Stereotactic ablative radiation therapy for operable early-stage lung cancer—considerations and controversies

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Contributions: (I) Conception and design: All authors; (II) Administrative support: None; (III) Provision of study materials or patients: D Moghanaki; (IV) Collection and assembly of data: CP Daniels; (V) Data analysis and interpretation: CP Daniels; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Stereotactic ablative radiation therapy (SABR) is the current standard of care for patients with stage I non-small cell lung cancer (NSCLC) who are not fit for surgery or who refuse an operation. The available evidence suggests that SABR is effective in obtaining durable local control in operable patients as well, but whether it can currently be recommended as an alternative to surgery in this population is contentious because of the absence of high quality long-term prospective randomized survival data. Retrospective comparisons of SABR with surgery are available, but have been subject to bias from the confounding effect of operability. Previous attempts to prospectively compare SABR with surgery in a randomized fashion have been unsuccessful due to poor accrual. From these efforts, the randomized data from two of these prematurely closed trials were combined to explore the potential outcome if they had completed accrual, though the analyses were largely dismissed by the academic community. In this review, we give a critical overview of the available data in this context, and address key areas of controversy which include the questioned importance of pathologic staging of the mediastinum, the appropriate thresholds for empiric treatment of suspicious lung nodules without biopsy confirmation, and the challenges of post-treatment surveillance of the irradiated lung. We also address design considerations aimed at maximising enrolment into ongoing prospective phase III trials of SABR versus surgery.

Keywords: Early stage; non-small cell lung cancer (NSCLC); radiation therapy; stereotactic body radiotherapy (SABR)

Received: 21 December 2018; Accepted: 25 December 2018; Published: 09 January 2019.
doi: 10.21037/tro.2019.01.01
View this article at: http://dx.doi.org/10.21037/tro.2019.01.01

SABR in early-stage non-small cell lung cancer (NSCLC)

Stereotactic ablative radiation therapy (SABR) for the treatment of early-stage NSCLC is a precise and safe radiation therapy technique (Figure 1) that has been available since the 1990s (1). It offers local tumour control rates greater than 90% at 5 years as demonstrated in the recently updated results of the RTOG 0236 study that was initially activated in the early 2000s (2). A pair of randomized studies that compared SABR to protracted conventionally fractionated radiotherapy in medically inoperable patients have been recently reported. These include the randomized SPACE trial (n=102), which prescribed 15 Gy ×3 to the periphery of the planning target volume (PTV) in the cohort randomized to SABR. It was
the first to complete and demonstrated that when compared to conventional long-course radiotherapy, patients treated with SABR had less dyspnea, chest pain, or cough; although, local control and overall survival (OS) rates were equivalent (3). Meanwhile, in initial findings from the randomized CHISEL trial (n=101), which prescribed 18 Gy ×3 or 12 Gy ×4 to the periphery of the PTV in the cohort randomized to SABR, patients were found to have superior local control and OS rates when compared to the longer course of protracted conventional radiotherapy (4).

Today, SABR is considered the standard of care for patients with stage I NSCLC whenever they are inoperable, or decline surgery (4,5). Yet, when delivered to a select series of operable patients, the results of SABR are surprisingly comparable to prospective surgical outcomes. Multiple prospective and retrospective series have now shown that whenever SABR is delivered to patients with a longer life expectancy, OS rates can be 77–95% (6-12) and 45–70% (8,10,13-15), at 3 and 5 years, respectively (Table 1). A deeper analysis of these operable series demonstrates local control rates between 86–97% can be achieved at 5 years (10,13-15) (Table 1), which once again represents results that are comparable with long-term surgical data (18,19). Such reports have led many to question the primacy of surgery over radiotherapy as a curative treatment for lung cancer, and continue to provide the foundation for multiple phase III trials that have attempted to compare these two treatments in a randomized fashion (NCT00687986, NCT00840749, NCT01336894).

**Potential advantages of SABR over surgery for stage I NSCLC**

Supported by the above efficacy data, the utilization of SABR for early NSCLC has continued to grow. A recently published analysis from the Surveillance, Epidemiology and End Results (SEER) database has shown an increase in utilization of definitive radiotherapy for stage I NSCLC from 13% to 29% between 2004 and 2012 that is coincident with a rise in the popularity with SABR (20). What factors may be driving physician and patient uptake of SABR? We believe that when applied to carefully selected patients, SABR presents a more attractive treatment proposition for patients and physicians when compared to an operation that requires a hospitalization that may result in a prolonged stay or complication. It is a convenient and safe outpatient procedure that does not expose patients to the known risks of early or delayed postoperative morbidity or mortality that can be seen following pulmonary resections when performed at low-volume hospitals by surgeons who are not specialized in thoracic surgery (21-24). Whilst it is true that very low 90-day postoperative mortality rates for stage I lung cancer of approximately 1–2% have been achieved in select series (25), these data come from specialized high volume thoracic surgical centres, and do not necessarily reflect outcomes in the general community. For example, in the UK National
Table 1: Published experience with SABR in operable patients with early NSCLC

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Study design</th>
<th>Dose/fraction</th>
<th>Size (n)</th>
<th>Age, median [range] (years)</th>
<th>3-y results</th>
<th>4-y results</th>
<th>5-y results</th>
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<td>OS, %</td>
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<tr>
<td>Uematsu et al. (12)†</td>
<td>2001</td>
<td>Retrospective</td>
<td>50–60 Gy/5–10#</td>
<td>29</td>
<td>71 [54–86]</td>
<td>86</td>
<td>–</td>
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<td>Chang et al. (STARS/ROSEL) (9)</td>
<td>2015</td>
<td>Prospective</td>
<td>54 Gy/3#; 50 Gy/4#; 60 Gy/5#</td>
<td>31</td>
<td>67.1 [43–82]</td>
<td>95</td>
<td>96</td>
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<td>Komiyama et al. (16)</td>
<td>2015</td>
<td>Retrospective</td>
<td>32–70 Gy/4–15#</td>
<td>661</td>
<td>75</td>
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<td>Timmerman et al. (RTOG 0618) (2)</td>
<td>2013, 2018</td>
<td>Prospective</td>
<td>54 Gy/3#</td>
<td>26</td>
<td>72.5 [54–88]</td>
<td>–</td>
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<td>57</td>
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<td>56</td>
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<td>Lagerwaard et al. (11)</td>
<td>2012</td>
<td>Retrospective</td>
<td>60 Gy/3#; 60 Gy/5#; 60 Gy/8#</td>
<td>177</td>
<td>76 [50–91]</td>
<td>84.7</td>
<td>81</td>
<td>51.3</td>
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<td>Onishi et al. (13)</td>
<td>2011</td>
<td>Retrospective</td>
<td>45–72.5 Gy/3–10#</td>
<td>87</td>
<td>74</td>
<td>–</td>
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<tr>
<td>Shibamoto et al. (15)†</td>
<td>2015</td>
<td>Prospective</td>
<td>44 Gy/4#; 48 Gy/4#; 52 Gy/4#</td>
<td>60</td>
<td>77 [29–89]†</td>
<td>–</td>
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<td>66</td>
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<td>74</td>
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<tr>
<td>Nagata et al. (JCOG 0403) (8,17)</td>
<td>2015, 2018</td>
<td>Prospective</td>
<td>48 Gy/4#</td>
<td>64 (3 y); 40 (5 y)</td>
<td>79§</td>
<td>76.5</td>
<td>54.5</td>
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<td>85.4§</td>
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<tr>
<td>Eriguchi et al. (10)</td>
<td>2017</td>
<td>Retrospective</td>
<td>40 Gy/5#; 50 Gy/5#; 60 Gy/5#</td>
<td>88</td>
<td>79 [55–88]</td>
<td>86</td>
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<td>69</td>
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<td>88</td>
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<tr>
<td>Schonewolf et al. (14)†</td>
<td>2018</td>
<td>Retrospective</td>
<td>BED ≥100 Gy/50</td>
<td>34</td>
<td>73 [55–92]</td>
<td>–</td>
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<td>45.3</td>
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<td>96.7</td>
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†, medically operable subgroup; †, ages for entire cohort (ages for medically operable subgroup not given); †, significant difference between SABR arm median age (79 years) and lobectomy arm median age (62 years), P<0.001; †, 10-y LC% remained at 85.4%, 10-y OS was 23.8% (58). y, year; LC, local control; PFS, progression-free survival; OS, overall survival; CSS, cancer-specific survival; SABR, stereotactic ablative radiation therapy; NSCLC, non-small cell lung cancer.
Lung Cancer Audit, 30-day mortality following surgery for stage IA NSCLC was 1.6%, rising to 3.4% by 90 days, and for stage IB 30-day mortality was 2.8%, rising to 5.5% by 90 days (26). In that same report, mortality rates increased with advancing age for all stages, with a 90-day mortality rate of 7.3% in patients aged 70–74 rising to 16.5% in patients aged 85 years or older (26). These increased 90-day mortality data are broadly consistent with other published surgical outcomes series, and have been summarized previously (27). In a similar fashion, a retrospective analysis of over 2,000 patients with stage I NSCLC from a high-volume academic hospital in North America showed that the non-cancer cumulative incidence of death after surgery was higher than cancer-related deaths until 1.5 years post-operatively, and in patients older than 75 years, this period was 2.5 years (25). This phenomenon of increased early mortality in patients undergoing thoracic surgery over radiotherapy has been coined “the head-start effect” (28), and given the efficacy of SABR now raises the question whether or not it is ethical to operate on patients who are at risk for premature mortality for treatment of an asymptomatic stage I NSCLC.

**SABR without biopsy confirmation**

Although it is demonstrably effective, there are several controversies in the application of SABR to patients with stage I NSCLC, whether patients are operable or not. A particular scenario in which SABR is sometimes recommended—and appropriately criticised—is in patients with unbiopsied lung lesions that carry a high clinical suspicion for malignancy. This naturally creates the potential for futile therapy in an empiric setting, unnecessary exposure to radiation-related toxicities, and may contribute to overestimations in the efficacy of SABR in patients with benign lung nodules. In patients with benign nodules it may also lead to a scenario where a patient has a complicated region of SABR-related fibrosis that requires additional invasive procedures in someone who never had lung cancer in the first place (29).

While the authors of this review believe that the first preference should be to always obtain a pre-treatment tissue diagnosis before SABR, there are numerous situations where this is not possible due to patient or technical factors, including lack of advanced endobronchial equipment or expertise. This dilemma can affect patients who are considered for either surgery or SABR. Recently published data inform us that the rate of benign disease at the time of pulmonary resection—where pre-operative biopsy was not performed—ranges from 11% to 20% (30,31). This includes a recent report from the Cancer and Leukaemia Group B (CALGB) 140503 trial of lobectomy versus sublobar resection trial that found the benign nodule rate at surgery was approximately 20% (32). While studies like these measure the incidence of futile surgery, and provide insights into the rate of potentially futile SABR, they might actually present an argument in favour of empiric SABR over a surgical biopsy given its lower risk of treatment-related complications. For example, in the NELSON lung cancer screening trial which reported a rate of minor and major complications after thoracotomy in 47% and 10% respectively, approximately 1 in 5 of these complications occurred following operations for benign disease which would have likely been avoided with empiric SABR (33).

Fortunately, there are nomograms that can predict the probability of malignancy when considering age, smoking history, and radiographic features; though there will always be times of uncertainty. As such, a threshold of 85% risk of malignancy to proceed with an intervention has been suggested as an appropriate level that achieves a balance between the risk of toxicity from an unnecessary procedure versus risk of untreated tumour progression (34); although, this same cut-off may not be appropriate in regions with a high risk of benign granulomatous disease. While discussions about surgical resection to satisfy a requirement for diagnosis have been largely unchallenged in the past, there are now many scenarios where the alternative option of empiric SABR might be more appropriate. As we have alluded to, these scenarios are quite complex, and warrant multidisciplinary discussions, especially if the risk of a surgical complication is high.

**SABR without mediastinal staging**

In a similar vein to concerns about irradiation of unbiopsied primary lesions, the lack of pathologic mediastinal staging with SABR has also attracted criticisms out of concerns that patients may miss out on the opportunity for life-prolonging adjuvant chemotherapy in those who would be upstaged at the time of surgery. This is even though the value of optimizing the discovery of occult mediastinal disease was unable to be measured in the American College of Surgeons Oncology Group (ACOSOG) Z0030 trial which randomized over 1,000 patients between mediastinal sampling vs. dissection and found no improvement in OS with a more thorough staging process (19). It is known from...
the lung adjuvant cisplatin evaluation (LACE) meta-analysis that there can be a 5% OS advantage in patients who are upstaged to pathologic stage II–III NSCLC after pulmonary resection and surgical lymph node staging (35). However, as Louie et al. have illustrated, even when assuming a 15% occult nodal metastasis rate, and an estimation of only 66% receiving guideline directed adjuvant chemotherapy, only 0.5 lives are prolonged for every 100 patients who undergo surgical staging of the mediastinum—a benefit that would be abrogated if the surgical mortality exceeded 0.5% (34). For now, it remains unclear why isolated nodal failures are rare in the context of SABR (36), though we postulate that incidental low-dose irradiation of mediastinal nodes, or potential immune activation and eradication of nodal deposits, are possible explanations that require further supporting evidence.

**Long-term outcomes with SABR**

An additional controversy about the idea of SABR in operable patients relates to concerns about the paucity of long-term tumour control rates, as many initial reports were limited to only 3 years of follow-up (37). However, as is presented in Table 1, contemporary series of operable patients have now reported up to 5-year data, with local tumour control rates in the range of 86–96% with SABR. In the long-awaited update from the RTOG 0236 study, additional cancer recurrences after 5 years were particularly found to occur in untreated locations in the chest (2).

**Management of relapse following SABR**

The management of patients with local or regional failure after SABR presents a challenge that is best addressed through a multidisciplinary approach. This is because patients are often still curable, as was recently demonstrated in a large series from MD Anderson that reported the outcomes for the 11.2% of patients who developed non-metastatic relapse following upfront SABR (38). Patients were managed with a variety of salvage strategies including repeat SABR, surgery, thermal ablation, chemotherapy, chemoradiotherapy, conventional radiotherapy, and even brachytherapy, though some patients did not receive any further treatment. Interestingly, the authors reported that patients who received salvage therapies for an isolated local relapse had similar survival when compared to those without recurrence. Survival was poorer for patients with isolated regional relapse, though their outcomes were similar to patients with stage III disease. Finally, survival was poorest for those who did not receive any salvage therapies.

With regard to the safety of salvage surgery after SABR, there are now multiple reports in the literature, including the use of minimally invasive resections with mediastinal sampling (39). In the largest series reported to date, Antonoff et al. detailed the outcomes of a selected series of 37 patients who underwent salvage surgery for an isolated local failure at a median of 16.2 months after SABR. Approximately half of the resections did not report any extensive adhesions, and negative margins were obtained in 100% (40). They reported a perioperative mortality rate of 0% related to previous SABR, and the 3-year OS was 71% which provides further support that a strategy of upfront SABR with reservation of surgery for treatment failure might be a viable strategy to investigate in prospective clinical trials. Particularly, as this is a treatment paradigm that has been adopted for routine oncological care for malignant tumours of the head and neck, cervix, and anal canal with good effect. It offers a favourable early toxicity profile of radiation therapy in the first instance, acknowledging that even a slightly inferior local control rate does not confer inferior survival because of the opportunity for surgical salvage intervention(s). Such a management strategy for stage I NSCLC is now inherently being tested in the ongoing randomized trials of surgery vs. SABR for operable patients who are likely to remain operable at time of relapse (NCT02984761, NCT02468024, NCT01753414).

**The trials and tribulations of comparing available data**

While we await the completion of randomized trials, we are left with retrospective comparisons that analyse datasets of convenience with statistical techniques, such as propensity score matching, that aim to reduce bias in non-randomized data. It is worth considering that such approaches might not actually achieve this aim, and so retrospective studies that used this approach should be interpreted with caution (41). That is because for any such comparisons to be meaningful, the data must first be established on a level playing field, without inherent differences in the life expectancy of each patient group, and assurances that interpretations of the analyses are devoid of specialty bias. This unfortunately cannot be achieved with a high degree of integrity given currently available retrospective analyses are confounded as a result of over 80 years of history that has marked...
surgical resection as the standard of care, with reservation of radiotherapy only for those who are frail, elderly, or have other conditions that deem them unsafe for surgery (42). By way of example, a recently published propensity matched retrospective analysis compared the outcomes of patients selected for video-assisted thoracic surgery (VATS) lobectomy or SABR for stage I NSCLC, and found a significantly higher rate of survival at 3 years among the group of patients who were offered surgery (43). But as Stokes and Rusthoven wrote in a related editorial, these data were “confounded by operability” which introduced limitations into modelling efforts to match the groups as 70% of patients in this propensity-matched SABR group were deemed medically inoperable, compared with 0% (by definition) in the surgical arm (44). There are now over two dozen similar publications, despite calls from editors to preserve caution about specialty bias whenever interpreting studies like these (45). Particularly as a recent meta-analysis of propensity score studies demonstrated that the first author specialty (thoracic surgery or radiation oncology) was one of the strongest predictors of survival in early lung cancer (46).

Another challenge with interpreting the retrospective literature concerns the assessment of local failure after SABR because of the scarring effects of radiation on normal lung tissue which can simulate or mask recurrence, making interpretation of imaging difficult. Radiographic findings predictive of local recurrence after SABR have been proposed, and include features such as cranio-caudal growth, serial enlargement, loss of air bronchogram and loss of linearity (47,48), but these are admittedly imperfect. Following surgery, definitions of local failure vary between published reports, and vary depending upon whether a lobectomy or sublobar resection was performed, and the rate of reporting of local failure can vary, depending on the reporting strategy used (18).

For now, the sole prospective randomized evidence we have to compare SABR and surgery for early-stage operable lung cancer is the controversial pooled analysis of the STARS and ROSEL trials, which combined the results of two phase III trials (n=58) that closed early due to poor accrual. Another phase III prospective trial, ACOSOG Z4099/RTOG 1021 (49), also closed early after enrolling only ten patients, and did not publish their results. The STARS-ROSEL pooled data were encouraging for SABR, showing a 3-year OS of 95% in that group with a median follow-up of 40 months; this OS result was 15% higher than the surgical group (9). However, this publication was appropriately criticised because of the higher than expected mortality in the surgical group, and high likelihood of a spurious finding given more than 1,400 additional patients needed still to be randomized (50). Notwithstanding the unexpected magnitude of the disparity in survival outcomes, the shape of the survival curves (parallel after 18 months following an initial postoperative decline in the surgical arm) is illustrative of the aforementioned head-start effect, in describing a survival benefit afforded to SABR, assuming an equivalent or near equivalent oncologic effect, simply due to the avoidance of acute and delayed postoperative mortality (28). The remarkable results in patients who received SABR in this series remain compelling, and invite speculation as to what findings might emerge in a larger well-powered randomized controlled trial (RCT) with better surgical outcomes in the comparator arm.

Today, there are three prospective randomized controlled trials ongoing that are comparing SABR vs. surgery for patients with operable early NSCLC (51–53). The VALOR trial (NCT02984761) (Figure 2) is open to patients with either peripheral or central biopsy-confirmed tumours up to 5 cm, and presents patients the opportunity to randomly receive either SABR or an anatomic resection (lobectomy or segmentectomy with mandatory lymph node sampling) with a primary outcome measure of 5-year OS (51). The POSTIL (NCT02468024) trial is enrolling high-risk operable patients with tumours up to 4 cm who are unable to tolerate lobectomy, and offers either SABR or a sublobar resection via randomized allocation or patient preference; wedge resections require a 1 cm margin, and lymph node sampling is recommended but not required, with a primary outcome of 3-year OS (52). The STABLE-MATES (NCT02984761) trial is limited to patients with tumours <3 cm and randomly allocates them to either SABR or sublobar resection with a 2 cm margin, with mandatory nodal sampling and a primary outcome of 2-year local control (53). Each of these studies provide a meaningful opportunity to have better balanced groups for comparisons that are meaningful, such that differences between treatments may be more reliably compared.

**Lessons learned from challenges with recruitment to closed randomized trials**

Key lessons were learned from the failures of previous RCT trials of SABR versus surgical resection. While many of
Insights into the future

As the above randomized studies continue to accrue, and may some day present final results, it deserves considering how the outcomes may influence practice in the future. Even if an OS advantage is demonstrated for patients treated with upfront SABR, it is inevitable that subgroups of operable patients will be better managed with upfront surgery instead. For now, the enthusiasm for SABR is raising the bar for thoracic surgeons to consider more thoughtful patient selection, minimally invasive resections, and surgical nodal staging. Yet, once published, there are three different scenarios to envision: (I) if the OS rate is superior with SABR, then it is likely that practice guidelines will promote SABR as the standard of care in early lung cancer, (II) if the OS rates are similar, then clinicians will more thoroughly consider secondary conditions such as surgical fitness and patient preferences, and engage in complex shared decisions about an optimal treatment decision for any given patient, and (III) if SABR is found to provide a lower probability of long-term survival, then we will for the first time have level I evidence that the risks of a pulmonary resection are justified if long-term survival beyond a few years is an important goal of care.

While we predict a day will come when adequately powered phase III data are available, it deserves emphasis that the history of medicine has shown us that clinical practice patterns can be slow to change even years after randomized evidence are published (58). However, considering the referral pathways of patients with radiographic evidence of stage 1 NSCLC, the influencers for this population will not be limited to any single specialty, and will need to consider pulmonologists, interventional radiologists, and primary care physicians who typically see...
these patients well before either of the treating physicians.

**Conclusions**

SABR is demonstrably effective and safe in controlling early NSCLC in inoperable patients. The limited available data for operable patients out to 5 years after treatment are compelling but incomplete. As such, they do not currently justify routinely offering this treatment as an alternative to surgical resection, which remains an appropriate treatment to prefer in the first instance. Despite some controversy, the increasing use of SABR in the operable setting suggests that patients and clinicians have started to challenge the current early NSCLC treatment paradigm in the absence of prospectively gathered evidence, so there is an imperative to test surgery and SABR prospectively in operable patients whilst clinical equipoise exists. There are indeed cultural challenges to this endeavour, but these are not insurmountable, so we keenly await the availability of prospectively gathered data. In the interim we would do well to keep in mind that even if a survival benefit is shown with SABR, there will undoubtedly be cases in which a surgical approach is preferred. Accordingly, we recommend treatment as per published guidelines and encourage the referral of suitable patients for STABLE-MATES, VALOR and POSTIL V clinical trial participation.

**Acknowledgements**

Jenny Donovan for her contribution to the discussion of challenges in recruitment to randomized controlled trials.

S Siva is supported by a National Health and Medical Research Council Early Career Fellowship APP1122347 and a Peter MacCallum Cancer Centre Clinical Fellowship.

**Footnote**

*Conflicts of Interest*: S Siva is the recipient of a grant from Varian Medical systems for research related to SABR in kidney cancer. D Moghanaki is employed by the Department of Veterans Affairs and receives support from the Veterans Affairs Cooperative Studies Program. He has received travel reimbursement and speaking honoraria from Varian Medical Systems. Dr. CP Daniels has no conflicts of interest to declare.

*Disclaimer*: The views expressed in this article do not necessarily represent those of the Department of Veterans Affairs, or the U.S. government.

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doi: 10.21037/tro.2019.01.01

Cite this article as: Daniels CP, Moghanaki D, Siva S. Stereotactic ablative radiation therapy for operable early-stage lung cancer—considerations and controversies. Ther Radiol Oncol 2019;3:3.