CPAG Summary Report for Clinical Panel – URN 1674: Stereotactic ablative radiotherapy for non-small cell lung cancer

The Benefits of the Proposition – Use of SABR vs open* surgery to treat NSCLC			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	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.
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Not measured	
11.	Delivery of	Not measured	

	intervention		

* 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.

Other health metrics determined by the evidence review: Use of SABR vs open* surgery to treat NSCLC			
No	Metric	Grade of evidence	Summary from evidence review
1.	Recurrence-free survival	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.
2.	Loco-regional recurrence	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.
3.	Distant recurrence	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.
4.	Global health status	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.
5.	Mean total productivity cost	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.
6.	Hindrance score	B	Louie et al 2015 do not define hindrance scores. They report mean hindrance scores for SABR 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.
7.	Procedure and follow-up cost	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.
8.	Yield of QALYs	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.
9.	Incremental cost effectiveness ratio	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.

* 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.

The Benefits of the Proposition – Use of SABR vs video-assisted thoracic surgery to treat NSCLC			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	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 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.
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Not measured	
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review: Use of SABR vs video-assisted thoracic surgery to treat NSCLC			
No	Metric	Grade of evidence	Summary from evidence review
1.	Recurrence-free survival	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.
2.	Cancer-specific survival	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.
3.	Local control	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.
4.	Regional lymph node control rate	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.
5.	Distant control rate	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.

The Benefits of the Proposition – Use of SABR vs particle therapy to treat NSCLC			
No	*Metric*	*Grade of evidence*	*Summary from evidence review*
1.	Survival	Not measured	
2.	Progression free survival	Not measured	
3.	Mobility	Not measured	
4.	Self-care	Not measured	
5.	Usual activities	Not measured	
6.	Pain	Not measured	
7.	Anxiety / Depression	Not measured	
8.	Replacement of more toxic treatment	Not measured	
9.	Dependency on care giver / supporting independence	Not measured	
10.	Safety	Not measured	
11.	Delivery of intervention	Not measured	

Other health metrics determined by the evidence review: Use of SABR vs particle therapy to treat NSCLC			
No	Metric	Grade of evidence	Summary from evidence review
1.	Procedure cost	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.
2.	Yield of quality-adjusted life-years (QALYs)	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. .