NHS England

Evidence review: Stereotactic Ablative Radiotherapy for Non Small Cell Lung Cancer

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1. Introduction

- Stereotactic ablative radiotherapy (SABR) is a radiotherapy technique which targets a lesion more precisely than conventional radiotherapy. It involves the use of a high radiation dose delivered in a small number of fractions, and allows sparing of the surrounding healthy normal tissues. It is associated with lower rates of acute and late morbidity. The technique requires specialist positioning equipment and imaging (NHS England 2013).
- Primary lung cancer, which means the cancer first appeared in the lungs, is one of the most common and serious types of cancer. Over 44,000 people are diagnosed with the condition every year in the UK (NHS Choices 2017). Lung cancer mainly affects older people. Although people who have never smoked can develop lung cancer, smoking is the main cause, accounting for about 90% of cases (NHS Choices 2017).
- Primary lung cancers fall into two histological categories, small cell and non small cell. Non small cell lung cancer (NSCLC), the subject of this evidence review, is more common than small cell lung cancer, and usually spreads more slowly.
- The appropriate treatment for NSCLC depends on how far it has spread (the stage) and the general health of the patient. Treatment options include surgery, radiotherapy and chemotherapy. Treatment may be curative or palliative (NICE 2011).
- Early NSCLC is often treated with curative intent, either with surgery or other ablative techniques. More advanced disease is often treated with palliative chemotherapy (NICE 2011).
- In 2013, NHS England published a commissioning policy (NHSCB/B01/P/a) on the use of SABR as a treatment option in the management of patients with early NSCLC not suitable for surgery (NHS England 2013). However, NHS England does not commission SABR for NSCLC in patients suitable for surgery.
- NICE does not include SABR among the treatments which it recommends in its clinical guideline for NSCLC (NICE 2011).

2. Summary of results

- We found three systematic reviews of the use of SABR for NSCLC: one of SABR versus open surgery, one of SABR vs video-assisted thoracic surgery and one of the incidence of lung toxicity after SABR. We also found two controlled studies of SABR versus open surgery (one a randomised trial which also reported economic results and one an unrandomised comparison), two controlled studies of SABR versus video-assisted thoracic surgery and three studies reporting health economic results.
- Six studies reported overall survival:
    - *SABR with video-assisted thoracic surgery*: An unrandomised controlled comparison of SABR with video-assisted thoracic surgery by Paul et al (2016) reported better survival after surgery (hazard ratio (HR) 1.80, 95% confidence interval (CI) 1.33 to 2.43; $p < 0.001$). Hamaji et al (2015) published a similar study with similar results (HR 0.39 (surgery better), 95% CI 0.20 to 0.76, $p = 0.0051$). In this study, the three-year, five-year, and ten-year survival rates in VATS lobectomy patients were 80.1%, 68.5%, and 61.6%, respectively, compared with 52.7%, 37.3%, and 20.7% in SABR patients respectively ($p = 0.0016$). However, the meta-analysis by Ma et al (2016) reported no significant survival differences between SABR and video-assisted thoracic surgery (HR 2.02, 95% CI 1.45 to 3.07, $p = 0.47$; the authors state this result is non-

significant, although the 95% CI excludes an HR of 1).

  - *SABR versus open surgery*: Li et al (2017) reported a meta-analysis of SABR versus open surgery. Surgery was associated with better overall survival (HR 1.40, 95% CI 1.21 to 1.61, p < 0.001). This was corroborated by an unrandomised comparison of SABR and wedge resection, in which five-year survival was 31.0% after SABR (95% CI 26.1% to 36.0%), and 49.9% after wedge resection (95% CI 45.1% to 54.6%) (p < 0.0001) (Yerukan et al 2017). Smith et al (2015) reported an unrandomised comparison of SABR, sub-lobar resection and lobectomy, with no significant differences in survival between SABR and sublobar resection (p = 0.81).

- Recurrence-free survival[1] was reported as better after surgery in Li et al (2017)'s meta-analysis (HR 1.84, 95% CI 1.26 to 2.68, p = 0.02). Hamaji et al (2015) also reported better recurrence-free survival after surgery (HR 0.32, 95% CI 0.17 to 0.58. p = 0.0002). However, Ma et al (2016) reported no significant differences in recurrence-free survival after SABR and video-assisted thoracoscopic surgery (HR 0.42, 95% CI 0.21 to 1.12, p = 0.52).
- There was no significant difference in loco-regional recurrence[2] after surgery and SABR reported in Li et al (2017)'s meta-analysis (HR 1.17, 95% CI 0.68 to 1.98, p = 0.57), nor in distant recurrence (HR 1.36, 95% CI 0.77 to 2.39, p = 0.29).
- Global health status was reported as better after SABR than after surgery in Louie et al (2015)'s randomised trial (HR 0.19, p = 0.038). However, the apparent statistical significance of this result may well be because of multiple comparisons and it should be regarded as arising from chance.
- No significant difference in cancer-specific survival[3] after surgery and SABR was reported by Paul et al (2016), while Hamaji et al (2015) reported longer survival after surgery (respectively HR 1.32, 95% CI 0.77 to 2.26, p = 0.32, and HR 0.228, 95% CI 0.09 to 0.62, p = 0.0035).
- Local[4] and distant[5] control was reportedly better after surgery (respectively HR 0.13, 95% CI 0.029 to 0.59, p = 0.0077 and HR 0.17, 95% CI 0.069 to 0.43, p = 0.0002) (Hamaji et al 2015). These authors reported no significant differences in regional lymph node control[6] after surgery and after SABR (HR 0.33, 95% CI 0.082 to 1.33, p = 0.12).
- The incidence of radiation-induced lung toxicity was reported as 10.4% (95% CI 9.8% to 15.2%) (Zhao et al 2016).
- We found four health economic analyses:
  - Louie et al (2015)'s randomised trial reported higher productivity costs after open surgery than after SABR (SABR: €95 (£86.80), surgery €3513 (£3210), p = 0.044). The productivity cost is calculated from the perspective of the participant's employer and is of limited relevance to NHS decision-making.
  - Smith et al (2015)'s uncontrolled comparison reported the following incremental costs per life-year gained: SABR vs sublobar resection $45,683 (£35,100), 95% CI

[1] Recurrence-free survival is the proportion of participants alive with no apparent recurrent tumour at specified intervals after completion of SABR.
[2] Loco-regional recurrence is the appearance of new tumour at the site of the primary or elsewhere in the lung, after initial treatment is complete.
[3] Cancer-specific survival is survival without death from SCLC. All other causes of death are censored (i.e. disregarded in the analysis).
[4] Local control is the absence of radiological evidence of further growth of the cancer at its site of origin.
[5] Distant control is the absence of radiological evidence of new metastases from the primary tumour.
[6] Regional lymph node control is the absence of radiological evidence of further growth of the cancer in regional lymph nodes which drain the primary tumour.

-US$325,572 to $269,807 (-£250,400 to £207,500); SABR vs lobectomy $28,645 (£22,000), 95% CI -$119,828 to $207,822 (-£92,200 to £159,900).

  - Shah et al (2013)'s modelling paper reported an incremental cost per QALY for lobectomy compared with SABR of US$13,215 (£10,200).
  - Finally, Grutters et al (2010)'s modelling paper reported that SABR dominated carbon ion treatment, being both more effective and less expensive (SABR: €8,485 (£7,800), 3.20 QALYs; carbon ions: €14,620 (£13,400), 3.16 QALYs).

- Taken together, the evidence that we found indicates that open or video-assisted thoracoscopic surgery is probably more effective than SABR in the treatment of early stage NSCLC. It appears to be associated with longer survival, and better tumour control on some metrics.
- The health economic analyses suggest that surgery is also more cost effective than SABR.
- SABR has adverse effects but they do not appear to be common or serious enough to cast doubt on its suitability for use.

3. Methodology

- The methodology to undertake this review is specified by NHS England in their 'Guidance on conducting evidence reviews for Specialised Commissioning Products' (2016).
- A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) to be included in this review was prepared by NHS England's Policy Working Group for the topic (see section 9 for the PICO).
- The PICO was used to search for relevant publications in EMBASE, MEDLINE and the Cochrane Library (see section 10 for search strategy).
- The search dates for publications were between 1 January 2007 and 2 August 2017.
- The titles and abstracts of the results from the literature searches were assessed using the criteria from the PICO. Full text versions of papers which appeared potentially useful were obtained and reviewed to determine whether they were appropriate for inclusion. Higher quality papers which matched the PICO were selected for inclusion in this review.
- Evidence from all papers included was extracted and recorded in evidence summary tables, critically appraised and their quality assessed using National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework (see section 7 below).
- The body of evidence for individual outcomes identified in the papers was graded and recorded in grade of evidence tables (see section 8 below).

4. Results

We found three systematic reviews: one of SABR versus open surgery (Li et al 2017, 15 studies, n=7810), one of SABR vs video-assisted thoracic surgery (Ma et al 2016, 37 studies, n=7869) and one of the incidence of lung toxicity after SABR (Zhao et al 2016, 54 studies, n=7752). We also found two controlled studies of SABR versus open surgery, one a randomised trial which also reported economic results (Louie et al 2015) and one an unrandomised comparison (Yerukan et al 2017), two controlled studies of SABR versus video-assisted thoracic surgery (Paul et al 2016 and Hamaji et al 2015) and three health economic studies (Smith et al 2015, Shah et al 2013 and

Grutters et al 2010). Most studies were of people with stage I NSCLC.

What is the evidence on clinical effectiveness of using SABR compared with existing treatments for non small cell lung cancer histology, stages 1-3?

The clinical efficacy outcomes reported in the studies were overall survival, recurrence-free survival, cancer-specific survival, local control, regional lymph node control rate, distant control rate and rates of radiation-induced lung toxicity, radiation pneumonitis and lung fibrosis.

Overall survival

We found six studies which reported this outcome.

In a meta-analysis comparing SABR with video-assisted thoracic surgery, Ma et al (2016) reported no significant difference in survival after SABR and after video-assisted thoracic surgery (hazard ratio (HR) 2.02, 95% confidence interval (CI) 1.45 to 3.07, p = 0.47). The authors state this is non-significant, although the 95% CI excludes a HR of 1.

By contrast, Paul et al (2016)'s unrandomised controlled comparison of SABR with video-assisted thoracic surgery reported better survival after surgery (HR 1.80, 95% CI 1.33 to 2.43; p < 0.001). The three-year estimated overall survival rates were 52.2% after SABR and 68.4% after surgery (significance test not reported).

Hamaji et al (2015) also reported an unrandomised controlled comparison of SABR with video-assisted thoracic surgery. The HR was 0.39 (surgery better), 95% CI 0.20 to 0.76, p = 0.0051. In this study, the three-year, five-year, and ten-year survival rates in VATS lobectomy patients were 80.1%, 68.5%, and 61.6%, respectively; three-year, five-year, and ten-year rates in SABR patients were 52.7%, 37.3%, and 20.7%, respectively (p = 0.0016).

Li et al (2017) reported a meta-analysis of SABR versus open surgery. Surgery was associated with better overall survival (HR 1.40, 95% CI 1.21 to 1.61, p < 0.001).

This was corroborated by the unrandomised comparison of SABR and wedge resection (Yerukan et al 2017). At five years, survival was 31.0% after SABR (95% CI 26.1% to 36.0%, median 3.4 years), and 49.9% after wedge resection (95% CI 45.1% to 54.6%, median 5.0 years, p < 0.0001).

Smith et al (2015) reported an unrandomised comparison of SABR, sub-lobar resection and lobectomy. There were no significant differences in survival between SABR and sublobar resection (SABR 3.6 years, sublobar resection 4.1 years, p = 0.95), nor between SABR and lobectomy (SABR 3.8 years, lobectomy 4.7 years, p = 0.81).

Recurrence-free survival

Li et al 2017's meta-analysis reported better recurrence-free survival after surgery (HR 1.84, 95% CI 1.26 to 2.68, p = 0.02).

There was a similar finding from Hamaji et al (2015), who also reported better recurrence-free survival after surgery (HR 0.32, 95% CI 0.17 to 0.58. p = 0.0002).

However, Ma et al (2016) reported no significant differences in recurrence-free after SABR and video-assisted thoracoscopic surgery (HR 0.42, 95% CI 0.21 to 1.12, p = 0.52).

Loco-regional recurrence

The meta-analysis by Li et al (2017) reported no significant difference in loco-regional recurrence after surgery and SABR (HR 1.17, 95% CI 0.68 to 1.98, p = 0.57).

Distant recurrence

The meta-analysis by Li et al (2017) reported no significant difference in distant recurrence after surgery and SABR (HR 1.36, 95% CI 0.77 to 2.39, p = 0.29).

Global health status

Louie et al (2015)'s randomised trial reported better global health status after SABR than after surgery (HR 0.19, p = 0.038). However, the apparent statistical significance of this result may well be because of multiple comparisons and it should be regarded as arising from chance.

Hindrance score

Louie et al (2015) also reported lower mean hindrance scores for SABR in paid and unpaid work after SABR than after surgery (1.9 vs 6.0, p = 0.010). The authors do not define hindrance scores and we were not able to interpret the reported difference.

Cancer-specific survival

Paul et al (2016) reported longer cancer-specific survival after surgery (HR 1.32, 95% CI 0.77 to 2.26, p = 0.32).

Hamaji et al (2015) also reported longer cancer-specific survival after surgery (HR 0.228, 95% CI 0.09 to 0.62, p = 0.0035).

Local control

Hamaji et al (2015) reported better local control after surgery (HR 0.13, 95% CI 0.029 to 0.59, p = 0.0077).

Regional lymph node control

Hamaji et al (2015) reported no significant differences in regional lymph node control after surgery and after SABR (HR 0.33, 95% CI 0.082 to 1.33, p = 0.12).

Distant control

Hamaji et al (2015) reported better distant control after surgery (HR 0.17, 95% CI 0.069 to 0.43, p = 0.0002.).

What is the evidence relating on the safety of SABR compared with existing treatments for non small cell lung cancer histology, stages 1-3?

We found one systematic review of the adverse effects of SABR on the lung (Zhao et al 2016).

It reported an incidence of radiation-induced lung toxicity of 10.4% (95% CI 9.8% to 15.2%). These authors also reported an incidence of grade 2 to 5 radiation pneumonitis of 9.5% (95% CI 7.8% to 11.3%), and of grade 3 to 5 radiation pneumonitis of 2.2% (95% CI 1.7% to 7.3%). They reported an incidence of grade 2 to 5 lung fibrosis of 0.2% (95% CI 0.008% to 4.7%), and of grade 3 to 5 fibrosis of 0.2% (95% CI 0.005% to 1.3%).

What is the evidence on the cost effectiveness of SABR compared with existing treatment for non small cell lung cancer histology, stages 1-3?

We found four health economic analyses, all of which reported different cost/cost effectiveness outcomes using different methodologies for estimating costs. These outcomes cannot therefore be easily assimilated. Louie et al (2015) reported cost results from their randomised trial, Smith et al (2015) reported costs and benefits from a comparison of SABR, sub-lobar resection and lobectomy, Shah et al (2013) reported a modelling paper about the cost utility of SABR and lobectomy and Grutters et al (2010) modelled the cost utility of treatment with SABR and carbon ions.

SABR vs open surgery: Louie et al (2015) reported higher productivity costs after open surgery than after SABR (SABR: €95 (£86.80), surgery €3513 (£3210), p = 0.044). The productivity cost is calculated from the perspective of the participant's employer. By convention, NHS economic evaluations take the perspective of the public sector and only include direct costs to the commissioners of NHS and social care, so this result is of limited relevance to NHS decision-making.

SABR vs sublobar resection or lobectomy: Smith et al (2015) reported the costs of SABR as US$55,120 (£42,400) and sublobar resection as $77,964 (£60,000). A separate comparison of SABR vs lobectomy reported SABR as costing $54,968 (£42,300) and lobectomy as costing $82,641 (£63,600). There were no reported tests of significance.

The incremental costs per life-year gained were higher for SABR when compared to sublobar resection than for lobectomy (Smith et al 2015).

- SABR vs sublobar resection $45,683 (£35,100), 95% CI -$325,572 to $269,807 (-£250,400 to £207,500);
- SABR vs lobectomy $28,645 (£22,000), 95% CI -$119,828 to $207,822 (-£92,200 to £159,900).

The incremental cost per quality adjusted life year (QALY) for lobectomy compared with SABR was $13,215 (£10,200) (Shah et al 2013). This was based on much lower procedure costs than were reported in Smith et al 2015 (SABR $40,107 (£30,900), lobectomy: $49,093 (£37,800)).

SABR vs carbon ion treatment: Finally, Grutters et al (2010) reported that SABR dominated carbon ion treatment, being both more effective and less expensive (SABR: €8,485 (£7,800), 3.20 QALYs; carbon ions: €14,620 (£13,400), 3.16 QALYs).

Does the evidence of clinical and cost-effectiveness identify any subgroups of patients with non small cell lung cancer who would gain greater benefit from using SABR compared with existing treatments?

No. We found no studies relevant to this question.

5. Discussion

The evidence we found was diverse, both in terms of study design and comparisons. However, there are some general points which emerge.

The studies reported either better or similar outcomes from surgery than from SABR. This was

true of both survival and of measures of disease control and metastasis.

One discrepancy from the general trend was the meta-analysis by Ma et al (2016), which produced non-significant results. These authors approach to adjustment for confounding used only age and the proportion of SABR participants deemed operable; this may have produced a spurious over-correction for the worse prognosis of SABR patients. In any case, the confidence intervals around these authors' hazard ratio estimates are wide, and consistent with those from the other comparisons.

A limitation of this review is the almost complete absence of randomised studies. The only randomised trial was terminated early with only 22 participants, and poorly analysed. The reliability of the numerous unrandomised studies depends on the adequacy of the adjustment for confounding; the consensus among them, despite varying designs, patient populations and statistical approaches, gives us confidence in their results.

The health economic analyses produced apparently contradictory conclusions, albeit with different metrics. Shah et al (2013) reported an incremental cost per quality-adjusted life-year for lobectomy compared with SABR of £10,200, well within NHS value-for-money thresholds. However, Smith et al (2015) reported incremental costs per unadjusted life-year gained of £35,100 for SABR vs sublobar resection and £22,000 for SABR vs lobectomy; normally, one would expect lower cost per unadjusted life-years than for QALYs. The confidence intervals around Smith et al (2015)'s estimates are so wide that we cannot be certain if SABR is more or less cost effective than the alternatives, so these studies are in fact compatible. Meanwhile, Grutters et al (2010) indicates that SABR is more cost-effective than seldom-used carbon ion treatment.

SABR is associated with lung toxicity. However, these adverse effects are not common.

Some would regard the unrandomised comparisons of SABR and surgery as adequate, but the risk of unmeasured and unadjusted confounding is material. Given the importance of this question, a randomised trial is indicated.

6. Conclusion

Taken together, the evidence that we found indicates that open or video-assisted thoracoscopic surgery is probably more effective than SABR in the treatment of early stage NSCLC. It appears to be associated with longer survival, and better tumour control on some metrics.

This conclusion is based on unrandomised comparisons. Although the studies' authors used appropriate techniques to adjust for the confounding inherent in such designs, these may not have been fully effective; this reduces the reliability of the review's conclusions.

The health economic analyses suggest that surgery is more cost effective than SABR.

SABR has adverse effects but they do not appear to be common or serious enough to cast doubt on its suitability for use.

7. Evidence Summary Tables

Use of SABR vs open* surgery to treat NSCLC									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Li et al 2017	S1 – Systematic review with meta-analysis. Search date 1 January 2017	7810 people in 15 controlled studies, of which 1 was randomised, with T1-3N0M0 NSCLC. Median age 66 to 79 years. Quality scores between 5 and 7 points, out of a maximum of 7.	SABR: 2986, open surgery 4719, video-assisted thoracic surgery 105. Median dose and fractionation not reported.	Primary Clinical effectiveness	Overall survival, SABR versus all surgical procedures (15 studies)	Hazard ratio (HR) 1.40 (surgery better), 95% confidence interval (CI) 1.21 to 1.61, p < 0.001. Heterogeneity I^2 = 59%, p = 0.002.[7]	9	Direct	Exclusion of each individual study one by one did not materially alter the results. The funnel plot for overall survival was symmetrical, indicating that publication bias was less likely. 11 of the 15 studies reduced confounding by using a propensity score or matched pair design. Significant heterogeneity, which indicates diversity among the constituent studies' results.
				Primary Clinical effectiveness	Recurrence-free survival[8], SABR versus all surgical procedures (6 studies)	HR 1.84 (surgery better), 95% CI 1.26 to 2.68, p = 0.02. Heterogeneity I^2 = 58%, p = 0.03.			
				Primary Clinical effectiveness	Loco-regional recurrence[9], SABR versus all surgical procedures (6 studies)	HR 1.17, 95% CI 0.68 to 1.98, p = 0.57. Heterogeneity I^2 = 69%, p = 0.007.			
				Primary Clinical effectiveness	Distant recurrence[10], SABR versus all surgical procedures (5 studies)	HR 1.36, 95% CI 0.77 to 2.39, p = 0.29. Heterogeneity I^2 = 77%, p = 0.001.			

[7] I^2 is a measure used to quantify heterogeneity. It describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value greater than 50% may be considered to represent substantial heterogeneity.
[8] Recurrence-free survival is the proportion of participants alive with no apparent recurrent tumour at specified intervals after completion of SABR.
[9] Loco-regional recurrence is the appearance of new tumour at the site of the primary or elsewhere in the lung, after initial treatment is complete.
[10] Distant recurrence is the appearance of new tumour outside the lung, after initial treatment is complete.

				Primary Clinical effectiveness	Overall survival, SABR versus lobectomy (5 studies)	HR 1.46, 95% CI 1.03 to 2.06, p = 0.03. Heterogeneity I^2 = 74%, P = 0.004.			
				Primary Clinical effectiveness	Overall survival, SABR versus sub-lobectomy (5 studies)	HR 1.40, 95% CI 1.09 to 1.80, p = 0.008. Heterogeneity I^2 = 66%, P = 0.02.			
				Primary Clinical effectiveness	Overall survival, SABR versus wedge resection (3 studies)	HR 1.48, 95% CI 1.01 to 2.16, p = 0.04. Heterogeneity I^2 = 52%, P = 0.12.			
Yeruka n et al 2017	P1 – Controlle d unrando mised study United States	6295 people with stage IA NSCLC (3rd edition). Median age about 72 years, 2497/6295 (40%) male. Median follow-up not reported.	SABR: 1778/6295 (28%), wedge resection (WR): 4517/6295 (72%). No information on SABR regimes reported.	Primary Clinical efficacy	Overall survival	At 5 years: SABR 31.0% (95% CI 26.1% to 36.0%), median 3.4 years, WR 49.9% (95% CI 45.1% to 54.6%), median 5.0 years, p < 0.0001. At 5 years in people older than 80 years: SABR 20.1% (95% CI 10.1% to 32.6%), median 3.2 years, WR 41.3% (95% CI 31.3 to 51.1%), median 4.4 years, p < 0.0001. At 5 years in people with a Charlson-Deyo comorbidity score[11] of 2 or more: SABR 21.1% (95% CI 12.3% to 37.2%), median 2.8 years, WR 44.0% (95% CI 32.5% to 55.0%), median 5.0 years, p < 0.0001.	7	Direct	3168 participants matched with propensity scoring, including age, sex, race, insurance status, Charlson-Deyo comorbidity score[10], facility type, histology type, tumour location, tumour size and distance to hospital. There may be residual confounding between the two groups.
Louie et al 2015	P1 – Randomi sed controlle d trial The	22 people with stage IA NSCLC. Median age not reported.	SABR: 11/22 (50%) (regime not reported), surgery: 11/22 (50%) (10 lobectomy, 1	Primary Clinical efficacy	Global health status	HR 0.19 (SABR better), p = 0.038.	7	Direct	Results from a randomised trial which ended early because of a low randomisation rate. The assessment of global health status was one of 5 quality-of-life measures assessed in the trial, without adjustment for multiple comparisons. The Bonferroni corrected p-value is 0.05/5 = 0.01 (calculated by
				Secondary	Mean total productivity cost	SABR: €95 (£86.80), surgery €3513 (£3210),			

[11] The Charlson Co-morbidity Index predicts 10-year survival in patients with multiple comorbidities.

	Netherlands	Median follow-up: 42 months	wedge resection).	Cost utility		p = 0.044.			SPH), indicating that the apparent statistical significance of the global health status result may well be because of multiple comparisons and should be regarded as arising from chance. The productivity cost is indirect, and calculated from the perspective of the participant's employer. By convention, NHS economic evaluations take the perspective of the public sector and only include direct costs to the commissioners of NHS and social care, so this result is of limited relevance to NHS decision-making. Hindrance scores are not defined; we were not able to interpret the reported difference Costs from the Dutch economy, exact source not reported. UK costs may differ.
				Secondary Cost utility	Hindrance score in paid and unpaid work	SABR: 1.9, surgery 6.0, p = 0.010).			
Smith et al 2015	P1 – Controlled unrandomised study United States	9093 people aged at least 66 years with T1 or T2A NSCLC, from which 543 matched pairs were formed. Median age 78 years (SABR vs sublobar resection), 77 years (SABR vs lobectomy).	SABR, sub-lobar resection and lobectomy. Surgical procedures included open and thoracoscopic approaches. Costs and benefits over 5 years	Primary Clinical efficacy	Overall survival	SABR vs sublobar resection: SABR 3.6 years, sublobar resection 4.1 years, p = 0.95. SABR vs lobectomy: SABR 3.8 years, lobectomy 4.7 years, p = 0.81	8	Direct	Participants matched with propensity scoring, including age, sex, race, use of supplementary oxygen, Charlson Comorbidity Score[12], performance status, T-stage, use of pathological staging of the mediastinum and use of pre-treatment PET scanning. The authors' assumptions are in line with the evidence. Costs were based on healthcare reimbursement claims in the US, NHS costs may differ. Analysis was confined to people at least 66 years old. A year of life after treatment for lung cancer is likely to be less than perfect, and so yield less than 1 QALY. Therefore, it is rational to be willing to pay less for a lifeyear than a QALY.
				Primary Cost utility	Cost and incremental cost effectiveness ratio.	SABR vs sublobar resection: SABR $55,120 (£42,400), sublobar resection: $77,964 (£60,000), incremental cost per life-year gained $45,683 (£35,100), 95% CI -$325,572 to $269,807 (-£250,400 to £207,500). SABR vs lobectomy: SABR $54,968 (£42,300), lobectomy: $82,641 (£63,600), incremental cost per life-year gained			

[12] The Charlson Co-morbidity Index predicts 10-year survival in patients with multiple comorbidities.

						$28,645 (£22,000), 95% CI -$119,828 to $207,822 (-£92,200 to £159,900).			
Shah et al 2013	S1 – meta analysis of existing data analysis	A Markov model to simulate the clinical trajectory of a 65-year-old patient with operable stage I NSCLC.	SABR and lobectomy	Primary Cost utility	Cost and yield of quality-adjusted life-years (QALYs) and incremental cost effectiveness ratio.	SABR: $40,107 (£30,900), 8.21 QALYs. Lobectomy: $49,093 (£37,800), 8.89 QALYs. Incremental cost per QALY for lobectomy compared with SABR: $13,215 (£10,200).	8	Direct	The authors modelled the treatment of marginally and clearly operable patients; we report here only the latter results. The authors' assumptions are in line with the evidence. Costs were those charged at the University of Pennsylvania, and included $14,821 (£11,340) for SABR and $16,206 (£12,500) plus physician fees for open surgery without complications or comorbidities. NHS costs may differ. Lobectomy had an ICER below £30,000 per QALY under every assumption except one in the authors' thorough sensitivity analysis.

* Li et al (2017) included 105 participants (1.3% of the total) who received video-assisted thoracic surgery. Although the review was therefore not strictly limited to open surgery, its results are reliable with respect to that intervention but not relevant to the assessment of video-assisted thoracic surgery.

Use of SABR vs video-assisted thoracic surgery to treat NSCLC									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Ma et al 2016	S1 – Systematic review with meta-analysis. Search date October 2015	7869 people with stage I or II NSCLC (7th edition staging criteria). The proportion of SABR patients deemed operable varied	4433 people in 24 uncontrolled studies of SABR (20 to 73.8 Gy) and 3436 people in 13 uncontrolled studies of video-assisted thoracic surgery (VATS).	Primary Clinical efficacy	Adjusted overall survival	HR 2.02 (SBRT better), 95% CI 1.45 to 3.07, p = 0.47. The authors state this is non-significant, although the 95% CI excludes a HR of 1.	8	Direct	Results adjusted for age and the proportion of SABR participants deemed operable. However, this adjustment may not be adequate for other confounding variables. Although most participants treated with SABR were inoperable and therefore outside the scope of this RER's PICO, we included this study because the authors adjust for the effects of inoperability on results.
				Primary Clinical efficacy	Cancer-free survival[13]	HR 0.42 (VATS better), 95% CI 0.21 to 1.12, p = 0.52.			

[13] Cancer-specific survival is survival without death from SCLC. All other causes of death are censored (ie disregarded in the analysis).

		between 0% and 48%, mean 18%. Median ages: SABR 74.5 years, VATS 67.1 years, p < 0.001. Median follow-up: SABR 27.8 months, VATS 41.3 months, significance test not reported.							
Paul et al 2016	P1 – Controlled unrandomised study United States	690 people with stage I SCLCs ≤ 2cm, treated between 2007 and 2012. Median age 76.4 years, 38% male. Median follow-up: 2.9 years.	SABR: 275/690 (40%), thoracoscopic sublobar resection 415/60 (60%), either wedge (87%) or segmental resection (13%). SABR regimes not reported.	Primary Clinical efficacy	Overall survival	HR: 1.80 (surgery better), 95% CI 1.33 to 2.43; p < 0.001. 3-year estimated overall survival: SABR 52.2%, surgery 68.4% (significance test not reported).	7	Direct	Participants matched with propensity scoring, including age, sex, race, marital status, income, residence location, tumour histology, size and stage, and comorbidities. There may be residual confounding between the two groups. Supplemental analysis with multivariable regression, instrumental variable analysis, and competing risk analysis confirmed findings from the primary and secondary analysis.
				Primary Clinical efficacy	Cancer-specific survival	HR 1.32 (surgery better), 95% CI 0.77 to 2.26, p = 0.32. 3-year estimated overall survival: SABR 82.6%, surgery 86.4% (significance test not reported).			
				Secondary Clinical efficacy	Overall survival, tumours ≤ 5 cm, 643 patients in each treatment arm	HR: 1.92 (surgery better), 95% CI 1.62 to 2.26, p < 0.001.			
				Secondary Clinical efficacy	Cancer-specific survival, tumours ≤ 5 cm, 643 patients in each treatment arm	HR 2.10 (surgery better), 95% CI 1.52 to 2.89, p < 0.001. 3-year estimated overall survival: SABR 80.0%, surgery 90.3% (significance test not			

						reported).			
Hamaji et al 2015	P1 – Controlled unrandomised study Kyoto, Japan	517 people with stage I SCLC, treated between 2003 and 2009. Median age 74 years, 77% male. Median follow-up: 55 months.	SABR: 104/517 (20%) 48 Gy[14] in 4 fractions, except for 1 patient with 56 Gy in 4 fractions and 4 patients with 60 Gy in 8 fractions; video-assisted thoracoscopic lobectomy: 413/517 (80%).	Primary Clinical efficacy	Overall survival	HR 0.39 (surgery better), 95% CI 0.20 to 0.76, p = 0.0051. 3-year, 5-year, and 10-year survival rates in VATS lobectomy patients were 80.1%, 68.5%, and 61.6%, respectively; 3-year, 5-year, and 10-year rates in SABR patients were 52.7%, 37.3%, and 20.7%, respectively, p = 0.0016.	7	Direct	Participants were matched with propensity scoring, including age, gender, tumour diameter, predicted % forced expiratory volume in 1 second and Charlson* comorbidity index. There may be residual confounding between the two groups.
				Primary Clinical efficacy	Cancer-specific survival	HR 0.228 (surgery better), 95% CI 0.09 to 0.62, p = 0.0035. 3-year, 5-year, and 10-year rates in VATS lobectomy patients were 94.5%, 83.5%, and 83.5%, respectively; 3-year, 5-year, and 10-year rates in SBRT patients were 71.5%, 56.7%, and 17.2%, respectively, p = 0.0015.			
				Primary Clinical efficacy	Recurrence-free survival	HR 0.32 (surgery better), 95% CI 0.17 to 0.58. p = 0.0002. 3-year, 5-year, and 10-year rates in VATS lobectomy patients were 72.6%, 60.4%, and 51.8%, respectively; 3-year, 5-year, and 10-year rates in SBRT patients were 29.0%, 19.5%, and			

[14] A gray is the unit of radiotherapy delivered, and is defined as the absorption of one joule of radiation energy per kilogram of matter.

						15.6%, respectively, p < 0.0001.			
				Primary Clinical efficacy	Local control rate[15]	HR 0.13 (surgery better), 95% CI 0.029 to 0.59, p = 0.0077.			
				Primary Clinical efficacy	Regional lymph node control rate[16]	HR 0.33 (surgery better), 95% CI 0.082 to 1.33, p = 0.12.			
				Primary Clinical efficacy	Distant control rate[17]	HR 0.17 (surgery better), 95% CI 0.069 to 0.43, p = 0.0002.			

Use of SABR vs particle therapy to treat NSCLC									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Grutters et al 2010	S1 – meta analysis of existing data analysis	People with operable stage I NSCLC, 5-year time horizon	Carbon ion therapy and SABR.	Primary Cost utility	Cost and yield of quality-adjusted life-years (QALYs)	SABR: €8,485 (£7,800), 3.20 QALYs. Carbon ions: €14,620 (£13,400), 3.16 QALYs.	7	Direct	The authors modelled the treatment of operable and inoperable patients; we report here only the former results. Costs were based on the Dutch manual for cost research 2004, NHS costs may differ. SABR dominated carbon ion treatment, being both more effective and less expensive.

[15] Local control is the absence of radiological evidence of further growth of the cancer at its site of origin.
[16] Regional lymph node control is the absence of radiological evidence of further growth of the cancer in regional lymph nodes which drain the primary tumour.
[17] Distant control is the absence of radiological evidence of new metastases from the primary tumour.

Use of SABR to treat NSCLC									
Study reference	**Study Design**	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**	**Critical Appraisal Summary**
Zhao et al 2016	S1 – meta analysis of existing data analysis. Search date December 2014	7752 people with lung cancer in 88 studies, of which 54 were of primary NSCLC. Median age 74 years, median tumour size 2.3cm. Median follow-up not reported.	SABR, median of 48 Gy in a median of 4 fractions.	Primary Safety	Grade 2-5 radiation-induced lung toxicity	In primary NSCLC: 10.4% (95% CI 9.8% to 15.2%).	8	Direct	This study was not confined to operable stage I to III NSCLC. However, we included it because the toxicity of SABR may not be closely related to the stage and operability of the tumour treated, and other studies did not report toxicity. Participants with primary lung cancers and lung metastases had rates of radiation-induced lung toxicity which did not differ significantly.
				Primary Safety	Radiation pneumonitis	In all tumours: grade 2 to 5 9.5% (95% CI 7.8% to 11.3%), grade 3 to 5 2.2% (95% CI 1.7% to 7.3%).			
				Primary Safety	Lung fibrosis	In all tumours: grade 2 to 5 0.2% (95% CI 0.008% to 4.7%), grade 3 to 5 0.2% (95% CI 0.005% to 1.3%).			

8. Grade of evidence tables

Use of SABR vs open* surgery to treat NSCLC					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Li et al 2017	9	Direct	A	Overall survival is the proportion of participants alive at specified intervals after completion of SABR. Li et al 2017 included 15 studies, reporting this outcome as follows: HR 1.40 (surgery better), 95% CI 1.21 to 1.61, p < 0.001. Heterogeneity I^2 = 59%, p = 0.002. This suggests that overall survival is about 40% better after open surgery than after SABR. Improved overall survival would be of great benefit to patients. This result's reliability is affected by the heterogeneity of the underlying studies.
	Yerukan et a; 2017	7			
	Smith et al 2015	8			
Recurrence-free survival	Li et al 2017	9	Direct	B	Recurrence-free survival is the proportion of participants alive with no apparent recurrent tumour at specified intervals after completion of SABR. Li et al 2017 included 6 studies, reporting this outcome as follows: HR 1.84 (surgery better), 95% CI 1.26 to 2.68, p = 0.02. Heterogeneity I^2 = 58%, p = 0.03. This suggests that recurrence-free survival is about 84% better after open surgery than after SABR. Improved recurrence-free survival would be of benefit to patients. This result's reliability is affected by the heterogeneity of the underlying studies.
Loco-regional recurrence	Li et al 2017	9	Direct	**B**	Loco-regional recurrence is the appearance of new tumour at the site of the primary or elsewhere in the lung, after initial treatment is complete. Li et al 2017 included 6 studies, reporting this outcome as follows: HR 1.17, 95% CI 0.68 to 1.98, p = 0.57.

					Heterogeneity I^2 = 69%, p = 0.007. This suggests that loco-regional recurrence is not significantly different after open surgery and after SABR. Improved loco-regional recurrence would benefit patients if it lead to fewer symptoms or better overall prognosis. We found no evidence that SABR improves loco-regional recurrence in NSCLC. This result's reliability is affected by the heterogeneity of the underlying studies.
Distant recurrence	Li et al 2017	9	Direct	**B**	Distant recurrence is the appearance of new tumour outside the lung, after initial treatment is complete. Li et al 2017 included 5 studies, reporting this outcome as follows: HR 1.36, 95% CI 0.77 to 2.39, p = 0.29. Heterogeneity I^2 = 77%, p = 0.001. This suggests that distant recurrence is not significantly different after open surgery and after SABR. Improved distant recurrence would benefit patients if it lead to fewer symptoms or better overall prognosis. We found no evidence that SABR improves distant recurrence in NSCLC. This result's reliability is affected by the heterogeneity of the underlying studies.
Global health status	Louie et al 2015	7	Direct	B	Global health status is a composite measure of quality of life. Louie et al reported a HR of 0.19 for this outcome, (SABR better), p = 0.038. This suggests that SABR may result in better global health status than surgery. However, the assessment of global health status was one of 5 quality-of-life measures assessed in the trial, without adjustment for multiple comparisons. The Bonferroni corrected p-value is 0.05/5 = 0.01 (calculated by SPH), indicating that the apparent statistical significance of the global health status result may well be because of multiple comparisons and should be regarded as arising from chance.

					Improved health status would greatly benefit patients. We found no reliable evidence that SABR improves health status in NSCLC.
Mean total productivity cost	Louie et al 2015	7	Direct	B	Total productivity loss was calculated by multiplying the number of hours reported absent by productivity costs. This was adjusted for productivity from the employer's perspective, and added to the number of hours of unpaid work substituted by other sources, multiplied by the average gross hourly wage of a domestic worker. Louie et al 2015 reported productivity costs as follows: SABR: €95 (£86.80), surgery €3513 (£3210), p = 0.044. The productivity cost is indirect, and calculated from the perspective of the participant's employer only. By convention, NHS economic evaluations take the perspective of the public sector and only include direct costs to the commissioners of NHS and social care, so this result is of limited relevance to NHS decision-making. Lower indirect costs are of value to employers and those patients in employment if their job security was enhanced. Lower direct costs to the NHS and social care would be of value to those agencies, but this study provides no evidence with respect to that outcome. Costs were from the Dutch economy and the exact source was not reported. UK costs may differ.
Hindrance score	Louie et al 2015	7	Direct	B	Louie et al 2015 do not define hindrance scores. They report mean hindrance scores for SABR in paid and unpaid work of 1.9, and for surgery of 6.0 (p = 0.010). The magnitude and clinical significance of this difference cannot be evaluated without a definition of what was measured by the authors. There is a high degree of uncertainty about the meaning and importance of this reported difference in hindrance

					scores.
Procedure and follow-up cost	Smith et al 2015	8	Direct	B	Cost is the cost of the healthcare provided to treat and follow-up the patient. Smith et al 2015 reported the costs of SABR as follows: SABR vs sublobar resection: SABR $55,120 (£42,400), sublobar resection: $77,964 (£60,000). SABR vs lobectomy: SABR $54,968 (£42,300), lobectomy: $82,641 (£63,600). Shah et al 2013 reported these costs: SABR $40,107 (£30,900), lobectomy: $49,093 (£37,800). This suggests that SABR is about 20% to 35% less expensive than surgery. Lower cost health interventions preserve resources for other patients' use, but this has no direct impact on individuals' health outcomes. Costs were based on healthcare reimbursement claims in the US, NHS costs may differ.
	Shah et al 2013	8			
Yield of QALYs	Shah et al 2013	8	Direct	B	Yield of QALYs is the extra number of quality adjusted life years (QALYs) resulting from one treatment's use in place of or in addition to another's. This measure is designed to take into account the quality as well as the duration of survival. Shah et al 2013 reported SABR yielded 8.21 QALYs and lobectomy yielded 8.89 QALYs. No significance testing was reported This study suggests that lobectomy produces more QALYs than SABR when used to treat NSCLC. Extra QALYs are of great benefit to patients. The lack of significance testing limits interpretation of this study. Costs were based on healthcare reimbursement claims in the US, NHS costs may differ.

Incremental cost effectiveness ratio	Smith et al 2015	8	Direct	B	An incremental cost effectiveness ratio is the ratio of the extra costs of an intervention, above that of alternatives, to the extra benefits it provides. Smith et al 2015 reported the following incremental costs per life-year gained: SABR vs sublobar resection $45,683 (£35,100), 95% CI -$325,572 to $269,807 (-£250,400 to £207,500); SABR vs lobectomy $28,645 (£22,000), 95% CI -$119,828 to $207,822 (-£92,200 to £159,900). Shah et al 2013 reported an incremental cost per QALY for lobectomy compared with SABR of $13,215 (£10,200). This suggests that the extra costs of lobectomy are low in proportion to its benefits. Costs were based on healthcare reimbursement claims in the US, NHS costs may differ. A lower incremental cost effectiveness ratio indicates better value for money. This does not directly benefit individual patients, but means that more patients can be treated with the resources available. NICE regards costs per QALY of less than £30,000 as good value for money.
	Shah et al 2013	8			

* Li et al (2017) included 105 participants (1.3% of the total) who received video-assisted thoracic surgery. Although the review was therefore not strictly limited to open surgery, its results are reliable with respect to that intervention but not relevant to the assessment of video-assisted thoracic surgery.

Use of SABR vs video-assisted thoracic surgery to treat NSCLC					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Overall survival	Ma et al 2016	8	Direct	A	Overall survival is the proportion of participants alive at specified intervals after completion of SABR. Ma et al 2016 reported a hazard ratio (HR) of 2.02 (SABR better), 95% CI 1.45 to 3.07, p = 0.47. The authors state this is non-significant, although the 95% CI excludes an HR of 1. This suggests that overall survival is not significantly different after video-assisted
	Paul et al 2016	7	Direct		
	Hamaji et al 2015	7	Direct		

					thoracic surgery and after SABR. Improved survival would benefit patients greatly. We found no evidence that SABR improves survival compared with video-assisted thoracic surgery in NSCLC.
Recurrence-free survival	Ma et al 2016	8	Direct	A	Recurrence-free survival is the proportion of participants alive with no apparent recurrent tumour at specified intervals after completion of SABR. Ma et al 2016 reported a HR of 0.42 (SBRT better), 95% CI 0.21 to 1.12, p = 0.52. This suggests that recurrence-free survival is not significantly different after video-assisted thoracic surgery and after SABR. Improved recurrence-free survival would benefit patients. We found no evidence that SABR improves recurrence-free survival compared with video-assisted thoracic surgery in NSCLC.
	Hamaji et al 2015	7	Direct		
Cancer-specific survival	Paul et al 2016	7	Direct	A	Cancer-specific survival is survival without death from NSCLC. All other causes of death are censored (ie disregarded in the analysis). Paul et al 2016 reported HR 1.32 (surgery better), 95% CI 0.77 to 2.26; p = 0.32. Hamaji et al 2015 reported HR 0.228 (surgery better), 95% CI 0.09 to 0.62, p = 0.0035. This suggests that cancer-specific survival may be better after video-assisted thoracic surgery than after SABR, though the studies' results are contradictory. Improved cancer-free survival would benefit patients. We found no evidence about whether SABR improves cancer-specific survival compared with video-assisted thoracic surgery in NSCLC, and some evidence that surgery leads to better cancer-specific survival. The results may be affected by residual confounding.
	Hamaji et al 2015	7	Direct		
Local control	Hamaji et al 2015	7	Direct	B	Local control is the absence of

					radiological evidence of further growth of the cancer at its site of origin. Hamaji et al 2015 reported HR 0.13 (surgery better), 95% CI 0.029 to 0.59, p = 0.0077. This suggests that rates of local control may be 73% better after video-assisted thoracic surgery than after SABR. Improved local control would benefit patients if it lead to fewer local symptoms or better overall prognosis. This evidence suggests that rates of local control are better after video-assisted thoracic surgery than after SABR. The results may be affected by residual confounding.
Regional lymph node control rate	Hamaji et al 2015	7	Direct	B	Regional lymph node control is the absence of radiological evidence of further growth of the cancer in regional lymph nodes which drain the primary tumour. Hamaji et al 2015 reported HR 0.33 (surgery better), 95% CI 0.082 to 1.33, p = 0.12. This suggests that regional lymph node control is not significantly different after video-assisted thoracic surgery and after SABR. Improved regional lymph node control would benefit patients if it lead to fewer local symptoms or better overall prognosis. We found no evidence that this was the case after SABR.
Distant control rate	Hamaji et al 2015	7	Direct	B	Distant control is the absence of radiological evidence of new metastases from the primary tumour. Hamaji et al 2015 reported HR 0.17 (surgery better), 95% CI 0.069 to 0.43, p = 0.0002. This suggests that rates of distant control may be 83% better after video-assisted thoracic surgery than after SABR. Improved distant control would benefit patients if it lead to fewer local symptoms or better overall prognosis.

					This evidence suggests that rates of distant control are better after video-assisted thoracic surgery than after SABR. The results may be affected by residual confounding.

Use of SABR vs particle therapy to treat NSCLC					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Procedure cost	Grutters et al 2010	7	Direct	B	Cost is the cost of the healthcare provided to treat and follow-up the patient. Grutters et al 2010 reported these costs: SABR: €8,485 (£7,800), carbon ion therapy: €14,620 (£13,400). This study suggests SABR is less expensive than carbon ion therapy. Lower cost health interventions preserve resources for other patients' use, but this has no direct impact on individuals' health outcomes. Costs were based on the Dutch manual for cost research 2004, NHS costs may differ.
Yield of quality-adjusted life-years (QALYs)	Grutters et al 2010	7	Direct	B	Yield of QALYs is the extra number of QALYs resulting from one treatment's use in place of another's (see definition in table above) Grutters et al 2010 reported these QALY yields: SABR: 3.20 QALYs, carbon ions: 3.16 QALYs. This study suggests that SABR dominates carbon ion treatment, being both more effective and less expensive Extra QALYs are of great benefit to patients. Costs were based on the Dutch manual for cost research 2004, NHS costs may differ. .

Use of SABR to treat NSCLC					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Grade 2-5 radiation-induced lung toxicity	Zhao et al 2016	8	Direct	B	This study reported the incidence of damage to the lungs resulting from radiation administered as part of SABR. Zhao et al 2016 reported an incidence of 10.4% (95% CI 9.8% to 15.2%). Radiation-induced lung toxicity can cause unpleasant and distressing symptoms and reduce quality of life. This study provides an estimate of the risk of this adverse effect of SABR.
Radiation pneumonitis	Zhao et al 2016	8	Direct	B	This study reported the incidence of pneumonitis resulting from radiation administered as part of SABR. Zhao et al 2016 reported an incidence of grade 2 to 5 radiation pneumonitis of 9.5% (95% CI 7.8% to 11.3%), and of grade 3 to 5 radiation pneumonitis of 2.2% (95% CI 1.7% to 7.3%). Radiation pneumonitis can cause unpleasant and distressing symptoms and reduce quality of life. This study provides an estimate of the risk of this adverse effect of SABR.
Lung fibrosis	Zhao et al 2016	8	Direct	B	This study reported the incidence of lung fibrosis resulting from radiation administered as part of SABR. Zhao et al 2016 reported an incidence of grade 2 to 5 lung fibrosis of 0.2% (95% CI 0.008% to 4.7%), and of grade 3 to 5 fibrosis of 0.2% (95% CI 0.005% to 1.3%). Lung fibrosis can cause unpleasant and distressing symptoms and reduce quality of life. This study provides an estimate of the risk of this adverse effect of SABR.

9. Literature Search Terms

P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Patients diagnosed with non small cell lung cancer histology, stages I-III (including central and / or peripheral disease)
I – Intervention Which intervention, treatment or approach should be used?	Stereotactic Ablative Radiotherapy (SABR)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	Any treatment for non small cell lung cancer histology, Stages I-III
O – Outcomes What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission; return to work, physical and social functioning, resource use.	Clinical effectiveness - Cancer specific survival - Overall survival - Local control - Adverse events/complications - Quality of life (including patient reported outcome measures) Cost effectiveness - Resource utilization - Attendances Any other outcome

Assumptions / limits applied to search	**Inclusion Criteria** All study designs except case reports published in peer-reviewed journals in the English language **Exclusion Criteria** Stage 4 non small cell lung cancer. Comparisons examining the clinical and cost effectiveness of SABR for indications already commissioned within the existing policy (NHSCB/B01/P/a): • Patients meeting all the following criteria will be routinely funded for SBRT / SABR: Multidisciplinary Team confirmed diagnosis of non small cell lung cancer based on findings of positive histology, positive PET scan or growth on serial CT scan AND clinical stages of: T1 N0 M0, or T2 (≤5cm) N0 M0, or T3 (≤5cm) N0 M0 AND not suitable for surgery because of medical co-morbidity or lesion is technically inoperable AND WHO performance status 0-2 AND peripheral lesions outside a 2cm radius of main airways and proximal bronchial tree (defined as 2cm from the bifurcation of the second order bronchus e.g. where the right upper lobe bronchus splits). Abstracts. Conference papers. Papers published greater than 10 years ago.

10. Search Strategy

We searched PubMed, Embase and Cochrane Library limiting the search to papers published in English and last 10 years. We excluded conference abstracts, commentaries, letters, editorials and case reports. We also searched TRIP and NICE Evidence Search.

Search date 2 August 2017

Embase search

1 *lung cancer/

2 *lung carcinoma/ or exp *non small cell lung cancer/ or *small cell lung cancer/

3 (((small cell or non small cell or nonsmall cell) adj2 (cancer? or carcinoma?)) or sclc or nsclc).ti,ab.

4 (lung adj2 (cancer? or carcinoma?)).ti.

5 1 or 2 or 3 or 4
6 stereotactic body radiation therapy/
7 stereotactic procedure/ and radiotherapy/
8 (stereotactic adj2 (radiotherap* or radiation therap*)).ti,ab.
9 (sbrt or sabr).ti,ab.
10 6 or 7 or 8 or 9
11 5 and 10
12 limit 11 to (english language and yr="2007 -Current")
13 conference*.pt.
14 12 not 13
15 limit 14 to "reviews (maximizes specificity)"
16 limit 14 to "therapy (best balance of sensitivity and specificity)"
17 limit 14 to "economics (maximizes sensitivity)"
18 mortality/ or cancer mortality/
19 survival/ or exp cancer survival/ or overall survival/
20 exp "quality of life"/
21 (mortality or death? or survival).ti,ab.
22 (complication? or adverse event? or adverse effect? or side effect? or harm*).ti.
23 ("quality of life" or qol or hrqol or hr-qol or hqol).ti,ab.
24 treatment outcome/ or exp treatment failure/
25 ((treatment or cancer) adj5 outcome?).ti,ab.
26 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25
27 14 and 26
28 15 or 16 or 17 or 27

11. Evidence Selection

- Total number of publications reviewed: 284
- Total number of publications considered potentially relevant: 32
- Total number of publications selected for inclusion in this briefing: 10

12. References

Grutters JPC, Pijls-Johannesma M, Ruysscher DD, Peeters A, Reimoser S, Severens JL, Lambin P, Joore MA 2010. The cost-effectiveness of particle therapy in non small cell lung cancer: exploring decision uncertainty and areas for future research. *Cancer Treatment Reviews* 36: 468-76.

Hamaji M, Chen F, Matsuo Y, Kawaguchi A, Morita S, Ueki N, Sonobe M, Nagata Y, Hiraoka M, Date H 2015. Video-assisted thoracoscopic lobectomy versus stereotactic radiotherapy for stage I lung cancer. *Annals of Thoracic Surgery* 99: 1122-9.

Li M, Chen Y, Yang X, Dai X, Sun F, Zhang L, Zhan C, Feng M, Wang Q 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. *OncoTargets and Therapy* 10: 2885-92.

Louie AV, van Werkhoven E, Chen H, Smit EF, Paul MA, Widder J, Groen HJM, van den Borne BEEM, De Jaeger K, Slotman BJ, Senan S 2015. Patient reported outcomes following stereotactic ablative radiotherapy or surgery for stage IA non small-cell lung cancer: results from the ROSEL multicenter randomized trial. *Radiotherapy and Oncology* 117: 44-8.

Ma L, Xiang J 2016. Clinical outcomes of video-assisted thoracic surgery and stereotactic body radiation therapy for early-stage non-small cell lung cancer: a meta-analysis. *Thoracic Cancer* 7: 442–451.

NHS Choices 2017. http://www.nhs.uk/conditions/Cancer-of-the-lung/Pages/Introduction.aspx (accessed 13 September 2017)

National Institute for Health and Care Excellence 2011. The diagnosis and treatment of lung cancer (update). Clinical guideline 121. https://www.nice.org.uk/guidance/cg121 accessed 1 September 2017.

Paul S, Lee PC, Mao J, Isaacs AJ, Sedrakyan A 2016. Long term survival with stereotactic ablative radiotherapy (SABR) versus thoracoscopic sublobar lung resection in elderly people: national population based study with propensity matched comparative analysis. *BMJ* 354: i3570.

Shah A, Hahn SM, Stetson RL, Friedberg JS, Pechet TTV, Sher DJ 2013. Cost-effectiveness of stereotactic body radiation therapy versus surgical resection for stage I non small cell lung cancer. *Cancer* 119: 3123-3132.

Smith BD, Jiang J, Chang JY, Welsh J, Likhacheva A, Buchholz TA, Swisher SG, Shirvani SM 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: 324-31.

Yerokun BA, Yang CFJ, Gulack BC, Li X, Mulvihill MS, Gu L, Wang X, Harpole DM, D'Amici TA, Berry MF, Hartwig MG 2017. A national analysis of wedge resection versus stereotactic body radiation therapy for stage IA non small cell lung cancer. *Journal of Thoracic and Cardiovascular Surgery* 154: 675-86.e4.

Zhao J, Yorke ED, Li L, Kavanagh BD, Li XA, Das S, Miften M, Rimner A, Campbell J, Xue J, Jackson A, Grimm J, Milano MT, Kong F-M 2016. Simple factors associated with radiation-

induced lung toxicity after stereotactic body radiation therapy of the thorax: a pooled analysis of 88 studies. *Int J Radiat Oncol Biol Phys* 95: 1357-66.