

Dose-escalation of locally advanced non-small cell lung cancer with proton beam therapy

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We appreciate the thoughtful comments by Drs. Hegde and Walker regarding the phase II study of concurrent chemotherapy and dose-escalated proton beam therapy (PBT) for locally advanced unresected non-small cell lung cancer (NSCLC) (1). There are several discussion points that we would like to add in tandem with the aforementioned correspondence.

We wish to initially emphasize that the utility of dose-escalated PBT for these cases is interdependent on several factors. First, as the authors point out, the importance of locoregional control is more important when distant metastatic disease is better controlled. To this extent, the increased adoption of adjuvant durvalumab going forward may be critical; whether concurrent immunotherapy and radiotherapy (RT) would also prove to be superior to concurrent chemotherapy and RT remains to be evaluated.

Second, the issue of dose-escalation with PBT is highly dependent on the ability to do so safely. The Radiation Therapy Oncology Group (RTOG) 0617 trial did not necessarily prove that dose-escalation is harmful, but rather that unsafe dose-escalation could indeed be. Indeed, the results of RTOG 0617 are rather contradictory to not only established radiotherapeutic and radiobiologic tenets, but also established RTOG data showing a direct relationship of dose-escalation with locoregional control and potentially even survival (2). Roughly half of patients in RTOG 0617 were treated with dose-escalated three-dimensional conformal RT, which is a very difficult task. Fortunately,

secondary analyses from that trial illustrated the benefits of intensity-modulated RT (IMRT); although there were no direct differences in survival between both techniques, the ability to better spare the heart may indirectly impact this endpoint (3). Additionally, IMRT better allows for safe dose-escalation by means of simultaneous integrated boosting of gross disease to a higher dose (e.g., 66–70 Gy in 30 fractions). This maintains the same dose (60 Gy in 30 fractions) to the planning target volume while avoiding protracted RT courses, which may increase immunosuppression along with reducing local control and/or survival (4).

It is important, therefore, to delineate subgroups that may benefit from safe dose-escalation to a greater extent. Perhaps this notion may encompass those with single-station N2 disease, who are expected to survive longer (5). Another thought is that patients with bulkier primary tumors may be better controlled with dose-escalation. Both of these conjectures imply the inherent heterogeneity of N2 NSCLC, but until subgroups are better identified, it could unfortunately be considered medical malpractice to deliver dose-escalated photon RT following the results of RTOG 0617.

Although this is a slippery slope on which to tread, PBT offers a safer ability to dose-escalate, provided it is combined with adequate image guidance in a well-selected population. Image guidance could explain the lack of differences between groups in the recent Bayesian randomized trial, while also explaining the decrease in salient endpoints

at more recent time periods (6). Additionally, it is well described that PBT, especially three-dimensional PBT (which was the technique utilized in the phase II trial), does not necessarily guarantee higher conformality than inverse-planned photon RT (7).

In fact, there is likely a highly overlooked enrollment bias onto prospective PBT trials in that the “highest-risk” patients may be enrolled, rather than a “standard” NSCLC population. This term may encompass disease in close apposition to organs-at-risk, bulky disease, and/or frail patients—the common notion being that clinicians may not feel that these patients could be treated safely with IMRT, and thus they are enrolled on protocol. Insurance issues are important as well, as younger/healthier patients may be more likely to have insurance denial, as compared to the more elderly Medicare cohort. As a result, the patients enrolled onto trials may be a much different population than the “typical” locally advanced NSCLC population.

Thus, for several aforementioned reasons, the authors’ claim that a randomized trial between PBT and IMRT would be a fair comparison may not be accurate—perhaps a randomized trial of intensity-modulated proton therapy (IMPT) versus IMRT would be a fairer comparison. To this extent, the accruing RTOG 1308 trial, which is dominated by passively scattered PBT, may not offer a definitive answer to the “protons versus photons” debate and may make the question even more divisive. We posit that separate trials would need to be constructed that specifically require IMPT; however, to date, the number of centers throughout the world (let alone the United States) offering IMPT is limited. IMPT also has several unique technical challenges such as dosimetric uncertainties from the interplay effect or tissue heterogeneities (8). It is also a difficult challenge following the eventual results of RTOG 1308, if suboptimal, that payers may consider any form of PBT to be economically suboptimal (9,10) and thus would cut coverage for IMPT and therefore hamper any hope of adequate accrual onto IMPT trials.

Taken together, the comments by Hegde and Walker are much appreciated and thought-provoking. The promising results of the phase II PBT trial must be contextualized by inherent biases against PBT as well as those of existing prospective photon RT trials. In order to effectively evaluate the utility of PBT in these cases, we must first more clearly decipher what the photon data really shows. We must also combine the application of biology and technology, as better biological (systemic) control leads to increased life expectancy and thus an increased emphasis on local control

with fewer toxicities. The continued advancement of technology and experience with PBT will also undoubtedly play a major role in its perceived effectiveness by patients, payers, and providers.

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Footnote

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

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