Editorial

The Great Debate: Surgery versus Stereotactic radiotherapy for early stage Non-small cell lung cancer.

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Stereotactic ablative radiotherapy (SABR) for primary early stage non-small cell lung cancer (NSCLC) is a precision therapy given over 3-8 fractions delivering a high dose to the tumour whilst minimising the dose to surrounding non-malignant tissues. SABR offers several advantages over conventionally fractionated radiotherapy which is given daily for 4-6.5 weeks. Importantly, due to improved radiotherapy conformality, SABR allows a higher biologically effective dose (BED) to be given compared to 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 to 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 the hazard ratio (HR) for death for those who received SABR was 0.69 compared with conventionally fractionated radiotherapy (2).

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

frailty and/or the presence of co-morbidities. 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 regards to patient outcome. Unfortunately, this strategy can be prone to significant bias due to the absence of key clinical data resulting in residual confounding.

In this issue, Khakwani *et al.* make use of the 2015 NLCA database and link this with the Hospital Episode Statistics (HES) and the Radiotherapy Dataset (RTDS) to compare the post-treatment survival between stage I NSCLC patients 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 receiving SABR have a worse OS even when adjusting for identifiable confounders and restricting analysis to those aged under 80 and with PS 0-1. Third, the median difference between the date of diagnosis and date of treatment for surgery was 17 days while for SABR it 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 the Systemic Anti-Cancer Therapy Dataset (SACT) to indirectly identify patients whose death may have resulted from cancer recurrence as opposed to death from a non-malignant cause. The data reflects 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 MDT, and considers anatomical location, the probability of a complete resection and the risk of postoperative 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 operable NSCLC patients, 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 sixteen CER studies, which all utilise 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. Thirdly, in order to match patients, these large cohorts are reduced to a subset of those initially analysed for the final comparison. Khakwani *et al.* should be praised for recognizing that there was insufficient data for a PSM analysis.

The authors attempted to calculate a Charlson co-morbidity score for patients by using the HES dataset to identify hospital admissions that were the result of a clinical code associated with a co-morbidity that forms part of this index. They found that patient receiving SABR were likely to have a higher co-morbidity score but when adjusting for this in their outcome

analysis, OS remained higher in patients who underwent surgery. Unfortunately, co-morbidities that did not result in hospital admission would be unreturnable meaning that there was an incomplete account of co-morbidities in the two populations.

The authors found that patients receiving SABR waited much longer for treatment from diagnosis compared to 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 onco-geriatricians. 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 versus 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 computed tomography (CT) scanning, volumetric-modulated arc radiotherapy (VMAT) 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 (VATS) offers potential advantages over conventional thoracotomy and the recently completed 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 (JCOG 0804; CALGB 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 operable or borderline operable stage I lung cancer patients. For the current time, surgery should continue to be regarded as the preferred treatment for patients with operable stage I lung cancer.

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