Editorial

Stage III non-small cell lung cancer: escalation matters, but how?

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Concurrent chemoradiation (CRT) as the standard treatment for unresectable stage III non-small cell lung cancer (NSCLC) has reached a therapeutic plateau. Variations in the chemotherapy backbone and addition of consolidation chemotherapy have failed to improve survival (1). Attempts to escalate radiation dose have been met with failure as well (2). As a result, the 5-year overall survival of locally advanced NSCLC has stagnated at 30–40% over the past 10–15 years. While there has been an explosion of new therapeutic strategies for metastatic NSCLC in recent years, locally advanced NSCLC is very much in need of innovation.

Curing stage III NSCLC can broadly be thought of in three terms—eradication of locoregional disease, eradication of systemic micro-metastasis and enriching the treatment population for benefit. Radiation therapy is crucial for eradication of locoregional disease. Early studies of radiation dose escalation showed promising rates of locoregional control and overall survival in comparison with results from the landmark RTOG 9410 trial (3,4). However, in the phase III RTOG 0617 study, dose escalation to 74 Gy led to inferior outcomes. While the reasons for failure of the high dose arm to improve survival have not been delineated entirely, excessive toxicity to surrounding normal tissue appears to have undone any benefit that dose escalation might have had. This is where proton beam therapy (PBT), with its Bragg peak effect seems appealing. Theoretically, with PBT, one should be able to escalate radiation dose to the tumor while sparing surrounding normal tissue. Doing so should ideally result in greater locoregional control and overall survival.

Early phase studies of high dose PBT with concurrent chemotherapy suggested some gain in overall survival in comparison to the standard set by RTOG 9410 (5,6). Recently, in *JAMA Oncology*, Chang *et al.* reported the final results of their phase II study evaluating concurrent chemotherapy and PBT in unresectable stage III NSCLC (7). Patients received weekly carboplatin (AUC =2) and paclitaxel (50 mg/m^2) along with 74 Gy relative biological effectiveness (RBE) of PBT. At a median follow up of 79.6 months for alive patients, median overall survival was 26.5 months and 5-year overall survival was 29%. While it was noted that there were fewer overall toxicities than in studies using intensity-modulated radiation therapy (IMRT) or 3D conformal radiation therapy (3D CRT), close to a third of the patients developed long term pulmonary toxicity. Distant recurrence remained the most common cause of treatment failure (62% of all failures). This study was designed in 2004 and aimed to improve upon the 17-month median overall survival reported by RTOG 9410. Technically the goal was met. But, there have been significant improvements in IMRT technology over the years. The long-term results of RTOG 0617 (3D CRT or IMRT) established a median overall survival of 28.7 months and 5-year overall survival of 32.1% with a standard dose of 60 Gy as the new standard in unresectable stage III NSCLC. Thus, the Chang *et al.* PBT study did not improve upon this new median and 5-year survival standard with conventional IMRT/3D CRT.

A randomized trial of PBT versus IMRT would be a fairer comparison. A recent phase II study published in the *Journal of Clinical Oncology* compared IMRT and PBT at a dose of 74 or 66 Gy (RBE) (8). Primary endpoints were first occurrence of severe (grade ≥3) radiation pneumonitis or

local failure. At a median follow up of 36.4 months for alive patients, there was no statistically significant difference in severe radiation pneumonitis and local failure rate between the two modalities. Although overall survival was not a primary endpoint, no significant difference was found between the two modalities. Radiation dose escalation using PBT doesn't appear to raise the bar for locoregional control and certainly does not address the issue of distant recurrence. At present, there appears to be no survival benefit for this rather expensive, yet popular radiation modality.

Radiation therapy was first developed for the purpose of direct cytotoxic effect. But abscopal responses after radiation therapy observed in a variety of tumor types cannot be explained by direct cytotoxic effect alone (9). In reality, the effects of radiation on the tumor, its microenvironment and the immune system is complex. Research in recent years has revealed a multitude of mechanisms, including neoantigen release leading to *in situ* tumor vaccination, increasing susceptibility to immunogenic cell death by altering tumor phenotype, increased infiltration by immune effector cells via changes in tumor microenvironment and reduction in tumor volume facilitating immunotherapy (10-12). Questions remain regarding the optimal dose and fractionation in order to harness the immunomodulating property of radiation. In preclinical studies, ablative radiation appears to be superior to conventional fractionated radiation in priming CD8+ T cells, leading to dramatic eradication of primary tumor and distant metastases (13). These responses are augmented by local immunotherapy. With increasing awareness of immunomodulating properties of ablative radiation, we really need to rethink the paradigm of CRT with conventional fractionation, be it IMRT or PBT.

Consolidation therapy with the anti-PD-L1 antibody, durvalumab, following CRT showed an unprecedented progression free survival (PFS) benefit in stage III NSCLC (14). The OS benefit of this approach remains to be seen. Other trials of conventionally fractionated radiation and concurrent or consolidation immune checkpoint blockade are ongoing (NCT02621398, NCT02434081, NCT02343952, NCT02525757, NCT03102242, NCT02768558). In locally advanced NSCLC, multiple phase I trials indicate feasibility of stereotactic ablative radiotherapy (SABR) boost to residual tumor following CRT (15-17). A review of our own institutional practice of using combined SABR to symptomatic metastatic sites and anti-PD-1 therapy in NSCLC showed significant lengthening of OS (18). But prospective trials combining SABR with immune checkpoint blockade in locally advanced NSCLC are lacking.

Immune checkpoint blockade for locally advanced NSCLC is a significant milestone but treatment failure remains a challenge in EGFR-mutated and ALK-translocated NSCLC. Just as in immunotherapy trials for metastatic NSCLC, the PACIFIC trial failed to show PFS benefit of consolidative durvalumab in EGFR-mutated NSCLC. EGFR inhibitors have been impactful in metastatic disease but studies of maintenance EGFR inhibitors in unresectable stage III NSCLC have been disappointing in terms of meaningful OS benefit. Unfortunately, in these trials, treatment arms were not enriched for benefit and outcome data according to EGFR mutation status have not been reported (19).

In the era of personalized therapy, well thought out biomarker driven trials are necessary to determine who needs what approach beyond CRT. Advances in next generation sequencing technology are enabling the detection of minimal residual disease (MRD) in solid tumors akin to hematologic malignancies. In a remarkable study conducted at Stanford University, in stages I–III NSCLC treated with curative intent, post-treatment circulating tumor DNA (ctDNA) analysis had a 100% positive predictive value and 93% negative predictive value for MRD (20). Three-year PFS and OS were significantly inferior for MRD positive when compared to MRD negative patients (0% *vs.* 92% and 8% *vs.* 75% respectively). Post-treatment ctDNA was detected a median of 5.2 months earlier than radiographic progression. In addition, the technology was able to identify mutation profiles associated with favorable outcomes with tyrosine kinase inhibitors or immune checkpoint blockade in 53% of patients with detectable ctDNA. Highly sensitive ctDNA assays would be incredibly useful, not only to detect microscopic disease in patients with radiographic complete responses or ambiguous radiographic findings following CRT, but also to determine the type of systemic therapy needed.

Well planned randomized clinical trials could determine the purported benefits of PBT as compared to the current standard of care. However, these trials would appear to be redundant with no expected elevation of the current plateaued survivals in surgically unresectable stage III NSCLC. The real step beyond the current outcome plateau will come from better distant disease eradication and more personalized treatment decisions guided by ctDNA. Certainly post-CRT immune checkpoint blockade with or

without consolidative SABR could arbitrarily be undertaken sequentially in the group. However, a paradigm of individualized treatment steps guided by ctDNA would be the real step forward of personalized oncology to maximize the curative outcome potential for each individual. If ctDNA is not persisting after conventional CRT, then further therapy would appear not to be a need. If ctDNA is persisting, then additional post-CRT therapy would clearly be a need with immune checkpoint blockade. If ctDNA would still be persisting with immune checkpoint blockade alone, then integrating SABR could well achieve further immune boosting benefits. This approach of incorporating the evolving understanding of the biological effects of radiation, emergence of immune checkpoint blockade and significant advances in ctDNA detection is far more enticing as a step forward in the curative outcome potential in locally advanced NSCLC than the redundant photon versus proton question.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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