Editorial

# Comparison of proton therapy and intensity modulated photon radiotherapy for locally advanced non-small cell lung cancer: considerations for optimal trial design

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*Provenance:* This is an invited Editorial commissioned by the Section Editor Jun Zhou (Department of Nuclear Medicine, Zhongshan Hospital, Fudan University, Shanghai, China).

*Comment on:* Liao Z, Lee JJ, Komaki R, *et al.* Bayesian Adaptive Randomization Trial of Passive Scattering Proton Therapy and Intensity-Modulated Photon Radiotherapy for Locally Advanced Non-Small-Cell Lung Cancer. J Clin Oncol 2018. [Epub ahead of print].

Submitted Mar 13, 2018. Accepted for publication Mar 30, 2018.
doi: 10.21037/jtd.2018.04.59
**View this article at:** http://dx.doi.org/10.21037/jtd.2018.04.59

The advent of proton therapy in the past years has generated many dosimetric studies comparing proton to photon radiation therapies (1-3). Proton therapy is able to deliver conformal, high dose radiation to the target site while sparing normal tissue. Although there is limited evidence on long term survival outcomes comparing photons versus protons (4-7), data suggests that proton therapy is better able to spare surrounding healthy tissue and thus has lower rates of adverse events (8-10). However, advances in technology have also led to the advent of intensity modulated radiation therapy (IMRT), which can deliver more conformal, high-dose radiation compared to traditional three-dimensional conformal photon techniques (11,12).

In lung cancer, pneumonitis, the most common radiation-related toxicity, negatively effects survival (12,13). Previous research has demonstrated that there is a significant dose-dependent relationship between radiation dose to the lung and pneumonitis (14,15).

As a result, IMRT and proton therapy have garnered interest as means of improving survival through both reduced toxicity rates and improved local control. To answer this important question, Liao *et al.* (16) initiated the first randomized controlled trial comparing IMRT and passive scattering proton therapy (PSPT) for locally advanced non-small cell lung cancer (NSCLC). The primary outcomes were radiation pneumonitis (RP) and local recurrence (LR). The trial utilized Bayesian adaptive modeling to detect differences between treatments, if they existed, during the trial, in order to allocate more patients to the more beneficial treatment plan if a difference was observed. Patients with stage II to IIIB; or stage IV disease with either a single brain metastasis or recurrent disease after surgical resection eligible to receive definitive chemoradiotherapy, were recruited. From historical data, the study anticipated RP rates of 15% and 5% in the IMRT and PSPT groups, respectively (11,17); LF rates were anticipated to be 25% in both groups. Each patient had evaluation of comparative PSPT and IMRT plans. If plans equally satisfied constraints on $V_{20}$ and mean lung dose, patients were randomized into either treatment group. Both groups received either 66 or 74 Gy* (relative biologic effectiveness, RBE).

Liao *et al.* (12) reported outcomes on 92 and 57 patients treated with IMRT and PSPT, respectively, with a median follow-up of 24.1 months. While there were no differences in mean doses to the lung or esophagus between groups, PSPT displayed reduced $V_{5–10}$ but increased lung $V_{20–80}$. PSPT also had significantly lower mean heart dose (P=0.002). There were six patients in each group that experienced grade ≥3 RP and no significant differences in RP between groups. One-year local failure rates were 10.9% for IMRT and 10.5 for PSPT (P=1.0). Median overall survival for IMRT and PSPT were 29.5 and 26.1

months, respectively (P=0.297).

To evaluate the effect of time of enrollment in the trial, however, the researchers found significant differences in LF and RP when comparing results before versus after the midpoint of the study, despite similar clinical characteristics between respective groups. The early IMRT group had combined rates of LF and RP at 1 year of 21.1% *vs.* 18.2% in the latter group (P=0.047). Similarly, the early PSPT group had a combined rate of LF and RP at 1 year of 31% compared to 13.1% in the latter group (P=0.027). The authors attributed these findings to improved IMRT and PSPT plans as the trial went on; during the first year of trial initiation, an in-house automated optimization algorithm was added to the existing IMRT planning system, which improved plan quality (18). In post hoc analysis, new treatment plans were generated for six patients in the early PSPT group also showed improved quality, suggesting a learning curve may, in part, explain the differences in RP and LF by time of enrollment. Multivariable cox proportional hazards modeling revealed no other significant variables for RP or LF. Although, there were no improvements in dose-volume indices for lung, PSPT significantly reduced the mean radiation dose to the heart (P=0.002). Similarly, other studies have demonstrated lower doses to the heart, but suggested that lower mean lung doses and $V_{20}$ could also be achieved with improving planning and delivery techniques over time (19,20).

In the era of combining radiation and immunotherapy, this is of particular interest. Research has demonstrated that proton therapy is associated with a 71% risk reduction in grade 4 lymphopenia (21), attributed to decreased irradiation of circulating lymphocytes. The increased conformity of proton therapy spares circulating lymphocytes through decreased radiation exposure and fractionation to major blood pools, such as the heart. Other research has shown that lymphopenia and post treatment circulating lymphocyte levels are independent predictors of survival (22,23). These collective findings suggest that proton therapy may improve outcomes through lymphocyte sparing. Furthermore, given lymphocytes are the vehicle in which immunotherapy enhances anti-tumor effects, we hypothesize that proton therapy may better synergize with immunotherapy than photon therapy (24). In line with this hypothesis, a recent phase 2 trial comparing stereotactic proton versus photon therapy found that 3-year overall survival was 90% and 27.8%, respectively (25). Unfortunately, the trial was closed early due to poor accrual, so the findings are incomplete.

Taken together, these findings suggest that IMRT and PSPT may have similar toxicity profiles and rates of LR in locally advanced NSCLC, but optimization of plans remains paramount for optimal results. It is remarkable that differences in the plans over a short period of time, within the same institution, can result in drastic improvements in both LF and RP. Liao *et al.'s* (12) findings in the unplanned analysis bring to light a broader issue. With the rapidly increasing pace of technology development, clinicians are likely to be experience a learning curve upon implementation. Research investigating the efficacy of newly developed or implemented technologies must seriously consider and evaluate dosimetric changes in plans over time, among other variables.

## Acknowledgements

None.

## Footnote

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

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**Cite this article as:** Cushman TR, Verma V, Rwigema JM. Comparison of proton therapy and intensity modulated photon radiotherapy for locally advanced non-small cell lung cancer: considerations for optimal trial design. J Thorac Dis 2018;10(Suppl 9):S988-S990. doi: 10.21037/jtd.2018.04.59

 