

LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Stereotactic Body Radiation Therapy in Advanced NSCLC



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H&O What is the standard first-line treatment in advanced non–small cell lung cancer (NSCLC)?

TW The standard treatment for unresectable, locally advanced stage III NSCLC is concomitant chemotherapy and radiation, followed by immunotherapy with durvalumab (Imfinzi, AstraZeneca). For metastatic NSCLC, we use an epidermal growth factor receptor (EGFR) inhibitor if the patient has an *EGFR* mutation, and chemotherapy, immunotherapy, or a combination of chemotherapy and immunotherapy if the patient does not have an *EGFR* mutation. Other types of systemic therapy, including small-molecule inhibitors, are available for less common subtypes of oncogene-driven NSCLC, such as those driven by mutations in *ALK*, *ROS*, or *BRAF*.

H&O What is stereotactic body radiation therapy (SBRT)?

TW SBRT, which is also known as stereotactic ablative body radiotherapy (SABR), pronounced “saber,” is an ablative radiation technique that is used to deliver highly conformal, accurately targeted radiation in high doses to extracranial sites. Compared with conventional radiation, it is delivered in a smaller number of fractions—typically no more than 5 in the United States.

H&O What is the mechanism of action behind SBRT in NSCLC?

TW SBRT induces tumor cell death by causing excessive DNA damage that cannot be repaired, along with vascular collapse that strips tumor cells of their blood

supply. We also believe that SBRT may cause the release of tumor antigens that help to prime an immune response against the tumor; this may in part be mediated by T cells, although other immune cell types are also being studied.

H&O Does SBRT affect the tumor microenvironment?

TW SBRT alters the tumor microenvironment by causing vascular collapse, the release of damage signals by inducing an acute and subacute proinflammatory state, and potentially a repair response involving a plethora of immune cell and progenitor cell types. It can sometimes induce a profibrotic response in the long term.

H&O When is SBRT used in NSCLC?

TW SBRT is commonly used in the setting of early-stage NSCLC for patients who are not fit to undergo surgery. It also is being increasingly used in metastatic NSCLC in the setting of oligometastasis or oligoprogression. SBRT is not used in stage III NSCLC; however, some studies have looked at the addition of SBRT to standard chemotherapy and radiation to treat residual disease or larger tumors, and others have examined how best to employ SBRT in the stage III setting.

H&O When is conventional radiation therapy used in advanced NSCLC?

TW Conventional radiation is used in the definitive treatment of NSCLC (eg, stage III) and is also useful to relieve pain from bone metastases and decrease bleeding,

and for other types of palliation in patients with stage IV disease.

Several small phase 2 randomized trials have provided evidence to support using SBRT in the metastatic setting. These include SABR-COMET, which was published by Palma and colleagues in 2019; work by Iyengar and colleagues at the University of Texas Southwestern Medical Center; and work by Gomez and colleagues at the MD Anderson Cancer Center. SABR-COMET included patients with multiple tumor types, whereas the other 2 trials specifically looked at patients with NSCLC. All of these trials showed that the addition of SBRT to systemic therapy improves progression-free survival in the oligo-metastatic setting, which is usually defined as the presence of no more than 3 to 5 metastases.

A newer, phase 3 trial called SINDAS, which tested the addition of SBRT to tyrosine kinase inhibition in patients with *EGFR*-mutant stage IV NSCLC, showed improved progression-free survival and overall survival in this patient population. Interim results were presented by Wang and colleagues at the 2020 American Society of Clinical Oncology Annual Meeting.

H&O Does the combination of SBRT and checkpoint inhibitors provide a synergistic effect?

TW A growing body of evidence from preclinical studies describes mechanistic synergy between ablative doses of radiation and immunotherapy. Evidence of this synergy was seen in the phase 2 PEMBRO-RT study, by Theelen and colleagues, in which 76 patients with metastatic NSCLC were treated with pembrolizumab (Keytruda, Merck) with or without SBRT to a single metastatic site within 7 days of the initiation of pembrolizumab. Radiation was given before immunotherapy in 3 fractions, at a dose of 8 gray (Gy) per fraction, for a total of 24 Gy. A trend was observed toward better results with the combination than with pembrolizumab alone (objective response rates of 36% and 18%, respectively), along with improved disease control, progression-free survival, and overall survival. None of these results reached statistical significance, however. No increase in toxicity was seen in the SBRT arm. In a subset analysis, the largest difference was seen in patients with programmed death ligand 1 (PD-L1)-negative tumors. We still need more data regarding synergy between SBRT and immunotherapy; ongoing clinical trials are addressing this topic.

H&O Are the recommended dose and fractionation of SBRT in clinical practice the same as those used in the PEMBRO-RT study?

TW For ablative doses of radiation, we typically administer

50 Gy in 5 fractions (or higher total doses when it is safe to do so) to achieve an appropriate, biologically effective dose of more than 100 Gy using an α/β ratio of 10. In the setting of metastatic disease, we typically are more conservative with dosing unless we are enrolling patients in clinical trials. Certainly, normal tissue tolerances need to be respected. PEMBRO-RT and other studies combining SBRT with checkpoint inhibitors to create a synergistic effect have often used more conservative, nonablative doses (eg, 8 Gy \times 3). It remains to be seen whether other radiation doses and fractionations will yield better effects.

H&O Why did the patients whose tumors were PD-L1-negative respond the best to SBRT and immunotherapy?

TW Although the results of the PD-L1-negative subset analysis also failed to reach statistical significance, they point to the possibility that SBRT may convert an “immunologically cold” tumor to an “immunologically hot” one, causing it to become “inflamed” and priming it for an immune response to the anti-PD-1 agent.

A number of trials to assess the optimal schedule for combining SBRT and checkpoint inhibitors are ongoing.

H&O How strong is the abscopal effect with SBRT in NSCLC?

TW The abscopal effect is rare with SBRT alone and more common when SBRT is combined with immunotherapy, such as a checkpoint inhibitor. More work needs to be done to establish how often the abscopal effect occurs and determine the optimal conditions (eg, radiation dose and fractionation, specific immunotherapy drug used, and sequencing of radiation and immunotherapy) under which it occurs.

H&O Is there a role for predictive biomarkers in determining whether patients will respond to SBRT?

TW We know that biomarkers such as the PD-L1 immunohistochemistry, tumor mutation burden, RNA

signatures, circulating tumor DNA, and microbiome can help us predict which patients will respond to immunotherapy, but we do not have any biomarkers to predict the radiographic overall response rate and disease control rate with SBRT. The good news is that large numbers of patients respond to SBRT; the response rate is at least 40% to 50%, with some studies suggesting that it is even higher, and the disease control rate with SBRT, which includes patients with stable disease, is higher still. For example, the RTOG 0813 trial by Bejjani and colleagues from the Radiation Therapy Oncology Group found a 2-year local control rate of 88% to 89% in patients with inoperable early-stage NSCLC. The most recent update of the RTOG 0236 study, first published by Timmerman and colleagues in 2010, found a 5-year primary control rate of approximately 93% in patients with inoperable early-stage NSCLC.

H&O What ongoing trials are looking at SBRT in NSCLC?

TW A number of trials to assess the optimal schedule for combining SBRT and checkpoint inhibitors are ongoing. For example, the phase 3 PACIFIC-4 trial, which is currently recruiting patients, is looking at the addition of durvalumab following SBRT in patients with unresected early-stage NSCLC (NCT03833154). Another phase 3 trial, SWOG/NRG S1914, is looking at the addition of atezolizumab (Tecentriq, Genentech) before, during, and after SBRT in early NSCLC (NCT04214262). Although both of these trials are looking at the early-stage disease setting, the results will be helpful in shedding light on SBRT in advanced disease. As more phase 1/2 trials examine combinations of SBRT and immunotherapy, we should be able to get a better handle on the frequency of abscopal responses, the timing of the combination of radiation and immunotherapy, and whether better immunotherapy regimens can be designed than just combinations of anti-programmed death 1, anti-PD-L1, and anti-cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) agents. Other trials that have been activated or are in development are addressing the role of SBRT in more advanced oligometastatic disease, and how best to combine SBRT with immunotherapy in the stage IV

setting. For example, SABR-COMET-10, a randomized phase 3 trial, is assessing whether SBRT improves clinical outcomes among patients with 4 to 10 oligometastatic tumors (multiple tumor types are allowed, including NSCLC). In addition, the phase 2/3 Alliance A082002 study will more comprehensively test whether SBRT alters clinical outcomes in patients receiving modern immunotherapy regimens for PD-L1–negative stage IV NSCLC.

Disclosure

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Suggested Readings

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