Editorial

Surgery versus SABR for early stage non-small cell lung cancer: the moving target of equipoise

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The notion that lobectomy is the standard treatment approach for operable early stage non-small cell cancer (ES-NSCLC) was recently challenged by the results from a combined analysis of two prematurely closed randomized controlled trials (STARS and ROSEL trials; NCT00840749 and NCT00687986) (1). In this study, Chang *et al.* pooled data from 58 patients with operable T1–2a (<4 cm) N0M0 NSCLC treated with lobectomy versus stereotactic ablative radiotherapy (SABR) and reported a similar 3-year recurrence-free survival between the two modalities and a 3-year overall survival (OS) in favour of SABR. Despite the numerous limitations inherent to post-hoc analysis of studies with a small sample size, these results have cast doubt over the superiority of surgery and supported SABR as a valid alternate option in operable patients with ES-NSCLC.

We read with interest the meta-analysis by Deng *et al.* from Sichuan University published in February 2017 in the *European Journal of Cardio-Thoracic Surgery* (2). This meta-analysis compared outcomes of SABR, lobectomy and sublobar resection based on the results of 12 matched cohort studies with a combined sample size of 13,598 patients. Results from this rigorously conducted study showed that SABR was associated with a significantly lower 3-year OS [relative risk for death (surgery/SABR) =0.78; 95% confidence interval (CI): 0.68–0.90, P=0.001] as well as increased hazard ratio (HR) for all-cause mortality compared to surgery [HR=1.60 (95% CI: 1.24–2.06), P<0.001]. Subgroup analysis revealed that SABR had significantly worse OS when compared to lobectomy [HR=1.68 (95% CI: 1.09–2.60]), but when SABR was compared with sublobar resection, the difference was not statistically significant [HR=1.52 (95% CI: 0.88–2.63)]. No statistically significant differences were found in the 3-year loco-regional control (LRC) achieved with either SABR or surgery. Although the authors concluded that "*lobectomy remains the best option for patients with stage I NSCLC who can tolerate it*", several limitations should be kept in mind when interpreting these results. Specifically, in the era of personalized medicine, other factors not examined in this study such as health-related quality of life (HRQoL), cost-effectiveness and treatment-related morality risk are highly relevant for optimal informed and shared decision-making.

Despite accurate methodology and efforts to reduce bias by strict inclusion of only high quality studies using matched analysis, the meta-analysis by Deng *et al.* remains limited by a selection bias inherent to retrospective comparisons. In fact, while the process of matching allows for compensation in imbalances in baseline patients and tumours factors, the data presented are limited by the availability of various factors in the retrospective setting. This is highlighted by the significant heterogeneity of matched variables across the studies included in this meta-analysis. As examples, only one study matched patients based on tumor

location (3), one study did not match for patient comorbidities (4) and over half did not match for pulmonary function (4-10). The omission of these and other unmeasured confounders may have influenced treatment allocation. The potential for confounding by indication is further illustrated by the high inter-study variation (as shown by the high I^2 scores) for their overall effect sizes. Furthermore, LRC rates were available in only 4 of the 12 included studies and were found to be similar at 3 years between SABR and surgery, as well as between SABR and lobectomy. Certainly additional data on rates of cancer recurrences, late toxicities, competing risks, causes of death, disease-free survival and LRC would be helpful in understanding potential OS differences between surgery and SABR.

To ensure a relevant contemporaneous interpretation of comparison of surgery and SABR, it is crucial that the debate reflect the best current SABR and surgical practice. Indeed, both have significantly evolved over the last decade, which do question the current validity of the results in the present meta-analysis. Regarding SABR, dose regimens across studies ranged from 32–60 Gy in 2–12 fractions, with several studies including patients treated below the guideline-recommended biologically effective (BED) tumour dose of 100 Gy_{10} (3,4,8,11). Of greater concern, some studies did not include radiation dose information (5,7,9). Doses ≥100 Gy_{10} have been adopted in most current radiotherapy practices, after studies on efficacy demonstrated decreased local control with doses below 100 Gy_{10} (12). Another change in SABR practice that may not be reflected in the current meta-analysis is the widespread application of risk-adapted schedules for centrally located tumors after reports of increased toxicities with use of standard 60 Gy in three fractions (13). With respect to surgery, the increasing use of video-assisted thoracoscopic surgery (VATS) appears to be associated with decreased morbidity and treatment-related mortality. Although this benefit appears to be particularly noteworthy for higher-risk surgical patients, the overall benefit of VATS remains controversial (14). Although Deng *et al.* accounted for potential differences between lobectomy and sublobar resection, they did not distinguish the outcomes of VATS and open surgery, with several studies including mixed VATS and open surgery cohorts (5,8,15) and other studies involving VATS only (3,16). This further contributes to the heterogeneity of data across studies.

Treatment related morbidity and 90-day post-treatment death are among the cornerstones of treatment decision-making in the borderline operable early-stage lung cancer population. A previously published Markov model-based decision analysis comparing SABR to surgery predicted a 5-year OS benefit in favour of surgery reaching 3% (17), consistent with the current meta-analysis. However, the model also predicted that the potential OS benefit was mitigated when post-surgical mortality risk exceeded 3%. In the pooled analysis from the STARS and ROSEL trials (1), 90-day mortality rates of surgery and SABR were 4% and 0%, respectively. In addition, the grade 3–4 toxicity rate was 44% with surgery and only 10% with SABR. Considering the generalizability of these results, a SEER study of 9,093 patients with ES-NSCLC aged ≥66 years reported unadjusted 90-day mortality of 4% with lobectomy and 1% with SABR (18). In a systematic review of higher risk patients with co-existing severe chronic obstructive pulmonary disease (COPD), 30-day mortality was 10% with surgery and 0% with SABR (19). Thus, although limited, the available current evidence suggests that SABR is associated with better tolerability and rare 90-day mortality. Therefore, we contend that in higher risk patients, such as elderly or patients with severe COPD, these considerations should be at the forefront of the treatment decision process.

Of equal importance, HRQoL data should be carefully considered and discussed as an integral part of the decision-making process. In a recently published systematic review of HRQoL after SABR for ES-NSCLC (20), 7 of 9 prospective cohorts of patients showed no clinically significant changes in HRQoL. A single study reported deterioration of fatigue after 135 days and another study described deterioration of dyspnea at 2 years. In contrast, a systematic review of HRQoL following lung cancer surgery (21) reported a meaningful decline in physical function 6 months post-operatively that persisted at 2 years. In this review, among 3 studies assessing long term HRQoL post-surgery, 1 reported persistent declines in physical functioning, dyspnea and fatigue at ≥2 years after surgery. Direct comparison of these data with the limited SABR literature is hindered by the inclusion of stage II–III NSCLC in the surgical systematic review, selection bias, heterogeneity of HRQoL assessments methods across studies, and possible improved HRQoL with VATS *vs.* open surgery. To date, the only available prospective comparison of HRQoL outcomes of SABR *vs.* surgery in ES-NSCLC is derived from the prematurely closed ROSEL randomized trial (22). In this hypothesis generating study, the HRQoL results from 22 randomized patients suggested that SABR was associated with better global health status and lower indirect costs of productivity loss.

Beyond considerations at the patient level, health care systems, insurance providers and governments are interested in the health economics of both treatment modalities. Cost-effectiveness evaluates the combined monetary cost and health impact of a given intervention and is a metric of increasing importance in the context of value-based oncologic care. The current literature on cost-effectiveness of surgery versus SABR in ES-NSCLC is limited and shows conflicting results. A recent Canadian cost-effectiveness study suggested that while SABR was preferred over sublobar resection and conventional radiotherapy, lobectomy remained the most cost-effective modality (23). In a propensity score matched study focusing on high-risk patients, although SABR was found to be less costly, surgery was found to be more cost-effective owing to the observed benefit in OS (7). Finally, in an American Markov model of cost-effectiveness, in patients who were clearly operable, surgery was more cost-effective, whereas in borderline operable patients, SABR was the most cost-effective approach (24). Ultimately, these findings suggest that the potential cost-effectiveness differences between surgery and SABR may be small, and may be most sensitive to patient preference, HRQoL, and short-term risk considerations—factors that are all proportional to a patient's risk category. Cost-effectiveness should be the subject of future prospective studies.

In summary, despite inherent selection bias and heterogeneity of patients across studies, Deng *et al.* successfully compiled the best retrospective survival data of patients with ES-NSCLC treated with surgery or SABR available. We agree that while surgery remains the standard of care in operable patients with ES-NSCLC, SABR also merits discussion as an alternate gold-standard option, especially in the era of shared decision-making. Perhaps the most striking evidence for the need of systematic discussions of these cases in a multidisciplinary setting emerges from a binary experiment in the Netherlands that demonstrated that pulmonologists, thoracic surgeons and radiation oncologists had poor consistency of treatment recommendation (SABR *vs.* surgery) when presented with various scenarios of ES-NSCLC (25).

Currently, at least four randomized controlled trials are on-going and will provide additional information in the debate between surgery and SABR for ES-NSCLC: (I) STABLE-MATES trial from the United States compares sublobar resection to SABR in high risk peripheral tumors (NCT02468024); (II) SABRTOOTH trial from the United Kingdom compares lobectomy/sublobar resection to SABR in high risk peripheral tumors (NCT02629458); (III) the POSTLIV trial from China compares radical resection to SABR in peripheral tumors (NCT01753414); and (IV) the VALOR Veterans Affairs study will compare lobectomy/segmentectomy to SABR in central and peripheral tumors. Meanwhile, as more robust randomized evidence is awaited, treatment decision should involve rigorous physician-to-patient discussions founded on transparent synthesis of the current evidence, multidisciplinary tumor board discussions and elicitation of patient values.

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Footnote

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