Editorial

# What is the role of stereotactic ablative radiotherapy in the management of surgically resectable and operable stage I non-small cell lung cancer?

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The use of stereotactic ablative radiotherapy (SABR) with the intention to cure stage I non-small cell lung cancer (NSCLC) in preference to surgical resection is currently a contentious and hotly debated topic. It may even be claimed that SABR could impact the future management of lung cancer in the same way that percutaneous coronary stents impacted the management of ischemic heart disease.

Treatment of lung cancer has evolved over recent decades with surgical advances such as minimally invasive surgery and enhanced recovery programmes along with new oncological technologies such as SABR and immunotherapy. SABR was initially intended for the management of early stage NSCLC in patients who despite being technically resectable, were physiological inoperable due to co-morbidities or whom had declined surgery.

In early studies, SABR demonstrated acceptable levels of local control but subsequent retrospective and phase II prospective trials reported overall survival (OS) results which were similar to patients undergoing surgical resection of stage I NSCLC (1-4). The Japanese Clinical Oncology Group 0403 trial and the Radiation Therapy Oncology Group Trial 0618, two prospective phase II trials focused on the OS following the use of SABR in operable stage I non-small cell lung cancer, reported OS at three years to be between 76% and 85% respectively (2,3). These results were equivalent to the OS outcomes of surgical patients (5). This equivalence led to suggestions that SABR should be considered as a standard treatment for stage I NSCLC especially in patients who despite co-morbidities would traditionally be surgical candidates.

However, despite these promising results, no high-level evidence has materialized to support the superiority of one treatment over the other. Randomized controlled trials have attempted to tackle the issue, including the STARS trial [NCT00840749] and the ROSEL trial [NCT00687986], but both studies closed early due to slow accrual. Chang *et al.* performed a pooled analysis of the data collected from STARS and ROSEL and reported, what they claimed to be, the first phase III randomized data comparing SABR and surgery (6). They found a significantly lower OS after surgery compared to SABR at 3 years and concluded that SABR had "emerged as a non-invasive standard treatment alternative to surgery". However, their analysis was potentially deceptive; it consisted of only 58 patients, it was retrospective and the ROSEL data included patients whose cancer diagnosis was based on radiological features alone without any histological confirmation. Within this small group, there were patients whose post resection histology confirmed benign lesions so the SABR arm could equally have been treating inappropriate patients.

A meta-analysis of six studies with 864 patients, published

in 2014, indicated that surgery had a superior three-year survival compared to SABR (7). This study was confounded by the surgical group consisting of an amalgamation of surgical patients irrespective of whether they had undergone a lobectomy, segmentectomy or wedge resection. These different procedures have historically been proven to have variable outcomes with regards to survival and recurrence and should not be treated as the same procedure (8).

The Deng *et al.* meta-analysis seeks to address these issues regarding the comparison of SABR versus surgery (9). Firstly, it tackles the lack of high-level evidence, namely randomized controlled trials, by performing a meta-analysis of the highest level of evidence available. Following a systematic review, they identified 12 observational studies that satisfied their inclusion criteria such as sufficient data on three-year survival, overall survival and loco-regional control (LRC). The unique aspect of this meta-analysis is its subgroup analysis where they compare SABR versus surgery overall but also specifically against lobectomy and sublobar resection.

The results of the overall analysis, irrespective of type of surgery, found that pooled three-year survival for patients treated with SABR and surgery were 47.7% and 68.1% respectively. There was a significantly lower three-year survival in the SABR group. Eleven studies reported OS; the SABR group had a significantly shorter OS versus the surgical cohort. Only four studies reported three-year LRC but they reported no difference between the SABR and surgical cohorts, 83.9% and 86.8% respectively.

In the subgroup analysis of SABR versus lobectomy, six studies reported adequate data to be included. The pooled three-year survival for the SABR and lobectomy groups was 61.3% and 70.6% respectively, which was not statistically different. They reported that SABR group had a significantly shorter OS compared to the lobectomy group. There was no difference between either group with respect to LRC.

The subgroup analysis of SABR versus sublobar resection reported the data from four studies, totaling 964 patients. The 3-year survival of the SABR and sublobar resection groups was 57.0% and 61.1% respectively, which had no statistical difference. Also, there was no significant difference in OS or three-year LRC between either group.

They concluded that their subgroup analysis helped to explain why other studies had reported such differing outcomes when comparing SABR and surgery due to the amalgamation of differing surgical procedures into one group. This broad grouping of surgical procedures was to the detriment of anatomical resections as the poorer outcomes of sublobar resections would negatively impact on surgical results. Based on their results, they recommend that surgery, particularly lobectomy, is superior to SABR regarding 3-year and overall survival but that SABR is comparable with regards to LRC across all subgroup analysis.

The authors should be commended as their study has tackled a highly contemporary and contentious debate, which is in need of high-level evidence. However, their study has several limitations, such as the quality of their data as it is extracted from retrospective cohort studies rather than RCTs and some studies were not ranked as high quality using the Newcastle-Ottawa scale. Also, the SABR group was heterogeneous with varying or unknown doses of radiation delivered. The sublobar group included segmentectomy and wedge resections together which is controversial as segmentectomies are anatomical resections and their outcomes have been shown to be superior to wedge resections (10). Finally, some of the cohorts had short follow up periods so they could not be included in the primary endpoint analysis of 3-year survival and LRC.

An important aspect of surgical management that Deng *et al.* does not address is the impact of whether the patients have undergone lung resection via thoracotomy or minimally invasive video assisted thoracic surgery (VATS). VATS lung resection is becoming the gold standard treatment for stage I lung cancer and for surgeons to engage and respect the results of studies comparing SABR and surgery, we believe that reporting specifically the results of VATS lung resections versus SABR would be necessary to reflect current practice.

A study by Paul *et al.* recently addressed this issue in a propensity matched analysis where they compared survival of stage I NSCLC patients who underwent SABR versus VATS sublobar and lobar lung resections (11). They extracted data from the Surveillance, Epidemiology, and End Results (SEER) registry in the US for patients aged over 66 with NSCLC with tumors ≤2 and ≤5 cm. The 3-year OS of patients with tumors ≤2 cm was 52.2% and 68.4% for the SABR and VATS groups respectively. In the group of tumors ≤5 cm, the cancer specific survival at three years was 80.0% and 90.2% in patients undergoing SABR and VATS respectively. Paul *et al.* concluded that patients undergoing VATS particularly for large tumors "might have improved cancer specific survival compared with patients undergoing

 

SABR".

Of note, 58.7% in the SABR group died during follow up of which 16.7% died from lung cancer. Similarly, in the VATS group 30.1% died during follow up but only 8.8% died from lung cancer. This highlights that the vast majority of stage I NSCLC patients who die during follow up, do not die of lung cancer. It could be assumed that these patients die from other co-morbidities commonly seen in a population highly populated with life-long smokers. This is an interesting area, which with further investigation could identify a certain patient group whom despite extensive co-morbidities are still eligible for surgery but in fact could benefit from the less invasive and low toxicity of SABR.

Impact on quality of life is rarely addressed when comparing these treatment modalities. Elderly patients faced with the option of surgical resection with a proven survival benefit versus outpatient radiotherapy treatment, would benefit from information detailing the impact that each treatment would have on their quality of life. Pre-operative counseling which informs them of the potential impact on their independence and baseline functioning might be just as, or even more, important to them as survival data. Some elderly patients may prefer "good" quality of life years versus additional survival years acquired at the cost of a lower quality of life or impaired independence.

Ultimately, this debate can only be moved forward by a RCT, which includes patient undergoing VATS resections and analysis of the impact on quality of life. Currently, lower level data is being complied and repackaged as high level data and inaccurate conclusions could be made about the role of SABR in stage I NCSLC. Everyone involved in the peri-diagnosis care of lung cancer patients needs to be pro-active to ensure that future RCTs do not succumb to the same fate as previous studies due to poor accrual. Fears of losing patients to another specialties treatments are likely to be groundless especially with advent to widespread screening programmes being introduced which could lead to a tenfold increase in the number of patients presenting with early stage lung cancer (12). SABR clearly has an important role in the treatment of stage I NSCLC but clinicians need to support future RCTs to ensure this role is accurately defined to ensure that patients appropriately benefit from this new and evolving technology.

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## Footnote

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

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