Purpose: Biological effect of radiation can be enhanced with hypofractionation, localized dose escalation, and controlled distribution of protonsâ€™ linear energy transfer (LET). We evaluate potential gain in therapeutic effect from delivery of daily inhomogeneous fractional dose distributions in pencil beam scanning proton therapy (PBS-PT).

Methods: For cases of prostate cancer, we considered a hypofractionated course of 20 fractions of 3 Gy (assuming $\frac{\alpha}{\beta}=1.5$, the equivalent dose in 2-Gy fractions (ED2Gy) is 77.1 Gy). Two sets of dose distributions were planned using two opposed lateral fields to deliver a uniform dose: (1) in full-target plans (FTP) each beam targeted the entire gland (2) in split-target plans (STP), beams targeted only the respective proximal hemispheres (prostate split sagittally). Linear combinations of optimized beam intensity maps from FTP and STP, for a variety of mixing weights, were used to evaluate inhomogeneous fractional dose (IFD) distributions. IFD delivered doses boosting either hemisphere in alternating fractions, e.g., alternating between 40% and 160% of the nominal fractional dose (1.2–4.8 Gy). The equivalent uniform dose (EUD) was calculated for ED2Gy distributions. IFD plans were rescaled so that the EUD of rectum and bladder did not increase. LET distributions were calculated with Monte Carlo, and compared for different plans.

Results: In the IFD courses, the whole prostate received a nearly uniform dose in every 2 fractions, however EUD was higher than in conventional FTP by up to 8%. Rectal EUD decreased by 2%, and bladder EUD was unchanged. The LET distributions of FTP and STP were distinctly different, thus, in IFD, LET depended strongly on the mixing weights.

Conclusions: In PBS-PT, modestly improved therapeutic outcome can be expected with delivery of inhomogeneous daily dose distributions, while administering the prescribed dose to target over the entire course. The biological effectiveness may be further enhanced by optimizing the LET distributions.

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