



Great debate: surgery versus stereotactic radiotherapy for early-stage non-small cell lung cancer

Crispin Hiley ^{1,2}, Ahmed Salem,^{1,3} Tim Batchelor,⁴ Fiona McDonald,⁵ Matthew Evison ^{6,7}

Stereotactic ablative radiotherapy (SABR) for primary early-stage non-small cell lung cancer (NSCLC) is a precision therapy given over three to eight fractions, delivering a high dose to the tumour while minimising the dose to surrounding non-malignant tissues. SABR offers several advantages over conventionally fractionated radiotherapy, which is given daily for 4.0–6.5 weeks. Importantly, due to improved radiotherapy conformality, SABR allows a higher biologically effective dose (BED) to be given compared with conventionally fractionated radiotherapy. The increased tumour control using a higher BED was demonstrated recently in the phase III randomised CHISEL trial, which reported significantly reduced local failure rates in patients with peripheral tumours treated with SABR compared with conventionally fractionated radiotherapy (14% vs 31%) and an improvement in overall survival (OS).¹ This is reflected in real-world data from the UK National Lung Cancer Audit (NLCA), which showed that the HR for death for those who underwent SABR was 0.69 compared with conventionally fractionated radiotherapy.²

The current National Institute for Clinical Excellence guidelines recommend that SABR should only be offered to patients who decline or are not suitable or considered at high risk for surgery with lobectomy. While patient preference for surgery or SABR does exist,³ UK patients undergoing SABR are predominantly those felt

to be unsuitable for surgery due to frailty and/or the presence of comorbidities. Despite the success of comparing SABR with conventionally fractionated radiotherapy, attempts to objectively compare SABR with surgery have failed with the early closure of several international (STARS and ROSEL) and a UK randomised trial (SABRTOOTH) due to poor recruitment. Other trials comparing surgery and SABR in operable patients with stage I NSCLC are ongoing (NCT02468024, STABLE-MATES, and NCT02984761, VALOR).

In the absence of high-quality data, clinical guidelines are forced to make recommendations based on lower levels of evidence. The lack of randomised data means that we need to rely on comparative effectiveness research (CER) to compare these two modalities. CER seeks to draw a causal inference between the use of one intervention over another with regard to patient outcome. Unfortunately, this strategy can be prone to significant bias due to the absence of key clinical data, resulting in residual confounding.

Khakwani *et al* make use of the 2015 NLCA database and link this with the Hospital Episode Statistics (HES) and the Radiotherapy Dataset to compare the post-treatment survival between patients with stage I NSCLC treated with lobectomy or SABR.⁴ The authors should be commended for their use of national datasets to add useful data where currently level I evidence is lacking. They draw several conclusions. First, older age and reduced performance (PS) were associated with having SABR rather than surgery. Second, patients undergoing SABR have a worse OS even when adjusting for identifiable confounders and restricting analysis to those aged under 80 years and with PS of 0–1. Third, the median difference between the date of diagnosis and the date of treatment for surgery was 17 days, while that for SABR was 73 days.

With respect to the comparison of the two modalities and outcomes, the authors acknowledge that they only have OS data and not disease-specific survival nor

do they make use of additional national datasets, such as the Systemic Anti-Cancer Therapy Dataset to indirectly identify patients whose deaths may have resulted from cancer recurrence as opposed to death from a non-malignant cause. The data reflect current national practice and therefore should be considered as a comparison between a predominantly operable population (treated with lobectomy) with a predominantly inoperable population (treated with SABR). Operability is a complex assessment, best made by a specialised lung cancer multidisciplinary team (MDT), and considers anatomical location, the probability of a complete resection and the risk of post-operative breathlessness or death while taking into account patient factors such as age, pulmonary function, cardiovascular disease and PS. The prognostic effect of inoperability cannot be overstated. In a retrospective Japanese series of SABR-treated patients, 5-year survival rates of medically operable and inoperable patients were 64.8% and 35.0%, respectively.⁵

Investigators of the prematurely terminated international STARS and ROSEL trials, comparing surgery with SABR in patients with operable NSCLC, published a pooled analysis of the 58 patients randomised, reporting that there was a significant improvement in OS at 3 years favouring SABR (HR 0.14), but with no difference in recurrence-free survival.⁶ However, due to the significant differences between treatment arms and the small number of analysed patients, these results should be interpreted with caution. With the lack of randomised data available currently, the report from Khakwani *et al* adds to the growing CER literature comparing surgery with SABR. A recent meta-analysis of 16 CER studies which all use propensity score matching (PSM) demonstrated that OS favoured surgery (HR 1.48), but lung cancer-specific survival was not significantly different.⁷ The PSM approach attempts to reduce patient characteristics for patient cohorts treated with different interventions to a single propensity score and matches patients to assess outcomes. However, there are several concerns with this approach. First, the validity of the comparison between the two interventions mandates there to be no inherent bias in patient selection. Second, important clinical confounders are not always universally measured in all patient cohorts, questioning the accuracy of the matching process. Third, in order to match patients, these large cohorts are reduced to a subset of those initially analysed for the final comparison. Khakwani

¹CRUK Lung Cancer Centre of Excellence, University College London & The University of Manchester, London & Manchester, UK

²Clinical Oncology, University College London Hospitals NHS Foundation Trust, London, UK

³Clinical Oncology, Christie NHS Foundation Trust, Manchester, UK

⁴Thoracic Surgery, Bristol Royal Infirmary, Bristol, UK

⁵Clinical Oncology, Royal Marsden NHS Foundation Trust, London, UK

⁶North West Lung Centre, University Hospital South Manchester, Manchester, UK

⁷Institute of Inflammation and Repair, University of Manchester, Manchester, UK

Correspondence to Dr Crispin Hiley, CRUK Lung Cancer Centre of Excellence, University College London, London WC1E 6BT, UK; Crispin.Hiley@crick.ac.uk

et al should be praised for recognising that there was insufficient data for a PSM analysis.

The authors attempted to calculate a Charlson comorbidity score for patients by using the HES dataset to identify hospital admissions that were the result of a clinical code associated with a comorbidity that forms part of this index. They found that patients undergoing SABR were likely to have a higher comorbidity score, but when adjusting for this in their outcome analysis, OS remained higher in patients who underwent surgery. Unfortunately, comorbidities that did not result in hospital admission would be unreturnable, meaning that there was an incomplete account of comorbidities in the two populations.

The authors found that patients undergoing SABR waited much longer for treatment from diagnosis compared with patients treated with surgery. This is an important finding. One cause for this delay may be because in clinical practice, some patients with lung lesions are surveyed for several months before a decision for SABR is made, particularly in those patients where a biopsy has a high risk of complications and patients are treated without histological confirmation. However, there is evidence of improved survival related to time to treatment.⁸ So, concern has to be raised about the impact of such delays on patient outcomes and experience. There are opportunities to minimise the decision time regarding operability through the use of standardised physiological work-up and MDT protocols to streamline borderline or high-risk surgical candidates into dedicated services. These services should permit joint consultations with thoracic surgeons and clinical oncologists, ideally with additional input from thoracic anaesthetists, respiratory physicians and oncogeriatricians. Our desire and the clinical need for efficient and timely decision-making is in line with the national optimal lung cancer pathway and the agenda to improve the effectiveness of MDT discussions.

The second possible cause for delay is the need to refer to a SABR commissioned centre once the decision has been made, as currently SABR is not available in 40% of UK radiotherapy centres. Lack

of access to SABR was also highlighted in the recent comparison of SABR with conventionally fractionated radiotherapy from the NLCA.² Due to the technical nature of SABR planning and delivery, commissioning was initially restricted to a small number of centres. However, the technical capacity of radiotherapy centres has improved with the widespread availability of four-dimensional CT scanning, volumetric-modulated arc radiotherapy and online cone beam CT imaging, which are all required for SABR planning and delivery. Any evidence suggesting a referral to a SABR commissioned centre is negatively affecting patient outcome is a strong argument that SABR should be considered routine and that access, with the commissioning of more centres, should be widened.

It should also be recognised that the face of surgery is changing, with modern operative approaches to care aimed at delivering the same oncological efficacy but with a reduced physiological impact on the patient. Video-assisted thoracic surgery offers potential advantages over conventional thoracotomy, and the recently completed Video Assisted Thoracoscopic Lobectomy Versus Conventional Open Lobectomy for Lung Cancer (VIOLET NCT03521375) trial will shed further light on this. Sublobar resections (principally segmentectomy) spare functional lung tissue and are becoming popular in stage IA disease. Two large trials comparing sublobar resection to lobectomy are currently collecting long-term outcomes (Japan Clinical Oncology Group 0804, Cancer and Leukemia Group B 14053). As a result, it is likely that the patient population eligible for surgery will expand, giving frailer patients more treatment options.

Unfortunately, this study will not settle the debate of surgery against SABR in patients with operable or borderline operable stage I lung cancer. For the current time, surgery should continue to be regarded as the preferred treatment for patients with operable stage I lung cancer.

Twitter Matthew Evison @matthewevison1

Contributors All authors contributed equally to this manuscript.

Funding This study was funded by UCLH Biomedical

Research Centre.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Commissioned; internally peer reviewed.

© Author(s) (or their employer(s)) 2020. No commercial re-use. See rights and permissions. Published by BMJ.



To cite Hiley C, Salem A, Batchelor T, *et al*. *Thorax* 2020;**75**:198–199.

Accepted 31 December 2019
Published Online First 21 January 2020



► <http://dx.doi.org/10.1136/thoraxjnl-2018-212493>

Thorax 2020;**75**:198–199.
doi:10.1136/thoraxjnl-2019-214014

ORCID iDs

Crispin Hiley <http://orcid.org/0000-0002-5869-0775>
Matthew Evison <http://orcid.org/0000-0003-4066-5253>

REFERENCES

- Ball D, Mai GT, Vinod S, *et al*. Stereotactic ablative radiotherapy versus standard radiotherapy in stage 1 non-small-cell lung cancer (TROG 09.02 CHISEL): a phase 3, open-label, randomised controlled trial. *Lancet Oncol* 2019;**20**:494–503.
- Phillips I, Sandhu S, Lüchtenborg M, *et al*. Stereotactic ablative body radiotherapy versus radical radiotherapy: comparing real-world outcomes in stage I lung cancer. *Clin Oncol* 2019;**31**:681–7.
- Franks K, Mcparland L, Webster J, *et al*. P2.16-16 SABRTOOTH: a Feasibility study of SABR versus surgery in patients with peripheral stage I NSCLC considered to be at higher risk for surgery. *J Thorac Oncol* 2018;**13**:S837.
- Khakwani A, Harden S, Beckett P, *et al*. Post-Treatment survival difference between lobectomy and stereotactic ablative radiotherapy in stage I non-small cell lung cancer in England. *Thorax* 2020;**75**:237–43.
- Onishi H, Shirato H, Nagata Y, *et al*. Hypofractionated radiotherapy for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. *J Thorac Oncol* 2007;**2**:S94–100.
- Chang JY, Senan S, Paul MA, *et al*. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. *Lancet Oncol* 2015;**16**:630–7.
- Chen H, Laba JM, Boldt RG, *et al*. Stereotactic ablative radiation therapy versus surgery in early lung cancer: a meta-analysis of propensity score studies. *Int J Radiat Oncol Biol Phys* 2018;**101**:186–94.
- Navani N, Nankivell M, Lawrence DR, *et al*. Lung cancer diagnosis and staging with endobronchial ultrasound-guided transbronchial needle aspiration compared with conventional approaches: an open-label, pragmatic, randomised controlled trial. *Lancet Respir Med* 2015;**3**:282–9.