Review Article

Surgery versus stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer: less is not more

Abby White, Scott J. Swanson

Division of Thoracic Surgery, Department of Surgery, Brigham and Women's Hospital, Boston, MA, USA

Contributions: (I) Conception and design: All authors; (II) Administrative support: All authors; (III) Provision of study materials or patients: A White; (IV) Collection and assembly of data: A White; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Abby White, DO. Associate Surgeon, Division of Thoracic Surgery, Instructor in Surgery, Harvard Medical School, Brigham and Women's Hospital, Mail: 75 Francis Street, Boston, MA 02115, USA. Email: awhite12@partners.org.

Abstract: High level evidence from randomized studies comparing surgery to stereotactic ablative radiotherapy (SABR) is lacking and available retrospective cohort and case control studies are highly variable in how thoroughly they define and stage lung cancer, in how they determine operability, and in the offered surgical approaches to operable lung cancer (open *vs*. video-assisted). This makes it difficult to compare best radiotherapy and best surgery approaches to treatment and to be confident in conclusions of equipoise between the two modalities. What has become clear from the controversy surrounding surgery versus SABR for early stage lung cancer is the desire to optimize treatment efficacy while minimizing invasiveness and morbidity. This review highlights the ongoing debate in light of these goals.

Keywords: Lobectomy; video-assisted thoracoscopic surgery (VATS); stereotactic; lung cancer

Submitted Feb 10, 2016. Accepted for publication Mar 10, 2016.
doi: 10.21037/jtd.2016.04.40
View this article at: http://dx.doi.org/10.21037/jtd.2016.04.40

Introduction

More than 1.8 million people are diagnosed with cancers of the lung and bronchus per year, and non-small cell lung cancer (NSCLC) remains the leading cause of cancer-related deaths worldwide (1). With increasing life expectancy and improvements in medical imaging, the number of affected patients is expected to escalate even further. While previous data suggested that only 25% of patients present with early-stage disease (2), the National Lung Screening Trial (NLST) (3) has confirmed that computed tomography (CT) screening leads to the detection of smaller and hence earlier stage lung cancers, resulting in a 20% mortality reduction. Standard therapy for operable, clinical stage 1 NSCLC is lobectomy with mediastinal lymph node dissection or sampling. That said, lung cancer is a disease of the elderly and a number of patients with early-stage lung cancer present with significant comorbid conditions. Tumor control in patients deemed too high risk to undergo surgery was suboptimal in the era of conventionally fractionated radiotherapy, with 5-year overall survival rates ranging from 6–32% (4). Dose escalation studies during that time-frame demonstrated modest improvement in local control and survival, but with undesirable toxicity profiles (5). In the last decade, stereotactic ablative radiotherapy (SABR) has emerged from applications in intracranial neoplasms and was evaluated in light of its ability to provide higher doses to more precisely targeted areas in a shorter timeframe than conventional radiotherapy. Unfortunately, high level evidence from randomized studies comparing surgery to SABR is lacking and available retrospective cohort and case control studies are highly variable in how they define and stage lung cancer, determine operability, and in the offered surgical approaches to operable lung cancer (open *vs*. video-assisted). This makes it difficult to compare best radiotherapy and best surgical approaches to treatment and to be confident in conclusions of equipoise between the two modalities. What has become clear from the controversy

surrounding surgery versus SABR for early stage lung cancer is the desire to optimize treatment efficacy while minimizing invasiveness and morbidity. This review attempts to highlight the ongoing debate in light of these goals.

Pre-treatment staging

Lung cancer survival is intimately linked to stage of disease (6) and well-established guidelines from the American Association of Chest Physicians (ACCP) (2) and National Cancer Care Network (NCCN) (7) highlight the importance of both tissue diagnosis and a complete metastatic workup in all stages of NSCLC. Pursuant to that and crucial to accurate staging is a thorough evaluation of the mediastinum. CT and 18-Fluoro-deoxyglucose positron emission tomography (FDG-PET) imaging is valuable to that evaluation. However, false-negative rates of 5–15% and false-positive rates of 0 to 53% make it an imperfect tool (8), and make more invasive approaches to mediastinal staging, such as endobronchial ultrasound-guided transbronchial needle aspiration (EBUS-TBNA) and cervical and video-assisted mediastinal lymph node sampling necessary. A large multi-institutional, prospective, randomized trial has demonstrated the importance of lymph node evaluation during the surgical treatment of NSCLC (9). Yet otherwise robust prospective studies evaluating SABR as primary therapy for both operable and inoperable early stage lung cancer have not consistently required tissue diagnosis and/or formal lymph node staging. This is despite the fact that there was a 16% incidence of occult N1 or N2 disease in the 525 patients who underwent lymph node dissection for early stage lung cancer in the randomized American College of Surgeons Oncology Group (ACOSOG) Z0030 trial (9). Even data for very small tumors (<1 cm) demonstrates an occult lymph node metastasis in 7% of patients (10). In the era of electronavigational bronchoscopy, EBUS, endoscopic ultrasound (EUS), and CT-guided biopsy, providing patients with the necessary counseling, expertise and tools to accurately diagnose and stage suspected lung cancer cannot be over-emphasized. Current and future studies designed to compare the effectiveness of surgical and non-surgical treatments of NSCLC should incorporate similar strategies in all treatment arms.

Defining operability

While the designation of operable versus inoperable lung cancer receives great press in the literature, working definitions within the context of comparing SABR to surgery are not consistently applied. The 2013 ACCP guidelines for the preoperative evaluation of lung cancer patients suggest that potential candidates for resection with either forced expiratory volume in one minute (FEV_1) or diffusing capacity of the lung for carbon monoxide (DLCO) less than sixty percent predicted undergo an estimation of the postoperative predicted volumes. Patients with postoperative predicted FEV_1 or DLCO between 30% and 60% are at increased operative risk and further simple exercise testing (six-minute walk, stair climbing) should be considered. Data from radiation oncology literature rarely includes this specific data for patients. Likewise, not all surgical data reports information relative to the oncology community regarding performance status, such as the Eastern Oncology Group (ECOG) Performance Scale. Ideally, studies comparing surgery and SABR would incorporate morbidity data which is mutually interpretable. While algorithms and scales are valuable benchmarks, when dealing with a persistently elderly and medically frail population, nothing supplants best real-time clinical judgment. Given geographical resource and skill set variations, surgeons themselves are charged with evaluating their own limitations before offering surgery to marginal lung cancer patients, and the authors would like to emphasize that the determination of operability should always be made by a board certified thoracic surgeon.

Surgery for early stage lung cancer

Dr. Evarts Graham (St Louis) reported the first successful pneumonectomy for lung cancer using a tourniquet technique in 1933 and subsequent adaptations including lobectomy and segmentectomy came much later. In 1992, Lewis and colleagues reported 100 consecutive patients who underwent video-assisted thoracoscopic surgery (VATS), including three lobectomies with anatomic hilar dissection (11). The Lung Cancer Study Group published results of a randomized trial, in 1995 that compared a sublobar resection versus a lobectomy for early stage lung cancer (12). This demonstrated a higher rate of recurrence and associated trend toward decreased disease-free survival when comparing lobar to sublobar resection for patients with cancer. This analysis of 247 patients set the tone for lobectomy as the standard of care for non-small cell lung cancer (NCSLC) for decades to come. Of note, both wedge resection and anatomic segmentectomy were included in the

sublobar analysis for this study and the majority of patients underwent open resection. There were no statistically significant differences among the treatment groups relative to prognostic factors, morbidity or mortality. In this study however, the VATS was ill-defined and included patients with mini-thoracotomy incisions and did not exclude rib spreading. At that time, patients considered high risk for thoracotomy, due to poor cardiopulmonary reserve, were being referred for radiation therapy, even for small peripheral (T1) tumors. In this light, a multicenter trial sponsored by the Cancer and Leukemia Group B (CALGB) 9335 aimed to evaluate the role of VATS wedge resection and adjuvant radiation in treating lung cancer patients considered to be high risk for thoracotomy (13). The study found VATS to be a reasonable approach with minimal morbidity and mortality for T1 lung cancers (tumors ≤3 cm).

In 2002, the first multicenter prospective trial (14) to standardize VATS lobectomy and evaluate it as a viable therapy for lung cancer was opened. It enrolled 128 patients for VATS lobectomy, intentionally defined as one access incision, two or three 5 mm port incisions, and no retractor use or rib spreading. The perioperative morbidity was 7.4% and 30-day mortality was 2.7%, both comparable to standards of open thoracotomy in patients with small peripheral tumors. Prolonged air leak and perioperative arrhythmia were both decreased in the VATS group relative to historical controls, affirming assumptions that would ultimately be corroborated by others: that VATS offered a sound oncologic operation at reduced morbidity, even in high risk patients. With the advent of VATS-specific instrumentation, improved techniques for lung isolation and retraction, and newer and better video equipment, those morbidity and mortality numbers have gotten even better and studies continue to show benefit with VATS versus open surgery with respect to hospital length of stay, perioperative complications, and greater likelihood of independent home discharge compared with open lobectomy for early-stage lung cancer (15). These results are reproducible in countries outside the United States, as fewer postoperative complications and shorter length of stay were recently corroborated in a European Society of Thoracic Surgery Database project which propensity matched over 2,000 patients who underwent VATS lobectomy (16). Recent studies suggest that VATS lobectomy can be accomplished in patients with significant COPD (17) or marginal pulmonary function tests with 30-day mortalities below 1% (18). VATS segmentectomy remains an option for patients whose lung function may not otherwise allow resection, and current randomized trials are underway to assess the oncologic equivalence of these sublobar resections (19,20) as they compare to standard lobectomy. Techniques for minimally invasive segmentectomy are well described and accomplishable in most VATS programs (21,22). Finally, the ACOSOG Z0030 trial (9), which included over 1,000 patients who underwent surgical treatment of early stage lung disease demonstrated that overall survival at 5 years was 72% for stage T1 tumors and 55% for stage T2 tumors. Local recurrence-free survival was 95% for stage T1 tumors and 91% for stage T2. As suggested by Su and colleagues in a 2014 analysis of the study, this robust, multi-institutional and meticulously verified data should serve as the benchmark against which non-surgical therapy for early stage lung cancer is compared (23).

Stereotactic ablative radiotherapy (SABR) for inoperable early stage lung cancer

Stereotactic radiotherapy for intracranial cancers has been in use since the 1950's (24). The first attempts to apply it outside of the central nervous system were pioneered in the 1990's. There are several platforms through which SABR for lung cancer is delivered. The key feature which makes SABR attractive for lung cancer therapy is the ability to deliver highly specific radiation using some form of image guidance to identify and compensate for tumor motion within the respiratory cycle. In systems where 2-D imaging is utilized, fiducial markers are placed in and around the tumor to facilitate motion of tracking throughout the treatment. Planning treatment volume (PTV) is chosen based on tumor volume and some additional margin, which varies from 2–5 mm. An advantage of SABR over conventional radiotherapy is the ability to deliver doses that would precipitate much higher rates of fibrosis and pneumonitis using conventional techniques. Enthusiasm was gained by a 2005 phase I trial of SABR and completed by Timmerman and colleagues at Indiana University (25). The trial included 47 patients with stage 1A or 1B NCSLC and concluded that pathologic diagnosis was required for accrual and patients had to be deemed inoperable by a thoracic surgeon. Local failure was defined as recurrence within the treated tumor volume only, so a recurrence within the same lobe but outside the treated area, would be considered regional recurrence. The local failure rate was 21% in this study. Overall and disease free survival were not reported, but the study was designed as a dose

Table 1 Summary of prospective studies of surgery and SABR for early-stage NSCLC

Study	Year	No. patients	5-year OS (%)	5-year DFS (%)	Local recurrence rate** (%)	Notes
ACOSOG Z0030 (Surgery)	2011	1,023			4.9	
Stage T1		578	72	77		
Stage T2		440	55	58		
RTOG	2014*					
Combined stage T1 and T2		55	40	26	23.6	
Bral *et al*.	2011					
Combined stage T1 and T2		40	NR	NR	7.5 (2 yr)	2 yr OS =56%, 2yr DFS =64%
Ricardi *et al*.	2010					
Combined stage T1 and T2		62	NR	NR	3.2 (2 yr)	35.5% had unknown histology, 3 yr OS =57.1%

*, the initial RTOG 0236 data was published in 2010 but longer-term data was presented by Timmerman *et al*. in 2014; **, defined as recurrence within the same lobe. SABR, stereotactic ablative radiotherapy; NSCLC, non-small cell lung cancer; OS, overall survival; DFS, disease free survival; RTOG, Radiation Oncology Group.

escalation study. Treatment toxicities were notable and included pneumonitis, pericardial effusion, tracheal necrosis and pneumonia. The maximum tolerated dose of radiation was determined to be 66 Gy delivered in three fractions. Because this was still considerably better than outcome data for untreated or conventional radiotherapy-treated early stage lung cancer, it sparked much interest and enthusiasm, prompting the phase II Radiation Oncology Group (RTOG) 0236 study (26). Fifty five patients were treated with SABR between 2004 and 2006 for histologically confirmed NCSLC, of which 80% were stage T1a. Inoperability was determined by a pulmonologist or a thoracic surgeon. Local failure was defined as those occurring within 1 cm of the planning target volume (1.5–2.0 cm from the gross tumor volume); however, disease free survival was reported and included separate assessments of local-regional failure (within the primary site, involved lobe, hilum, or mediastinum) and disseminated recurrence (failure beyond the local and regional sites). Three-year overall and disease-free survival were 55% and 48.3% respectively. The locoregional recurrence rate was 12.8% and 20% of patients had distant recurrence. Central tumors were exluded from this study because Timmerman and colleagues had identified the risk of treatment-related complications was higher in this cohort in a secondary analysis of the initial phase I study (27). Nearly 22% of patients had a rated Grade 3 or higher adverse event by the 90-day mark, which included reduction in PFTs, hypocalcemia, or pneumonitis (rib fracture and chest wall pain were not reported). There were no treatment-related deaths and SABR gained rapid popularity. Several retrospective studies emerged in the radiation oncology literature reporting similar three-year overall and disease-free survival data (28-30), though the standards of histologically confirmed cancer diagnosis and surgeon-led evaluation of operability were sparsely acknowledged or reported and local and regional failure definitions inconsistent.

Stereotactic ablative radiotherapy (SABR) for operable early stage lung cancer

Table 1 highlights characteristics of randomized data (26,31,32) comparing SABR to the benchmark ACOSOG Z0030 trial (9). With increasing concerns of extrapolating retrospective data on inoperable and high-risk patients to operable patients, two prospective randomized controlled studies enrolled to evaluate surgery versus SABR in operable stage 1 NSCLC patients. Both trials closed due to poor accrual and were not designed to compare best surgical practice to SABR, as open lobectomy was the most common approach, and morbidity and mortality rates were far below accepted international norms. The STARS trial included 28 sites in the USA, China and France but only seven ultimately enrolled a total of 31 patients. In the ROSEL trial, ten centers in the Netherlands were approved and only four enrolled a total of 22 patients. Chang *et al*. attempted

analysis and interpretation of the combined data from these two studies, citing similar inclusion criteria, though no histologic cancer diagnosis was required for enrollment in the ROSEL trial, and could positively affect survival data in favor of SABR (33). Of the 58 patients analyzed, 27 were assigned to surgery and 70% of them underwent open lobectomy. The authors declared equipoise between the two treatment modalities quoting the overall and disease-free survival data that favored SABR, yet the study was not designed as a non-inferiority project and was underpowered for both of these end points. Under highlighted was the 16% locoregional recurrence rate in the SABR-treated patients and surgical complication rates much higher than accepted standards. Two additional prospective randomized trials have been designed to help ascertain which patients stand to gain the most benefit from SABR. The VALOR study: Veterans Affairs Lung cancer surgery OR stereotactic Radiotherapy in the US and the SABRTooth study in the United Kingdom will aim to compare best surgical to best SABR treatments.

Treatment efficacy

Measures of treatment efficacy when comparing SABR and surgery are subject to similar constraints of comparing pathologic to clinical data, particularly as it relates to surveying for and defining disease recurrence. Pathologic data about tumor grade, margin and receptor status, pleural and lymphovascular invasion, and induction treatment effect have proven to be objective and insightful in the treatment of patients with early-stage NSCLC. Data in surgical literature suggests a relationship between surgical resection margin and local recurrence rates (34,35). A review of over 400 patients found that patients with a 10-mm margin distance had a 45% lower local recurrence risk than those with a 5-mm distance (34). Such information is available as a consequence of surgical resection, but unavailable within the context of nonsurgical therapies, including SABR. Evidence supports adjuvant chemotherapy for the 15–20% of patients with early stage NSCLC and occult lymph node metastasis on surgical pathologic review (36), information that is simply not available for patients without specimens to review. Post-treatment surveillance PET scanning will be important, but unlikely to provide timely insight until lymph node spread has become sufficient to produce avidity in mediastinal or hilar lymph node stations, at which point it is unclear whether adjuvant chemotherapy would still offer a survival benefit. The challenge of following SABR patients post-treatment has been studied (37). Recognition of imaging patterns and development of tools and technology to detect locoregional recurrence earlier and with better accuracy will be essential to assessing the efficacy of non-surgical therapies for lung cancer.

Discussion

Although surgery is the standard of care for early stage NSCLC, the rapid evolution of non-surgical therapies, such as SABR, has brought to light important concerns about patient selection, oncologic efficacy and treatment-related morbidity. Additionally, SABR has and will continue to have an important role to play in patients who cannot undergo or refuse surgery. Scientific and technological breakthroughs have expanded the diagnostic and therapeutic armamentarium for patients with lung cancer. The pace of innovation and discovery is promising, but must not outperform quality filtering and critical review of published data. Pathologic confirmation of disease is paramount when comparing surgical resection to SABR. In much the same way surgical survival data would have less impact if patients with hamartomas and granulomas were included, patients without confirmation of cancer should be excluded from SABR data. In the era of multidisciplinary tumor boards and clinics, electronavigational bronchoscopy, EBUS, EUS, imaged guided percutaneous biopsies, single-incision and even awake VATS lung and lymph node biopsies, it should be the exception to find patients who are unfit or unwilling to undergo tissue diagnosis and thorough mediastinal staging or restaging, not the norm. This is particularly true in light of targeted therapy and molecular sequencing advances, which necessitate at least a core of tissue for analysis. Review of current prospective randomized (most is not randomized) data as detailed in this review, highlights the need for large scale, multi-institution and multi-specialty collaborations to provide sound comparison between the standard of care and non-surgical therapies. Cost analyses will be critical to our understanding and long-term survival and quality of life data should be incorporated into well-designed clinical trials.

Conclusions

Surgical resection remains the standard of care for early-stage NCSLC. Minimally invasive approaches should be considered for all patients with operable tumors. Prospective data suggests improved morbidity and

equivalent oncologic efficacy in VATS approaches to lung cancer, even in populations considered high-risk. SABR is a safe and valuable treatment option for patients who cannot or will not undergo surgery, and operability should be determined by a board-certified thoracic surgeon. More robust data is needed before drawing conclusions about the applicability of SABR as primary therapy for patients with operable early stage NSCLC, and caution should be taken when extrapolating available data.

Acknowledgements

None.

Footnote

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

References

1. Torre LA, Bray F, Siegel RL, et al. Global cancer statistics, 2012. CA Cancer J Clin 2015;65:87-108.
2. Detterbeck FC, Lewis SZ, Diekemper R, et al. Executive Summary: Diagnosis and management of lung cancer, 3rd ed: American College of Chest Physicians evidence-based clinical practice guidelines. Chest 2013;143:7S-37S.
3. National Lung Screening Trial Research Team, Aberle DR, Adams AM, et al. Reduced lung-cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
4. Qiao X, Tullgren O, Lax I, et al. The role of radiotherapy in treatment of stage I non-small cell lung cancer. Lung Cancer 2003;41:1-11.
5. Dosoretz DE, Katin MJ, Blitzer PH, et al. Radiation therapy in the management of medically inoperable carcinoma of the lung: results and implications for future treatment strategies. Int J Radiat Oncol Biol Phys 1992;24:3-9.
6. Detterbeck FC, Boffa DJ, Tanoue LT. The new lung cancer staging system. Chest 2009;136:260-71.
7. National Cancer Care Network Guidelines. Non-small cell lung cancer. 2015. Available online: www.nccn.org
8. Puri V, Meyers BF. Optimal initial pathologic mediastinal staging of lung cancer: EUS, EBUS, mediastinoscopy. Difficult decisions in thoracic surgery. London: Springer, 2011:67-75.
9. Darling GE, Allen MS, Decker PA, et al. Randomized trial of mediastinal lymph node sampling versus complete lymphadenectomy during pulmonary resection in the patient with N0 or N1 (less than hilar) non-small cell carcinoma: results of the American College of Surgery Oncology Group Z0030 Trial. J Thorac Cardiovasc Surg 2011;141:662-70.
10. Miller DL, Rowland CM, Deschamps C, et al. Surgical treatment of non-small cell lung cancer 1 cm or less in diameter. Ann Thorac Surg 2002;73:1545-50; discussion 1550-1.
11. Lewis RJ, Caccavale RJ, Sisler GE, et al. One hundred consecutive patients undergoing video-assisted thoracic operations. Ann Thorac Surg 1992;54:421-6.
12. Ginsberg RJ, Rubinstein LV. Randomized trial of lobectomy versus limited resection for T1 N0 non-small cell lung cancer. Lung Cancer Study Group. Ann Thorac Surg 1995;60:615-22; discussion 622-3.
13. Shennib HA, Landreneau R, Mulder DS, et al. Video-assisted thoracoscopic wedge resection of T1 lung cancer in high-risk patients. Ann Surg 1993;218:555-8; discussion 558-60.
14. Swanson SJ, Herndon JE 2nd, D'Amico TA, et al. Video-assisted thoracic surgery lobectomy: report of CALGB 39802--a prospective, multi-institution feasibility study. J Clin Oncol 2007;25:4993-7.
15. Taylor MD, LaPar DJ, Isbell JM, et al. Marginal pulmonary function should not preclude lobectomy in selected patients with non-small cell lung cancer. J Thorac Cardiovasc Surg 2014;147:738-44; Discussion 744-6.
16. Falcoz PE, Puyraveau M, Thomas PA, et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg 2016;49:602-9.
17. Nwogu CE, D'Cunha J, Pang H, et al. VATS lobectomy has better perioperative outcomes than open lobectomy: CALGB 31001, an ancillary analysis of CALGB 140202 (Alliance). Ann Thorac Surg 2015;99:399-405.
18. Burt BM, Kosinski AS, Shrager JB, et al. Thoracoscopic lobectomy is associated with acceptable morbidity and mortality in patients with predicted postoperative forced expiratory volume in 1 second or diffusing capacity for carbon monoxide less than 40% of normal. J Thorac Cardiovasc Surg 2014;148:19-28, dicussion 28-29.e1.
19. Nakamura K, Saji H, Nakajima R, et al. A phase III randomized trial of lobectomy versus limited resection for small-sized peripheral non-small cell lung

cancer (JCOG0802/WJOG4607L). Jpn J Clin Oncol 2010;40:271-4.
20. Fox N, Bauer T. CALGB 140503: A randomized phase III trial of lobectomy versus sublobar resection for small (<2cm) peripheral non-small cell lung cancer. Oncology Issues November/December 2008. (Status: Active).
21. McKenna RJ, Mahtabifard A, Swanson SJ. Atlas of minimally invasive thoracic surgery (VATS). 1st edition. Philadelphia: Elsevier/Saunders, 2011.
22. White A, Swanson SJ. Video-assisted thoracic surgery (VATS) segmentectomy: state of the art. Minerva Chir 2016;71:61-6.
23. Su S, Scott WJ, Allen MS, et al. Patterns of survival and recurrence after surgical treatment of early stage non-small cell lung carcinoma in the ACOSOG Z0030 (ALLIANCE) trial. J Thorac Cardiovasc Surg 2014;147:747-52: Discussion 752-3.
24. Leksell L. The stereotaxic method and radiosurgery of the brain. Acta Chir Scand 1951;102:316-9.
25. McGarry RC, Papiez L, Williams M, et al. Stereotactic body radiation therapy of early-stage non-small-cell lung carcinoma: phase I study. Int J Radiat Oncol Biol Phys 2005;63:1010-5.
26. Fakiris AJ, McGarry RC, Yiannoutsos CT, et al. Stereotactic body radiation therapy for early-stage non-small-cell lung carcinoma: four-year results of a prospective phase II study. Int J Radiat Oncol Biol Phys 2009;75:677-82.
27. Timmerman R, McGarry R, Yiannoutsos C, et al. Excessive toxicity when treating central tumors in a phase II study of stereotactic body radiation therapy for medically inoperable early-stage lung cancer. J Clin Oncol 2006;24:4833-9.
28. Onishi H, Shirato H, Nagata Y, et al. Hypofractionated stereotactic radiotherapy (HypoFXSRT) for stage I non-small cell lung cancer: updated results of 257 patients in a Japanese multi-institutional study. J Thorac Oncol 2007;2:S94-100.
29. Grills IS, Hope AJ, Guckenberger M, et al. A collaborative analysis of stereotactic lung radiotherapy outcomes for early-stage non-small-cell lung cancer using daily online cone-beam computed tomography image-guided radiotherapy. J Thorac Oncol 2012;7:1382-93.
30. Guckenberger M, Allgäuer M, Appold S, et al. Safety and efficacy of stereotactic body radiotherapy for stage 1 non-small-cell lung cancer in routine clinical practice: a patterns-of-care and outcome analysis. J Thorac Oncol 2013;8:1050-8.
31. Bral S, Gevaert T, Linthout N, et al. Prospective, risk-adapted strategy of stereotactic body radiotherapy for early-stage non-small-cell lung cancer: results of a Phase II trial. Int J Radiat Oncol Biol Phys 2011;80:1343-9.
32. Ricardi U, Filippi AR, Guarneri A, et al. Stereotactic body radiation therapy for early stage non-small cell lung cancer: results of a prospective trial. Lung Cancer 2010;68:72-7.
33. Chang JY, Senan S, Paul MA, et al. Stereotactic ablative radiotherapy versus lobectomy for operable stage I non-small-cell lung cancer: a pooled analysis of two randomised trials. Lancet Oncol 2015;16:630-7.
34. Mohiuddin K, Haneuse S, Sofer T, et al. Relationship between margin distance and local recurrence among patients undergoing wedge resection for small (≤2 cm) non-small cell lung cancer. J Thorac Cardiovasc Surg 2014;147:1169-75; discussion 1175-7.
35. El-Sherif A, Fernando HC, Santos R, et al. Margin and local recurrence after sublobar resection of non-small cell lung cancer. Ann Surg Oncol 2007;14:2400-5.
36. Winton T, Livingston R, Johnson D, et al. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352:2589-97.
37. Eradat J, Abtin F, Gutierrez A, et al. Evaluation of treatment response after nonoperative therapy for early-stage non-small cell lung carcinoma. Cancer J 2011;17:38-48.

Cite this article as: White A, Swanson SJ. Surgery versus stereotactic ablative radiotherapy (SABR) for early-stage non-small cell lung cancer: less is not more. J Thorac Dis 2016;8(Suppl 4):S399-S405. doi: 10.21037/jtd.2016.04.40

