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Lung Cancer Update

Evidence reviews for the clinical and cost effectiveness of different radiotherapy regimens with curative intent for NSCLC

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Evidence reviews

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Draft for Consultation

These evidence reviews were developed by the NICE Guideline Updates Team

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Evidence reviews for the clinical and cost effectiveness of different radiotherapy regimens with curative intent for NSCLC

Review questions

RQ3.2: What is the clinical and cost effectiveness of different radiotherapy regimens with curative intent for NSCLC?

Introduction

New evidence on stereotactic ablative radiotherapy (SABR) for people with early stage NSCLC has become available. The aim of this review is to assess which radiotherapy regimens with curative intent are most effective for people with NSCLC.

Table 1: PICO table

Population	People with NSCLC
Interventions	• SABR • Other radical radiotherapy regimens including continuous hypofractionated accelerated radiotherapy (CHART)
Comparators	• Each other • Placebo or usual care • The same radiotherapy technique with a different total dose and fractionation • Surgery (where indicated)
Outcomes	• Mortality • Quality of life • Length of stay • Exercise tolerance • Adverse events • Treatment-related dropout rates • Pain

Methods and process

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

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

Clinical evidence

Included studies

This review was conducted as part of a larger update of the NICE Lung cancer: diagnosis and management guideline (CG121).

Randomised controlled trials

A systematic literature search for randomised controlled trials (RCTs) and systematic reviews of RCTs with a date limit of 2005 yielded 10,142 references. A date limit of 2005 was chosen because of advances in radiotherapy technology. For example, more common usage of multileaf collimators to focus beams and imaging to direct the focus.

Papers returned by the literature search were screened on title and abstract, with 70 full-text papers ordered as potentially relevant systematic reviews or RCTs. Studies were excluded if they did not meet the criteria of enrolling participants with non-small cell lung cancer (NSCLC).

Seventeen papers representing 13 unique RCTs were included after full text screening.

Table of included RCTs

Study	Number of patients	NSCLC stages included	Interventions	Follow-up period	Study location
Baumann 2011	406	Stages I to IIIB	CHARTWEL[1] vs conventional fractionation	The median follow-up period was 3.3 years in one arm and 3.4 years in the other	Poland, Germany and the Czech Republic
Belani 2005	112	Stages IIIA, IIIB	Chemotherapy, conventional fractionation vs chemotherapy, HART[2]	The minimum follow-up period was 36 months for surviving participants	USA
Bradley 2015	495	Stages IIIA, IIIB	Chemotherapy, conventional fractionation 60 Gy vs chemotherapy, conventional fractionation 74 Gy	The median follow-up period was 22.9 months	USA and Canada
Chang 2015	58	Stage I	SABR vs lobectomy	The median follow-up period was 40.2 months	The Netherlands, USA, China and France
Curran 2011	382	Stages II to IIIB	Chemotherapy, conventional fractionation vs chemotherapy, conventional fractionation	The median follow-up was 11 years	USA
Eberhardt 2015	161	Stages IIIA, IIIB	Chemotherapy, conventional fractionation, conventional fractionation boost vs chemotherapy, conventional fractionation, surgery	Follow-up was a minimum of 1 year	Germany
Girard 2010	46	Stage IIIA	Chemotherapy, conventional fractionation, surgery vs chemotherapy, surgery	The median follow-up period was 31.4 months	France
Katakami 2012	56	Stage IIIA	Chemotherapy, conventional fractionation, surgery vs chemotherapy, surgery	The median follow-up period was 61 months	Japan
Nyman 2016	102	Stage I	SABR vs conventional fractionation	The median follow-up period was 37 months	Sweden and Norway
Pless 2015	231	Stage IIIA	Chemotherapy, conventional fractionation, surgery vs chemotherapy, surgery	The median follow-up period was 52.4 months	Switzerland, Germany and Serbia
van Meerbeeck 2007	308	Stage IIIA	Chemotherapy, conventional fractionation vs chemotherapy, surgery	The median follow-up period was 6 years	The Netherlands
Videtic 2015	82	Stage I	SABR 34 Gy in 1 fraction vs SABR 48 Gy in 4 fractions	The median follow-up period was 30.2 months	USA
Wang 2016	50	Stages I to IV	SABR vs conventional fractionation	The "average" follow-up period was 32.5 months	China

1. CHARTWEL, Continuous Hyperfractionated Accelerated RadioTherapy WeekEndLess
2. HART, Hyperfractionated Accelerated RadioTherapy

Observational studies

The committee agreed that there was insufficient evidence to judge the effectiveness of SABR based on the randomised controlled trials alone. Therefore, a systematic literature search for all observational studies (having at least two arms) with a date limit of 2005 yielded 16,595 references.

Papers were screened on title and abstract, with 99 full-text papers ordered as potentially relevant systematic reviews or observational studies. Studies were excluded if they did not meet the criteria of enrolling people with non-small cell lung cancer (NSCLC).

Ten papers representing 3 systematic reviews covering 23 observational studies and 7 further individual observational studies not included in the systematic reviews were included after full text screening.

Table of included observational studies

Study	Number of patients	NSCLC stages included	Interventions	Follow-up period	Study location
Bryant 2018	4069	Stage I	SABR vs lobectomy and SABR vs sublobar resection	The median follow-up period for lobectomy, sublobar resection, and SBRT people was 2.9, 2.6, and 1.5 years, respectively	USA
Chen 2018 (systematic review of 13 studies)	19992	Stages I, II	SABR vs lobectomy and SABR vs sublobar resection	The median follow-up periods of the 12 relevant observational studies ranged from 16 months to 80 months. This is a systematic review	Japan, USA, Canada, the Netherlands
Cornwell 2018	183	Stage I	SABR vs lobectomy	The median follow-up period was 3.7 years	USA
Grills 2010	124	Stage I	SABR vs sublobar resection	The median potential follow-up for all patients was 2.5 years	USA
Jeppesen 2013	132	Stage I	SABR vs conventional fractionation	The follow-up period was 5 years	Denmark
Koshy 2015	13036	Stage I	SABR vs conventional fractionation and SABR vs no therapy	The median follow-up period was 68 months	USA
Lanni 2011	86	Stage I	SABR vs conventional fractionation	The median potential follow-up period was 36 months	USA
Nakagawa 2014	218	Stage I and aged 75 years or older	SABR vs surgery (any)	5 years	Japan
Puri 2012	114	Stage I	SABR vs surgery (any)	4 years	USA
Tong 2015	68	Stage I	SABR vs conventional fractionation	The follow-up period was 1 year	China
Tu 2017	238	Stage I	SABR vs conventional fractionation	The median follow-up period was 28 months	Taiwan
Van den Berg 2015	340	Stage I	SABR vs surgery (any)	The duration of follow-up was not mentioned	The Netherlands
Wang 2016	70	Stage I	SABR vs surgery (any)	5 years	China
Widder 2011	229	Stage I	SABR vs conventional fractionation	The median follow-up period was 13 months	The Netherlands

For the search strategy, please see appendix C. For the clinical evidence study selection flowchart, see appendix D.

Outcomes

The reported outcomes with extractable data were mortality, adverse events caused by radiotherapy and quality of life.

For the full evidence tables and full GRADE profiles for included studies, please see appendices E and F.

Excluded studies

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

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 3,465 citations was returned. Details of the literature search are provided in Appendix C. Following review of titles and abstracts, 26 full-text studies were retrieved for detailed consideration. In total, 5 cost–utility analyses were identified and one cost-effectiveness study. In total, 6 studies were included in the initial review. A final up-to-date rerun of the evidence base uncovered an additional cost-utility study. This brought the total number of studies to 7.

PET-ART vs Conventional Fixed-Dose CTG-Based Radiation Therapy Treatment (CRT)

Bongers et al. (2015) created a micro-simulation multi-state statistical model to evaluate long-term health effects, costs, and cost-effectiveness of positron emission tomography (PET)-based isotoxic accelerated radiation therapy treatment (PET-ART) compared with conventional fixed-dose CT-based radiation therapy treatment (CRT) in non-small cell lung cancer (NSCLC) for NSCLC patients with inoperable stage I-IIIB cancer. Primary model outcomes were the difference in life-years (LYs), quality-adjusted life-years (QALYs), costs, and the incremental cost-effectiveness and cost/utility ratio (ICER and ICUR) of PET-ART versus CRT. The model had a time-horizon of 3 years and consisted of four health states. All patients started in the “alive” state and either had a “local occurrence”, a distant “metastases”, or “died”.

With the CRT regimen, patients received a radiation dose of either 70 Gy (stage I-II) or 60 Gy (stage III), in daily 2-Gy fractions in a mean overall treatment time of 42 days. With the PET-ART regimen, patients received a radiation dose of 54.0-79.2 Gy, delivered in 1.8-Gy fractions, twice daily, depending on the mean lung dose or spinal cord dose constraint. The mean overall treatment time was 25 days.

Treatment effects, tumour characteristics, toxicity and follow-up data were based on data of 200 patients from the Maastro Clinic data, collected between 2002 and 2009 (Dehing-Oberije (2009). Resource use estimates were also based on the data of the Maastro Clinic and the literature (Pompen (2009), Peeters (2010), Grutters (2010). Costs were based on the Dutch Manual for Costing in Economic Evaluations, the Dutch Healthcare Board, or the Pharmacotherpeutical Compass and the literature (Ploder (2006), Oosterbrink (2004), Dutch Healthcare Authority Tarrif (2016) and Zorginstituut Nederland (2012)). All costs were reported in Euros and the price year was 2012. Costs and outcomes discounted at 3% beyond the first year.

The utility estimates for the model were obtained from a meta-analysis of 23 studies of utilities in NSCLC patients (Sturza et al. (2010)) and from a cost-effectiveness study (Grutters et al. (2010)).

Model outcomes were obtained from averaging the predictions for 50,000 simulated patients. For the probabilistic analysis, distributions were assigned to all the model input parameters. 1000 parameter sets were randomly created, and for each set of parameters, 50,000 patients were simulated. Model predictions for the difference in costs and LYs between PET-ART and CRT, and for the difference in costs and QALYs were represented on a cost-effectiveness plane.

The results of the model are shown in Table 2.

Table 2. Costs and effects taken from Bongers et al. (2015)

	Absolute		Incremental		
Strategy	**Cost**	**Effect**	**Cost**	**Effect**	**ICER**
CRT	€ 24,879	1.07 QALYs 1.39 Lys			
PET-ART	€ 25,449	1.40 QALYs 1.82 Lys	€ 569	0.33 QALYs 0.42 LYs	€ 1,360/LY €1,744/QALY

The authors found that incremental life years and incremental QALYs were 0.42 and 0.33 in favour of PET-ART. PET-ART was slightly more expensive; incremental costs of PET-ART compared with CRT were € 569. The incremental costs and effects resulted in an ICER of €1,360/LY and €1,744/QALY. For PET-ART, the proportions of local recurrence, distant metastases, and death after three years were smaller than for CRT. However, proportions of severe toxicity were smaller for CRT.

Of 1000 ICER replicates for both QALYs and LYs, the authors found that 36% of the replicates are in the lower right quadrant, indicating that PET- ART both improves outcomes and reduces costs. The remaining 64% were located in the upper right quadrant, indicating that PET-ART improves outcomes at increased costs compared with CRT. The cost-effectiveness acceptability curve showed that at a threshold value of €18,000 per QALY, there is a 95% probability that PET- ART is cost-effective.

The authors concluded that according to the data available to them, PET-ART is likely to be more effective than CRT and seems to be cost-effective as well. There is a 64% probability that PET-ART is more costly, but the additional cost is limited. These findings can support decision makers to implement PET-ART schemes in radiation therapy treatment planning.

SABR modelled with the CRMM

The model in **Louie et al. (2014)** measured the financial and health impact of introducing stereotactic ablative radiotherapy (SABR) for stage I non-small cell lung cancer (NSCLC) in in the context of the publically funded Canadian health care system. SABR was compared against radiotherapy (RT), best supportive care (BSC), sublobar resection and lobectomy.

The whole-system model had the capability to simulate the impact of different oncologic health policies such as risk factor modification, screening interventions, and new treatment modalities for common malignancies. The relative merits of these strategies could be analysed by forecasting their influence on cancer incidence, mortality, costs, quality-adjusted life-years (QALYs), and accordingly, cost-effectiveness. This model used discrete-event, continuous-time, Monte Carlo microsimulation of millions of individual biographies of all Canadians from birth to death.

In the model, patients were evaluated by their family physician and referred for investigation by a specialist, after which stage- and histology appropriate treatment is initiated. The proportion of patients receiving alternative treatments due to advanced age, comorbidity, and/or poor performance status are informed by provincial patterns of practice. Survival by stage and histology were extracted from a review of the medical literature, and follow-up procedures were conducted in accordance with published provincial guidelines (Evans et al. (2013)).

To model outcomes for SABR patients who previously received no treatment or conventional RT, the Radiation Therapy Oncology Group (RTOG) 0236 multi-institutional SABR trial was used.

The model was validated internally using Statistics Canada data and externally with Canadian Cancer Registry data to ensure that all demographics, economics, risk factors, incidence of cancer, and oncologic outcomes reflected observed levels in the Canadian population before 2007 (Evans et al. (2012)).

Professional fees were obtained from the most recent edition of the Ontario schedule of fees and benefits (http://www.health.gov.on.ca/en/). Other direct and indirect health care costs abstracted in the previous version of the model were adjusted to reflect 2013 Canadian dollars using the consumer price index from the Bank of Canada. A 10-year time horizon was used, and both costs and QALYs were discounted at a 3% rate.

The CRMM did not allow for probabilistic or deterministic sensitivity analyses.

The results of the model are shown in Table 3.

Table 3. Costs and effects taken from Louie et al. (2014)

Scenario in which SABR is introduced	Incremental Cost	Incremental Effect	ICER (in QALYs)
Radiotherapy	- $25,187,816	2,510 LY 1,693 QALYs	**Dominated by SABR**
Best supportive care	-$29,951,612	875 LY 660 QALYs	**Dominated by SABR**
Sublobar resection	-$23,288,656	3,385 LY 2,353 QALYs	**Dominated by SABR**
Lobectomy	-$164,370,264	-570 LY -294 QALYs	$55,909/QALY vs SABR

In patients who were eligible for SABR, BSC and sublobar resection, SABR was found to be more effective and produce a saving and therefore is the dominant treatment option. In patients who were eligible for both SABR and lobectomy, SABR produced a saving but also resulted in the loss of QALYs. At a willingness-to-pay threshold of $100,000/QALY, lobectomy would be the preferred treatment option.

The authors concluded that while SABR is cost-effective for medically inoperable and borderline operable patients, lobectomy is preferred for those who are eligible. The use of SABR is thus projected to result in significant cost and survival gains at the population level.

SBRT vs CFRT

Mitera et al. (2014) conducted a cost-effectiveness study using data collected from a clinical database comparing conventionally fractionated radiotherapy (CFRT) and stereotactic body radiotherapy (SBRT) in patients with stage I non-small cell lung cancer (NSCLC) who were either ineligible or refused surgery. Data were retrospectively collected from an in-house research ethics board–approved prospective clinical database of patients treated at the Princess Margaret Cancer Centre in Toronto, Ontario, Canada, from March 2002 to June 2010. All patients (n=168) were included if they received either a full course of CFRT (n=50) or SBRT (n=118), defined as having completed their prescribed dose of radiation. Overall, 58% of patients were men, and 42% were women, whilst median age of patient was 74 years (ranging from 48 to 94 years).

In the conventionally fractionated radiotherapy (CFRT) regimen, patients received a total dose of approximately 50 to 70 Gy over25 to 35 treatment sessions. In the stereotactic body radiotherapy (SBRT) regimen, patients received 48 to 60 Gy in three to eight treatments.

Probabilities for hospitalization for esophagitis, pneumonitis (grade ≥3), and chest pain were obtained from Sher et al. (2011) and Grutters et al. (2010).

Utilities, and therefore QALYs, were not measured in this study. Instead, outcomes as a result of treatment effects were measured in life years (LY). Overall survival was estimated using Kaplan-Meier estimates of an assumed exponential distribution from the start of treatment to either the date of death or of last follow-up (censored). Mean survival time was calculated as the area under the survival curve, with 95% Cs calculated using SEM survival, assuming a Gaussian distribution.

The authors conducted a one-way and two-way sensitivity analysis around the variables associated with each treatment technique to account for any variability over time.

The base case results from the public payer perspective are shown in Table 4 whilst only radiation costs are shown in Table 5.

Table 4: Costs and effects from the public payer perspective – taken from Mitera et al. (2014).

Strategy	Mean		Incremental		
	Cost	Effect	Cost	Effect	ICER
CFRT	$6,886	2.83 LY	-	-	-
SBRT	$8,042	3.86 LY	$1,156	1.03 LY	$1,120 per LYG

Table 5: Costs and effects from the hospital perspective (radiation treatment delivery only) – taken from Mitera et al. (2014).

Strategy	Mean		Incremental		
	Cost	Effect	Cost	Effect	ICER
CFRT	$5,989	2.83 LY	-	-	-
SBRT	$6,962	3.86 LY	$973	1.03 LY	$942 per LYG

Mean overall survival was 2.83 years (95% CI, 1.8 to 4.1) for CFRT and 3.86 years (95% CI, 3.2 to not reached) for SBRT (P = .06). Mean costs for CFRT were $6,886 overall and $5,989 for radiation treatment delivery only versus $8,042 and $6,962, respectively, for SBRT. Incremental costs (incremental cost-effectiveness ratio [ICER]) per LYG for SBRT versus CFRT were $1,120 for the public payer and $942 for radiation treatment alone. Varying survival and labour costs individually (±20%) created the largest changes in the ICER, and simultaneous adjustment (± 5% to ± 30%) confirmed cost effectiveness of SBRT.

In a one-way sensitivity analysis from the MOHLTC perspective, varying costs by ±20%, the biggest drivers to influence the ICER were survival differences and direct labour costs. When survival for CFRT was decreased by 20%, the ICER became $742 per LYG; it became $4,558 per LYG when survival for SBRT was decreased by 20%. When survival was increased by 20% for CFRT, the ICER became $2,541 per LYG, it became $657 per LYG when survival for SBRT was increased by 20%. When the costs of direct labour for CFRT were both decreased and increased by 20%, the ICER was accordingly reflected as $1,845 and $452 per LYG, respectively; it was $253 and $2,940 per LYG when direct labour costs for SBRT were increased and decreased by 20%. Results for the two-way sensitivity analysis produced similar results. When the total cost for SBRT and incremental effectiveness were varied simultaneously by ±30%, the ICER ranged from a $936 cost savings per LYG for using SBRT to an incurred cost of $4,938 per LYG.

The authors acknowledged that the clinical data set used in the study were not taken from a randomised controlled trial, as this data comparing SBRT and CFRT does not yet exist, and that the robustness of the results would be improved if a controlled trial data was used to inform treatment effects.

The authors concluded that using a threshold of $50,000 per LYG, SBRT seems cost effective and that the results require confirmation with randomized data.

SBRT compared with surgical resection

Shah et al. (2013) created a Markov model to compare the cost-effectiveness of stereotactic body radiation therapy (SBRT) with wedge resection (WR) and lobectomy for marginally operable (MO) and clearly operable (CO) patients, respectively, using a payer (Medicare) perspective. The patient population eligible for treatment were 65 year old patients with medically operable stage I non-small cell lung cancer (NSCLC). The model compared three treatment strategies. For patients who are MO, SBRT and wedge resection were compared.

For patients who are CO, the cost-effectiveness of SBRT and lobectomy were compared. The model had a time-horizon of five years.

The local recurrence rate (LR) for SBRT was taken from Lagerwaard et al. (2012), a three-year study of potentially operable patients in The Netherlands. The probability for no evidence of disease (NED) to LR for wedge resection was taken from Grills et al. (2010). The probability values for NED to locoregional recurrence (LRR) were taken from Carr et al. (2012) and Arrigada et al. (2010).

Costs used in the model were taken from Medicare payment schedules. All costs were inflated to 2012 US dollars using the Consumer Price Index (US Department of Labor. Bureau of Labor Statistics.) if necessary. All costs and outcomes beyond first year discounted at 3% annually

Utility scores used in the model were taken from Doyle et al. (2008), who used the EQ-5D (via the visual analogue scale and standard gamble techniques – not the time trade off technique as per NICE's preferred methods).

The authors conducted one-way sensitivity analysis (OWSA), two-way sensitivity analyses and a probabilistic sensitivity analyses (PSA).

The base case results of the MO patients are shown in Table 4 and CO people shown are shown in Table 7.

Table 6: Costs and effects for MO people – taken from Shah et al. (2013).

Strategy	Absolute		Incremental		
	Cost	Effect	Cost	Effect	ICER
Wedge resection-MO	$51,487	7.93			
SBRT-MO	$42,094	8.03	$-9,393	0.1	**Dominant**

Table 7. Costs and effects for CO patients – taken from Shah et al. (2013).

Strategy	Absolute		Incremental		
	Cost	Effect	Cost	Effect	ICER
SBRT-CO	$40,107	8.21			
Lobectomy-CO	$49,093	8.89	$8,986	0.68	$13,214

SBRT-MO, SBRT-CO, wedge resection, and lobectomy were associated with a mean cost and quality-adjusted life expectancy of $42,094/8.03, $40,107/8.21, $51,487/7.93, and $49,093/8.89, respectively. In patients who are MO, SBRT was the dominant strategy and thus the most cost-effective. For patients who are CO, lobectomy was the cost-effective treatment option (ICER=$13,200/QALY).

When an open-only surgical approach was considered in the base model, wedge resection and lobectomy were associated with a mean cost of $53,570 and $49,428, respectively. Similarly, wedge resection and lobectomy were associated with a mean cost of $50,669 and $48,713, respectively, when a VATS-only analysis was performed; the ICERs were essentially unchanged.

For OWSA of SBRT-MO vs wedge resection, in almost any scenario, SBRT was the dominant (and thus the most cost-effective) strategy compared with wedge resection. SBRT remained borderline cost-effective when the cost associated with wedge resection was only $10,000 (ICER = $57,000/QALY). Wedge resection did become the cost-effective strategy when its 5-year risk of LR was 2% (ICER = $18,400/QALY) or the LR risk associated with SBRT was 20% (ICER = $5500/QALY).

For OWSA of SBRT-CO vs lobectomy, under every assumption used in the model, lobectomy was more cost-effective compared with SBRT for patients who are CO. The ICER for lobectomy was below $50,000/QALY, well below any accepted societal willingness to pay (WTP) in the US. Lobectomy was the clearly dominant strategy when the prevalence of nodal disease (N1 or N2) was 50%, cost of SBRT was $50,000, or cost of lobectomy was $10,000. None of these scenarios are likely, however.

For the two-way sensitivity analyses, the authors varied the probability that dyspnea and pain were permanent, as well as the disutility associated with them (ranging between 50% to 200% for the assumed disutility). In the MO comparison, SBRT was still the dominant strategy, even with the assumption of no permanent morbidity and a small disutility for pain and dyspnea. In the CO comparison, lobectomy was cost-effective versus SBRT (ie., ICER below $50,000/QALY) in nearly every scenario except the most extreme: permanent pain and dyspnea, with a disutility twice that of the base case. This case resulted in an ICER of lobectomy of $90,000/QALY.

The PSA assumed 2 conditions favourable to wedge resection: its local control rate relative to SBRT varied between 0.65 and 1, and its MS-DRG payment was the lowest possible between 50% and 75% of cases. Even with these favourable assumptions, SBRT was most likely to be the cost-effective strategy up to a WTP well beyond $500,000/QALY.

The authors acknowledged study limitations including that clinical outcomes were based on the results of retrospective and phase 2 data. Furthermore, the model horizon was only 5 years, and cost data was used from only one hospital.

The authors concluded that SBRT was nearly always the most cost-effective treatment strategy for MO patients with stage I NSCLC. In contrast, for patients with CO disease, lobectomy was the most cost-effective option.

Paix et al (2018) conducted an economic evaluation modelling study of stereotactic body radiotherapy (SBRT) and video assisted thoracoscopic surgery (VATS) lobectomy for patients with operable stage I non-small cell lung cancer.

The authors derived probabilities of transition from PFS to LR-RR and DR for SBRT and lobectomy from the pooled analysis of STARS and ROSEL, two randomized studies that compared SBRT and video assisted thoracoscopic surgery (VATS) lobectomy for operable stage I non-small cell lung cancer Statistical method described by Guyot et al (2012) were used to retrieve raw data. The starting age of the model cohort was 67 years old, as reported in the pooled results of STARS and ROSEL, which was consistent with WHO data.

The SBRT initial cost was estimated based on the preparation of the treatment and the treatment in 5 fractions. The paper included travel costs which we could not eliminate from the analysis. All costs and QALYs were discounted at an annual rate of 4% beyond the first year. The perspective of the analysis was a French public payers' perspective using the price year of 2017. All costs were expressed in Euros.

The Markov model cycle length was one month whilst the model considered a patient lifetime horizon. The cohort starting age was 67 years. Progression free survival and recurrence health state utilities were from Doyle et al. (2008), a UK study, which used the EQ-5D.

Table 4 shows the results from the study.

Table 8: Costs and effects taken from Paix et al. (2018)**Strategy**	**Mean**		**Incremental**		
	Cost	**QALYs**	**Cost**	**QALYs**	**ICER**
SBRT	€ 9,234.15	16.35	-	-	-
VATS	€ 10,726.98	15.80	€ 1,492.83	-0.55	**Dominated**

The model found 3-year overall survival rates were 88% and 84.5% for SBRT and lobectomy, respectively. In the base case, SBRT was associated with a mean cost of €9,234.15, including a cost of initial treatment of €8,030, a cost induced by complications of initial treatment of €615.14 and a cost for follow-up of €589.01. Lobectomy was associated with a mean cost of €10,726.98 including a cost of initial treatment of €9,958.48, a cost induced by complications of initial treatment of €140.52 and a cost for follow-up of €627.98. SBRT and lobectomy were associated with a quality-adjusted life expectancy of 16.35 and 15.80 QALYs, respectively. SBRT appeared to be €1,492.84 cheaper with an increase in quality adjusted life expectancy of 0.54 QALYs; hence, SBRT was dominant over lobectomy in early stage NSCLC treatment.

The one-way sensitivity analysis found that the parameters that the model was most sensitive to were the initial cost of both SBRT and lobectomy, to the utility decrement caused by SBRT and lobectomy associated complications, distant recurrences, and chemotherapy; and to chemotherapy probability. For each of those assumptions, SBRT remained dominant over lobectomy, except for extremes initial costs. The ICER was not sensitive to the other variables tested in this sensitivity analysis.

The probabilistic sensitivity analysis showed that most of the 1000 simulated patients were either in the north-west quadrant (57.1%), which means that lobectomy is more expensive and less effective than SBRT, or in the north-east quadrant (38.3%), which means that lobectomy is more expensive and more effective than SBRT. The proportion of patients in the south-west and the south-east quadrant were 3.1% and 1.5% respectively. The acceptability curve showed that for willingness to pay threshold of €30,000 and €100,000 per QALY, SBRT had the highest probability of cost-effectiveness compared to lobectomy.

SBRT compared with RFA and 3D-CRT

Sher et al. (2011) created a Markov model comparing the cost-effectiveness of Stereotactic Body Radiotherapy (SBRT), Radiofrequency Ablation (RFA) and Conventional Radiotherapy (3D-CRT) for patients with medically inoperable stage 1 NSCLC. Efficacy data for SBRT was derived from long-tern follow-up data from the Indiana University Phase II SBRT trial. The local recurrence rate for RFA was obtained from Brown University. The 3D-CRT was derived from data from Washington University and Duke University.

The model had 8 states and took a patient life time horizon perspective. Patients began in the model in the well state (no evidence of disease [NED]) having received either 3d-CRT, RFA or SBRT. Patients in the model could have recurrence of the disease and die of the disease, or die of other causes at any state in the model. Both costs and QALYs beyond the first year were discounted at 3%.

Costs accrued in each of the health states were largely derived from publicly available 2009 Medicare payment schedules. A US Medicare payer perspective was used in this analysis.

The authors performed both deterministic and probabilistic sensitivity analyses.

The results of the model are shown in Table 4.

Table 9: Costs and effects from Sher et al. (2011).

	Absolute		Incremental		
Strategy	**Cost**	**Effect**	**Cost**	**Effect**	**ICER**
RFA	$ 44,648	1.45			
3D-CRT	$ 48,842	1.53	$ 4,194	0.08	$ 52,425
SBRT	$ 51,133	1.91	$ 2,291	0.38	$ 6,029

In the base case, 3D-CRT had an ICER of $52,425 compared to RFA. SBRT had an ICER of $6,029 compared to 3D-CRT. If all three treatment options were available to a clinician, the authors found SBRT to be clearly the most cost-effective treatment option, followed by RFA.

The one-way sensitivity analysis showed that in almost any scenario, SBRT was the most cost-effective option whilst RFA dominated the other two treatment options when its associated 3-year risk of local recurrence was 10%. A two-way sensitivity analysis used to estimate the cost-effective of these treatments for small and large primaries. When only the tumour size was varied, SBRT was cost-effective for both T1 and T2 Cancers. SBRT was still found to be the most cost-effective treatment option.

The probabilistic sensitivity analysis showed that the probability that SBRT was cost-effective at a societal WTP of $50,000/QALY was 70%. SBRT was cost-effective in the majority of trials above a WTP of $30,000/QALY.

The authors concluded that given the data used in the model, SBRT is the most cost-effective treatment for medically inoperable Stage I NSCLC. They also found that the results of the model are robust over a wide range of assumptions, including the efficacy of each treatment modality, natural history of Stage I Lung Cancer, health state utilities values, and costs.

Comparison of five different regimens of radiotherapy

Ramaekers et al. (2013) developed a probabilistic decision-analytic Markov cohort model comparing the cost-effectiveness of Conventional Fractionation Radiotherapy (CRT), Identical Hyperfractionated Radiotherapy (HRTI), Higher Hyperfractionated Radiotherapy (HRTH), Very Accelerated Radiotherapy (VART) and Moderately Accelerated Radiotherapy (MART) for patients with unresected NSCLC. Data for treatment effects was taken from the Meta-analysis of Radiotherapy in Lung Cancer (MAR-LC) database that compared conventional and modified fractionated radiotherapies (RT's). The number of trials for each strategy and the resulting regimen modelled are shown in Table 10.

Table 10. Each strategy considered by the Ramaekers model (taken from Ramaekers et al. 2013)

Strategy	Number of trials from MAR-LC database	Regimen
Conventional Fractionation Radiotherapy	(CRT; 10 trials; N = 944)	Five weekly fractions of 1.8 to 2.0 Gy, accumulating to a total treatment dose (TTD) of 60 to 70 Gy.
Very accelerated RT	(VART; 6 trials; N = 700)	Reduced overall treatment time (OTT) with more than or equal to 50%, using an identical (±5%) or lower (5%–10%) TTD compared with CRT (OS HR, 0.88 [95% confidence interval (CI) 0.78–0.98] versus CRT)
Moderately accelerated RT	(MART; 1 trial; N = 29)	Reduced OTT with 14% to 49%, using a TTD identical (±5%) to CRT (OS HR, 0.90 (95% CI, 0.52–1.54) versus CRT).
Hyperfractionated RT using identical TTD	(HRTI; 2 trials, N = 164)	The average dose per fraction is decreased to 1.75 Gy or lesser, using a TTD identical (±5%) to CRT (OS HR: 0.87 (95% CI, 0.69–1.10) versus CRT).
Hyperfractionated RT using higher TTD	(HRTH; 1 trial; N = 163)	The average dose per fraction is decreased to 1.75 Gy or lesser, using a higher (5%–15%) TTD than CRT (OS HR, 0.92 [95% CI, 0.74–1.15] versus CRT).

The model had 8 states and took a patient life time horizon perspective. The cycle length in the model was 1 month, with half-cycle correction applied. Both costs and

QALYs beyond the first year were discounted at 4% and 1.5% respectively, in accordance with the Dutch pharmacoeconomic guideline.

Costs and resource use in the model were taken from the MAR-LC database, the Dutch NSCLC guideline and expert opinion. Costs were calculated using the Dutch health care perspective and converted to the 2011 price level, based on price indices from Statistics Netherlands (CBS).

The authors performed probabilistic sensitivity analyses to test parameter uncertainty using Monte Carlo simulation (of 15,000 iterations).

The results of the model are shown in Table 4.

Table 11: Costs and effects from Ramaekers et al. 2013

Strategy	Absolute			Incremental analysis compared to Conventional Fractionation Radiotherapy (CRT)		
	Cost (95% CI)	Effect (95% CI)	Net Monetary Benefit (95% CI)	Cost (95% CI)	Effect (95% CI)	ICER
Conventional Fractionation Radiotherapy (CRT)	€24,360 (€21,173 – €28,110)	1.12 (1.00 – 1.24)	€65,125 (€54,663– €75,537)	-	-	-
Identical Hyperfractionated Radiotherapy (HRTI) vs CRT	€ 29,683 (€25,536 – €35,208)	1.14 (0.90 – 1.42)	€61,663 (€40,967– €84,360)	€5,323 (€3,907 – €7,533)	0.02 (−0.20 to 0.28)	€228,852
Higher Hyperfractionated Radiotherapy (HRTH) vs CRT	€26,199 (€22,714 – €30,523)	1.27 (1.00 – 1.57)	€75,170 (€53,320– €99,989)	€1,839 (€1212 – €2,699)	0.15 (−0.11 to 0.44)	€12,379
Very Accelerated Radiotherapy (VART) vs CRT	€25,746 (€22,370 – €29,861)	1.30 (1.14 – 1.47)	€78,347 (€64,635– €92,526)	€1,386 (€957 – €1,982)	0.18 (0.05 to 0.32)	€7,592
Moderately Accelerated Radiotherapy (MART) vs CRT	€26,208 (€22,690 – €30,571)	1.32 (0.78 – 1.99)	€79,322 (€35,478– €133,648)	€1,848 (€895 – €2,845)	0.20 (−0.35 to 0.87)	€9,214

The authors found that all modified fractionations were more effective and costlier than CRT (1.12 QALYs, €24,360). VART and MART were most effective (1.30 and 1.32 QALYs) and cost €25,746 and €26,208, respectively. HRTI and HRTH yielded less QALYs than the accelerated schemes (1.27 and 1.14 QALYs), and cost €26,199 and €29,683, respectively. MART had the highest NMB (€79,322; 95% confidence interval [CI], €35,478-€133,648) and was the most cost-effective treatment followed by VART (€78,347; 95% CI, €64,635- €92,526). CRT had an NMB of €65,125 (95% CI, €54,663-€75,537).

The probabilistic sensitivity analysis showed that MART had the highest probability of being cost effective (43%), followed by VART (31%), HRTI (24%), HRTH (2%), and CRT. The comparison of MART versus VART resulted in a 51% probability for MART and 49% probability for VART of being cost effective.

The authors concluded that implementing accelerated RT is almost certainly more cost-effective than current practice CRT and should be recommended as standard RT for the curative treatment of unresected NSCLC patients not receiving concurrent chemo-radiotherapy.

Evidence statements

Randomised controlled trials

Studies that only included people who were operable

Operable, stage I: Stereotactic ablative radiotherapy (SABR) peripheral: 54 Gy in 3 x 18 Gy fractions; central: 50 Gy in 4 x 12.5 Gy fractions vs lobectomy

Low to moderate-quality evidence from 1 RCT reporting data on 58 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio). However, there were a greater number of participants who experienced adverse events grade 3 or above in the surgery group compared to the SABR group. The data could not differentiate for treatment-related death or dyspnoea.

Operable, stage IIIA: chemotherapy, conventional fractionation (CF) 60-62.5 Gy (1.95-2.05 Gy in 30-32 fractions over 40-46 days) vs chemotherapy, surgery

Moderate-quality evidence from 1 RCT reporting data on 332 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio) nor for participants dropping out during treatment.

Operable, stage IIIA: chemotherapy, CF 40-46 Gy (1 or 2 fractions per day, 5 days a week), surgery vs chemotherapy, surgery

Very low to moderate-quality evidence from 3 RCTs reporting data on 333 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio and risk ratio for survival at 1, 2 and 3 years), stomatitis, dyspnoea and pneumonitis (adverse events grade 3 or above).

Operable stage IIIA and IIIB: chemotherapy, CF 45 Gy (1.5 Gy, 2x per day, 5 days a week), CF boost 20-26 Gy (2 Gy, 2x per day, 5 days a week) vs chemotherapy, CF 45 Gy (1.5 Gy, 2x per day, 5 days a week), surgery

Moderate-quality evidence from 1 RCT reporting data on 161 people with NSCLC found that the data could not differentiate for mortality (risk ratio for survival at 1, 2, 3, 4, 5 and 6 years), oesophagitis, mucositis/stomatitis, pulmonary, other gastrointestinal or renal, cardiac (adverse events grade 3 or above) or dropout during treatment.

Studies that only included people who were inoperable or refused surgery

Inoperable or refused surgery, stage I: SABR 34 Gy in 1 fraction vs SABR 48 Gy in 4 consecutive daily fractions

Low-quality evidence from 1 RCT reporting data from 84 people with NSCLC found that the data could not differentiate for mortality (risk ratio of survival at 1 and 2 years) or respiratory disorders (adverse events grade 3 or above).

Inoperable or refused surgery, stage I: SABR 66 Gy (3x 22 Gy during 1 week) vs CF 70 Gy (2 Gy, daily, 5 days a week)

Low-quality evidence from 1 RCT reporting data from 101 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio), pneumonitis, dyspnoea, pulmonary fibrosis, cough or skin reactions (adverse events grade 3 or above).

Inoperable or refused surgery, stage I to IIIB: continuous hyperfractionated accelerated radiotherapy weekend less (CHARTWEL) 60 Gy (1.5 Gy, 3x per day, 5 days a week) vs CF 66 Gy (2 Gy, daily, 5 days a week)

Low to moderate-quality evidence from 1 RCT reporting data from 406 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio, cancer-related risk ratio of death and treatment-related risk ratio of death). However, the CHARTWEL group had a greater number of people who experienced early dysphagia at 2 weeks and 4 weeks (adverse events grade 3 or above) compared to the CF group. The data could not differentiate for early dysphagia at 8 weeks, 12 weeks, 16 weeks and 20 weeks, nor for clinical pneumonitis at 8 weeks and 12 weeks (adverse events grade 3 or above) nor for global quality of life.

Inoperable or refused surgery, stage I to IV: SABR 64-66 Gy (6-8 Gy, 3 times a week) vs CF 68-70 Gy (unspecified fractions, 5 times a week)

Low-quality data from 1 RCT reporting data from 50 people who had NSCLC could not differentiate mortality (risk ratio for survival at 1 and 2 years).

Studies that only included people who were inoperable

Inoperable, stage II, IIIA, IIIB: chemo, CF 63 Gy (1.8 Gy, daily, 5 days a week) vs chemo, CF 69.6 Gy (1.2 Gy, 2x per day, 5 days a week)

Moderate to high-quality evidence from 1 RCT reporting data from 380 people who had NSCLC could not differentiate mortality (all-cause hazard ratio). However, there were a greater number of people who experienced acute oesophageal toxicity and acute mucositis in the CF 69.6 (1.2 Gy, 2x per day) group compared to the CF 63 Gy (1.8 Gy, daily) group (adverse events grade 3 or above). The data could not differentiate acute pulmonary or cardiac toxicity nor late pulmonary, oesophageal nor cardiac toxicity (adverse events grade 3 or above).

Inoperable, stage IIIA and IIIB: chemotherapy, CF 60 Gy (2 Gy, daily, 5 days a week) vs chemotherapy, CF 74 Gy (2 Gy, daily, 5 days a week)

High to moderate-quality evidence from 1 RCT reporting data from 495 people who had NSCLC found that mortality (all-cause hazard ratio) favoured the CF 60 Gy group compared to the CF 74 Gy group. In addition, there were a greater number of people who experienced dysphagia, oesophagitis and radiation recall reaction (dermatological) within 90 days in the 74 Gy group compared to the 60 Gy group (adverse events grade 3 or above). However, the data could not differentiate radiation dermatitis, dyspnoea, pneumonitis, desquamating rash within 90 days, nor dysphagia, dyspnoea or pneumonitis after day 90 (adverse events grade 3 or above).

Inoperable, stage IIIA and IIIB: chemotherapy, IMRT 60 or 74 Gy (2 Gy, daily, 5 days a week) vs chemotherapy, 3D-CRT 60 or 74 Gy (2 Gy, daily, 5 days a week)

Low to moderate-quality evidence from 1 non-randomised subgroup analysis of an RCT reporting data from 482 people with NSCLC found that the data could not differentiate mortality (risk ratio for survival at 2 years). However, there were a greater number of people who experienced pneumonitis in the 3D-CRT group compared to the IMRT group (adverse events grade 3 or above). The data could not differentiate for oesophagitis/dysphagia nor for cardiovascular adverse events (grade 3 or above)

Inoperable, stage IIIA and IIIB: chemotherapy, CF 64 Gy (2 Gy, daily, 5 days a week) vs chemotherapy, hyperfractionated accelerated radiotherapy (HART) 57.6 Gy (1.5 Gy, 3x per day, 5 days a week) (similar to CHARTWEL)

Moderate-quality evidence from 1 RCT reporting data from 113 people with NSCLC could not differentiate mortality (risk ratio for survival at 1 and 2 years), overall incidences of adverse events, oesophagitis, pulmonary adverse events and skin adverse events (grade 3 or above).

Observational studies

Studies that included people who were operable, inoperable or refused surgery

Stage I: SABR vs lobectomy

Very low-quality evidence from 9 observational studies reporting data on 5220 people with NSCLC found that mortality (all-cause hazard ratio) favoured the lobectomy group compared to the SABR group. Very low-quality evidence from 1 observational study reporting data on 74 people with NSCLC found that mortality all-cause risk ratio at 3 years favoured lobectomy. However, the data could not differentiate for mortality all-cause risk ratio at 1 year.

Stage I or II: SABR vs lobectomy

Very low-quality evidence from 1 observational study reporting data on 128 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio).

Stage I: SABR vs sublobar resection

Very low-quality evidence from 6 observational studies reporting data on 10328 people with NSCLC found that mortality (all-cause hazard ratio) favoured the sublobar resection group compared to the SABR group. Very low-quality evidence from 1 observational study reporting data on 124 people with NSCLC found that the data could not differentiate for mortality (risk ratio at 30 months).

Stage I or II: SABR vs sublobar resection

Very low-quality evidence from 1 observational study reporting data on 2243 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio).

Stage I: SABR vs surgery (any)

Very low-quality data from 3 observational studies reporting data on 524 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio, risk ratio at 1, 3, 4 and 5 years).

People aged 75 years or older: stage I: SABR vs surgery (any)

Very low-quality data from 1 observational studies reporting data on 218 people with NSCLC found that the data could not differentiate for mortality (all-cause hazard ratio).

Studies that only included people who were inoperable or refused surgery

Inoperable or refused surgery, stage I or T1-T2 N0 M0: Stereotactic ablative radiotherapy (SABR) vs conventional fractionation (CF)

Very low-quality evidence from 2 observational studies reporting data from 218 people with NSCLC found that mortality favoured SABR over CF (risk ratio of survival at a median potential follow-up of 3 years and cancer-specific risk ratio at 5 years). Very low-quality evidence from 4 observational studies reporting data from 2101 people with NSCLC could not differentiate for mortality (all-cause hazard ratio, all-cause risk ratio at 1 year and cancer-specific risk ratio at 1 year). However, for the all-cause hazard ratio, the statistical means favoured SABR over CF and the random effects model only touched the line of no effect (please refer to the meta-analysis for further details). Very low-quality evidence from 3 observational studies reporting data on 429 people with NSCLC could not differentiate adverse events grade 3 or above (oesophagitis and radiation pneumonitis) or health-related quality of life.

Inoperable or refused surgery, stage I: SABR vs no therapy

Very low-quality evidence from 1 observational study reporting data on 7661 people with NSCLC stage I found that mortality (all-cause hazard ratio) favoured the SABR group compared to the no therapy group.

Health economics evidence statements

One partially applicable Dutch health economic modelling study with potentially serious limitations compared the cost-effectiveness of positron emission tomography (PET)-based isotoxic accelerated radiation therapy treatment (PET-ART) compared with conventional fixed-dose CT-based radiation therapy treatment (CRT) in non-small cell lung cancer (NSCLC) for NSCLC patients with inoperable stage I-IIIB cancer. PET-ART was found to have an ICER of €1,744/QALY compared to CRT. The cost-effectiveness acceptability curve showed that at a threshold value of €18,000 per QALY, there is a 95% probability that PET- ART is cost-effective.

One partially applicable Canadian population level model with very serious limitations compared SABR compared against radiotherapy (RT), best supportive care (BSC), sublobar resection and lobectomy. The study found that SABR costs less and produced more QALYs than RT, BSC and sublobar resection and was therefore a dominant treatment option in these cases. However, when SABR was compared against lobectomy in patients who were eligible for both, SABR was found to produce a saving in costs but also produce less QALYs, resulting in an ICER of $55,909/QALY. At a willingness-to-pay of $100,000/QALY, lobectomy was therefore cost-effective.

One partially applicable Canadian cost-effectiveness study with very serious limitations compared conventionally fractionated radiotherapy (CFRT) and stereotactic body radiotherapy (SBRT) in patients with stage I non-small cell lung cancer (NSCLC) who were either ineligible or refused surgery. (It is worth to note that SBRT and with stereotactic ablative radiotherapy (SABR) are the same treatment). In the base case, the incremental cost of SBRT compared to CFRT was $1,156 but produced an additional 1.03 life years, resulting in an ICER of $1,120 per life year gained. None of the one-way or two-way sensitivity analyses resulted in an ICER above a stated threshold of $50,000 per LYG.

One partially applicable Dutch modelling study with potentially serious limitations created a Markov model comparing the cost-effectiveness of Conventional Fractionation Radiotherapy (CRT), Identical Hyperfractionated Radiotherapy (HRTI), Higher Hyperfractionated Radiotherapy (HRTH), Very Accelerated Radiotherapy (VART) and Moderately Accelerated Radiotherapy (MART) for patients with unresected NSCLC. The authors found that all modified fractionations were more effective and costlier than CRT. VART and MART were most effective whilst HRTI and HRTH yielded less QALYs than the accelerated schemes. MART was found to have the highest NMB. The probabilistic sensitivity analysis found that MART had the highest probability of being cost effective, followed by VART, HRTI, HRTH, and CRT.

One partially applicable US study using a Markov model with potentially serious limitations compared compare the cost-effectiveness of stereotactic body radiation therapy (SBRT) with wedge resection (WR) and lobectomy for marginally operable (MO) and clearly operable (CO) patients with stage I NSCLC. For patients who were MO, SBRT was cheaper than wedge resection and produced more QALYs and was therefore the dominant strategy. In sensitivity analysis, SBRT for MO patients was nearly always the most cost-effective treatment strategy. In contrast, for patients with CO disease, lobectomy was the most cost-effective option.

One partially applicable US study of a Markov model with potentially serious limitations compared Stereotactic Body Radiotherapy (SBRT), Radiofrequency Ablation (RFA) and Conventional Radiotherapy (3D-CRT) for patients with medically inoperable stage 1 NSCLC. The authors found SBRT to be the most cost-effective treatment option under most willingness-to-pay thresholds per QALY gained in the base-case, probabilistic sensitivity analyses and deterministic sensitivity analyses.

One partially applicable French study with potentially serious limitations used a Markov model to compare the cost-effectiveness of stereotactic body radiotherapy (SBRT) and video assisted thoracoscopic surgery (VATS) lobectomy for operable stage I non-small cell lung cancer. The authors found that VATS was more expensive and produced fewer QALYs than SBRT, which resulted VATS to be a dominated strategy. A one-way sensitivity analysis found that the parameter that the model was most sensitive to be the initial cost of SBRT and VATS. The probabilistic sensitivity analysis and cost-effectiveness acceptability curve showed that SBRT was always more likely to be more cost-effective comparted to VATS at both willingness to pay threshold of €30,000 and €100,000 per QALY.

Recommendations

Surgery

1.4.20 For people with NSCLC who are well enough and for whom treatment with curative intent is suitable, offer lobectomy (either open or thoracoscopic). [2019]

Surgery or radiotherapy for people not having lobectomy

1.4.24 For people with stage I–IIA (T1a–T2b, N0, M0) NSCLC who decline lobectomy or in whom it is contraindicated, offer radical radiotherapy with stereotactic ablative radiotherapy (SABR) or sublobar resection. [2019]

Radical radiotherapy for people not having surgery

1.4.25 For people with stage I–IIA (T1a–T2b, N0, M0) NSCLC who decline surgery or in whom any surgery is contraindicated, offer SABR. If SABR is contraindicated, offer alternative radical radiotherapy. [2019]

1.4.26 For eligible people with stage IIIA NSCLC who cannot tolerate or who decline chemoradiotherapy (with or without surgery), consider radical radiotherapy (either conventional or hyperfractionated). [2019]

1.4.27 For eligible people with stage IIIB NSCLC who cannot tolerate or who decline chemoradiotherapy, consider radical radiotherapy (either conventional or hyperfractionated). [2019]

1.4.28 If conventionally fractionated radical radiotherapy is used, offer either:

- 55 Gy in 20 fractions over 4 weeks **or**
- 60–66 Gy in 30–33 fractions over 6–6½ weeks. [2019]

Research recommendation

1.4.30 What is the effectiveness and cost effectiveness of SABR compared to surgery (for example, sublobar, wedge resection, lobectomy) for operable patients with NSCLC (stage I and II)?

Rationale and impact

Why the committee made the recommendations

For people with non-small-cell lung cancer (NSCLC) who are well enough and for whom treatment with curative intent is suitable, the evidence showed that lobectomy provides better survival outcomes than stereotactic ablative radiotherapy (SABR). Lobectomy is a good compromise between preserving pulmonary function and being more likely to remove cancerous cells compared to sublobar resection..

For people with stage I-IIA (T1a–T2b, N0, M0) NSCLC, the evidence showed that:

- if they decline lobectomy or it is contraindicated, sublobar resection and SABR both provide better survival outcomes than conventionally fractionated radiotherapy, and it is not clear which of these 2 is better
- if they decline any surgery or it is contraindicated, SABR provides better survival outcomes than conventionally fractionated radiotherapy, and people often prefer it because it involves fewer hospital visits
- if surgery and SABR are contraindicated, conventionally fractionated radiotherapy provides better survival outcomes than no radiotherapy.

For people with stage IIIA or IIIB NSCLC who cannot tolerate chemoradiotherapy or who decline it, the evidence was not strong enough to recommend conventional radiotherapy over hyper-fractionated regimens or vice versa. However, people who cannot tolerate chemoradiotherapy may also be unable to tolerate radical radiotherapy, so this will not be an option for everyone with stage IIIA or IIIB NSCLC. For an explanation of the recommendations covering surgery in this group, see the rationale on management of stage IIIA-N2 NSCLC.

55 Gy in 20 fractions is the most common conventional radical radiotherapy regimen in the UK. If conventionally fractionated radiotherapy is used, a total radiation dose of 60 Gy provides better survival outcomes and fewer adverse events than 74 Gy. A total dose of 60–66 Gy is also normal NHS practice.

There are not many randomised controlled trials comparing SABR with surgery (lobectomy or sublobar resection). SABR is non-invasive, so if it is as effective as surgery then it may be a preferable option for many people with lung cancer. It is also possible that SABR, which is usually delivered as outpatient treatment, is more cost-effective than surgery. There might also be subgroups for whom different forms of surgery or SABR might be the most cost-effective options. The committee made a research recommendation to investigate these uncertainties.

How the recommendations might affect practice

The new recommendations on SABR are a change from the 2011 guideline and improve choice for people with NSCLC. However, practice has also changed since 2011, and SABR is now widely used, so implementing the recommendations may not involve a significant change in practice. The remaining changes to the recommendations reflect current practice.

Interpreting the evidence

The outcomes that matter most

The committee agreed that mortality was the most important outcome, closely followed by adverse events grade 3 or above. This is because most people who have lung cancer value being able to spend as much time with their family as possible.

The quality of the evidence

There was a sparseness of RCT evidence that led to the inclusion of observational studies: The committee agreed that the findings from Chang 2015 were of insufficient quality to recommend SABR as an alternative to lobectomy for people who are medically fit and suitable for lobectomy with curative intent. It combined two small RCTs, only having 58 people in total. In addition, in the opinion of the committee, the mortality rate of the people in the surgery arm was relatively high compared to the mortality rate of similar people in the UK. The risk of bias was assessed as high because there is limited information on the inclusion criteria. The committee agreed that the findings from Nyman 2016 were of insufficient quality to recommend conventional fractionation (CF) as an alternative to SABR for stage I people who are inoperable or who have refused surgery. The CF arm of this study had a higher number of T1 people and a lower number of T2 people compared to the SABR arm. Therefore, the arms were not comparable. Such a large difference is unusual for an RCT. Nyman 2016 included 101 people whereas in contrast, the observational studies Jeppesen 2013, Koshy 2015, Tu 2017 and Widder 2011 had a combined total of 2,101 people for the comparison of SABR vs CF. For this comparison, Koshy 2015 had the greatest number of people (n = 1,502) and therefore the largest weighting. This study was well conducted for an observational study and the SABR and CF arms were balanced. The data in the RCT Wang 2016 suggests that SABR has a similar risk ratio for survival at 1 and 2 years compared to CF. However, this study is not directly applicable to the recommendations made because this study has people who are stage I to IV.

The observational data are all very low quality evidence. This is because they are non-randomised and therefore have a high risk of bias. For example, clinicians may be tempted to place patients who are more easily resectable on imaging into the surgery arms compared to the SABR arms. Patients with comorbidities and worse performance status may be placed into the SABR arms compared to the surgery arms. This is because of concerns regarding anaesthesia and postoperative recovery. Such biases may occur consciously and subconsciously. Propensity matching may go some way to reducing this bias. However, it may not be possible to measure comorbidities and performance status comprehensively for every patient.

Benefits and harms

1.4.20 and 1.4.24: The committee agreed that for people with NSCLC who are well enough and for whom treatment with curative intent is suitable, lobectomy (either open or thoracoscopic) should be offered. Evidence for this comes from the meta-analysis of observational studies for people for whom treatment with curative intent is suitable: the data favours the lobectomy group compared to the SABR group with regards to mortality (all-cause hazard ratio). In addition, in Cornwell 2018, the data favours lobectomy compared to SABR for mortality all-cause risk ratio at 3 years. The committee acknowledged that the data in the Chang 2015 RCT for a similar population nearly favoured SABR compared to lobectomy for mortality (all-cause hazard ratio) and favoured SABR compared to lobectomy for adverse events grade 3 or above. However, the committee agreed that the overall quality of this RCT is low because of small participant numbers (58 in total) and because this RCT is actually a combination of two separate RCTs (ROSEL and STARS) and details of the eligibility and exclusion criteria are missing from the supplementary information.

The committee acknowledged that in the meta-analyses comparing SABR vs lobectomy and SABR vs sublobar resection, the mortality (all-cause hazard ratio) data favoured both forms of surgery compared to SABR. However, the committee agreed that lobectomy is preferred to sublobar resection if patients are well enough to have lobectomy. This is because lobectomy is a good compromise between preserving pulmonary function and being more likely to remove cancerous cells compared to sublobar resection. In addition, other studies that could not be included in this meta-analysis could not differentiate for mortality (Ezer 2015, van den Berg 2015, Wang 2016, Puri 2012 and Nakagawa 2014). Therefore, the committee agreed that SABR and sublobar resection are comparable treatments for people who cannot or do not want to undergo lobectomy.

Although the evidence reviewed only had participants who were early stage NSCLC, the committee were keen to avoid excluding people with different NSCLC stages who are medically fit and suitable for surgery. Therefore, the committee agreed to keep the original wording of the first sentence of the 2011 recommendation. Previously, this recommendation had a second sentence that read “For patients with borderline fitness and smaller tumours (T1a–b, N0, M0), consider lung parenchymal-sparing operations (segmentectomy or wedge resection) if a complete resection can be achieved.” This sentence has now been superseded by a new recommendation, 1.4.25, which is discussed below.

The committee agreed that for people with stage I-IIa (T1a–T2b, N0, M0), who are unfit for lobectomy or who refuse lobectomy, radical therapy via SABR or sublobar resection should be offered. The committee agreed to replace ‘segmentectomy or wedge resection’ with ‘sublobar resection’ which encompasses both procedures and is widely recognised.

Jeppesen 2013 and a meta-analysis of Koshy 2015, Tu 2017 and Widder 2011 demonstrate that these studies’ data favour SABR over CF for people with stage I-IIa (T1a–T2b, N0, M0) who are unsuitable for surgery for medical reasons or who have refused surgery.

The committee recommended that for people who have T1a-T2b N0 M0 NSCLC, SABR offers additional treatment choice. SABR is particularly beneficial for people who cannot have surgery or wish to have an alternative treatment option.

The committee agreed that people often prefer SABR to CF because SABR requires fewer hospital visits: SABR requires 1 to 8 hospital visits compared to CF that requires 20-32.

1.4.25: The committee recommended that SABR should be offered to people who are unsuitable for surgery for medical reasons with stage I-IIa (T1a-T2b N0 M0) NSCLC if technically feasible. Evidence for this comes from Jeppesen 2013, Koshy 2015, Tu 2017 and Widder 2011. These studies' data favours SABR over CF for mortality (all-cause). The committee agreed that if SABR is contraindicated, alternative radical radiotherapy should be offered. Koshy 2015 has data that favours SABR over CF for mortality (all-cause). This study also has data that favours CF over no therapy. The committee agreed to widen the potential options from CF to 'alternative radical radiotherapy'. This is because the data in Bauman 2011 suggests that Continuous Hyperfractionated Accelerated Radiotherapy WeekEndLess (CHARTWEL) has similar results to CF. The committee agreed that CHART is a very similar therapy to CHARTWEL and that 'alternative radical radiotherapy' includes CF, CHART and CHARTWEL.

1.4.26 and 1.4.27: The committee agreed that for people with stages IIIA or IIIB NSCLC who cannot tolerate or do not wish to have chemoradiotherapy, radical radiotherapy should be considered. These recommendations differ from the 2011 recommendations in a number of ways. Firstly, "offer" has been changed to "consider". This is because the committee agreed that if a patient cannot tolerate chemoradiotherapy, they might not tolerate radical radiotherapy. Secondly, CHARTWEL is now a treatment option as well as CHART. The evidence for this was reviewed in Baumann 2011. The committee agreed that both CHART and CHARTWEL should be treatment options because of the explanations given in the paragraph above. Thirdly, the committee agreed that people with stage IIIA NSCLC have the possible option of having surgery. Evidence for this comes from a network meta-analysis and health economic model conducted for RQ 3.1. Details of this evidence can be found in the relevant economics sections.

1.4.28: The committee agreed that if conventionally fractionated radiotherapy is used, 55 Gy in 20 fractions over 4 weeks or 60 Gy to 66 Gy in 30 to 33 fractions over 6 to 6 ½ weeks should be offered. This is because data in Bradley 2015 favours 60 Gy rather than 74 Gy for mortality (all-cause hazard ratio), dysphagia, oesophagitis and radiation recall reaction within 90 days (adverse events grade 3 or above). In addition, the committee agreed that it is normal NHS clinical practice to have either a total radiation dose of 60 Gy to 66 Gy over 6–6½ weeks or 55 Gy over 4 weeks.

Cost effectiveness and resource use

The committee noted that while SABR is currently significantly more expensive than CF (average ~£5,200 vs ~£2,500), this is because it is currently being commissioned using a special Commissioning through Evaluation tariff that has been designed to promote uptake. The techniques use the same machines, with SABR requiring some additional software and setup. The committee therefore thought it highly plausible that the cost of SABR would decrease as adoption increased. Given that SABR only involves an average of five sessions, as opposed to 20 or more with CF, they also thought it highly plausible that SABR would become a dominant intervention in time.

The published cost-effectiveness studies in this review were mostly based on observational evidence and were all conducted outside the UK setting. The committee noted that, while none of these studies were directly applicable enough to base their decision on, they broadly supported the use of SABR.

CHART and CHARTWEL are also much more expensive than CF (~£5,900) because people usually stay in the hospital or attached accommodation over the course of their treatment. Without formal assessment in the UK context the relative cost-effectiveness of the two interventions is uncertain, however. The committee noted that only a very small proportion of people are still receiving these regimens and that they might still be a good treatment option for some people.

Other factors the committee took into account

The committee agreed that the new recommendations on SABR are in alignment with the SABR UK Consortium's document Stereotactic Ablative Body Radiation Therapy (SABR): A Resource 2016, which has been endorsed by the Royal College of Radiologists. The committee noted that SABR already has a great deal of support from patients and professionals; the National Lung Cancer Audit data shows that SABR is used in at least 36% of radical radiotherapy cases in NSCLC the UK. The committee agreed that people generally prefer SABR over CF. This is because SABR only requires an average of 5 visits to hospital. By contrast, CF requires approximately 20 to 33 visits.

For people with stage 1 lung cancer that are unsuitable for surgery or who choose not to have surgery, the committee discussed the preliminary findings for the CHISEL RCT. This has been published as a conference abstract, Ball 2017. This RCT compares SABR (n=66) to chemoradiotherapy using CF (n=35). So far, all participants have been followed for a minimum of 2 years and mortality all-cause hazard ratio favours SABR: HR 0.51 (95% CI 0.51, 0.911) p=0.02.

The previous NICE guideline recommendations regarding CHART were informed by Saunders 1997 and Saunders 1999, which were not within the date limits set in the review protocol for this update. The committee agreed that CHART should still remain as a treatment option even though it is rarely used. There was agreement that some people prefer CHARTWEL to CHART because CHARTWEL does not involve treatment at the weekends. In addition, choice is likely to be governed partly by local availability. The relative effectiveness of the various radical radiotherapy regimens in people who cannot have SABR (due to tumour size and/or location, for example) is unknown.

Appendix A – Review protocols

Review protocol for the clinical and cost effectiveness of different radiotherapy regimens with curative intent for NSCLC

Field (based on PRISMA-P	Content
Review question	What is the clinical and cost effectiveness of different radiotherapy regimens with curative intent for NSCLC?
Type of review question	Intervention
Objective of the review	The review question was identified as requiring updating in the 2016 surveillance review, due to new evidence being available that could impact on current recommendations. Recommendations may cover whether Stereotactic body radiotherapy is clinically and cost effective for people with NSCLC.
Eligibility criteria – population/ disease/ condition/ issue/ domain	People with NSCLC
Eligibility criteria – intervention(s)/expos	• Stereotactic body radiotherapy (SABR)

ure(s)/ prognostic factor(s)	• Other radical radiotherapy regimens including continuous hypofractionated accelerated radiotherapy (CHART)
Eligibility criteria – comparator(s)/control or reference (gold) standard	1. Each other 2. Placebo or usual care (surgery, conventional fractionation or no therapy) 3. The same radiotherapy technique with a different total dose and fractionation
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

	○ dyspnoea ○ hypoxia and need for home oxygen ○ stroke ○ cardiovascular disease ○ pneumonitis ○ oesophagitis • Treatment-related dropout rates
Eligibility criteria – study design	• RCT data. • Systematic reviews of RCTs • If no RCT data available, then retrospective observational data will be considered.
Other inclusion exclusion criteria	• Non English-language papers • Unpublished evidence/ conference proceedings • Palliative treatments, such as brachytherapy
Proposed sensitivity/sub-group analysis, or meta-regression	Pre-existing performance status defined by ECOG and Karnofsky performance status scale
Selection process – duplicate screening/selection/analysis	10% of the abstracts were reviewed by two reviewers, with any disagreements resolved by discussion or, if necessary, a third independent reviewer. If meaningful disagreements were found between the different reviewers, a further 10% of the abstracts were reviewed by two reviewers, with this process continued until

	agreement is achieved between the two reviewers. From this point, the remaining abstracts will be screened by a single reviewer. This review made use of the priority screening functionality with the EPPI-reviewer systematic reviewing software. See Appendix B for more details.
Data management (software)	See 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.

Identify if an update	Update. Original Question (linked): What is the most effective treatment for people with resectable non-small cell lung cancer? **Recommendations that may be affected:** 1.4.27 Patients with stage I or II NSCLC who are medically inoperable but suitable for radical radiotherapy should be offered the CHART regimen. **[2005]**
Author contacts	[Add link to in development page for the guideline]
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 F of the full guideline
Data collection process – forms/ duplicate	A standardised evidence table format will be used, and published as appendix G (clinical evidence tables) or H (economic evidence tables) of the full guideline.
Data items – define all variables to be collected	For details please see evidence tables in appendix G (clinical evidence tables) or H (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 – Current management	For details please see the introduction to the evidence review in the full guideline.
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

1.1 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.

1.2 Incorporating published systematic reviews

There was a deviation in the protocol: originally, the protocol stated that we would search for prospective non-randomised studies if there were insufficient RCT evidence available. So few RCT and prospective non-randomised studies were available that we expanded our inclusion criteria to retrospective studies that had at least two arms. The search for retrospective studies was limited to those comparing SABR either to a different radiotherapy technique or to surgery. This is because the committee were interested in how SABR performs relative to alternative mainstream treatments or usual care. Because of time constraints, we used the most recent moderate quality systematic review for the SABR versus surgery comparison. We used the quality ratings in the systematic review for reporting the findings in the GRADE tables. We extracted the data from the studies in the systematic review and used the data for our own meta-analysis. We included any relevant studies not included in the systematic review. Concerning other systematic reviews found, we screened all included studies to identify any additional relevant primary studies not found as part of the initial search.

1.2.1 Quality assessment

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

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

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

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

1.2.2 Using systematic reviews as a source of data

If systematic reviews were identified as being sufficiently applicable and high quality, and were identified sufficiently early in the review process (for example, from the surveillance review or early in the database search), they were used as the primary source of data, rather than extracting information from primary studies. The extent to which this was done depended on the quality and applicability of the review, as defined in Table 12. When systematic reviews were used as a source of primary data, and unpublished or additional data included in the review which is not in the primary studies was also included. Data from these systematic reviews was then quality assessed and presented in GRADE/CERQual tables as described below, in the same way as if data had been extracted from primary studies. In questions where data was extracted from both systematic reviews and primary studies, these were cross-referenced to ensure none of the data had been double counted through this process.

Table 12: Criteria for using systematic reviews as a source of data

Quality	Applicability	Use of systematic review
High	Fully applicable	Data from the published systematic review were used instead of undertaking a new literature search or data analysis. Searches were only done to cover the period of time since the search date of the review.
High	Partially applicable	Data from the published systematic review were used instead of undertaking a new literature search and data analysis for the relevant subsection of the protocol. For this section, searches were only done to cover the period of time since the search date

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

1.3 Evidence synthesis and meta-analyses

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

1.4 Evidence of effectiveness of interventions

1.4.1 Quality assessment

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

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

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

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

1.4.2 Methods for combining intervention evidence

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

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

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

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

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

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

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

1.4.3 Minimal clinically important differences (MIDs)

The Core Outcome Measures in Effectiveness Trials (COMET) database was searched to identify published minimal clinically important difference thresholds relevant to this guideline. However, no relevant MIDs were found. In addition, the Guideline Committee were asked to specify any outcomes where they felt a consensus MID could be defined from their experience. In particular, any questions looking to evaluate non-inferiority (that one intervention is not meaningfully worse than another) required an MID to be defined to act as a non-inferiority margin. However, the committee agreed that in their experience, they could not define any MIDs. This is because the committee agreed that the protocol outcomes were objective rather than subjective measures and the committee were not aware of evidence supporting the use of MIDs for the protocol's outcomes. Therefore, the line of no effect was used as the MID for risk ratios, hazard ratios and mean differences.

1.4.4 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. If non-RCT evidence was included for intervention-type systematic reviews then these were initially rated as either moderate quality (quasi-randomised studies) or low quality (cohort studies) and the quality of the evidence for each outcome was further downgraded or not from this point, based on the criteria given in Table 13.

Table 13: Rationale for downgrading quality of evidence for intervention studies

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

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

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

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

1.4.5 Publication bias

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

1.4.6 Evidence statements

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

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

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

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

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

1.5 Health economics

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

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

There are 2 parts of the appraisal process. The first step is to assess applicability (that is, the relevance of the study to the specific guideline topic and the NICE reference case); evaluations are categorised according to the criteria in Table 14.

Table 14 Applicability criteria

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

In the second step, only those studies deemed directly or partially applicable are further assessed for limitations (that is, methodological quality); see categorisation criteria in Table 15.

Table 15 Methodological criteria

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

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

Appendix C – Literature search strategies

Scoping search strategies

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

Guidelines/website
American Cancer Society
American College of Chest Physicians
American Society for Radiation Oncology
American Thoracic Society
Association for Molecular Pathology
British Lung Foundation
British Thoracic Society
Canadian Medical Association Infobase
Canadian Task Force on Preventive Health Care
Cancer Australia
Cancer Care Ontario
Cancer Control Alberta
Cancer Research UK
Care Quality Commission
College of American Pathologists
Core Outcome Measures in Effectiveness Trials (COMET)
Department of Health & Social Care
European Respiratory Society
European Society for Medical Oncology
European Society of Gastrointestinal Endoscopy

Guidelines/website
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
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 18th January 2018 (main search), 3rd April 2018 (2005-2011 published papers), 24th May 2018 (observational studies)
Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Strategy:
1 exp Lung Neoplasms/
2 ((lung* or pulmonary or bronch*) adj3 (cancer* or neoplasm* or carcinoma* or tumo?r* or lymphoma* or metast* or malignan* or blastoma* or carcinogen* or adenocarcinoma* or angiosarcoma* or chrondosarcoma* or sarcoma* or teratoma* or microcytic*)).tw.
3 ((pancoast* or superior sulcus or pulmonary sulcus) adj4 (tumo?r* or syndrome*)).tw.
4 ((lung* or pulmonary or bronch*) adj4 (oat or small or non-small) adj4 cell*).tw.
5 (SCLC or NSCLC).tw.
6 or/1-5
7 exp Radiotherapy/
8 Radiation Oncology/
9 radiotherapy.fs.
10 (radiotherap* or radiotreat* or roentgentherap* or radiosurg*).tw.
11 ((radiat* or radio* or irradiat* or roentgen or x-ray or xray) adj4 (therap* or treat* or repair* or oncolog* or surg*)).tw.
12 (RT or RTx or XRT).tw.
13 Stereotaxic Techniques/
14 ((stereotac* or stereotax*) adj4 (radiat* or surg* or procedure* or method* or technique* or technic*)).tw.
15 (SABR or SBRT or SRS).tw.
16 ((hypofraction* or hyperfraction*) adj4 (dose* or dosage* or accelerat* or expedite* or hasten* or quick* or radical* or modulat* or adjust* or regulat* or intens*)).tw.
17 (HFSRT or CAHRT or CHARTWEL or IMRT or AHRT or A-HYPO or HypoTRT).tw.
18 or/7-17
19 6 and 18

Medline Strategy, searched 18th January 2018 (main search), 3rd April 2018 (2005-2011 published papers), 24th May 2018 (observational studies)
Database: Ovid MEDLINE(R) 1946 to Present with Daily Update
Search Strategy:
20 limit 19 to english language
21 Animals/ not Humans/
22 20 not 21
23 (201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013* or 2014* or 2015* or 2016* or 2017* or 2018*).ed.
24 22 and 23

Note: In-house RCT, observational studies and systematic review filters were appended. Original search was conducted on 18th January 2018 with a date limit of April 2011 onwards. An additional search was then requested for papers published between 2005 and April 2011, this was conducted on 3rd April 2018. A final search of observational studies to support RCT evidence was conducted on 24th May 2018

Study Design Filters

The MEDLINE SR, RCT, and observational studies filters are presented below.
Systematic Review
1. Meta-Analysis.pt.
2. Meta-Analysis as Topic/
3. Review.pt.
4. exp Review Literature as Topic/
5. (metaanaly$ or metanaly$ or (meta adj3 analy$)).tw.
6. (review$ or overview$).ti.
7. (systematic$ adj5 (review$ or overview$)).tw.
8. ((quantitative$ or qualitative$) adj5 (review$ or overview$)).tw.
9. ((studies or trial$) adj2 (review$ or overview$)).tw.
10. (integrat$ adj3 (research or review$ or literature)).tw.
11. (pool$ adj2 (analy$ or data)).tw.
12. (handsearch$ or (hand adj3 search$)).tw.
13. (manual$ adj3 search$).tw.
14. or/1-13
15. animals/ not humans/
16. 14 not 15
RCT
1 Randomized Controlled Trial.pt.
2 Controlled Clinical Trial.pt.
3 Clinical Trial.pt.
4 exp Clinical Trials as Topic/
5 Placebos/
6 Random Allocation/
7 Double-Blind Method/
8 Single-Blind Method/
9 Cross-Over Studies/
10 ((random$ or control$ or clinical$) adj3 (trial$ or stud$)).tw.
11 (random$ adj3 allocat$).tw.
12 placebo$.tw.

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

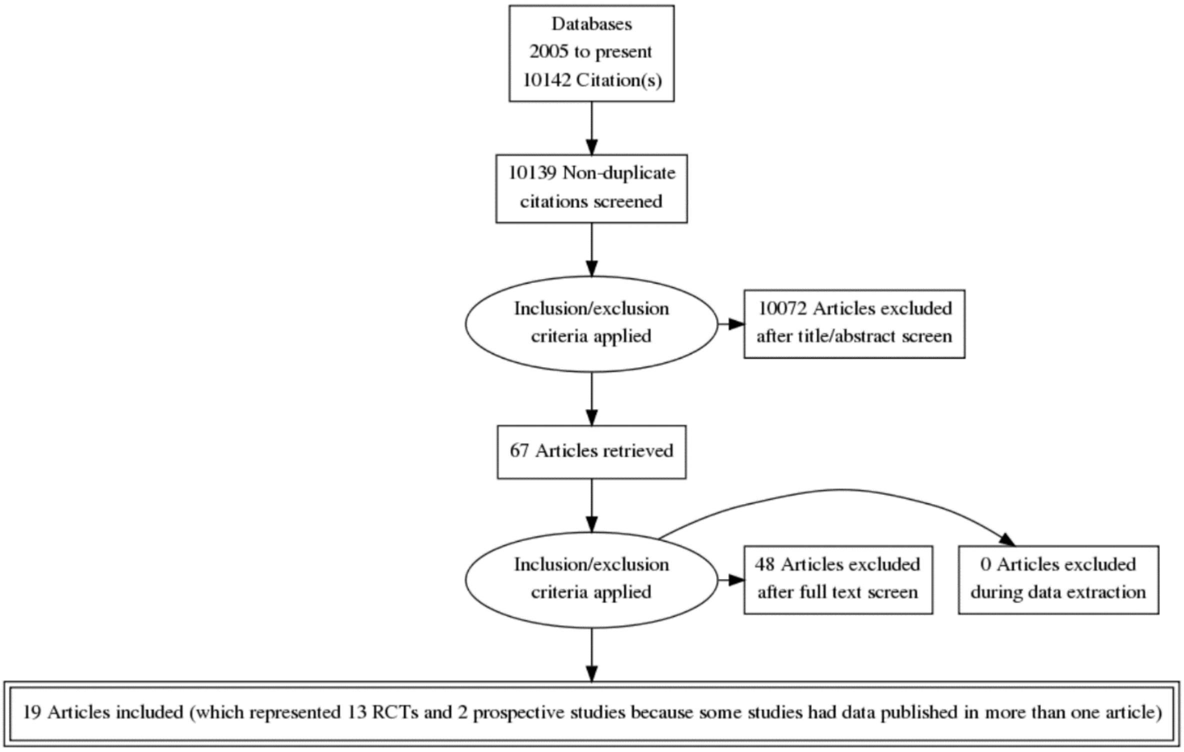
Medline Strategy
Economic evaluations 1 Economics/ 2 exp "Costs and Cost Analysis"/ 3 Economics, Dental/ 4 exp Economics, Hospital/ 5 exp Economics, Medical/ 6 Economics, Nursing/ 7 Economics, Pharmaceutical/ 8 Budgets/ 9 exp Models, Economic/ 10 Markov Chains/ 11 Monte Carlo Method/ 12 Decision Trees/ 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. 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.

Medline Strategy	
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

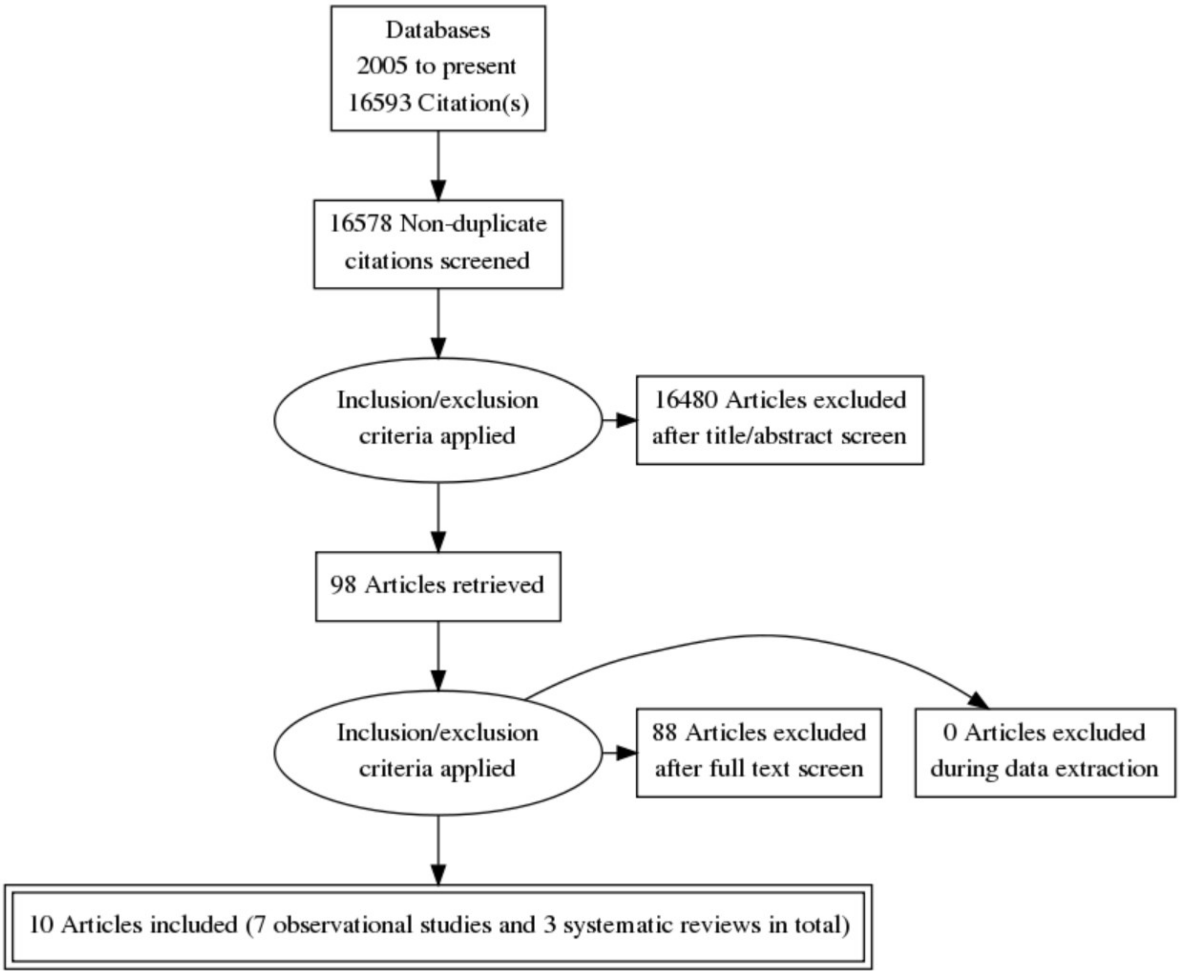
Clinical Evidence study selection

Randomised controlled trials



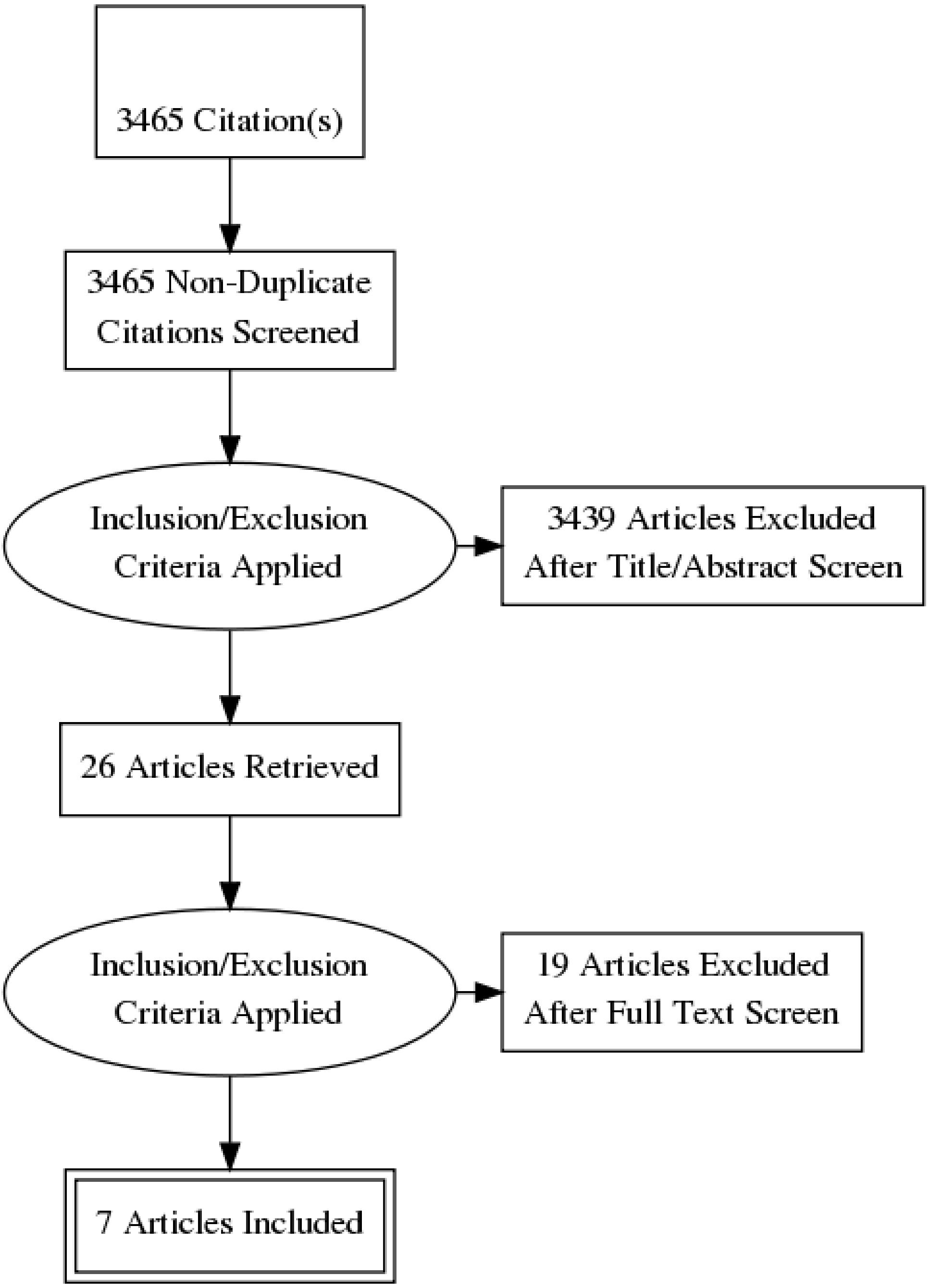
286

287 **Observational studies**



288
289

Economic Evidence study selection



293 # Appendix E – Clinical evidence tables

294 ## Randomised controlled trials

Short Title	Title	Study Characteristics	Risk of Bias
Baumann 2011 (Includes Soliman 2013 and Hechtner 2018)	Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC)	**Study type** • Randomised controlled trial *This is the CHARTWEL study includes Baumann 2011, Soliman 2013 and Hechtner 2018* **Study details** • Study location *Poland, Germany, Czech Republic* • Study setting *Hospitals* • Study dates *Recruitment occurred between 1997 to 2005* • Duration of follow-up *Follow-up examinations were at 8 weeks and 3 months after start of radiotherapy, followed by three-monthly visits up to 2 years, and 6-monthly visits up to 5 years. The median follow-up times for surviving people were 3.3 years for CF and 3.4 years for CHARTWEL.* • Sources of funding *The German Cancer Foundation* **Inclusion criteria** • Inoperable NSCLC or surgery refused • Histological confirmation of NSCLC by biopsy or cytological evaluation	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias *This study has no blinding. However, this may not be feasible because many of the participants are stage IIIA and IIIB. Good communication may take precedence over blinding.* Blinding of participants and personnel • Unclear risk of bias *This study has no blinding. However, this may not be feasible because many of the participants are stage IIIA and IIIB. Good communication may take precedence over blinding.* Blinding of outcome assessment • Unclear risk of bias *This study has no blinding. However, this may not be feasible because many of the participants are stage IIIA and IIIB. Good communication may take precedence over blinding.*

Short Title	Title	Study Characteristics	Risk of Bias
		• Tumour volume allowing curatively intended radiotherapy **Exclusion criteria** • WHO performance status >2 • >15% weight loss within the previous 6 months that was not intentional • Other disease that is expected to limit short term life expectancy • FEV1 <1 under optimised treatment • Previous radiotherapy • Prior malignancy other than non-melanoma skin cancer or adequately treated stage I in situ cervical cancer And also not including cancer of the glottis • Surgical resection other than biopsy • Age <18 years • Unsuitable for radical radiotherapy • Unsuitable for follow-up • Distant metastases • Supraclavicular lymph node metastases • Pleural effusion (if not cytologically negative or very small and explainable by other reasons) • Cardiac pacemaker in the irradiation field unless the cardiologist agrees with radiotherapy • Patient involvement with any other clinical trial testing pharmaceutical products • Impossibility of being able to conduct follow-up procedures • No co-operation from the patient **Sample characteristics** • Sample size	Incomplete outcome data • High risk of bias *After 1 year, over 20% of participants were not returning their QoL questionnaire. The adverse event measurements were limited to snapshots at 2, 4, 8, 12, 16 and 20 weeks for dysphagia and 8 and 12 weeks for radiation induced pneumonitis. Splitting adverse events into snapshots could be exploited to ensure that statistical significance is not reached. It is possible that by having snapshots, some instances were missed. In addition, some incidents may have been counted more than once if they passed through more than one 'snapshot'. The usual way of measuring adverse events is cumulative incidence - either of episodes or people experiencing events. This is particularly true of the grade 3 or higher adverse events that everyone is particularly interested in. This is because by their definition they require attention from a healthcare professional who would then document it. The study only measured dysphagia and radiation induced pneumonitis. There may have been additional adverse events that were not reported.* Selective reporting • Low risk of bias Other sources of bias • Unclear risk of bias *Approximately a quarter of participants in both arms received chemotherapy before radiotherapy. The*

Short Title	Title	Study Characteristics	Risk of Bias
		406 people • Split between study groups *CHARTWEL = 203; conventional fractionation = 203* • Loss to follow-up *None for mortality and adverse events. However, the drop-out rate for the QoL outcome was above 20% beyond 1 year in both arms. At 5 years, compliance was 12.5% (1/8) in the CF arm and 21.4% (3/14) in the CHARTWEL arm.* • %female *CHARTWEL = 9%; conventional fractionation = 12%* • Average age *Median (range): CHARTWEL = 66 years (47-84); conventional fractionation = 66 years (38-87)* **Interventions** • Conventional fractionation (CF) 66 Gy (2 Gy, daily, 5 days a week) *The prescribed treatment in the conventional fractionation arm was a daily dose of 2 Gy at five days per week to 50 Gy in planning target volume 1 and an additional boost dose of 16 Gy to planning target volume 2, resulting in a total dose of 66 Gy in 33 fractions. Planning target volume 1 included the mediastinum and the primary tumour with a margin of 1–1.5 cm ipsilaterally and 1 cm contralaterally. The mediastinum, defined as an area from fossa jugulare to 3 cm below the carina included the target volume of the primary tumour, the ipsilateral hilum, the subcarinal lymph node and the ipsi- and contralateral paratracheal lymph node. Supraclavicular irradiation was allowed for tumours of the upper lobes and irradiation of the contralateral hilum was included if positive. Planning target volume 2 included the primary tumour and positive lymph node with a margin of 1 cm. Positive lymph nodes were defined as lymph node with the short axis measuring greater than or equal to 1 cm in CT scans.*	*chemotherapy was not specified and was left to the discretion of the clinicians. This introduces an element of potential bias.* Overall risk of bias • Moderate Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Overall treatment time was 6.5 weeks in the CF arm. Missing fractions were to be compensated wherever possible by by applying a second fraction at another treatment day. Recommended dose constraints were: the maximum dose to the spinal cord had to be less than 44 Gy and in any case less than 48 Gy in the CF arm; not more than 30% of the contralateral lung should receive a dose of more than 20 Gy and not more than 20% of more than 30 Gy; not more than 50% of the total lung should receive more than 20 Gy and not more than 35% more than 30 Gy. • Continuous Hyperfractionated Accelerated RadioTherapy WeekEnd-Less (CHARTWEL) 60 Gy (1.5 Gy, 3x per day, 5 days a week) *For the CHARTWEL arm, a dose per fraction of 1.5 Gy was given three times per day at five days per week, excluding the weekends, to a dose in PTV1 of 39 Gy and a boost dose to PTV2 of 21 Gy, resulting in a total dose of 60 Gy. The interfraction-interval was at least 6 hours. Overall treatment time was 18 days in the CHARTWEL arm. Missing fractions were to be compensated wherever possible by irradiation at weekends. Recommended dose constraints were: the maximum dose to the spinal cord had to be less than 40 Gy and in any case less than 44 Gy in the CHARTWEL arm; not more than 30% of the contralateral lung should receive a dose of more than 20 Gy and not more than 20% of more than 30 Gy; not more than 50% of the total lung should receive more than 20 Gy and not more than 35% more than 30 Gy.* **Outcome measures** • Mortality *This data was reported in Baumann 2011* • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	

Short Title	Title	Study Characteristics	Risk of Bias
		This data is in Baumann 2011 • Quality of life *This data is in Hechtner 2018. The assessment of QoL was not obligatory for the participating study sites. Consequently, the proportion of patients with at least one QoL assessment available was relatively small (59.9%, n = 243). Therefore, in order to minimize selection effects and structural inequalities between the treatment groups, only patients from the Department of Radiation Oncology at the University Hospital Carl Gustav Carus (Technische Universität Dresden, Germany), in which QoL assessment was performed consistently over the course of the study, were included. This subgroup represents the largest monocentric sample of the trial and comprises 163 patients of the intention-to-treat population, 82 randomly assigned to CHARTWEL and 81 to CF. QoL questionnaires were administered at baseline, 8 weeks, 6 months, 1 year, and yearly thereafter until five years after randomisation. QoL was assessed with the European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire (EORTC QLQ-C30, Version 3.0).*	
Belani 2005	Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with	**Study type** • Randomised controlled trial **Study details** • Study location *USA* • Study setting *Hospitals* • Study dates *Recruitment was from 1998 to 2001* • Duration of follow-up *Minimum follow-up of 36 months for surviving participants.*	**Quality assessment (RCT)** Random sequence generation • Unclear risk of bias *The method of randomisation was not provided. However, the baseline characteristics of the two arms appear well balanced.* Allocation concealment • Unclear risk of bias *There was no blinding in this study. However, blinding might not be feasible because participants were stage IIIA and IIIB. Openness and good communication would probably be a priority.*

Short Title	Title	Study Characteristics	Risk of Bias
	unresectable stage IIIA and B non-small-cell lung cancer	• Sources of funding *Eastern Cooperative Oncology Group* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Unresectable • Stage IIIA • Stage IIIB **Exclusion criteria** • ECOG performance status >2 • Previous chemotherapy or thoracic radiotherapy • Prior malignancy other than non-melanoma skin cancer or adequately treated stage I in situ cervical cancer During the preceding 5 years • Age <18 years • Pleural effusion on chest X-ray • Collapse of an entire lung • Active peptic ulcer disease, oesophageal reflux, or hiatal hernia • No consent to abstain from smoking during radiotherapy • Tumour location was such that 100% of the cardiac volume would not receive more than 45 Gy, or if 50% or more of the cardiac volume would receive no more than 50 Gy **Sample characteristics** • Sample size *112 people* • Split between study groups	Blinding of participants and personnel • Unclear risk of bias *There was no blinding in this study. However, blinding might not be feasible because participants were stage IIIA and IIIB. Openness and good communication would probably be a priority.* Blinding of outcome assessment • Unclear risk of bias *There was no blinding in this study. However, blinding might not be feasible because participants were stage IIIA and IIIB. Openness and good communication would probably be a priority.* 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 Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		HART = 56; CF = 56 • Loss to follow-up *HART = 2; CF = 1* • %female *HART = 38%; CF = 41%* • Average age *Median (range): HART = 65.7 years (45-77); CF = 63.4 years (40-77)* **Interventions** • Chemotherapy, conventional fractionation (CF) 64 Gy (2 Gy, daily, 5 days a week) *The chemotherapy regimen consisted of two cycles of carboplatin (days 1 and 22) area under the time-concentration curve 6 mg/mL/min and paclitaxel 225 mg/m2 during a 3-hour period on day 1 administered 3 weeks apart and delivered before radiotherapy. Dose reductions were permitted for both haematologic and nonhaematologic effects. Growth factor support was not routinely used, but was permitted as secondary prophylaxis. After the completion of two cycles of chemotherapy, patients were reassessed with chest CT to ensure the absence of metastatic progression.* *In the absence of metastatic progression, patients were randomly assigned to one of two different radiotherapeutic regimens, with treatment to begin between days 43 and 50.* *In the CF arm, the total dose was 64 Gy in 32 fractions of 2 Gy each, delivered 5 days per week. For most patients, an initial anteroposterior field arrangement was used for approximately 40 Gy; this covered the primary tumour and all enlarged lymph nodes. In addition, elective nodal radiation of selected stations was allowed, based on tumour location and nodal status. Subsequently, this region received a total dose of 50 Gy, using either lateral or oblique portals, and a final cone-down boost increased the dose to 64 Gy for the tumour and all*	

Short Title	Title	Study Characteristics	Risk of Bias
		enlarged lymph nodes, with a 1- to 1.5-cm margin. Postchemotherapy CT scans were used for tumour definition. Electrons were permitted for treating the supraclavicular fossae only, and all photon energies had to be a minimum of 4 MV. CT-based treatment planning was recommended, but lung density corrections were not used; the prescription was to the isocenter and not to an isodose surface, and dose heterogeneity within the tumour was limited to 10%. A system of rapid port review was used and provided immediate feedback to the treating physician for therapy modification as needed. Standard dose limitations were used for normal tissues. • Chemotherapy, Hyperfractionated Accelerated Radiotherapy (HART) 57.6 Gy (1.5 GY, 3x per day, 5 days a week) (Most similar to CHARTWEL) *The chemotherapy regimen consisted of two cycles of carboplatin (days 1 and 22) area under the time-concentration curve 6 mg/mL/min and paclitaxel 225 mg/m2 during a 3-hour period on day 1 administered 3 weeks apart and delivered before radiotherapy. Dose reductions were permitted for both haematologic and nonhaematologic effects. Growth factor support was not routinely used, but was permitted as secondary prophylaxis. After the completion of two cycles of chemotherapy, patients were reassessed with chest CT to ensure the absence of metastatic progression.* *In the absence of metastatic progression, patients were randomly assigned to one of two different radiotherapeutic regimens, with treatment to begin between days 43 and 50.* *In the experimental (HART) arm, the total dose was 57.6 Gy on the 3 times a day fractionation schedule. Simulation and CT-based treatment planning were used, and oesophageal contrast was used at simulation to define the location of the oesophagus. Corrections for lung transmission were not used for dosimetric calculations. The minimum interval between fractions was 4 hours. The first and third fraction of each day consisted of anteroposterior-posteroanterior fields*	

Short Title	Title	Study Characteristics	Risk of Bias
		encompassing the primary tumour and draining lymphatics with a 1- to 1.5-cm margin; the fraction size for these fields was 1.5 Gy. The second fraction of each day used lateral or oblique photon fields, encompassed all gross disease (primary tumour and involved nodes) with a 1-cm margin, and excluded the spinal cord. The fraction was interdigitated between fraction 1 and fraction 3, and the fraction size was 1.8 Gy. Attempts were made to design the fraction 2 field to minimize the volume of oesophagus treated without compromising the margin around tumour or spinal cord. Treatment began on a Monday and finished on the third Tuesday, for a total of 12 planned treatment days during 15 elapsed days. **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
Bradley 2015	Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-	**Study type** • Randomised controlled trial **Study details** • Study location *USA and Canada* • Study setting *Hospitals* • Study dates *Recruitment was from 2007 to 2011* • Duration of follow-up	**Quality assessment (RCT)** Random sequence generation • Low Allocation concealment • Low risk of bias Blinding of participants and personnel • Unclear risk of bias *There was no blinding. However, blinding might not be feasible given that participants were stage IIIA or IIIB. Good communication and transparency might be more of a priority.*

Short Title	Title	Study Characteristics	Risk of Bias
	two factorial phase 3 study	*Follow-up assessments were every 3 months for the first year, every 4 months for year 2, every 6 months for years 3–5, then every year. The median follow-up was 22·9 months (IQR 27·5–33·3).* • Sources of funding *National Cancer Institute and Bristol-Myers Squibb* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Unresectable • Stage IIIA • Stage IIIB **Exclusion criteria** • Zubrod performance status >2 • >10% weight loss within the previous month • Previous or current other malignancy During the last 3 years • Pulmonary function (before or after bronchodilation) of 1·2 L per second or higher • Age <18 years • Pleural effusion (if not cytologically negative or very small and explainable by other reasons) *Transudative were allowed* • Contralateral hilar or supraclavicular adenopathy or Pancoast tumours (because of the risk of lung or brachial plexus toxic effects) • Low haemoglobin • Low neutrophil count • Low platelet count	Blinding of outcome assessment • Unclear risk of bias *There was no blinding. However, blinding might not be feasible given that participants were stage IIIA or IIIB. Good communication and transparency might be more of a priority.* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		• Abnormal serum creatinine • Abnormal bilirubin • Abnormal aspartate aminotransferase 2·5 times or lower the upper institutional normal limit • Abnormal alanine aminotransferase 2·5 times or lower the upper institutional normal limit **Sample characteristics** • Sample size *495 people* • Split between study groups *CF 60 Gy = 288; CF 74 Gy = 207* • Loss to follow-up *None* • %female *CF 60 Gy = 41%; CF 74 Gy = 42%* • Average age *Median (range): CF 60 Gy = 64 years (38-83); CF 74 Gy = 64 years (41-83)* **Interventions** • Chemotherapy, conventional fractionation (CF) 60 Gy (2 Gy, daily, 5 days a week) *Radiation therapy was given 5 days per week (i.e., Monday to Friday with the weekend off) in 2 Gy fractions daily by use of 6–18 MV x-rays. Use of image-guided radiation therapy was encouraged. Both three-dimensional conformal and intensity-modulated radiation therapy were allowed. Compliance with normal tissue dose constraints was encouraged but not necessary. Radiation doses were prescribed to the*	

Short Title	Title	Study Characteristics	Risk of Bias
		planning target volume. Motion management was required, and internal target volumes, clinical target volumes, and planning target volumes depended on which motion management method was used. Use of PET or CT and four-dimensional CT for radiation therapy planning was encouraged. Elective nodal irradiation was not permitted. The gross tumour volume was defined as the primary tumour and any regionally involved nodes on CT (>1 cm on short axis) or pre-treatment PET scan (standardised uptake value >3). The internal target volume was defined as the envelope that encompasses the gross tumour volume plus ventilatory motion. Clinical target volume margins were 0·5–1·0 cm beyond the internal target volume. Planning target volume margins were 0·5–1·5 cm beyond the clinical target volume, depending on the use of four-dimensional CT for planning and image-guided radiation therapy for delivery. Radiation therapy plans were reviewed centrally and scored for both target delineation and dose and normal tissue delineation and dose on submitted plans. Per-protocol planning target volume coverage was achieved when more than 99% of the planning target volume received 93% or more of the prescribed dose and when minimum margin values for both clinical target volume and planning target volume were achieved. *Chemotherapy consisted of weekly paclitaxel (45 mg/m² per week) and carboplatin (area under the curve [AUC] 2 per week) during radiation therapy. Two weeks after chemoradiation, two cycles of consolidation chemotherapy separated by 3 weeks were given consisting of paclitaxel (200 mg/m²) and carboplatin (AUC 6). Paclitaxel was given for 3 hours 30 minutes after diphenhydramine (25–50 mg), followed by an H2 blocker, and dexamethasone (oral or intravenous administration allowed). Carboplatin was given for 30 minutes with standard anti-emetics after paclitaxel. 137/288 received cetuximab. Patients in the cetuximab groups received the agent during both concurrent and consolidative phases. Cetuximab was given at 400 mg/m² intravenously on day 1, with concurrent chemoradiation starting on day 8. Weekly cetuximab dosing was 250 mg/m², given before*	

Short Title	Title	Study Characteristics	Risk of Bias
		chemotherapy and radiation therapy that day. Consolidation cetuximab (250 mg/m² per week) was given weekly during consolidation. • Chemotherapy, conventional fractionation (CF) 74 Gy (2 Gy, daily, 5 days a week) *Radiation therapy was given 5 days per week (i.e., Monday to Friday with the weekend off) in 2 Gy fractions daily by use of 6–18 MV x-rays. Use of image-guided radiation therapy was encouraged. Both three-dimensional conformal and intensity-modulated radiation therapy were allowed. Compliance with normal tissue dose constraints was encouraged but not necessary. Radiation doses were prescribed to the planning target volume. Motion management was required, and internal target volumes, clinical target volumes, and planning target volumes depended on which motion management method was used. Use of PET or CT and four-dimensional CT for radiation therapy planning was encouraged. Elective nodal irradiation was not permitted. The gross tumour volume was defined as the primary tumour and any regionally involved nodes on CT (>1 cm on short axis) or pretreatment PET scan (standardised uptake value >3). The internal target volume was defined as the envelope that encompasses the gross tumour volume plus ventilatory motion. Clinical target volume margins were 0·5–1·0 cm beyond the internal target volume. Planning target volume margins were 0·5–1·5 cm beyond the clinical target volume, depending on the use of four-dimensional CT for planning and image-guided radiation therapy for delivery. Radiation therapy plans were reviewed centrally and scored for both target delineation and dose and normal tissue delineation and dose on submitted plans. Per-protocol planning target volume coverage was achieved when more than 99% of the planning target volume received 93% or more of the prescribed dose and when minimum margin values for both clinical target volume and planning target volume were achieved.*	

Short Title	Title	Study Characteristics	Risk of Bias
		Chemotherapy consisted of weekly paclitaxel (45 mg/m² per week) and carboplatin (area under the curve [AUC] 2 per week) during radiation therapy. 2 weeks after chemoradiation, two cycles of consolidation chemotherapy separated by 3 weeks were given consisting of paclitaxel (200 mg/m²) and carboplatin (AUC 6). Paclitaxel was given for 3 hours 30 minutes after diphenhydramine (25–50 mg), followed by an H2 blocker, and dexamethasone (oral or intravenous administration allowed). Carboplatin was given for 30 min with standard anti-emetics after paclitaxel. *Patients in the cetuximab groups received the agent during both concurrent and consolidative phases. 107/207 participants received cetuximab. Cetuximab was given at 400 mg/m² intravenously on day 1, with concurrent chemoradiation starting on day 8. Weekly cetuximab dosing was 250 mg/m², given before chemotherapy and radiation therapy that day. Consolidation cetuximab (250 mg/m² per week) was given weekly during consolidation.* • Chemotherapy, Intensity Modulated Radiation Therapy (IMRT) 60 or 74 Gy (2 Gy, daily, 5 days a week) • Chemotherapy, 3-Dimensional Conformal external beam Radiation Therapy (3D-CRT) 60 or 74 Gy (2 Gy, daily, 5 days a week) **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
Chang 2015 (includes	Stereotactic ablative radiotherapy versus lobectomy for	**Study type** • Randomised controlled trial *This is a pooling of two RCTs. It includes Louie 2015*	**Quality assessment (RCT)** Random sequence generation • Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
Louie 2015)	operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials.[Erratum appears in Lancet Oncol. 2015 Sep;16(9):e427; PMID: 26370351]	**Study details** • Study location *ROSEL RCT: The Netherlands STARS RCT: USA, China and France* • Study setting *Hospitals / cancer centres* • Study dates *ROSEL: 2008 to 2014 STARS: 2009 to 2014* • Duration of follow-up *ROSEL: follow-up every 3 months for the first year. Then every 6 months for the following 5 years. Each follow-up visit included contrast-enhanced CT scans of the thorax and upper abdomen. STARS: follow-up every 6 months for 2 years, and then annually thereafter. Contrast-enhanced CT of the chest and upper abdomen or PET-CT images were obtained at the 6-month and subsequent follow-up visits. Median follow-up for all patients was 40·2 months (Interquartile Range 23·0–47·3) in the SABR group and 35·4 months (IQR 18·9–40·7) in the surgery group.* • Sources of funding *Accuracy and Varian Medical Systems (radiotherapy manufacturers), the Netherlands Organisation for Health Research and Development, NCI Cancer Center Support (Core) Grant and NCI Clinical and Translational Science Award* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation This was required in the STARS trial but was not mandatory in the ROSEL protocol.	Allocation concealment • High risk of bias *No allocation concealment* Blinding of participants and personnel • High risk of bias *There was no blinding* Blinding of outcome assessment • High risk of bias *There was no blinding* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Unclear risk of bias *The authors wrote that detailed eligibility and exclusion criteria are included in the appendix. However, there are no further details in the appendix. This makes it more difficult to assess how homogeneous or heterogeneous the combined RCTs are.* Overall risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		• New or growing pulmonary lesion with radiological features consistent with malignant disease and avidity on ^{18}F-fluorodeoxyglucose PET This was the case for the ROSEL trial, not the STARS trial. This is because in the ROSEL trial, the likelihood of a benign diagnosis in such cases in the Dutch population is less than 6%. • Staging chest CT • ^{18}F-FDG-PET • Imaging that suggests T1-2a (<4cm), N0 M0, operable disease • Participants with radiologically suspicious lymph nodes underwent endobronchial ultrasonography or mediastinoscopy **Exclusion criteria** • None reported *The authors wrote that detailed eligibility and exclusion criteria are included in the appendix. However, there are no further details in the appendix.* • Performance status >2 *This was mentioned in the results section* **Sample characteristics** • Sample size *58 people* • Split between study groups *SABR = 31; surgery = 27* • Loss to follow-up *None* • %female *SABR = 55%; surgery = 59%* • Average age	• High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Interventions • Stereotactic ablative radiotherapy (SABR) peripheral: 54 Gy in 3 x 18 Gy fractions; central: 50 Gy in 4 x 12.5 Gy fractions. Otherwise known as stereotactic body radiotherapy *In the STARS protocol, the CyberKnife system was used for all radiotherapy sessions for patients randomly assigned to receive SABR. Implanted fiducial markers were used to verify and track tumour motion. Patients with peripherally located lesions (i.e., those located >2 cm in any direction from the proximal bronchial tree, major vessels, oesophagus, heart, tracheal, vertebral body, pericardium, mediastinal pleural, and brachial plexus) received a total radiation dose of 54 Gy in three 18 Gy fractions (BED 151·2 Gy), calculated with a Monte Carlo or equivalent algorithms or its equivalent dose if other algorithms were used and heterogeneity correction. For central lesions (i.e., those within 2 cm of these structures), 50 Gy in four 12·5 Gy fractions (BED 112·5 Gy) was used. The SABR dose was prescribed to the highest isodose line, which was required to cover 100% of the gross tumour volume (defined as visible disease in CT images with use of lung window) and more than 95% of the planning target volume (defined as the gross tumour volume plus a 3 mm margin). Coverage of 100% of the planning target volume by at least the prescription dose was encouraged. The normal tissue constraints were met for all cases. Treatment delivery was recommended to be complete within 5 days of its initiation. In the ROSEL protocol, linear-accelerator-based SABR from multiple vendors was used for patients randomly assigned to receive radiotherapy. Only lesions located 2 cm or more from the hilar structures on the diagnostic CT scan were eligible. A toxicity risk-adapted fractional scheme was used in which a total dose of 54 Gy in three 18 Gy fractions (BED 151·3 Gy), calculated with a Monte Carlo or equivalent algorithms or its equivalent doses if other algorithms were used and heterogeneity correction, and given over 5–8 days;*	

Short Title	Title	Study Characteristics	Risk of Bias
		alternatively, a total dose of 60 Gy at five 12 Gy fractions (BED 132·0 Gy), was given over 10–14 days (to account for different treatment delivery practices in Dutch centres). The SABR dose prescription was chosen such that 95% of the planning target volume, the internal target volume (based on four dimensional CT), or other equivalent approaches to take tumour motion into consideration - plus a 3–5 mm margin for setup and motion uncertainty - would receive at least the nominal fraction dose, and 99% of the planning target volume would receive at least 90% of the fraction dose. The preferred maximum dose within the planning target volume was between 110% and 140% of the prescribed dose. • Surgery (lobectomy) *For patients randomly assigned to receive surgery, acceptable surgical techniques included anatomic lobectomy by open thoracotomy or video-assisted thoracotomy. All accessible hilar (level 10) lymph nodes had to be dissected from the specimen. All patients who had a lobectomy also underwent dissection or sampling of mediastinal lymph nodes in both trials (for right-sided lesions, including levels 4R, 7, and 9; for left-sided lesions, including 5, 6, 7, and 9).* **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
Curran (2011)	Sequential vs. concurrent chemoradiation for stage III non-small cell lung cancer:	**Study type** • Randomised controlled trial **Study details** • Study location	**Quality assessment (RCT)** Random sequence generation • Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
	randomized phase III trial RTOG 9410	*USA* • Study setting *Hospital* • Study dates *Recruitment was from 1994 to 1998* • Duration of follow-up *Median follow-up was 11 years* • Sources of funding *Radiation Therapy Oncology Group and the National Cancer Institute* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Unresectable • Stage II • Stage IIIA • Stage IIIB **Exclusion criteria** • Karnofsky performance status <70 • >5% weight loss over the previous 3 months • Previous chemotherapy or thoracic radiotherapy *Or neck radiotherapy* • Surgical resection other than biopsy • Age <18 years • Evidence of metastatic disease • Pleural effusion on chest X-ray • Pleural effusion with malignant cytology	*The method of randomisation was not given. However, the baseline characteristics were similar for each group* Allocation concealment • Unclear risk of bias *No allocation concealment. However, this may not have been feasible* Blinding of participants and personnel • Unclear risk of bias *No blinding. However, this may not have been feasible given that many participants were stage IIIA or IIIB* Blinding of outcome assessment • Unclear risk of bias *There were 3 blinded interim analyses. Nothing else had blinding. However, blinding may not have been feasible* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		• Low haemoglobin • Low granulocyte count • Low platelet count • Abnormal serum creatinine • Abnormal bilirubin • Abnormal serum glutamic oxaloacetic transaminase • Pregnant • Other *Patients were ineligible if they could be enrolled on an RTOG phase III trial for patients with confirmed N2 lymph node involvement evaluating the role of surgery for such patients (RTOG 9309)* **Sample characteristics** • Sample size *382 people* • Split between study groups *CF, 63 Gy, daily = 195; CF 69.6 Gy, twice daily = 187* • Loss to follow-up *4 participants were lost to follow-up in each arm* • %female *CF, 63 Gy, daily = 36%; CF 69.6 Gy, twice daily = 34%* • Average age *Median (range): CF, 63 Gy, daily = 60 years (33-79); CF 69.6 Gy, twice daily = 63 years (35-80)* **Interventions** • Chemotherapy, conventional fractionation 63 Gy (1.8 Gy, daily, 5 days a week)	Overall risk of bias • Low Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Cisplatin chemotherapy was delivered intravenously at a dose of 100 mg/m2 over a 30- to 60-minute period on day 1 or 2, and vinblastine was delivered at a dose of 5 mg/m2 weekly for five consecutive weeks beginning on day 1. Radiotherapy started on day 1. The initial radiotherapy target volume consisted of the primary pulmonary tumour, the regional draining lymph nodes, and any intrathoracic or supraclavicular lymph nodes measuring greater than 2.5 cm. Radiotherapy was delivered to this volume at a daily dose of 1.80 Gy to a total dose of 45.00 Gy over 5 weeks. The sixth and seventh weeks of radiotherapy were delivered to a smaller target volume encompassing the primary tumour and lymph nodes known to be involved with disease and any lymph node measuring greater than 2.0 cm. This treatment was delivered in a technique avoiding the spinal cord at a daily dose of 2.00 Gy for nine fractions to 18.00 Gy. The total radiotherapy dose to the tumour was 63.00 Gy, and the total dose to the spinal cord was restricted to 48.00 Gy or less. • Chemotherapy, conventional fractionation 69.6 Gy (1.2 Gy, 2x per day, 5 days a week) *Cisplatin was delivered intravenously at 50 mg/m2 over 30–60 minutes on days 1, 8, 29, and 36, and oral etoposide was administered at a dose of 50 mg twice daily on days 1–5, 8–12, 29–33, and 36–40. The dosing of oral etoposide was reduced to 75 mg/d if the patient's body surface area was less than 1.7 m2. Radiotherapy was delivered twice daily in 20 Gy fractions to a total dose of 69.60 Gy separated with an interfraction time interval of 6–8 hours. Target volume definitions were identical to the other arm, and the total dose was 50.40 Gy for the initial volume and 19.20 Gy for the secondary target volume. Spinal cord dose was also restricted to 48.00 Gy or less.* **Outcome measures** • Mortality	

Short Title	Title	Study Characteristics	Risk of Bias
		• Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
Eberhardt (2015)	Phase III Study of Surgery Versus Definitive Concurrent Chemoradiotherapy Boost in Patients With Resectable Stage IIIA(N2) and Selected IIIB Non-Small-Cell Lung Cancer After Induction Chemotherapy and Concurrent Chemoradiotherapy (ESPATUE)	**Study type** • Randomised controlled trial **Study details** • Study location *Germany* • Study setting *Hospitals* • Study dates *Recruitment was from 2004 to 2013* • Duration of follow-up *Follow-up visits were scheduled every 3 months after random assignment. Follow-up was a minimum of 1 year.* • Sources of funding *German Cancer Aid* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Potentially resectable stage IIIA (N2) or selected stage IIIB *N2 disease had to be pathologically proven during mediastinoscopy (recommended), endobronchial ultrasonography, or parasternal mediastinotomy. Selected resectable IIIB disease was defined as N3 disease with contralateral mediastinal nodes and proven T4 disease with involvement of the pulmonary artery, carina, left atrium, vena cava, or mediastinum. Positron emission tomographic (PET) or PET–*	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC* Blinding of participants and personnel • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC* Blinding of outcome assessment • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC* Incomplete outcome data • Low risk of bias Selective reporting

Short Title	Title	Study Characteristics	Risk of Bias
		computed tomographic staging, which was performed in 97%, and brain imaging investigations were routinely recommended. **Exclusion criteria** • ECOG performance status >2 • >10% weight loss in the 6 months before diagnosis • Inadequate renal, hepatic or haematologic functions **Sample characteristics** • Sample size *161 people* • Split between study groups *Induction chemotherapy, chemoradiotherapy + surgery = 81; induction chemotherapy, chemoradiotherapy (radiotherapy boost) = 80* • Loss to follow-up *None* • %female *Induction chemotherapy, chemoradiotherapy + surgery = 31%; induction chemotherapy, chemoradiotherapy (radiotherapy boost) = 34%* • Average age *Median (range): Induction chemotherapy, chemoradiotherapy + surgery = 58 years (33-72); induction chemotherapy, chemoradiotherapy (radiotherapy boost) = 59 years (42-74)* **Interventions** • Chemotherapy, conventional fractionation (CF) 45 Gy (1.5 Gy, 2x per day, 5 days a week), surgery	• Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Induction chemotherapy consisted of three cycles of dose-dense cisplatin and paclitaxel in a 21-day cycle. Neoadjuvant radiotherapy was delivered to a total cumulative dose of 45 Gy, as two 1.5-Gy fractions per day, given 5 days a week. The minimum interval between daily fractions was 6 hours. Three dimensional treatment planning was mandatory. Intensity-modulated radiotherapy was not allowed. Concurrent chemotherapy consisted of one cycle of cisplatin and vinorelbine: cisplatin 50 mg/m2 on days 2 and 9 and vinorelbine 20 mg/m2 on days 2 and 9 of neoadjuvant radiotherapy. • Chemotherapy, conventional fractionation (CF) 45 Gy (1.5 Gy, 2x per day, 5 days a week), boost CF 20-26 Gy (2 Gy, 2x per day, 5 days a week) *Induction chemotherapy consisted of three cycles of dose-dense cisplatin and paclitaxel in a 21-day cycle. Neoadjuvant radiotherapy was delivered to a total cumulative dose of 45 Gy, as two 1.5-Gy fractions per day, given 5 days a week. The minimum interval between daily fractions was 6 hours. Three dimensional treatment planning was mandatory. Intensity-modulated radiotherapy was not allowed. Concurrent chemotherapy consisted of one cycle of cisplatin and vinorelbine: cisplatin 50 mg/m2 on days 2 and 9 and vinorelbine 20 mg/m2 on days 2 and 9 of neoadjuvant radiotherapy. The chemoradiotherapy boost was risk adapted to between 65 and 71 Gy. This was done in the following way: Definitive boost radiotherapy was given at 2 Gy per fraction, five fractions per week, to a cumulative dose of 20 to 26 Gy without a treatment break from neoadjuvant radiotherapy. A 26-Gy boost dose was recommended if deliverable within the normal tissue constraints. Specific radiation parameters, techniques, concurrent chemotherapy application given to the boost (cisplatin 40 mg/m2 on day 2 and vinorelbine 15mg/m2 on days 2 and 9 of the boost radiotherapy). The maximum allowed mean dose to the lung was 18 Gy, and the maximum dose at the spinal cord had to be*	

Short Title	Title	Study Characteristics	Risk of Bias
		less than 42 Gy. To avoid increased toxicities during the concurrent chemoradiotherapy boost, and given the previous experience in the pilot phase II study, concurrent chemotherapy to the boost was reduced in doses of cisplatin and vinorelbine. **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy) • Dropout during treatment	
Girard 2010	Is neoadjuvant chemoradiotherapy a feasible strategy for stage IIIA-N2 non-small cell lung cancer? Mature results of the randomized IFCT-0101 phase II trial	**Study type** • Randomised controlled trial **Study details** • Study location *France* • Study setting *Hospitals* • Study dates *Recruitment was from 2003 to 2007* • Duration of follow-up *Median follow-up of 31.4 months.* • Sources of funding *Programme Hospitalier de Recherche Clinique, Ligue National contre le Cancer and the Lilly Laboratories.* **Inclusion criteria**	**Quality assessment (RCT)** Random sequence generation • High risk of bias *Randomisation was stratified by clinical centre and histological type (squamous cell carcinoma vs. others). However, the 3 groups were not balanced in terms of gender or pN2/cN2. This might be because of the relatively low numbers of participants. Nevertheless, they were not balanced.* Allocation concealment • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC* Blinding of participants and personnel • Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		• Histological confirmation of NSCLC by biopsy or cytological evaluation • Staging CT of chest, abdomen, head CT brain or MRI brain. Fiberoptic bronchoscopy, mediastinoscopy. • Potentially resectable stage IIIA (N2, T1-3) **Exclusion criteria** • ECOG performance status >2 • Inadequate renal, hepatic or haematologic functions • Unsatisfactory medical condition for chemotherapy, thoracic radiotherapy and surgery • History of respiratory, cardiac failure, or invasive cancer • Predicted post-operative FEV1 <35% of predicted value • Previous chemotherapy or thoracic radiotherapy • Age <18 years • Age >70 years • High probability of stage IIIB NSCLC *In other words, if the tumour was suspected to invade the carina, the superior vena cava, the phrenic nerves, the aorta, the oesophagus, the vertebrae, the heart, the chest wall, or the contra-lateral mediastinal or supra-clavicular lymph nodes.* **Sample characteristics** • Sample size *46 people* • Split between study groups *Induction chemotherapy, surgery = 14; chemo, CF = 32* • Loss to follow-up *None*	*No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC* Blinding of outcome assessment • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC* 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 Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		• %female *Induction chemotherapy, surgery = 35.7%; chemo, CF = 12.5%* • Average age *Not provided* **Interventions** • Chemotherapy, surgery *This arm consisted of chemotherapy with cisplatin (80mg/m2 on days 1, 22, 43) and gemcitabine (1250mg/m2 on days 1, 8, 22, 29, 43, 50). Surgery was scheduled between week 11 and week 14 after randomisation. Lobectomy or pneumonectomy was performed. After surgery, post-operative treatment depended on the completion of the resection. In case of complete resection (R0), no adjuvant treatment was administered; in case of microscopically incomplete resection (R1), adjuvant radiotherapy was done to a total dose of 60 Gy for patients assigned this arm. After macroscopically incomplete resection (R2), radiotherapy was administered to a total dose of 60 Gy after a pneumonectomy, and of 66Gy after a lobectomy for patients in this arm.* • Chemotherapy, conventional fractionation (CF) 46 Gy (2 Gy, daily, 5 days a week), surgery *Participants received induction chemotherapy followed by chemoradiotherapy. Half of the participants received the combination of cisplatin (80mg/m2 on days 1, 22, 43) and vinorelbine (25mg/m2 on days 1, 8, 15, and 15mg/m2 on days 22, 29, 43, 50). The other half received carboplatin (Calvert AUC 6 on day 1, and AUC 2 on days 22, 29, 36, 43, 50) and paclitaxel (200mg/m2 on day 1, and 40mg/m2 on days 22, 29, 36, 43, 50). All participants in this arm underwent radiotherapy to a total dose of 46 grays delivered from week 4 to week 8. Conformal radiotherapy was delivered using a standard fractionation*	

Short Title	Title	Study Characteristics	Risk of Bias
		scheme (2 Gy/day, 5 days/week), after a three-dimensional treatment planning. Patients were immobilized using a cervico-thoracic immobilization device. The gross tumor volume (GTV) was defined as the primary tumor mass including any hilar or mediastinal lymph node ≥1 cmin short axis dimension. A 6–8mmmargin was added to the GTV to account for microscopic extension. Additional margins for tumor motion, ranging from 10 to 20mm were added based on radioscopy to define the Planned Tumor Volume (PTV). Dose–volume histograms for normal lung were calculated using total lung volume excluding the PTV. The lung V20 had to be lower than 30%. Total dose to the spinal cord was limited to 46 Gy. The maximal dose delivered to more than 15cm of the oesophagus was 40 Gy. Treatment plans included corrections for lung tissue inhomogeneity. The 100%-isodose line was defined at the isocenter of the treatment plan, and total dose was prescribed to this point. Beam-eye-view display was used to ensure optimal target volume coverage and normal tissue sparing. After surgery, post-operative treatment depended on the completion of the resection. In case of complete resection (R0), no adjuvant treatment was administered; in case of microscopically incomplete resection (R1), a dose of 14 Gy was delivered post-operatively. After macroscopically incomplete resection (R2), radiotherapy was administered to a total dose of 60 Gy after a pneumonectomy. For patients initially assigned to this arm, the decision about adjuvant treatment was left to the discretion of the local investigator. **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
Katakami 2012	A phase 3 study of induction treatment	**Study type** • Randomised controlled trial	**Quality assessment (RCT)** Random sequence generation

Short Title	Title	Study Characteristics	Risk of Bias
	with concurrent chemoradiotherapy versus chemotherapy before surgery in patients with pathologically confirmed N2 stage IIIA nonsmall cell lung cancer	**Study details** • Study location *Japan* • Study setting *Multiple academic and community hospitals.* • Study dates *2000 to 2005* • Duration of follow-up *Patients were scheduled for a chest CT scan 4 to 6 weeks after completion of the last chemotherapy cycle and were followed up every 2 months for at least 5 years. During this time, the patients received CT scans of the chest and upper abdomen, CT or MRI scans of the brain, and bone scans every 6 months. Median follow-up times for surviving patients in the chemo, surgery and chemo, radiotherapy, surgery arms were 60.7 months (range 1.8 to 86.5 months) and 60.8 months (range 44.5 to 87.5 months), respectively.* • Sources of funding *No specific funding was disclosed.* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Staging CT of chest, abdomen, head Also included a bone scan. CT brain or MRI brain. • Potentially resectable stage IIIA (N2, T1-3) **Exclusion criteria** • ECOG performance status >2	• Unclear risk of bias *The randomisation method was not provided. However, the baseline characteristics of both arms were roughly equal* Allocation concealment • Unclear risk of bias *There was no blinding in this study. However, blinding might not be realistically possible for these participants because they were stage III and therefore transparency and communication might be more important.* Blinding of participants and personnel • Unclear risk of bias *There was no blinding in this study. However, blinding might not be realistically possible for these participants because they were stage III and therefore transparency and communication might be more important.* Blinding of outcome assessment • Unclear risk of bias *There was no blinding in this study. However, blinding might not be realistically possible for these participants because they were stage III and therefore transparency and communication might be more important.* Incomplete outcome data

Short Title	Title	Study Characteristics	Risk of Bias
		• >10% weight loss within the previous 6 months • Inadequate renal, hepatic or haematologic functions • Unsatisfactory cardiac function • Uncontrolled angina pectoris or a history of congestive heart failure or myocardial infarction within 3 months • Pulmonary fibrosis detectable by CT scan • Partial pressure of arterial oxygen <70 Torr • FEV1 <1.5 L • COPD (FEV1 <65%) • Prior malignancy other than non-melanoma skin cancer or adequately treated stage I in situ cervical cancer • Age <20 years • Age >70 years **Sample characteristics** • Sample size *56 people* • Split between study groups *Induction chemotherapy, surgery = 29; induction chemoradiotherapy (conventional fractionation), surgery = 31* • Loss to follow-up *None* • %female *Induction chemotherapy, surgery = 32%; induction chemoradiotherapy (conventional fractionation), surgery = 34%* • Average age *Median age (range): Induction chemotherapy, surgery = 58.0 years (34-69); induction chemoradiotherapy (conventional fractionation), surgery = 57.0 years (36-70)*	• Low risk of bias Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Low Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Interventions • Chemotherapy, surgery *Induction chemotherapy involved 2 cycles of carboplatin (area under the receiver operating curve [AUC] = 5 on days 1, 22, intravenous infusions) and docetaxel (60 mg/m2 on days 1, 22, intravenous infusions). The patients were reassessed using CT scan plus repeat pulmonary function tests 2 to 4 weeks after completion of the induction therapy. The response to induction was assessed by WHO criteria without the need for a second confirmation of response. If the disease had not progressed and the patient remained medically healthy, a complete surgical resection with a mediastinal lymph node dissection was performed 3 or 4 weeks after the induction therapy was completed. No consolidation chemotherapy was administered after surgery. Dose reduction guidelines were specified in the protocol.* • Chemotherapy, conventional fractionation (CF) 40 Gy (2 GY, daily, 5 days a week), surgery *Induction chemotherapy involved 2 cycles of carboplatin (area under the receiver operating curve [AUC] = 5 on days 1, 22, intravenous infusions) and docetaxel (60 mg/m2 on days 1, 22, intravenous infusions). Thoracic radiotherapy (40 Gy in 20 fractions of 2 Gy over 4 weeks) was also administered from day 1. All patients were treated with a linear accelerator photon beam of 6MV or more. At the commencement of this multi-institutional study, a 3-dimensional (3D) treatment planning system using CT was not available at some of the participating institutions. Hence, 2-dimensional (2D) treatment planning techniques were allowed. Radiation doses were specified at the centre of the target volume, and doses were calculated assuming tissue homogeneity without correction for lung tissues. The primary tumour and involved nodal disease received 40 Gy in 2 Gy fractions over 4 weeks via the anterior and posterior opposing portals. Radiation fields*	

Short Title	Title	Study Characteristics	Risk of Bias
		included the primary tumour with a margin of at least 1.0 cm, and the ipsilateral hilum and mediastinal nodal areas with a margin of 0.5 to 1.0 cm from the paratracheal lymph nodes (#2) to 4.5 cm below the tracheal bifurcation including subcarinal lymph nodes (#7). The contralateral hilum was not included. The supraclavicular areas were not treated routinely, but the ipsilateral supraclavicular area was treated when the primary tumour was located in the upper lobe. *The patients were reassessed using CT scan plus repeat pulmonary function tests 2 to 4 weeks after completion of the induction therapy. The response to induction was assessed by WHO criteria without the need for a second confirmation of response. If the disease had not progressed and the patient remained medically healthy, a complete surgical resection with a mediastinal lymph node dissection was performed 3 or 4 weeks after the induction therapy was completed.* *No consolidation chemotherapy was administered after surgery. Dose reduction guidelines were specified in the protocol. Patients in the CRS arm who could not be treated surgically within 6 weeks after induction therapy received further radiotherapy of up to 66 Gy in 33 fractions in total. In this boost radiotherapy procedure, the spinal cord was excluded from the radiation fields.* **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
			Quality assessment (prospective, non-randomised cohort study) Did the study address a clearly focused issue? • Yes

Short Title	Title	Study Characteristics	Risk of Bias
			Was the cohort recruited in an acceptable way? • No *There was no discussion of how participants were selected for each arm* Was the exposure accurately measured to minimise bias? • Unclear *The two groups have similar baseline characteristics with regards to the clinical stage of the NSCLC and performance status. However, there is no discussion as to whether this was planned or happened by chance alone.* Was the outcome accurately measured to minimise bias? • No *Mortality is measured as the overall survival at a median potential follow-up of 36 months. However, the average values could be different for each arm. In addition, this is an unusual measurement for mortality. Normally, overall survival is measured at yearly intervals or preferably as a hazard radio.* Have the authors identified all important confounding factors? • Unclear *There was no discussion of confounding factors*

Short Title	Title	Study Characteristics	Risk of Bias
			Have they taken account of the confounding factors in the design and/or analysis? • No Was the follow up of subjects complete enough? • Unclear *There was no mention of adverse events. However, this is an economic study* Was the follow up of subjects long enough? • Yes Overall risk of bias • High Directness • Directly applicable
Nyman 2016	SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC	**Study type** • Randomised controlled trial **Study details** • Study location *Sweden and Norway* • Study setting *Hospitals* • Study dates *Recruitment was between 2007 to 2011* • Duration of follow-up	**Quality assessment (RCT)** Random sequence generation • High risk of bias *The method of randomisation was not given. The SABR arm had more T2 participants than the CF arm: T1: SABR = 53%; CF = 75%. T2: SABR = 47%; CF = 25%* Allocation concealment • High risk of bias *There was no blinding*

Short Title	Title	Study Characteristics	Risk of Bias
		The same schedule was used for both study groups consisting of follow-up at 7 weeks, 3, 6, 12, 18, 24 and 36 months. Toxicity was scored using CTC version 3.0 by the investigators. The median follow-up was 37 months. • Sources of funding *Nordic Cancer Union and King Gustav V Jubilee Clinic Cancer Foundation* **Inclusion criteria** • Inoperable NSCLC or surgery refused • Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage I *T1-2 N0 M0* **Exclusion criteria** • WHO performance status >2 • Previous or current other malignancy Within the last 5 years • Previous radiotherapy *To the thorax* • Central tumour growth adjacent to the trachea, main bronchus or oesophagus • Tumour diameter >6 cm **Sample characteristics** • Sample size *102 people* • Split between study groups	Blinding of participants and personnel • High risk of bias *There was no blinding* Blinding of outcome assessment • High risk of bias *There was no blinding* Incomplete outcome data • High risk of bias *Quality of life was measured. However, the data was presented in a qualitative or semi-quantitative format such that comparisons between the two arms are difficult to make. For example, charts without error bars and p-values without point estimates. In addition, they did not give the overall values for quality of life, which is the most important quality of life data.* Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • High Directness

Short Title	Title	Study Characteristics	Risk of Bias
		SABR = 49; CF = 53 • Loss to follow-up *None* • %female *SABR = 55%; CF = 64%* • Average age *Mean (range): SABR = 73 years (57-86); CF = 75 years (62-85)* **Interventions** • Stereotactic body radiotherapy (SABR) 66 Gy (3x 22 Gy during 1 week) *A stereotactic body frame with vacuum-pillow was used for setup and fixation, respectively, with lasers being set to skin marks. If tumour movements were larger than 10 mm during fluoroscopy, abdominal pressure was applied to reduce movements. The tumour tissue visible on CT constituted the gross tumour volume (GTV) and clinical target volume (CTV) comprised the GTV including diffuse margins at the tumour border. Planning target volume (PTV) was defined as the CTV with a 5 mm margin in the transversal plane and 10 mm in the longitudinal direction. A dose plan was created normally with 5–7 static coplanar or non-coplanar fields with 6 MV photons. In addition to the CT used for dose planning, a second CT was performed before the first treatment to verify tumour reproducibility with predefined tolerance limits. CBCT (cone beam CT) and 4DCT was allowed but only available at a few sites. A heterogeneous dose distribution within the PTV was used. The prescribed dose was 22 Gy times three at the isocentre during one week (15 Gy at the periphery of PTV, corresponding to the 68% isodose).* • *Conventional fractionation 70 Gy (2 Gy, daily, 5 days a week)*	• Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		A vacuum-pillow was used for fixation and set-up, with lasers being set to skin marks. GTV and CTV were delineated in the same way as in arm A and the PTV was defined as the CTV with a 20 mm margin in all directions. Three to four coplanar fields with 6 MV photons were used with a homogeneous dose distribution. The prescribed dose was 70 Gy with 2.0 Gy per fraction, five days a week for seven weeks. The 95% isodose was required to cover 95% of the PTV. Portal imaging with bone and soft tissue matching was used for set-up verification with 5 mm deviation as the action level. Dose constrains were set for the spinal cord with 21 Gy in arm A and 48 Gy in arm B, no other constraints were used but doses to organs at risk were registered. **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
Pless 2015	Induction chemoradiation in stage IIIA/N2 non-small-cell lung cancer: a phase 3 randomised trial	**Study type** • Randomised controlled trial **Study details** • Study location *Switzerland, Germany and Serbia* • Study setting *Cancer centres* • Study dates *Enrolment was from 2001 to 2012* • Duration of follow-up *Patients attended follow-up visits 1 month after surgery, then every 3 months for 2 years, every 6 months for 2 years, and then every 12*	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC.* Blinding of participants and personnel • Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		months. During visits patients were assessed for toxic effects. They also underwent chest radiography or chest CT at alternate visits for 5 years. The trial was stopped after the third interim analysis and 134 events, on the advice of the independent data monitoring board, because the futility boundary had been crossed. At the time of data cut-off, the median follow-up time was 52·4 months (IQR 32·0–85·2). • Sources of funding *This study was funded by the Swiss State Secretariat for Education, Research and Innovation, the Swiss Cancer League and Sanofi.* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage IIIA (T1-3, N2, M0) • Staging PET-CT and brain MRI **Exclusion criteria** • ECOG performance status >2 • Unsatisfactory cardiac function • Unsatisfactory lung function • Unsatisfactory liver function • Unsatisfactory bone marrow function • Unsatisfactory kidney function *Creatinine clearance less than 1·00 mL/s [60 mL/min]* • Age <18 years • Age >75 years **Sample characteristics** • Sample size	*No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC.* Blinding of outcome assessment • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC.* 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 Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		231 people • Split between study groups *Induction chemotherapy, surgery = 115; induction chemoradiotherapy, surgery = 117* • Loss to follow-up *Induction chemotherapy, surgery = 8; induction chemoradiotherapy, surgery = 2* • %female *Induction chemotherapy, surgery = 33%; induction chemoradiotherapy, surgery = 33%* • Average age *Median age (range): Induction chemotherapy, surgery = 59.0 years (30.0-74.0); induction chemoradiotherapy, surgery = 60.0 years (37.0-76.0)* **Interventions** • Chemotherapy, surgery *Chemotherapy consisted of three cycles of 100 mg/m² intravenous cisplatin and 85 mg/m² docetaxel given every 3 weeks. The administration of prophylactic granulocyte-colony stimulating factor was compulsory. Dose reductions were not allowed for cisplatin. Switch to carboplatin (target area under the curve 6) was possible if patients developed renal insufficiency (creatinine clearance lower than 0·83 mL/s [50 mL/ min]), hearing loss worse than grade 1, or peripheral neuropathy worse than grade 2. Dose reductions for docetaxel to 55 mg/m² were possible if patients developed impaired liver function (worse than grade 1), grade 3 diarrhoea, or peripheral neuropathy (worse than grade 1). If toxic effects did not recover to grade 1 severity or resolve within 2 weeks, chemotherapy was stopped. Surgery was scheduled 21 days after the last chemotherapy cycle for patients in the chemotherapy group.*	

Short Title	Title	Study Characteristics	Risk of Bias
		Surgery included tumour resection and systematic lymph node dissection. Patients in the chemotherapy group in whom resection was incomplete (R1 or R2) were allowed to receive postoperative radiotherapy. • Chemotherapy, conventional fractionation (CF) 44 Gy in 22 fractions over a 3 week period, surgery *Chemotherapy consisted of three cycles of 100 mg/m² intravenous cisplatin and 85 mg/m² docetaxel given every 3 weeks. The administration of prophylactic granulocyte-colony stimulating factor was compulsory. Dose reductions were not allowed for cisplatin. Switch to carboplatin (target area under the curve 6) was possible if patients developed renal insufficiency (creatinine clearance lower than 0·83 mL/s [50 mL/ min]), hearing loss worse than grade 1, or peripheral neuropathy worse than grade 2. Dose reductions for docetaxel to 55 mg/m² were possible if patients developed impaired liver function (worse than grade 1), grade 3 diarrhoea, or peripheral neuropathy (worse than grade 1). If toxic effects did not recover to grade 1 severity or resolve within 2 weeks, chemotherapy was stopped.* *Three weeks after day 1 of the last planned date of chemotherapy, radiotherapy was started in patients in the chemoradiotherapy group. Patients received 44 Gy in 22 fractions over a 3 week period, delivered with a concomitant boost technique. Planning target volumes were defined according to the results of CT scans done after induction chemotherapy. Planning target volume 1, representing the original volume, included the primary tumour, lymph nodes, ipsilateral hilus, and ipsilateral and contralateral mediastinum at risk of subclinical disease, with a 1·5–2·0 cm margin. Planning target volume 2 included the primary tumour (gross disease) with a 1·5–2·0 cm margin and lymph node metastases in the mediastinum and represented the boost volume. Arrangement of fields was at the discretion of the investigators as long as the target volumes were clearly outlined. The dose to the*	

Short Title	Title	Study Characteristics	Risk of Bias
		spinal cord had to remain lower than 36 Gy. The prescribed dose was specified at the International Commission on Radiation Units and Measurements reference point. Computer assisted three-dimensional treatment planning was used in all cases, and the selection of a collapsed cone or Monte Carlo algorithm was recommended for photon energies greater than 6 MV. The reference isodose had to be within 10% of that prescribed, and hot spots were delineated and recorded. Central review of three random patients from each centre was done to ensure radiotherapy quality control. *Surgery was scheduled 21–28 days after completion of radiotherapy for patients in the chemoradiotherapy group. Surgery included tumour resection and systematic lymph node dissection.* **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
van Meerbeeck 2007	Randomized controlled trial of resection versus radiotherapy after induction chemotherapy in stage IIIA-N2 non-small-cell lung cancer	**Study type** • Randomised controlled trial **Study details** • Study location *The Netherlands* • Study setting *Hospitals* • Study dates *Recruitment was from 1994 to 2002* • Duration of follow-up	**Quality assessment (RCT)** Random sequence generation • Low risk of bias Allocation concealment • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC.* Blinding of participants and personnel • Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		Patients underwent follow-up visits every 3 months for 2 years and every 6 months thereafter, which included clinical evaluation, a chest-x-ray, and additional investigations when clinically indicated. The median follow-up was approximately 6 years. • Sources of funding *National Cancer Institute. The study was supported by unrestricted educational grants of Eli Lilly, Bristol-Myers Squibb and Aventis.* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation *Eligible patients had to have cytologic or histologic proof of unresectable stage IIIA-N2 NSCLC.* • Staging CT of chest, abdomen, head *Guidelines for unresectability were as follows: 1) any N2 involvement by a non-squamous carcinoma; 2) in case of squamous cell carcinoma, any N2 nodal involvement exceeding level 4R for a right-sided tumour and level 5 and 6 for a left-sided tumour. N2 found only at thoracotomy after a negative staging mediastinoscopy was not necessarily considered to be unresectable. Tumours and/or any involved mediastinal lymph node(s) had to be unidimensionally measurable on CT scan.* **Exclusion criteria** • WHO performance status >2 • Unsatisfactory medical condition for chemotherapy, thoracic radiotherapy and surgery • Pulmonary fibrosis • Pre-existing neurotoxicity • Pre-existing infection	*No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC.* Blinding of outcome assessment • Unclear risk of bias *No blinding. However, this is probably not possible in this instance. This is because of the relatively high stage of the NSCLC.* Incomplete outcome data • High risk of bias *The adverse events are reported narratively in such a way that it is not possible to compare the arms of the trial.* Selective reporting • Low risk of bias Other sources of bias • Low risk of bias Overall risk of bias • Moderate Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		• Previous or current other malignancy • Previous therapy for NSCLC • Age <18 years **Sample characteristics** • Sample size *308 people* • Split between study groups *Chemotherapy, surgery = 154; chemotherapy, radiotherapy = 154* • Loss to follow-up *None* • %female *Chemotherapy, surgery = 29%; chemotherapy, radiotherapy = 23%* • Average age *Median (range): chemotherapy, surgery = 61 years (29-78); chemotherapy, radiotherapy = 62 years (33-76)* **Interventions** • Chemotherapy, surgery *Induction chemotherapy consisted of three cycles of cisplatin, at a dose of at least 80 mg/m 2 per cycle, or carboplatin, at a target area under the curve of at least 5 per cycle, combined with at least one other chemotherapy drug. Response was evaluated with CT scan after at least two cycles of induction chemotherapy and scored according to WHO criteria, but confirmation was not required. Eligibility was reassessed before random assignment. Only patients showing a response (complete, partial, or minor) to induction chemotherapy were eligible for random assignment. Surgery had to start within 6 weeks of random assignment. Postoperative radiotherapy consisting of 56 Gy in once-daily fractions of 2 Gy was recommended in cases of incomplete*	

Short Title	Title	Study Characteristics	Risk of Bias
		resection and had to start between the 4th and 10th postoperative week. • Chemotherapy, conventional fractionation (CF) 60-62.5 Gy (1.95-2.05 Gy in 30-32 fractions over 40-46 days) *Induction chemotherapy consisted of three cycles of cisplatin, at a dose of at least 80 mg/m 2 per cycle, or carboplatin, at a target area under the curve of at least 5 per cycle, combined with at least one other chemotherapy drug. Response was evaluated with CT scan after at least two cycles of induction chemotherapy and scored according to WHO criteria, but confirmation was not required. Eligibility was reassessed before random assignment. Only patients showing a response (complete, partial, or minor) to induction chemotherapy were eligible for random assignment. Radiotherapy had to start within 6 weeks of random assignment. The dosage administered to the primary tumour and involved mediastinum was 60–62.5 Gy and to the uninvolved mediastinum it was 40–46 Gy. The fractionation size was 1.95 – 2.05 Gy. A number of fractions were 30-322 Gy. The total treatment duration was 40-46 days.* **Outcome measures** • Mortality • Dropout during treatment	
Videtic 2015	A Randomized Phase 2 Study Comparing 2 Stereotactic Body Radiation Therapy Schedules for Medically Inoperable Patients	**Study type** • Randomised controlled trial **Study details** • Study location *USA* • Study setting	**Quality assessment (RCT)** Random sequence generation • Unclear risk of bias *The method of randomisation is not given. However, the baseline characteristics of each arm are reasonably well balanced.* Allocation concealment

Short Title	Title	Study Characteristics	Risk of Bias
	With Stage I Peripheral Non-Small Cell Lung Cancer: NRG Oncology RTOG 0915 (NCCTG N0927)	*Hospitals* • Study dates *Recruitment was from 2009 to 2011* • Duration of follow-up *Patients were seen 6 and 12 weeks after SABR, then every 3 months for 2 years, every 6 months for next 2 years, and annually thereafter. The median follow-up time was 30.2 months.* • Sources of funding *The National Cancer Institute* **Inclusion criteria** • Inoperable NSCLC or surgery refused *The protocol-specified indicators of medically inoperability included baseline forced expiratory volume in the first second of expiration (FEV1) <30% of predicted; carbon monoxide diffusing capacity (DLCO) <40% of predicted; baseline hypoxemia or hypercapnia; severe pulmonary hypertension; diabetes mellitus with end-organ damage; severe cerebral, cardiovascular, or peripheral vascular disease; or severe chronic heart disease.* • Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage I *T1 to T2 (under or equal to 5 cm) N0 M0. Tumours were required to be >2 cm in all directions from the proximal bronchial tree, which was defined as the distal 2 cm of the trachea, carina, and named major lobar bronchi up to their first bifurcation.* **Exclusion criteria** • WHO performance status >2 • Previous or current other malignancy	• High risk of bias *There was no allocation concealment* Blinding of participants and personnel • High risk of bias *There was no blinding* Blinding of outcome assessment • High risk of bias *There was no blinding* 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 • High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		Within the last 2 years • Previous radiotherapy • Age <18 years • Other *Planned use of concomitant (whether induction, concurrent, or adjuvant) antineoplastic therapy during the protocol.* **Sample characteristics** • Sample size *82 people* • Split between study groups *SABR 34 Gy in 1 fraction = 39; SABR 48 Gy in 4 fractions = 45* • Loss to follow-up *None* • %female *SABR 34 Gy in 1 fraction = 59.0%; SABR 48 Gy in 4 fractions = 51.1%* • Average age *Median (range): SABR 34 Gy in 1 fraction = 75 years (57-89); SABR 48 Gy in 4 fractions = 75 (52-87)* **Interventions** • Stereotactic body radiation therapy (SABR) 34 Gy in 1 fraction *Patients were immobilized in a stable position with a device that permitted accurate reproducibility of the target position from treatment to treatment. A variety of rigid immobilisation systems were allowed as long as they could be referenced to a pre-specified stereotactic coordinate system. All positioning systems were validated and accredited by the Radiation Therapy Oncology Group's (RTOG's) Advanced Technology Consortium (ATC) before patients were enrolled*	

Short Title	Title	Study Characteristics	Risk of Bias
		on this trial. To account for the effect of internal organ motion (e.g. from breathing) on target positioning and reproducibility, manoeuvres including reliable abdominal compression, accelerator beam gating with the respiratory cycle, tumour tracking, and active breath-holding techniques were allowed. All systems used to account for internal organ motion were also validated and accredited by the ATC. The full extent of tumour motion was to be quantified using fluoroscopy or 4-dimensional (4D) CT scanning. Image guidance capable of confirming the position of the target at the time of treatment delivery was required; permitted imaging approaches included planar kV imaging devices, in-room helical CT, tomotherapy helical CT, and cone beam CT equipment, in association with standard electronic portal imaging device verification. The target lesion was outlined by an appropriately trained physician and designated the gross tumour volume (GTV). The target was generally drawn using CT pulmonary windows; however, soft tissue windows with contrast medium could be used to avoid including adjacent vessels, atelectasis, or chest wall structures within the GTV. No additional margin was added for possible microscopic extension, and thus the clinical target volume (CTV) was considered equivalent to the GTV. Two acceptable methods were used to define the planning target volume (PTV) depending on the method of CT simulation: 1. conventional (helical) CT simulation (i.e. non-4DCT): the PTV included the GTV plus an additional 0.5-cm margin in the axial plane and a 1.0-cm margin in the longitudinal plane (craniocaudal); or 2. 4DCT simulation: an internal target volume (ITV) around the GTV, accounting for tumour motion as defined from the 4D CT dataset. The PTV included the ITV plus an additional 0.5-cm margin uniformly applied to the ITV. *Patients enrolled on NRG Oncology RTOG 0915 were randomized to 1 of 2 dose/fractionation schemes (arms 1 or 2). Patients on arm 1 received 34 Gy in 1 fraction to the prescription line at the edge of the PTV, whereas patients on arm 2 received 4 fractions at 12 Gy per fraction, for a total dose of 48 Gy to the prescription line at the edge of*	

Short Title	Title	Study Characteristics	Risk of Bias
		the PTV, with treatments given over 4 consecutive days. This protocol required the use of validated tissue density heterogeneity corrections for dose planning. With respect to maximum dose, all treatment plans had to be created so that 100% corresponded to the maximum dose delivered and this point existed within the PTV. The prescription isodose surface had to be >60% and <90% of the maximum dose. Adequate target coverage was achieved when 95% of the PTV was covered by the assigned total dose and when 99% of the PTV received >90% of the prescription dose. High dose conformality was controlled in such a manner that the volume of tissue outside of the PTV receiving a dose >105% of the prescription dose had to be <15% of the PTV and the target conformality index (ratio of the volume receiving total prescription dose to the planning target volume) was <1.2. Treatment plans had to meet contoured organ dose constraints as specified per treatment arm. • Stereotactic body radiation therapy (SABR) 48 Gy in 4 consecutive daily fractions *As above* **Outcome measures** • Mortality • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
Wang 2016	Effect of image-guided hypofractionated stereotactic radiotherapy on peripheral non-small-cell lung cancer	**Study type** • Randomised controlled trial **Study details** • Study location *China* • Study setting	**Quality assessment (RCT)** Random sequence generation • High risk of bias *The method of randomisation was not given. The two arms were not balanced. For example the numbers of participants in each arm having various stages of*

Short Title	Title	Study Characteristics	Risk of Bias
		Hospital • Study dates *Recruitment was from 2010 to 2016* • Duration of follow-up *Monthly during the first 6 months after the radiotherapy. After the first 6 months, patients were followed up every 3 months. The two groups of patients were followed up for 4–61 months ("average" 32.5 months).* • Sources of funding *The National Natural Science Foundations of China, Program for New Century Excellent Talents in University, Scientific and Technological Research Foundation of Shaanxi Province, and Scientific Research Foundation for the Returned overseas Chinese Scholars of State Education Ministry.* **Inclusion criteria** • Inoperable NSCLC or surgery refused • Histological confirmation of NSCLC by biopsy or cytological evaluation **Exclusion criteria** • None reported **Sample characteristics** • Sample size *50 people* • Split between study groups *SABR = 23; CF = 27* • Loss to follow-up *None*	*NSCLC was: SABR: Ia, 7; IIb, 1; IIIa, 1; IIIb, 1; IV, 9. CF: Ia, 2; IIb, 4; IIIa, 4; IIIb, 12; IV, 2* Allocation concealment • Unclear risk of bias *There was no blinding. However, this study had participants with stage III and IV. Transparency and good communication would probably be more of a priority.* Blinding of participants and personnel • Unclear risk of bias *There was no blinding. However, this study had participants with stage III and IV. Transparency and good communication would probably be more of a priority.* Blinding of outcome assessment • Unclear risk of bias *There was no blinding. However, this study had participants with stage III and IV. Transparency and good communication would probably be more of a priority.* Incomplete outcome data • Low risk of bias Selective reporting • Low risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		• %female *SABR = 39%; CF = 19%* • Average age *Median (range): SABR = 68 years (49-80); CF = 66 years (33-80)* **Interventions** • Hypofractionated stereotactic radiotherapy (SABR) 64-66 Gy (6-8 Gy, 3x per week) *Radiation therapy was given using an Elekta Synergy medical linear accelerator. The position of each patient's body was fixed by body positioning phantom. CT simulation was performed by enhanced CT scanning with patients breathing quietly. Patients were scanned from the thoracic entrance to the level of the costophrenic angle, with a 5 mm scanning thickness. The scanned electronic images were transmitted to the treatment planning system. Tumour target volume was delineated by the radiotherapy and imaging physicians together in accordance with the standard definition stipulated in documents of the International Radiation Units and Measurement Committee. Gross target volume (GTV) is the entire tumour area detected by clinical and radiographic examination, including gross target volume-primary tumour (GTV-P) and including gross target volume-regional metastasis lymph node (GTV-N). Lymph nodes with a diameter greater than 1 cm in the CT scan were judged as positive lymph node. GTV-P was delineated in lung window setting while GTV-N was delineated in mediastinal window setting. The clinical target volume was judged based on the size of tumour and lymph node prior to chemotherapy. The planning target volume was determined based on the position error and the patient's respiratory motion. The field direction, the field weight, and the field fraction were designed through the Beam-field Equation Vision (BEV) and Reaction Equation Vision (REV).* *X-ray examination was performed on a weekly basis during the treatment and was compared with the simulated images and digitally*	Other sources of bias • Low risk of bias Overall risk of bias • Moderate Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		reconstructed images to determine the accuracy of target area and the patient position. Group A patients underwent hypofractionated radiotherapy with 6–8 Gy/time, once every other day, three times per week, with a total dose of 64–66 Gy. *Stereotactic radiotherapy plans included intensity-modulated radiation therapy (IMRT) and volumetric-modulated arc therapy (VMAT) plans. The treatment plan is selected based on whether this plan is capable or not of achieving a better target coverage, and organs at risk protection. IMRT plan: The IMRT optimisation was performed by applying a direct machine parameter optimisation (DMPO) algorithm in our treatment planning system. For each plan, five or seven coplanar beams were used depending on the tumour location. In the plan generation, maximum iterations and maximum number of segments in the plan optimization were 50 and 80, respectively, and the maximum MUs and segment area were 5 MU and 5 cm2, respectively. Plans were generated for the Elekta Beam Modulator with 10 MV X-ray beams. VMAT plan: The VMAT planning was done by applying the SmartArc planning algorithm in Pinnacle3 version 9.2. Single or dual arcs were employed depending on the tumour location. The accelerator used automatic dose rate was chosen for each individual segment of the arc. Plans were generated with 10 MV X-ray beams.* *Plan evaluation: The quality of plans was evaluated by three radiation oncologists. Dose–volume histograms (DVHs) and the corresponding dose distributions of plans were independently reviewed by each oncologist. Images acquisition technology during the treatment Elekta Synergy system integrates the treatment accelerator with the image acquisition guiding system which is based on the principle of X-ray volume imaging. Synergy system is designed to provide three-dimensional (3D) X-ray volume imaging (XVI) with kV level. XVI is an advanced imaging system, which can obtain two-dimensional (2D) and 3D kV-level images of treatment position during the treatment. XVI can use the image management tools to automatically and remotely correct the bed position. The image guidance functions of Elekta Synergy*	

Short Title	Title	Study Characteristics	Risk of Bias
		system include the function of obtaining the real-time images of accelerator using iViewGT. The PlanarView software supports the acquisition of static 2D planar high-quality kV-level images. Under this image mode, the positioning mark can be clearly seen. The image processing tool supports the comparison of the collected 3D volumetric imaging data with the planning CT data, and also supports the online and offline adaptive radiotherapy technology. Error analysis and adjustment before and during the treatment The first XVI image, was obtained before the treatment. The acquired volume images and planning images were matched through the automatic matching function of the system, and the errors of the target centre in the X, Y, Z directions were acquired and corrected. The second volume image was obtained after the error adjustment. The irradiation was implemented if the error was less than 2 mm. The third XVI image, was obtained after the treatment. Matching images of four patients were randomly selected and are shown in Figure 3, which shows the image matching results during the treatment. Multileaf collimator system: Multileaf collimator equipment of Elekta Synergy system is a full built-in integrated fine field forming system, providing an accurate collimator system used universally for the 3D radiotherapy and accurate IMRT technology. Irradiation field of the small multileaf system comprises 80 independently controlled blades and the field size is 16×21 cm. The trip distance of every blade is more than 21 cm. Since the thickness of the blade is 0.4 cm (at the isocentre), the blade can form the "fork finger" and the relative blades insert into each other's slots. The little multileaf can form many little fields in one field in one step. • Conventional fractionation (CF) 68-70 Gy (unspecified fractions, 5 times a week) *These participants received conventional fractionated radiotherapy, with a total dose of 68–70 Gy.*	

Short Title	Title	Study Characteristics	Risk of Bias
		Outcome measures • Mortality • Adverse events (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy) *There were no grade 3 or above adverse events in either arm*	

Observational studies

Short Title	Title	Study Characteristics	Risk of Bias
Bryant 2018	Stereotactic Body Radiation Therapy Versus Surgery for Early Lung Cancer Among US Veterans	**Study type** Retrospective cohort study **Study details** • Study location *USA* • Study setting *Hospital* • Study dates *Radiotherapy occurred from 2006 to 2015* • Duration of follow-up *The median follow-up for lobectomy, sublobar resection, and SBRT patients was 2.9, 2.6, and 1.5 years, respectively.* • Sources of funding *This project was supported by the National Institutes of Health* **Inclusion criteria**	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors?

Short Title	Title	Study Characteristics	Risk of Bias
		• Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage T1 or T2a (<5 cm in greatest dimension) And N0 **Exclusion criteria** • Previous or current other malignancy • Other *Missing cause or date of death data. Patients treated more than 6 months after diagnosis. Biologically effective dose <100 Gy.* **Sample characteristics** • Sample size *4,069 people* • Split between study groups *SABR = 449; lobectomy = 2,986; sublobar resection = 634* • Loss to follow-up Not reported • %female *SABR = 3%; lobectomy = 4%; sublobar resection = 4%* • Average age *Mean (SD) years: SABR = 71 (7.6); lobectomy = 66 (7.8); sublobar resection = 69 (8.5)* **Interventions** • Stereotactic ablative radiotherapy (SABR) *Investigators identified patients treated with radiation through a US Veterans Affairs Informatics and Computing Infrastructure (VINCI) registry, then manually reviewed charts to extract radiation dose and*	• Unclear *It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Have they taken account of the confounding factors in the design and/or analysis? • Unclear *It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Moderate *It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.*

Short Title	Title	Study Characteristics	Risk of Bias
		fractionation information, and to ensure patients received radiation directed at the lung as opposed to another site. Patients in the SABR group received a biologically equivalent dose of 124 Gy10 with a range from 100 to 216 Gy10. • Surgery (lobectomy group and a separate sublobar resection group) *Patients who underwent lobectomy or sublobar resection were identified were identified by searching perioperative clinical notes for keywords related to that surgery type. The sublobar resection group included patients who underwent wedge or segmental resections.* **Outcome measures** • Mortality	Directness • Directly applicable
Chen 2018	Stereotactic Ablative Radiation Therapy Versus Surgery in Early Lung Cancer: A Meta-analysis of Propensity Score Studies	**Study type** Systematic review *Systematic review of prospective and retrospective observational studies.* **Study details** • Dates searched *Databases were queried up to December 2016* • Databases searched *MEDLINE and Embase* • Sources of funding *This study was supported by a university research grant* **Inclusion criteria** • Early stage NSCLC *Specific cancer staging not specified.*	**Quality assessment (systematic review)** Study eligibility criteria • Low risk of bias *The specific cancer staging was not specified in the inclusion criteria. However, we looked at each study and recorded the cancer staging. They were all early stage (stage I-II) (see table).* Identification and selection of studies • Unclear risk of bias *The investigators did not search reference lists for possible includes. However, we conducted our own search and found that there were no further relevant studies up to December 2016.* Data collection and study appraisal • Unclear risk of bias

Short Title	Title	Study Characteristics	Risk of Bias
		• Compared SABR to surgery • Observational studies • All studies used propensity score matching methods • Report hazard ratios **Exclusion criteria** • Not reported **Sample characteristics** *Observational studies reporting hazard ratios of comparisons between SABR and surgery for treating early-stage NSCLC (specific cancer staging not specified). All studies used propensity score matching methods.* *The included studies* <table><tr><th>Study</th><th>Stage of participants</th><th>Design of study</th><th>Newcastle-Ottawa Scale score</th><th>No. in SABR arm</th><th>No. in lobectomy arm</th><th>No. in sublobar resection arm</th><th>Location of study</th></tr><tr><td>Eba 2016</td><td>Ia</td><td>Case-match</td><td>7</td><td>21</td><td>21</td><td>-</td><td>Japan</td></tr><tr><td>Ezer 2015</td><td>I-II</td><td>Retrospective cohort</td><td>7</td><td>362</td><td>-</td><td>1881</td><td>USA, Canada</td></tr><tr><td>Hamaji 2015</td><td>I (T1a-T2a)</td><td>Case-match</td><td>8</td><td>41</td><td>41</td><td>-</td><td>Japan</td></tr></table>	*For quality assessment, the Newcastle-Ottawa Scale for cohort studies was used to assess the risk of bias of individual studies. Details of each individual study are presented in tables in the paper and in the supplemental information.* *Shirvani 2012 and Shirvani 2014 have overlapping recruitment dates (2001-2007 and 2003-2009). Therefore, some of these participants have probably been double-counted in the meta-analysis. However, removing either study from the meta-analysis does not change the results.* Synthesis and findings • Low risk of bias Overall quality • Moderate Applicability as a source of data • Fully applicable

Short Title	Title	Study Characteristics								Risk of Bias
		Matsuo 2014	*I*	*Case-match*	*8*	*53*	*-*	*53*	*Japan*	
		Mokhles 2015	*Ia-Ib*	*Case-match*	*7*	*73*	*73*	*-*	*The Netherlands*	
		Paul 2016	*I (T1-T2)*	*Case-match*	*8*	*201*	*-*	*201*	*USA*	
		Puri 2015	*I*	*Case-match*	*7*	*4555*	*-*	*4555*	*USA*	
		Robinson 2013	*I*	*Case-match*	*7*	*76*	*76*	*-*	*USA*	
		Rosen 2016	*I*	*Case-match*	*7*	*1781*	*1781*	*-*	*USA*	
		Shirvani 2012	*Ia-Ib*	*Case-match*	*8*	*99 and 112*	*99*	*112*	*USA*	
		Shirvani 2014	*I (T1a-T2a)*	*Case-match*	*8*	*251*	*251*	*-*	*USA*	
		Smith 2015	*I (T1a-T2a)*	*Case-match*	*7*	*300 and 243*	*300*	*243*	*USA*	
		Verstegen 2013	*I-II*	*Case-match*	*7*	*64*	*64*	*-*	*The Netherlands*	
		Total numbers of participants				***2706 and 5526***	***2642***	***7045***		

Short Title	Title	Study Characteristics	Risk of Bias
		Interventions • Stereotactic ablative radiotherapy (SABR) • Lobectomy • Sublobar resection **Outcome measures** • Mortality	
Cornwell 2018	Video-assisted thoracoscopic lobectomy is associated with greater recurrence-free survival than stereotactic body radiotherapy for clinical stage I lung cancer	**Study type** Prospective case-control study **Study details** • Study location *USA* • Study setting *Hospital* • Study dates *2009 to 2014* • Duration of follow-up *Median of 3.7 years* • Sources of funding *Self-funded* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage I	**Quality assessment (case-control study)** Did the study address a clearly focused issue? • Yes Did the authors use an appropriate method to answer their question? • Unclear. *It is difficult to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Were the cases recruited in an acceptable way? • Yes Were the controls selected in an acceptable way? • No. *The controls were operable, unlike the SABR patients.* Was the exposure accurately measured to minimise bias?

Short Title	Title	Study Characteristics	Risk of Bias
		• Treated by SABR or thoracic lobectomy **Exclusion criteria** • Previous or current other malignancy • Inadequate follow-up • Underwent any procedure more or less extensive than lobectomy • Oxygen dependence • Central tumours • Biologically effective dose <100 Gy **Sample characteristics** • Sample size *74 propensity matched participants* • Split between study groups *SABR = 37; lobectomy = 37* • Loss to follow-up *Not reported* • %female *SABR = 2.7%; lobectomy = 2.7%* • Average age *SABR = 66 (63-72); lobectomy = 68 (63-73)* **Interventions** • Surgery (lobectomy) *All resections involved hilar and mediastinal lymph node dissection by one surgeon. The operation generally involved a 3-incision approach and full dissection and individual division of hilar structures. No conversions to open surgery were performed.*	• Unclear. *This is difficult to do in a study that attempts to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Have the authors taken account of potential confounding factors in the design and/or in their analysis? • Unclear *This is difficult to do in a study that attempts to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Overall risk of bias • High. *The participants were propensity matched. This was a comparison of largely medically inoperable participants vs operable participants.* Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		• Stereotactic ablative radiotherapy (SABR) *All patients received fiducial markers, placed under CT or bronchoscopic guidance. Standard pre-treatment included invasive mediastinal staging with hilar and mediastinal lymph node sampling via endobronchial ultrasonography-guided transbronchial needle aspiration. As real-time tumour tracking was used during each treatment, there were no margin expansions to account for presumed macroscopic disease, nor internal target volume to account for tumour motion. Each participant received dexamethasone prophylaxis 30 minutes before each treatment. SABR was delivered once daily on consecutive days. Treatment was delivered in 4 or 5 fractions, with doses and fractionation regimens chosen by the treating radiation oncologists. SABR was delivered with noncoplanar beams using the CyberKnife robotic delivery system with 6MV photons and cone collimation. Image guidance was accomplished with fiducial marker tracking and a respiratory tracking system for real-time intra-fraction tumour motion tracking.* **Outcome measures** • Mortality	
Grills 2010	Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer	**Study type** • Retrospective cohort study **Study details** • Study location *USA* • Study setting *Hospital* • Study dates	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No *All those who had surgery were medically operable but of those receiving SBRT, 95% were medically inoperable. There was no propensity matching.*

Short Title	Title	Study Characteristics	Risk of Bias
		Recruitment was from 2003 to 2008 • Duration of follow-up *The median potential follow-up for all patients was 2.5 years* • Sources of funding *Not mentioned* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage I *T1-2 N0 M0* • Stage T1-2 N0 M0 **Exclusion criteria** • None reported **Sample characteristics** • Sample size *124 people* • Split between study groups *SABR = 55; sublobar resection = 69* • Loss to follow-up *None* • %female *SABR = 60%; sublobar resection = 62%* • Average age *Median (range): SABR = 78 years (55-89); sublobar resection = 74 years (69-78)*	Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Unclear. *It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Have they taken account of the confounding factors in the design and/or analysis? • Unclear. *It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes

Short Title	Title	Study Characteristics	Risk of Bias
		Interventions • Stereotactic ablative radiotherapy (SABR) All patients were simulated immobilized in a stereotactic body frame, or alpha cradle. Respiratory tumour motion was screened using fluoroscopy. At study outset, a four-dimensional CT was performed in patients with poorly visualized tumours or motion more than 5 mm. After the first several patients enrolled, four-dimensional CT and free-breathing CT were always obtained. Abdominal compression was used in five patients (2%) with tumour excursion more than 1.0 cm. CT data were transferred to the planning workstation, registered, and fused with a planning PET. SBRT plans consisted of six to nine coplanar and noncoplanar beams and limited number of couch angles. A function of the Pinnacle software originally designed for intensity-modulated radiotherapy was adapted to inversely optimize the beam aperture and weighting but constrained to allow only a single segment per beam. Intensity-modulated radiotherapy was only used in rare cases where required to meet normal tissue dose objectives. The gross tumour volume (GTV) was equivalent to the tumour on CT lung windows with consideration of the registered PET. Forty-eight Gy in four fractions (12 Gy x 4) or 60 Gy in five fractions (12 Gy x 5) was prescribed to the planning target volume (PTV) edge (60% to 90% isodose line, but typically 80% for T1 or T2 tumours, respectively, with greater than or equal to 40 hours and greater than or equal to 4 days between fractions. • Surgery (sublobar resection) The degree of lung resection, without lobectomy, to achieve adequate surgical margin while still tolerable in view of medical and/or pulmonary reserve was determined by an experienced thoracic surgeon. All surgeries were performed with curative intent and a goal of negative oncologic margins. Resection was performed either via open thoracotomy or thoracoscopically (video-assisted thoracoscopic	Overall risk of bias • High. *It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		surgery [VATS]) depending on tumour depth, location, and year of operation. Thirty-six patients (52%) underwent VATS; 14 patients (20%) underwent open thoracotomy; and 19 patients (28%) were planned to undergo thoracoscopic, but converted to open thoracotomy intraoperatively. Forty-three of 69 patients had a mediastinal lymph node dissection; 21 of 69 patients had preoperative mediastinoscopy; 49 patients (71%) had mediastinoscopy or lymph node dissection or both. **Outcome measure** • Mortality	
Jeppesen 2013	Stereotactic body radiation therapy versus conventional radiation therapy in patients with early stage non-small cell lung cancer: an updated retrospective study on local failure and survival rates	**Study type** Retrospective cohort study **Study details** • Study location *Denmark* • Study setting *Hospital* • Study dates *Recruitment was from August 2005 to June 2012* • Duration of follow-up *For both groups of patients follow-up was performed five weeks after treatment, every third month in two years, and then in six-month intervals until a five-year follow-up period.* • Sources of funding • Not mentioned **Inclusion criteria**	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No *The mean tumour volume was on average twice as large for the CF group compared to the SABR group. (27.3 cm3 vs 12.9 cm3). In addition, the most patients in the SABR group were T1 but most patients in the CF group were T2. The proportion of genders in each arm is not equal.* Was the exposure accurately measured to minimise bias? • No *As above*

Short Title	Title	Study Characteristics	Risk of Bias
		• Histological confirmation of NSCLC by biopsy or cytological evaluation • Medically inoperable • Stage T1-2 N0 M0 **Exclusion criteria** • None reported **Sample characteristics** • Sample size *132 people* • Split between study groups *SABR = 100; CF = 32* • Loss to follow-up *Not mentioned* • %female *SABR = 55%; CF = 31%* • Average age *Mean (range): SABR = 73.3 years (52-88); CF = 70.4 years (51-87)* **Interventions** • Stereotactic ablative radiotherapy (SABR) 45 or 66 Gy, 3 fractions *Patients treated with SBRT were immobilized in a Lax-Blomgreen stereotactic body frame using a VacFix vacuum bag or similar fi xation device. The patients were scanned with normal and uncoached respiration and without the use of abdominal compression. In 2007 four-dimensional (4D) CT scans were introduced to visualise the time dependence of the geometrical positions of the target volumes. The gross tumour volume (GTV) was contoured using a pulmonary CT*	Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		window. Clinical target volume (CTV) is identical to GTV. Planning target volume (PTV) is defi ned as the CTV with a margin of 5 mm in the transversal plan and 10 mm in the longitudinal plan. The prescribed dose was 45 Gy/3F with GTV covered by 95% (prior to October 2008) or 66 Gy/3 F in a peak in GTV. At each fraction the PTV was covered with 15 Gy. The GTV was encompassed by the 95% isodose. 32 patients were treated with the prescribed dose 45 Gy/3F with GTV covered by 95%. One patient with 50 Gy/3F because of tumour position in close relation to diaphragm and pleura. The treatment duration was nine days (whenever possible). Initially, the preferable treatment technique was at least six (typically 10) different coplanar beam directions with no overlapping skin entries to avoid severe skin toxicity. Since 2011 volumetric modulated arc therapy (VMAT) in two uninterrupted arcs around the patient was introduced as the preferable treatment technique. 4D cone-beam was used at each fraction to check for reproducibility of the tumour. Organs at risk (OAR) were spinal cord, oesophagus, lungs, heart and nearest ribs and vertebras. • Conventional fractionation (CF) 80 Gy, 35-40 fractions, 5 times a week *Patients treated with CF received treatment five times per week. A 3D conformal radiotherapy technique was used. The Pinnacle3 system was used for treatment planning and the doses were calculated with the collapsed-cone algorithm. Only two patients (those treated in 2011) had 4D scan performed. The GTV was contoured using a pulmonary CT window. CTV was identical to GTV. PTV was defined as a margin of 2 cm in all directions. The prescribed dose was 80 Gy in 35–40 F to cover 95% of the PTV. The treatment was without elective mediastinal nodal irradiation. Patients did not receive any chemotherapy. OAR was identical to those treated with SBRT.* **Outcome measures**	

Short Title	Title	Study Characteristics	Risk of Bias
		• Mortality	
Koshy 2015	Stereotactic body radiotherapy and treatment at a high volume facility is associated with improved survival in patients with inoperable stage I non-small cell lung cancer	**Study type** Retrospective cohort and case-control study **Study details** • Study location *USA* • Study setting *Hospital* • Study dates *They included patients in the National Cancer Database from 2003 to 2006* • Duration of follow-up *The median follow up was 68 months (interquartile range: 35–83 months)* • Sources of funding *None* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage I • Received all or part of their first course of treatment at CoC-accredited facilities (if treated at all) **Exclusion criteria** • For the CF cohort, excluded if they received less than 60 Gy using 1.8-2 Gy fraction sizes	**For the SABR vs no therapy comparison: quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes *Patients not meeting criteria for one of the cohorts were excluded from the analysis* Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • No *There is no measurement of performance score.* Have they taken account of the confounding factors in the design and/or analysis? • No *In the no therapy arm, 46.7% were T2 compared to 32.3% in the SABR arm.*

Short Title	Title	Study Characteristics	Risk of Bias
		• For the no therapy cohort, excluded if they survived less than 4 months to exclude patients ineligible for any therapy **Sample characteristics** • Sample size *13,036 people* • Split between study groups *SABR = 773; CF = 5,375; no therapy = 6,888* • Loss to follow-up *Not mentioned* • %female *SABR = 55.5%; CF = 49.5%; no therapy = 49.6%* • Average age *Age at diagnosis % (18-59, 60-69, 70-79, 80+): SABR = 7.6%, 20.8%, 44.0%, 27.6%; CF = 6.6%, 22.4%, 41.9%, 29.1%; no therapy = 10.2%, 22.8%, 38.4%, 28.6%* • Cancer staging *Before case-matching (T1, T2): no therapy 53.3%, 46.7%; CF 53.7%, 46.3%; SABR 67.7%, 32.3%. After case-matching the CF and SABR arms had 50% for both T1 and T2.* **Interventions** • Stereotactic ablative radiotherapy (SABR) • Conventional fractionation (CF) at least 60 Gy in 1.8-2 Gy per fraction • No therapy **Outcome measures** • Mortality	Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • High Directness • Directly applicable **For the SABR vs CF comparison: quality assessment (case-control study)** Did the study address a clearly focused issue? • Yes Did the authors use an appropriate method to answer their question? • Yes Were the cases recruited in an acceptable way? • Yes *Patients not meeting criteria for one of the cohorts were excluded from the analysis.* Were the controls selected in an acceptable way?

Short Title	Title	Study Characteristics	Risk of Bias
			• Yes Was the exposure accurately measured to minimise bias? • No *There is no measurement of performance score.* Have the authors taken account of potential confounding factors in the design and/or in their analysis? • Yes *After propensity matching, the NSCLC stages, comorbidity scores, ages and histology are balanced in each arm.* Overall risk of bias • Moderate Directness • Directly applicable
Lanni 2011	Stereotactic Radiotherapy Reduces Treatment Cost While Improving Overall Survival and Local Control Over Standard Fractionated Radiation Therapy	**Study type** • Prospective cohort study *This is an economic study. However, it has some mortality data.* **Study details** • Study location *USA* • Study setting *Hospital*	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No *There was no discussion of how participants were selected for each arm.*

Short Title	Title	Study Characteristics	Risk of Bias
	for Medically Inoperable Non-Small-Cell Lung Cancer	• Study dates *Radiotherapy occurred from 2002 to 2008* • Duration of follow-up *People had multiple routine follow-up history and physical examinations along with chest x-rays and/or CT scans, and 18-fluorodeoxyglucose Positron Emission Tomography scans. The first of these appointments was performed 6 weeks and 16 weeks after final radiotherapy treatment followed by every 3 to 6 months post-treatment appointments thereafter. The median potential follow-up period was 36 months.* • Sources of funding *Not mentioned* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Unresectable • Stage I *IA T1 N0 M0 or IB T2 N0 M0* **Exclusion criteria** • None reported **Sample characteristics** • Sample size *86 people* • Split between study groups *SABR = 45; CF = 41* • Loss to follow-up	Was the exposure accurately measured to minimise bias? • Unclear *The two groups have similar baseline characteristics with regards to the clinical stage of the NSCLC and performance status. However, there is no discussion as to whether this was planned or happened by chance alone.* Was the outcome accurately measured to minimise bias? • No *Mortality is measured as the overall survival at a median potential follow-up of 36 months. However, the average values could be different for each arm. In addition, this is an unusual measurement for mortality. Normally, overall survival is measured at yearly intervals or preferably as a hazard radio.* Have the authors identified all important confounding factors? • Unclear *There was no discussion of confounding factors.* Have they taken account of the confounding factors in the design and/or analysis? • No Was the follow up of subjects complete enough? • Unclear

Short Title	Title	Study Characteristics	Risk of Bias
		None • %female *SABR = 60%; CF = 56%* • Average age *SABR = 76 (63-90); CF = 76 (53-85). There is no explanation as to what sort of average or variance these values are.* **Interventions** • Stereotactic ablative radiotherapy (SABR) 48 Gy (4 x 12 Gy) for T1 tumours or 60 Gy (5 x 12 Gy) for T2 tumours. Otherwise known as stereotactic body radiotherapy *Patient treatment plans were formulated using virtual computed tomography (CT) simulation with subsequent 3D dose calculation including heterogeneity correction and dose volume histogram generation. SABR people received a dose of 12 Gy per fraction for a median of 4 fractions. The prescribed dose for SABR was 48 Gy in 4 fractions for T1 tumours and 60 Gy in 5 fractions for T2 tumours prescribed to the edge of the planning target volume with approximately 20% target heterogeneity.* • Conventional fractionation (CF) 70 Gy (1.8-2 Gy, daily, 5 days a week) *Patient treatment plans were formulated using virtual computed tomography (CT) simulation with subsequent 3D dose calculation including heterogeneity correction and dose volume histogram generation. CF (3D-CRT) people received a dose of 1.8 to 2Gy per fractions, and the median dose delivered for all people was 70 Gy (median 35 fractions) with a range of 29 to 70 Gy. For 3D-CRT people (some treated before the availability of 4D CT at our institution), tumour motion was initially observed using fluoroscopy and tumour respiratory motion was recorded in 3 dimensions followed by a free-breathing*	*There was no mention of adverse events. However, this is an economic study.* Was the follow up of subjects long enough? • Yes Overall risk of bias • High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		planning CT scan. The gross tumour target volume (GTV) was then defined on CT lung windows, with a 5 mm GTV to clinical target volume expansion, and planning target volume (PTV) expansion equivalent to 5 mm for set-up error plus appropriate margin for observed respiratory motion, unless a GTV_1TV (Internal Target Volume) could be formulated from 4D CT. Dose was typically prescribed to the isocentre, but sometimes the 90% to 95% isodose line depending on PTV coverage. **Outcome measures** • Mortality	
Nakagawa 2014	Comparison of the outcomes of stereotactic body radiotherapy and surgery in elderly patients with cT1-2N0M0 non-small cell lung cancer	**Study type** • Retrospective cohort study **Study details** • Study location *Japan* • Study setting *Hospital* • Study dates *January 2001 to December 2011* • Duration of follow-up *5 years* • Sources of funding *Not mentioned* **Inclusion criteria** • Stage I • Stage T1-2 N0 M0	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No *There was no propensity matching. This is important because 22/35 SABR participants were medically inoperable. People undergoing surgery had a better performance status.* Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias? • Yes

Short Title	Title	Study Characteristics	Risk of Bias
		• 75 years of age or older **Exclusion criteria** • Coexisting malignancies • Previous malignancy during the last 5 years **Sample characteristics** • Sample size *218 participants* • Split between study groups *SABR = 35; surgery = 183* • Loss to follow-up *None* • %female *SABR = 29%; surgery = 33.3%* • Average age *Mean (SD): SABR = 79.8 years (2.8); surgery 78.3 years (2.5)* **Interventions** • Stereotactic ablative radiotherapy (SABR) *SBRT was administered at total doses ranging from 48 to 60 Gy that were delivered in 4–8 fractions to the isocenter.* • Surgery *The details of surgery were not provided.* **Outcome measure** • Mortality	Have the authors identified all important confounding factors? • Unclear *It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Have they taken account of the confounding factors in the design and/or analysis? • No *There was no propensity matching. This is important because 22/35 SABR participants were medically inoperable. People undergoing surgery had a better performance status. In the SABR arm, 49% were performace status 0. In the surgery arm, 83% were performance status 0.* Was the follow up of subjects long enough? • Yes Overall risk of bias • High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
Puri 2012	A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis	**Study type** • Retrospective case-control study **Study details** • Study location *USA* • Study setting *Hospital* • Study dates *All surgical patients with clinical stage I lung cancer treated between 1 January 2000 to 31 December 2006 and all patients between 1 February 2004 to 5 May 2007 with clinical stage I lung cancer undergoing treatment with SBRT were included.* • Duration of follow-up *4 years* • Sources of funding *Not mentioned* **Inclusion criteria** • Stage I **Exclusion criteria** • None reported **Sample characteristics** • Sample size *114 people* • Split between study groups	**Quality assessment (case-control study)** Did the study address a clearly focused issue? • Yes Did the authors use an appropriate method to answer their question? • Unclear. *It is difficult to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Were the cases recruited in an acceptable way? • Yes Were the controls selected in an acceptable way? • No. *The controls were operable, unlike the SABR patients.* Was the exposure accurately measured to minimise bias? • Unclear. *This is difficult to do in a study that attempts to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Have the authors taken account of potential confounding factors in the design and/or in their analysis? • Unclear

Short Title	Title	Study Characteristics	Risk of Bias
		SABR = 57; surgery (81% lobectomy, 19% sublobar resection) = 57 • Loss to follow-up *None* • %female *SABR = 60%; surgery = 40.4%* • Average age *Mean (SD): SABR = 71.79 years (10.6); surgery = 71.54 years (7.9)* **Interventions** • Stereotactic ablative radiotherapy (SABR) *Current standard SBRT dosing at their centre delivered 54 Gy in 3 fractions over 8 to 14 days. The vast majority of patients undergoing SBRT had been refused resection by the surgical team. They attempted to address this using propensity scoring methods.* • Surgery *81% had a lobectomy and 19% had a sublobar resection.* **Outcome measure** • Mortality	*This is difficult to do in a study that attempts to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Overall risk of bias • High *The participants were propensity matched. This was a comparison of largely medically inoperable participants vs operable participants.* Directness • Directly applicable
Tong 2015	Advantages of cyber knife for inoperable stage I peripheral non-small-cell lung cancer compared to three-dimensional conformal radiotherapy	**Study type** Retrospective cohort study **Study details** • Study location *China* • Study setting *Hospital* • Study dates	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Yes Was the exposure accurately measured to minimise bias? • Yes

Short Title	Title	Study Characteristics	Risk of Bias
		2012 to 2013 • Duration of follow-up *1 year* • Sources of funding *The China Postdoctoral Science Foundation* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage I *Peripheral* **Exclusion criteria** • None reported **Sample characteristics** • Sample size *68 people* • Split between study groups *SABR = 30; CF = 38* • Loss to follow-up *None reported* • %female *SABR = 33%; CF = 47%* • Average age *Number with age (years) <70, >70: SABR = 13, 17; CF = 16, 22* **Interventions**	Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • Low Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		• Stereotactic ablative radiotherapy (SABR) 42-60 Gy *In the SABR arm, they treated a group of patients with the CyberKnife frameless robotic radiosurgery system. They obtained fine-cut (1.5-mm) treatment planning CTs 7-10 days following fiducial placement during a full-inhalation breath-hold. Gross tumour volume (GTV) was contoured with lung windows. The GTV margin was expanded by 5 mm to set the planning treatment volume (PTV). All the critical thoracic structures and the lungs were contoured to ensure that incidental radiation delivered to these structures was limited according to the reports of the American Association of Physicists in Medicine Task Group 101. A treatment plan from MultiPlan software was made using the CyberKnife non-isocentric, inverse-planning ray-tracing algorithm with tissue density heterogeneity corrections for lung. Lower doses within the range of 42-60 Gy in three fractions were prescribed when concerns regarding adjacent critical structures arose and when patients were considered to exhibit severe pulmonary dysfunction. The biologically effective dose (BED) was 100.8-180 Gy for patients undergoing CK treatment. The radiation dose was prescribed to an isodose line that covered ≥95% of the PTV and caused the 30-Gy isodose contour to extend a minimum of 1 cm from the GTV. The percentage of the total lung volume receiving ≥15 Gy (V15) was limited to 15%.* • Conventional fractionation (CF) 60 Gy, 2 Gy per fraction *Radiation was delivered with photon beams of 6 MV from a linear accelerator in the 3DCRT group. Each of the patients was irradiated for 60 Gy, 2 Gy/fraction, once per day, 5 days per week. The BED was 72 Gy for the patients receiving 3DCRT treatment. Radiation Therapy Planning software was used to design the radiation plan. In the 3DCRT plans, due to the unavailability of 4DCT imaging, larger margins were used to defi ne the PTV (10, 10 and 15 mm in the latero-lateral,*	

Short Title	Title	Study Characteristics	Risk of Bias
		antero -posterior and cranio -caudal directions, respectively) to account for respiratory motion. The lungs, heart and spinal cord were considered as organs at risk (OARs). The planning objective was to cover 95% of the volume with 95% of the dose for the PTV. The constraints for the OARs were Dmax <20 Gy for the spinal cord and Dmax <30 Gy for the heart. For the joint lungs, exclusive of PTV, the following constraints were set: V30Gy <20% and a mean lung dose <4 Gy. The BED was calculated with the following linear quadratic formula: BED = (nd) [1+d/(α/β)]. Factor α/β was assumed to be 10 Gy, with the variables n and d representing the number of fractions and the dose per fraction, respectively. **Outcome measures** • Adverse events grade 3 and above (For example: respiratory, stroke, cardiovascular, oesophagitis, dysphagia, dermatological and adverse events that investigators attribute to radiotherapy)	
Tu 2017	A population-based study of the effectiveness of stereotactic ablative radiotherapy versus conventional fractionated radiotherapy for clinical stage i non-small cell lung cancer patients	**Study type** Retrospective cohort study **Study details** • Study location *Taiwan* • Study setting *Hospital* • Study dates *Patients received therapy between 2007 to 2013* • Duration of follow-up *The median follow-up time was 28 months.* • Sources of funding *Not mentioned*	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • Uncertain *There were a greater number of participants in the SABR arm who had comorbidities compared to the CF arm (87% vs 75%). 60% of participants in the SABR arm had an ECOG performance status of 3 or 4. To our knowledge, no other study includes participants with a performance status of 4 (bedbound, completely disabled, cannot carry on any self-care, totally to bed or chair). Status 5 is death.*

Short Title	Title	Study Characteristics	Risk of Bias
		Inclusion criteria • Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage I **Exclusion criteria** • Surgical resection other than biopsy **Sample characteristics** • Sample size *238 people* • Split between study groups *SABR = 69; CF = 169* • Loss to follow-up *Not mentioned* • %female *SABR = 30%; CF = 40%* • Average age *Mean (SD): SABR = 77.5 years (8.26); CF = 77.8 years (9.79)* **Interventions** • Stereotactic ablative radiotherapy (SABR): 25-34 Gy in 1 fraction, 45-60 Gy in 3 fractions, 48-50 Gy in 4 fractions, 50-55 Gy in 5 fractions, 60-70 Gy in 8-10 fractions *There was no further information.* • Conventional fractionation (CF) 60-70 Gy in 1.8-2 Gy per fractions *There was no further information.*	Was the exposure accurately measured to minimise bias? • *No. Performance score values were not available for the CF arm. This is a large omission given that so many participants in the SABR arm had a performance score of 3 or 4.* Was the outcome accurately measured to minimise bias? • Yes Have the authors identified all important confounding factors? • No *Performance score was only considered retrospectively.* Have they taken account of the confounding factors in the design and/or analysis? • No *Performance score was only considered retrospectively.* Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes

Short Title	Title	Study Characteristics	Risk of Bias
		Outcome measures • Mortality	Overall risk of bias • High *There were a greater number of participants in the SABR arm who had comorbidities compared to the CF arm (87% vs 75%). 60% of participants in the SABR arm had an ECOG performance status of 3 or 4. To our knowledge, no other study includes participants with a performance status of 4 (bedbound, completely disabled, cannot carry on any self-care, totally to bed or chair). Status 5 is death.* Directness • Directly applicable
Van den Berg 2015	Patterns of Recurrence and Survival after Surgery or Stereotactic Radiotherapy for Early Stage NSCLC	**Study type** • Retrospective cohort study **Study details** • Study location *The Netherlands* • Study setting *Hospital* • Study dates *2007 to 2010* • Duration of follow-up *Not mentioned* • Sources of funding *Not mentioned* **Inclusion criteria**	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No. Patients treated with surgery were 10 years younger, had a better performance status, less comorbidity, and better lung function tests. Those who had SABR were effectively a different population to those undergoing surgery. Was the exposure accurately measured to minimise bias? • Yes Was the outcome accurately measured to minimise bias?

Short Title	Title	Study Characteristics	Risk of Bias
		• Histological confirmation of NSCLC by biopsy or cytological evaluation • Stage T1 or T2a (<5 cm in greatest dimension) **Exclusion criteria** • None reported **Sample characteristics** • Sample size *340 people* • Split between study groups *SABR = 197; surgery = 143* • Loss to follow-up *None* • %female *SABR = 27%; surgery = 33%* • Average age *Median (range): SABR = 77 years (52-93); surgery = 67 years (40-84)* **Interventions** • Stereotactic ablative radiotherapy (SABR) SABR was based on a 4D-planning CT. The planning target volume (PTV) was defined as the envelope including the moving gross tumor volume plus a margin in all directions of 5 mm. After the institutional protocol, a risk-adapted fractionation schedule of 3 to 12 fractions to 60 Gy was administered. In brief, lesions completely surrounded by lung tissue and not located within 2 cm of the central airways received three fractions of 20 Gy. Lesions located within the 2 cm corridor of trachea and main bronchi received eight fractions of 7.5 Gy or 12 fractions of 5	• Yes Have the authors identified all important confounding factors? • Unclear *It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Have they taken account of the confounding factors in the design and/or analysis? • Unclear *The SABR arm had people who were mostly not medically suitable for surgery. This population will be different to the patients who had surgery. It would be difficult to adjust for all confounding factors.* Was the follow up of subjects complete enough? • Unclear. The duration of follow-up was not mentioned. Was the follow up of subjects long enough? • Yes Overall risk of bias • High Directness

Short Title	Title	Study Characteristics	Risk of Bias
		Gy, whereas lesions adjacent to the thoracic wall received five times 12 Gy. During the study period, a pencil-beam dosecalculation algorithm with tissue heterogeneity correction had been used and the dose was prescribed at 80% isodose comprising periphery of the PTV. • Surgery Surgery was performed via open thoracotomy (94% of the cases) or video-assisted thoracic surgery and included wedge resection, lobectomy, bilobectomy, or pneumonectomy, the latter three operations with hilar and mediastinal lymph-node dissection. **Outcome measure** • Mortality	• Directly applicable
Wang 2016	A propensity-matched analysis of surgery and stereotactic body radiotherapy for early stage non-small cell lung cancer in the elderly	**Study type** • Retrospective case-control study **Study details** • Study location *China* • Study setting *Hospital* • Study dates *2002 to 2010* • Duration of follow-up *5 years* • Sources of funding *Not provided* **Inclusion criteria** • Stage I	**Quality assessment (case-control study)** Did the study address a clearly focused issue? • Yes Did the authors use an appropriate method to answer their question? • Unclear *It is difficult to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Were the cases recruited in an acceptable way? • Yes Were the controls selected in an acceptable way? • No

Short Title	Title	Study Characteristics	Risk of Bias
		Exclusion criteria • Previous radiotherapy • Surgical resection other than biopsy • <60 years of age • Past history of lung cancer • Previous chemotherapy **Sample characteristics** • Sample size *70 people* • Split between study groups *SABR = 35; surgery = 35* • Loss to follow-up *None* • %female *SABR = 5.7%; surgery = 5.7%* • Average age *Mean (SD): SABR = 77.1 years (5.2); surgery = 74.8 (6.6)* **Interventions** • Stereotactic ablative radiotherapy (SABR) *SBRT was administered as an outpatient or inpatient treatment based on risk-adapted fractionation schemes. The internal target volume (ITV) was determined using CT with a slow scan or 4D CT technique, and tumour motion was assessed using fluoroscopy. The planning target volume was defined as the ITV plus a 5-mm margin. Irradiation was performed with 6-MV x-ray beams from a linear accelerator in multiple non-coplanar static ports. The dose of SBRT was prescribed*	*The controls were operable, unlike the SABR patients.* Was the exposure accurately measured to minimise bias? • Unclear *This is difficult to do in a study that attempts to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Have the authors taken account of potential confounding factors in the design and/or in their analysis? • Unclear *This is difficult to do in a study that attempts to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.* Overall risk of bias • High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		to the highest isodose line that was required to cover 100% of the ITV and >95% of the planning target volume. • Surgery *In the surgery patients, performance of a lobectomy, sublobectomy, thoracotomy, or video-assisted thoracic surgery was discussed within the MDT prior to the procedure.* **Outcome measure** • Mortality	
Widder 2011	Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer	**Study type** Retrospective cohort study **Study details** • Study location *The Netherlands* • Study setting *Hospital* • Study dates *Therapy was between 2006 to 2009* • Duration of follow-up *Median follow-up was 13 months* • Sources of funding *Not mentioned* **Inclusion criteria** • Histological confirmation of NSCLC by biopsy or cytological evaluation • Medically inoperable • Stage T1-2 N0 M0	**Quality assessment (cohort study)** Did the study address a clearly focused issue? • Yes Was the cohort recruited in an acceptable way? • No *The patients in the SABR arm were sicker compared to the CF arm. Twice as many patients in the CF arm had a normal performance status. Three times as many patients in the SABR arm had a performance status of 2-3.* Was the exposure accurately measured to minimise bias? • Unclear As above Was the outcome accurately measured to minimise bias? • Yes

Short Title	Title	Study Characteristics	Risk of Bias
		Exclusion criteria • Technically unresectable **Sample characteristics** • Sample size *229 people* • Split between study groups *SABR = 202; CF = 27* • Loss to follow-up *Not mentioned* • %female *SABR = 27%; CF = 19%* • Average age *Median (range): SABR = 76 years (46-93); CF = 71 years (47-82)* **Interventions** • Stereotactic ablative radiotherapy (SABR) 60 Gy, 3-8 fractions *Patients were positioned in a vacuum-mattress and underwent a 4D-planning CT scan without intravenous contrast. An internal target volume was derived by delineating the visible gross tumour volume as maximum-intensity-projection reconstructed from 4-6 respiratory phases. Then, a 5-mm margin was added in all directions to yield the planning target volume (PTV). In this manner, an individual target volume was generated for every patient, depending on the patient's respiratory pattern and tumour location. Three fractionation schedules were used. Lesions completely surrounded by lung tissue and not located within 2 cm of the central airways received three fractions of 20 Gy (biologically equivalent dose [BED] = 180 Gy for tumour effects). Lesions located within the 2 cm corridor of trachea and main bronchi*	Have the authors identified all important confounding factors? • Yes Have they taken account of the confounding factors in the design and/or analysis? • Yes Was the follow up of subjects complete enough? • Yes Was the follow up of subjects long enough? • Yes Overall risk of bias • High Directness • Directly applicable

Short Title	Title	Study Characteristics	Risk of Bias
		received eight fractions of 7.5 Gy (BED = 105 Gy), whereas lesions adjacent to the thoracic wall received 5 x 12 Gy (BED = 132 Gy). The total dose of 60 Gy was prescribed at the margin of the PTV, constituting 80% of the dose at the isocenter and following the dose-conformity guidelines as used in the Radiation Therapy Oncology Group 0236 trial. Treatment was delivered using four noncoplanar dynamic arcs. • Conventional fractionation (CF) 70 Gy, 35 fractions *The PTV comprising the tumour as seen on a slow 3D-planning CT with a margin of 20 mm (15 mm to CTV; 5 mm to PTV) was treated to 46 Gy, thereafter portals were reduced to tumour plus 5 mm as PTV to the total dose of 70 Gy, which results in a BED of 84 Gy for tumour effects. In 17 of 27 patients (63%), a two-field technique was used in the initial setup, 10 patients (37%) started with a three-field technique. The boost volumes were administered using two portals in 14 patients and three portals in 13 patients, respectively.* **Outcome measures** • Mortality • Quality of life	

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Appendix F – GRADE tables

Randomised controlled trials

Studies that only included people who were operable

Operable, stage I: SABR peripheral: 54 Gy in 3 x 18 Gy fractions; central: 50 Gy in 4 x 12.5 Gy fractions vs lobectomy

Quality assessment						No of people		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Surgery**	**Summary of results**	
Mortality: hazard ratio (values under 1 favour SABR)									
1 (Chang 2015[1])	RCT	Serious[2]	Not serious	N/A	Serious[3]	31	27	HR 0.14 (0.02, 1.17)	Low
Mortality: risk ratio of survival at 1 year (values over 1 favour SABR)									
1 (Chang 2015[1])	RCT	Serious[2]	Not serious	N/A	Serious[3]	31	27	RR 1.13 (0.97, 1.30)	Low
Mortality: risk ratio of survival at 3 years (values over 1 favour SABR)									
1 (Chang 2015[1])	RCT	Serious[2]	Not serious	N/A	Serious[3]	31	27	RR 1.20 (0.96, 1.50)	Low
Mortality: risk ratio of treatment-related death (values under 1 favour SABR)									
1 (Chang 2015[1])	RCT	Serious[2]	Not serious	N/A	Serious[3]	31	27	RR 0.29 (0.01, 6.88)	Low
Adverse events grade 3 or above: risk ratio of participants experiencing grade 3 or above adverse events (values below 1 favour SABR)									
1 (Chang 2015[1])	RCT	Serious[2]	Not serious	N/A	Not serious	31	27	RR 0.22 (0.07, 0.69)	Moderate
Adverse events grade 3 or above: dyspnoea (values below 1 favour SABR)									
1 (Chang 2015[1])	RCT	Serious[2]	Not serious	N/A	Serious[3]	31	27	RR 0.35 (0.07, 1.65)	Low

1. Includes Louie 2015
2. No allocation concealment. There was no blinding. The authors wrote that detailed eligibility and exclusion criteria are included in the appendix. However, there are no further details in the appendix. This makes it more difficult to assess how homogeneous or heterogeneous the combined RCT data is.
3. 95% CI of the effect size crosses the line of no effect

Operable, stage IIIA: chemotherapy, CF 60-62.5 Gy (1.95-2.05 Gy in 30-32 fractions over 40-46 days) vs chemotherapy, surgery

Quality assessment						No of people		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Chemo, surgery**	**Chemo, CF**	**Summary of results**	
Mortality: all cause hazard ratio (values over 1 favour chemotherapy, CF)									
1 (van Meerbeeck 2007)	RCT	Not serious	Not serious	N/A	Serious[1]	165	167	HR 1.06 (0.85, 1.33)	Moderate
Dropout during treatment (values over 1 favour chemotherapy, CF)									
1 (van Meerbeeck 2007)	RCT	Not serious	Not serious	N/A	Serious[1]	165	167	RR 0.86 (0.40, 1.86)	Moderate
1. 95% CI of the effect size crosses the line of no effect									

Operable, stage IIIA: chemotherapy, CF 40-46 Gy (1 or 2 fractions per day, 5 days a week), surgery vs chemotherapy, surgery

Quality assessment						No of people		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Chemo, surgery**	**Chemo, CF, surgery**	**Summary of results**	
Mortality: all-cause hazard ratio (values below 1 favour chemotherapy, CF, surgery)									
2 (Katakami 2012, Pless 2015)	RCT	Not serious	Not serious	Not serious	Serious[1]	149	138	HR 0.94 (0.69, 1.27)	Moderate
Mortality: risk ratio for survival at 1 year (values below 1 favour chemotherapy, CF, surgery)									
1 (Girard 2010)	RCT	Serious[2]	Not serious	Not serious	Serious[1]	14	32	RR 1.10 (0.89, 1.36)	Low
Mortality: risk ratio for survival at 2 years (values below 1 favour chemotherapy, CF, surgery)									
1 (Girard 2010)	RCT	Serious[2]	Not serious	Not serious	Serious[1]	14	32	RR 0.87 (0.52, 1.46)	Low
Mortality: risk ratio for survival at 3 years (values below 1 favour chemotherapy, CF, surgery)									
2 (Girard 2010, Katakami 2012)	RCT	Serious[2]	Not serious	Serious[4]	Serious[1]	42	60	RR 0.76 (0.49, 1.18)	Very low
Adverse events grade 3 or above: stomatitis (values above 1 favour chemotherapy, CF, surgery)									
1 (Pless 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	121	110	RR 4.55 (0.54, 38.30)	Moderate
Adverse events grade 3 or above: dyspnoea (values above 1 favour chemotherapy, CF, surgery)									

Quality assessment						No of people		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Chemo, surgery**	**Chemo, CF, surgery**	**Summary of results**	
2 (Katakami 2012, Pless 2015)	RCT	Not serious	Not serious	Not serious	Serious[1]	149	138	RR 8.19 (0.45, 150.38)	Moderate
Adverse events grade 3 or above: pneumonitis (values above 1 favour chemotherapy, CF, surgery)									
1 (Girard 2010)	RCT	Serious[2]	Not serious	Not serious	Serious[1]	14	32	RR 0.73 (0.03, 16.97)	Low

1. 95% CI of the effect size crosses the line of no effect
2. Girard 2010: Randomisation was stratified by clinical centre and histological type (squamous cell carcinoma vs. others). However, the groups were not balanced in terms of gender or pN2/cN2. This might be because of the relatively low numbers of participants. Nevertheless, they were not balanced.

Operable stage IIIA and IIIB: chemotherapy, CF 45 Gy (1.5 Gy, 2x per day, 5 days a week), CF boost 20-26 Gy (2 Gy, 2x per day, 5 days a week) vs chemotherapy, CF 45 Gy (1.5 Gy, 2x per day, 5 days a week), surgery

Quality assessment						No of people		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**Chemo, chemorad + surgery**	**Chemo, chemorad boost**	**Summary of results**	
Mortality: risk ratio for survival at 1 year (values below 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 0.94 (0.81, 1.10)	Moderate
Mortality: risk ratio for survival at 2 years (values below 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.07 (0.84, 1.37)	Moderate
Mortality: risk ratio for survival at 3 years (values below 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.08 (0.75, 1.56)	Moderate
Mortality: risk ratio for survival at 4 years (values below 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.23 (0.75, 2.04)	Moderate
Mortality: risk ratio for survival at 5 years (values below 1 favour chemo, chemorad boost)									

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	Chemo, chemorad + surgery	Chemo, chemorad boost	Summary of results	
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.23 (0.69, 2.21)	Moderate
Mortality: risk ratio for survival at 6 years (values below 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.12 (0.60, 2.08)	Moderate
Adverse events grade 3 or above: oesophagitis (values above 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 0.52 (0.27, 1.00)	Moderate
Adverse events grade 3 or above: mucositis/stomatitis (values above 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.48 (0.25, 8.63)	Moderate
Adverse events grade 3 or above: pulmonary (values above 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.78 (0.62, 5.07)	Moderate
Adverse events grade 3 or above: other gastrointestinal or renal (values above 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.58 (0.54, 4.62)	Moderate
Adverse events grade 3 or above: cardiac (values above 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.98 (0.37, 10.48)	Moderate
Dropout during treatment risk ratio (values above 1 favour chemo, chemorad boost)									
1 (Eberhardt 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	81	80	RR 1.65 (0.41, 6.66)	Moderate
1. 95% CI of the effect size either crosses or touches the line of no effect									

Studies that only included people who were inoperable or refused surgery

Inoperable or refused surgery, stage I: SABR 34 Gy in 1 fraction vs SABR 48 Gy in 4 consecutive daily fractions

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR 34 Gy in 1 fraction	SABR 48 Gy in 4 fractrions	Summary of results	
Mortality: risk ratio of survival at 1 year (values below 1 favour 48 Gy in 4 fractions)									
1 (Videtic 2015)	RCT	Serious[1]	Not serious	N/A	Serious[2]	39	45	RR 0.93 (0.79, 1.09)	Low
Mortality: risk ratio of survival at 2 years (values below 1 favour 48 Gy in 4 fractions)									
1 (Videtic 2015)	RCT	Serious[1]	Not serious	N/A	Serious[2]	39	45	RR 0.79 (0.59, 1.06)	Low
Adverse events grade 3 or above: respiratory disorders (values above 1 favour 48 Gy in 4 fractions)									
1 (Videtic 2015)	RCT	Serious[1]	Not serious	N/A	Serious[2]	39	45	RR 0.10 (0.01, 1.83)	Low

1. There was no allocation concealment nor blinding
2. 95% CI of the effect size crosses the line of no effect

Inoperable or refused surgery, stage I: SABR 66 Gy (3x 22 Gy during 1 week) vs CF 70 Gy (2 Gy, daily, 5 days a week)

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	CF	Summary of results	
Mortality: all-cause hazard ratio (values above 1 favour SABR)									
1 (Nyman 2016)	RCT	Serious[1]	Not serious	N/A	Serious[2]	48	53	HR 0.75 (0.43, 1.30)	Low
Adverse events grade 3 or above: pneumonitis (values below 1 favour SABR)									
1 (Nyman 2016)	RCT	Serious[1]	Not serious	N/A	Serious[2]	48	53	RR 0.37 (0.02, 8.81)	Low
Adverse events grade 3 or above: dyspnoea (values below 1 favour SABR)									
1 (Nyman 2016)	RCT	Serious[1]	Not serious	N/A	Serious[2]	48	53	RR 1.10 (0.34, 3.58)	Low
Adverse events grade 3 or above: pulmonary fibrosis (values below 1 favour SABR)									
1 (Nyman 2016)	RCT	Serious[1]	Not serious	N/A	Serious[2]	48	53	RR 0.37 (0.02, 8.81)	Low
Adverse events grade 3 or above: cough (values below 1 favour SABR)									
1 (Nyman 2016)	RCT	Serious[1]	Not serious	N/A	Serious[2]	48	53	RR 3.31 (0.14, 79.28)	Low
Adverse events grade 3 or above: skin reactions (values below 1 favour SABR)									

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	CF	Summary of results	
1 (Nyman 2016)	RCT	Serious[1]	Not serious	N/A	Serious[2]	48	53	RR 3.31 (0.14, 79.28)	Low

1. The method of randomisation was not given. The SABR arm had more T2 participants than the CF arm: T1: SABR = 53%; CF = 75%. T2: SABR = 47%; CF = 25%. There was no blinding.
2. 95% CI of the effect size crosses the line of no effect

310 ***Inoperable or refused surgery, stage I to IIIB: CHARTWEL 60 Gy (1.5 Gy, 3x per day, 5 days a week) vs CF 66 Gy (2 Gy, daily, 5 days a week)***

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	CHARTWEL	CF	Summary of results	
Mortality: all-cause hazard ratio (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Not serious	Not serious	N/A	Serious[2]	203	203	HR 0.92 (0.75, 1.13)	Moderate
Mortality: cancer-related risk ratio of death (locoregional recurrence, supraclavicular or neck lymph node metastasis or distant metastasis) (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Not serious	Not serious	N/A	Serious[2]	203	203	RR 0.95 (0.80, 1.13)	Moderate
Mortality: treatment-related risk ratio of death (radiation injury) (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Not serious	Not serious	N/A	Serious[2]	203	203	RR 1.00 (0.14, 7.03)	Moderate
Adverse events grade 3 and above: risk ratio of early dysphagia at 2 weeks (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Serious[3]	Not serious	N/A	Not serious	199	200	RR 10.05 (3.12, 32.40)	Moderate
Adverse events grade 3 and above: risk ratio of early dysphagia at 4 weeks (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Serious[3]	Not serious	N/A	Not serious	198	199	RR 2.45 (1.57, 3.81)	Moderate
Adverse events grade 3 and above: risk ratio of early dysphagia at 8 weeks (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Serious[3]	Not serious	N/A	Serious[2]	194	191	RR 1.12 (0.65, 1.91)	Low
Adverse events grade 3 and above: risk ratio of early dysphagia at 12 weeks (values below 1 favour CHARTWEL)									

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	CHARTWEL	CF	Summary of results	
1 (Baumann 2011)[1]	RCT	Serious[3]	Not serious	N/A	Serious[2]	181	179	RR 2.23 (0.70, 7.09)	Low
Adverse events grade 3 and above: risk ratio of early dysphagia at 16 weeks (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Serious[3]	Not serious	N/A	Serious[2]	161	155	RR 2.89 (0.59, 14.09)	Low
Adverse events grade 3 and above: risk ratio of early dysphagia at 20 weeks (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Serious[3]	Not serious	N/A	Serious[2]	157	147	RR 2.81 (0.30, 26.70)	Low
Adverse events grade 3 and above: risk ratio of clinical pneumonitis at 8 weeks (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Serious[3]	Not serious	N/A	Serious[2]	194	191	RR 1.48 (0.54, 4.07)	Low
Adverse events grade 3 and above: risk ratio of clinical pneumonitis at 12 weeks (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Serious[3]	Not serious	N/A	Serious[2]	203	203	RR 0.70 (0.34, 1.42)	Low
Quality of life: Global QoL mean difference between CF and CHARTWEL at 3 years (from EORTIC QLQ-C30) (values below 1 favour CHARTWEL)									
1 (Baumann 2011)[1]	RCT	Not serious	Not serious	N/A	Serious[2]	203	203	MD -5.40 (-13.60, 2.80)	Moderate

1. This CHARTWEL study also includes Soliman 2013 and Hechtner 2018)
2. 95% CI of the effect size crosses the line of no effect
3. Adverse events should be measured using cumulative incidence. Particularly grade 3 adverse events because by definition they require assistance from a healthcare professional. Using snapshots might miss some adverse events.

Inoperable or refused surgery, stages I to IV: SABR 64-66 Gy (6-8 Gy, 3 times a week) vs CF 68-70 Gy (unspecified fractions, 5 times a week)

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	CF	Summary of results	
Mortality: risk ratio for survival at 1 year (values above 1 favour SABR)									
1 (Wang 2016)	RCT	Serious[1]	Not serious	N/A	Serious[2]	23	27	RR 1.38 (0.99, 1.92)	Low
Mortality: risk ratio for survival at 2 years (values above 1 favour SABR)									

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	CF	Summary of results	
1 (Wang 2016)	RCT	Serious[1]	Not serious	N/A	Serious[2]	23	27	RR 1.17 (0.72, 1.91)	Low

1. The method of randomisation was not given. The two arms were not balanced. For example the numbers of participants in each arm having various stages of NSCLC was: SABR: Ia, 7; IIb, 1; IIIa, 1; IIIb, 1; IV, 9. CF: Ia, 2; IIb, 4; IIIa, 4; IIIb, 12; IV, 2
2. 95% CI of the effect size crosses the line of no effect

Studies that only included people who were inoperable

Inoperable, stage II, IIIA, IIIB: chemo, CF 63 Gy (1.8 Gy, daily, 5 days a week) vs chemo, CF 69.6 Gy (1.2 Gy, 2x per day, 5 days a week)

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	CF 63 Gy (1.8 Gy, daily)	CF 69.6 Gy (1.2 Gy, 2x per day)	Summary of results	
Mortality: all-cause mortality hazard ratio (values above 1 favour CF 69.6 Gy (1.2 Gy, twice daily)									
1 (Curran 2011)	RCT	Not serious	Not serious	N/A	Serious[1]	193	187	HR 0.90 (0.73, 1.11)	Moderate
Adverse events grade 3 or above: acute toxicity: pulmonary (values above 1 favour CF 69.6 Gy (1.2 Gy, 2x per day))									
1 (Curran 2011)	RCT	Not serious	Not serious	N/A	Serious[1]	193	187	RR 1.70 (0.50, 5.70)	Moderate
Adverse events grade 3 or above: acute toxicity: oesophageal (values above 1 favour CF 69.6 Gy (1.2 Gy, 2x per day))									
1 (Curran 2011)	RCT	Not serious	Not serious	N/A	Not serious	193	187	RR 0.52 (0.38, 0.71)	High
Adverse events grade 3 or above: acute toxicity: cardiac (values above 1 favour CF 69.6 Gy (1.2 Gy, 2x per day))									
1 (Curran 2011)	RCT	Not serious	Not serious	N/A	Serious[1]	193	187	RR 0.14 (0.02, 1.11)	Moderate
Adverse events grade 3 or above: acute toxicity: mucositis (values above 1 favour CF 69.6 Gy (1.2 Gy, 2x per day))									
1 (Curran 2011)	RCT	Not serious	Not serious	N/A	Not serious	193	187	RR 0.48 (0.30, 0.79)	High
Adverse events grade 3 or above: late toxicity: pulmonary (values above 1 favour CF 69.6 Gy (1.2 Gy, 2x per day))									
1 (Curran 2011)	RCT	Not serious	Not serious	N/A	Serious[1]	193	187	RR 0.74 (0.44, 1.22)	Moderate
Adverse events grade 3 or above: late toxicity: oesophageal (values above 1 favour CF 69.6 Gy (1.2 Gy, 2x per day))									
1 (Curran 2011)	RCT	Not serious	Not serious	N/A	Serious[1]	193	187	RR 0.93 (0.31, 2.83)	Moderate
Adverse events grade 3 or above: late toxicity: cardiac (values above 1 favour CF 69.6 Gy (1.2 Gy, 2x per day))									
1 (Curran 2011)	RCT	Not serious	Not serious	N/A	Serious[1]	193	187	RR 0.46 (0.14, 1.52)	Moderate

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	CF 63 Gy (1.8 Gy, daily)	CF 69.6 Gy (1.2 Gy, 2x per day)	Summary of results	
1. 95% CI of the effect size crosses the line of no effect									

Inoperable, stage IIIA and IIIB: chemotherapy, CF 60 Gy (2 Gy, daily, 5 days a week) vs chemotherapy, CF 74 Gy (2 Gy, daily, 5 days a week)

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	CF 60 Gy	CF 74 Gy	Summary of results	
Mortality: all cause hazard ratio (values less than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Not serious	288	207	HR 1.38 (1.09, 1.75)	High
Adverse events grade 3 or above: radiation dermatitis within 90 days (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	288	207	RR 0.43 (0.10, 1.78)	Moderate
Adverse events grade 3 or above: dysphagia within 90 days (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Not serious	288	207	RR 0.26 (0.12, 0.54)	High
Adverse events grade 3 or above: dyspnoea within 90 days (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	288	207	RR 1.50 (0.77, 2.91)	Moderate
Adverse events grade 3 or above: oesophagitis within 90 days (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Not serious	288	207	RR 0.41 (0.24, 0.69)	High
Adverse events grade 3 or above: pneumonitis within 90 days (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	288	207	RR 1.75 (0.74, 4.13)	Moderate
Adverse events grade 3 or above: radiation recall reaction (dermatological) within 90 days (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Not serious	288	207	RR 0.09 (0.01, 0.71)	High
Adverse events grade 3 or above: desquamating rash within 90 days (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	288	207	RR 1.08 (0.31, 3.77)	Moderate
Adverse events grade 3 or above: dysphagia after day 90 (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	288	207	RR 0.74 (0.05, 11.70)	Moderate
Adverse events grade 3 or above: dyspnoea after day 90 (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	288	207	RR 0.74 (0.28, 1.93)	Moderate

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	CF 60 Gy	CF 74 Gy	Summary of results	
Adverse events grade 3 or above: pneumonitis after day 90 (values greater than 1 favour CF 74 Gy)									
1 (Bradley 2015)	RCT	Not serious	Not serious	N/A	Serious[1]	288	207	RR 1.47 (0.27, 7.96)	Moderate
1. 95% CI of the effect size crosses the line of no effect									

Inoperable, stage IIIA and IIIB: chemotherapy, CF 64 Gy (2 Gy, daily, 5 days a week) vs chemotherapy, HART 57.6 Gy (1.5 Gy, 3x per day, 5 days a week) (similar to CHARTWEL)

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	HART	CF	Summary of results	
Mortality: risk ratio for survival at 1 year (values above 1 favour HART)									
1 (Belani 2005)	RCT	Not serious	Not serious	N/A	Serious[1]	56	57	RR 1.32 (0.82, 2.10)	Moderate
Mortality: risk ratio for survival at 2 years (values above 1 favour HART)									
1 (Belani 2005)	RCT	Not serious	Not serious	N/A	Serious[1]	56	57	RR 1.30 (0.62, 2.72)	Moderate
Adverse events grade 3 and above: overall incidences (values below 1 favour HART)									
1 (Belani 2005)	RCT	Not serious	Not serious	N/A	Serious[1]	56	57	RR 0.73 (0.45, 1.19)	Moderate
Adverse events grade 3 and above: oesophagitis (values below 1 favour HART)									
1 (Belani 2005)	RCT	Not serious	Not serious	N/A	Serious[1]	56	57	RR 1.58 (0.75, 3.36)	Moderate
Adverse events grade 3 and above: pulmonary (values below 1 favour HART)									
1 (Belani 2005)	RCT	Not serious	Not serious	N/A	Serious[1]	56	57	RR 0.08 (0.00, 1.36)	Moderate
Adverse events grade 3 and above: skin (values below 1 favour HART)									
1 (Belani 2005)	RCT	Not serious	Not serious	N/A	Serious[1]	56	57	RR 0.34 (0.01, 8.15)	Moderate
1. 95% CI of the effect size crosses the line of no effect									

319 **Observational studies**

320 **Inoperable or refused surgery, stage I: SABR vs CF**

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	CF	Summary of results	
Mortality: all-cause hazard ratio (values below 1 favour SABR)									
3 (Koshy 2015, Tu 2017, Widder 2011)	Case-control, retrospective cohort, retrospective cohort	Serious[1]	Not serious	Very serious[2]	Serious[3]	1022	947	HR 0.61 (0.37, 1.00)	Very low
Mortality: all-cause risk ratio at 1 year (values below 1 favour SABR)									
1 (Jeppesen 2013)	Retrospective cohort	Very serious[4]	Not serious	N/A	Serious[3]	100	32	RR 0.72 (0.35, 1.50)	Very low
Mortality: all-cause risk ratio at 5 years (values below 1 favour SABR)									
1 (Jeppesen 2013)	Retrospective cohort	Very serious[4]	Not serious	N/A	Serious[3]	100	32	RR 0.73 (0.61, 0.87)	Very low
Mortality: cancer-specific risk ratio at 1 year (values below 1 favour SABR)									
1 (Jeppesen 2013)	Retrospective cohort	Very serious[4]	Not serious	N/A	Serious[3]	100	32	RR 0.48 (0.14, 1.60)	Very low
Mortality: risk ratio of survival at a median potential follow-up of 3 years									
1 (Lanni 2011)	Prospective cohort study	Serious[5]	Not serious	N/A	Not serious	45	41	RR 1.72 (1.14, 2.58)	Very low
Mortality: cancer-specific risk ratio at 5 years (values below 1 favour SABR)									

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	CF	Summary of results	
1 (Jeppesen 2013)	Retrospective cohort	Very serious[4]	Not serious	N/A	Not serious	100	32	RR 0.57 (0.40, 0.80)	Very low
Adverse events: all severe (severe oesophagitis) (values below 1 favour SABR)									
1 (Jeppesen 2013)	Retrospective cohort	Very serious[4]	Not serious	N/A	Serious[3]	100	32	RR 0.11 (0.00, 2.61)	Very low
Adverse events grade 3 or above: radiation pneumonitis (values below 1 favour SABR)									
1 (Tong 2015)	Retrospective cohort	Not serious	Not serious	N/A	Serious[3]	30	38	RR 0.18 (0.01, 3.35)	Very low
Health-related quality of life: change per year (values below 1 favour SABR)									
1 (Widder 2011)	Retrospective cohort	Very serious[6]	Not serious	N/A	Serious[2]	202	27	MD -3.80 (-9.34, 1.74)	Very low

1. Tu 2017: 87% of participants have comorbidities in the SABR arm compared to 75% in the CF arm. 60% of participants in the SABR arm have ECOG performance status 3 or 4. Performance status was not reported for the CF arm. Widder 2011: In the SABR arm, 21% had a WHO performance status of 2 or 3 compared to 7% in the CF arm. In Koshy 2015, performance status was not recorded.
2. The I^2 is 71% (over 50%)
3. 95% CI of the effect size either touches or crosses the line of no effect
4. Retrospective study. The mean tumour volume was on average twice as large for the CF group compared to the SABR group. (27.3 cm3 vs 12.9 cm3). In addition, the most people in the SABR group were T1 but most people in the CF group were T2
5. There was no discussion of how participants were selected for each arm. Mortality is measured as the overall survival at a median potential follow-up of 36 months. However, the average values could be different for each arm. In addition, this is an unusual measurement for mortality
6. Retrospective study. The people in the SABR arm were sicker compared to the CF arm: Twice as many people in the CF arm had a normal performance status. Three times as many people in the SABR arm had a performance status of 2-3

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Inoperable or refused surgery, stage I: SABR vs no therapy

Quality assessment						No of people		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	No therapy	Summary of results	
Mortality: all-cause risk ratio at 3 years (values below 1 favour SABR)									
1 (Koshy 2015)	Retrospective cohort	Serious[1]	Not serious	N/A	Not serious	773	6888	RR 0.72 (0.67, 0.77)	Very low

1. In the no therapy arm, 46.7% were T2 compared to 32.3% in the SABR arm.

Stage I: SABR vs lobectomy

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Lobectomy	Summary of results	
Mortality: all-cause hazard ratio (values above 1 favour lobectomy)									
9 (In Chen 2018: Eba 2016, Hamaji 2015, Mokhles 2015, Robinson 2013, Rosen 2016, Shirvani 2012, Shirvani 2014, Smith 2015. Not in Chen 2018: Bryant 2018)	Case-matched and retrospective cohort studies	Not serious	Not serious	Very serious[1]	Not serious	2642	2578	HR 1.62 (1.29, 2.04)	Very low
Mortality: all-cause risk ratio at 1 year (values above 1 favour lobectomy)									
1 (Cornwell)	Retrospective cohort	Very serious[2]	Not serious	N/A	Serious[3]	37	37	RR 2.00 (0.39, 10.26)	Very low
Mortality: all-cause risk ratio at 3 years (values above 1 favour lobectomy)									

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Lobectomy	Summary of results	
1 (Cornwell)	Retrospective cohort	Very serious[2]	Not serious	N/A	Not serious	37	37	RR 1.77 (1.07, 2.93)	Very low

1. The I^2 is 73% (over 66.7%)
2. Propensity matching in order to compare an arm that is largely medically inoperable (SABR) vs a medically operable arm. It is unlikely that everything can be adjusted for.
3. 95% CI of the effect size crosses the line of no effect.

325 **Stage I or II: SABR vs lobectomy**

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Lobectomy	Summary of results	
Mortality: all-cause hazard ratio (values above 1 favour lobectomy)									
1 (In Chen 2018: Verstegen 2013)	Case-match	Not serious	Not serious	N/A	Serious[1]	64	64	HR 1.09 (0.50, 2.37)	Very low

1. 95% CI of the effect size crosses the line of no effect.

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327 **Stage I: SABR vs sublobar resection**

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Sublobar resection	Summary of results	
Mortality: all-cause hazard ratio (values above 1 favour sublobar resection)									
6 (In Chen 2018: Matsuo 2014, Paul 2016, Puri 2015, Shirvani 2012, Smith 2015. Not in Chen 2018: Bryant 2018)	Case-matched and retrospective cohort studies	Not serious	Not serious	Serious[1]	Not serious	5164	5164	HR 1.35 (1.17, 1.56)	Very low

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Sublobar resection	Summary of results	
Mortality: risk ratio of mortality at 30 months (values above 1 favour sublobar resection)									
1 (Grills 2010)	Retrospective cohort study	Serious[2]	Not serious	N/A	Serious[3]	55	69	RR 2.09 (0.99, 4.41)	Very low

1. The I^2 is 47% (between 33.6% and 66.7%)
2. It is difficult to adjust for all confounders using a multivariate analysis in a study that compares participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.
3. 95% CI of the effect size crosses the line of no effect.

Stage I or II: SABR vs sublobar resection

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Sublobar resection	Summary of results	
Mortality: all-cause hazard ratio									
1 (In Chen 2018: Ezer 2015)	Retrospective cohort	Not serious	Not serious	N/A	Serious[1]	362	1881	HR 1.00 (0.85, 1.18)	Very low

1. 95% CI of the effect size crosses the line of no effect.

Stage I: SABR vs surgery (any)

Quality assessment						No of patients		Effect estimate	Quality
No of studies	Design	Risk of bias	Indirectness	Inconsistency	Imprecision	SABR	Surgery	Summary of results	
Mortality: all-cause hazard ratio (values over 1 favour surgery)									
1 (Van den Berg 2015)	Retrospective cohort	Very serious[1]	Not serious	N/A	Serious[2]	197	143	HR 1.07 (0.74, 1.54)	Very low
Mortality: risk ratio at 1 year (values over 1 favour surgery)									

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Surgery**	**Summary of results**	
1 (Wang 2016)	Case-control	Serious[3]	Not serious	N/A	Serious[2]	35	35	RR 2.00 (0.19, 21.06)	Very low
Mortality: risk ratio at 3 years (values over 1 favour surgery)									
1 (Wang 2016)	Case-control	Serious[3]	Not serious	N/A	Serious[2]	35	35	RR 2.14 (1.00, 4.61)	Very low
Mortality: risk ratio at 4 years (values over 1 favour surgery)									
1 (Puri 2012)	Case-control	Serious[3]	Not serious	N/A	Serious[2]	57	57	RR 1.25 (0.98, 1.59)	Very low
Mortality: risk ratio at 5 years (values over 1 favour surgery)									
1 (Wang 2016)	Case-control	Serious[3]	Not serious	N/A	Serious[2]	35	35	RR 1.64 (0.91, 2.94)	Very low

1. The SABR arm had people who were mostly not medically suitable for surgery. This population will be different to the patients who had surgery. It would be difficult to adjust for all confounding factors. The duration of follow-up is not mentioned.
2. 95% CI of the effect size crosses the line of no effect.
3. It is difficult to propensity match participants who are likely to be mostly medically inoperable in one arm (SABR) and operable in the other.

People aged 75 years or older, Stage I: SABR vs surgery (any)

Quality assessment						No of patients		Effect estimate	Quality
No of studies	**Design**	**Risk of bias**	**Indirectness**	**Inconsistency**	**Imprecision**	**SABR**	**Surgery**	**Summary of results**	
Mortality: all-cause hazard ratio									
1 (Nakagawa 2014)	Case-control	Serious[1]	Not serious	N/A	Serious[2]	35	183	HR 1.71 (0.98, 2.98)	Very low

1. There was no propensity matching. This is important because 22/35 SABR participants were medically inoperable. People undergoing surgery had a better performance status.
2. 95% CI of the effect size crosses the line of no effect.

Appendix G – Meta-analyses

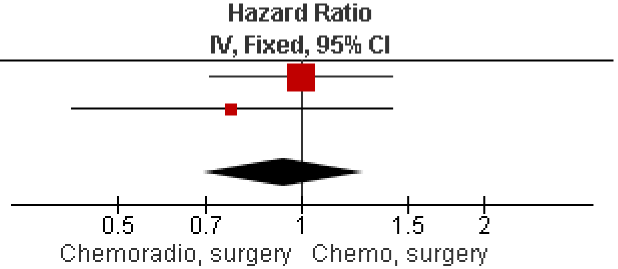
Randomised controlled trials

Operable, stage IIIA: chemotherapy, CF 40-46 Gy (1 or 2 fractions per day, 5 days a week), surgery vs chemotherapy, surgery

Mortality: all-cause hazard ratio

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Pless 2015	0	0.176823	75.3%	1.00 [0.71, 1.41]
Katakami 2012	-0.26136	0.308952	24.7%	0.77 [0.42, 1.41]
Total (95% CI)			**100.0%**	**0.94 [0.69, 1.27]**

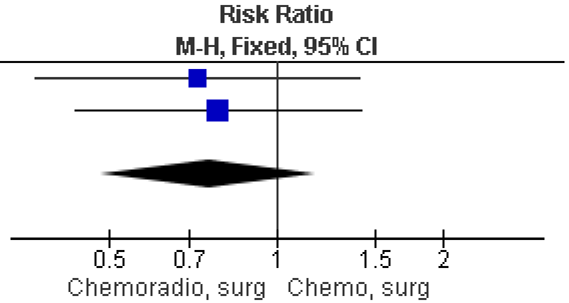
Heterogeneity: Chi² = 0.54, df = 1 (P = 0.46); I² = 0%
Test for overall effect: Z = 0.42 (P = 0.67)



Mortality: risk ratio for survival at 3 years

Study or Subgroup	Chemo, surgery Events	Chemo, surgery Total	Chemoradio, surg Events	Chemoradio, surg Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Girard 2010	6	14	19	32	45.2%	0.72 [0.37, 1.41]
Katakami 2012	11	28	14	28	54.8%	0.79 [0.44, 1.42]
Total (95% CI)		**42**		**60**	**100.0%**	**0.76 [0.49, 1.18]**
Total events	17		33			

Heterogeneity: Chi² = 0.03, df = 1 (P = 0.85); I² = 0%
Test for overall effect: Z = 1.23 (P = 0.22)



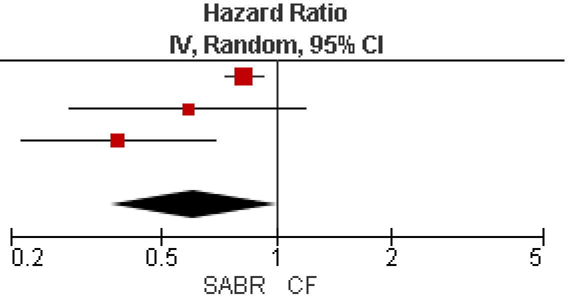
Observational studies

Inoperable or refused surgery, stage I or T1-T2 N0 M0: SABR vs CF

Mortality: all-cause hazard ratio

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
Koshy 2015	-0.19845	0.059013	46.6%	0.82 [0.73, 0.92]
Tu 2017	-0.53444	0.364292	24.3%	0.59 [0.29, 1.20]
Widder 2011	-0.95551	0.296723	29.1%	0.38 [0.22, 0.69]
Total (95% CI)			**100.0%**	**0.61 [0.37, 1.00]**

Heterogeneity: Tau² = 0.14; Chi² = 6.96, df = 2 (P = 0.03); I² = 71%
Test for overall effect: Z = 1.95 (P = 0.05)

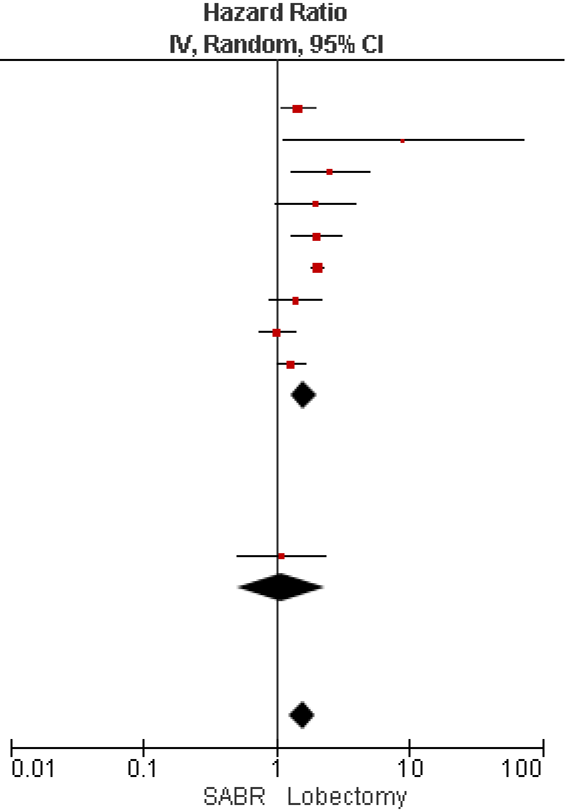


A randomised effects model was used because the I^2 is 71% (over 50%).

Stage I or II: SABR vs lobectomy

Mortality: all-cause hazard ratio

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Random, 95% CI
27.1.1 Stage I participants				
Bryant 2018	0.371564	0.147069	13.8%	1.45 [1.09, 1.93]
Eba 2016	2.197225	1.054136	1.1%	9.00 [1.14, 71.04]
Hamaji 2015	0.940007	0.341686	6.8%	2.56 [1.31, 5.00]
Mokhles 2015	0.678034	0.351057	6.6%	1.97 [0.99, 3.92]
Robinson 2013	0.693147	0.220042	10.7%	2.00 [1.30, 3.08]
Rosen 2016	0.708036	0.060006	17.1%	2.03 [1.80, 2.28]
Shirvani 2012	0.34359	0.230323	10.3%	1.41 [0.90, 2.21]
Shirvani 2014	0.00995	0.158977	13.3%	1.01 [0.74, 1.38]
Smith 2015	0.262364	0.128284	14.6%	1.30 [1.01, 1.67]
Subtotal (95% CI)			**94.4%**	**1.62 [1.29, 2.04]**
Heterogeneity: Tau² = 0.07; Chi² = 30.07, df = 8 (P = 0.0002); I² = 73%				
Test for overall effect: Z = 4.11 (P < 0.0001)				
27.1.2 Stage I and II participants				
Verstegen 2013	0.086178	0.39587	5.6%	1.09 [0.50, 2.37]
Subtotal (95% CI)			**5.6%**	**1.09 [0.50, 2.37]**
Heterogeneity: Not applicable				
Test for overall effect: Z = 0.22 (P = 0.83)				
Total (95% CI)			**100.0%**	**1.58 [1.27, 1.98]**
Heterogeneity: Tau² = 0.07; Chi² = 31.45, df = 9 (P = 0.0002); I² = 71%				
Test for overall effect: Z = 4.05 (P < 0.0001)				
Test for subgroup differences: Chi² = 0.92, df = 1 (P = 0.34), I² = 0%				



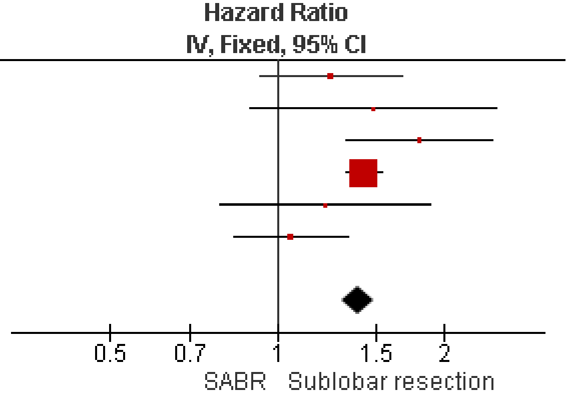
A randomised effects model was used because the I^2 is 71% (over 50%).

Stage I: SABR vs sublobar resection

Mortality: all-cause hazard ratio

Study or Subgroup	log[Hazard Ratio]	SE	Weight	Hazard Ratio IV, Fixed, 95% CI
Bryant 2018	0.223144	0.150858	5.2%	1.25 [0.93, 1.68]
Matsuo 2014	0.398776	0.258576	1.8%	1.49 [0.90, 2.47]
Paul 2016	0.587787	0.153753	5.0%	1.80 [1.33, 2.43]
Puri 2015	0.357674	0.03905	77.4%	1.43 [1.32, 1.54]
Shirvani 2012	0.198851	0.222525	2.4%	1.22 [0.79, 1.89]
Smith 2015	0.058269	0.119139	8.3%	1.06 [0.84, 1.34]
Total (95% CI)			**100.0%**	**1.40 [1.31, 1.49]**

Heterogeneity: $Chi^2 = 9.42$, $df = 5$ ($P = 0.09$); $I^2 = 47\%$
Test for overall effect: $Z = 9.73$ ($P < 0.00001$)



A fixed effects model was used because the I^2 is 47% (under 50%).

Appendix H – Excluded Studies

Excluded clinical studies

Randomised controlled trials

Study	Title	Reason for exclusion
Auperin 2010	Meta-analysis of concomitant versus sequential radiochemotherapy in locally advanced non-small-cell lung cancer	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Brock 2008	Review of hypofractionated small volume radiotherapy for early-stage non-small cell lung cancer	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Burdett 2005	Postoperative radiotherapy in non-small-cell lung cancer: update of an individual patient data meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Cardona 2008	Palliative endobronchial brachytherapy for non-small cell lung cancer	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Chen 2015	Meta-analysis of postoperative adjuvant chemotherapy without radiotherapy in early stage non-small cell lung cancer	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Chi 2017	Comparison of particle beam therapy and stereotactic body radiotherapy for early stage non-small cell lung cancer: A systematic review and hypothesis-generating meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Chun 2017	Impact of Intensity-Modulated Radiation Therapy Technique for Locally Advanced Non-Small-Cell Lung Cancer: A Secondary Analysis of the NRG Oncology RTOG 0617 Randomized Clinical Trial	This is a non-randomised subgroup analysis of Bradley 2015
Crabtree 2014	Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy	Retrospective study. For example, a database was searched (it is not possible to know the decision behind which intervention they received)
Deng 2017	Radiotherapy, lobectomy or sublobar resection? A meta-	This systematic review includes studies that do not match the protocol (pre-

Study	Title	Reason for exclusion
	analysis of the choices for treating stage I non-small-cell lung cancer	2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Fairchild 2008	Palliative thoracic radiotherapy for lung cancer: a systematic review	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Falkson 2017	Radiotherapy With Curative Intent in Patients With Early-stage, Medically Inoperable, Non-Small-cell Lung Cancer: A Systematic Review	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Gomez 2016	Local consolidative therapy versus maintenance therapy or observation for patients with oligometastatic non-small-cell lung cancer without progression after first-line systemic therapy: a multicentre, randomised, controlled, phase 2 study	This study compared radiotherapy to surgery. The radiotherapy technique used was left to the discretion of the clinical radiologist. The supplementary document shows that different methods of radiotherapy were used using diverse dosing regimens
Grills 2010	Outcomes after stereotactic lung radiotherapy or wedge resection for stage I non-small-cell lung cancer	The control arm participants were selected retrospectively
Grutters 2010	Comparison of the effectiveness of radiotherapy with photons, protons and carbon-ions for non-small cell lung cancer: a meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Kaster 2015	Radical-intent hypofractionated radiotherapy for locally advanced non-small-cell lung cancer: a systematic review of the literature	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Li 2017	Stereotactic body radiotherapy or stereotactic ablative radiotherapy versus surgery for patients with T1-3N0M0 non-small cell lung cancer: a systematic review and meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Liang 2010	Chemo-radiotherapy for advanced non-small cell lung cancer: concurrent or sequential? It's no longer the question: a systematic review	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Lin 2013	Dose escalation of accelerated hypofractionated three-dimensional conformal radiotherapy (at 3 Gy/fraction) with concurrent vinorelbine and carboplatin chemotherapy in unresectable	This is a small dose escalation study. All participants were in the same arm

Study	Title	Reason for exclusion
	stage III non-small-cell lung cancer: A phase I trial	
Mauguen 2012	Hyperfractionated or accelerated radiotherapy in lung cancer: an individual patient data meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Palma 2012	Curative treatment of Stage I non-small-cell lung cancer in patients with severe COPD: stereotactic radiotherapy outcomes and systematic review	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Patel 2014	Evidence supporting contemporary post-operative radiation therapy (PORT) using linear accelerators in N2 lung cancer	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Pezzetta 2005	Comparison of neoadjuvant cisplatin-based chemotherapy versus radiochemotherapy followed by resection for stage III (N2) NSCLC	Non-RCT and does not involve SABR
Port 2014	A propensity-matched analysis of wedge resection and stereotactic body radiotherapy for early stage lung cancer	Retrospective study. For example, a database was searched (it is not possible to know the decision behind which intervention they received)
Pottgen 2017	Definitive radiochemotherapy versus surgery within multimodality treatment in stage III non-small cell lung cancer (NSCLC) - a cumulative meta-analysis of the randomized evidence	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Puri 2012	A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis	Retrospective study. For example, a database was searched (it is not possible to know the decision behind which intervention they received)
Ramroth 2016	Dose and Fractionation in Radiation Therapy of Curative Intent for Non-Small Cell Lung Cancer: Meta-Analysis of Randomized Trials	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Ren 2015	Randomized controlled trials of induction treatment and surgery versus combined chemotherapy and radiotherapy in stages IIIA-N2 NSCLC: a systematic review and meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Rowell 2017	Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or	This review was withdrawn

Study	Title	Reason for exclusion
	declining surgery (medically inoperable)	
Sakib 2018	Effect of postoperative radiotherapy on outcome in resectable stage IIIA-N2 non-small-cell lung cancer: An updated meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Shah 2012	Induction chemoradiation is not superior to induction chemotherapy alone in stage IIIA lung cancer	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Singh 2017	A Phase 2 Randomized Study of 2 Stereotactic Body Radiation Therapy Regimens for Medically Inoperable Patients With Node-Negative, Peripheral Non-Small Cell Lung Cancer	Conference abstract
Stephens 2005	A randomised controlled trial of pre-operative chemotherapy followed, if feasible, by resection versus radiotherapy in patients with inoperable stage T3, N1, M0 or T1-3, N2, M0 non-small cell lung cancer	This study compared radiotherapy to surgery. The radiotherapy technique used was left to the discretion of the clinical radiologist. The regimens varied between 28 Gy in 8 fractions to 50 Gy in 20 fractions. There are no details of how many participants received what regimen
Wang 2005	Late course three-dimensional conformal radiotherapy in patients with stage III non-small cell lung cancer	Not written in English
Wang 2008	Three-dimensional conformal radiotherapy combined with stereotactic radiotherapy for locally advanced non-small cell lung cancer: efficacy and complications	Not written in English
Wang 2017	Cardiac Toxicity After Radiotherapy for Stage III Non-Small-Cell Lung Cancer: Pooled Analysis of Dose-Escalation Trials Delivering 70 to 90 Gy	Non-systematic review of dose escalation studies. The reference list was searched for studies that might meet our inclusion criteria
Wang 2017	Sublobar resection is associated with improved outcomes over radiotherapy in the management of high-risk elderly patients with Stage I non-small cell lung cancer: a systematic review and meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Wen 2017	A Propensity-Matched Analysis of Outcomes of Patients with Clinical Stage I Non-Small Cell Lung Cancer Treated surgically or with	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria

Study	Title	Reason for exclusion
	stereotactic radiotherapy: A Meta-Analysis	
Widder 2011	Survival and quality of life after stereotactic or 3D-conformal radiotherapy for inoperable early-stage lung cancer	The control arm was gathered prospectively 10 years before the treatment arm. Therefore, the control arm is a retrospective selection
Xu 2015	Is There a Survival Benefit in Patients With Stage IIIA (N2) Non-small Cell Lung Cancer Receiving Neoadjuvant Chemotherapy and/or Radiotherapy Prior to Surgical Resection: A Systematic Review and Meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Yu 2014	Accelerated hypofractionated 3-dimensional conformal radiotherapy vs conventional radiotherapy in locally advanced non-small cell lung cancer using PET/CT-derived plan: a prospectively randomized controlled trial	Not written in English
Yu 2017	Survival Outcome after Stereotactic Body Radiation Therapy and Surgery for Early Stage Non-Small Cell Lung Cancer: A Meta-Analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Zhang 2011	Which is the optimal biologically effective dose of stereotactic body radiotherapy for Stage I non-small-cell lung cancer? A meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Zhang 2012	Non-conventional radiotherapy versus conventional radiotherapy for inoperable non-small-cell lung cancer: A meta-analysis of randomized clinical trials	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Zhang 2014	Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Zhang 2015	A meta-analysis comparing hyperfractionated vs. conventional fractionated radiotherapy in non-small cell lung cancer	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Zhang 2015	Full-dose pemetrexed plus cisplatin combined with concurrent thoracic radiotherapy for previously untreated advanced nonsquamous non-small cell lung cancer	Retrospective study. For example, a database was searched (it is not possible to know the decision behind which intervention they received)

Study	Title	Reason for exclusion
Zhao 2016	Treatment-Related Death during Concurrent Chemoradiotherapy for Locally Advanced Non-Small Cell Lung Cancer: A Meta-Analysis of Randomized Studies	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Zheng 2014	Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/retrospective/single arm). However, the reference list was searched for studies that match the criteria
Zhu 2014	Sequential chemoradiotherapy with accelerated hypofractionated radiotherapy compared to concurrent chemoradiotherapy with standard radiotherapy for locally advanced non-small cell lung cancer	The two prospective arms were selected retrospectively from different studies

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367 **Observational studies**

Study	Title	Reason for exclusion
Alite 2016	Local control dependence on consecutive vs. nonconsecutive fractionation in lung stereotactic body radiation therapy	Study looks at timings using the same radiotherapy technique, dose and fractionation
Alongi 2018	Stereotactic body radiotherapy for lung oligometastases: Literature review according to PICO criteria	This systematic review has single-arm studies. However, the reference list was searched for studies that meet our inclusion criteria.
Annede 2017	Flattening Filter Free vs. Flattened Beams for Lung Stereotactic Body Radiation Therapy	Both arms have SABR with a small technical difference in each arm
Anonymous 2014	PL03.05 An intergroup randomized phase III comparison of standard-dose (60 Gy) vs high-dose (74 Gy) chemoradiotherapy (CRT) +/- cetuximab (cetux) for stage III non-small cell lung cancer (NSCLC): results on cetux from RTOG 0617	Conference abstract
Bi 2016	Comparison of the Effectiveness of Radiofrequency Ablation With Stereotactic Body Radiation Therapy in Inoperable Stage I Non-Small Cell Lung Cancer: A Systemic Review and Pooled Analysis	This systematic review includes studies that do not match the protocol (pre-2005/single arm). However, the reference list was searched for studies that match the criteria
Borst 2009	Radiation pneumonitis in patients treated for malignant pulmonary lesions with hypofractionated radiation therapy	Study includes malignant pulmonary lesions from all causes

Study	Title	Reason for exclusion
Chen 2013	Involved-field radiotherapy versus elective nodal irradiation in combination with concurrent chemotherapy for locally advanced non-small cell lung cancer: a prospective randomized study	Does not involve SABR
Chi 2016	Definitive Upfront Stereotactic Ablative Radiotherapy Combined with Image-Guided, Intensity Modulated Radiotherapy (IG-IMRT) or IG-IMRT Alone for Locally Advanced Non-Small Cell Lung Cancer	Single arm study
Counago 2018	Neoadjuvant treatment followed by surgery versus definitive chemoradiation in stage IIIA-N2 non-small-cell lung cancer: A multi-institutional study by the oncologic group for the study of lung cancer (Spanish Radiation Oncology Society)	Does not involve SABR
Crabtree 2010	Stereotactic body radiation therapy versus surgical resection for stage I non-small cell lung cancer	This study has already been included in the included systematic reviews
Crabtree 2014	Analysis of first recurrence and survival in patients with stage I non-small cell lung cancer treated with surgical resection or stereotactic radiation therapy	This study has already been included in the included systematic reviews
Daly 2011	Impact of neoadjuvant chemoradiotherapy followed by surgical resection on node-negative T3 and T4 non-small cell lung cancer	Does not involve SABR
Deng 2017	Radiotherapy, lobectomy or sublobar resection? A meta-analysis of the choices for treating stage I non-small-cell lung cancer	We have already included the studies in this systematic review
Donovan 2018	Stereotactic body radiation therapy (SBRT) in the management of non-small-cell lung cancer: Clinical impact and patient perspectives	We have already included the studies in this systematic review
Eba 2016	Stereotactic body radiotherapy versus lobectomy for operable clinical stage IA lung adenocarcinoma: comparison of survival outcomes in two clinical	This study has already been included in the included systematic reviews

Study	Title	Reason for exclusion
	trials with propensity score analysis (JCOG1313-A)	
Ezer 2015	Outcomes after Stereotactic Body Radiotherapy versus Limited Resection in Older Patients with Early-Stage Lung Cancer	This study has already been included in the included systematic reviews
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	This is a study on SCLC, not NSCLC
Falkson 2017	Radiotherapy With Curative Intent in Patients With Early-stage, Medically Inoperable, Non-Small-cell Lung Cancer: A Systematic Review	This systematic review has single-arm studies. However, the reference list was searched for studies that meet our inclusion criteria.
Fang 2006	Comparison of outcomes for patients with medically inoperable Stage I non-small-cell lung cancer treated with two-dimensional vs. three-dimensional radiotherapy	Does not involve SABR
Fernandez 2012	Sublobar resection versus definitive radiation in patients with stage IA non-small cell lung cancer	Does not involve SABR
Fitzgerald 2016	A comparison of three different VMAT techniques for the delivery of lung stereotactic ablative radiation therapy	No outcomes of interest. This study only looked at dose statistics.
Fujii 2013	A retrospective comparison of proton therapy and carbon ion therapy for stage I non-small cell lung cancer	Does not involve SABR
Graham 2006	Stage I non-small cell lung cancer: Results for surgery in a patterns-of-care study in Sydney and for high-dose concurrent end-phase boost accelerated radiotherapy	Does not involve SABR
Gudbjartsson 2008	Early surgical results after pneumonectomy for non-small cell lung cancer are not affected by preoperative radiotherapy and chemotherapy	Does not involve SABR
Guo 2016	Neoadjuvant Chemoradiotherapy vesus Chemotherapy alone Followed by Surgery for Resectable Stage III Non-Small-Cell Lung Cancer: a Meta-Analysis	Does not involve SABR

Study	Title	Reason for exclusion
Hamaji 2015	Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage i lung cancer	This study has already been included in the included systematic reviews
Hansen 2017	A randomized phase II trial of concurrent chemoradiation with two doses of radiotherapy, 60Gy and 66Gy, concomitant with a fixed dose of oral vinorelbine in locally advanced NSCLC	Does not involve SABR
Harris 2014	A population-based comparative effectiveness study of radiation therapy techniques in stage III non-small cell lung cancer	Does not involve SABR
He 2016	119P: Feasibility and efficacy of helical IMRT for stage III non-small cell lung cancer in comparison with conventionally fractionated 3D-CRT	Conference abstract and does not involve SABR
Hegi 2018	Comparing the Outcomes of Stereotactic Ablative Radiotherapy and Non-Stereotactic Ablative Radiotherapy Definitive Radiotherapy Approaches to Thoracic Malignancy: A Systematic Review and Meta-Analysis	This systematic review has single-arm studies. However, the reference list was searched for studies that meet our inclusion criteria.
Hsia 2014	A population-based study of primary chemoradiotherapy in clinical stage III non-small cell lung cancer: intensity-modulated radiotherapy versus 3D conformal radiotherapy	Does not involve SABR
Hsie 2009	Definitive treatment of poor-risk patients with stage I lung cancer: a single institution experience	Does not involve SABR
Hu 2016	Is IMRT Superior or Inferior to 3DCRT in Radiotherapy for NSCLC? A Meta-Analysis	Does not involve SABR
Iwata 2010	High-dose proton therapy and carbon-ion therapy for stage I nonsmall cell lung cancer	Does not involve SABR
Jegadeesh 2016	Evaluating Intensity-Modulated Radiation Therapy in Locally Advanced Non-Small-Cell Lung Cancer: Results From the National Cancer Data Base	Does not involve SABR
Jeppesen 2018	Survival of localized NSCLC patients without active treatment or treated with SBRT	This study was not available at the time of the review but a copy has been requested. The

Study	Title	Reason for exclusion
		reported findings in the abstract will not change the recommendations.
Jeremic 2008	From conventionally fractionated radiation therapy to hyperfractionated radiation therapy alone and with concurrent chemotherapy in patients with early-stage nonsmall cell lung cancer	Does not involve SABR
Jeremic 2018	Induction Therapies Plus Surgery Versus Exclusive Radiochemotherapy in Stage IIIA/N2 Non-Small Cell Lung Cancer (NSCLC)	Does not involve SABR
Kale 2016	Cost of Intensity-modulated Radiation Therapy for Older Patients with Stage III Lung Cancer	Does not involve SABR
Kastelijn 2015	Clinical Outcomes in Early-stage NSCLC Treated with Stereotactic Body Radiotherapy Versus Surgical Resection	This study has already been included in the included systematic review
Kilburn 2016	Image guided radiation therapy may result in improved local control in locally advanced lung cancer patients	Does not involve SABR
Lagerwaard 2008	Outcomes of risk-adapted fractionated stereotactic radiotherapy for stage I non-small-cell lung cancer	Single arm study
Li 2017	Stereotactic body radiotherapy or stereotactic ablative radiotherapy versus surgery for patients with T1-3N0M0 non-small cell lung cancer: a systematic review and meta-analysis.	We have already included the studies in this systematic review
Ling 2016	Comparison of Toxicity Between Intensity-Modulated Radiotherapy and 3-Dimensional Conformal Radiotherapy for Locally Advanced Non-small-cell Lung Cancer	Does not involve SABR
Liu 2013	Chemotherapy and late course three dimensional conformal radiotherapy for treatment of patients with stage III non- small cell lung cancer	Does not involve SABR
Lucas 2014	Comparison of accelerated hypofractionation and stereotactic body radiotherapy for Stage 1 and	Single arm study

Study	Title	Reason for exclusion
	node negative Stage 2 non-small cell lung cancer (NSCLC)	
Ma 2016	Clinical outcomes of video-assisted thoracic surgery and stereotactic body radiation therapy for early-stage non-small cell lung cancer: A meta-analysis	This systematic review includes studies that do not match the protocol (pre-2005/single arm). However, the reference list was searched for studies that match the criteria
Matsuo 2014	Comparison of long-term survival outcomes between stereotactic body radiotherapy and sublobar resection for stage I non-small-cell lung cancer in patients at high risk for lobectomy: A propensity score matching analysis	This study has already been included in the included systematic reviews
Miyazaki 2017	Surgery or stereotactic body radiotherapy for elderly stage I lung cancer? A propensity score matching analysis	Single arm study
Mokhles 2015	Comparison of clinical outcome of stage I non-small cell lung cancer treated surgically or with stereotactic radiotherapy: results from propensity score analysis	This study has already been included in the included systematic reviews
Monirul 2013	Outcomes following surgical treatment compared to radiation for stage I NSCLC: a SEER database analysis	Does not involve SABR
Movsas 2016	Quality of Life Analysis of a Radiation Dose-Escalation Study of Patients With Non-Small-Cell Lung Cancer: A Secondary Analysis of the Radiation Therapy Oncology Group 0617 Randomized Clinical Trial	Does not involve SABR
Palma 2011	Treatment of stage I NSCLC in elderly patients: a population-based matched-pair comparison of stereotactic radiotherapy versus surgery	This study has already been included in the included systematic reviews
Pan 2013	Clinical study on gefitinib combined with gamma-ray stereotactic body radiation therapy as the first-line treatment regimen for senile patients with adenocarcinoma of the lung (final results of JLY20080085)	Study involves a treatment that is not usual care
Paul 2016	Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population based	This study has already been included in the included systematic reviews

Study	Title	Reason for exclusion
	study with propensity matched comparative analysis	
Pezzi 2017	Radiation Therapy is Independently Associated with Worse Survival After R0-Resection for Stage I-II Non-small Cell Lung Cancer: An Analysis of the National Cancer Data Base	Does not involve SABR
Port 2014	A propensity-matched analysis of wedge resection and stereotactic body radiotherapy for early stage lung cancer	The selection criteria for the two arms of interest were not the same
Pottgen 2013	Accelerated hyperfractionated radiotherapy within trimodality therapy concepts for stage IIIA/B non-small cell lung cancer: Markedly higher rate of pathologic complete remissions than with conventional fractionation	Does not involve SABR
Robinson 2013	Patterns of failure after stereotactic body radiation therapy or lobar resection for clinical stage I non-small-cell lung cancer	This study has already been included in the included systematic reviews
Rosen 2016	Lobectomy versus stereotactic body radiotherapy in healthy patients with stage I lung cancer	This study has already been included in the included systematic reviews
Rowell 2015	Radical radiotherapy for stage I/II non-small cell lung cancer in patients not sufficiently fit for or declining surgery (medically inoperable)	Does not involve SABR
Semik 2004	Preoperative chemotherapy with and without additional radiochemotherapy: benefit and risk for surgery of stage III non-small cell lung cancer	Does not involve SABR
Shirvani 2012	Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly	This study has already been included in the included systematic reviews
Shirvani 2014	Lobectomy, sublobar resection, and stereotactic ablative radiotherapy for early-stage non-small cell lung cancers in the elderly	This study has already been included in the included systematic reviews
Smith 2015	Cost-effectiveness of stereotactic radiation, sublobar resection, and lobectomy for early non-small cell lung cancers in older adults	This study has already been included in the included systematic reviews

Study	Title	Reason for exclusion
Stephans 2009	A comparison of two stereotactic body radiation fractionation schedules for medically inoperable stage I non-small cell lung cancer: the Cleveland Clinic experience	This study did not compare SABR against a different radiotherapy technique nor against surgery
Stokes 2018	Post-treatment mortality after surgery and stereotactic body radiotherapy for early-stage non-small-cell lung cancer	Single arm study
Sun 2017	Comparison of 3D intensity-modulated radiation therapy and 3D conformal radiation therapy concurrently combined with chemotherapy for stage III non-small cell lung cancer	Does not involve SABR
Toyooka 2012	Induction chemoradiotherapy is superior to induction chemotherapy for the survival of non-small-cell lung cancer patients with pathological mediastinal lymph node metastasis	Does not involve SABR
Van Schil 2005	Morbidity and mortality in the surgery arm of EORTC 08941 trial	Does not involve SABR
Varlotto 2013	Matched-pair and propensity score comparisons of outcomes of patients with clinical stage I non-small cell lung cancer treated with resection or stereotactic radiosurgery	No outcomes of interest: The SABR and surgery arms had the most different participants of any study we have seen in this review. For example, the SABR arm had people with stages T1-T2 but the surgery arms had people who were T1-T4. Therefore, the only meaningful data are from matched-pairs. For the matched-pair comparisons, the percentage survivals are given but without providing the number of participants in the matched-pairs, it is not possible to calculate a measure of certainty, which is required to give the data meaning.
Verstegen 2013	Stage I-II non-small-cell lung cancer treated using either stereotactic ablative radiotherapy (SABR) or lobectomy by video-assisted thoracoscopic surgery (VATS): outcomes of a propensity score-matched analysis	This study has already been included in the included systematic reviews
Wang 2016	Intensity-Modulated Radiation Therapy May Improve Local-Regional Tumor Control for Locally Advanced Non-Small Cell Lung Cancer Compared With Three-Dimensional Conformal Radiation Therapy	Does not involve SABR

Study	Title	Reason for exclusion
Wang 2016	Prospective Study of Patient-Reported Symptom Burden in Patients With Non-Small-Cell Lung Cancer Undergoing Proton or Photon Chemoradiation Therapy	Does not involve SABR
Wang 2018	Stereotactic ablative radiotherapy versus lobectomy for stage I non-small cell lung cancer: A systematic review	We have already included the studies in this systematic review
Wijsman 2017	Comparison of toxicity and outcome in advanced stage non-small cell lung cancer patients treated with intensity-modulated (chemo-)radiotherapy using IMRT or VMAT	Does not involve SABR
Wolff 2018	Differences in Longitudinal Health Utility between Stereotactic Body Radiation Therapy and Surgery in Stage I Non-Small Cell Lung Cancer	No outcomes of interest. The quality of life data is not provided in numerical form. It is presented as very small graphs.
Yang 2015	Clinical outcomes of surgery after induction treatment in patients with pathologically proven N2-positive stage III non-small cell lung cancer	Does not involve SABR
Yendamuri 2007	Comparison of limited surgery and three-dimensional conformal radiation in high-risk patients with stage I non-small cell lung cancer	Does not involve SABR
Yu 2017	Survival Outcome after Stereotactic Body Radiation Therapy and Surgery for Early Stage Non-Small Cell Lung Cancer: A Meta-Analysis	One of the studies in this systematic review does not meet our inclusion criteria: the inclusion criteria were different for each arm in Port 2014. We have already included the remaining studies in this systematic review.
Yuan 2007	A randomized study of involved-field irradiation versus elective nodal irradiation in combination with concurrent chemotherapy for inoperable stage III nonsmall cell lung cancer	Does not involve SABR
Zhang 2011	Which is the optimal biologically effective dose of stereotactic body radiotherapy for stage I non-small-cell lung cancer? A meta-analysis	This systematic review has single-arm studies. However, the reference list was searched for studies that meet our inclusion criteria.
Zhang 2014	Matched-pair comparisons of stereotactic body radiotherapy (SBRT) versus surgery for the treatment of early stage non-small cell lung cancer: a systematic review and meta-analysis	This systematic review has single-arm studies. However, the reference list was searched for studies that meet our inclusion criteria.

Study	Title	Reason for exclusion
Zheng 2014	Survival outcome after stereotactic body radiation therapy and surgery for stage I non-small cell lung cancer: a meta-analysis	This systematic review has single-arm studies. However, the reference list was searched for studies that meet our inclusion criteria.

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369 Excluded economic studies

Paper	Primary reason for exclusion
Bijlani, A., Aguzzi, G., Schaal, D. and Romanelli, P., 2013. Stereotactic radiosurgery and stereotactic body radiation therapy cost-effectiveness results. Frontiers in oncology, 3, p.77.	Not a cost-utility analysis that met the PICO criteria.
Boily, G., Filion, É., Rakovich, G., Kopek, N., Tremblay, L., Samson, B., Goulet, S., Roy, I. and Comité de l'évolution des pratiques en oncologie, 2015. Stereotactic ablative radiation therapy for the treatment of early-stage non–small-cell lung cancer: CEPO review and recommendations. Journal of Thoracic Oncology, 10(6), pp.872-882.	Not a cost-utility analysis that met the PICO criteria.
Bongers, M.L., de Ruysscher, D., Oberije, C., Lambin, P., Uyl-de Groot, C.A., Belderbos, J. and Coupé, V.M., 2017. Model-based cost-effectiveness of conventional and innovative chemo-radiation in lung cancer. International journal of technology assessment in health care, 33(6), pp.681-690.	Not a cost-utility analysis that met the PICO criteria.
Chang, J.Y., Senan, S., Paul, M.A., Mehran, R.J., Louie, A.V., Balter, P., Groen, H.J., McRae, S.E., Widder, J., Feng, L. and van den Borne, B.E., 2015. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. The Lancet Oncology, 16(6), pp.630-637.	Not a cost-utility analysis that met the PICO criteria.
Chang, J.Y., Senan, S., Smit, E.F. and Roth, J.A., 2016. Stereotactic radiotherapy or surgery for early-stage non-small-cell lung cancer–Authors' reply. The Lancet Oncology, 17(2), pp.e42-e43.	Not a cost-utility analysis that met the PICO criteria.
Chang, J.Y., Senan, S., Smit, E.F. and Roth, J.A., 2016. Stereotactic radiotherapy or surgery for early-stage non-small-cell lung cancer–Authors' reply. The Lancet Oncology, 17(2), pp.e42-e43.	Not a cost-utility analysis that met the PICO criteria.
Chen, H., Louie, A.V., Boldt, R.G., Rodrigues, G.B., Palma, D.A. and Senan, S., 2016. Quality of life after stereotactic ablative radiotherapy for early-stage lung cancer: a systematic review. Clinical lung cancer, 17(5), pp.e141-e149.	Not a cost-utility analysis that met the PICO criteria.
Chouaid, C., Atsou, K., Hejblum, G. and Vergnenegre, A., 2009. Economics of treatments for non-small cell lung cancer. Pharmacoeconomics, 27(2), pp.113-125.	

Paper	Primary reason for exclusion
Claassens, L., Van Meerbeeck, J., Coens, C., Quinten, C., Ghislain, I., Sloan, E.K., Wang, X.S., Velikova, G. and Bottomley, A., 2011. Health-related quality of life in non–small-cell lung cancer: An update of a systematic review on methodologic issues in randomized controlled trials. Journal of Clinical Oncology, 29(15), p.2104.	Not a cost-utility analysis that met the PICO criteria.
Hechtner, M., Krause, M., König, J., Appold, S., Hornemann, B., Singer, S. and Baumann, M., 2017. Long-term quality of life in inoperable non-small cell lung cancer patients treated with conventionally fractionated compared to hyperfractionated accelerated radiotherapy–Results of the randomized CHARTWEL trial. Radiotherapy and Oncology.	Not a cost-utility analysis that met the PICO criteria.
Lanni Jr, T.B., Grills, I.S., Kestin, L.L. and Robertson, J.M., 2011. Stereotactic radiotherapy reduces treatment cost while improving overall survival and local control over standard fractionated radiation therapy for medically inoperable non-small-cell lung cancer. American journal of clinical oncology, 34(5), pp.494-498.	Not a cost-utility analysis that met the PICO criteria.
Lester-Coll, N.H., Dosoretz, A.P., Magnuson, W.J., Laurans, M.S., Chiang, V.L. and Yu, J.B., 2016. Cost-effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for up to 10 brain metastases. Journal of neurosurgery, 125(Supplement 1), pp.18-25.	Not a cost-utility analysis that met the PICO criteria.
Lievens, Y., Kesteloot, K. and Van den Bogaert, W., 2005. CHART in lung cancer: economic evaluation and incentives for implementation. Radiotherapy and oncology, 75(2), pp.171-178.	Not a cost-utility analysis that met the PICO criteria.
Miller, J.A., Kotecha, R. and Suh, J.H., 2016. Comparative effectiveness of stereotactic radiosurgery versus whole-brain radiation therapy for patients with brain metastases from breast or non–small cell lung cancer. Cancer, 122(20), pp.3243-3244.	Not a cost-utility analysis that met the PICO criteria.
Puri, V., Crabtree, T.D., Kymes, S., Gregory, M., Bell, J., Bradley, J.D., Robinson, C., Patterson, G.A., Kreisel, D., Krupnick, A.S. and Meyers, B.F., 2012. A comparison of surgical intervention and stereotactic body radiation therapy for stage I lung cancer in high-risk patients: a decision analysis. The Journal of thoracic and cardiovascular surgery, 143(2), pp.428-436.	Not a cost-utility analysis that met the PICO criteria.
Shirvani, S.M., Jiang, J., Chang, J.Y., Welsh, J.W., Gomez, D.R., Swisher, S., Buchholz, T.A. and Smith, B.D., 2012. Comparative effectiveness of 5 treatment strategies for early-stage non-small cell lung cancer in the elderly. International Journal of Radiation Oncology• Biology• Physics, 84(5), pp.1060-1070.	Not a cost-utility analysis that met the PICO criteria.
Smith, B.D., Jiang, J., Chang, J.Y., Welsh, J., Likhacheva, A., Buchholz, T.A., Swisher, S.G. and Shirvani, S.M., 2015. Cost-effectiveness of stereotactic radiation, sublobar resection, and lobectomy for early non-small cell lung cancers in older adults. Journal of geriatric oncology, 6(4), pp.324-331.	Not a cost-utility analysis that met the PICO criteria.

Paper	Primary reason for exclusion
van den Hout, W.B., Kramer, G.W., Noordijk, E.M. and Leer, J.W.H., 2006. Cost–Utility Analysis of Short-Versus Long-Course Palliative Radiotherapy in Patients With Non–Small-Cell Lung Cancer. Journal of the National Cancer Institute, 98(24), pp.1786-1794.	Not a cost-utility analysis that met the PICO criteria.
van Loon, J., Grutters, J.P., Wanders, R., Boersma, L., Dingemans, A.M.C., Bootsma, G., Geraedts, W., Pitz, C., Simons, J., Brans, B. and Snoep, G., 2010. 18FDG-PET-CT in the follow-up of non-small cell lung cancer patients after radical radiotherapy with or without chemotherapy: an economic evaluation. European Journal of Cancer, 46(1), pp.110-119.	Not a cost-utility analysis that met the PICO criteria.
Wernicke, A.G., Yondorf, M.Z., Parashar, B., Nori, D., Chao, K.C., Boockvar, J.A., Pannullo, S., Stieg, P. and Schwartz, T.H., 2016. The cost-effectiveness of surgical resection and cesium-131 intraoperative brachytherapy versus surgical resection and stereotactic radiosurgery in the treatment of metastatic brain tumors. Journal of neuro-oncology, 127(1), pp.145-153.	Not a cost-utility analysis that met the PICO criteria.

Appendix I – References

Clinical studies - randomised controlled trials - included

Baumann M, Herrmann T, Koch R, Matthiessen W, Appold S, Wahlers B, Kepka L, Marschke G, Feltl D, Fietkau R, Budach V, Dunst J, Dziadziuszko R, Krause M, and Zips D (2011) Final results of the randomized phase III CHARTWEL-trial (ARO 97-1) comparing hyperfractionated-accelerated versus conventionally fractionated radiotherapy in non-small cell lung cancer (NSCLC). Radiotherapy and oncology 100(1), 76-85

Belani C P, Wang W, Johnson D H, Wagner H, Schiller J, Veeder M, Mehta M, Eastern Cooperative Oncology, and Group (2005) Phase III study of the Eastern Cooperative Oncology Group (ECOG 2597): induction chemotherapy followed by either standard thoracic radiotherapy or hyperfractionated accelerated radiotherapy for patients with unresectable stage IIIA and B non-small-cell lung cancer. Journal of Clinical Oncology 23(16), 3760-7

Bradley J D, Paulus R, Komaki R, Masters G, Blumenschein G, Schild S, Bogart J, Hu C, Forster K, Magliocco A, Kavadi V, Garces Y I, Narayan S, Iyengar P, Robinson C, Wynn R B, Koprowski C, Meng J, Beitler J, Gaur R, Curran W, Jr , and Choy H (2015) Standard-dose versus high-dose conformal radiotherapy with concurrent and consolidation carboplatin plus paclitaxel with or without cetuximab for patients with stage IIIA or IIIB non-small-cell lung cancer (RTOG 0617): a randomised, two-by-two factorial phase 3 study. Lancet Oncology 16(2), 187-99

Chang J Y, Senan S, Paul M A, Mehran R J, Louie A V, Balter P, Groen H J, McRae S E, Widder J, Feng L, van den Borne , B E, Munsell M F, Hurkmans C, Berry D A, van Werkhoven , E , Kresl J J, Dingemans A M, Dawood O, Haasbeek C J, Carpenter L S, De Jaeger , K , Komaki R, Slotman B J, Smit E F, and Roth J A (2015) Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials.[Erratum appears in Lancet Oncol. 2015 Sep;16(9):e427; PMID: 26370351]. Lancet Oncology 16(6), 630-7

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Nyman J, Hallqvist A, Lund J A, Brustugun O T, Bergman B, Bergstrom P, Friesland S, Lewensohn R, Holmberg E, and Lax I (2016) SPACE - A randomized study of SBRT vs conventional fractionated radiotherapy in medically inoperable stage I NSCLC. Radiotherapy & Oncology 121(1), 1-8

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Clinical studies - observational studies - included

Bryant A K, Mundt R C, Sandhu A P, Urbanic J J, Sharabi A B, Gupta S, Daly M E, and Murphy J D (2018) Stereotactic Body Radiation Therapy Versus Surgery for Early Lung Cancer Among US Veterans. Annals of Thoracic Surgery 105(2), 425-431

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Appendix J – Health Economics Evidence Tables

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
			3D-CRT vs RFA				
Sher (2011) Patients with medically inoperable stage 1 NSCLC United States **Partially applicable** [a,b,c,d] **Potentially serious limitations** [e]	**Treatment effects** Local recurrence rate for Stereotactic Body Radiotherapy (SBRT) treatment was derived from long-tern follow-up data from the Indiana University Phase II SBRT trial. Local recurrence rate for Radiofrequency Ablation (RFA) obtained from Brown University. Conventional Radiotherapy (3D-CRT) from Washington University and Duke University. **Costs and resource use** Costs accrued in each health state were largely derived from publicly	Patient lifetime Markov model with 8 states Model created in TreeAge Pro. Both costs and outcomes discounted at 3% No conflicts of interest declared.	$ 4,194.00	0.08	$ 52,425.00	Given the data used in the model, SBRT is the most cost-effective treatment for medically inoperable Stage I NSCLC. The results are robust over a wide range of assumptions, including the efficacy of each treatment modality, natural history of Stage I Lung Cancer, health state utilities values, and costs.	The deterministic sensitivity analysis showed that in almost any scenario, SBRT was the most cost-effective option whilst RFA dominated the other two treatment options when its associated 3-year risk of local recurrence was 10%. The probabilistic sensitivity analysis consisting of 1,000 iterations showed that the probability that SBRT was cost-effective at a societal WTP of
			SBRT vs 3D-CRT				
			$ 2,291.00	0.38	$ 6,028.95		

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
	available 2009 Medicare payment schedules and related studies. Costs expressed in 2009 US dollars. **Utility** Utilities taken from Doyle et al. (2008). Utilities elicited from an English and Welsh population using the EQ-5D VAS and SG methods.						$50,000/QALY was 70%. SBRT was cost-effective in the majority of trials above a WTP of $30,000/QALY.

(a) US Study.
(b) Medicare perspective.
(c) Discount rate not in line with NICE reference case.
(d) QALYs derived using VAS and SG, not TTO.
(e) The cycle length of the model is not given.

Study, population, country and quality	**Data sources**	**Other comments**	**Scenario in which SABR is introduced**			**Conclusions**	**Uncertainty**
			Incremental Cost	**Incremental Effect**	**ICER (in QALYs)**		
Louie et al. (2014) Patients with stage I non-small cell lung cancer (NSCLC). Canada **Partially applicable** [a] **Very serious limitations** [b, c, d, e]	**Treatment effects** Survival by stage and histology were extracted from a review of the medical literature, and follow-up procedures were conducted in accordance with published provincial guidelines (Evans et al. (2013)). The Radiation Therapy Oncology Group (RTOG) 0236 multi-institutional SABR trial was used to model outcome for SABR patients. **Costs and resource use** Professional fees were obtained from the most recent edition of the Ontario schedule of fees and benefits (http://www.health.gov.on.ca/en/). Other direct and indirect health care costs abstracted in the previous version of the CRMM model were adjusted to reflect 2013 Canadian dollars using the consumer price index from the Bank of Canada.	Both costs and QALYs discounted annually at 3%. The model used a 10-year time horizon.	Radiotherapy			The authors concluded that while SABR is cost-effective for medically inoperable and borderline operable patients, lobectomy is preferred for those who are eligible. The use of SABR is thus projected to result in significant cost and survival gains at the population level.	The CRMM did not allow for probabilistic or deterministic sensitivity analyses.
			- $25,187,816	2,510 LY 1,693 QALYs	**Dominated**		
			Best supportive care				
			-$29,951,612	875 LY 660 QALYs	**Dominated**		
			Sublobar resection				
			-$23,288,656	3,385 LY 2,353 QALYs	**Dominated**		
			Lobectomy				
			-$164,370,264	-570 LY -294 QALYs	$55,909/QALY		

Study, population, country and quality	Data sources	Other comments	Scenario in which SABR is introduced			Conclusions	Uncertainty
			Incremental Cost	Incremental Effect	ICER (in QALYs)		
	Utility QALYs used in the model were derived using The Classification and Measurement System of Functional Health (CLAMES) from Evans et al. (2005).						

a) Canadian study
b) QALYs not derived using NICE's preferred methods.
c) Not clear which medical literature was used to inform the treatment effects.
d) This was a population level study rather than an individual patient level study.
e) The choice of the distributions for survival was not discussed.

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
Mitera et al. (2014) Patients with stage I NSCLC either ineligible or refused surgery. Canada **Partially applicable** [a,b,] **Very serious limitations** [c, d]	**Treatment effects** Data were retrospectively collected from an in-house research ethics board–approved prospective clinical database of patients with stage I medically inoperable NSCLC treated at the Princess Margaret Cancer Centre in Toronto, Ontario, Canada, from March 2002 to June 2010. All patients (n=168) were included if they received either a full course of CFRT (n=50) or SBRT (n=118), defined as having completed their prescribed dose of radiation. The median follow up of patients was 24 months. **Costs and resource use** Physician billing codes were derived from the Ontario Schedule of Benefits for Physician Services. Equipment costs, including the linear accelerator machine, computed tomography (CT) scanner, planning system, and abdominal compression board, were obtained using 2010 provincial costs.	The primary analysis conducted from the perspective of the Ontario Ministry of Health and Long-Term Care (MOHLTC; ie., public payer). A sub-analysis was conducted from the hospital perspective. Conventionally fractionated radiotherapy (CFRT) – patients received a total dose of approximately 50 to 70 Gy in over25 to 35 treatment sessions. Stereotactic body	SBRT vs CFRT (public payer perspective)			The authors concluded that using a threshold of $50,000 per LYG, SBRT seems cost effective and that the results require confirmation with randomized data.	In a one-way sensitivity analysis from the MOHLTC perspective, varying costs by 20%, the biggest drivers to influence the ICER were survival differences and direct labour costs. When survival for CFRT was decreased by 20%, the ICER became $742 per LYG; it became $4,558 per LYG when survival for SBRT was decreased by 20%. When survival was increased by 20% for CFRT, the ICER became $2,541 per LYG, it became $657 per LYG when survival for SBRT was increased by 20%. When the costs of direct labour for CFRT were both decreased and increased by 20%, the ICER was accordingly reflected as $1,845 and $452 per LYG, respectively; it was $253 and $2,940 per LYG when direct labour costs for SBRT were increased and decreased by 20%. Results for the two-way sensitivity analysis produced similar results. When the total cost for SBRT and incremental effectiveness were varied simultaneously by_30%, the
			$1,156	1.03 LY	$1,120 per LYG		
			SBRT vs CFRT (hospital perspective (radiation treatment delivery only))				
			$973	1.03 LY	$942 per LYG		

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
	Costs for the carbon fiber lung board were retrieved from the manufacturer. **Utility** Utility was not measured in this study. Instead, outcomes as a result of treatment effects were measured in life years (LY).	radiotherapy (SBRT) - patients received 48 to 60 Gy in three to eight treatments.					ICER ranged from a $936 cost savings per LYG for using SBRT to an incurred cost of $4,938 per LYG.

(a) Canadian study.
(b) QALYs are not used as an outcome measurement
(c) Treatment effect data were not from a randomised controlled trial.
(d) No discussion of the choice of survival assumptions

Study, population, country and quality	Data sources	Other comments	Incremental Cost (95% CI)	Incremental Effect (95% CI)	ICER	Conclusions	Uncertainty
Ramaekers et al. (2013) Patients with unresected NSCLC The Netherlands	**Treatment effects** Taken from the Meta-analysis of Radiotherapy in Lung Cancer (MAR-LC) database. This consist of 12 RCT's that compared conventional and modified fractionated RT's. **Costs and resource use** Costs and resource use in the model were taken from the MAR-LC database, the Dutch NSCLC guideline and expert opinion. Costs were calculated using the Dutch health care perspective and converted to the 2011 price level, based on price indices from Statistics Netherlands (CBS). **Utility** Utility scores were derived	Patient lifetime Markov model with 8 states. Cycle length of 1 month. Costs and outcomes discounted at 4% and 1.5% beyond the first year. No conflicts of interest declared.	Conventional Fractionation Radiotherapy (CRT)			The authors concluded that implementing accelerated RT is almost certainly more efficient than current practice CRT and should be recommended as standard RT for the curative treatment of unresected NSCLC patients not receiving concurrent chemo-radiotherapy.	MART had the highest probability of being cost effective (43%), followed by VART (31%), HRTI (24%), HRTH (2%), and CRT. The comparison of MART versus VART resulted in a 51% probability for MART and 49% probability for VART of being cost effective.
			-	-	-		
			Identical Hyperfractionated Radiotherapy (HRT[I]) vs CRT				
			€5,323 (€3,907 – €7,533)	0.02 (−0.20 to 0.28)	€228,852		
			Higher Hyperfractionated Radiotherapy (HRT[H]) vs CRT				
			€1,839 (€1212 – €2,699)	0.15 (−0.11 to 0.44)	€12,379		
			Very Accelerated Radiotherapy (VART) vs CRT				
			€1,386 (€957 – €1,982)	0.18 (0.05 to 0.32)	€7,592		
			Moderately Accelerated Radiotherapy (MART) vs CRT				
			€1,848 (€895 – €2,845)	0.20 (−0.35 to 0.87)	€9,214		

Study, population, country and quality	Data sources	Other comments	Incremental Cost (95% CI)	Incremental Effect (95% CI)	ICER	Conclusions	Uncertainty
Partially applicable [a] **Potentially serious limitations** [b, c]	from a Dutch cross-sectional study Grutters et al. 2011 (n = 260), which used the EQ-5D.						

a) Costs and outcomes discounted at 4% and 1.5% beyond the first year respectively.
b) Expert opinion used to elicit some of the model parameters.
c) The authors did not discuss their choice of distributions for survival analysis.

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
Shah et al. (2013) 65 year old patients with clearly operable (CO) and marginally operable (MO) stage I non-small cell lung cancer (NSCLC). United States **Partially applicable** [a,b,c] **Potentially serious limitations** [d,e]	**Treatment effects** The local recurrence rate (LR) for SBRT taken from Lagerwaard et al. (2012), a three-year study of potentially operable patients in The Netherlands. Probability for no evidence of disease (NED) to LR for wedge resection taken from Grills et al. (2010). Probability values for NED to locoregional recurrence (LRR) taken from Carr et al. (2012) and Arrigada et al. (2010). **Costs and resource use** Costs taken from Medicare payment schedules. All costs were inflated to 2012 US dollars using the Consumer Price Index (US Department of Labor. Bureau of Labor Statistics.) if necessary.	Model horizon 5 years. All costs and outcomes beyond first year discounted at 3% annually. Model created in TreeAge Pro 2010. Three treatment strategies in the model were lobectomy which is only considered for clearly operable patients (CO), wedge resection (WR) which is only considered for marginally operable patients (MO), and	SBRT-MO vs Wedge resection (base case)			The authors concluded that SBRT was nearly always the most cost-effective treatment strategy for MO patients with stage I NSCLC. In contrast, for patients with CO disease, lobectomy was the most cost-effective option.	<u>OWSA SBRT-MO vs Wedge resection</u> In almost any scenario, SBRT was the dominant (and thus the most cost-effective) strategy compared with wedge resection. SBRT remained borderline cost-effective when the cost associated with wedge resection was only $10,000 (ICER = $57,000/QALY). Wedge resection did become the cost-effective strategy when its 5-year risk of LR was 2% (ICER = $18,400/QALY) or the LR risk associated with SBRT was 20% (ICER = $5500/QALY).
			$-9,393	0.1	**Dominant**		
			Lobectomy vs SBRT-CO (base case)				
			$8,986	0.68	$13,214		

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
	Utility Utility scores taken from Doyle et al. (2008), who used the EQ-5D (via VAS and SG – not TTO as per NICE's preferred methods).	stereotactic body radiation therapy (SBRT). Analysis took a payer (Medicare) perspective.					OWSA SBRT-CO vs Lobectomy Under every assumption used in the model, lobectomy was more cost-effective compared with SBRT for patients who are CO. The ICER for lobectomy was below $50,000/QALY, well below any accepted societal WTP. Lobectomy was the clearly dominant strategy when the prevalence of nodal disease (N1 or N2) was 50%, cost of SBRT was $50,000, or cost of lobectomy was $10,000. None of these scenarios are likely, however.

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
							<u>PSA Wedge resection</u> The PSA assumed 2 conditions favorable to wedge resection: its local control rate relative to SBRT varied between 0.65 and 1, and its MS-DRG payment was the lowest possible between 50% and 75% of cases. Even with these favourable assumptions, SBRT was most likely to be the cost-effective strategy up to a WTP well beyond $500,000/QALY.

(a) US Study.
(b) Medicare perspective.
(c) Discount rate not in line with NICE reference case.
(d) The cycle length of the model is not given.
(e) Effectiveness data not from a randomised controlled trial.

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty

Study, population, country and quality	Data sources	Other comments	Incremental Cost (95% CI)	Incremental Effect (95% CI)	ICER	Conclusions	Uncertainty
Bongers et al. (2015) NSCLC patients with inoperable stage I-IIIB receiving curative sequential che- moradiation or radiation therapy alone. The Netherlands **Partially applicable** [a,b] **Potentially serious limitations** [c]	**Treatment effects** Treatment effects, tumour characteristics, toxicity and follow-up data were based on data of 200 patients from the Maastro Clinic data, collected between 2002 and 2009 (Dehing-Oberije (2009). **Costs and resource use** Resource use estimates were based on the data of the Maastro Clinic and the literature (Pompen (2009), Peeters (2010), Grutters (2010). Costs were based on the Dutch Manual for Costing in Economic Evaluations, the Dutch Healthcare Board, or the Pharmacotherpeutical Compass and the literature (Ploder (2006), Oosterbrink (2004), Dutch Healthcare Authority Tarrif (2016)	This study took a hospital perspective. The micro-simulation multi-state statistical model contained four health states and had a time horizon of 3 years. Treatments being compared are positron emission tomography (PET)-based isotoxic accelerated radiation therapy treatment (PET-ART) and conventional fixed-dose CT-based	PET-ART vs CRT €569	0.33 QALYs	€1,744/QALY	The authors concluded that according to the data available to them, PET-ART is likely to be more effective than CRT and seems to be cost-effective as well. There is a 64% probability that PET-ART is more costly, but the additional cost is limited. These findings can support decision makers to implement PET-ART schemes in radiation therapy treatment planning.	Of 1000 ICER and ICUR replicates, 36% of the replicates are in the lower right quadrant, indicating that PET- ART both improves outcomes and reduces costs. The remaining 64% is located in the upper right quadrant, indicating that PET-ART improves outcomes at increased costs compared with CRT. The cost-effectiveness acceptability curve shows that at a threshold value of €18,000 per QALY, there is a 95% probability that PET-ART is cost-effective.

Study, population, country and quality	Data sources	Other comments	Incremental Cost (95% CI)	Incremental Effect (95% CI)	ICER	Conclusions	Uncertainty
	and Zorginstituut Nederland (2012)). All costs were reported in Euros and the price year was 2012. **Utility** The utility estimates for the model were obtained from a meta-analysis of 23 studies of utilities in NSCLC patients (Sturza et al. (2010)) and from a cost-effectiveness study (Grutters et al. (2010)).	radiation therapy treatment (CRT). Costs and outcomes discounted at 3% beyond the first year. No conflicts of interest declared.					

(a) Costs and outcomes discounted at 3% beyond the first year.
(b) Not a UK study
(c) Model time horizon was 3 years and not patient life time.

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
Paix et al (2018) Patients with medically operable early stage non-small cell lung cancer. France **Partially applicable** a,b, **Very serious limitations** c,d	**Treatment effects** The authors derived probabilities of transition from PFS to Local Recurrence – Regional Recurrence and Distant Recurrence for SBRT and lobectomy from the pooled analysis of STARS and ROSEL, two randomized studies that compared SBRT and video assisted thoracoscopic surgery (VATS) lobectomy for operable stage I non-small cell lung cancer. Statistical method described by Guyot et al (2012) were used to retrieve raw data. **Costs and resource use** The SBRT initial cost was estimated based on the preparation of the treatment and the treatment in 5 fractions. Price year used was 2017 and all costs were expressed in Euros.	Markov model with cycle length of one month whilst using a patient lifetime horizon. No conflicts of interest were declared by any of the authors. The authors considered a willingness to pay ratio of €100,000/QALY The starting age of the cohort was 67 years old, as reported in the pooled results of STARS and ROSEL, which was	VATS vs SBRT VATS € 1,492.83 more expensive than SBRT	VATS -0.55 QALYs compared to SBRT	**VATS dominated compared to SBRT**	The authors concluded that their analyses suggest that SBRT is dominant over lobectomy in operable early-stage NSCLC treatment. Deterministic and probabilistic sensitivity analyses confirmed that this result was robust and that it was not modified by the assumptions made in the Markov model building.	A one-way sensitivity analysis found that the parameter that the model was most sensitive to be the initial cost of SBRT and VATS. The probabilistic sensitivity analysis and cost-effectiveness acceptability curve showed that SBRT was always more likely to be more cost-effective comparted to VATS at both willingness to pay threshold of €30,000 and €100,000 per QALY.

Study, population, country and quality	Data sources	Other comments	Incremental Cost	Incremental Effect	ICER	Conclusions	Uncertainty
	Utilities Progression free survival and recurrence health state utilities were from Doyle et al. (2008), a UK study. Utilities in this paper were derived using the EQ-5D.	consistent with WHO data.					

(a) French study
(b) Study conducted from a French payers perspective.
(c) The study included patient travel costs which we could not remove from the analysis.
(d) Both costs and QALYs were discounted at 4% per annum beyond the first year of the model.

Appendix K – Research recommendations

Question	What is the effectiveness and cost effectiveness of SABR compared to surgery (for example, sublobar, wedge resection, lobectomy) for operable patients with NSCLC (stage I and II)?
Population	Operable patients with NSCLC (stage I and II)
Characteristics of interest	• Overall survival • Health-related quality of life • Adverse events grade 3 or above • Safety
Study design	Randomised controlled trial

Potential criterion	Explanation
Importance to patients, service users or the population	Twenty seven percent of NSCLC are at stage 1A-2B at diagnosis, and therefore eligible for potentially radical treatment with curative intent. However, 47% of these patients are performance status 2 or more at diagnosis, and in 2016 of patients with a performance status of 0-1, only 61% received surgery (National Lung Cancer Audit, 2016). If a less invasive or more acceptable treatment than surgery was available with equivalent outcomes then more patients could receive potentially curative treatment.
Relevance to NICE guidance	Medium priority: a recommendation was made on the use of SABR for people with stage I–IIa (T1a–T2b, N0, M0) NSCLC in whom lobectomy is contraindicated or who decline it. Furthermore SABR has been recommended for people with stage I–IIa (T1a-T2b N0 M0) NSCLC in whom any surgery is contraindicated or who decline it. The additional information provided by an RCT study will strengthen the case for an

Potential criterion	Explanation
	additional treatment option to people with NSCLC (T1-2b, N0) in whom surgery is contraindicated or who decline it.
Current evidence base	There is a lack of RCT studies comparing SABR radiotherapy and surgery, either lobectomy or sublobar resections (wedge or segmentectomy procedures) therefore identifying a need for further research.
Equality	This study could improve equality of access to SABR and ensure that more people receive this potentially curative treatment.
Feasibility	There is a large enough population of people with this condition and SABR is available in current clinical practice.