Stereotactic Body Radiation Therapy for Early-Stage Lung Cancer

Are We “All In”

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Stereotactic body radiation therapy (SBRT) has rapidly been adopted into clinical practice as an option for patients with medically inoperable early-stage non-small cell lung cancer (NSCLC) based on reports of excellent outcomes, often with local tumor control ≥90%, from centers in North America, Europe, and Asia. Although data for metastatic lung tumors are less robust, experience supporting SBRT as a viable alternative to surgical resection in this patient population is growing, and Siva et al. provide a comprehensive review of SBRT for pulmonary (oligo) metastases in this issue of the journal. They conclude that SBRT seems both effective and safe in the metastatic setting as a 2-year local tumor control approached 80%, whereas severe toxicity was observed in less than 5% of patients.

Although several prospective single-arm SBRT trials have been conducted, the recently reported results of the multicenter prospective Radiation Therapy Oncology Group (RTOG) 0236 trial for early-stage NSCLC are nothing short of remarkable—particularly for a treatment approach just starting to appear on the radar screen at the start of this decade. Fifty-five high-risk patients with T1 or T2 N0 NSCLC were treated with SBRT to a dose of 6000 cGy in three fractions of 2000 cGy (a 10-fold increase in the dose per fraction given with conventionally fractionated radiotherapy). With intermediate-term follow-up of 34.4 months (range 4.8–49.4 months), only one relapse in the primary site was observed. Local tumor control in the involved lobe was 90.6% and estimated 3-year survival exceeded 50%. At the same time, treatment seemed tolerable with protocol-specified grade 3 and grade 4 toxic events in 14% and 4% of patients, respectively. It should be kept in mind in assessing these results that all patients had FDG-PET imaging as a part of initial staging evaluation, only lesions located in the lung periphery were treated, and institutions were required to undergo a rigorous quality assurance process to participate. The treated population consisted predominantly of women (62%) and T1 lesions (80%).

Although many reports suggest SBRT for early-stage NSCLC is associated with limited toxicity, mature prospective results are just starting to appear in the literature. Perhaps the most influential SBRT data come from a prospective phase II study performed at Indiana University. This trial in essence served as the basis for RTOG 0236, but unlike RTOG 0236 tumor location (e.g., central versus peripheral) was not a condition for eligibility. An increased risk of toxic deaths after SBRT for centrally located lesions was initially reported, although a statistically significant difference in severe toxicity was not seen between central and peripheral lesions with longer follow-up. In addition to tumor location, size of the gross tumor volume was a significant predictor of severe toxicity in the Indiana University trial. In other experiences, pulmonary fatalities after SBRT have been observed secondary to fistula (tracheoesophageal or bronchopulmonary), pneumonitis, and hemoptysis, and tumor location as well as a history of prior radiotherapy and/or...
chemotherapy have been linked to toxicity.\(^1\) It should be acknowledged that assigning a direct cause for pulmonary toxicity in a population with baseline pulmonary dysfunction is challenging at best, with some suggesting that aggravation of dyspnea after SBRT reflects exacerbations of underlying pulmonary disease rather than treatment-related toxicity.\(^7\) Moreover, fatal toxicity has also been observed after alternative treatment approaches for this population including sublobar resection and radiofrequency ablation.\(^8,9\)

Although the potential toxic effects of SBRT for centrally located lesions have been emphasized, several recent reports raise concerns about the treatment of very peripheral lesions that may be in proximity to the rib and chest wall. In this setting, unexpected high rates of skin, rib, and brachial plexus toxicity after SBRT have now been reported even from institutions with substantial SBRT experience and expertise.\(^10–13\) In fact, on the RTOG 0236 study, six patients were classified as having adverse events that were not classified prospectively as protocol specified (as they were not likely anticipated when the trial opened in 2004), including three patients with grade 3 soft tissue (skin or rib) treatment-related complications.\(^3\) Given these observations, specific dose constraints for SBRT regimens have been updated by the RTOG and the National Comprehensive Cancer Network has published SBRT guidelines for NSCLC.\(^14,15\)

In this issue of the journal, Devisetty and Salama\(^16\) report two cases of severe lung cavitation that developed during the course of image-guided SBRT for peripheral NSCLC. Although these changes were not associated with clinical sequelae, the authors raised concerns given experience correlating cavitation with fatal bleeding in patients receiving the antivascular endothelial growth factor receptor bevacizumab with chemotherapy in advanced NCSLC.\(^17\) Interestingly, fatal toxicity (from fistula formation) has also been reported after administration of bevacizumab in patients with a history of thoracic radiotherapy.\(^18\) Although both patients in this report had medical comorbidities including vascular disease and diabetes mellitus, similar factors are present in the majority of patients with stage I NSCLC deemed ineligible for lobectomy. As such, it is not clear which factors may have precipitated these unique radiographic changes.

In fact, it is perhaps most surprising that there have been relatively few reports of unusual and severe reactions after the extreme doses delivered with SBRT. Although the comfort level has risen with SBRT regimens, there is still much to learn regarding the biology of very large radiotherapy fractions and potential complications of therapy. As opposed to conventionally fractionated radiotherapy, which presumably follows classic radiobiologic principles predicting preferential tumor cell killing and relative protection of normal structures, SBRT uses doses that are theorized to have a direct ablative effect on both tumors and surrounding tissue. Therefore, the use of advanced technology such as (respiratory) motion management and image guidance are critical to ensuring that radiation dose is applied only to the intended target.

The development of SBRT for early-stage NSCLC is a great success story for the field of radiation oncology in that we can now offer patients a high-tech, noninvasive treatment that can be completed in a minimum of visits with a high expectation of success. For the most part, the question has become: Which medically inoperable patients should not receive SBRT? Nevertheless, there remains much work to be done in identifying factors that place patients at high risk for severe toxicity, and this may be particularly challenging given marked variation in SBRT fractionation, dose, technique, target determination, and dose calculation algorithm.

And although outcomes for SBRT have been impressive, alternative treatments options also seem quite promising. For example, single institution series have reported excellent local tumor control after sublobar resection and brachytherapy in high-risk T1N0 NSCLC, and the American College of Surgeons Oncology Group recently completed a phase III study assessing the addition of I-125 brachytherapy to sublobar resection in this population.\(^19\) At this time, a phase III trial comparing sublobar resection and SBRT is being considered by the RTOG and American College of Surgeons Oncology Group. Accelerated hypofractionated radiation regimens that preserve some degree of fractionation may also have merit. The Cancer and Leukemia Group B recently reported mature results of accelerated conformal radiotherapy to a dose of 70 Gy for node-negative NSCLC up to 4 cm. With median follow-up of 53 months, only three local failures were identified in 39 patients, whereas grade 3 toxic effects were observed in only two patients.\(^20\) An additional prospective trial from the NCI Canada testing a regimen of 60 Gy in 15 fractions more than 3 weeks for peripheral NSCLC lesions up to 5 cm completed accrual and results should be reported in the near future.\(^21\)

Advances in the past decade have radically changed expectations for patients with medically inoperable early-stage NSCLC. Phase III comparative studies will be necessary to provide definitive information regarding the therapeutic ratio of SBRT and alternative treatment options. In the meantime, meticulous radiation treatment planning and delivery is essential for centers performing SBRT, and vigilance is required in carefully monitoring and reporting patient outcomes.

REFERENCES


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