Editorial Commentary

Accelerated hypofractionated chemoradiation followed by stereotactic ablative radiotherapy boost for locally advanced, unresectable non-small cell lung cancer

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The goal of treatment for patients with locally advanced unresectable non-small cell lung cancer (NSCLC) is cure. The current standard therapy for these patients is a combination of radiotherapy to all sites of disease given concurrently with chemotherapy, usually carboplatin and paclitaxel (chemo-radiation), followed by 1 year of immunotherapy with durvalumab. This regimen yielded a median progression-free survival (PFS) of 16.8 months [95% confidence interval (CI): 13.0 to 18.1 months] and a median overall survival (OS) of 47.5 months (95% CI: 38.1 to 52.9 months) in the PACIFIC trial (1,2). While these outcomes were significantly better than those seen with the prior standard of care treatments, only 42.9% of patients in the intervention arm of the PACIFIC trial were alive at 5 years, highlighting the need for further improvements to the treatment regimen (3,4). Further, recurrences after chemo-radiation +/– durvalumab occur at local as well as distant sites (3-5). For example, in a recent study of concurrent chemo-radiation followed by immunotherapy, local failure occurred in 48/119, and of those with local failure, 58% were in field (5). Thus, improvements in local therapy as well as systemic therapy are needed to improve cure rates. However, attention to the effects of local radiation on immune reactions must also be considered (6,7).

In the article that accompanies this commentary, Wu *et al.* evaluated the use of hypofractionated concurrent chemoradiation with a PET-adapted stereotactic ablative radiotherapy (SABR) boost in patients with locally advanced, unresectable NSCLC (3). This was a non-randomized trial that enrolled 28 patients who all received a base dose of radiotherapy of 10 fractions of 4 Gy. After the 8th or 9th fraction, each patient underwent a repeat positron emission tomography (PET) scan and 4-dimensional computed tomography (CT) simulation. The radiotherapy treatment fields were narrowed based on these scans. All patients then received a SABR boost in 5 fractions with either 5 Gy (low-dose cohort), 6 Gy (intermediate-dose cohort), or 7 Gy (high-dose cohort) per fraction. All radiotherapy was given concurrently with chemotherapy consisting of carboplatin and paclitaxel. The authors report a local control rate of 74.1%, 85.7%, and 100.0% after 2 years in the low-, intermediate-, and high-dose cohorts, respectively. They also report survival rates of 30.0%, 76.2%, and 55.6% after 2 years in the low-, intermediate-, and high-dose cohorts, respectively. Only 3 acute (1 in the low-dose cohort, 2 in the high-dose cohort) and 2 late (1 each in the low- and high-dose cohorts) grade ≥3 adverse events (AEs) were reported in the whole trial population, although it is notable that the 2 acute AEs reported in the high-dose cohort were treatment-related deaths. The authors conclude that the

intermediate dose regimen is a safe and effective treatment for patients with locally advanced, unresectable NSCLC.

The small sample size in this trial makes it difficult to draw any definitive conclusions from the results. There are a number of factors that limit its applicability to current practice. First, this trial was largely done in the time before the PACIFIC regimen became the standard of care for patients with locally advanced, unresectable NSCLC. Only 1 patient in the trial received durvalumab. It is therefore unclear how the addition of an immune checkpoint inhibitor (ICI) like durvalumab would affect the reported efficacy and safety of the proposed radiotherapy regimen. These questions must be answered in future trials and the authors do note that some such trials are already ongoing. There is also evidence that higher doses of radiotherapy to the immune system may worsen treatment outcomes in NSCLC, which will have to be weighed against any potential benefit from using higher radiation doses in the treatment of NSCLC (4-6). Second, the trial had three dose levels and it is not clear which is preferable due to the small numbers, although the high dose may be too toxic. A larger, randomized trial using the low- and intermediate-dose regimens from this trial in that patient population would be useful. Third, the use of PET to adapt radiotherapy during treatment is not currently standard practice in most treatment settings, although its use has been explored elsewhere and may make its way into standard practice in the future (8,9). Finally, this trial illustrates one of the inherent difficulties in any radiotherapy dose escalation study, namely the challenge of establishing dose-limiting toxicities (DLTs). In this trial only toxicities that occurred during treatment or within 90 days after treatment were captured. The maximum tolerated dose (MTD) as defined by the trial protocol was not reached in any cohort, but there were 2 treatment-related deaths in the high-dose cohort. The authors are correct to recommend against the high-dose regimen under these circumstances. In the RTOG 0813 trial testing dose escalation for stereotactic body radiation therapy (SBRT) in centrally located tumors, the DLT observation period was 1 year from the start of SBRT, but likely treatment-related severe toxicities were observed even beyond that timeframe (10).

In conclusion, there is a need for improved treatments for locally advanced, unresectable NSCLC and this trial begins to address that need. Its applicability to current clinical practice is limited and extensive further study will be required to establish a role for accelerated hypofractionated chemoradiation and SABR boost in the standard treatment of this disease state.

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Footnote

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