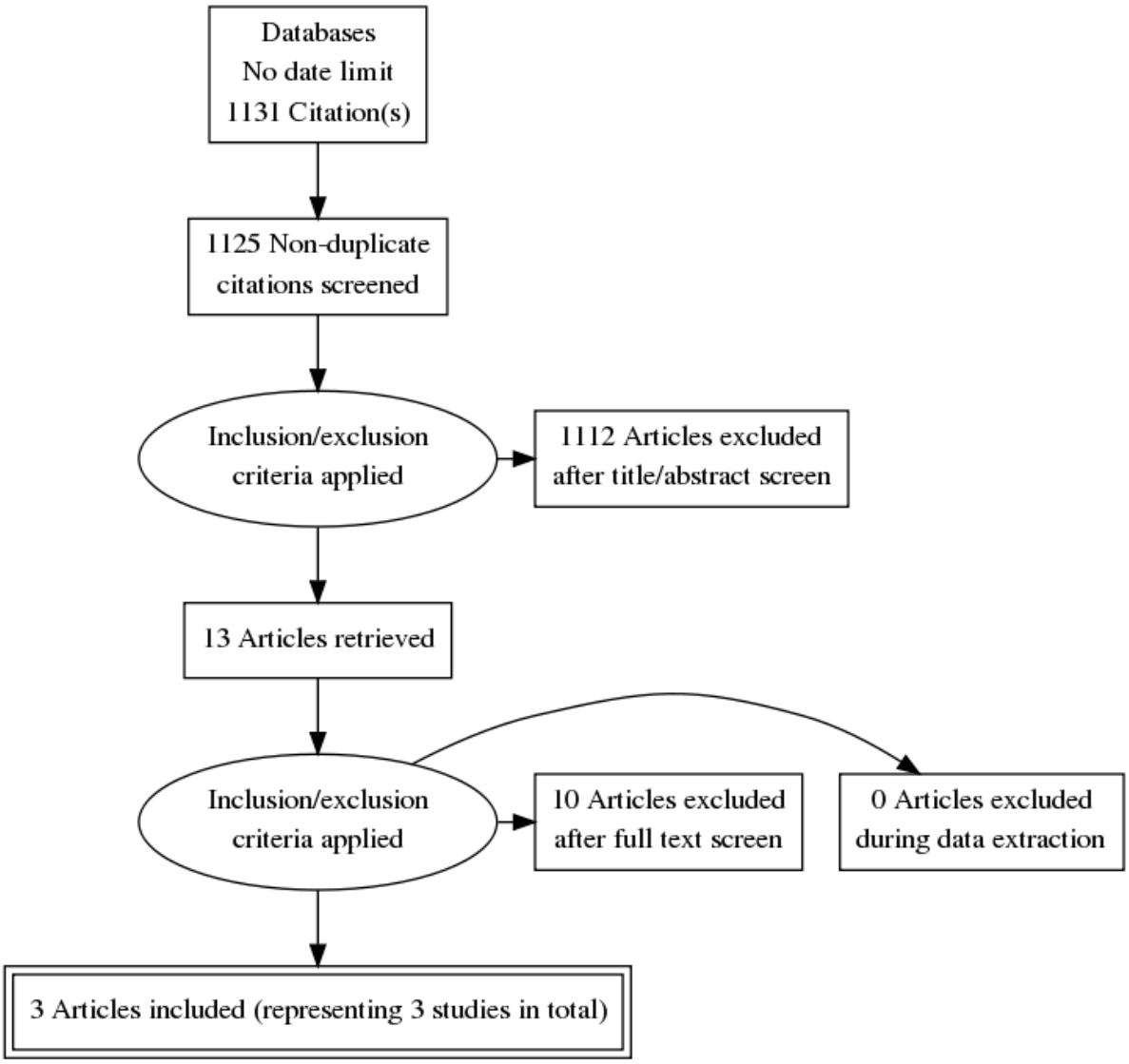
Medline Strategy
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

264 **Health economics search strategy**

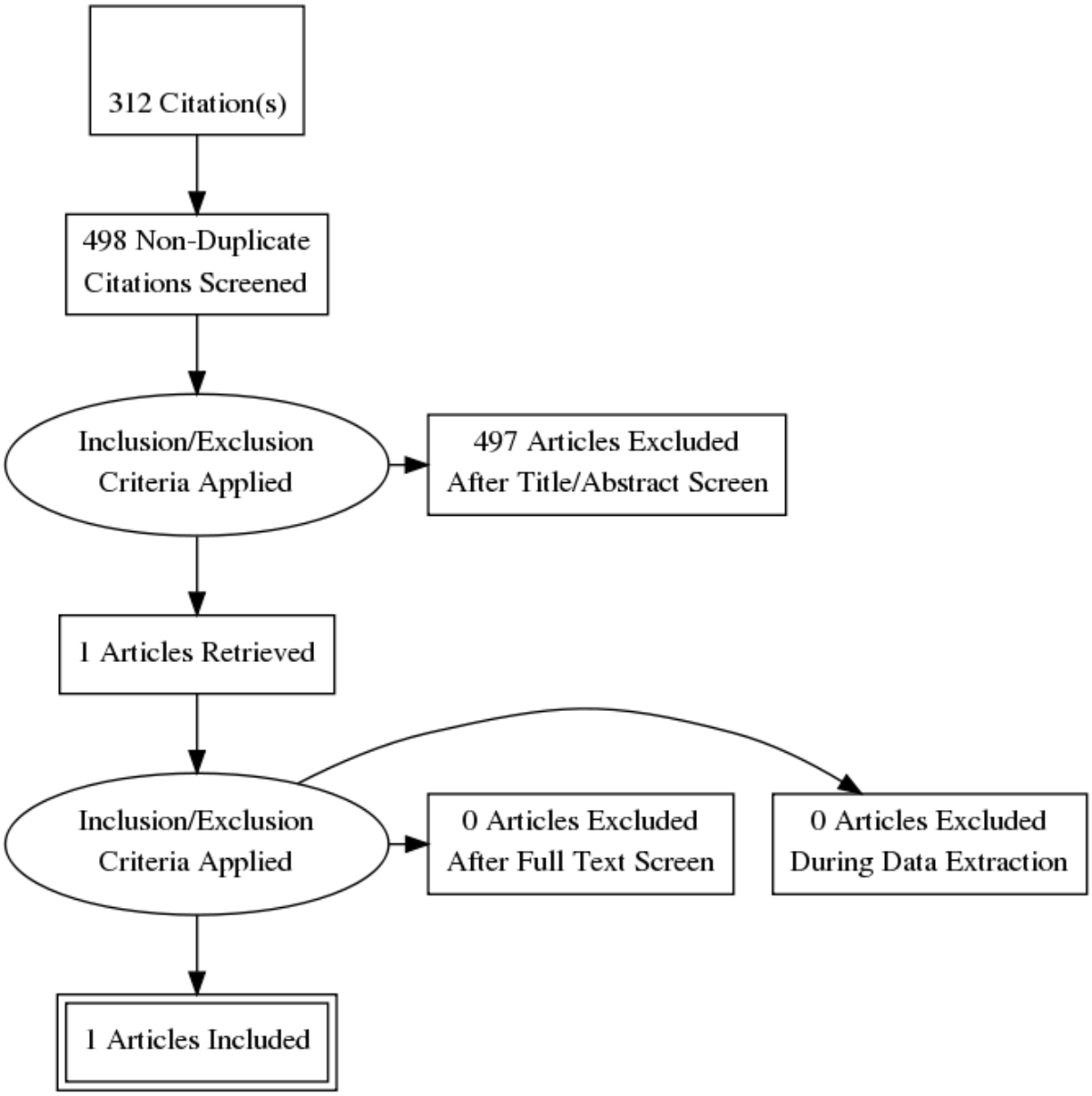
Medline Strategy, searched 13th February 2018 **Database: Ovid MEDLINE(R) 1946 to Present with Daily Update** **Search Strategy:**
1 Small Cell Lung Carcinoma/
2 Carcinoma, Small Cell/
3 SCLC.tw.
4 ((pancoast* or superior sulcus or pulmonary sulcus) adj4 (tumo?r* or syndrome*)).tw.
5 or/1-4
6 ((small or oat or reserve or round) adj1 cell adj1 (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.
7 (non adj1 small adj1 cell adj1 (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.
8 6 not 7
9 5 or 8
10 exp Radiotherapy/
11 Radiation Oncology/
12 exp Radiography, Thoracic/
13 radiotherapy.fs.
14 (radiotherap* or radiotreat* or roentgentherap* or radiosurg*).tw.
15 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw.
16 (RT or RTx or XRT or TRT or TCRT).tw.
17 or/10-16
18 9 and 17
19 limit 18 to english language
20 Animals/ not Humans/
21 19 not 20

Appendix D – Evidence study selection

Clinical Evidence study selection



270 **Economic Evidence study selection**



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272 Appendix E – Clinical evidence tables

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
Gore (2017)		Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extracranial Irradiation for Extensive-Disease Small Cell Lung Cancer (ED SCLC): NRG Oncology RTOG 0937	**Study type** • Randomised controlled trial **Study details** • Study location *USA* • Study setting *Various hospitals in the USA* • Study dates *Recruitment was between 2010 to 2015* • Duration of follow-up *Trial was stopped prematurely because futile. Median follow-up was 9 months. At planned interim analysis, the study crossed the futility boundary for OS and was closed before meeting the accrual target. The original plan was to evaluate participants after therapy at 2 weeks; at 1, 2, 6, 9, and 12 months; every 6 months for 2 to 3 years; and then annually. CT of the chest/abdomen or PET/CT and brain imaging were to be required at each visit starting at 2 months.* • Sources of funding *National Cancer Institute* • Details of first-line treatment with systemic anti-cancer therapy *4 to 6 cycles of platinum-based chemotherapy at a minimum of one site of disease.* **Inclusion criteria** • Pathologically proven SCLC	**Quality assessment (RCT)** Random sequence generation • High risk of bias *Although the randomisation technique use have worked, in practice those randomised cRT + PCI arm were on average 5 years o (comparing median ages of the two groups cRT + PCI arm, 54.5% of the participants v years old or over, compared to 28.6% for t only group.* Allocation concealment • High risk of bias *Not mentioned* Blinding of participants and personnel • Unclear risk of bias *Not possible* Blinding of outcome assessment • High risk of bias *None* Incomplete outcome data • Low risk of bias

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			• Staging CT of chest and abdomen showing extensive SCLC • Bone scan or PET/CT • Brain imaging • Partial or complete response to chemotherapy • Restaging within 8 weeks of study entry (CT of chest & abdomen or PET/CT, bone scan or PET, MRI brain or CT brain if contraindicated) **Exclusion criteria** • Brain metastases • 5 or more (extracranial) metastases • Evidence of progression at any site • Evidence of progression at the 8-week re-staging • Zubrod performance status above 2 • Serum aspartate transaminase level beyond 2.5 times the upper limit of normal • Aspartate transaminate level beyond 2.5 times the upper limit of normal • Bilirubin level 1.5 times or greater than the upper limit of normal • Serum creatinine level 1.5 times or more than the upper limit of normal for people with renal or perirenal metastases • Absolute neutrophil count of lower than 1000 cells/mm3 • Platelet count of lower than 75,000 cells/mm3 • Haemoglobin level lower than 8 g/dL **Sample characteristics** • Sample size *86 participants* • Split between study groups	Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • High Directness • Directly applicable

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			Consolidative extracranial irradiation + PCI group = 44; PCI group = 42 • Loss to follow-up *2 participants were lost to follow-up in the PCI group.* • %female *Consolidative extracranial irradiation + PCI group = 52.3%; PCI group = 57.1%* • Average age *Median age (range): consolidative extracranial irradiation + PCI group = 66 years (35-86); PCI group = 60.5 years (47-81)* • Performance status *Zubrod performance status (0, 1, 2): consolidative extracranial irradiation + PCI group = 40.9%, 56.8%, 2.3%; PCI group = 50%, 50%, 0%* • Response to first-line treatment with systemic anti-cancer therapies *Complete response, complete thoracic response and partial metastatic response elsewhere, partial thoracic response and partial metastatic response elsewhere or stable: consolidative extracranial irradiation + PCI group = 15.9%, 13.6%, 70.5%; PCI group = 23.8%, 11.9%, 64.3%* • Number of metastatic lesions *1, 2-4: consolidative extracranial irradiation + PCI group = 31.8%, 68.2%; PCI group = 40.5%, 59.5%* **Interventions** • Consolidative extracranial irradiation (cRT) + prophylactic cranial irradiation (PCI) *25 Gy of PCI at 2.5 Gy per fraction. Thoracic radiation therapy to the primary and involved regional nodes was required for all participants unless they had had palliative radiation therapy to the primary at diagnosis. Radiation was delivered to postchemotherapy volumes,*	

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			including to the site of the primary and involved nodal regions at diagnosis. Metastases were treated if they did not have a complete response to chemotherapy. The recommended radiation dose to all extracranial sites was 45 Gy delivered in 15 daily fractions of 3 Gy. From 30 to 40 Gy was acceptable if dose reduction was necessary to meet normal tissue dose constraints. It was recommended that PCI be started concurrently with cRT, although sequential therapy was allowed at the discretion of the treating physician. The median time from diagnosis to start of radiation was 22 weeks. The median time from end of chemotherapy to start of radiation was 6.9 weeks. Of the participants treated with cRT, 90.5% received thoracic radiation per protocol (30–45 Gy). Two participants received less than 30 Gy (22.5 Gy and 24 Gy) and two participants received more than 45 Gy (50 and 65 Gy), with 95.3% of all participants receiving PCI per protocol. • Prophylactic cranial irradiation *25 Gy of PCI at 2.5 Gy per fraction. The median time from diagnosis to start of radiation was 22 weeks. The median time from end of chemotherapy to start of radiation was 5.9 weeks.* **Outcome measures** • Mortality: hazard ratio • Mortality: 1 year overall survival • Response to treatment: hazard ratio for time to progression • Response to treatment: percentage whose cancer had progressed at 3 months • Response to treatment: percentage whose cancer had progressed at 1 year • Adverse events: number of people who experienced a grade 3 or higher adverse event	

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
Jeremic (1999)		Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study	**Study type** • Randomised controlled trial *Participants who had the best response to chemotherapy, in other words, those who had a complete response outside the thorax, were randomised to either (group 1:) accelerated hyperfractionated radiation therapy and concurrent low-dose daily chemotherapy consisting of carboplatin and etoposide, followed by prophylactic cranial irradiation and then by two additional cycles of cisplatin/etoposide or (group 2:) four additional cycles of cisplatin/etoposide and PCI.* **Study details** • Study location *Yugoslavia* • Study setting *University Hospital, Kragujevac, Yugoslavia* • Study dates *1988 to 1993* • Duration of follow-up *Follow-up was ongoing - no follow-up stop duration. Participants were examined fully at the end of their treatment, every month for 6 months after the end of the treatment, every 2 months for 2 years thereafter, and every 4 to 6 months thereafter.* • Sources of funding *Japanese Ministry of Education* • Details of first-line treatment with systemic anti-cancer therapy *Three cycles of a standard-dose cisplatin/etoposide regimen given at 3-week intervals (cisplatin 80 mg/m2 on day 1 and etoposide 80 mg/m2 on days 1 through 3). No dose reductions were allowed for the first three cycles of cisplatin/etoposide. After three cycles of*	**Quality assessment (RCT)** Random sequence generation • Unclear risk of bias *The method of randomisation is not given. the characteristics of the participants in gr 2 are reasonably well balanced.* Allocation concealment • High risk of bias *Not performed* Blinding of participants and personnel • Unclear risk of bias *Not performed. However, this is probably n possible.* Blinding of outcome assessment • High risk of bias *Not performed* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			cisplatin/etoposide, complete patient re-evaluation and restaging were performed. Depending on how they responded, they were allocated different interventions. **Inclusion criteria** • Pathologically proven SCLC • Staging procedures: chest X-rays, tomography, bronchoscopy, bone marrow biopsy, radionuclide scans of brain, bone, liver. Abdominal ultrasonography. CT abdomen, thorax and brain. Showed extensive SCLC *CT abdomen, thorax and brain were performed in all participants since 1989. Extensive SCLC was defined as tumour beyond the confines of the hemithorax, mediastinum, and ipsilateral or contralateral supraclavicular nodes. Participants with tumours that could not be encompassed within a tolerable RT field were also considered to have ED SCLC, as were participants who had an "isolated" pleural effusion with positive cytology.* **Exclusion criteria** • Brain metastases • Negative cytology in an isolated pleural effusion • Previous or concurrent malignancy except skin nonmelanoma • Karnofsky performance score <70 • Age <18 years • Age >70 years • WBC count <4,000/mm3 • Platelet count <150,000/mm3 • Serum creatinine 2.0 mg/dL or more • Bilirubin level 2.0 mg/dL or more	• High risk of bias *The RCT aspect of the trial does not look a radiotherapy in isolation: the chemotherap are not quite the same. Group 1 had 1x carboplatin/etoposide (+ radiotherapy) and cisplatin/etoposide. Group 2 had 2x cisplatin/etoposide and 2x cisplatin/etopos* Overall risk of bias • High *A total radiotherapy dose of 54 Gy is relati compared to UK practice.*

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			Unless low because of liver metastases • Recent or concurrent severe, uncontrolled, cardiovascular or pulmonary disease • Impairment of mental status **Sample characteristics** • Sample size *171 participants* • Split between study groups *Group 1 = 55; group 2 = 54; group 3 = 34; group 4 = 28* • Loss to follow-up *None* • %female *Group 1 = 40%; group 2 = 40.7%; group 3 = 38.2%; group 4 = 39.3%* • Average age *Median age (range): group 1 = 59 years (38-70); group 2 = 59 years (39-71); group 3 = 58 (41-70); group 4 = 60 (44-69)* • Performance status *No meaningful data provided* • Response to first-line treatment with systemic anti-cancer therapies *See 'Split between study groups' heading above* **Interventions** • Group 1 (RCT): For participants who had a complete response outside the thorax: accelerated hyperfractionated radiation therapy + carboplatin/etoposide + PCI + 2x cisplatin/etoposide *Participants who had the best response to chemotherapy, in other words, those who had a complete response outside the thorax (and*	

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			had either a complete or partial response inside the thorax), were randomised to group 1 and group 2. *A complete response was defined as the disappearance of all disease for at least 4 weeks, including negative bone marrow examination results, and the absence of new lesions (for all measurable or assessable disease). For bone metastasis, bone lesions visible on plane radiographs were required only to be improved or stable, and no finding on radionuclide bone scan could have interfered with the designated type of response. For measurable disease, a partial response was defined as a 4-week reduction of greater than 50% of the sum of the products of the cross-sectional diameters of all measurable disease, together with the absence of new lesions. For assessable lesions, a partial response was defined as a decrease in tumour size for at least 8 weeks.* *Group 1 had accelerated hyperfractionated radiation therapy and concurrent low-dose daily chemotherapy consisting of carboplatin and etoposide, followed by prophylactic cranial irradiation and then by two additional cycles of cisplatin/etoposide. PCI was administered to the whole brain at a total tumour dose of 25 Gy in 10 daily fractions in 2 weeks via two parallel-opposed lateral fields.* • Group 2 (RCT): For participants who had a complete response outside the thorax: 2x cisplatin/etoposide + PCI + 2x cisplatin/etoposide *Participants who had the best response to chemotherapy, in other words, those who had a complete response outside the thorax (and had either a complete or partial response inside the thorax). Group 2 had four additional cycles of cisplatin/etoposide and PCI. PCI was administered to the whole brain at a total tumour dose of 25 Gy in 10 daily fractions in 2 weeks via two parallel-opposed lateral fields.* • Details of accelerated hyperfractionated radiation therapy for groups 1, 3 and 4	

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			Radiotherapy was administered with 6 to 10 MV photons from linear accelerators. The target volume included all gross disease and ipsilateral hilum with a 2-cm margin and the entire mediastinum with a 1-cm margin. Both supraclavicular fossae were routinely irradiated, and anteroposterior/posteroanterior fields were used to deliver 36 Gy in 24 fractions in 12 treatment days over 2.5 weeks. After this, the anterior, lateral, and/or posterior oblique fields were used to give an additional 18 Gy in 12 fractions in 6 treatment days. The total TD was 54 Gy in 36 fractions in 18 treatment days in 3.5 weeks. Doses were specified at middepth at the central axis for parallel-opposed fields and at the intersection of the central axes for oblique techniques. The maximum dose was 36 Gy for the spinal cord and the entire heart, 54 Gy for the oesophagus, and 18 Gy for the contralateral lung. Two daily fractions of 1.5 Gy were used with an interfraction interval of 4.5 to 6 hr. No dose corrections were made for lung inhomogeneities. During accelerated hyperfractionated radiation therapy, 50 mg of carboplatin and 50 mg of etoposide were given on each RT day between the two daily fractions (3 to 4 hr after the first one, ie, 1 to 2 hr before the second one). • Details of cisplatin/etoposide treatment for groups 1, 2, 3 and 4 *Dose reductions and/or treatment delays were allowed during any subsequent treatment. Adjustments in drug dosage were made according to nadir and treatment-day blood counts. A 25% reduction in the dosage of both drugs was made if the nadir granulocyte count was less than 0.5 x 10 9/L or the nadir platelet count was less than 75 x 10 9/L. A similar reduction was made if the pretreatment granulocyte count was between 1.5 and 2.0 x 10 9/L or the pretreatment platelet count was between 100 and 125 x 10 9/L. If the pretreatment granulocyte count or platelet count fell below these levels that required a 25% dosage reduction, treatment was delayed for 1 week until the blood counts recovered.*	

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			Outcome measures • Mortality: yearly survival rates for 5 years *Participants who died during cycles 1 through 3 were considered induction deaths and were included in all analyses.* • Response to treatment: percentage thoracic and extra-thoracic recurrence-free survival each year for 5 years *Participants were evaluated for response after three cycles of cisplatin/etoposide (week 9), then after either accelerated hyperfractionated radiation therapy or two additional cisplatin/etoposide cycles (week 15), and at the end of treatment (week 21). A complete response was defined as the disappearance of all disease for at least 4 weeks, including negative bone marrow examination results, and the absence of new lesions (for all measurable or assessable disease). For bone metastasis, bone lesions visible on plane radiographs were required only to be improved or stable, and no finding on radionuclide bone scan could have interfered with the designated type of response. For measurable disease, a partial response was defined as a 4-week reduction of greater than 50% of the sum of the products of the cross-sectional diameters of all measurable disease, together with the absence of new lesions. For assessable lesions, a partial response was defined as a decrease in tumor size for at least 8 weeks. Stable disease was defined as a reduction of less than 50% or an increase of less than 25% in the sum of the products of the cross-sectional diameters of all measurable lesions and no clear pattern of either regression or progression of disease for at least 8 weeks. Disease progression was defined as an increase of greater than 25% in the sum of the products of the cross-sectional diameters of measured lesions, together with an increase in assessable disease or the appearance of new lesions.* • Response to treatment: median time to first relapse	

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			• Response to treatment: complete response rate at thoracic and extra-thoracic sites • Response to treatment: duration of response • Adverse events *Chemotherapy-induced toxicity was evaluated using the criteria of the Eastern Cooperative Oncology Group. Toxicity attributable to accelerated hyperfractionated radiation therapy was evaluated according to the criteria of the Radiation Therapy Oncology Group/European Organization for the Research and Treatment of Cancer.*	
Slotman (2015)		Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial	**Study type** • Randomised controlled trial **Study details** • Study location *The Netherlands, UK, Norway and Belgium.* • Study setting *42 hospitals: 16 in Netherlands, 22 in the UK, 3 in Norway and 1 in Belgium.* • Study dates *Recruitment was from 2009 to 2012* • Duration of follow-up *Participants in both groups were followed up at 6 weeks and 12 weeks, then once every 3 months, then once every 6 months after 1 year. All participants were followed up until death. The median follow-up was 24 months.* • Sources of funding *Dutch Cancer Society (CKTO), Dutch Lung Cancer Research Group, Cancer Research UK, Manchester Academic Health Science Centre*	Random sequence generation • Low risk of bias Allocation concealment • High risk of bias *No allocation concealment.* Blinding of participants and personnel • Unclear risk of bias *No blinding but this is probably not possibl situation.* Blinding of outcome assessment • High risk of bias *No blinding of outcome assessment.* Incomplete outcome data • Low risk of bias

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			Trials Coordination Unit, and the UK National Cancer Research Network. • Details of first-line treatment with systemic anti-cancer therapy *4 to 6 cycles of platinum etoposide chemotherapy, which was standard chemotherapy. 488/495 participants had this, 7/495 received other platinum-based regimens.* **Inclusion criteria** • Extensive SCLC *Defined as disease beyond the hemithorax, hilar, mediastinal, and supraclavicular nodes.* • Partial or complete response to chemotherapy *Assessed by the local investigators using the RECIST 1.1 criteria.* **Exclusion criteria** • Brain metastases *Or leptomeningeal metastases* • Age <18 years • WHO performance status >2 • Not considered treatable using acceptable radiation fields as judged by a radiation oncologist • More than 6 weeks between chemotherapy and randomisation • Pleural metastases • Previous radiotherapy to the brain or thorax • Ability to comply with protocol and follow-up schedules **Sample characteristics** • Sample size	Selective reporting • Low risk of bias Other sources of bias • High risk of bias *After the intervention, treatment for diseas progression was not part of the protocol ar to each centre's policy. The potential differ might have an effect on the outcomes. Wh study was registered, the investigators onl to report on data at 1 year follow-up. There is the prospect of cherry-picking data.* Overall risk of bias • High Directness • Directly applicable

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			495 participants • Split between study groups *Thoracic radiotherapy + PCI group = 247; PCI group = 248* • Loss to follow-up *None* • %female *Thoracic radiotherapy + PCI group = 45%; PCI group = 45%* • Average age *Median age (interquartile range): thoracic radiotherapy + PCI group = 63 years (58-69); PCI group = 63 (57-69)* • Performance status *WHO performance score (0, 1, 2): thoracic radiotherapy + PCI group = 39%, 49%, 12%; PCI group = 28%, 63%, 9%* • Response to first-line treatment with systemic anti-cancer therapies *Complete response, partial response, good response: thoracic radiotherapy + PCI group = 5%, 73%, 22%; PCI group = 5%, 69%, 26%.* **Interventions** • Thoracic radiotherapy + PCI *Thoracic radiotherapy was delivered to a dose of 30 Gy in 10 fractions. The planning target volume included the post-chemotherapy volume with a 15 mm margin to account for microscopic disease and setup errors. Hilar and mediastinal nodal stations that were considered involved pre-chemotherapy were always included, even in case of response. Both 2D and 3D radiotherapy planning techniques were allowed. For 3D planning, the volume of normal lung tissue, minus planning target volume receiving more than 20 Gy, should be less than 35% and correction for tissue heterogeneity was mandatory. Treatment*	

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			was delivered with a linear accelerator (4–10 MV) and all fields were treated daily (4 or 5 fractions per week). Prophylactic cranial irradiation was given as 20 Gy in 5 fractions, 25 Gy in 10 fractions, or 30 Gy in 10, 12, or 15 fractions. Each centre had to preselect one prophylactic cranial irradiation scheme for all participants. Treatment was delivered with two opposed lateral fields (4–10 MV). Prophylactic cranial irradiation and thoracic radiotherapy preferably had to start within 6 weeks, but not later than 7 weeks after chemotherapy, and not within 2 weeks after chemotherapy or if acute grade 2 or higher toxic effects of chemotherapy had not yet resolved. In the thoracic radiotherapy group, 7 participants did not receive and 6 did not complete thoracic radiotherapy, because of disease progression (n=5), deterioration of general condition (n=3), patient refusal (n=4), or treatment-related toxic effects (n=1). • Prophylactic cranial irradiation *Prophylactic cranial irradiation (PCI) was given as 20 Gy in 5 fractions, 25 Gy in 10 fractions, or 30 Gy in 10, 12, or 15 fractions. Each centre had to preselect one prophylactic cranial irradiation scheme for all participants. Treatment was delivered with two opposed lateral fields (4–10 MV). PCI preferably had to start within 6 weeks, but not later than 7 weeks after chemotherapy, and not within 2 weeks after chemotherapy or if acute grade 2 or higher toxic effects of chemotherapy had not yet resolved.* **Outcome measures** • Mortality: hazard ratio • Mortality: 1 year overall survival • Mortality: 1.5 year overall survival • Mortality: 2 year overall survival • Response to treatment: intrathoracic control	

Short Title		Title	Study Characteristics	Risk of Bias: quality assessment
			• Response to treatment: pattern of failure • Response to treatment: progression-free survival • Adverse events	

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Appendix F – GRADE tables

For all participants who had at least a partial response to chemotherapy: thoracic radiation + PCI vs PCI only

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	RT + PCI	PCI	Summary of results (95% CI)	
Mortality: all-cause hazard ratio (values below 1 favour thoracic radiotherapy + PCI)									
2 (Gore 2017, Slotman 2015)	RCT	Very serious[1]	Not serious	Very serious[2]	Serious[3]	291	290	HR 1.03 (0.62, 1.71)[3]	Very low
Mortality: risk ratio of participants still alive at 1.5 years (values over 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Not serious	247	248	RR 1.83 (1.12, 2.98)	Low
Mortality: risk ratio of participants still alive at 2 years (values over 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Not serious	247	248	RR 4.59 (2.07, 10.20)	Low
Response to treatment: hazard ratio for progression (values below 1 favour thoracic radiotherapy + PCI)									
2 (Gore 2017, Slotman 2015)	RCT	Very serious[1]	Not serious	Not serious	Not serious	291	290	HR 0.68 (0.52, 0.88)	Low
Response to treatment: risk ratio whose cancer had progressed at 3 months (values under 1 favour radiotherapy + PCI)									
1 (Gore 2015)	RCT	Very serious[1]	Not serious	N/A	Not serious	44	42	RR 0.26 (0.12, 0.58)	Low
Response to treatment: progression-free survival at 6 months (values over 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 1.18 (0.85, 1.65)	Very low
Response to treatment: risk ratio whose cancer had progressed at 1 year (values below 1 favour thoracic radiotherapy + PCI)									
1 (Gore 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	44	42	RR 0.95 (0.76, 1.20)	Very low
Adverse events: risk ratio of people who experienced a grade 3 or higher adverse event (values below 1 favour thoracic radiotherapy + PCI)									
1 (Gore 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	44	42	RR 1.53 (0.78, 2.98)	Very low
Adverse events: risk ratio of people experiencing cough grade 3 or above (values below 1 favour thoracic radiotherapy + PCI)									

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	RT + PCI	PCI	Summary of results (95% CI)	
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 0.33 (0.01, 8.18)	Very low
Adverse events: risk ratio of people experiencing dysphagia grade 3 or above (values below 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 3.01 (0.12, 73.58)	Very low
Adverse events: risk ratio of people experiencing dyspnoea grade 3 or above (values below 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 0.75 (0.17, 3.33)	Very low
Adverse events: risk ratio of people experiencing oesophagitis grade 3 or above (values below 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 9.04 (0.49, 166.95)	Very low
Adverse events: risk ratio of people experiencing fatigue grade 3 or above (values below 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 1.23 (0.52, 2.91)	Very low
Adverse events: risk ratio of people experiencing insomnia grade 3 or above (values below 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 1.51 (0.25, 8.94)	Very low
Adverse events: risk ratio of people experiencing nausea or vomiting grade 3 or above (values below 1 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 3.01 (0.12, 73.58)	Very low
Adverse events: risk ratio of people experiencing headache grade 3 or above (values below 0 favour thoracic radiotherapy + PCI)									
1 (Slotman 2015)	RCT	Very serious[1]	Not serious	N/A	Serious[3]	247	248	RR 1.51 (0.25, 8.94)	Very low

1. For Gore 2017: Those randomised to the thoracic radiotherapy arm were a median of 5 years older. There was no allocation concealment and no blinding of outcome assessment. For Slotman 2015: No blinding of outcome assessment. Treatment of disease progression was left to the discretion of each of the participating centres and there were 4 different countries involved. The authors' protocol was to look at outcomes at 1 year. However, other time intervals were also looked at so there is the possibility of cherry-picking data.
2. There is significant statistical heterogeneity in the meta-analysis ($I^2 \geq 66.7\%$).

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	RT + PCI	PCI	Summary of results (95% CI)	

3. The effect size crosses the line of no effect.
4. Random effects model used because the total dose of thoracic radiation was: Slotman 2015, 30 Gy; Gore 2017, 45 Gy. In addition, in Gore 2017, those randomised to the thoracic radiation + PCI arm were on average 5 years older compared to the PCI arm.

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277 **For people who had a complete extra-thoracic response (and who had either a complete or partial thoracic response) to**
278 **chemotherapy: Accelerated hyperfractionated radiation therapy + carboplatin/etoposide + PCI + 2x cisplatin/etoposide vs 2x**
279 **cisplatin/etoposide + PCI + 2x cisplatin/etoposide**

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	RT + 2x chemo + PCI + 2x chemo	2x chemo + PCI + 2x chemo	Summary of results (95% CI)	
Mortality: risk ratio of participants still alive at 1 year (values over 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 1.41 (1.00, 2.00)	Very low
Mortality: risk ratio of participants still alive at 2 years (values over 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 1.37 (0.80, 2.37)	Very low
Mortality: risk ratio of participants still alive at 3 years (values over 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 1.47 (0.65, 3.32)	Very low
Mortality: risk ratio of participants still alive at 4 years (values over 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 2.29 (0.62, 8.40)	Very low
Mortality: risk ratio of participants still alive at 5 years (values over 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 2.45 (0.50, 12.11)	Very low
Response to treatment: thoracic recurrence-free survival at 5 years (values over 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 2.70 (0.92, 7.96)	Very low
Response to treatment: extra-thoracic metastases-free survival at 5 years (values over 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 1.84 (0.85, 3.98)	Very low

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	RT + 2x chemo + PCI + 2x chemo	2x chemo + PCI + 2x chemo	Summary of results (95% CI)	
Adverse events: risk ratio of people experiencing leukopenia grade 3 or above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 0.74 (0.51, 1.07)	Very low
Adverse events: risk ratio of people experiencing thrombocytopenia grade 3 or above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 0.67 (0.39, 1.15	Very low
Adverse events: risk ratio of people experiencing anaemia grade 3 and above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 0.54 (0.21, 1.35)	Very low
Adverse events: risk ratio of people experiencing infection grade 3 and above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 0.75 (0.41, 1.39)	Very low
Adverse events: risk ratio of people experiencing nausea and vomiting grade 3 and above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Not serious	55	54	RR 0.27 (0.11, 0.68)	Low
Adverse events: risk ratio of people experiencing alopecia grade 3 or above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Not serious	55	54	RR 0.22 (0.11, 0.46)	Low
Adverse events: risk ratio of people experiencing kidney toxicity grade 3 or above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Not serious	55	54	RR 0.04 (0.00, 0.65)	Low
Adverse events: risk ratio of people experiencing oesophageal toxicity grade 3 or above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Not serious	55	54	RR 30.45 (1.85, 496.43)	Low
Adverse events: risk ratio of people experiencing bronchopulmonary toxicity grade 3 or above (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 6.88 (0.36, 130.01)	Very low
Adverse events: risk ratio of people requiring hospital admission for an adverse event (values below 1 favour RT + 2x chemo + PCI + 2x chemo)									
1 (Jeremic 1999)	RCT	Very serious[1]	Not serious	N/A	Serious[2]	55	54	RR 0.54 (0.21, 1.35)	Very low

1. The chemotherapy interventions are different for each arm of the trial. In addition, participants were selected for the RCT because they were expected to have a better outcome: they had a complete extra-thoracic response to the chemotherapy before they were randomised. People who were thought to have a worse prognosis (partial extra-thoracic response) were placed into cohort study arms where comparison was not possible.
2. The effect size crosses or touches the line of no effect.

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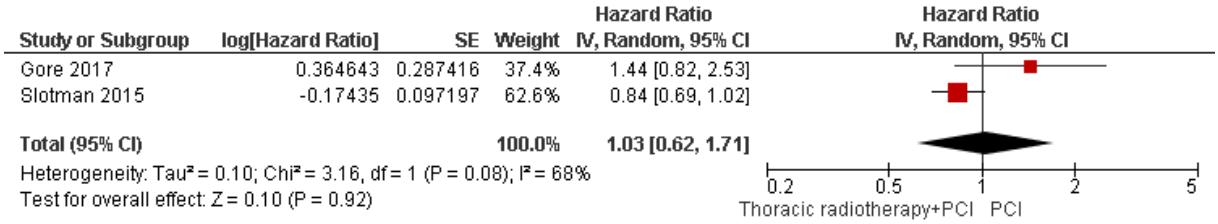
Appendix G – Forest plots

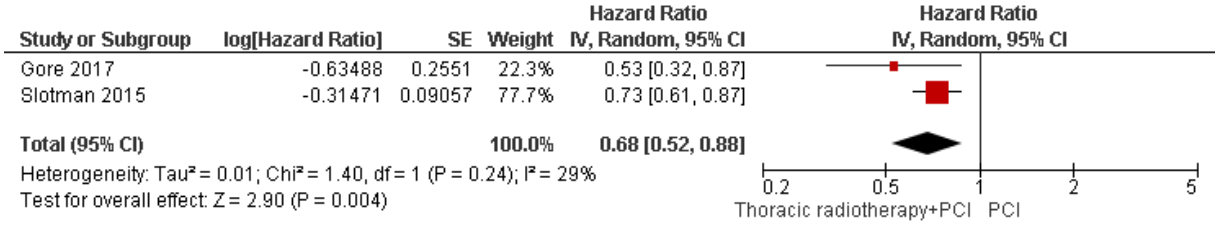
For all participants who had at least a partial response to chemotherapy: thoracic radiotherapy + PCI vs PCI

Mortality: all-cause hazard ratio



Random effects model used because the total dose of thoracic radiation was: Slotman 2015, 30 Gy; Gore 2017, 45 Gy. The median follow-up times were 9 months for Gore 2017 and 24 months for Slotman 2015.

Response to treatment: hazard ratio for progression



Random effects model used because the total dose of thoracic radiation was: Slotman 2015, 30 Gy; Gore 2017, 45 Gy.

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298 Appendix H – Excluded Studies

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Short Title	Title	Reason for exclusion
Giuliani (2011)	Clinical outcomes of extensive stage small cell lung carcinoma patients treated with consolidative thoracic radiotherapy	Study outcome data included participants whose extensive SCLC did not respond to initial chemotherapy
Li-Ming (2017)	Receipt of thoracic radiation therapy and radiotherapy dose are correlated with outcomes in a retrospective study of three hundred and six patients with extensive stage small-cell lung cancer	Study outcome data included participants whose extensive SCLC did not respond to initial chemotherapy
Luan (2015)	Efficacy of 3D conformal thoracic radiotherapy for extensive-stage small-cell lung cancer: A retrospective study	Study outcome data included participants whose extensive SCLC did not respond to initial chemotherapy
Luo (2017)	Timing of thoracic radiotherapy in the treatment of extensive-stage small-cell lung cancer: important or not?	Study outcome data included participants whose extensive SCLC did not respond to initial chemotherapy *This study included an unknown number of participants who had a stable response after chemotherapy. Our protocol inclusion criteria specify a partial response. This is an important distinction because there might not be much difference between an effect of radiotherapy that is statistically significant and one that is not for people who have had a partial response.*
Mahmoud (2016)	Intrathoracic extensive-stage small cell lung cancer: assessment of the benefit of thoracic and brain radiotherapy using the SEER database	Study outcome data included people whose extensive SCLC did not respond to initial chemotherapy

Palma (2016)	Thoracic Radiotherapy for Extensive Stage Small-Cell Lung Cancer: A Meta-Analysis	This systematic review was searched for relevant studies. This systematic review was considered for inclusion. However, it meta-analyses studies that we believe are not comparable.
Slotman (2015)	[Letter regarding the study:: Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial (Slotman 2015)]	This is a non-peer reviewed letter
Xu (2017)	Thoracic radiotherapy (TRT) improved survival in both oligo- and polymetastatic extensive stage small cell lung cancer	Study outcome data included people whose extensive SCLC did not respond to initial chemotherapy
Yee (2012)	Clinical trial of post-chemotherapy consolidation thoracic radiotherapy for extensive-stage small cell lung cancer	Single-arm study
Zhu (2011)	Thoracic radiation therapy improves the overall survival of patients with extensive-stage small cell lung cancer with distant metastasis	Study outcome data included people whose extensive SCLC did not respond to initial chemotherapy *Although only 9/60 participants had either stable disease or progressive disease after chemotherapy, this small number of participants might make a difference to the outcomes that we are trying to assess. This is because for the people with extensive SCLC who respond to chemotherapy, the effect of radiotherapy might be borderline between statistically significant and not statistically significant.*

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Appendix H – References

Clinical Studies - Included

Gore E M (2017) Randomized Phase II Study Comparing Prophylactic Cranial Irradiation Alone to Prophylactic Cranial Irradiation and Consolidative Extracranial Irradiation for Extensive-Disease Small Cell Lung Cancer (ED SCLC): NRG Oncology RTOG 0937. Journal of Thoracic Oncology 12(10), 1561-70

Jeremic B (1999) Role of radiation therapy in the combined-modality treatment of patients with extensive disease small-cell lung cancer: A randomized study. J Clin Oncol 17(7), 2092-9

Slotman B J (2015) Use of thoracic radiotherapy for extensive stage small-cell lung cancer: a phase 3 randomised controlled trial. Lancet 385(9962), 36-42

Clinical studies – Excluded

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Health Economic studies – Included

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Health Economic studies – Excluded

None.

352 **Appendix I – Health Economics Evidence Tables**
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Study, population, country and quality	Data sources	Other comments	Results			Conclusions	Uncertainty
			Cos	**Effect**			
Patrice (2017) Cost-utility study (Partitioned Survival Model) Patients with Extensive-Stage Small Cell Lung Cancer (ES-SCLC) (as per the CREST RCT) United States **Partially Applicable** [a] **Minor Limitations** [b]	**Effects** A single-study estimate of effectiveness was used - CREST RCT (Nederlands Trial Register, number NTR1527). n=498. Patients who demonstrated any response to induction chemotherapy to receive Thoracic Radiation Therapy (TRT) and Prophylactic Cranial Irradiation (PCI) or PCI alone. **Costs and resource use** TRT costs were obtained from the 2016 Centers for Medicare & Medicaid Services Physician Fee Schedule (CMSPFS) national payment amount. Post-treatment surveillance costs associated with the PFS health state were obtained from the 2016 CMSPFS. Costs were inflated to 2016 US dollars using the medical care component of the US Chained Consumer Price Index.	A discount rate of 3% was used for costs and outcomes beyond the first year. The analysis used a US health care payer perspective. The base case analysis took a 24 month time horizon, matching that of CREST. The second analysis took a patient lifetime horizon. Patient lifetime horizon's ICER was in excess of $100,000 per QALY due to the high cost of salvage therapy regimens.	***Incremental comparison of TRT compared to Standard Therapy*** ***24 month analysis***			"By use of the actual follow-up interval reported in the CREST, adding TRT to chemotherapy and PCI strongly dominates a strategy of chemotherapy and PCI alone in patients with ES SCLC. Since the long-term incremental survival benefit of TRT is small relative to ongoing incremental costs to manage progressive metastatic disease, the ICER of TRT is less favorable and situated near the upper boundary of contemporary thresholds for cost-effectiveness	24 months one-way deterministic sensitivity analysis found that the TRT ICER was most sensitive to changes in the parameters of the TRT and ST PFS and OS distributions. Patient lifetime one-way deterministic sensitivity analysis, the use of alternative PFS distributions resulted in the TRT ICERs ranging from $79,291 to $381,264. For the 24-month time horizon probabilistic sensitivity analysis, TRT was expected to be cost-effective and preferred over the ST strategy in 68%, 81%, and 96% of the simulations at
			-$538	0.049 QALYs	Dominant		
			Incremental comparison of TRT compared to Standard Therapy ***Lifetime Analysis***				
			$17,583	0.090 QALYs	$194,726/QALYs		

Study, population, country and quality	Data sources	Other comments	Results			Conclusions	Uncertainty
			Cos	Effect			
	Utility Patient preferences for the PFS and PPS health states associated with metastatic lung cancer were obtained from the literature and were elicited from members of the general public using standard gamble techniques (Nafees, 2008). Utility values for metastatic non-SCLC were used as a proxy for the comparable ES-SCLC health states based on available data					when evaluating a lifetime scenario."	willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and 200,000/QALY, respectively. In contrast, when a lifetime horizon was assumed, ST was expected to be cost-effective and preferred over the TRT strategy in 89%, 82%, and 55% of the simulations at willingness-to-pay thresholds of $50,000/QALY, $100,000/QALY, and 200,000/QALY, respectively.

a) US Study.

b) Not clear if the unit costs of resources from the best available sources.

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