Encouraging Long-Term Outcomes Reported in Patients With Stage I Non-Small Cell Lung Cancer Treated With Stereotactic Ablative Radiotherapy

A new study provides evidence that patients with medically inoperable, stage I non-small cell lung cancer (NSCLC) treated with stereotactic ablative radiotherapy (SABR) enjoy long-term outcomes that are similar to those of patients undergoing surgery for similar lung cancers (Cancer [published online ahead of print March 27, 2017]. doi: 10.1002/cncr.30693). Although SABR has become an accepted treatment of patients with medically inoperable, early-stage NSCLC, data regarding outcomes with more than 5 years of follow-up are lacking. The current study helps to fill that knowledge gap. This information may become more clinically relevant as more patients are diagnosed with early-stage NSCLC in the era of modern lung cancer screening. “Our data confirmed that SABR achieved the low incidence of local recurrence, regional recurrence, and distant metastasis in 7 years, comparable to surgery in stage I NSCLC,” says Joe Y. Chang, MD, PhD, corresponding author and professor of radiation oncology at The University of Texas MD Anderson Cancer Center in Houston.

Study Details
Researchers at The University of Texas MD Anderson Cancer Center conducted a phase 2 clinical trial investigating SABR among patients with medically inoperable stage IA or stage IB NSCLC from 2005 through 2013. A staging positron emission tomography/computed tomography (CT) scan was performed before treatment. Patients received image-guided SABR to a dose of 50 grays in 4 fractions. Follow-up included chest CT scans every 3 months for 2 years, every 6 months for the next 3 years, and then annually. Local disease recurrence (LR) was classified as a recurrence in the radiation field, regional recurrence (RR) was defined as an intrathoracic lymph node recurrence outside of the radiation field, and distant metastasis (DM) was defined as recurrence in a different lobe of the lung or outside the thorax.

A total of 65 patients were included in the final analysis. At a median of 7.2 years of follow-up (range, 3.1-10.2 years), a total of 18 patients (27.7%) developed recurrence. The initial disease recurrence manifested as LR in 5 patients, RR in 8 patients, and DM in 8 patients, with 2 patients experiencing simultaneous failure. The median time to any recurrence was 14.5 months. It is interesting to note that 2 of the patients with RR and 4 of the patients with DM had short intervals (approximately 4-6 months) to their recurrence. Estimated 5-year rates of LR, RR, and DM were 8.1%, 10.9%, and 11%, respectively. At 7 years, these risks increased to 8.1%, 13.6%, and 13.8%, respectively. The estimated 5-year progression-free survival rate was 49.5%, decreasing to 38.2% at 7 years. The overall survival estimates were 55.7% at 5 years and 47.5% at 7 years. The 5 patients who experienced an initial LR only exhibited larger tumor volumes, with a median volume of 20.76 cm³ compared with a median volume of 8.3 cm³ for the whole group. However, because of the small number of events, the authors believed they could not draw conclusions from their data regarding risk factors for any type of recurrence.

A second primary lung cancer was detected in 12 of the 65 patients at a median of 35 months after SABR. Ten of these patients underwent a biopsy; among new tumors that occurred in the same lobe as the first one, 2 were found to have a different histology.
thereby underscoring the need for continued screening and biopsy for histological confirmation. The most common toxicities were dermatitis (32.3%), radiation pneumonitis (87.7%), and chest wall pain (45.4%). These toxicities were mostly of grade 1 and 2, with only 3 patients developing grade 3 toxicity and none developing grade 4 or 5 toxicities (toxicity was graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events [version 3.0]). The bulk of the radiation pneumonitis cases were of grade 1 (75.4%) in which the patients were asymptomatic but had interstitial lung abnormalities noted on surveillance imaging.

**Implications**

The study authors believed their data shed light on some important points. One-third of the patients with RR and/or DM experienced their recurrence within 6 months of undergoing SABR, suggesting that occult tumor was present at the time of diagnosis and that the disease was destined to recur despite any local treatment. More accurate imaging than the positron emission tomography/CT technology currently available may be useful, as well as approaches to better treat occult cancer cells at the time of local treatment, such as systemic treatment with chemotherapy or immunotherapy. “We will activate our phase 2 randomized study in early-stage NSCLC to compare SABR versus SABR plus PD-1 immunotherapy in June 2017 (ClinicalTrials.gov identifier NCT03110978). The idea is to reduce LR, RR, DM, and secondary cancers,” says Dr. Chang. “The major questions for SABR are regarding optimal combination with systemic treatment including timing, sequencing, and dosage, as well as potentially applying it in stage IV disease. There is a thought that cancer cells killed by SABR can release tumor-associated antigen and activate immunity to function as a tumor-specific vaccine. Combined systemic treatment and SABR may open a new window to improve both local and systemic control for early-stage and advanced-stage cancers,” he adds.

Charles R. Thomas Jr., MD, professor and chair of radiation medicine at the Oregon Health and Science University in Portland, agrees, and states that the use of adjuvant therapy currently is a poorly defined research space and clinical trials are ongoing and necessary to define its role in conjunction with SABR.

Patient selection for SABR is a key area of research as well. “The indications for broadening eligibility criteria will depend on the type of patient. For example, patients with operable disease may have other comorbidities which preclude safe surgical resection. In such cases, SABR is commonly used and will continue to be a treatment option,” says Dr. Thomas. Whether SABR will benefit patients with a higher stage of disease or should be performed in operable patients requires careful study. “The most important thing to stress is that these patients should be evaluated in a multidisciplinary forum with a dedicated thoracic surgeon, pulmonary medicine specialist, radiation oncologist, and imaging expert,” he says.

The study authors also believed it was interesting to note that second primary lung cancer often is curable and, in their study, that approximately one-half of the patients who experienced LR or RR did not have a subsequent recurrence after receiving salvage therapy. This information underscored that patients should be followed closely after SABR so as not to miss a window of opportunity in which a second lung cancer or limited recurrence can be cured. Last, methods of SABR are improving. “Current practices have emerged that can deliver high doses in much shorter time with improved efficiency and accuracy,” says Dr. Chang.

doi: 10.3322/caac.21375