Editorial Commentary

Stereotactic ablative radiotherapy for operable stage I non-small cell lung cancer: not ready for prime time

James G. Connolly, Gregory D. Jones, Raul Caso, David R. Jones

Thoracic Surgery Service, Memorial Sloan Kettering Cancer Center, New York, NY, USA

Correspondence to: David R. Jones, MD. Professor & Chief, Thoracic Surgery Service, Fiona & Stanley Druckenmiller Chair for Lung Cancer Research, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, USA. Email: jonesd2@mskcc.org.

Provenance: This is an invited article commissioned by the Section Editor Dr. Song Xu (Department of Lung Cancer Surgery, Tianjin Medical University General Hospital, Tianjin Key Laboratory of Lung Cancer Metastasis and Tumor Microenvironment, Lung Cancer Institute, Tianjin, China).

Comment on: Palma DA, Nguyen TK, Louie AV, *et al*. Measuring the integration of stereotactic ablative radiotherapy plus surgery for early-stage non-small cell lung cancer: a phase 2 clinical trial. JAMA Oncol 2019;5:681-8.

Submitted Jul 31, 2019. Accepted for publication Aug 08, 2019.
doi: 10.21037/atm.2019.08.40
View this article at: http://dx.doi.org/10.21037/atm.2019.08.40

Stereotactic ablative radiotherapy (SABR) is a well-accepted treatment modality for patients with early-stage non-small cell lung cancer (NSCLC) who are thought to be inoperable or who decide not to undergo surgery (1). Some groups have recently suggested that SABR is a noninferior treatment approach for patients with operable stage I NSCLC (2,3). Surprisingly, there are no available data demonstrating the effectiveness of SABR at achieving pathologic complete response (pCR) in patients with NSCLC, a highly relevant point for all patients and perhaps particularly so for those who are candidates for surgery. To address this gap in knowledge, Palma *et al*. recently conducted a prospective single-arm phase II clinical trial at a single tertiary-care center to evaluate pCR in patients with clinical stage I (T1-T2aN0M0) NSCLC undergoing SABR followed 10 weeks later by surgery (4). The primary endpoint was pCR rate; secondary endpoints were locoregional and distant control, toxicity, and quality of life. On the basis of previously published imaging-based studies, the authors hypothesized that SABR would result in a pCR rate of 90% (2,4,5). Power analysis suggested that 40 patients would be needed to achieve a 95% confidence interval of ±10 percentage points for pCR. Pathologic assessment was performe d via uptake of hematoxylin and eosin staining and the morphologic appearance of tumor cells on microscopy.

In all, 36 patients underwent SABR followed by R0 resection. Four subjects were excluded from primary endpoint analysis but were included in the intent-to-treat analysis of oncologic outcomes. A majority of patients (81%) underwent video-assisted thoracic surgery (VATS), 72% underwent lobectomy, and a median of 6 (range, 0–16) lymph nodes were sampled. The conversion rate from VATS to thoracotomy was 15%. Pathologic nodal upstaging occurred in 3 of 36 patients (8%). The pCR rate was 60%, meaning that 40% of patients had persistent viable tumor cells 10 weeks after SABR. Toxicity was relatively minor, and there were no perioperative deaths.

The primary finding of this study is the pCR rate of only 60%, which is significantly lower than response rates in previous reports that used only imaging-based assessments (2,4,6). The authors address several factors they believe led to the variability in these findings. They recognized that prior imaging-based studies likely did not accurately reflect the presence or absence of residual tumor. Because of the high doses of radiotherapy focally delivered, a small local recurrence may be difficult to distinguish from the background of radiotherapy-ablated lung parenchyma (7), which would falsely underestimate true-response rates. To counter this, the authors employed thin-slice dynamic contrast-enhanced computed tomography (CT) and dynamic fluorodeoxyglucose–positron emission tomography to better distinguish benign and malignant pathologic findings after SABR. CT findings were assessed

using standard response evaluation criteria in solid tumors (RECIST) criteria and are as follows: complete response, 1 patient (2%); partial response, 17 patients (43%); stable disease, 20 patients (50%); and progressive disease, 2 patients (5%). Unfortunately, the authors did not correlate posttreatment CT findings with pathologic results at the time of surgery (10 weeks after SABR). A comparison of these results would have provided insight into the validity of either modality to assess tumor recurrence.

A specific issue raised in this report is how to best determine pathologic response following therapy. pCR may not be the best indicator of treatment efficacy. Major pathologic response, defined as ≥90% tumor cell death, is commonly used as a surrogate for efficacy in the setting of neoadjuvant therapy for NSCLC (8). However, the field of determining pathologic response is quickly evolving with the increasing use of induction immunotherapy (9). Lessons learned here could perhaps be applied to the uncommon cases of SABR followed by surgical resection. Another concern in this study is the use of a single pathologist to assess pCR, as well as the need for a more robust description of the methodology used to calculate pCR. Several studies, most notably in hepatobiliary cancer, have used graded criteria to qualify pathologic response after SABR (10,11). Finally, although RECIST criteria were underexplored in this study, they do not appear to be adequate for detection of residual disease. If tumor recurrence is misinterpreted as benign fibrosis, a patient may not receive the immediate salvage treatment they require. If fibrosis is diagnosed as cancer recurrence, the patient may be subjected to undue interventions, including further imaging, biopsy, chemotherapy, or surgery.

Oncologic outcomes were a secondary endpoint in this study. With a median follow-up of 19 months, local, regional, and distant control rates for the 36 patients who completed both SABR and surgery were 100%, 53%, and 76%, respectively. However, these data should be interpreted with caution, as the median follow-up was relatively short, and it is likely that not all late recurrences were detected, given that only 70% to 80% of NSCLC recurrences occur within the first two years (12). Perhaps a more troubling concern—that has nothing to do with SABR—is the very high rate of regional recurrence, which was defined by the authors as new hilar, mediastinal, or supraclavicular lymphadenopathy. Forty-four percent of patients had regional recurrence at a median follow-up of 19 months, which raises concerns about inadequate intraoperative nodal assessment, ultimately resulting in pathologic understaging. For example, only 50% of patients had level 7 nodes sampled at the time of surgery. These results continue to remind the thoracic surgical community of the importance of systematic nodal sampling/dissection when performing NSCLC resections (13). Finally, a conversion rate of 15% from VATS to thoracotomy is high, and although the potential reasons for this are not specifically discussed, scarring and fibrosis related to prior SABR likely play a significant role, particularly for more centrally located tumors. Such a scenario suggests that a significant number of patients who could have undergone initial straightforward R0 minimally-invasive resection for clinical stage I NSCLC will instead undergo open thoracotomy when their cancer recurs.

Despite the limitations and caveats detailed herein, this is an important study, and it should be recognized as the first prospective clinical trial to evaluate pCR after SABR in patients with NSCLC. Clearly, if 40% of patients have viable cancer after SABR, then SABR should not be used as a local treatment modality for patients with operable NSCLC. Important challenges remain, including defining the optimal noninvasive assessment(s) of tumor viability after SABR, improving nodal assessment strategies before SABR, and designing future studies that will confirm or refute the very modest post-SABR pCR rate of 60% for patients with clinical stage I NSCLC.

Acknowledgments

The authors thank Mr. David Sewell for excellent editorial assistance.

Footnote

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

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Timmerman R, Paulus R, Galvin J, et al. Stereotactic body radiation therapy for inoperable early stage lung cancer. JAMA 2010;303:1070-6.
2. Senthi S, Lagerwaard FJ, Haasbeek CJ, et al. Patterns of

disease recurrence after stereotactic ablative radiotherapy for early stage non-small-cell lung cancer: a retrospective analysis. Lancet Oncol 2012;13:802-9.
3. Nguyen NP, Garland L, Welsh J, et al. Can stereotactic fractionated radiation therapy become the standard of care for early stage non-small cell lung carcinoma. Cancer Treat Rev 2008;34:719-27.
4. Palma DA, Nguyen TK, Louie AV, et al. Measuring the integration of stereotactic ablative radiotherapy plus surgery for early-stage non-small cell lung cancer: a phase 2 clinical trial. JAMA Oncol 2019;5:681-8.
5. Timmerman RD, Hu C, Michalski JM, et al. Long-term results of stereotactic body radiation therapy in medically inoperable stage I non-small cell lung cancer. JAMA Oncol 2018;4:1287-8.
6. Timmerman RD, Paulus R, Pass HI, et al. Stereotactic body radiation therapy for operable early-stage lung cancer: findings from the NRG oncology RTOG 0618 trial. JAMA Oncol 2018;4:1263-6.
7. Huang K, Dahele M, Senan S, et al. Radiographic changes after lung stereotactic ablative radiotherapy (SABR)--can we distinguish recurrence from fibrosis? A systematic review of the literature. Radiother Oncol 2012;102:335-42.
8. Hellmann MD, Chaft JE, William WN Jr, et al. Pathological response after neoadjuvant chemotherapy in resectable non-small-cell lung cancers: proposal for the use of major pathological response as a surrogate endpoint. Lancet Oncol 2014;15:e42-50.
9. Forde PM, Chaft JE, Smith KN, et al. Neoadjuvant PD-1 blockade in resectable lung cancer. N Engl J Med 2018;378:1976-86.
10. Rajagopalan MS, Heron DE, Wegner RE, et al. Pathologic response with neoadjuvant chemotherapy and stereotactic body radiotherapy for borderline resectable and locally-advanced pancreatic cancer. Radiat Oncol 2013;8:254.
11. Katz AW, Chawla S, Qu Z, et al. Stereotactic hypofractionated radiation therapy as a bridge to transplantation for hepatocellular carcinoma: clinical outcome and pathologic correlation. Int J Radiat Oncol Biol Phys 2012;83:895-900.
12. Lou F, Huang J, Sima CS, et al. Patterns of recurrence and second primary lung cancer in early-stage lung cancer survivors followed with routine computed tomography surveillance. J Thorac Cardiovasc Surg 2013;145:75-81; discussion 81-2.
13. Lardinois D, De Leyn P, Van Schil P, et al. ESTS guidelines for intraoperative lymph node staging in non-small cell lung cancer. Eur J Cardiothorac Surg 2006;30:787-92.

Cite this article as: Connolly JG, Jones GD, Caso R, Jones DR. Stereotactic ablative radiotherapy for operable stage I non-small cell lung cancer: not ready for prime time. Ann Transl Med 2019;7(Suppl 6):S234. doi: 10.21037/atm.2019.08.40

