Surgery or stereotactic body radiotherapy for early-stage lung cancer: two sides of the same coin?

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Stereotactic body radiotherapy (SBRT) seems a promising alternative to surgery in high-risk patients; however, more robust clinical data are needed, especially when considering SBRT for low-risk early-stage NSCLC patients http://bit.ly/2Ytibks

Cite this article as: Berzenji L, Van Schil PE. Surgery or stereotactic body radiotherapy for early-stage lung cancer: two sides of the same coin? *Eur Respir J* 2019; 53: 1900711 [https://doi.org/10.1183/13993003.00711-2019].

Currently, the standard of care for resectable, early-stage and functionally operable nonsmall cell lung cancer (NSCLC) is complete surgical resection [1]. However, for elderly patients and patients with multiple comorbidities, surgery may not be the preferred option due to higher surgical morbidity and mortality [2]. An alternative treatment for this group of patients is stereotactic body radiotherapy (SBRT), which administers a high local dose of radiation in fewer fractions as an ablative treatment [3]. In recent years, SBRT has gained in popularity as it has shown better local control rates and less toxicity to surrounding structures when compared to conventional fractionated radiotherapy (CFRT). This was confirmed by the recently published CHISEL phase III randomised controlled trial (RCT) [4]. Due to these promising results and the expected rise in early detected tumours as a result of more lung cancer screening initiatives, an increasing amount of studies investigate whether SBRT could be an acceptable alternative to surgery in operable, early-stage NSCLC [5]. Although initial data from studies concerning SBRT for early-stage lung cancer seem to obtain good clinical outcomes and acceptable safety profiles, concrete data and large studies are still lacking. To date, no large phase III trials have been published. Three RCTs comparing surgery and SBRT in higher risk patients (Radiosurgery Or Surgery for operable Early-stage nonsmall cell Lung cancer (ROSEL); Stereotactic Radiotherapy *versus* Surgery (STARS); and Radiation Therapy Oncology Group (RTOG) 1021) attempted to compare these two treatment modalities but had to close early due to poor accrual [6]. A pooled intention-to-treat analysis of data from the ROSEL and the STARS trials suggested improved overall survival and recurrence-free survival with SBRT after 3 years [6]. However, these results were based on a small sample size and a short follow-up period, which warrants caution when interpreting these data [7, 8].

Due to the lack of high-level evidence, clinicians can currently only rely on retrospective and observational data. A fundamental problem with these types of studies is the heterogeneity of the study cohorts. In an intention-to-treat analysis by Spencer *et al.* [9], a total of 468 patients who underwent surgery (316 patients), SBRT (99 patients) or CFRT (53 patients) were analysed for treatment outcomes. Surgical treatment in this study consisted of either pneumonectomy, lobectomy or sublobar resection. Although

Received: April 08 2019 | Accepted: April 09 2019

overall survival was inferior in the SBRT group compared with surgery, the authors found no difference in cancer-specific, and combined cancer and treatment-related survival between SBRT and surgery [9]. In the propensity matched comparative analysis by Detillon *et al.* [10], the authors aimed at removing the ambiguity regarding surgical treatment by only including patients who were treated by a lobectomy using video-assisted thoracoscopic surgery (VATS). A total of 792 patients aged ⩾65 years with clinical stage I NSCLC underwent VATS lobectomy or SBRT. In this study, median overall survival rates were significantly better in the surgical group for unmatched (surgery: 77 months; SBRT: 38 months) and matched (surgery: 77 months; SBRT: 33 months) patients. The authors suggest that elderly patients with stage I NSCLC undergoing VATS lobectomy have better overall survival rates than patients undergoing SBRT [10]. Other recent retrospective studies comparing surgical resection to SBRT have found similar conflicting results [11, 12].

A number of attempts have been made to summarise the plethora of these non-randomised propensity score analyses. A meta-analysis by Chen *et al.* [13] combined results from 16 propensity score studies comparing surgery and stereotactic ablative radiation therapy for early-stage NSCLC. In this analysis, overall survival favoured surgery, but lung cancer-specific survival did not differ between SBRT and surgery. On further stratification, overall survival favoured lobectomy and sublobar resections over SBRT, but no significant results were found for cancer-specific survival [13]. In a recent systematic review and meta-analysis by Cao *et al.* [14] 23 patient cohort studies were included for quantitative analysis. Their results showed that overall survival, cancer-specific survival, disease-free survival and freedom from locoregional recurrence rates were better after surgery when compared to SBRT. On stratification, both lobectomy and sublobar resections showed superior overall survival rates when compared to SBRT. These data suggest that surgery provides better long-term clinical patient outcomes [14]. However, in both meta-analyses, the authors have emphasised that these findings could partially be a result of an inherent selection bias that is present due to different baseline characteristics for SBRT and surgical patients. So, at the present time, a clear consensus has not been reached and this topic remains hotly debated at major thoracic oncology conferences, also because long-term follow-up data are not yet available.

The MISSILE study (NCT02136355) provides an interesting study design [15]. In this original phase II trial SBRT and surgery are sequentially applied. Patients are initially treated with SBRT followed by surgery 10 weeks later. Updated results were presented at the 19th World Conference on Lung Cancer in 2018 in Toronto [16]. Out of 40 patients enrolled, 35 patients undergoing SBRT followed by surgery, could be assessed. Pathologically complete response rate was only 60%, demonstrating that 40% of patients still have viable tumour cells after high-dose SBRT.

It is evident that additional prospective clinical trials are necessary to shed more light on the controversies surrounding this topic. Currently, there are three ongoing RCTS that aim at comparing surgical resection and SBRT for stage I NSCLC: the Veterans Affairs Lung Cancer Or Stereotactic Radiotherapy (VALOR; NCT02984761), the JoLT-Ca Sublobar Resection *Versus* Stereotactic Ablative Radiotherapy for Lung Cancer (STABLEMATES; NCT02468024), and the Radical Resection *versus* Ablative Stereotactic Radiotherapy in Patients With Operable Stage I NSCLC (POSTILV; NCT01753414). Hopefully, these trials will be able to recruit a sufficient number of patients to provide more definitive answers regarding the treatment efficacy of SBRT compared to surgical resection. In addition, the Lung Cancer STARS trial (NCT02357992) aims to investigate 3-year survival outcomes and the safety profile of SBRT. Equally, integration of immunotherapy in our treatment algorithms will have a major impact in the near future [17].

In conclusion, although SBRT seems a promising alternative treatment to surgery for high-risk patients and patients who refuse surgical treatment, more robust clinical data are necessary to adequately compare these treatment modalities, especially when considering SBRT for low-risk patients with early-stage NSCLC. At the present time, an individual patient-oriented treatment proposal should be made by an experienced multidisciplinary team, taking into consideration morbidity and long-term results of each treatment modality, or a combination thereof.

Conflict of interest: None declared.

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