Letter to the Editor

Considerations in randomized trials to test technologies

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

Response to: 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:S988-90.

Submitted Jul 26, 2018. Accepted for publication Aug 13, 2018.

doi: 10.21037/jtd.2018.08.61

View this article at: http://dx.doi.org/10.21037/jtd.2018.08.61

I appreciate the opportunity to comment on the editorial by Cushman and colleagues, which reviewed our trial, the first randomized trial to directly compare proton therapy with intensity-modulated photon (X-ray) radiation therapy (IMRT) for lung cancer (https://doi.org/10.1200/JCO.2017.74.0720). One of the take-home messages from our trial was that ongoing improvements in technology and experience with using proton therapy will significantly enhance the clinical benefit of proton therapy. Cushman et al. concluded that any future clinical trials that compare two technologies must consider these factors in both the design of the trial and the choice of the trial endpoints to reliably demonstrate any clinical benefit from the tested technologies.

Our trial was conducted between 2009 and 2014, when proton therapy was just beginning to be used to treat thoracic tumors. The state of the art at the time the trial was designed was passive-scattered proton therapy (PSPT); the technique of proton treatment has evolved since then and has largely been replaced by the current state of the art, intensity-modulated proton therapy (IMPT), which is delivered with scanning beams of protons. The dose distributions from PSPT are now known to be inferior to those from IMPT, and IMPT allows more flexibility in the design of those dose distributions than was possible with passively scattered protons. It is our hope that IMPT will facilitate tighter conformality of the radiation dose to the tumor, which would result in significant reductions in dose to nearby organs at risk and would minimize or eliminate the low-dose bath associated with IMRT, which would further reduce radiation-induced toxicity.

Other critical considerations in the design of comparative proton-photon trials include feasibility of patient accrual and the need for biomarker-directed patient selection. The cost of proton therapy and inconsistent policies for reimbursement of those costs by insurance companies can result in imbalances in accrual and in the numbers of patients assigned to receive proton versus photon therapy, which can render some comparative trials difficult or impossible to carry out. However, in the end the true clinical benefits of proton therapy can be established only through direct comparative trials, and the radiation oncology profession is obligated to accomplish this mission.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

Cite this article as: Liao Z. Considerations in randomized trials to test technologies. J Thorac Dis 2018;10(Suppl 26):S3308. doi: 10.21037/jtd.2018.08.61