Editorial

Guidelines for stereotactic body radiation therapy treatment of lung cancer highlight important research questions: what is the next step?

Lorraine D. Cornwell[1], Melissa L. Korb[2], Bryan M. Burt[2]

[1]Division of Cardiothoracic Surgery, [2]Division of General Thoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, Houston, TX, USA

Correspondence to: Lorraine D. Cornwell. Division of Cardiothoracic Surgery, Michael E. DeBakey Department of Surgery, Baylor College of Medicine, 1 Baylor Plaza, Houston, TX 77030, USA. Email: Cornwell@bcm.edu.

Provenance: This is an invited Editorial commissioned by the Section Editor Xiaozheng Kang (Department of Thoracic Surgery, Beijing Cancer Hospital, Peking University, Beijing, China).

Comment on: Schneider BJ, Daly ME, Kennedy EB, *et al.* Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline. J Clin Oncol 2018;36:710-9.

Submitted Feb 10, 2018. Accepted for publication Feb 21, 2018.
doi: 10.21037/jtd.2018.03.36
View this article at: http://dx.doi.org/10.21037/jtd.2018.03.36

Over the past decade, stereotactic body radiation therapy (SBRT) has become increasingly accepted as a safe and effective therapy for stage I lung cancer for medically inoperable patients. The American Society for Radiation Oncology (ASTRO) clinical guidelines concerning the use of SBRT for the treatment of stage I non-small cell lung cancer (NSCLC) were recently endorsed by the American Society of Clinical Oncology (ASCO) (1,2). Both the ASTRO guidelines and the ASCO endorsement are thorough and clear, and summarize the current state of evidence. ASCO has recommended certain modifications and qualifications that emphasized the importance of the multidisciplinary cancer care team discussions, shared decision-making, and the importance of adequate staging. An underappreciated advantage of establishing clinical guidelines is the resultant light that is shined on the many unanswered questions, which should guide the focus of further clinical research.

Of the 4 key questions addressed by the guidelines (*Table 1*), the first question is the most important and potentially controversial: "*When is SBRT appropriate for patients with T1-2 N0 NSCLC who are medically operable*?" Traditional first line treatment for this cohort of patients is surgical resection with lobectomy and systematic lymph node evaluation, a recommendation endorsed by all major guidelines, including the National Comprehensive Cancer Network (NCCN), and now by ASTRO and ASCO. Concerning trends, however, have shown increased use of SBRT with a concomitant decrease in surgical utilization (3), suggesting that patients with potentially operable early stage NSCLC are choosing SBRT over surgery. As thoracic surgeons, it is gratifying to see that 2 of the major organizations for our colleagues in cancer care recognize that the current state of research does not yet support recommending the use of SBRT instead of surgery for operable patients outside of clinical trials.

Two areas highlighted by the ASCO proceeding are in need of further research: (I) importance given to invasive tissue diagnosis for biopsy and staging; and (II) use of SBRT in operable high risk patients. The importance of invasive staging of the hilum and mediastinum before SBRT, especially in the case of central tumors and multiple primary lung cancers (MPLC) is emphasized in the ASCO qualifying statements. Increasing the accuracy of staging for patients considered for SBRT can be predicted to improve appropriate management strategies and decrease inappropriate usage of SBRT in cases more advanced than stage I. Reciprocally, whether the upstaging of medically inoperable patients with suspected stage I NSCLC, who are less able to tolerate any invasive procedure, will improve

Table 1 Summary of ASTRO guidelines concerning SBRT use for stage I lung cancer, with ASCO additions in bold print (in parentheses, strength of recommendation, quality of evidence)

1. Recommendations for patients with T1-2N0 NSCLC who are medically operable:
   a. should be evaluated by a thoracic surgeon to determine operability. (strong, moderate)
   b. for patients with standard operative risk, SBRT is not recommended as an alternative to surgery outside of a clinical trial. (strong, high)
   c. for patients with high operative risk, discussions about SBRT as a potential alternative to surgery are encouraged within the multidisciplinary cancer care team. (conditional, moderate)
2. Recommendations for SBRT for medically inoperable patients with T1-2N0 NSCLC, and with special circumstances:
   a. SBRT as treatment of central tumors may pose significant risks. The use of 3 fraction regimen is not recommended in this setting. (strong, high)
   b. caution is needed for use of SBRT for central tumors. The use of 4 or 5 fractions may reduce risk of toxicity. (conditional, moderate)
   c. for select tumors >5 cm diameter, SBRT may be an appropriate option. (conditional, low)
   d. whenever possible, obtain a biopsy prior to treatment with SBRT to confirm a histologic diagnosis. (strong, high)
   e. SBRT may be delivered to patients without a tissue diagnosis after consensus within a multidisciplinary care team setting (with qualifying features stated by ASCO). (strong, moderate)
   f. MPLC, synchronous primary or multifocal, pose unique issues and should be discussed within a multidisciplinary cancer care team setting. (strong, moderate)
   g. patients with MPLC should have PET/CT and brain MRI to help distinguish intrathoracic metastatic lung cancer. Invasive mediastinal/hilar staging with EBUS/mediastinoscopy should be strongly considered. (strong, moderate)
   h. SBRT may be considered for patients with synchronous MPLC; (conditional, low)
   i. SBRT may be considered for patients with metachronous MPLC; (strong, moderate)
   j. SBRT may be considered in the post-pneumonectomy setting. (conditional, low)
3. Recommendations for patients with tumors with intimal proximity/involvement of mediastinal structures:
   a. SBRT for tumors in close proximity to the bronchial tree should be considered with caution. Delivery of SBRT in 4–5 fractions may reduce the risks of severe toxicity. (strong, low)
      a) ASCO qualifying statement: appropriate staging, including PET/CT and invasive mediastinal/hilar staging, is recommended because of high risk for nodal disease in this population
   b. SBRT near esophagus poses risk for severe toxicity, and plans should meet constraints defined in prospective studies. (strong, low)
   c. SBRT for tumors in close proximity to heart or pericardium should be delivered in 4–5 fractions, with volumetric and dose constraints defined in prospective trials, with a low incidence of serious toxicities observed. (strong, low)
   d. SBRT may be offered for cT1-2 tumors abutting the chest wall. (strong, high)
   e. ASCO deferred a decision for or against the use of SBRT for cT3 disease due to chest wall invasion. (until further data available)
4. Recommendations for the role of SBRT in medically inoperable patients as salvage therapy:
   a. SBRT may be offered following discussion of the multidisciplinary care team. (conditional, low)
   b. selection is highly individualized. (strong, low)

ASTRO, American Society for Radiation Oncology; SBRT, stereotactic body radiation therapy; MPLC, multiple primary lung cancer; NSCLC, non-small cell lung cancer; ASCO, American Society of Clinical Oncology; PET, positron emission tomography; MRI, magnetic resonance imaging.

long-term outcomes is an area in need of clinical research.

The next area in need of more evidence is the recommendation for the potential use of SBRT in medically operable patients with stage I lung cancer. Although the guidelines state that surgical resection remains the treatment of choice at this time, both ASTRO and ASCO agree that SBRT can be considered for patients with "high" operative risk (*Table 1*, recommendation 1c). However, it is well recognized among physicians caring for cancer patients that risk assessment can be subjective. The ASTRO guideline recommendation states: "*Operative risk should be assessed by a thoracic surgeon who specializes in lung resection*", and defined standard operative risk as "*anticipated operative mortality <1.5%*;" while further elaborating on "high operative risk" by risk factors used for clinical trials, including "*FEV1 <50% predicted*, *DLCO <50% predicted*, *or a combination of advanced age*, *impaired pulmonary function*, *pulmonary hypertension*, *and poor left ventricular function*". ASCO removed the mortality risk definition in their endorsement and added "*there is no universally accepted definition*," to the definition of high operative risk, and also added further qualifying statements: namely, emphasizing that limited lung resection is more often selected than SBRT in patients with high operative risk, and adding the longer term data from RTOG 0236 phase II trial of inoperable stage I NSCLC to the discussion points (with overall survival at 5 years 40% with SBRT) (4).

In sum, we find the ASCO proceeding to present a balanced view of the current state of the literature concerning operable patients. But it is clear that more data is needed. No large multicenter phase III clinical trial comparing results of surgical resection to SBRT for lung cancer has been completed. Recent attempts at randomized comparisons of SBRT to surgery were not able to accrue patients and were published as only underpowered, preliminary findings (5). Nevertheless, innumerable retrospective analyses comparing the 2 treatments continue to be published (6,7). Despite propensity matching and use of large databases, the effect of selection bias and residual confounding can never be eliminated in looking at retrospective data. SBRT has traditionally been reserved for patients with comorbidities, poor performance status, poor lung function, and high to prohibitive surgical risk and thus shorter life expectancies. Meanwhile, data is accumulating for first-line SBRT in operable patients. Series report 5 years overall survivals of 51% to 74% for SBRT, which rivals surgical results (8-12).

Three ongoing clinical trials are expected to provide a higher level evidence regarding SBRT for medically operable patients with stage I NSCLC: the VA Clinical Studies Program VALOR (Veterans Affairs Lung Cancer Or Stereotactic Radiotherapy NCT02984761) trial, POSTILV (Radical Resection *vs.* Ablative Stereotactic Radiotherapy in Patients with Operable Stage I NSCLC NCT01753414) and STABLE-MATES (A Randomized Phase III Study of Sublobar Resection *vs.* Stereotactic Ablative Radiotherapy in High Risk Patients with Stage I NSCLC, NCT01622621). It is critically important that clinicians of all disciplines who treat lung cancer patients support and enroll in these trials which may become the basis for the standard of care in early stage NSCLC.

The ASTRO and ASCO guidelines point to inadequate data for evidence-based decision-making for stage I NSCLC. These and critical research questions must be answered for us to honestly and completely inform our patients. Cancer care should always be centered on options for enrollment in clinical trials, so that we can continue to improve and enhance treatment paradigms. The collaboration of thoracic surgeons, radiation oncologists, medical oncologists, pulmonologists, and radiologists is necessary at this time to maximize our ability to answer these important questions.

Acknowledgements

K. Macellaro, PhD, a member of the Baylor College of Medicine Michael E. DeBakey Department of Surgery Research Core Team, assisted with the editing of this editorial.

Footnote

Conflicts of Interest: Dr. Cornwell receives research funding from the Department of Veteran Affairs Cooperative Studies Program at the Michael E. DeBakey VA Medical Center in support of the VALOR trial. The other authors have no conflicts of interest to declare.

References

1. Videtic GM, Donington J, Giuliani M, et al. Stereotactic body radiation therapy for early-stage non-small cell lung cancer: Executive Summary of an ASTRO Evidence-Based Guideline. Pract Radiat Oncol 2017;7:295-301.
2. Schneider BJ, Daly ME, Kennedy EB, et al. Stereotactic Body Radiotherapy for Early-Stage Non-Small-Cell Lung Cancer: American Society of Clinical Oncology

Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline. J Clin Oncol 2018;36:710-9.
3. Haque W, Szeja S, Tann A, et al. Changes in Treatment Patterns and Overall Survival in Patients With Early-Stage Non-Small Cell Lung Cancer in the United States After the Incorporation of Stereotactic Ablative Radiation Therapy: A Population-based Analysis. Am J Clin Oncol 2018;41:259-66.
4. Timmerman RD, Hu C, Michalski J, et al. Long-term Results of RTOG 0236: A Phase II Trial of Stereotactic Body Radiation Therapy (SBRT) in the Treatment of Patients with Medically Inoperable Stage I Non-Small Cell Lung Cancer. International Journal of Radiation Oncology 2014;90:S30.
5. 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.
6. Cornwell LD, Echeverria AE, Samuelian J, et al. Video-assisted thoracoscopic lobectomy is associated with greater recurrence-free survival than stereotactic body radiotherapy for clinical stage I lung cancer. J Thorac Cardiovasc Surg 2018;155:395-402.
7. Yerokun BA, Yang CJ, Gulack BC, et al. A national analysis of wedge resection versus stereotactic body radiation therapy for stage IA non-small cell lung cancer. J Thorac Cardiovasc Surg 2017;154:675-686.e4.
8. Nagata Y, Hiraoka M, Shibata T, et al. Prospective Trial of Stereotactic Body Radiation Therapy for Both Operable and Inoperable T1N0M0 Non-Small Cell Lung Cancer: Japan Clinical Oncology Group Study JCOG0403. Int J Radiat Oncol Biol Phys 2015;93:989-96.
9. Eriguchi T, Takeda A, Sanuki N, et al. Stereotactic body radiotherapy for operable early-stage non-small cell lung cancer. Lung Cancer 2017;109:62-7.
10. Lagerwaard FJ, Verstegen NE, Haasbeek CJ, et al. Outcomes of stereotactic ablative radiotherapy in patients with potentially operable stage I non-small cell lung cancer. Int J Radiat Oncol Biol Phys 2012;83:348-53.
11. Shibamoto Y, Hashizume C, Baba F, et al. Stereotactic body radiotherapy using a radiobiology-based regimen for stage I non-small-cell lung cancer: five-year mature results. J Thorac Oncol 2015;10:960-4.
12. Onishi H, Shirato H, Nagata Y, et al. Stereotactic body radiotherapy (SBRT) for operable stage I non-small-cell lung cancer: can SBRT be comparable to surgery? Int J Radiat Oncol Biol Phys 2011;81:1352-8.

Cite this article as: Cornwell LD, Korb ML, Burt BM. Guidelines for SBRT treatment of lung cancer highlight important research questions: what is the next step? J Thorac Dis 2018;10(3):1339-1342. doi: 10.21037/jtd.2018.03.36