Xuemin Bai, Gino Lim, Hans-Peter Wieser, Mark Bangert, David Grosshans, Radhe Mohan and Wenhua Cao, 2019, Robust optimization to reduce the impact of biological effect variation from physical uncertainties in intensity-modulated proton therapy *Physics in Medicine and Biology*, **64** 025004.

Abstract Robust optimization (RO) methods are applied to intensity-modulated proton therapy (IMPT) treatment plans to ensure their robustness in the face of treatment delivery uncertainties, such as proton range and patient setup errors. However, the impact of those uncertainties on the biological effect of protons has not been specifically considered. In this study, we added biological effect-based objectives into a conventional RO cost function for IMPT optimization to minimize the variation in biological effect.

One brain tumor case, one prostate tumor case and one head & neck tumor case were selected for this study. Three plans were generated for each case using three different optimization approaches: planning target volume (PTV)-based optimization, conventional RO, and RO incorporating biological effect (BioRO). In BioRO, the variation in biological effect caused by IMPT delivery uncertainties was minimized for voxels in both target volumes and critical structures, in addition to a conventional voxel-based worst-case RO objective function. The biological effect was approximated by the product of dose-averaged linear energy transfer (LET) and physical dose. All plans were normalized to give the same target dose coverage, assuming a constant relative biological effectiveness (RBE) of 1.1. Dose, biological effect, and their uncertainties were evaluated and compared among the three optimization approaches for each patient case.

Compared with PTV-based plans, RO plans achieved more robust target dose coverage and reduced biological effect hot spots in critical structures near the target. Moreover, with their sustained robust dose distributions, BioRO plans not only reduced variations in biological effect in target and normal tissues but also further reduced biological effect hot spots in critical structures compared with RO plans.

Our findings indicate that IMPT could benefit from the use of conventional RO, which would reduce the biological effect in normal tissues and produce more robust dose distributions than those of PTV-based optimization. More importantly, this study provides a proof of concept that incorporating biological effect uncertainty gap into conventional RO would not only control the IMPT plan robustness in terms of physical dose and biological effect but also achieve further reduction of biological effect in normal tissues. (p.1)

… This approach follows the principles of info-gap decision theory (Ben-Haim 2006, Matrosov et al 2013), which seeks to maximize the robustness of a decision given minimum performance requirements. In other words, only the robustness of biological effect is optimized; biological effect itself is not maximized or minimized in either target or normal tissues. (p.3)

Keywords IMPT, linear energy transfer, robust optimization, biological effect.

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