Commentary

Is it time for SABR to overtake surgery as the treatment of choice for stage I non-small cell lung cancer?

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The role of surgery as the standard of care for early stage non-small cell lung cancer (NSCLC) is being called into question. Lobectomy has traditionally been the accepted standard of care for early stage NSCLC; supported by a randomized trial that found that patients undergoing a sublobar resection in stage IA NSCLC had a local recurrence rate three times that of lobectomy (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).

More recent evidence has suggested that sublobar resection could yield equal results in high-risk patients with small peripheral tumors. Furthermore, 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 shown that 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 non-small cell lung cancer, have reported overall survival data which is equivalent to that of surgery. They reported overall survival at three years to be between 76% and 85% respectively (4,5).

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. This debate will become more potent following the decision made by Medicare to cover lung cancer screening using CT scans following the results of the US National Lung Cancer Screening Trial (7). The introduction of widespread screening has already led to predictions that the number of patients presenting with resectable lung cancer will increase by ten times current numbers (8). This potential increase, in most likely elderly patients with significant comorbidities, will increase the demand for clarity regarding the optimal treatment in this patient group.

Unfortunately, there is a lack of high-level evidence to support the superiority of surgery versus oncological treatment. Several randomized controlled trials have sought to address this debate including the STARS trial [NCT00840749] and the ROSEL trial [NCT00687986]. Sadly, both of these studies were closed early due to slow accrual. Chang *et al*. collated the data from these two trials and performed a pooled analysis and reported, what they claimed to be, 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".

However, their data had many limitations. The pooled analysis only contained 58 patients, it was retrospective and the ROSEL data included patients whom had a cancer diagnosis based on clinical features alone and no histology. Even in that small group, there were patients whose post lung resection histology reported benign lesions so the SABR arm could equally have been treating patients with benign disease.

The majority of the evidence comparing the two treatments has including patients undergoing lung resection via thoracotomy. Any results from these studies would be rejected by surgeons as this does not reflect current practices where resections and especially sublobar or wedge resection are commonly 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.

Paul *et al*. have attempted to address this limitation in previous studies by comparing survival of patients with stage I NSCLC with SABR versus 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 United States and subjected the data to 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 should be commended for highlighting again that this important and contemporary debate still does not have high-level evidence to support or enable fully informed patient centered decision making. However, the study has many limitations; ultimately it is not a randomized controlled trial, which is what this debate desperately needs. Clinicians may be uneager to recommend SABR to treat operable stage I lung cancer without the backing of a RCT especially as it could leave them vulnerable to litigation if a cancer recurs after 'curative' SABR treatment.

Accurate cancer staging is another limitation within this study. The SABR group was clinically staged whereas the surgical group benefit from pathological staging, which may lead to stage migration within the surgical group. Also, 13% of patients in this cohort did not have any lymph nodes sampled during surgery, which could be argued to reflect rather poor surgical practice. Additionally, the analysis combines 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).

An interesting aspect of this study is that the vast majority of patients, who died during the follow up period, did not die from lung cancer. Whilst the actual cause of deaths was not reported, it can be assumed that these patients died from their co-morbidities. In view of that, future studies should collect data regarding quality of life and assessing which treatment maintains, as closely as possible, the pre-treatment quality of life. This outcome measure would be undeniably an important factor when counselling 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, is it time for SABR to overtake surgery as the treatment of choice for stage I lung cancer? No, but

it is time for high quality evidence to guide our multi-disciplinary teams and support our patients in their decision making process.

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None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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