Letter to the Editor

Controversies in dose-escalation for locally advanced non-small cell lung cancer and the role of proton beam therapy

Vivek Verma[1], Joe Y. Chang[2]

[1]Department of Radiation Oncology, University of Nebraska Medical Center, Omaha, NE, USA; [2]Department of Radiation Oncology, University of Texas M.D. Anderson Cancer Center, Houston, TX, USA

Correspondence to: Joe Y. Chang, MD, PhD. Department of Radiation Oncology, Unit 97, University of Texas M.D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030, USA. Email: jychang@mdanderson.org.

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We appreciate the insightful commentary by Drs. Choi and Simone regarding the phase II study of concurrent chemotherapy and dose-escalated proton beam therapy (PBT) for locally advanced non-resected non-small cell lung cancer (NSCLC) (1). We wish to add several discussion points that are in concord with the aforementioned piece.

Dose-escalation mediated by PBT is highly dependent on doing so safely. The Radiation Therapy Oncology Group (RTOG) 0617 trial did not necessarily demonstrate that dose-escalation is deleterious, but rather that unsafe dose-escalation could indeed be. As pointed out in the commentary, the findings of RTOG 0617 contradict not only established radiotherapeutic and radiobiologic doctrines, but also other RTOG data displaying a direct relationship between dose-escalation and locoregional control and even survival (2). Roughly half of patients in RTOG 0617 were treated with dose-escalated three-dimensional conformal RT, which is technically very cumbersome. As mentioned by the authors, secondary analyses from that trial illustrated that intensity-modulated RT (IMRT) can better spare the heart and thus may indirectly impact survival, although no direct and independent survival advantage was appreciated by technique alone (3). In addition to the increasing use of IMRT in contemporary times, it is also highly important to consider that modern target margins and utilization of image guidance is remarkably improved over the time period when RTOG 0617 accrued. Thus, the most modern assessment of toxicities with dose-escalated radiotherapy could very well be lower than those reported by RTOG 0617. Additionally, IMRT may afford safer dose-escalation by simultaneously boosting gross disease to a higher dose (e.g., 66–70 Gy in 30 fractions). This results in the same planning target volume dose (60 Gy in 30 fractions) and avoids prolonged radiotherapy courses, which can reduce local control and/or survival and increase immunosuppression (4).

Given the notable ambiguity in the current status of dose-escalation in locally advanced NSCLC, a prime goal of further research should be to highlight subgroups that may benefit to a greater extent from safe dose-escalation with advanced radiotherapeutic techniques and modalities. For instance, the difficulty of controlling bulkier primary disease with a given dose of radiation is well known, and hence well-selected instances of such could theoretically benefit. Additionally, it clear that stage III NSCLC is a clearly heterogeneous population with diverse prognoses; thus, because death is a competing risk factor for locoregional recurrence, patients with poor risk factors may benefit proportionally less from dose-escalated radiotherapy. In addition to age and performance status, other prognostic factors that could impact the differential benefit to dose-escalated RT include single versus multi-station N2 disease, individual patient anatomy (e.g., proximity

of the primary disease to the heart), and histopathologic considerations.

In light of RTOG 0617, use of PBT to dose-escalate these patients remains controversial. Although based on the lesson learned from RTOG 0617, PBT allows for safe dose-escalation, it is also well described that PBT, especially passively scattered PBT (the technique utilized in the phase II trial), clearly does not guarantee higher conformality than inverse-planned photon therapy, especially for complicated cases (5). To this extent, there is probably an enrollment bias onto prospective PBT trials that is very often overlooked. The "highest-risk" patients may be enrolled, which does not represent a "standard" NSCLC population. These patients may have disease with close relationship to organs-at-risk, bulky disease, and/or frail patients. Because providers may not be comfortable with safety profiles afforded by IMRT, they may preferentially be enrolled on protocol. Additionally, because Medicare is more likely to cover PBT, the proportion of younger and healthier patients enrolled onto these trials may be comparatively lower.

Collectively, these and other factors have implications on the currently accruing RTOG 1308 trial of largely passively scattered PBT versus IMRT, with the primary endpoint of overall survival. First, a randomized trial between forward-planned PBT and IMRT would not be a fair comparison, but intensity-modulated proton therapy (IMPT) versus IMRT would be fairer. As a result, RTOG 1308 may not offer a definitive solution to the "protons versus photons" debate and may potentially create less consensus. Separate trials would need to be implemented that specifically require IMPT, but there are altogether few facilities offering IMPT presently. IMPT also carries distinct technical challenges such as dosimetric uncertainties from tissue heterogeneities or the interplay effect (6).

Additionally, the only known randomized study of three-dimensional PBT versus IMRT in locally advanced NSCLC has recently reported no differences in the primary endpoint (local failure and radiation pneumonitis) (7). Although the aforementioned caveats to patient enrollment likely exist and could have contributed to the findings, it is also crucial to underscore advancements in IMRT in contemporary periods that may have contributed. For instance, increased implementation of image guidance could have explained the lack of differences between cohorts along with the decrease incidences of the primary endpoint events in more recent time periods.

A final thought is related to the evolving management of locally advanced NSCLC. The basic paradigms of the phase II PBT trial, RTOG 0617, the aforementioned randomized trial, and RTOG 1308 are no longer the standard of care, as adjuvant durvalumab has displayed a large progression-free survival benefit that may very well translate to an overall survival improvement in a future publication (8). Although dose-escalation is delivered for purposes of increasing locoregional control, this parameter means comparatively less if distant disease is suboptimally controlled. To this extent, adjuvant immunotherapy may better control distant disease by priming of the immune system and allow patients to experience longer survival with which to experience beneficial effects of more durable locoregional control. In other words, future research must fuse the application of biology and technology – better biologic (systemic) control results in increased life expectancy, and hence an increased emphasis on local control with fewer adverse events.

Taken together, both the role of dose-escalation and the role of PBT as a means for such is a slippery slope. With the already tenuous status of dose-escalation from RTOG 0617, together with the major caveats of forward-planned PBT as well as the aforementioned randomized trial (the highest level of evidence to date), payers may evaluate the economic aspects (9,10) and may further cut coverage for PBT (including IMPT) in the future if RTOG 1308 results are suboptimal. Viewpoints like those of Choi and Simone are hence much appreciated and thought-provoking and a notable step in understanding the untold story of these controversial notions.

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Footnote

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

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