Should stereotactic ablative radiotherapy be considered as an equal to surgical resection in the management of operable stage I lung cancer?

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Lobectomy is the accepted standard of care for early stage non-small cell lung cancer (NSCLC); supported by a randomized trial which reported a local recurrence rate three times that of lobectomy in patients undergoing sublobar resection for stage IA NSCLC (1). However, not all patients have the performance status to tolerate a lobectomy; they are technically resectable but not physically operable candidates. The American College of Chest Physicians guidelines recommend that such patients should be offered, based on decreasing levels of performance status, segmentectomy, wedge resection and stereotactic ablative radiotherapy (SABR) (2).

Recent evidence suggests that sublobar resection could yield equal results in high-risk patients with small peripheral tumors. Also, SABR has been shown to provide acceptable local control in patients with both operable and inoperable stage I NSCLC. Retrospective and phase 2 prospective trials have reported that the overall survival is similar in patients with operable stage I NSCLC irrespective of treatment with SABR or surgery (3-6). The Japanese Clinical Oncology Group 0403 trial and the Radiation Therapy Oncology Group Trial 0618, two prospective phase II trials studying SABR in operable stage I NSCLC have reported overall survival at 3 years to be between 76% and 85% respectively (4,5). These survival results are equivalent to those from surgical resection.

This evidence suggesting equipoise between SABR and surgical excision has led to an emerging debate regarding what should be the standard treatment for stage I NSCLC especially in elderly patients with multiple comorbidities. The results of the US National Lung Cancer Screening Trial has led to a decision by Medicare to cover lung cancer screening using CT scans (7). There have already been predictions that the introduction of widespread screening will lead to a tenfold increase in the number of patients presenting with resectable lung cancer (8). This potential increase, potentially in elderly patients with significant comorbidities, will increase the demand for a conclusion to this debate and clarity regarding the optimal treatment for this patient group.

There is a lack of high-level evidence to support the superiority or even the non-inferiority of oncological treatment over surgery. Several randomized controlled trials have sought to address this debate including the STARS trial [NCT00840749] and the ROSEL trial [NCT00687986]. Both studies were closed early due to poor accrual. Chang *et al.* amalgamated the data from these two trials to perform a pooled analysis and reported the "first phase 3 randomized data comparing SABR and surgery" (9). They reported that there was a significantly lower overall survival with surgery compared to SABR at 3 years. They concluded that SABR had "emerged as a non-invasive standard treatment alternative to surgery". Their data had many limitations; it only contained 58 patients, it was retrospective and the ROSEL data included patients who had a cancer diagnosis based on clinical features alone and no histology. Within this small group, there were surgical patients whose post resection histology confirmed benign

lesions so the SABR arm could equally have been treating inappropriate patients.

The majority of the evidence comparing the two treatments has including patients undergoing lung resection via thoracotomy. However, this does not reflect current practices as many resections, especially lung parenchyma sparing resections, are performed via minimally invasive video assisted thoracic surgery (VATS). VATS lung resection is becoming the gold standard treatment for stage I lung cancer and is associated with less morbidity and improved outcomes. Hence, evidence comparing SABR versus resection via thoracotomy will struggle to be recognized and accepted by thoracic surgeons.

Paul *et al.* aimed to address this limitation by comparing survival of patients with stage I NSCLC treated with SABR as compared VATS sublobar and lobar lung resection in patients aged over 66 (10). They collated data from the Surveillance, Epidemiology, and End Results (SEER) registry linked with the Medicare database in the US and performed propensity matching comparative analysis. The objective was to compare cancer specific survival after VATS sublobar (segmentectomy or wedge) resection and SABR for tumors ≤2 cm in size and VATS resection (sublobar or lobectomy) for tumors ≤5 cm in size.

The 3-year follow up of the patients with tumors ≤2 cm, in the propensity matched cohort, found that the overall survival was 52.2% and 68.4% for patients undergoing SABR and VATS sublobar resection respectively and the cancer specific survival was 82.6% and 86.4% respectively. In the full cohort, 144 (52.4%) patients undergoing SABR died during follow up, with 37 (13.5%) dying from lung cancer; 138 (33.3%) patients undergoing VATS died during follow up, with 44 (10.6%) dying from lung cancer.

The 3-year follow up of patients with tumors ≤5 cm found, in the propensity matched cohort, that the cancer specific survival at 3 years was 80.0% and 90.2% in patients undergoing SABR and VATS respectively. In the full cohort, 419 (58.7%) in the SABR group died during follow up with 119 (16.7%) dying from lung cancer. In the surgical group, 680 (30.1%) died during follow up of which 198 (8.8%) dying from lung cancer.

The authors concluded that patients undergoing VATS, particularly for larger tumors, "might have improved cancer specific survival compared with patients undergoing SABR". The authors have commendably highlighted that this critical and contemporary debate still does not have high-level evidence to support fully informed patient centered decision making. However, their study has many limitations involving staging, poor lymph node sampling and pooling of surgical patients irrespective of procedure.

The SABR group was clinically staged whereas the surgical group benefit from pathological staging, which may lead to stage migration within the surgical group. Lymph nodes were not sampled in 13% of the surgical cohort, which could be argued to reflect poor surgical practice and impact on the accuracy of their final staging. The analysis pooled the results of the surgical patients irrespective of whether they have undergone a lobectomy, segmentectomy or wedge resection. A wedge resection is known to be an inferior cancer operation compared to lobectomy or segmentectomy so these results should be reported separately to avoid undermining the results of anatomical resections or falsely inflating the results of wedge resections (1).

Ultimately, Paul *et al.* have not managed to provide clinicians with a randomized controlled trial, something which this debate desperately needs. Clinicians would be cautious to support SABR as an equal treatment to surgery for operable stage I lung cancer without the backup of a RCT, which could leave them vulnerable to litigation if a cancer recurs after 'curative' SABR treatment.

Intriguingly, the vast majority of patients in this study, who died during the follow up period, did not die from lung cancer. The actual cause of death are not reported but it can be assumed that these patients died from their co-morbidities. In view of that, future studies should collect quality of life data and assess which treatment maintains, as closely as possible, the pre-treatment quality of life. This outcome measure would be an important factor when counseling elderly patients about their treatment options.

Ultimately, SABR and VATS techniques have increased the size of the curative playing field for elderly patients with significant comorbidities. Failure of engagement, surgical complacency or even fears of a turf war have all potentially played a role in the failure of completion of RCTs into this subject. As clinicians, it should be a source of shame if future RCTs also fail to adequately recruit as we could be depriving a vulnerable group of patients from treatment options that are both adequate in terms of disease control but also maintaining a good quality of life.

So, should SABR be considered as an equal surgery for the treatment for stage I lung cancer? Not yet, but it clearly will have an important role, especially in patients with comorbidities, which can only be further defined if clinicians involved with the management of lung cancer support future RCTs. It is imperative that high quality

evidence is established to guide both our multi-disciplinary teams and to ensure that patients appropriately benefit from new and evolving technologies.

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