Radiation Therapy as a Backbone of Treatment of Locally Advanced Non-Small Cell Lung Cancer

Aaron M. Laine, Kenneth D. Westover, and Hak Choy

Locally advanced non-small cell lung cancer (LA-NSCLC) is a heterogeneous disease, encompassing stage IIIA, for which surgery in combination with chemotherapy and/or radiation therapy (RT) represents a potential treatment approach for select patients, and stage IIIB, for which chemoradiation represents the standard of care. Recent advances in systemic cytotoxic and molecularly targeted therapies coupled with technologic innovations in radiotherapy have the potential to improve outcomes for this patient population. Many ongoing clinical trials use specific genetic mutations or histologic status to determine the combination of targeted therapies and RT, as well as to determine the optimal chemoradiotherapy platforms. Additionally, use of modern RT techniques has improved outcomes for some patients with limited metastatic disease, thereby prompting further studies on how to best integrate aggressive management of oligometastases using RT with chemotherapeutic regimens.
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Identifying lung cancer patients before they progress to locally advanced disease remains one of the foremost challenges to improving outcomes for lung cancer patients. Forty to fifty thousand patients with locally advanced non-small cell lung cancer (LA-NSCLC) are diagnosed annually in the United States, representing approximately 35% of all newly diagnosed cases.[1] Many of the advances in the treatment of this disease have come from studies involving combined modality therapy (CMT), where a combination of chemotherapy with radiation treatments have made a significant impact in the outcome of these patients.[2] However, despite encouraging improvements in survival, the absolute overall survival (OS) of patients with LA-NSCLC remains poor. Improving outcomes for patients with locally advanced disease is an area of ongoing research and significant advances have been made in the treatment of this patient population over the past few decades. Active areas of research include determining the appropriate sequencing of systemic treatments with radiation therapy (RT) in the combined modality setting, discovery of novel agents, and technological advances aimed at improving delivery of radiation treatments. Treatment paradigms now incorporate factors beyond age, performance status (PS), and non-small cell histology into the decision-making process such as genetic alterations. We have arrived at an era where patients benefit from individualized therapeutic strategies based on the molecular characteristics of tumor tissue.[3] The handful of success stories in this regard provide reason to expect that additional research will lead to better outcomes and more effective clinical trial design for a greater number of patients in the future. In addition, technological improvements in RT are expanding the ability to target tumors with more precision and higher doses, enhancing treatment options for patients. This has effectively expanded the number of clinical situations where RT may be beneficial. In this review, we will discuss the role of radiotherapy in the treatment of LA-NSCLC, current strategies for combined modality therapy, the role of targeted therapies, the treatment of limited metastatic disease, and potential future directions under investigation.

Department of Radiation Oncology, University of Texas Southwestern Medical Center, Dallas, TX.
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Address correspondence to Hak Choy, MD, Department of Radiation Oncology, University of Texas Southwestern Medical Center, 5801 Forest Park Rd, Dallas, TX 75390-9183. E-mail: hak.choy@utsouthwestern.edu.
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ROLE OF RADIOTHERAPY

Definitive RT was the standard of care for patients with LA-NSCLC until clinical trials demonstrated improved survival with CMT. RT without chemotherapy remains the preferred definitive approach

for poor-risk patients who are not candidates for CMT. RT can also have a role in selected patients with isolated thoracic recurrence after previous therapy. Other benefits of RT include palliation of tumor-related symptoms, local control of tumor growth and a potential survival advantage.

Dose Escalation

The use of RT alone for LA-NSCLC consistently resulted in a median survival of about 10 months and 5-year survival rates of 5%.[4–7] In the 1970s, the Radiation Therapy Oncology Group (RTOG) performed a phase III trial (RTOG 73-01) to evaluate the role of RT dose on local control rates and OS.[8] Patients were randomly assigned to treatment with 40, 50, or 60 Gy in 2-Gy daily fractions. Local control rates were significantly better with the highest dose (52% *v* 62% *v* 73%, respectively), although median survival rates were similar (10.6 months *v* 9.5 months *v* 10.8 months, respectively).[8] This established 60 Gy in 30 fractions as the standard RT dose-fractionation schema.

Early RT portals were designed to cover primary tumor, ipsilateral supraclavicular nodes, ipsilateral hilum, and contralateral mediastinum. This approach was termed elective nodal radiation therapy (ENI). However, as it became apparent that ENI results in additional toxicity and that local failure is closely related to poor patient outcomes, treatment planning shifted towards involved field irradiation (IFI).[9] Concerns over the potential for nodal recurrences with IFI were answered by a prospective randomized trial from China where LA-NSCLC patients were treated with 68–74 Gy IFI or 60–64 Gy ENI.[10] At 5 years, significant improvements were seen in the IFI arm with regard to overall response rates (90% *v* 79%), local control (51% *v* 36%), and the rates of pneumonitis (17% *v* 29%). OS was improved for patients treated with IFI with 2-year rates at 39.4% versus 25.6%. While there are limitations to this study, the results are intriguing and suggest that failure to cover elective nodes is unlikely to compromise clinical outcomes.

In addition to determining the optimal treatment volume, there was interest in exploring the role of dose escalation in the improvement of local control rates.[11] Early phase I/II trials suggested that increasing the dose to 74 Gy could improve the median survival times to 24 months.[12–15] These promising results, in addition to a pooled analysis of cooperative group studies,[16] suggested the need to compare, with the backdrop of CMT, dose-escalated RT to standard RT doses in a randomized trial. This question was addressed in a phase III trial (RTOG 06-17) that randomly assigned patients with LA-NSCLC to one of two chemotherapy regimens and to either standard-dose RT (60 Gy in 30 daily fractions) or high-dose RT (74 Gy in 37 daily fractions). Survival was compared between the 74-Gy group and the 60-Gy group, and OS was better in the lower dose group (median survival of 28.7 months in 60-Gy group *v* 19.5 months in 74-Gy group and an estimated 18-month OS of 66.9% *v* 53.9%).[17] Patients in the high-dose group had a 56% greater risk for death than those in the standard-dose group and a 37% greater risk for local progression. However, even though 17 patients died in the 74-Gy arm compared with seven in the 60-Gy arm, the toxicity rates were no different between the two dose groups. The final results of this trial will surely be scrutinized, but the standard dose of RT for LA-NSCLC remains 60 Gy.

Altered Fractionation Schedules

Multiple trials have explored the use of altered dose fractionation schedules to improve the therapeutic index of RT. These approaches have included hyperfractionation (two or three fractions per day with a lower dose per fraction over the standard treatment duration), accelerated fractionation (using a standard fraction size and total radiation dose, given over a shorter overall time) or a combination of both.

Randomized studies have not shown a survival benefit to hyperfractionated radiation with concurrent chemotherapy delivered either continuously or as a split course compared with standard chemoradiotherapy.[18,19] However, studies have demonstrated improved outcomes when using a hyperfractionated accelerated radiotherapy (HART) approach. Continuous HART, delivering 54 Gy in 36 fractions of 1.5 Gy over 12 days, resulted in improved survival compared with conventional RT alone (2-year OS 29% *v* 20%).[20] Similarly, Eastern Cooperative Oncology Group (ECOG) 2597, which randomly assigned patients to HART (1.5 Gy three times per day for 2.5 weeks) after two cycles of carboplatin/paclitaxel or standard RT (64 Gy in 2 Gy daily fractions) with the same chemotherapy, revealed an numerically improved median survival for the HART arm (20.3 *v* 14.9 months, $P = .28$) and 3-year OS (23% *v* 14%).[21]

The most informative results come from a meta-analysis of eight randomized trials that examined individual patient data from 2,000 patients, in which patients were randomly assigned to an altered regimen or conventional fractionation.[22] The analysis was limited to trials where chemotherapy was identical in both treatment arms. Modified fractionation resulted in a small, but significant, improvement in 5-year OS (10.8% *v* 8.3%; hazard ratio 0.88). A higher rate of severe esophageal toxicity (19% *v* 9%) was observed in the modified fraction group.