National Institute for Health and Care Excellence

Final

Lung cancer update

[F] Evidence reviews for the most clinically and cost-effective regimen of chemoradiotherapy for people with limited-stage SCLC

NICE guideline NG122

Evidence reviews

March 2019

Final

These evidence reviews were developed by the NICE Guideline Updates Team

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RQ3.4: What is the most clinically and cost effective regimen of chemoradiotherapy for people with limited-stage SCLC?

Introduction

New evidence on chemoradiotherapy dosing for people with limited-stage SCLC has become available. Therefore, the aim of this review is to review all evidence from randomised controlled trials (RCTs) in this area to provide clearer guidance regarding the optimal regimen.

Table 1: PICO table

Population	People with stage limited-stage SCLC
Interventions	Drug regimens, number of cycles and duration of treatment. The timing of radiotherapy in relation to chemotherapy (early/late), the fractionation of radiotherapy, the radiotherapy regiment (e.g. once/twice daily
Comparators	• Each regimen with the other.
Outcomes	• Mortality (cancer-related, treatment-related, all-cause) • Quality of life (for example, ECOG, EORTC, EQ-5D) • Length of stay (Hospital, ICU) • Exercise tolerance • Adverse events (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.

During screening of potential papers it was noted that a large amount of the evidence came from studies taking place before 2000, with the likely potential for the treatment used in these studies to now be outdated. The protocol specified no date limit for searches, however upon discussion with the committee it was agreed that there have been considerable advancements in the treatment of lung cancer over recent decades. As a result, the protocol was changed: all studies that took place prior to 1999 were excluded from the evidence review. The limit of 1999 was agreed upon as

to include the Turrisi (1999) paper for which current practice is guided by regarding the usage of twice-daily radiotherapy. Those studies taking place in 1999 were included but marked down for indirectness. This is because the committee agreed that higher doses of radiotherapy are now used.

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 with a no date limit yielded 2,145 references.

Papers returned by the literature search were screened on title and abstract, with 44 full-text papers ordered as potentially relevant systematic reviews or RCTs.

Nineteen papers representing 16 unique RCTs were included after full text screening. Following application of the 1999-present date limit, an additional seven papers were excluded, leaving 12 papers representing ten unique RCTs. The RCTs were:

- Faivre-Finn 2017: CONVERT trial, N=547, follow-up period median 45 months.
- Turrisi 1999: N=417, follow-up 5 years.
- Bonner 1999: Also reported in Schild 2004, N=262, follow-up median 8 years.
- Gronberg 2016: Also reported in Halvorsen 2016, N=157, follow-up median 81 months.
- Spiro 2006: N=325, follow-up 5 years.
- Skarlos 2001: N=219, follow-up median 3 years.
- Sun 2013: N= 219, follow-up 5 years.
- Takada 2002: N=224, follow-up 5 years (minimum)
- Blackstock 2005: N=224, follow-up 10 years (minimum)
- Lebeau 1999: N= 156, follow up median 66 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 appendices E and G.

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

Study locations

One randomised controlled trial was from the UK (Spiro 2006), 1 was from Greece (Skarlos 2001), 3 were from the USA (Blackstock 2005, Bonner 1999, Turrisi 1999), 1 was from Norway (Gronberg 2016), 1 was from France (Lebeau 1999), 1 was from South Korea (Sun 2013), and 1 was from Japan (Takada 2002). The CONVERT trial took place across Belgium, the UK, The Netherlands, France, Spain, Canada, Poland and Slovenia.

Outcomes and sample sizes

The reported outcomes with extractable data were mortality, adverse events and quality of life. The sample sizes ranged from 64 participants to 547 across studies.

See full evidence tables and Grade profiles in appendices E and G.

Quality assessment of clinical studies included in the evidence review

See appendix E for full GRADE tables.

Economic evidence

Standard health economic filters were applied to the clinical search for this question, and a total of 376 citations were returned. Following review of titles and abstracts, no full text studies were retrieved for detailed consideration. Therefore, no relevant cost–utility analyses were identified for this question.

Evidence statements

Once-daily versus twice-daily radiotherapy (with concomitant chemotherapy in both arms)

Moderate quality evidence from two RCTs reporting data on 906 people with limited-stage small cell lung cancer found a greater length of time to any-cause mortality in people given twice-daily radiotherapy than those given once-daily radiotherapy.

Very-low- to low-quality evidence from up to 3 RCTs reporting data on up to 1,170 people with limited-disease small cell lung cancer could not differentiate rates of grade 3 or above adverse events (oesophagitis, pneumonitis or cardiac toxicity) or rates of mortality (2, 3 or 5-years) between people given twice-daily radiotherapy and those given once-daily radiotherapy.

Once-daily hypofractionated radiotherapy versus twice-daily hypofractonated radiotherapy (with concomitant chemotherapy in both arms)

Low- to moderate-quality evidence from 1 RCT reporting data on 157 people with limited-stage small cell lung cancer could not differentiate time to any-cause mortality or rates of grade 3 or above adverse events (oesophagitis and pneumonitis) between those give once-daily hypofractionated radiotherapy and those given twice-daily hyperfractionated radiotherapy.

Early versus late radiotherapy (with concomitant chemotherapy in both arms)

Early radiotherapy began on weeks 1 to 3. Late radiotherapy began on weeks 9 to 15.

Very low- to low-quality evidence from up to 4 RCTs reporting data on up to 853 people with limited-stage small-cell lung cancer could not differentiate rates of mortality at 12 months, 24 months, 36 months or 60 months, or rates of grade 3 or above adverse events (oesophagitis, cardiac, pneumonitis) between people given early and those given late radiotherapy.

Continuous versus alternating radiotherapy (with concomitant chemotherapy in both arms)

Moderate quality evidence from up to 2 RCTs reporting data on up to 266 people could not differentiate rates of mortality (2, 3 or 5 years) or grade 3 or above adverse events (oesophagitis) between those people receiving continuous radiotherapy and those receiving alternating radiotherapy.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

Overall survival is particularly important due to the low survival rates associated with small cell lung cancer. In addition, adverse events (toxicity) are of importance due to the impact these have on quality of life and the ability of patients to complete treatment following radiotherapy, including the remainder of the chemotherapy course and prophylactic cranial irradiation. Quality of life is also an important outcome and the lack of quality of life evidence available for this review question was noted by the committee.

The quality of the evidence

The evidence available for this review was of moderate to very-low quality. All studies were likely to have been non-blinded because of the nature of the interventions. This is unlikely to have had a major impact on the reporting of overall survival but may have created bias in the reporting of adverse events.

The committee noted that the survival data from the Turrisi 1999 study and the CONVERT 2017 trial was homogeneous (0% heterogeneity), which provides sufficient support to recommend twice daily over once daily radiotherapy.

There was a very high level of heterogeneity in many of the analyses. This was likely a result of the large time gaps between studies and differences in radiotherapy dosages and dose frequency. In particular, rates of adverse events were difficult to interpret due to high levels of heterogeneity in results, despite the relatively large sample sizes for rates of grade 3 or above oesophagitis. All included RCTs had sample sizes of at least 100 participants.

Benefits and harms

A recommendation of twice-daily radiotherapy was made because the survival data favours twice-daily radiotherapy over once-daily. The adverse events data could not differentiate between the two. In the committee's experience, people who are not well enough to tolerate twice-daily radiotherapy should be offered once-daily radiotherapy.

Cost effectiveness and resource use

The committee discussed the suggestion made in the CONVERT trial that twice-daily radiotherapy is potentially cost saving due to patients requiring less travel time to treatment because the total number of days attending hospital would be lower. They felt, however, that there was insufficient evidence for the cost saving potential of twice-daily therapy and noted that people may require overnight stays due to longer hospital time per session, which could incur costs to the system. They also noted that the overall number of fractions, and therefore the radiotherapy costs, would be similar between the two options. Although there were some clinical benefits associated with twice daily treatment, the committee felt that the potential for symptomatic burden and associated downstream consequences from more intense treatment meant it was highly uncertain which schedule was the more cost-effective. Additionally, they felt it was not possible to select a subgroup (based on patient fitness, for example) in which this could be determined.

Other factors the committee took into account

Although evidence shows a survival benefit from twice-daily radiotherapy compared with once daily, the committee noted that some patients would find the practicalities of the twice-daily treatment schedule and the associated side effects and travel burdensome. The committee agreed that it was important for patients to be able to complete chemotherapy and be fit enough to undergo subsequent prophylactic cranial irradiation.

The committee noted that higher doses of radiotherapy are now used compared to doses reported in most of the pre-1999 trials. In addition, the radiotherapy techniques used for small cell lung cancer have changed dramatically since 1999. Therefore, it was agreed that a pre-1999 cap be applied to the inclusion criteria, to remove older studies but keep the Turrisi (1999) paper, which was seen as the first clinically relevant study using treatment methods relevant to current practice. Additionally, papers reported in 1999 were likely to have used outdated procedures and were rated down for indirectness.

Appendix A – Review protocols

Review protocol for the most clinically and cost-effective regimen of chemoradiotherapy for people with limited-stage SCLC?

What is the most clinically and cost-effective regimen of chemoradiotherapy for people with limited-stage SCLC?

Field (based on PRISMA-P	Content
Review question	This question was identified as requiring updating through the 2016 surveillance review. The review will aim to address the most clinical and cost effective chemoradiotherapy regimen for people with limited-stage SCLC.
Type of review question	Intervention
Objective of the review	To provide clearer guidance regarding the treatment of limited-stage SCLC.
Eligibility criteria – population/ disease/ condition/ issue/ domain	People with limited- stage SCLC.
Eligibility criteria – intervention(s)/	Consider drug regimens and number of cycles and duration of treatment. Timing and fractionation.

exposure(s)/ prognostic factor(s)	For example: Concurrent once-daily versus twice-daily chemoradiotherapy (either 45 Gy radiotherapy in 30 twice-daily fractions of 1·5 Gy over 19 days, or 66 Gy in 33 once-daily fractions of 2 Gy over 45 days, starting on day 22 after commencing cisplatin–etoposide chemotherapy (given as four to six cycles every 3 weeks)
Eligibility criteria – comparator(s)/ control or reference (gold) standard	Each regimen with the other (once daily versus twice daily regimen of chemo-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

	○ Oesophagitis ○ pneumonitis ○ Dyspnoea ○ Hypoxia and need for home oxygen ○ Stroke ○ Cardiovascular disease • 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	Pre-existing performance status defined by ECOG and Karnofsky performance status scale
Selection process – duplicate screening/selection/analysis	

Data management (software)	See appendix B.
Information sources – databases and dates	No date limit. 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. Note. There was a post-hoc amendment to the protocol to exclude studies prior to 1999
Identify if an update	New question.

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 H (clinical evidence tables) or I (economic evidence tables) of the full guideline.
Data items – define all variables to be collected	For details please see evidence tables in appendix H (clinical evidence tables) or I (economic evidence tables) of the full guideline.
Methods for assessing bias at outcome/study level	Standard study checklists were used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence was evaluated for each outcome using an adaptation of the 'Grading of

	Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/ For further detail see Appendix B.
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	For details please see the methods chapter of the full guideline. See appendix B.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. See appendix B.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual See appendix B.
Rationale/ context –	For details please see the introduction to the evidence review in the full guideline.

Current management	
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by NICE Guideline Updates Team and chaired by Gary McVeigh in line with section 3 of Developing NICE guidelines: the manual. Staff from NICE Guideline Updates Team undertook systematic literature searches, appraised the evidence, conducted meta-analysis and cost-effectiveness analysis where appropriate, and drafted the guideline in collaboration with the committee. For details please see the methods chapter of the full guideline.
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

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.

Evidence synthesis and meta-analyses

Where possible, meta-analyses were conducted to combine the results of studies for each outcome. For mean differences, where change from baseline data were reported in the studies 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. All studies were assessed to ensure that baseline values were balanced across the treatment/comparison groups; if there were significant differences in important confounding variables at baseline these studies were not included in any meta-analysis and were reported separately.

When averages were given as medians, no meta-analysis of the data were performed.

Evidence of effectiveness of interventions

Quality assessment

Individual RCTs were quality assessed using the Cochrane Risk of Bias Tool. Each individual study was classified into one of the following three groups:

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

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

- Direct – No important deviations from the protocol in population, intervention, comparator and/or outcomes.
- Partially indirect – Important deviations from the protocol in one of the population, intervention, comparator and/or outcomes.
- Indirect – Important deviations from the protocol in at least two of the following areas: population, intervention, comparator and/or outcomes.

Methods for combining intervention evidence

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

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

A pooled relative risk was calculated for dichotomous outcomes (using the Mantel–Haenszel method). 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.

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 v 5.3.

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, for pooled mean differences, a MID of 0.2 SD was used because this corresponds to the threshold for a small effect size initially suggested by Cohen et al. (1988). The line of no effect was used as a MID for risk ratios and hazard ratios.

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 RCTs was initially rated as high quality and the quality of the evidence for each outcome was downgraded or not from this initial point.

Table 2: 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.

GRADE criteria	Reasons for downgrading quality
	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.
Imprecision	The line of no effect was defined as the MID for risk ratios and hazard ratios. Risk ratios and hazard ratios were downgraded once if the 95% confidence interval of the effect size crossed the line of no effect. For pooled mean differences, a MID of 0.2 SD was used. If the 95% confidence interval of the effect size crossed one line of no effect, the outcome was downgraded once. If the 95% confidence interval crossed both lines of no effect, the outcome was downgraded twice. The committee agreed that a sample size of 40 or less would result in one downgrade for imprecision. A sample size of 25 or less would result in two downgrades for imprecision. 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.

Publication bias

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

Evidence statements

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

- Situations where the data are only consistent, at a 95% confidence level, with an effect in one direction (i.e. one that is ‘statistically significant’), and the magnitude of that effect is most likely to meet or exceed the MID (i.e. the point estimate is not in the zone of equivalence). In such cases, we state that the evidence showed that there is an effect.

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

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 8th March 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 Chemoradiotherapy/
11 (chemoradiotherap* or radiochemotherap* or chemoradiation*).tw.
12 (chemo adj1 (radiotherap* or radiation)).tw.
13 ((chemotherap* or antineoplastic* or anti-neoplastic* or polychemotherap* or CTX) adj4 combin* adj4 (radiotherap* or radiotreat* or irradiat* or RT or RTx or XRT or TRT or TCRT)).tw.
14 Combined Modality Therapy/
15 (combine* adj4 modal* adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw.
16 ((tri-modal* or trimodal* or multi-modal* or multimodal*) adj4 (treat* or therap* or regimen* or manag* or intervention*)).tw.
17 TMT.tw.
18 or/10-17
19 Drug Therapy/
20 exp Drug Therapy, Combination/
21 exp Antineoplastic Protocols/
22 exp Antineoplastic Agents/
23 Chemotherapy, Adjuvant/
24 (chemotherap* or antineoplastic* or anti-neoplastic* or polychemotherap* or CTX).tw.
25 ((anticancer* or anti-cancer* or antitumo?r or anti-tumo?r or anticarcinogen* or anti-carcinogen*) adj4 (drug* or agent* or therap* or treat* or medicat* or protocol*)).tw.
26 or/19-25
27 (concurrent* or follow* or after* or with or consecutiv* or alongside or synchroni?ed or parallel or coexisting or concomitant or accompan*).tw.
28 exp Radiotherapy/
29 Radiation Oncology/
30 exp Radiography, Thoracic/
31 radiotherapy.fs.
32 (radiotherap* or radiotreat* or roentgentherap* or radiosurg*).tw.

Medline Strategy, searched 8th March 2018 Database: Ovid MEDLINE(R) 1946 to Present with Daily Update Search Strategy:
33 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw.
34 (RT or RTx or XRT or TRT or TCRT).tw.
35 ((chest* or thorac* or thorax) adj4 irradiat*).tw.
36 or/28-35
37 26 and 27 and 36
38 18 or 37
39 9 and 38
40 Animals/ not Humans/
41 39 not 40
42 limit 41 to english language

Note: In-house RCT and systematic review filters were appended. No date limit was used as this was 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/

The MEDLINE SR, RCT, and observational studies filters are presented below.	
10	((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
11	(random$ adj3 allocat$).tw.
12	placebo$.tw.
13	((singl$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).tw.
14	(crossover$ or (cross adj over$)).tw.
15	or/1-14
16	animals/ not humans/
17	15 not 16
Observational	
1	Observational Studies as Topic/
2	Observational Study/
3	Epidemiologic Studies/
4	exp Case-Control Studies/
5	exp Cohort Studies/
6	Cross-Sectional Studies/
7	Controlled Before-After Studies/
8	Historically Controlled Study/
9	Interrupted Time Series Analysis/
10	Comparative Study.pt.
11	case control$.tw.
12	case series.tw.
13	(cohort adj (study or studies)).tw.
14	cohort analy$.tw.
15	(follow up adj (study or studies)).tw.
16	(observational adj (study or studies)).tw.
17	longitudinal.tw.
18	prospective.tw.
19	retrospective.tw.
20	cross sectional.tw.
21	or/1-20

Health Economics literature search strategy

Sources searched to identify economic evaluations

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

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

Searches were re-run in May 2018.

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

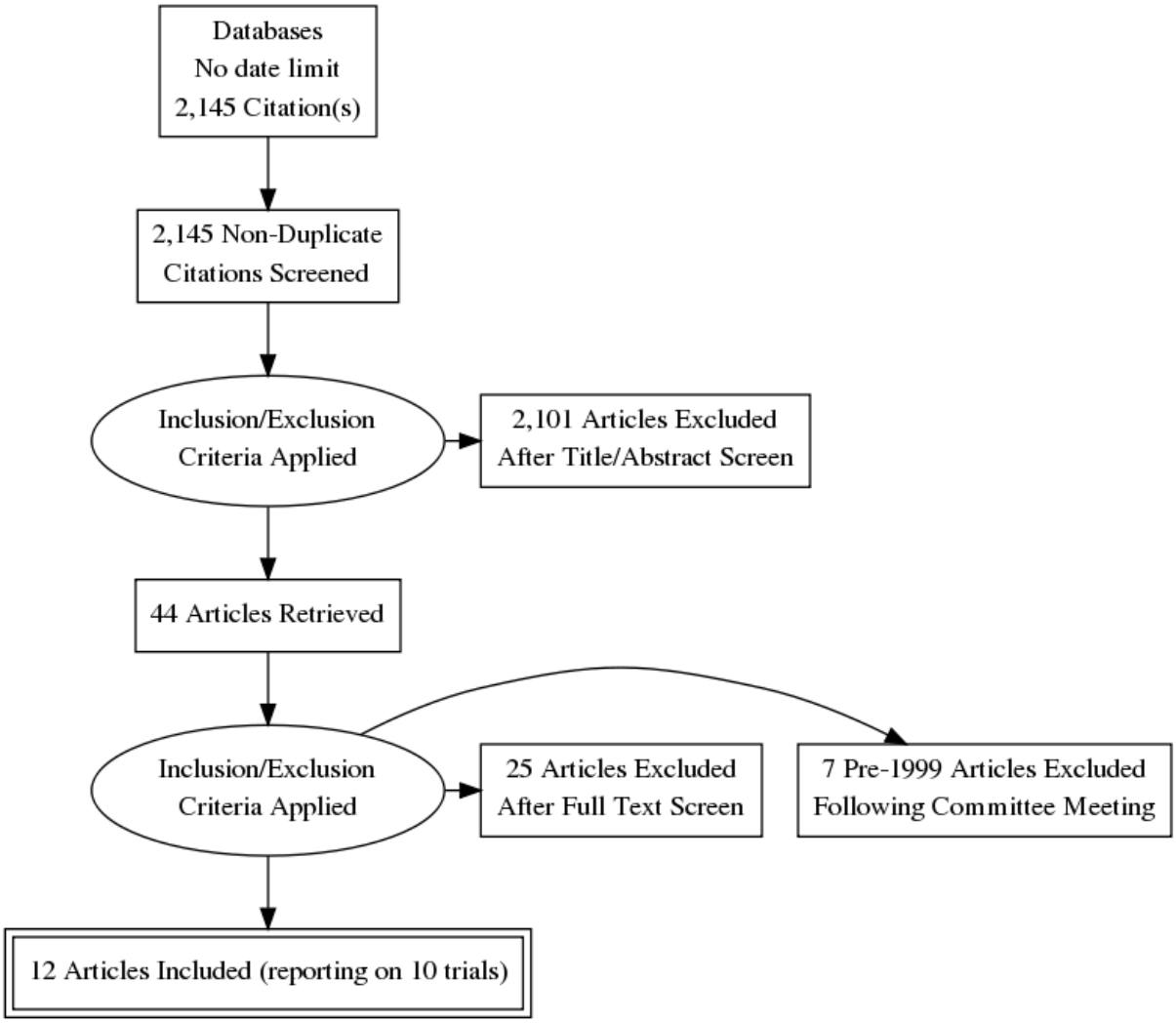
Economic evaluation and quality of life filters

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

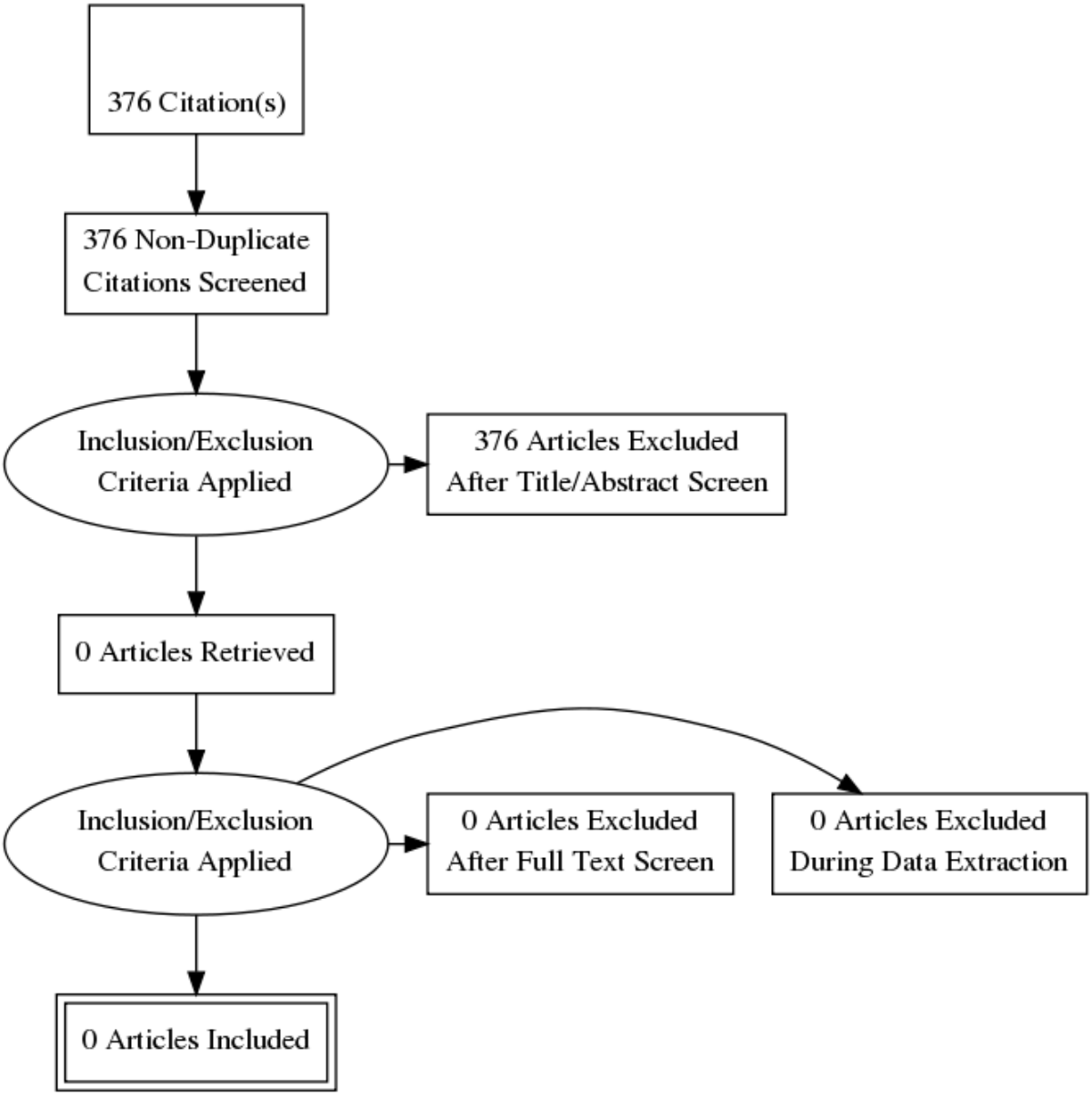
Medline Strategy
13 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.
14 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).tw.
15 (euroqol or euro qol or eq5d or eq 5d).tw.
16 (qol or hql or hqol or hrqol).tw.
17 (hye or hyes).tw.
18 health$ year$ equivalent$.tw.
19 utilit$.tw.
20 (hui or hui1 or hui2 or hui3).tw.
21 disutili$.tw.
22 rosser.tw.
23 quality of wellbeing.tw.
24 quality of well-being.tw.
25 qwb.tw.
26 willingness to pay.tw.
27 standard gamble$.tw.
28 time trade off.tw.
29 time tradeoff.tw.
30 tto.tw.
31 or/1-30

Appendix D – Evidence study selection

Clinical Evidence study selection



Economic Evidence study selection



Appendix E – Clinical evidence tables

Study	Title	Study characteristics	Risk of bias
Blackstock (2005)	Split-course versus continuous thoracic radiation therapy for limited-stage small-cell lung cancer: final report of a randomized phase III trial	Study type • Randomised controlled trial Study details • Study location USA • Study setting Multiple medical centres • Study dates Inclusion period: 1987 - 1992 • Duration of follow-up After the completion of treatment, patients were scheduled for evaluation every 2 months for 1 year, then every 4 months to a median of 14.7 months. For survival analysis minimum follow-up was 10.8 years for arm A and 12.8 years for arm B • Sources of funding Not mentioned. Inclusion criteria • Histologically proven small cell lung cancer • Acceptable radiotherapy target volume Exclusion criteria • ECOG performance status >3 • White blood cell count <4,000 /micro L • Platelet count <150,000 / micro L • Bilirubin concentration >1.5mg • Serum creatine concentration >1.5mg • aspartate aminotransferase concentration > 60 IU	Random sequence generation • Low risk of bias Randomised, non-stratified Allocation concealment • Unclear risk of bias Unlikely concealed Blinding of participants and personnel • High risk of bias non-blinded Blinding of outcome assessment • High risk of bias unlikely to have been blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Unclear allocation concealment; non-blinded.

Study	Title	Study characteristics	Risk of bias
		• Age <18 years • When febrile neutropenia or severe nonhematologic toxicity occurred Sample characteristics • Sample size 114 people • Split between study groups 57 in each arm • Loss to follow-up 13 lost to follow-up or excluded following randomization • %female arm 1: 52% female arm 2: 26% female • Average age Arm 1: median age 63 (44-78) Arm 2: median age 60 (41-75) Interventions • Radiotherapy Cranial irradiation: All patients experiencing a complete response (CR) at the completion of treatment received prophylactic cranial irradiation (PCI) beginning 3 weeks after the last cycle of chemotherapy. • Chemotherapy All patients received same chemotherapy, which began on day 1 of therapy. Chemo was given over 6 cycles. Cycles 1, 2, and 5: given on weeks 0, 3 and 12 consisted of IV cisplatin 60 mg/m2 on day 1 after prehydration and IV etopside 120 mg/m2 on days 1, 2, and 3. Cycles 3, 4, and 6: Given on weeks 6, 9, and 15 and consisted of IV cyclophosphamide 750 mg/m2 on day 1, IV vincristine 2.0 mg on day 1, and doxorubicin 60 mg/m2 on day 1 • Continuous radiotherapy Given to arm 1: 50 Gy radiation (25 x 2.0gy) given 5 days	Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		per week concomitantly (day 1) with the first 2 cycles of the cisplatin/ etoposide chemotherapy. • Alternating radiotherapy Arm 2: 50 Gy (20 x 2.5gy) given concurrently on days 8-17 during the first two 21-day cycles of chemotherapy and on days 8 and 11 during the third 21-day cycle. Outcome measures • Survival • Adverse events (grade 3 or above)	
Bonner (1999)	Phase III comparison of twice-daily split-course irradiation versus once-daily irradiation for patients with limited stage small-cell lung carcinoma	Study type • Randomised controlled trial Study details • Study location USA • Study setting Multiple medical centres • Duration of follow-up Median: 39 (range 2 - 89) months Inclusion criteria • ECOG performance ECOG 0-2 • Other minimal pleural effusions • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • White blood cell count <3,500 cells/mm3 • Platelets <100,000 cells/mm3	Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias Unclear allocation concealment procedures Blinding of participants and personnel • Unclear risk of bias Unclear, likely not possible/done Blinding of outcome assessment • Unclear risk of bias Unclear, likely not possible/done Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias

Study	Title	Study characteristics	Risk of bias
		• History of another malignancy except a curatively resected non-melanoma skin cancer or in situ cervical cancer Unless 3-year period disease-free prior to study • Hemoglobin <9.5 g/dL • Creatine over 1.5 times upper limit of normal Sample characteristics • Sample size 324; 311 randomized • Split between study groups Once daily: 132 Twice daily: 130 • Loss to follow-up 62 lost to follow-up before receiving first three cycles of chemotherapy (due to death, progression, withdrawal and toxicity) • %female 42% female • Average age Average not reported Interventions • Radiotherapy Once daily: 48 Gy in 32 fractions, with a 2.5-week break after the initial 24 Gy Twice daily: 50.4Gy in 28 fractions • Chemotherapy All patients received three cycles of EP prior to any RT, each cycle consisting of three days EP. Two cycles were given concurrent with RT and one cycle was given post-RT Outcome measures • Survival Bonner 1999: 2 and 3-year survival rates Schild 2004: 5-	Other sources of bias • Low risk of bias Overall risk of bias • Moderate Lack of clarity regarding use of any blinding/allocation concealment procedures; likely not performed/not possible. Directness • Partially directly applicable Participants were only randomized after 3 cycles of chemotherapy, at which point radiotherapy began. In addition, treatment advancement relating to dosage and technique have been made since this study took place.

Study	Title	Study characteristics	Risk of bias
		year survival rates • Adverse events (grade 3 or above) Pneumonitis and eosphagitis	
Faivre-Finn (2017)	Concurrent once-daily versus twice-daily chemoradiotherapy in patients with limited-stage small-cell lung cancer (CONVERT): an open-label, phase 3, randomised, superiority trial	Study type • Randomised controlled trial Study details • Study location Belgium, Canada, France, Netherlands, Poland, Slovenia, Spain, UK. • Study setting 73 centres in 8 countries • Study dates 2008-2017 • Duration of follow-up Inclusion criteria • Age 18 years plus • ECOG performance status of 0-1 or; status of 2 due to disease-related symptoms (not co-morbidities) • Histologically proven small cell lung cancer Disease encompassed within a radical radiation portal • Acceptable radiotherapy target volume According to local radiotherapist Exclusion criteria • Other malignant pleural or pericardial effusions; > one adverse biochemical factor; Malignancy in past 5 years (except non-melanomatous skin or insitu cervix carcinoma) or	Random sequence generation • Low risk of bias Allocation concealment • Low risk of bias Allocation via phone by recruiting centre to Trails coordination unit Blinding of participants and personnel • Low risk of bias Not possible Blinding of outcome assessment • Low risk of bias Unlikely to have been blind Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate

Study	Title	Study characteristics	Risk of bias
		previous/concomitant illness or treatment that, in the opinion of the investigator, would interfere with the trial treatments or comparisons. • FEV/1s < 1 L or 40% of predicted value Sample characteristics • Sample size 547 randomly assigned • Split between study groups Once daily: 273 allocated, 240 received concurrent chemoradiotherapy, 270 were included in survival analysis Twice daily: 274 allocated, 249 received concurrent chemoradiotherapy, 273 were included in survival analysis • Loss to follow-up 4 lost to follow-up • %female Once daily: 45% Twice daily: 46% • Average age Once daily: 63 (34-81) Twice daily: 62 (29-84) • Smoking status Once daily: 39% current smoker, 60% ex-smoker, 2% never smoker. Twice daily: 34% current smoker, 64% ex-smoker, 1% never smoker. Interventions • Radiotherapy Once daily: 66 Gy (33 x 2Gy fractios) over 45 days given on 5 consecutive days. Twice daily: 45Gy in 30 x 1.5 Gy fractions with a minimum of 6h beween fractions, over 19 days, given on 5 consecutive days a week. • Chemotherapy	Non-blinded however allocation was likely concealed. Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		Outcome measures • Survival Overall and progression-free • Adverse events (grade 3 or above) Acute chemo toxicity (Nausea, vomiting, Mucositis, fatigue, motor and sensory neuropathy, infection, anaemia, febrile neutropenia, neutropenia, anorexia, other) Acute radiotherapy toxicity (Oesophagitis, pneumonitis) Late toxicity (Dermatitis, oesophagitis, oesophageal stricture or fistula, pulmonary fibrosis, pneumonitis, myelitis, other)	
Gronberg (2016)	Randomized phase II trial comparing twice daily hyperfractionated with once daily hypofractionated thoracic radiotherapy in limited disease small cell lung cancer	Study type • Randomised controlled trial Study details • Study location Norway • Study setting 18 Hospitals in Norway • Study dates Inclusion period: 2005-2011 • Duration of follow-up PFS outcome: Median follow-up 59 months (range: 29-97), 34 patients were progression free at time of analysis (July, 2013). OS outcome: Median follow-up 81 months (range: 52-119), 34 patients were alive at time of the analysis (April, 2015). • Sources of funding "supported by the Central Norway Regional Health Authority (RHA), the Norwegian University of Science and Technology (NTNU) and the Norwegian Cancer Society."	Random sequence generation • Low risk of bias Randomised in blocks of 8 and stratified for the five Norwegian health care regions. Allocation concealment • Unclear risk of bias unclear whether allocation was concealed, unlikely to have been. Blinding of participants and personnel • Unclear risk of bias unclear blinding, unlikely to be blinded Blinding of outcome assessment • Unclear risk of bias unclear blinding, unlikely to be blinded Incomplete outcome data • Low risk of bias

Study	Title	Study characteristics	Risk of bias
		Inclusion criteria • Histologically proven small cell lung cancer measurable disease according to RECIST v1.0 • Other WHO performance status 0-2 • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • None reported • Pleural effusion unless one negative cytology • History of another malignancy except a curatively resected non-melanoma skin cancer or in situ cervical cancer • Previous treatment with systemic chemotherapy or radiation therapy • Platelets <100,000 /micro L • Age <18 years • White blood cell count <3,000 / micro L • Bilirubin >1.5 x ULN • Creatine >125 umol/l Sample characteristics • Sample size 171 enrolled, 157 analysed • Split between study groups Once daily: 89 randomized, 84 analysed Twice daily: 82 randomized, 73 analysed • Loss to follow-up 14 • %female 48% female • Average age	Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Unlikely to have been blinded or have had allocation concealed. Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		Median age 63 years Interventions • Radiotherapy All participants received 3d-CRT 5x/week beginning 3-4 weeks after day 1 of first PE-course. Once daily hypofractionated: 42Gy (15 x 2.8gy) Twice daily conventional: 45Gy (30 x 1.5gy) • Chemotherapy All participants were to receive four courses of cisplatin (75 mg/m2 IV day 1) and etoposide (100 mg/m2 IV days 1-3 every 3 weeks). Outcome measures • Survival PFS and OS, 1-year • Adverse events (grade 3 or above) Pneumonitis, oesophagitis • QoL HR-QoL using EORTC quality of life questionnaire.	
Lebeau (1999)	A randomized clinical trial comparing concurrent and alternating thoracic irradiation for patients with limited small cell lung carcinoma. "Petites Cellules" Group	Study type • Randomised controlled trial Study details • Study location France • Study setting Multiple medical centres • Study dates Inclusion period 1988 - 1994 • Duration of follow-up	Random sequence generation • Low risk of bias randomized by a centralized telephone assignment procedure, stratified by center. Allocation concealment • Unclear risk of bias Unclear however possibly done as participants were randomized by a centralized telephone assignment procedure

Study	Title	Study characteristics	Risk of bias
		Median 66 months, minimum 19 months Inclusion criteria • ECOG performance 0-3 • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • Other history of neoplasm in last 5 years; renal, hepatic, or respiratory failure; or serious cardiac disease • Previous treatment with systemic chemotherapy or radiation therapy or curative surgery • Age >70 years Sample characteristics • Sample size 164; 156 randomized • Split between study groups Continuous: 82 Alternating: 74 • Loss to follow-up 36 patients originally included were either deemed ineligible or did not receive at least 80% of planned treatment. • Average age Mean 57.5 years Interventions • Chemotherapy Treatment consisted of IV combination of cyclophosphamide (1000 mg/m2 on Day 1), doxorubicin	Blinding of participants and personnel • High risk of bias non-blinded Blinding of outcome assessment • High risk of bias non-blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Unclear allocation concealment; non-blinded Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		(45 mg/m2 on Day 1), and etoposide (150 mg/m2 on Days 1 and 2); doxorubicin was replaced by vindesine (3 mg/m2 on Day 1) for the second and third courses of chemotherapy to avoid the cardiotoxicity of the combination of doxorubicin and thoracic radiotherapy • Continuous radiotherapy 50Gy (20 x 2.5gy): 40Gy given in 16 fr over 28 days followed by 10gy in 4 fr over 7 days. Took place between days 30 - 64, covering 2nd and 3rd cycles of chemotherapy. • Alternating radiotherapy 55gy (22 x 2.5gy): first and second courses 20gy (8 x 2.5gy) over 12 days each, third course 15 gy (6x 2.5gy) over 10 days. Treatment was intercalated with 1-week rest periods before and after 2nd, 3rd, 4th and 5ht course of chemotherapy. Outcome measures • Survival	
Skarlos (2001)	Randomized comparison of early versus late hyperfractionated thoracic irradiation concurrently with chemotherapy in limited disease small-cell lung cancer: a randomized phase II study of the Hellenic Cooperative Oncology Group (HeCOG)	Study type • Randomised controlled trial Study details • Study location Greece • Study setting Multiple medical centres • Study dates Inclusion period 1993 - 1999 • Duration of follow-up A full re-evaluation included full blood count, liver and renal function tests, CT scan of the brain, thorax and abdomen	Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias Centrally randomized; unclear whether allocation was concealed Blinding of participants and personnel • High risk of bias Unlikely to have been blinded

Study	Title	Study characteristics	Risk of bias
		was performed every two cycles of chemotherapy. After completion of the treatment, the same re-evaluation was repeated every three months for the first year, every four months for the second year and every six months thereafter. The median follow-up was 35 months. • Sources of funding Not mentioned Inclusion criteria • Histologically proven small cell lung cancer Limited disease (confined to one hemithorax with involvement of mediastinal and/or ipsilateral supraclavicular lymphnodes) • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • Other Patients with pleural effusion; history of malignancy (except curatively resected non-melanoma skin cancer or in situ cervical cancer); those previously treated with systemic chemotherapy or radiotherapy • Pleural effusion • Contralateral supraclavicular lymph node involvement • ECOG performance status >2 • White blood cell count <3,500 cells/mm3 • Platelets <100,000 cells/mm3 • Hb <10 g/dl • Creatinine clearance <60 ml/min • History of another malignancy except a curatively resected non-melanoma skin cancer or in situ cervical cancer • Previous treatment with systemic chemotherapy or	Blinding of outcome assessment • High risk of bias Unlikely to have been blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • High risk of bias Greater drop-out rate in early-arm, partly due to toxicity. Overall risk of bias • High Unlikely to have been blinded, unclear allocation concealment procedures, higher attrition in early arm. Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		radiation therapy Sample characteristics • Sample size 81 people • Split between study groups Early radiotherapy + chemo = 42; Late radiotherapy + chemo = 39 • Loss to follow-up Early radiotherapy + chemo = 1; Late radiotherapy + chemo = 0 • %female Early radiotherapy + chemo = 7%; Late radiotherapy + chemo = 10% • Average age Median (range): Early radiotherapy + chemo = 61 years (40-76); Late radiotherapy + chemo = 60 years (37.5-76) Interventions • Radiotherapy Early: Received RT concurrently with first cycle of chemotherapy; Late: Received RT concurrently with fourth cycle All patients received 45Gy (30 x 1.5Gy, twice daily). • Chemotherapy "Chemotherapy consisted of carboplatin administered at an area under the curve (AUC) of six, I v by 1-hour infusion on day 1 immediately followed by etoposide at a dose of 100 mg/m2 i v by two-hour infusion for three consecutive days Treatment chemotherapy was repeated every three weeks up to a total of six cycles" • Early radiotherapy + chemo Early radiotherapy was done weeks 0 to 3. Chemotherapy consisted of carboplatin administered at an area under the curve (AUC) of six, IV by 1-hour infusion on day 1	

Study	Title	Study characteristics	Risk of bias
		immediately followed by etoposide at a dose of 100 mg/m2 IV by two-hour infusion for three consecutive days Treatment chemotherapy was repeated every three weeks up to a total of six cycles. Radiotherapy was given at a dose of 1.5 Gy per fraction twice daily up to a total of 45 Gy. Patients in this arm received radiotherapy concurrently with the first cycle of chemotherapy. An interval of at least four or, preferably, six hours between the two fractions was mandatory. Anterior- posterior fields were used The target volume for the first 30 Gy included the initial tumor area plus the bilateral medustinal and the ipsilateral hilar lymphnodes. The ipsilateral supraclavicular area was included in the radiation field, only in case of nodal involvement. The spinal cord was limited to 30 Gy The remaining 15 Gy were delivered to the primary tumor In group B, radiation fields were also determined by the initial tumor volume Dose correction was made for lung dishomogeneity. Prophylactic cranial irradiation (PCI) was delivered to patients who achieved a complete response. The whole brain was irradiated by using two lateral opposed fields to 20 Gy in five consecutive daily fractions of four Gy each. • Late radiotherapy + chemo Late radiotherapy was from weeks 9 to 12. Chemotherapy consisted of carboplatin administered at an area under the curve (AUC) of six, IV by 1-hour infusion on day 1 immediately followed by etoposide at a dose of 100 mg/m2 IV by two-hour infusion for three consecutive days. Treatment chemotherapy was repeated every three weeks up to a total of six cycles. Radiotherapy was given at a dose of 1.5 Gy per fraction twice daily up to a total of 45 Gy. Patients in this arm received radiotherapy concurrently with the fourth cycle of chemotherapy. An interval of at least four or, preferably, six hours between the two	

Study	Title	Study characteristics	Risk of bias
		fractions was mandatory. Anterior- posterior fields were used The target volume for the first 30 Gy included the initial tumor area plus the bilateral medustinal and the ipsilateral hilar lymphnodes. The ipsilateral supraclavicular area was included in the radiation field, only in case of nodal involvement. The spinal cord was limited to 30 Gy The remaining 15 Gy were delivered to the primary tumor In group B, radiation fields were also determined by the initial tumor volume Dose correction was made for lung dishomogeneity. Prophylactic cranial irradiation (PCI) was delivered to patients who achieved a complete response. The whole brain was irradiated by using two lateral opposed fields to 20 Gy in five consecutive daily fractions of four Gy each. Outcome measures • Survival overall and progression-free • Adverse events (grade 3 or above) Oesophagitis toxicity grade 3	
Spiro (2006)	Early compared with late radiotherapy in combined modality treatment for limited disease small-cell lung cancer: a London Lung Cancer Group multicenter randomized clinical trial and meta-analysis	Study type • Randomised controlled trial Study details • Study location UK • Study setting Multiple medical centres • Study dates Inclusion period: 1993 - 1999 • Duration of follow-up The median follow-up time for all patients was 63 months.	Random sequence generation • Low risk of bias Patients were randomly assigned using minimization, with stratification by center,ECOG performance status, sex, and whether or not they had undergone a CT brain scan. Allocation concealment • Unclear risk of bias unlikely to have been concealed

Study	Title	Study characteristics	Risk of bias
		• Sources of funding None reported Inclusion criteria • Histologically proven small cell lung cancer measurable/assessable and limited disease (within one hemithorax, mediastinum, or ipsilateral supraclavicular fossa) • Limited disease (within one hemithorax, mediastinum or ipsilateral supraclavicular fossa) Exclusion criteria • Previous treatment with systemic chemotherapy or radiation therapy • Age >75 years • ECOG performance status >3 • White blood cell count <3,000 /micro L • Platelets <100,000 /micro L • Bilirubin >34.2 mmol/L • Creatinine clearance <50 ml/min • Disease could not be encompassed within the radiotherapy field • Condition that would exclude the use of thoracic radiotherapy Sample characteristics • Sample size 325 people • Split between study groups Early radiotherapy + chemo = 159; Late radiotherapy + chemo = 166 • Loss to follow-up Early radiotherapy + chemo = 1; Late radiotherapy +	Blinding of participants and personnel • High risk of bias non-blinded Blinding of outcome assessment • High risk of bias Non-blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • High risk of bias 83 participants did not finish all six courses of chemotherapy, with greater drop-out in early arm. In particular, toxicity and being deemed unfit were more likely to cause drop-out in the early arm. Overall risk of bias • High High attrition, differing between arms and toxicity-related. Non-blinded and allocation unlikely to have been concealed. Directness • Partially directly applicable Used a once-daily, very high dose-per-fraction regimen

Study	Title	Study characteristics	Risk of bias
		chemo = 2 • %female Early radiotherapy + chemo = 40%; Late radiotherapy + chemo = 43% • Average age Median (range): Early radiotherapy + chemo = 62 years (34-74); Late radiotherapy + chemo = 62 years (33-74) Interventions • Early radiotherapy + chemo Patients were randomly assigned to early thoracic radiotherapy administered concurrently with the first cycle of EP (week 3). The third cycle of chemotherapy (cyclophosphamide, doxorubicin, and vincristine) in the early radiotherapy arm was delayed for 1 week to allow patients to recover from the effects of radiotherapy and chemotherapy. All patients received the following chemotherapy administered intravenously: cyclophosphamide 1,000 mg/m2, doxorubicin 50 mg/m2, and vincristine 2mg total dose administered on day 1 of a 3-week cycle (cyclophosphamide, doxorubicin, and vincristine [CAV]), alternating with etoposide (100 mg/m2) and cisplatin (25 mg/m2) administered on days 1 to 3 (EP). A total of six cycles were intended, with each chemotherapy combination administered three times. Dose modification schedules were based on either the pretreatment or nadir neutrophils and platelets (whichever were the lowest), the pretreatment serum creatinine, or creatinine clearance and bilirubin. All drugs were reduced to 75% of the dose if the nadir neutrophil count was less than 0.2 X 109/L and/or the platelet count was less than 50 X 109/L or if the pretreatment neutrophil count was less than 2.0 X 109/L and/or the platelet count was less than 100 X 109/L. If the pretreatment neutrophil count was less	

Study	Title	Study characteristics	Risk of bias
		than 1.5 X 109/L and/or the platelet count was less than 75 X 109/L, the cycle would be delayed by 1 week or until neutrophils and platelets had recovered. If the serum creatinine was between the upper limit of normal (ULN) and less than 1.3 X ULN or creatinine clearance was 50 to 70 mL/min, the dose of cisplatin was reduced to 60%. If the serum creatinine was more than 1.3 X ULN or creatinine clearance was less than 50 mL/min, the cisplatin dose was omitted. Doxorubicin was reduced by 25% if the bilirubin level was between 20 and 25.9 TRT consisted of 40 Gy in 15 fractions over 3 weeks using cobalt-60 or a linear accelerator. The radiation began on day 1 of the first course of EP (ie, week 3) provided there was no evidence of progressive disease. The technique used was anterior and parallel-opposed fields with shielding of uninvolved lung. The thoracic spine was shielded to minimize the dose to the spinal cord to 35 Gy. The field size, which was based on the prechemotherapy tumour, was to be planned to encompass the primary tumor with a minimum 2 cm margin plus the entire mediastinum, with the supraclavicular lymph nodes if they were thought to be involved. Radiotherapy was continued regardless of the neutrophil count unless there was severe toxicity. Prophylactic cotrimoxazole (2 tablets bid) was administered from day 1 of each cycle of chemotherapy in which the patient received concomitant radiotherapy until the beginning of the next cycle prophylactic cranial irradiation. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to responding patients who had a negative CT brain scan after completion of radiotherapy and all chemotherapy. Parallel opposing 20 X 17 cm fields were used, with a cobalt-60 or a linear accelerator. The whole brain was irradiated (with the inferior border following a line drawn to avoid the	

Study	Title	Study characteristics	Risk of bias
		eyes), including the temporal fossae and the intracranial portion of the cranial nerves. Treatment began on approximately day 8 of the third cycle of EP in the early radiotherapy group. • Late radiotherapy + chemo Patients were randomly assigned to late radiotherapy administered concurrently with the sixth cycle of chemotherapy (ie, third cycle of EP; week 15). All patients received the following chemotherapy administered intravenously: cyclophosphamide 1,000 mg/m2, doxorubicin 50 mg/m2, and vincristine 2mg total dose administered on day 1 of a 3-week cycle (cyclophosphamide, doxorubicin, and vincristine [CAV]), alternating with etoposide (100 mg/m2) and cisplatin (25 mg/m2) administered on days 1 to 3 (EP). A total of six cycles were intended, with each chemotherapy combination administered three times. Dose modification schedules were based on either the pretreatment or nadir neutrophils and platelets (whichever were the lowest), the pretreatment serum creatinine, or creatinine clearance and bilirubin. All drugs were reduced to 75% of the dose if the nadir neutrophil count was less than 0.2 X 109/L and/or the platelet count was less than 50 X 109/L or if the pretreatment neutrophil count was less than 2.0 X 109/L and/or the platelet count was less than 100 X 109/L. If the pretreatment neutrophil count was less than 1.5 X 109/L and/or the platelet count was less than 75 X 109/L, the cycle would be delayed by 1 week or until neutrophils and platelets had recovered. If the serum creatinine was between the upper limit of normal (ULN) and less than 1.3 X ULN or creatinine clearance was 50 to 70 mL/min, the dose of cisplatin was reduced to 60%. If the serum creatinine was more than 1.3 X ULN or creatinine clearance was less than 50 mL/min, the cisplatin dose was	

Study	Title	Study characteristics	Risk of bias
		omitted. Doxorubicin was reduced by 25% if the bilirubin level was between 20 and 25.9 TRT consisted of 40 Gy in 15 fractions over 3 weeks using cobalt-60 or a linear accelerator. The radiation began on day 1 of the third course of EP (i.e., week 15) provided there was no evidence of progressive disease. The technique used was anterior and parallel-opposed fields with shielding of uninvolved lung. The thoracic spine was shielded to minimize the dose to the spinal cord to 35 Gy. The field size, which was based on the prechemotherapy tumour, was to be planned to encompass the primary tumor with a minimum 2 cm margin plus the entire mediastinum, with the supraclavicular lymph nodes if they were thought to be involved. Radiotherapy was continued regardless of the neutrophil count unless there was severe toxicity. Prophylactic cotrimoxazole (2 tablets bid) was administered from day 1 of each cycle of chemotherapy in which the patient received concomitant radiotherapy until the beginning of the next cycle prophylactic cranial irradiation. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to responding patients who had a negative CT brain scan after completion of radiotherapy and all chemotherapy. Parallel opposing 20 X 17 cm fields were used, with a cobalt-60 or a linear accelerator. The whole brain was irradiated (with the inferior border following a line drawn to avoid the eyes), including the temporal fossae and the intracranial portion of the cranial nerves. Treatment began on approximately 2 weeks after the end of radiotherapy in the late group. Outcome measures • Survival overall and progression-free	

Study	Title	Study characteristics	Risk of bias
		• Adverse events (grade 3 or above) aesophagitis	
Sun (2013)	Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer.[Erratum appears in Ann Oncol. 2014 Aug;25(8):1672]	Study type • Randomised controlled trial Study details • Study location South Korea • Study setting Multiple medical centres in South Korea • Study dates Inclusion period: 2003- 2010 • Duration of follow-up Median 59.4 months • Sources of funding None reported Inclusion criteria • Histologically proven small cell lung cancer Limited disease (confined to one hemithorax, the mediastinum, and the bilateral supraclavicular fossae). • Other At least one measurable tumorous legion; adequate hematological, hepatic and renal function Exclusion criteria • Other Previous treatment with chemotherapy or radiation therapy • FEV/1s inadequate	Random sequence generation • Low risk of bias "randomly assigned in a 1:1 ratio into the early and late TRT arms. Treatment was assigned using block randomization with variable block sizes. At randomization, patients were stratified by center." Allocation concealment • Unclear risk of bias unclear whether allocation was concealed Blinding of participants and personnel • High risk of bias Unlikely to have been blinded Blinding of outcome assessment • High risk of bias Unlikely to have been blinded Incomplete outcome data • High risk of bias almost 20% of patients did not receive allocated radiotherapy and chemotherapy schedule. However, it is worth noting that this rate was similar between groups. Selective reporting • Low risk of bias

Study	Title	Study characteristics	Risk of bias
		Sample characteristics • Sample size 222 • Split between study groups Early: 113 (2 excluded following assignment) Late: 109 (one excluded following assignment) • Loss to follow-up 43 of originally assigned 222 participants were lost to follow-up/did not receive treatment. • %female 11% female • Average age Median age 60 years (39-75 years) Interventions • Early radiotherapy + chemo Participants received 4 cycles of chemotherapy every 21 days. Participants in this arm were assigned to receive radiotherapy with the first cycle of chemotherapy. Chemotherapy was administered every 3 weeks for four cycles. Etoposide (100 mg/m2 per day on days 1–3) and cisplatin (70 mg/m2 on day 1; EP) of each cycle were given by intravenous infusion. After the first cycle of chemotherapy, dose adjustments were allowed according to renal, hematologic, or other toxic effects. All radiotherapy was commenced using photons generated from linear accelerators following contrast-enhanced CT simulation and computerised treatment planning. The planning target volume encompassed the clinical target volume (CTV) with adequate margins in all directions (usually 1–1.5 cm). Three-dimensional conformal radiation therapy (3D-CRT) was planned in all patients, and dose constraints for lung were <20 Gy for MLD (mean lung dose) and 35% for V20. Pencil beam convolution algorithm	Other sources of bias • Low risk of bias Overall risk of bias • Moderate Unlikely that any blinding or allocation concealment was performed; high dropout rate. Directness • Partially directly applicable Used a once-daily, high dose-per-fraction regimen

Study	Title	Study characteristics	Risk of bias
		was used for dose calculation and lung tissue correction was applied. Total dose radiotherapy was 52.5 Gy with 2.1 Gy per fraction in once a day and five times a week for consecutive 5 weeks. All gross tumours were fully covered by prescribed dose and spinal cord dose was limited to 50 Gy. Radiotherapy was to begin on day 1 in this 'early' arm. Radiotherapy was to be continued, unless there was an uncontrollable severe toxic effect. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to the patients who achieved complete response or very good partial response following the planned treatment course. • Late radiotherapy + chemo Participants received 4 cycles of chemotherapy every 21 days. Participants in this arm were assigned to receive radiotherapy with the third cycle of chemotherapy (at week 9). Chemotherapy was administered every 3 weeks for four cycles. Etoposide (100 mg/m2 per day on days 1–3) and cisplatin (70 mg/m2 on day 1; EP) of each cycle were given by intravenous infusion. After the first cycle of chemotherapy, dose adjustments were allowed according to renal, hematologic, or other toxic effects. All radiotherapy was commenced using photons generated from linear accelerators following contrast-enhanced CT simulation and computerised treatment planning. The planning target volume encompassed the clinical target volume (CTV) with adequate margins in all directions (usually 1–1.5 cm). Three-dimensional conformal radiation therapy (3D-CRT) was planned in all patients, and dose constraints for lung were <20 Gy for MLD (mean lung dose) and 35% for V20. Pencil beam convolution algorithm was used for dose calculation and lung tissue correction was applied. Total dose radiotherapy was 52.5 Gy with 2.1 Gy per fraction in once a day and five times a week for	

Study	Title	Study characteristics	Risk of bias
		consecutive 5 weeks. All gross tumours were fully covered by prescribed dose and spinal cord dose was limited to 50 Gy. Radiotherapy was to begin on the third cycle of EP chemotherapy in this arm. In this 'late' arm, the CTV modification reflecting tumour shrinkage following chemotherapy was done with reference to the postchemotherapy chest CT images. The initially involved mediastinal nodal stations, however, were to be included within the CTV even though a significant clinical response had occurred. Radiotherapy was to be continued, unless there was an uncontrollable severe toxic effect. Prophylactic cranial irradiation (25 Gy in 10 fractions over 2 weeks) was administered to the patients who achieved complete response or very good partial response following the planned treatment course. Outcome measures • Survival Overall, progression-free • Adverse events (grade 3 or above) Toxic effects as according to National Cancer Institute Common Toxicity Criteria	
Takada (2002)	Phase III study of concurrent versus sequential thoracic radiotherapy in combination with cisplatin and etoposide for limited-stage small-cell lung cancer: results of the Japan Clinical Oncology Group Study 9104	Study type • Randomised controlled trial Study details • Study location Japan • Study setting 16 medical centres/hospitals across Japan • Study dates Enrolment period: May 1991 to January 1995. Final	Random sequence generation • Low risk of bias Randomization was performed centrally using the minimization method of balancing institution and PS at the JCOG Data Center. Allocation concealment • Low risk of bias Performed centrally and therefore likely to have

Study	Title	Study characteristics	Risk of bias
		analysis was performed in August 2000 • Duration of follow-up Follow-up between 5 and 9 years • Sources of funding Supported in part by Grants-in-Aid for Cancer Research 2S-1, 5S-1, 8S-1, 11S-2, and 11S-4 and by the Second Term Comprehensive 10-Year Strategy for Cancer Control, all from the Ministry of Health, Labor, and Welfare. Inclusion criteria • ECOG performance 0-2 • Histologically proven small cell lung cancer • Other Adequate organ function • Limited disease (within one hemithorax, with or without mediastinal, supraclavicular or hilar lymph node involvement) Exclusion criteria • Other Arterial oxygen pressure <70 mmHg; stage I disease according to the tumour-node-metastasis staging method; symptomatic cardiac disease or history of MI in previous 3 months. • Pleural effusion • Age >75 years • Platelets <100,000 /micro L • White blood cell count <4,000 /micro L • Hemoglobin 11 g/dL or less • Creatine > 1.5 mg/dL • Serum AST and ALT levels over 2 x ULN • Serum bilirubin over 2.0 mg/dL	been concealed Blinding of participants and personnel • Unclear risk of bias Likely non-blinded Blinding of outcome assessment • Unclear risk of bias Likely non-blinded Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Non-blinded however allocation was likely concealed and blinding is unlikely to affect primary outcome (Survival) Directness • Directly applicable

Study	Title	Study characteristics	Risk of bias
		• 24-hour creatine clearance < 60 mL/min/m2 Sample characteristics • Sample size 231; 224 analysed • Split between study groups 114 early 114 late • Loss to follow-up 3 excluded post-randomisation; a further 9 did not have toxicity data. • %female Early: 20% female Late: 18% female • Average age Early: median age 64 (range 30-74) Late: median age 65 (range 39-74) Interventions • Chemotherapy Chemotherapy was given in a 28-day cycle in the concurrent arm and a 21-day cycle in the sequential arm. Chemotherapy consisted of cisplatin (80 mg/m2 IV) on day 1 and etoposide (100 mg/m2 IV) on days 1, 2, and 3. If leukocyte decreased to< 3,000/mm3 or the platelet count < 75,000/mm3 on the first day of next cycle, chemotherapy was withheld until the counts recovered. During cycles 3 and 4, the dose of etoposide was reduced to 75% of the initial dosage for patients who experienced grade 4 hematologic toxicity in the previous cycle. Study chemotherapy was terminated in patients with serum creatinine levels of 2.0 mg/dL or higher, serum bilirubin levels of 2.0 mg/dL or higher, or failure of the hepatic transaminase level to fall below 100 IU/L after 6 weeks of the prior cycle. • Early radiotherapy + chemo	

Study	Title	Study characteristics	Risk of bias
		Began on day-2 of first cycle. Administered twice-daily for 1.5Gy per fraction to a total of 45Gy in 3 weeks. After TRT, prophylactic whole-brain irradiation was administered to patients with a complete or near-complete response, to a dose of 24 Gy in 1.5-Gy fractions twice daily, 5 days per week. • Late radiotherapy + chemo Began on day-2 of fourth cycle. Administered twice-daily for 1.5Gy per fraction to a total of 45Gy in 3 weeks. After TRT, prophylactic whole-brain irradiation was administered to patients with a complete or near-complete response, to a dose of 24 Gy in 1.5-Gy fractions twice daily, 5 days per week. Outcome measures • Survival Overall survival • Adverse events (grade 3 or above) oesophagitis; Treatment-related death	
Turrisi (1999)	Twice-daily compared with once-daily thoracic radiotherapy in limited small-cell lung cancer treated concurrently with cisplatin and etoposide	Study type • Randomised controlled trial Study details • Study location USA • Study setting Medical centre • Study dates Inclusion period: 1989-1992 • Duration of follow-up Median follow-up 8 years, 5 years minimum follow-up • Sources of funding	Random sequence generation • Low risk of bias "Randomized according to a permuted-block scheme, stratified according to Eastern Cooperative Oncology Group performance status (0 or 1 vs. 2), sex, and weight loss during the six months before entry (less than 5 percent of body weight vs. 5 percent or more)" Allocation concealment • Unclear risk of bias Unclear whether steps were taken to conceal

Study	Title	Study characteristics	Risk of bias
		Supported in part by Public Health Service grants (NCI, NIH and department of health and human services) Inclusion criteria • Histologically proven small cell lung cancer confined to one hemithorax, the ipsilateral supraclavicular fossa, or both. Exclusion criteria • Other pleural effusions found on chest films; contralateral hilar or supraclavicular adenopathy; Symptomatic cardiac disease or a myocardial infarction within the previous six months; Patients with prior cancer or prior treatment with either chemotherapy or radiotherapy Sample characteristics • Sample size 419 patients • Split between study groups Once daily: 206 Twice daily: 211 • Loss to follow-up 36 excluded from the analysis of eligible patients, 7 withdrew and never received therapy, and 29 were found to be ineligible • %female Once daily: 41% female Twice daily: 42% female • Average age Once daily: median 63 years (range 34 - 80) Twice daily: median 61 years (range 30 - 82) Interventions • Radiotherapy	allocation. Blinding of participants and personnel • High risk of bias Unlikely any blinding was done Blinding of outcome assessment • High risk of bias Unlikely any blinding was done Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Balanced groups Overall risk of bias • Moderate Likely to have been Non-blinded, allocation concealment procedures unclear. Directness • Partially directly applicable Study took place before 2000 with more recent studies of this nature using higher dose radiotherapy.

Study	Title	Study characteristics	Risk of bias
		Once daily: 45 Gy (25 x 1.8 Gy) over 5 weeks. Twice daily: 45 Gy (30 x 1.5 Gy) over 3 weeks. All patients received prophylactic cranial irradiation lasting 12 weeks • Chemotherapy "patients received four cycles of chemotherapy. Each three-week cycle consisted of 60 mg of cisplatin per square meter of body-surface area on day 1 and 120 mg of etoposide per square meter on days 1, 2, and 3." Outcome measures • Survival Overall, disease-progression free • Adverse events (grade 3 or above) Myelotoxicity (decrease in marrow-derived cells in peripheral blood counts), esophagitis, other, weight loss, fever, vomiting, pulmonary effects, infection, anaemia, thrombocytopenia, granulocytpoenia, leukopenia.	

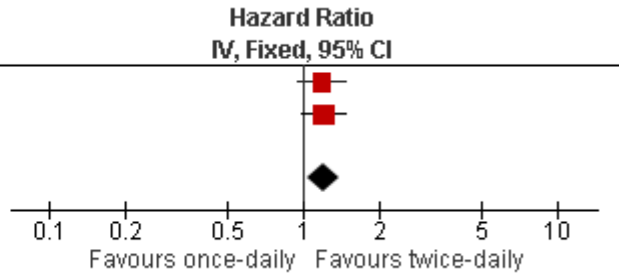
Appendix F – Forest plots

Once- versus twice-daily radiotherapy with concomitant chemotherapy for the treatment of limited-disease small cell lung cancer

Mortality: All-cause hazard ratio

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
CONVERT 2017	0.165514	0.107872	47.9%	1.18 [0.96, 1.46]
Turrisi 1999 (1)	0.18633	0.103435	52.1%	1.20 [0.98, 1.48]
Total (95% CI)			**100.0%**	**1.19 [1.03, 1.38]**

Heterogeneity: Chi² = 0.02, df = 1 (P = 0.89); I² = 0%
Test for overall effect: Z = 2.36 (P = 0.02)

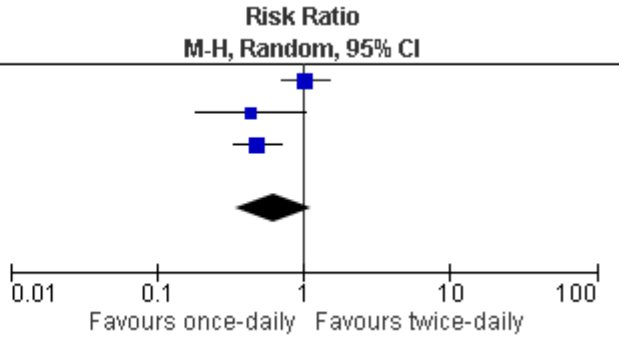


Adverse events grade 3 or above (oesophagitis, pneumonitis)

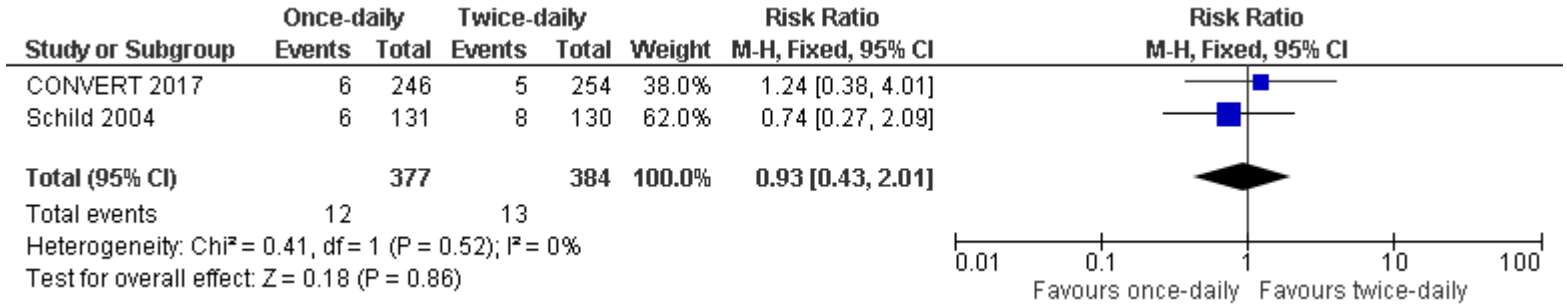
Oesophagitis

Study or Subgroup	Once-daily Events	Once-daily Total	Twice-daily Events	Twice-daily Total	Weight	Risk Ratio M-H, Random, 95% CI
CONVERT 2017	47	246	47	254	38.5%	1.03 [0.72, 1.49]
Schild 2004	7	131	16	130	23.3%	0.43 [0.18, 1.02]
Turrisi 1999	32	203	67	206	38.2%	0.48 [0.33, 0.70]
Total (95% CI)		**580**		**590**	**100.0%**	**0.63 [0.35, 1.15]**
Total events	86		130			

Heterogeneity: Tau² = 0.21; Chi² = 9.27, df = 2 (P = 0.010); I² = 78%
Test for overall effect: Z = 1.51 (P = 0.13)

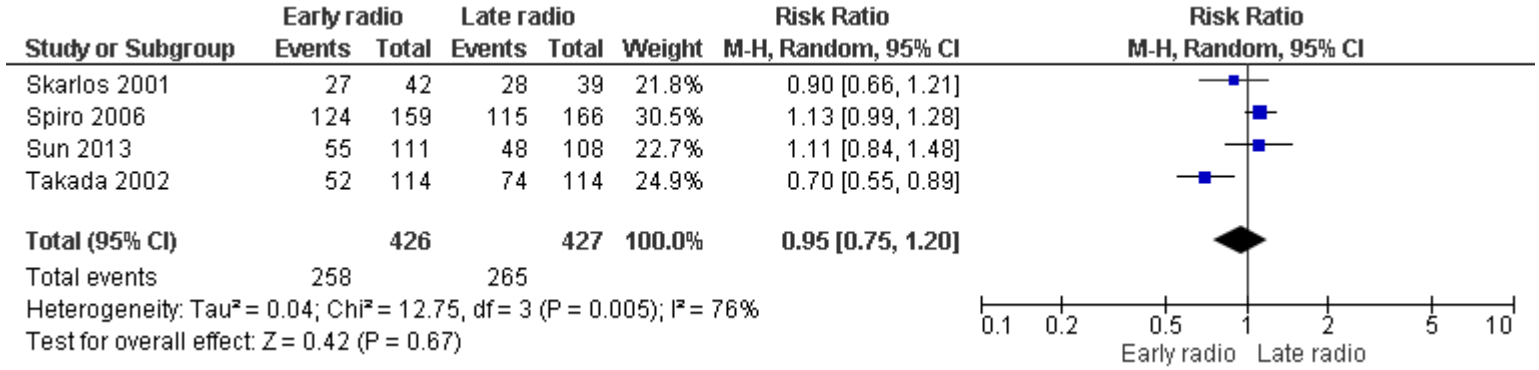


Pneumonitis



Early versus late radiotherapy with concomitant chemotherapy for the treatment of limited-disease small cell lung cancer

Mortality: Risk ratio for mortality at 24 months

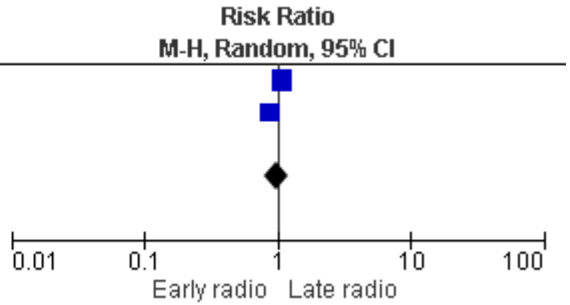


Lung cancer: diagnosis and management: Evidence reviews for the most clinically and cost-effective regimen of chemoradiotherapy for people with limited-stage SCLC (March 2019)

Mortality: Risk ratio for mortality at 36 months

Study or Subgroup	Early radio Events	Total	Late radio Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Spiro 2006	134	159	129	166	53.4%	1.08 [0.98, 1.21]
Takada 2002	80	114	91	114	46.6%	0.88 [0.76, 1.02]
Total (95% CI)		**273**		**280**	**100.0%**	**0.98 [0.80, 1.21]**
Total events	214		220			

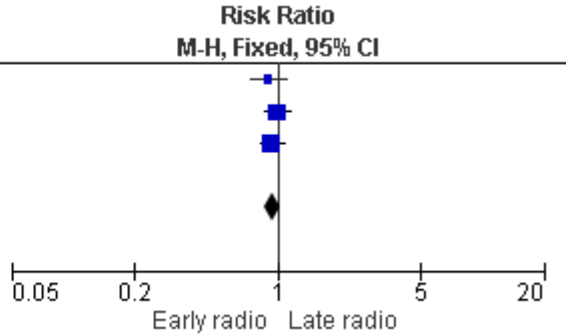
Heterogeneity: Tau² = 0.02; Chi² = 5.08, df = 1 (P = 0.02); I² = 80%
Test for overall effect: Z = 0.16 (P = 0.87)



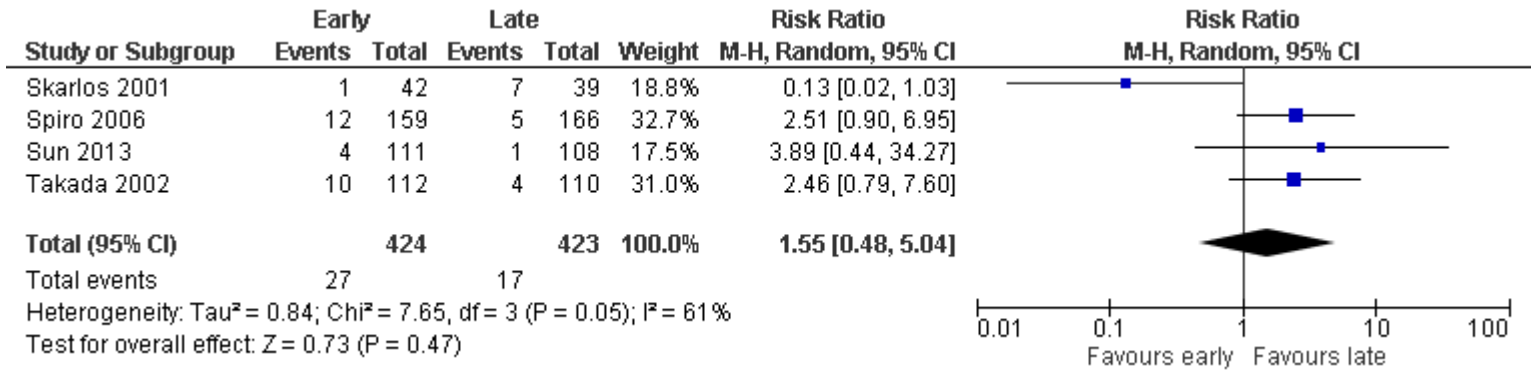
Mortality: Risk ratio for mortality at 60 months

Study or Subgroup	Early radio Events	Total	Late radio Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Skarlos 2001	33	42	34	39	16.7%	0.90 [0.74, 1.10]
Sun 2013	84	111	82	108	39.3%	1.00 [0.86, 1.16]
Takada 2002	87	114	93	114	44.0%	0.94 [0.82, 1.07]
Total (95% CI)		**267**		**261**	**100.0%**	**0.95 [0.87, 1.04]**
Total events	204		209			

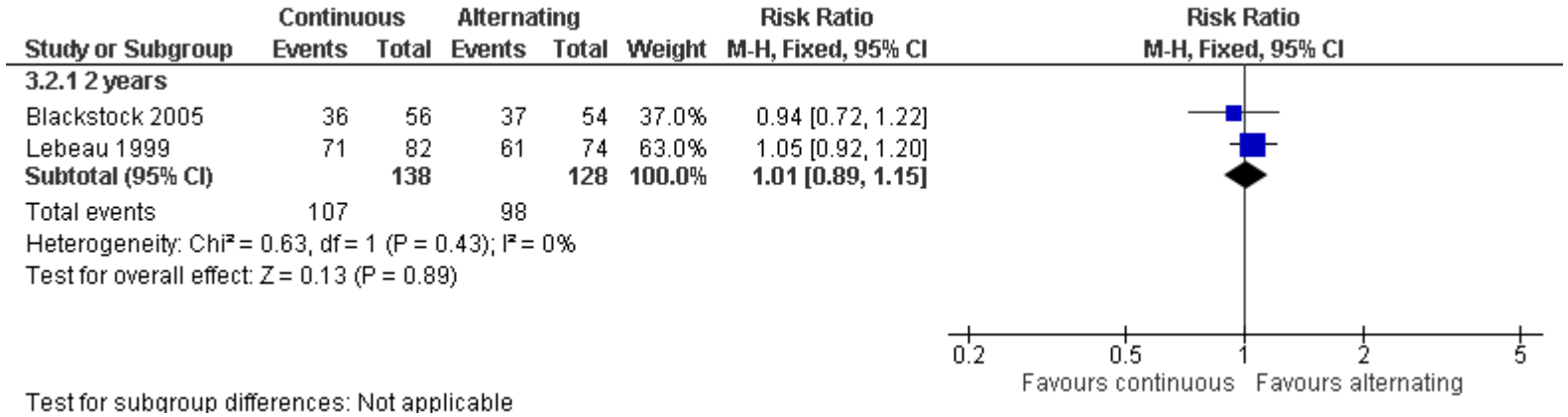
Heterogeneity: Chi² = 0.72, df = 2 (P = 0.70); I² = 0%
Test for overall effect: Z = 1.03 (P = 0.30)



Adverse events grade 3 or above: oesophagitis



Continuous versus alternating radiotherapy for the treatment of limited-disease small cell lung cancer



Appendix G – GRADE tables

Once- versus twice-daily radiotherapy with concomitant chemotherapy for the treatment of limited-disease small cell lung cancer

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Once-daily	Twice-daily	Summary of results (95% CI)	
Mortality: all-cause hazard ratio (values greater than 1 favour twice-daily)									
2 studies (CONVERT 2017; Turrisi 1999*)	RCT	Not serious	Serious[5]	Not serious	Not serious	446	460	HR 1.19 (1.03, 1.38)	Moderate
Mortality: risk ratio for mortality at 2 years (values greater than 1 favour twice-daily)									
1 study Bonner 1999	RCT	Not serious	Serious[1]	N/A	Serious[2]	132	130	RR 0.95 (0.76, 1.19)	Low
Mortality: risk ratio for mortality at 3 years (values greater than 1 favour twice-daily)									
1 study Bonner 1999	RCT	Not serious	Serious[1]	N/A	Serious[2]	132	130	RR 0.93 (0.79, 1.10)	Low
Mortality: risk ratio for mortality at 5 years (values greater than 1 favour twice-daily)									
1 study Schild 2004	RCT	Not serious	Serious[1]	N/A	Serious[2]	132	130	RR 1.01 (0.89, 1.15)	Low
Adverse events grade 3 or above: Risk ratio for oesophagitis (values greater than 1 favour twice-daily)									
3 studies Turrisi 1999 Schildd 2004 Convert 2017	RCT	Serious[4]	Serious[5]	Very serious[3]	Serious[2]	580	590	RR 0.68 (0.35, 1.15)	Very low
Adverse events grade 3 or above: Risk ratio for pneumonitis (values greater than 1 favour twice-daily)									
2 studies Schildd 2004	RCT	Serious[4]	Serious[5]	Not serious	Serious[2]	377	384	RR 0.93 (0.43, 2.01)	Very low

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Once-daily	Twice-daily	Summary of results (95% CI)	
Convert 2017									
Adverse events grade 3 or above: Risk ratio for cardiac toxicity (values greater than 1 favour twice-daily)									
1 study Schild	RCT	Serious[4]	Serious[1]	N/A	Serious[2]	131	130	RR 0.20 (0.02, 1.68)	Very low

1. Partially directly applicable: Participants were delayed in being randomized to and receiving radiotherapy until after 3 cycles of chemotherapy.
2. 95% CI of the effect size crosses the line of no effect.
3. I^2 >66.6%.
4. Studies were not blinded and this had the potential to bias reporting of outcome.
5. Long length of time difference between the studies resulting in differences in standard of care.

* Hazard ratio data taken from De Ruysscher 2016 meta-analysis as Estimate in original paper is inconsistent with confidence intervals

Once-daily hypofractionated versus twice-daily hyperfractionated radiotherapy for the treatment of limited-disease small cell-lung cancer

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Once-daily	Twice-daily	Summary of results (95% CI)	
Mortality: Any-cause hazard ratio (values greater than 1 favour twice-daily)									
1 study Halvorsen 2016	RCT	Not serious	Not serious	N/A	Serious[2]	84	73	RR 1.19 (0.79, 1.79)	Moderate
Adverse events grade 3 or above: Risk ratio for oesophagitis (values greater than 1 favour twice-daily)									
1 study Gronberg 2016	RCT	Serious[1]	Not serious	N/A	Serious[2]	84	73	RR 0.94 (0.60, 1.49)	Low
Adverse events grade 3 or above: Risk ratio for Pneumonitis (values greater than 1 favour twice-daily)									
1 study Gronberg 2016	RCT	Serious[1]	Not serious	N/A	Serious[2]	84	73	RR 1.45 (0.36, 5.85)	Low

1. Studies were not blinded and this had the potential to bias reporting of outcome.

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Once-daily	Twice-daily	Summary of results (95% CI)	
2. 95% CI of the effect size crosses the line of no effect.									

Early versus late radiotherapy with concomitant chemotherapy for the treatment of limited-disease small cell lung cancer

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Early	Late	Summary of results (95% CI)	
Mortality: risk ratio for mortality at 12 months (values greater than 1 favour late)									
1 study Spiro 2006	RCT	Not serious	Serious[5]	N/A	Serious[3]	159	166	RR 1.12 (0.87, 1.46)	Low
Mortality: risk ratio for mortality at 24 months (values greater than 1 favour late)									
4 studies Skarlos 2001 Spiro 2006 Sun 2013 Takada 2002	RCT	Not serious	Serious[1]	Very serious[2]	Serious[2]	426	427	RR 0.95 (0.75, 1.20)	Very low
Mortality: risk ratio for mortality at 36 months (values greater than 1 favour late)									
2 studies Spiro 2006 Takada 2002	RCT	Not serious	Serious[5]	Very serious[2]	Serious[2]	273	280	RR 0.98 (0.80, 1.21)	Very low
Mortality: risk ratio for mortality at 60 months (values greater than 1 favour late)									
3 studies Skarlos 2001 Sun 2013 Takada 2002	RCT	Not serious	Serious[1]	Not serious	Serious[3]	267	261	RR 0.95 (0.87, 1.04)	Low
Adverse events grade 3 or above: Oesophagitis (values greater than 1 favour late)									

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Early	Late	Summary of results (95% CI)	
4 studies Skarlos 2001 Spiro 2006 Sun 2013 Takada 2002	RCT	Serious[4]	Serious[1]	Serious[6]	Serious[3]	424	423	RR 1.55 (0.48, 5.04)	Very low
Adverse events grade 3 or above: Pneumonitis (values greater than 1 favour late)									
1 study Sun 2013	RCT	Serious[4]	Serious[5]	N/A	Serious[3]	111	108	RR 1.62 (0.40, 6.62)	Very low
Adverse events grade 3 or above: Cardiac (values greater than 1 favour late)									
1 study Spiro 2006	RCT	Serious[4]	Serious[5]	N/A	Serious[3]	159	166	RR 9.39 (0.51, 173.08)	Very low

1. Partially directly applicable: Two or more studies used a once-daily, very high dose-per-fraction regimen.
2. I^2 >66%.
3. 95% CI of the effect size crosses the line of no effect.
4. Non-blinded and this had the potential to bias reporting of outcome.
5. Partially directly applicable: Study used a once-daily regimen.
6. I^2 >33%.

Continuous versus alternating radiotherapy for the treatment of limited-disease small cell lung cancer

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Continuous	Alternating	Summary of results (95% CI)	
Mortality: risk ratio for staying mortality at 2 years (values greater than 1 favour alternating)									
2 studies	RCT	Not serious	Not serious	Not serious	Serious[2]	138	128	RR 1.01 (0.89, 1.15)	Moderate

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Continuous	Alternating	Summary of results (95% CI)	
Blackstock 2005 Lebeau 1999									
Mortality: risk ratio for mortality at 3 years (values greater than 1 favour alternating)									
1 study Lebeau 1999	RCT	Not serious	Not serious	N/A	Serious[2]	82	74	RR 1.05 (0.96, 1.16)	Moderate
Mortality: risk ratio for mortality at 5 years (values greater than 1 favour alternating)									
1 study Blackstock 2005	RCT	Not serious	Not serious	N/A	Serious[2]	56	54	RR 1.03 (0.86, 1.24)	Moderate
Adverse events grade 3 or above: Risk ratio for oesophagitis (values greater than 1 favour alternating)									
1 study Blackstock 2005	RCT	Serious[1]	Not serious	N/A	Serious[2]	56	54	RR 2.41 (0.49, 11.90)	Low

1. Study was not blinded and this had the potential to bias reporting of outcome.
2. 95% CI of the effect size crosses the line of no effect.

Appendix H – Excluded Studies

Study	Title	Reason for exclusion
Anonymous (1983)	Cytotoxic chemotherapy before and after radiotherapy compared with radiotherapy followed by chemotherapy in the treatment of small-cell carcinoma of the bronchus: the results up to 36 months	• Excluded post committee meeting Pre-1999
Choi (1998)	Phase I study to determine the maximum-tolerated dose of radiation in standard daily and hyperfractionated-accelerated twice-daily radiation schedules with concurrent chemotherapy for limited-stage small-cell lung cancer	• Non-RCT Non-randomised
De Ruysscher (2006)	Time between the first day of chemotherapy and the last day of chest radiation is the most important predictor of survival in limited-disease small-cell lung cancer	• More recent systematic review included that covers the same topic
De Ruysscher (2012)	Radiation-induced oesophagitis in lung cancer patients. Is susceptibility for neutropenia a risk factor?	• Non-RCT Non-randomized
De Ruysscher (2016)	Impact of thoracic radiotherapy timing in limited-stage small-cell lung cancer: usefulness of the individual patient data meta-analysis	• Systematic review with all data taken from individual studies
Fried (2004)	Systematic review evaluating the timing of thoracic radiation therapy in combined modality therapy for limited-stage small-cell lung cancer	• Systematic review with all data taken from individual studies
Gregor (1995)	Acute toxicity of alternating schedule of chemotherapy and irradiation in limited small-cell lung cancer in a pilot study (08877) of the EORTC Lung Cancer Cooperative Group	• More recent update of this study
Gregor (1997)	Randomized trial of alternating versus sequential radiotherapy/chemotherapy in limited-disease patients with small-cell lung cancer: a European Organization for Research and Treatment of Cancer Lung Cancer Cooperative Group Study	• Excluded post committee meeting Pre-1999
Hackshaw (2007)	The timing of radiotherapy when given with chemotherapy in patients with limited-disease small cell lung cancer	• Full text paper not available
Halvorsen (2016)	Tumour size reduction after the first chemotherapy-course and outcomes of chemoradiotherapy in limited disease small-cell lung cancer	• More recent update of this study
Hu (2010)	A prospective randomized study of the radiotherapy volume for limited-stage	• Study does not contain any relevant

Study	Title	Reason for exclusion
	small cell lung cancer: a preliminary report	interventions
Huncharek (2004)	A meta-analysis of the timing of chest irradiation in the combined modality treatment of limited-stage small cell lung cancer	• More recent systematic review included that covers the same topic
Jeremic (1997)	Initial versus delayed accelerated hyperfractionated radiation therapy and concurrent chemotherapy in limited small-cell lung cancer: a randomized study	• Excluded post committee meeting Pre-1999
Kraft (1990)	Role of thoracic radiotherapy combined with chemotherapy in limited stage small cell lung cancer (SCLC). A randomized multicenter phase III trial	• Excluded post committee meeting Pre-1999
Le Chevalier (1988)	Combination of chemotherapy and radiotherapy in limited small cell lung carcinoma: Results of alternating schedule in 109 patients	• Non-RCT Non-randomized
Lee (2002)	Randomized Trial of Early Versus Late Alternating Radiotherapy/ Chemotherapy in Limited-Disease Patients with Small Cell Lung Cancer	• Study not reported in English
Liu (2010)	Whole brain radiotherapy concomitant or sequential Vm26/DDP in treating small cell lung cancer patients with brain metastases	• Study does not contain any relevant interventions
Lu (2014)	A meta-analysis of randomized controlled trials comparing early and late concurrent thoracic radiotherapy with etoposide and cisplatin/carboplatin chemotherapy for limited-disease small-cell lung cancer	• Systematic review with all data taken from individual studies
Lueza (2014)	Phase III trial of concurrent thoracic radiotherapy with either first- or third-cycle chemotherapy for limited-disease small-cell lung cancer	• Conference abstract
Murray (1993)	Importance of timing for thoracic irradiation in the combined modality treatment of limited-stage small-cell lung cancer. The National Cancer Institute of Canada Clinical Trials Group	• Excluded post committee meeting Pre-1999
Park (1996)	The effects according to the timing of thoracic radiotherapy in limited stage small cell lung cancer	• Study not reported in English
Perez (1981)	Thoracic and elective brain irradiation with concomitant or delayed multiagent chemotherapy in the treatment of localized small cell carcinoma of the lung: a randomized prospective study by the Southeastern Cancer Study Group	• Study does not contain any relevant interventions

Study	Title	Reason for exclusion
Pijls-Johannesma (2004)	Early versus late chest radiotherapy in patients with limited-stage small cell lung cancer	• Systematic review with all data taken from individual studies
Pijls-Johannesma (2007)	Timing of chest radiotherapy in patients with limited stage small cell lung cancer: a systematic review and meta-analysis of randomised controlled trials	• Systematic review with all data taken from individual studies
Qiao (2004)	Concurrent radiotherapy combined with carboplatin and etoposide in limited stage small cell lung cancer	• Study not reported in English
Samson (2007)	Evidence for management of small cell lung cancer: ACCP evidence-based clinical practice guidelines (2nd edition)	• More recent systematic review included that covers the same topic
Sculier (2008)	A phase III randomised study of concomitant induction radiochemotherapy testing two modalities of radiosensitisation by cisplatin (standard versus daily) for limited small-cell lung cancer	• Study does not contain any relevant interventions
Seidenfeld (2006)	Management of small cell lung cancer	• Study does not contain any relevant interventions
Sheikh (2011)	Use of G-CSF during concurrent chemotherapy and thoracic radiotherapy in patients with limited-stage small-cell lung cancer safety data from a phase II trial	• Study does not contain any of the outcomes of interest
Work (1997)	Randomized study of initial versus late chest irradiation combined with chemotherapy in limited-stage small-cell lung cancer. Aarhus Lung Cancer Group	• Excluded post committee meeting Pre-1999
Ye (2011)	Three-dimensional conformal radiotherapy or intensity-modulated radiotherapy combined with concurrent sequential chemotherapy for limited stage small cell lung cancer	• Study not reported in English

Appendix I – References

Clinical Studies - Included

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Health Economic studies – Included

None

Health Economic studies – Excluded

None