

Invited Commentary

Dose Escalation Optimization in Patients With Locally Advanced Non-Small-Cell Lung Cancer

The Right Dose, in the Right Location, to the Right Patient, at the Right Time

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Results from RTOG 0617, comparing conventionally fractionated 60 Gy vs 74 Gy with concurrent chemotherapy in patients with unresectable non-small-cell lung cancer (NSCLC),



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informed us that uniform dose escalation over the entire tumor volume in an unselected population to 74 Gy led to inferior survival compared with 60 Gy.¹ The exact cause of inferior survival in the higher-dose arm is unclear; however, local failure remains a considerable problem in radiation therapy (RT) for locally advanced NSCLC, with local failure rates of 31% to 39% at 2 years reported in RTOG 0617, consistent with other studies. Kong et al² attempt to address this problem with the phase 2 trial reported in this issue of *JAMA Oncology*.

In this trial, patients with unresectable/inoperable NSCLC received definitive radiation in 30 fractions that was dose-escalated to their during-RT metabolically active tumor volume (positron emission tomography coupled with computed tomography [PET/CT] scan around 40-50 Gy) to as high as 86 Gy, while respecting standard normal tissue constraints, including keeping lung normal tissue complication probability, a measure of the likelihood of radiation-induced pulmonary complications, to less than 17.2%. Pretreatment planning target volume received 50 Gy or more, and the during-RT metabolically active volume received 70 Gy or more, with 94% of patients receiving more than 74 Gy equivalent dose in 2 Gy fractions (EQD2). The authors² were able to report 2-year local-regional tumor control of 82% (in field). There were no grade 4 or 5 adverse events, with acceptable rates of grade 3 events, although 4 patients (10%) died from massive hemorrhage, thought to be related to massive pulmonary artery invasion.

The local control results of this study compare favorably with historical controls and warrant further investigation, but we must interpret phase 2, single-arm results with caution because the phase 2 trial results that led to RTOG 0617 were also very encouraging compared with historical controls at the time.³ It should be noted that the 82% local control reported by Kong et al² did not appear to translate into an improvement in survival because the 2-year overall survival was 52%, similar to the 2-year survival of 57.6% in patients enrolled in RTOG 0617's 60 Gy arm. Although the 2 trials cannot be directly compared owing to differences in eligibility, etc, the ultimate goal of dose escalation is to improve overall survival. It should be noted that RTOG 0617 found heart dose to be a significant predictor for overall survival on multivariate analy-

ses, and this trial, designed prior to the publication of RTOG 0617, does not specifically constrain heart dose beyond standard parameters. The RTOG 1106 trial is a randomized phase II clinical trial comparing the dose escalation strategy employed by Kong et al² with standard 60 Gy in 30 fractions, with results expected in the near future.

Multiple alternate strategies of dose escalation using PET/CT-based tumor volume and response assessments are actively being pursued. One strategy would be to escalate radiation dose for selected patients deemed to be at high risk of local failure. Since not all patients experience local failure, only patients who are at risk of failure locally are expected to benefit from increased local therapy, whereas all other patients will only potentially be harmed by radiation doses that are beyond those required to control their tumor. The challenge is to identify these patients likely to experience local failure either a priori or early on during treatment. Data from van Elmpt et al⁴ may provide some insight. They reported that for patients receiving definitive conventionally fractionated radiation therapy for stages II to IV NSCLC, early PET/CT responders (>15% partial metabolic response) have 2-year OS of 92%, whereas early nonresponders have 2-year OS of 33%. To maximize the therapeutic benefit, one could argue that a patient group with 2-year OS of more than 90% does not need further therapy escalation, where a group with 2-year OS of only 33% could withstand further risk of toxic effects to potentially increase treatment efficacy. Our center has used this observation to inform a strategy of selective escalation of radiation dose for those patients believed to be at high risk of local failure in an ongoing phase 2 clinical trial [NCT02773238](#) (clinicaltrials.gov), for patients with unresectable NSCLC receiving definitive chemoradiation. This trial uses assessment of tumor response on an early-treatment PET/CT scan at 24 Gy (2.5 weeks into treatment) to stratify patients into early responders and early nonresponders, and only escalates dose to patients who are in the nonresponder group.

Other strategies of dose escalation include using a pretreatment PET/CT scan to guide dose escalation because pretreatment PET/CT imaging has also been correlated with sites of local failure posttreatment.⁵ Location of residual 18F-fluorodeoxyglucose (FDG)-uptake in tumor after radiotherapy corresponds with the high FDG-uptake tumor subregions preradiotherapy, which also corresponds with future areas of local failure. Therefore, targeted dose escalation to only areas of high FDG-uptake on the pretreatment PET/CT imaging is another strategy of increasing treatment efficacy without substantial

increase in toxic effects. Beyond FDG, other tracers, such as ^{18}F -fluoromisonidazole (F-MISO) for hypoxia imaging, are also being explored, including as part of RTOG 1106. Vera et al⁶ report on a phase II trial of dose escalation to 86 Gy in patients with hypoxic lesions identified by F-MISO PET/CT imaging. Patients with hypoxia on F-MISO scans had worse disease-free survival at 1-year than patients who did not have hypoxia (50%; 95% CI, 32%-65% vs 85%; 95% CI, 60%-95%; $P = .004$), and radiation dose escalation did not seem to be able to reverse the poor prognosis conferred by the presence of hypoxia, perhaps owing to hypoxia also being a marker of distant failure.⁷

In addition to imaging biomarkers, search is also under way for other methods of identifying patients at high risk of local failure or intrinsic tumor radiation resistance. For example,

Scott and colleagues⁸ have developed a 10-gene “radiosensitivity index,” which has been tested in over 8000 tissue samples and found to be correlated with radiation response and clinical outcomes across several cancer types, leading to the possibility of individualizing radiation doses based on tumor radiosensitivity.

Radiation therapy for locally advanced NSCLC is currently at a cross roads. We know our outcomes remain poor with median survival of less than 3 years, but we have also proven that uniform tumor dose escalation for all patients is detrimental. Therefore, moving forward, we must develop methods of individualizing therapy to deliver the right radiation dose, to the right patient, in the right location, at the right time.

ARTICLE INFORMATION

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