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LET-Optimized IMPT Planning for Dominant Intraprostatic Lesion Boost in Prostate Cancer: A Feasibility Study Comparing Two-Field and Four-Field Beam Arrangements with Variable RBE Dose Analysis

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Objectives

Local recurrence in prostate cancer often originates from the dominant intraprostatic lesion (DIL), a hypoxic sub-volume within the prostate. Dose escalation to the DIL has been correlated with improved local control. This study investigates the feasibility of applying dose-average linear energy transfer (LETd)-based with RBE-based optimization objectives to escalate dose to the DIL using two-field (2F) and four-field (4F) proton beam arrangements. The dose to the targets and organs-at-risk (OARs) was assessed using RBE 1.1 and a variable RBE model.

Methods

Five prostate cancer patients previously treated with proton therapy were retrospectively selected (Study approved by local ethics). Each patient had hydrogel spacer and fiducial markers placed before same-day CT-simulation and mpMRI imaging for target delineation. Three IMPT plans were generated per patient: a 2F-non-boost as reference (2F-NB; G270°, G90°), a 2F-boost (2F-B), and a 4F-boost (4F-B; G260°, G300°, G60°, and G100°). Plans were created in RayStation 2024B (non-clinical version). Plans were based on 60 GyRBE in 20 fractions and were robustly optimized using a 5 mm setup and 3.5% range uncertainties. LETd-based objective of 5 keV/μm was applied to the DIL, with RBE-based objectives to achieve a DIL Dmean of ≥66 GyRBE, while limiting urethra PRV dose to <67.8 GyRBE for the boost plans. MFO-technique was used for the boost plans, assuming an RBE of 1.1. Variable RBE dose distributions were calculated using the McNamara model. Statistical analysis was performed with the Wilcoxon signed-rank test ($p<0.05$).

Results

Both 2F-B and 4F-B achieved comparable D95% to the prostate substrate DIL, with 4F-B showing significantly higher DIL dose, $p<0.05$ (Table 1). The 4F-B also achieved lower dose to the rectum, bladder (excluding the highest dose range), and femurs compared to 2F-B, $p<0.05$. Including the LETd objective increased DIL LETd by ≥0.7 keV/μm over the 2F-NB. 4F-B further enhanced DIL LETd by ~0.5 keV/μm over 2F-B (Fig.1). Variable RBE-based analysis revealed significantly higher RBE-weighted dose to the DIL and lower dose to the urethraPRV2 in 4F-B compared to 2F-B, $p<0.05$ (Table 2).

Conclusions

Both 2F-B and 4F-B LETd-based optimizations for DIL dose escalation in prostate IMPT are feasible and clinically promising. The 4F-B plans offer higher LETd and variable RBE dose to the DIL without compromising on plan robustness, supporting the role of biologically optimized IMPT in improving outcomes for focal boost in prostate radiotherapy.

Table 1: Target coverage and OAR doses for 2-field boost (2F-B) and 4-field boost (4F-B) were compared using RBE-weighted dose metrics, reported as mean and standard deviations (SD).

Targets/ OARs	Metrics	2F-B	4F-B	Dose diff, (4F-B minus 2F-B)	p-value
Pros-DIL	D98 % (GyRBE)	60.21 ± 0.07	60.52 ± 0.32	0.31 ± 0.39	p = 0.14
	D95 % (GyRBE)	60.53 ± 0.11	60.84 ± 0.30	0.31 ± 0.38	p = 0.23
	Dmean (GyRBE)	62.17 ± 0.15	62.45 ± 0.36	0.29 ± 0.32	**p < 0.05**
Prostate	Volume (cc)	51.61 ± 11.90			
DIL	D90 % (GyRBE)	66.87 ± 0.23	67.51 ± 0.12	0.63 ± 0.19	**p < 0.05**
	Dmean (GyRBE)	68.50 ± 0.46	69.22 ± 0.16	0.72 ± 0.53	p = 0.08
	Volume (cc)	3.00 ± 3.29			
Rectum	V60 GyRBE (%)	1.23 ± 1.41	0.98 ± 1.24	- 0.25 ± 0.38	p = 0.27
	V56 GyRBE (%)	1.79 ± 1.70	1.49 ± 1.60	- 0.30 ± 0.36	p = 0.08
	V52 GyRBE (%)	2.62 ± 2.19	2.05 ± 2.07	- 0.56 ± 0.30	**p < 0.05**
	V48 GyRBE (%)	3.29 ± 2.27	2.75 ± 2.34	- 0.54 ± 0.43	**p < 0.05**
	V40 GyRBE (%)	5.07 ± 2.79	4.22 ± 2.83	- 0.86 ± 0.64	p = 0.07
	V32 GyRBE (%)	7.40 ± 2.73	6.01 ± 3.55	- 1.39 ± 1.10	**p < 0.05**
	V24 GyRBE (%)	10.83 ± 2.83	8.94 ± 4.25	- 1.88 ± 1.78	**p < 0.05**
Bladder	V60 GyRBE (%)	5.77 ± 1.92	5.57 ± 1.42	- 0.21 ± 0.75	p = 0.50
	V48 GyRBE (%)	15.28 ± 4.41	11.59 ± 2.56	- 3.32 ± 3.14	**p < 0.05**
	V40 GyRBE (%)	19.62 ± 5.43	15.76 ± 3.21	- 3.86 ± 3.60	**p < 0.05**
Urethra PRV2	D0.1 cc (GyRBE)	63.50 ± 0.76	63.48 ± 0.68	- 0.02 ± 0.28	p = 0.89
Femurs	Dmean (GyRBE)	17.10 ± 2.71	10.81 ± 2.00	- 6.29 ± 1.05	**p < 0.05**

Table 2: Target coverage and OAR doses calculated using the McNamara variable RBE model, with tissue-specific α/β ratio for 2-field non-boost (2F-NB), 2-field boost (2F-B) and 4-field boost (4F-B) were compared. RBE-weighted dose metrics, including mean and standard deviation (SD) were reported

Targets/ OARs	Metrics	2F-NB (Reference)	2F-B	4F-B	Dose diff, (4F-B minus 2F-B)	p-value
Pros-DIL, α/β: 1.5 Gy	Dmean (GyRBE)	65.94 ± 0.23	66.58 ± 0.40	67. 16 ± 0.50	0.58 ± 0.61	p = 0.08
Pros-DIL, α/β: 3 Gy	Dmean (GyRBE)	64.18 ± 0.22	64.81 ± 0.39	65.36 ± 0.48	0.55 ± 0.59	p = 0.08
DIL, α/β: 1.5 Gy	Dmean (GyRBE)	65.81 ± 0.41	74.48 ± 0.98	75.36 ± 1.26	0.88 ± 1.58	**p = 0.05**
Rectum α/β: 3 Gy	V60 GyRBE (%)	2.02 ± 1.86	1.58 ± 1.64	1.38 ± 1.52	-0.20 ± 0.26	p = 0.89
Bladder α/β: 3 Gy	V60 GyRBE (%)	10.94 ± 2.71	9.04 ± 2.71	7.85 ± 2.04	- 1.19 ± 0.95	p = 0.07
Urethra PRV2 α/β: 3 Gy	D0.1 cc (GyRBE)	65.35 ± 0.44	66.15 ± 0.61	66.11 ± 1.34	- 0.04 ± 0.97	**p < 0.05**

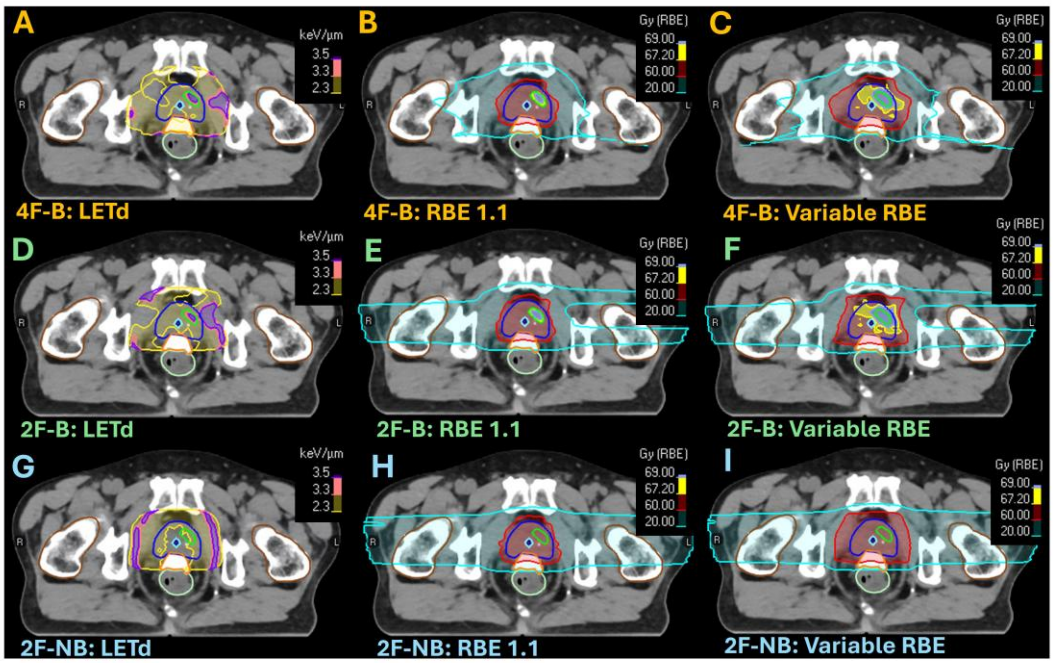

Figure 1: Dose analysis for LET_d (A, D, G), RBE of 1.1 (B, E, H) and variable RBE (C, F, I) using the McNamara Model for the 4-field boost (4F-B), 2-field boost (2F-B) and 2-field non-boost (2F-NB) plans for one prostate case. The prostate (blue), urethra PRV2 mm (cyan), DIL (green), rectum (green) and spacer (orange) are illustrated.