LUNG CANCER IN FOCUS

Current Developments in the Management of Lung Cancer

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Radiation Therapy and MRI-Based Treatments in Non–Small Cell Lung Cancer

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H&O How has the role of radiation therapy in non–small cell lung cancer (NSCLC) evolved in recent years?

PL Historically, radiation therapy with concurrent chemotherapy in lung cancer was used mostly in stage III, unresectable NSCLC. This is an area in which radiation oncologists are still integrally involved in the treatment paradigm. In addition, stereotactic body radiotherapy (SBRT)—a form of radiation delivered in 5 or fewer sessions at a high dose—has become one of the standards of care for stage I, node-negative NSCLC that is considered inoperable for medical reasons, frailty, or age.

Immunotherapy has long been a big component of treatment in locally advanced NSCLC and is used after chemoradiation. We have seen a lot of enthusiasm and data regarding the use of neoadjuvant chemo-immunotherapy before resection. Although neoadjuvant chemo-immunotherapy has improved patient outcomes, it has made decision making more complex. We have no head-to-head comparison to determine whether surgery or radiation is the superior approach in cases of borderline-operable stage III NSCLC, such as in patients with multi-station nodal disease. In addition, defining which patients with stage III disease are operable or inoperable is a currently a topic of considerable controversy and debate.

Among patients with stage IV NSCLC, radiation historically has been used primarily in a palliative fashion. We still use radiation as palliative therapy; however, radiotherapy is increasingly being used in the treatment of metastatic or oligometastatic disease in the consolidation setting to eradicate residual disease or disease that is resistant to systemic therapy. For patients who have limited sites of metastases and have responded well to systemic therapy, we often consolidate those metastatic sites with radiation therapy to improve local control and potentially improve progression-free survival (PFS) or overall survival (OS). We have randomized phase 2 data, particularly in patients with targetable mutations, suggesting that this approach may improve PFS and potentially OS.

H&O What are the current best practices for integrating radiation therapy with systemic treatments?

PL The historical standard of care for stage III disease is concurrent chemoradiation over 6 weeks followed by consolidation immunotherapy, per the regimen used in the PACIFIC trial.[1]

For early-stage disease, ongoing studies are evaluating the role of SBRT combined with immunotherapy. Some of these studies have closed early owing to a lack of observed benefit, but the PACIFIC-4 study is ongoing.[2]

In stage IV disease, the role of radiation therapy depends on whether the patient has oligometastatic or oligoprogressive disease. Typically, patients receive systemic therapy first—chemotherapy, immunotherapy, or targeted therapy. If they show disease control after 3 to

6 months, we consolidate all sites of initial disease with radiation therapy when feasible and safe. The decision on the timing and integration of systemic therapy depends on toxicity considerations because some newer drugs—such as antibody-drug conjugates—may have synergistic toxicity with radiation. Immunotherapy, in contrast, is generally well tolerated with radiation therapy.

For oligoprogressive disease, meaning that a patient has systemic disease but only 1 to 5 sites with progression of disease, we often consider radiating those sites while continuing systemic therapy. This approach, studied in phase 2 trials such as CURB, has shown benefit for lung cancer histology, but not for breast cancer.[3]

> We do not yet have level 1 evidence proving that MRI-guided adaptive radiation improves long-term survival compared with convention radiation.

H&O What are the advantages of magnetic resonance imaging (MRI)–guided radiation therapy vs traditional computed tomography (CT)–based planning?

PL MRI-guided radiation therapy offers several advantages over CT-guided radiation therapy. First, MRI provides superior soft-tissue imaging contrast of tumor vs normal tissue in comparison with CT, making it easier to delineate tumors. Second, MRI does not use ionizing radiation, so we can acquire images daily without worrisome radiation exposure. This allows us to update treatment plans according to anatomical changes while the patient is on the treatment console just before the radiation therapy is delivered, a process known as online or real-time adaptive radiation therapy. Adaptive therapy allows us to modify radiation plans in real time to optimize dose delivery while sparing normal tissue from high-dose radiation therapy. This approach is advantageous because anatomy can change daily, especially in cases in which tumors shrink or nearby organs move between treatment days. This is particularly relevant for treating tumors near a critical structure like the trachea, esophagus, or heart.

During treatment, MRI can also be used for real-time tumor tracking. That is, the MRI is continuously creating a cine movie of the internal tumor and surrounding tissue while the radiation beam is on. For example, we can employ gated treatment—in which radiation is delivered only when the tumor is in the correct position—within a small margin beyond the tumor itself. Gated treatment is particularly useful for mobile tumors in the lung or abdomen. The use of real-time MRI guidance for radiotherapy facilitates control of the beam and accuracy of the delivery of ablative doses of radiation therapy, allowing the radiation oncologist to treat the tumor only when it is in the intended target zone while the patient holds their breath. This significantly reduces the amount of healthy tissue irradiated and ensures that the tumor is not underdosed owing to uncertainty in the tumor position during radiotherapy.

H&O What are the challenges encountered in implementing MRI-based radiation therapy?

PL Several challenges are involved in implementing MRI-based radiation therapy. The first is the cost. MRI-guided linear accelerators are significantly more expensive than standard CT-guided machines, given that they are early in the clinical adoption cycle; this limits their accessibility primarily to academic centers and large institutions.

The second challenge is efficiency. Treatment times are longer with MRI-guided radiation therapy than with standard CT-guided therapy, at approximately 45 to 90 minutes per session vs 15 to 30 minutes per session, respectively, so that the number of patients who can be treated per day is reduced.

The third challenge is staff training. Radiation oncologists, physicists, and radiation therapists typically are trained in CT-based planning, so transitioning to MRI requires extensive education and training. It took our team approximately a year to become proficient in the use of MRI-based radiation therapy.

The final challenge is the issue of evidence. Although we have promising early data, we do not yet have level 1 evidence proving that MRI-guided adaptive radiation improves long-term survival in comparison with conventional radiation. More clinical trials are needed, but radiation oncology trials are difficult to conduct because we are modifying how an existing treatment is delivered rather than introducing a new drug.

H&O What clinical trial data should oncologists be aware of in lung cancer?

PL Several trials have shaped current practice. The phase 3 PACIFIC trial showed that consolidation treatment with the anti–programmed death ligand 1 antibody durvalumab (Imfinzi, AstraZeneca) after chemoradiation significantly

improved OS in patients with stage III NSCLC who did not have disease progression after 2 or more cycles of platinum-based chemoradiotherapy.[1]

For limited-stage small cell lung cancer, the recently published phase 3 ADRIATIC trial demonstrated significantly longer OS and PFS with consolidative durvalumab than with placebo following chemoradiation in patients with limited-stage small cell lung cancer.[4]

The recent phase 3 LAURA trial, which focused on *EGFR*-mutant stage III NSCLC, found that the third-generation epidermal growth factor receptor (EGFR)–tyrosine kinase inhibitor osimertinib (Tagrisso, AstraZeneca), rather than durvalumab, is the preferred consolidation therapy for these patients, demonstrating superior PFS.[5]

For oligometastatic disease, studies like the phase 2 CURB trial—which I mentioned earlier—suggest that consolidative radiation can dramatically improve outcomes in patients with oligoprogressive NSCLC. In this trial, the addition of SBRT to standard of care led to more than a 4-times increase in PFS in comparison with standard of care only.[3]

Finally, my own study, published in *JAMA Oncology*, explored the use of hypofractionated chemoradiation in patients with stage III, unresectable NSCLC and suggested better local control with higher biological doses of radiation therapy delivered in a shorter amount of time (3 weeks vs the traditional 6 weeks).[6] This was an early-phase, dose-escalation nonrandomized controlled trial. We showed the benefit and safety of chemoradiation with an adaptive stereotactic ablative radiotherapy (SABR) boost of up to 70 Gy in 15 fractions with concurrent chemotherapy.

H&O What are the uses of artificial intelligence (AI) in radiation therapy?

PL AI is already being used for contouring and treatment planning, but accuracy and reliability remain limitations, so human oversight as well as insight and clinical judgment or intuition are essential. In MRI-guided radiation therapy, AI can help streamline adaptive treatment by automating contouring and dose calculation, which reduces planning time. If AI becomes more reliable, I envision a future in which every session of radiation therapy for each patient is individually optimized and personalized in real time. I think this will further enhance the therapeutic ratio of radiation therapy, augmenting efficacy and reducing short- and long-term side effects of treatment.

Barriers to the more widespread use of AI in radiation therapy include workflow efficiency and reimbursement models. The extra time required for adaptive planning is not always reimbursed, currently making widespread adoption challenging.

Disclosures

Dr Lee has done consulting for Varian, ViewRay, AstraZeneca, Genentech, Johnson & Johnson, Roche, and the RTOG Foundation; has served on the speakers' bureau of Varian, ViewRay, and AstraZeneca; has received travel reimbursement from the Radiosurgery Society; and has served on the Data and Safety Monitoring Board or advisory board of Genentech, ViewRay, AstraZeneca, and Roche.

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