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Genitourinary Cancers

Can We Advance Proton Therapy for Prostate? Considering Alternative Beam Angles and Relative Biological Effectiveness Variations When Comparing Against Intensity Modulated Radiation Therapy

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Summary

Because of its low α/β value, models predict that the prostate should be highly sensitive to elevations in proton relative biological effectiveness (RBE) (both relative to the typically assumed value of 1.1 and with increasing linear energy transfer across a spread-out Bragg peak). Here we investigate the extent to which modeled RBE variations

Purpose: For prostate treatments, robust evidence regarding the superiority of either intensity modulated radiation therapy (IMRT) or proton therapy is currently lacking. In this study we investigated the circumstances under which proton therapy should be expected to outperform IMRT, particularly the proton beam orientations and relative biological effectiveness (RBE) assumptions.

Methods and Materials: For 8 patients, 4 treatment planning strategies were considered: (A) IMRT; (B) passively scattered standard bilateral (SB) proton beams; (C) passively scattered anterior oblique (AO) proton beams, and (D) AO intensity modulated proton therapy (IMPT). For modalities (B)-(D) the dose and linear energy transfer (LET) distributions were simulated using the TOPAS Monte Carlo platform and RBE was calculated according to 3 different models.

Results: Assuming a fixed RBE of 1.1, our implementation of IMRT outperformed SB proton therapy across most normal tissue metrics. For the scattered AO proton plans, application of the variable RBE models resulted in substantial hotspots in rectal RBE weighted dose. For AO IMPT, it was typically not possible to find a plan that

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affect proton versus IMRT comparisons. Additionally, we demonstrate that, for a cohort without rectal spacer gels, anterior beams do not prove robust to the application of variable RBE modeling.

simultaneously met the tumor and rectal constraints for both fixed and variable RBE models.

Conclusion: If either a fixed RBE of 1.1 or a variable RBE model could be validated in vivo, then it would always be possible to use AO IMPT to dose-boost the prostate and improve normal tissue sparing relative to IMRT. For a cohort without rectum spacer gels, this study (*1*) underlines the importance of resolving the question of proton RBE within the framework of an IMRT versus proton debate for the prostate and (*2*) highlights that without further LET/RBE model validation, great care must be taken if AO proton fields are to be considered for prostate treatments.

Purpose

The application of proton therapy to prostate cancer remains one of the most controversial issues within radiation oncology (1-4). Whereas evidence has shown the standard bilateral proton beam technique to be safe and effective (5), data reported thus far have not demonstrated clear clinical benefit relative to the substantially cheaper photon alternative, intensity modulated radiation therapy (IMRT) (6, 7). As treatment planning studies typically report that passively scattered proton therapy does not reduce high-dose (>70 Gy) coverage of the rectum (8, 9), arguably it should not be expected to reduce the incidence of rectal bleeding (10). However, proton plans reduce rectal coverage at lower dose levels (<50 Gy) (8, 9), and it has been hypothesized that this may lead to reduced bowel urgency and frequency (10). The lower integral dose associated with proton therapy is also likely to correspond to a reduced risk of secondary cancer (11, 12).

Nonetheless, the high cost associated with prostate proton therapy will require further justification if the technique is to compete over coming years. Its implementation is still evolving rapidly, particularly through the expansion of intensity modulated proton therapy (IMPT) programs. Recent studies have demonstrated the dosimetric benefit of prostate-rectum spacer gels (13-15). Additionally, further prostate-specific areas for development have been highlighted (16), including hypofractionation, which would bring down the treatment cost; the application of simultaneous dose-boosts to prostate subvolumes; improved knowledge and use of proton relative biological effectiveness (RBE); and the use of alternative beam angles. This study focuses on the latter 2 possibilities.

Assuming a constant RBE of 1.1, range-verified anterior oblique (AO) proton beams offer the potential to reduce the mean dose to the rectum, anterior rectal wall, and penile bulb by a factor of ~2 relative to standard bilateral (SB) proton beam arrangements (17). Furthermore, AO beams targeted at the prostate avoid the femoral heads and so form an appealing option for patients with hip prostheses. By means of a cautious approach with restricted beam weightings, AO proton fields have already been applied clinically by a consortium of 3 centers, which recently published a study reporting on the treatment of 20 prostate patients with hip prostheses (18). However, AO proton beams are associated with 2 major concerns. The first is range uncertainty: variations in patient setup and anatomy (eg, bladder filling) may result in substantial proton overshoot. The second relates to proton linear energy transfer (LET): even if range uncertainty could be eliminated, for AO beams the substantially elevated LET values found at spread-out Bragg peak (SOBP) distal edges would coincide with the boundary between the prostate and sensitive rectal tissue.

In vitro, cell survival experiments performed at different depths within a proton SOBP report significantly higher levels of cell kill toward the SOBP distal edge (19). Additionally, such in vitro data suggest that (*1*) the RBE for prostate cancer cells is likely to be greater than 1.1 at all SOBP positions, assuming standard fractionation (20, 21); and (*2*) disregarding RBE variation in treatment plan comparison may lead to bias in favor of proton plans (22). It was recently reported that a proton trial for prostate therapy with a prescription dose of 82 Gy appeared to hit upon a surprisingly low dose limit (photons have been used to deliver even higher doses successfully), suggesting that the proton RBE question should be reopened (16). Nonetheless, no clinical data have yet been found to indicate that a proton RBE of 1.1 results in significant patient underdosage or overdosage.

In this study we applied 3 published RBE models (20, 23, 24) to investigate whether the previously reported dosimetric benefits associated with AO proton plans prove robust to variable RBE modeling. Additionally, we considered the impact of such modeling on SB proton plans and AO IMPT plans, the latter having increased conformity relative to the passively scattered proton technique. In each case, the proton plans were compared against IMRT.

Methods and Materials

Eight patients with low-risk to intermediate-risk prostate cancer were considered, all treated with passively scattered SB proton beams to 79.20 Gy(RBE) to the prostate and 50.40 Gy(RBE) to the proximal 5 to 15 mm of seminal vesicles. Endorectal balloons were applied.

Four different treatment planning strategies were analyzed (Table 1).

Table 1 Summary of the 4 treatment planning strategies considered

Treatment planning strategy	Beam angles	Unit of rectal dose constraints	CTV to PTV expansion margins	Range uncertainty/ aperture margins	Treatment planning system
(A) 7-field IMRT	0°, 60°, 100°, 135°, 225°, 260°, 300°	Physical dose	5 mm laterally/ anteriorly and 4 mm posteriorly	Not applicable	RayStation (Raysearch Laboratories, Sweden): multicriteria optimization
(B) Standard bilateral (SB) passively scattered protons; 4 fields planned (1 pair per day to either the 79.20 Gy(RBE) or 50.40 Gy(RBE) target)	±90°	Gy(RBE) assuming RBE = 1.1	5 mm laterally/ anteriorly and 4 mm posteriorly	Range: 3.5% + 1 mm; lateral aperture margins of 1.2 cm	XiO (Elekta, Sweden)
(C) Anterior oblique (AO) passively scattered protons; 4 fields planned (1 pair per day to either the 79.20 Gy(RBE) or 50.40 Gy(RBE) target volume)	±35°: selected to avoid femoral heads, avoid beam overlap on skin surface, and reduce bladder dose relative to smaller angular separations	Gy(RBE) assuming RBE = 1.1	Best-case scenario assuming in vivo range verification with millimeter accuracy; PTV not considered	100% isodose conformed to the CTV distal edge (0% range uncertainty); lateral aperture margins of 1.2 cm	XiO (Elekta, Sweden)
(D) Anterior oblique IMPT; 4 fields planned (1 pair per day to either the 79.20 Gy(RBE) or 50.40 Gy(RBE) target volume)	As for (C)	Gy(RBE) assuming variable RBE, considering the worst-case LET/ RBE model for the rectum maximum dose and $\alpha/\beta = 3$ Gy	Best-case scenario assuming in vivo range verification with millimeter accuracy; PTV not considered	0% (100% isodose conformed to the CTV distal edge)	Astroid (in-house): multicriteria optimization; in-air spot sigma values of 12 mm at 60 MeV to 4.6 mm at 230 MeV

Abbreviations: CTV = clinical target volume; IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; PTV = planning target volume.

It has been reported previously that in vivo range verification could be implemented for AO proton beams with millimeter accuracy, by means of diodes attached to an endorectal balloon (17, 25). Consequently, whereas a 3.5% range uncertainty margin was applied to the SB plans, accurate in vivo range verification (0% range uncertainty) was assumed for the AO plans. Diode-based range verification remains at a preclinical stage, but the primary purpose of this study was to test whether AO proton plans proved biologically robust under a physical dose best-case scenario.

For all proton plans (treatment planning strategies, Table 1), dose and dose-averaged LET (26) distributions were calculated using TOPAS (TOol for PArticle Simulations, version beta 8) (27). It has been demonstrated that, relative to Monte Carlo (MC) simulations, the proton pencil beam algorithm within the XiO TPS overestimates the mean dose delivered to deep-seated targets such as the prostate by approximately 2% while underestimating the scattered dose to normal tissues (28). Consequently, in this study, proton plan-specific scaling factors were applied to the MC dose distributions so that the median dose received by a patient's clinical target volume (CTV) 79.20 volume matched that for their IMRT plan.

Proton RBE was calculated voxel-by-voxel according to 3 different models (20, 23, 24). All use (*1*) isoeffective proton/photon surviving fraction equations based on the linear quadratic formulation and (*2*) LET dependencies drawn from in vitro data. The models predict tissues with the lowest α/β values to be the most sensitive to LET-related increases in biological dose. As outlined in the QUANTEC organ-specific report on rectal side effects (29), whereas a rectal α/β of 5.4 Gy has been previously

proposed (30), the choice of 3 Gy forms a more conservative estimate (29). Within the QUANTEC bladder report, an α/β of 3 Gy is also considered (31). Thus, for normal tissues we typically considered an α/β of 3 Gy but also tested a range of 2 to 6 Gy. For the prostate, evidence indicates a lower α/β of approximately 1.5 Gy (32-34). Within our analysis we took 3 Gy as a conservative estimate but also considered a range of 0.5 to 4 Gy.

Results

Assuming a fixed proton RBE of 1.1 for planning strategies (A) through (C)

Figure 1 compares dose-volume histogram (DVH) data from treatment planning strategies A through C (as described in Table 1). All of the proton data in Figure 1 assume a fixed RBE of 1.1. The 3 modalities are well matched in terms of target dose coverage, as shown in Figure 1(i). For the rectum, IMRT (A) performs worst in the low-dose region (<20 Gy) but outperforms SB proton beams (B) in the high-dose region in a consistent manner across all patients. Considering penile bulb and bladder statistics, IMRT (A) appears preferable to SB proton beams (B). Passively scattered AO proton beams (C) and IMRT (A) are generally well matched in terms of normal tissue sparing, except that IMRT (A) results in a greater rectal low-dose bath, and scattered AO proton beams (C) generally lead to increased bladder dose.

The intermodality trends evident in Figure 1 are further reflected and analyzed statistically in Table 2, where it is also apparent that AO proton beams reduce the integral energy deposited within normal tissue relative to IMRT and SB proton plans.

What is the impact of potential variation in RBE on SB (B) versus AO (C) passively scattered proton plans?

Figure 2(i) shows dose and LET simulations for a simple SOBP. For $\alpha/\beta = 3$ Gy, the Wedenberg model predicts that the substantially elevated LET values found at

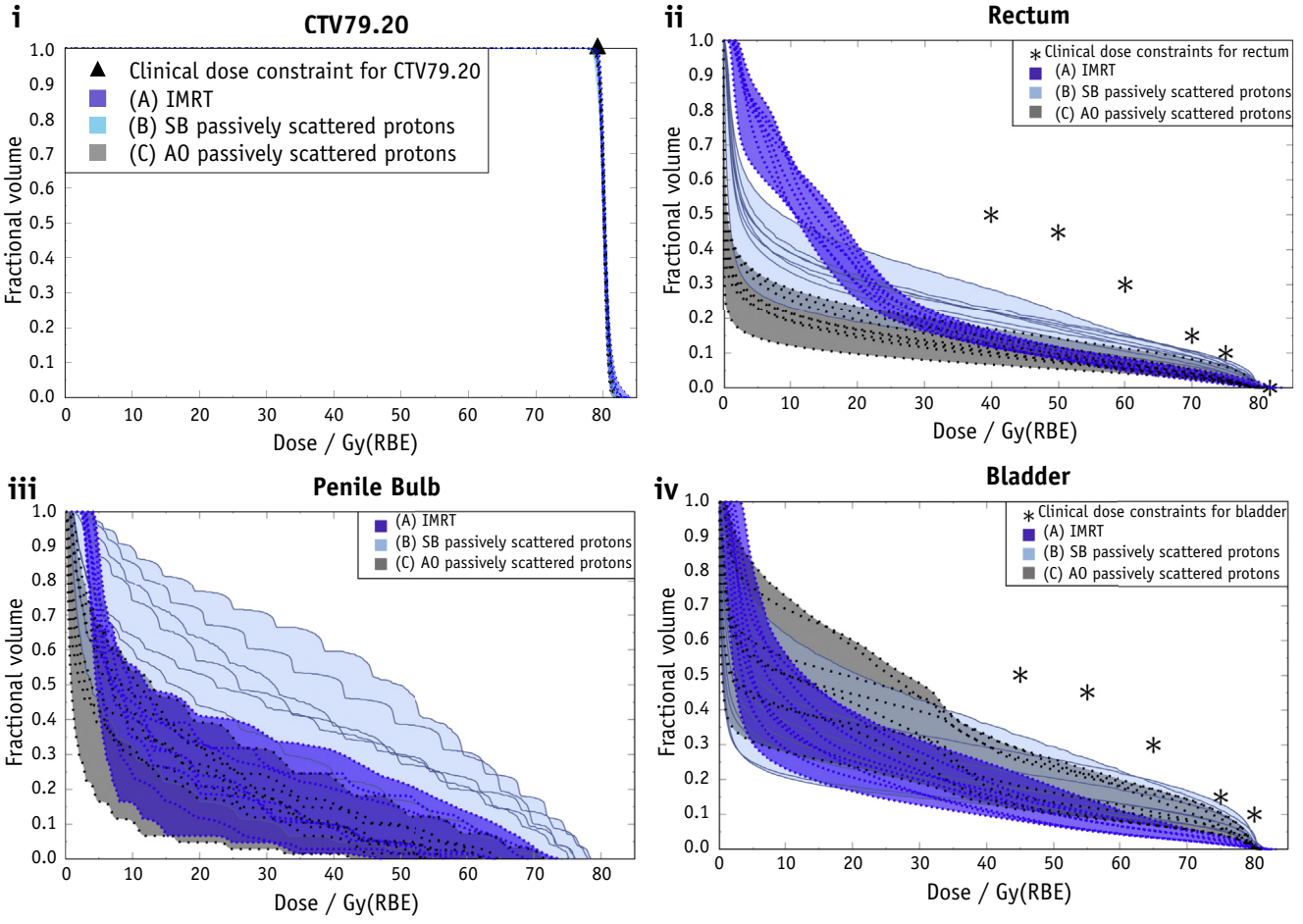

Fig. 1. Dose-volume histogram (DVH) comparison between treatment planning strategies (A) through (C) (Table 1) for all 8 patients across four different structures: (i) the CTV79.20, (ii) the rectum, (iii) the penile bulb, and (iv) the bladder.. Each solid/dashed line corresponds to a DVH plot for an individual patient; the shaded regions indicate the interpatient range for each plan type. *Abbreviations:* AO = anterior oblique; CTV = clinical target volume; IMRT = intensity modulated radiation therapy; RBE = relative biological effectiveness; SB = standard bilateral.

Table 2 Normal tissue metric comparison between treatment planning strategies (A)-(C) (see Table 1)

	(A) 7-field IMRT	(B) SB passively scattered protons	Sig $P=.05$?	(C) AO passively scattered protons	Sig $P=.05$?
Rectum					
Mean dose	19.7 (17.3-21.8)	18.5 (12.1-23.7)	No	10.5 (5.9-14.6)	Yes: (C)
EUD, a = 5	43.8 (40.8-46.6)	49.9 (46.3-51.9)	Yes: (A)	43.4 (39.4-49.0)	No
V30	0.203 (0.165-0.234)	0.255 (0.162-0.343)	No	0.144 (0.080-0.201)	No
V40	0.139 (0.118-0.164)	0.214 (0.138-0.287)	No	0.118 (0.067-0.170)	No
V50	0.098 (0.083-0.117)	0.171 (0.114-0.222)	Yes: (A)	0.094 (0.055-0.142)	No
V60	0.067 (0.048-0.085)	0.130 (0.089-0.156)	Yes: (A)	0.070 (0.042-0.114)	No
V70	0.039 (0.022-0.055)	0.088 (0.062-0.107)	Yes: (A)	0.044 (0.027-0.083)	No
V80	0.006 (0.000-0.017)	0.006 (0.001-0.010)	No	0.001 (0.000-0.004)	Yes: (C)
Maximum dose to 1 cc	79.1 (76.0-81.0)	79.8 (79.3-80.1)	No	78.1 (78.0-79.7)	No
Rectal wall					
Mean dose	19.7 (17.7-22.6)	18.3 (14.3-21.6)	No	12.7 (9.6-17.0)	Yes: (C)
EUD, a = 5	48.0 (45.0-50.3)	52.3 (50.8-53.7)	Yes: (A)	48.1 (45.5-52.3)	No
V30	0.212 (0.187-0.250)	0.249 (0.192-0.300)	Yes: (A)	0.177 (0.133-0.236)	No
V40	0.167 (0.147-0.200)	0.218 (0.173-0.262)	Yes: (A)	0.155 (0.120-0.208)	No
V50	0.133 (0.120-0.161)	0.186 (0.153-0.220)	Yes: (A)	0.134 (0.107-0.180)	No
V60	0.103 (0.08-0.126)	0.153 (0.131-0.176)	Yes: (A)	0.111 (0.090-0.151)	No
V70	0.071 (0.046-0.091)	0.117 (0.105-0.131)	Yes: (A)	0.081 (0.056-0.119)	No
V80	0.014 (0.000-0.037)	0.012 (0.004-0.021)	No	0.002 (0.000-0.008)	Yes: (C)
Maximum dose to 1 cc	79.0 (76.0-81.0)	79.7 (79.3-80.1)	No	78.1 (76.5-79.7)	No
Bladder					
Mean dose	17.4 (10.4-23.0)	19.0 (11.6-30.5)	No	23.7 (12.8-31.4)	Yes: (A)
EUD, a = 7	50.8 (47.3-54.1)	57.7 (54.1-61.4)	Yes: (A)	56.7 (52.5-59.9)	Yes: (A)
V30	0.218 (0.128-0.314)	0.258 (0.157-0.429)	No	0.360 (0.189-0.477)	Yes: (A)
V50	0.110 (0.067-0.180)	0.190 (0.116-0.295)	Yes: (A)	0.192 (0.101-0.259)	Yes: (A)
V60	0.073 (0.043-0.113)	0.154 (0.095-0.226)	Yes: (A)	0.149 (0.080-0.201)	Yes: (A)
V70	0.043 (0.025-0.060)	0.114 (0.071-0.169)	Yes: (A)	0.104 (0.056-0.145)	Yes: (A)
Penile bulb					
Mean dose	16.1 (7.8-25.2)	30.9 (10.4-43.9)	Yes: (A)	13.2 (3.7-21.6)	No
Femoral heads					
Mean dose	13.5 (11.6-17.3)	21.8 (25.6-28.0)	Yes: (A)	0.2 (0-0.7)	Yes: (C)
Normal tissue					
Mean integral energy	100.7 (77.5-135.2)	65.6 (52.1-79.7)	Yes: (B)	39.6 (26.9-51.8)	Yes: (C)

Abbreviations: AO = anterior oblique; EUD = equivalent uniform dose, calculated according to the method described previously by Trofimov et al (8); IMRT = intensity modulated radiation therapy; SB = standard bilateral.

For each metric the mean value and range (across all 8 patients) are quoted. The fourth and sixth table columns include results from a sign test, testing modalities (B)/(C) against modality (A). Where a significant difference was found (at the 5% level) the letter corresponding to the preferable modality is shown. Constraints reported as VX refer to the fractional volume of the structure receiving X Gy(RBE). Integral energy deposition was calculated for the whole body minus the IMRT planning target volumes (assuming a body composition of water).

the distal edges of the SOBP correspond to increases in RBE-weighted (RBEw) dose of up to 20% (relative to the assumption that RBE = 1.1).

Figures 2(ii) and (iii) exemplify the impact of such variable-RBE modeling on DVHs and biological dose distributions for planning strategies B and C (Table 1). The results are presented for a single (conservative) α/β value of 3 Gy for all structures and the RBE model with the most extreme effect on rectal maximum RBEw dose (23).

Considering the DVH plots on the left-hand side of Figures 2(ii) and (iii): for both (B) and (C), application of the variable RBE model suggests that coverage of the CTV79.20 is underestimated when a fixed RBE value of 1.1 is assumed. For the SB plan (B), the mean dose to the CTV79.20 is boosted by $\geq$ 3% when $\alpha/\beta \leq 3$ Gy. For the AO plans (C), the increased LET within the target leads to a more substantial boost to the mean CTV79.20 dose ($\geq$8% when $\alpha/\beta \leq 3$ Gy). Furthermore, for the SB planning strategy (B), the maximum dose to the rectum remains relatively robust to the consideration of a variable RBE. This is not the case for the AO plans (C), where the rectal dose increases by over 10 Gy(RBE) (assuming $\alpha/\beta = 3$ Gy) when the RBE model is applied, such that the clinical constraint is clearly exceeded. Thus, whereas AO scattered proton plans (C) offer femoral head sparing, modeling indicates that they may lead to substantial hotspots in rectal biological dose. These 2 trends were evident across all 8 patients, all 3 RBE models, and broad ranges of α/β (the latter 2 points being reported in detail for planning strategy D in the next section).

The right-hand plot of Figure 2(ii) demonstrates that for the standard bilateral proton beams (B), high LET and

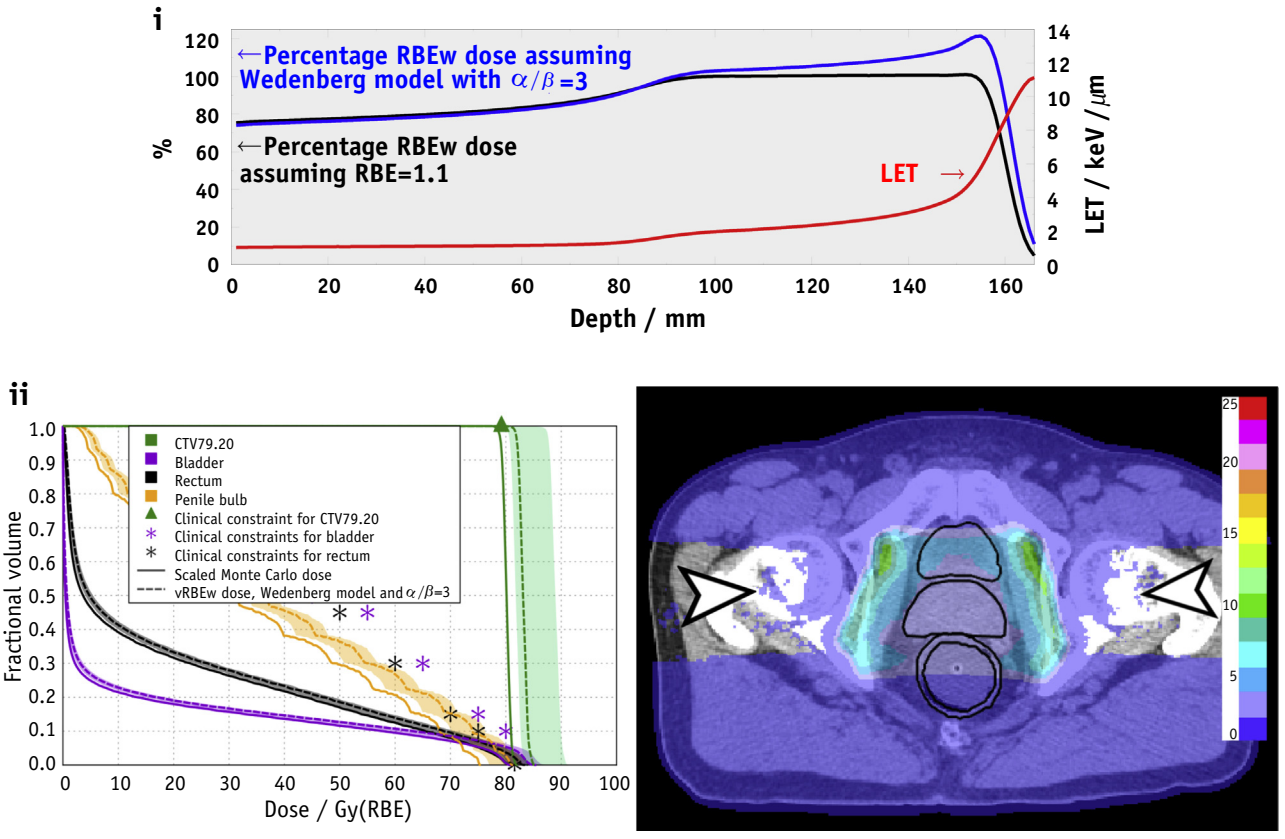

Fig. 2. (i) Example of modeled weighted relative biological effectiveness (RBEw) dose across a simple spread-out Bragg peak (SOBP) in water. (ii) through (iv) Single-patient analysis for treatment planning strategies (B) through (D) and the Wedenberg model. The dose-volume histogram plots in the left-hand column demonstrate the impact of the model application for normal tissue α/β values of 3 Gy (dashed lines) and 2 to 6 Gy (colored bands). For the prostate clinical target volume CTV79.20, an α/β of 3 Gy is considered (dashed line) along with a range 0.5 to 4 Gy (green bands). The images on the right show the difference in each treatment plan's dose [Gy(RBE)] when calculated assuming fixed versus variable RBE: [RBEw dose assuming vRBE] − [RBEw dose assuming RBE = 1.1]. A fixed α/β of 3 Gy is considered throughout the patient. The regions without dose color-wash correspond to voxels where the calculated RBE is < 1.1. From top to bottom the contours correspond to the bladder, CTV79.20, and rectal wall. (ii) Strategy (B), standard bilateral passively scattered protons. (iii) Strategy (C), anterior oblique passively scattered protons. (iv) Strategy (D), anterior oblique intensity modulated proton therapy. (A color version of this figure is available at www.redjournal.org.)

RBEw dose values mainly fall within the range uncertainty margins to the left and right of the CTV79.20 target. For the AO proton beams (C), the situation is more critical: the high LET and RBE regions coincide with the boundary between the prostate and the rectum. The boost in biological dose arising from a transition between fixed (1.1) and variable RBE (shown in the right-hand figures) is substantial: for this model and $\alpha/\beta = 3$ Gy it exceeds 20 Gy(RBE) within certain rectal regions.

Can IMPT plans provide adequate target coverage assuming RBE = 1.1, yet still prove robust to increases in rectal dose considering potential RBE variations?

Figure 2(iii) demonstrates that an AO passively scattered proton plan (C) that met the target coverage constraints, assuming a fixed RBE of 1.1, led to substantial rectal hotspots when variable RBE models were applied. Consequently, we investigated whether the increased conformity offered by IMPT could adequately spare the rectum in a manner robust to variable RBE modeling.

For AO IMPT (Table 1, strategy D), the DVH results for an example patient are included as the left-hand plot of Figure 2(iv). Here a conservative planning strategy was adopted: target coverage was maximized subject to the constraint that no 1 cc of the rectum should receive more than 103% of the prescription dose, assuming $\alpha/\beta = 3$ Gy and the Wedenberg RBE model. For the plans generated according to this constraint, it was not possible to maintain full target coverage when considering a fixed RBE of 1.1. However, assuming validity of the Wedenberg model with a conservative $\alpha/\beta \leq 3$ Gy for the prostate, then at least 99% of the target volume received the full prescription dose across all 8 patients considered. According to the

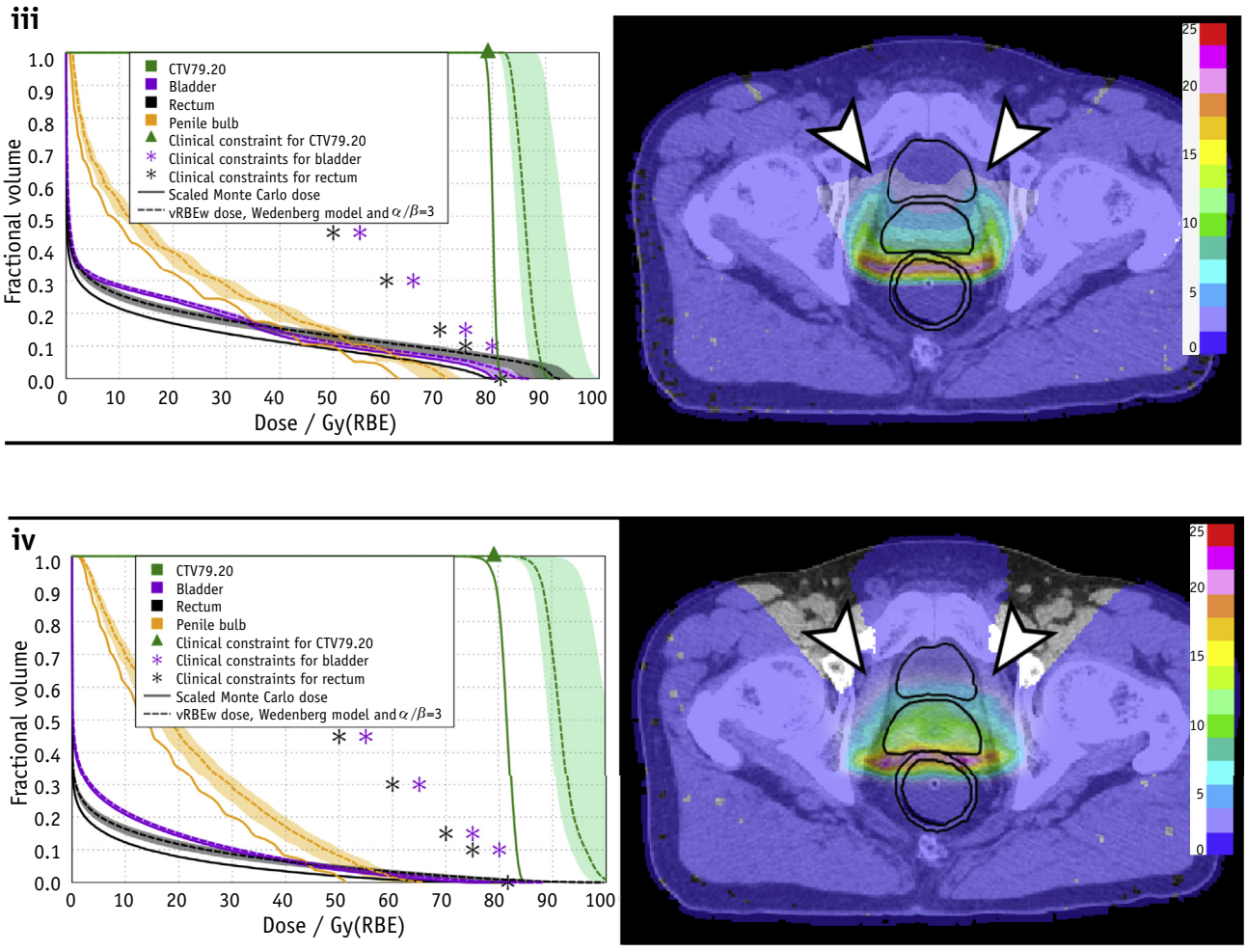

Fig. 2. (*continued*).

Wedenberg model, the AO IMPT plans outperformed the IMRT plans (at a statistically significant level) across almost all normal tissue metrics (Table 3).

The results presented in the figures and tables thus far considered only the most conservative RBE model in terms of biological dose to the rectum, with a fixed α/β of 3 Gy for both the normal tissues and the tumor. Yet, as demonstrated in Figure 3, the same trends were observed for all 3 RBE models and persisted across a range of α/β values. Figure 3 demonstrates that the lower the α/β the greater the predicted RBE boost: because of the prostate's low α/β, AO proton therapy may ultimately facilitate substantial dose escalation.

Discussion

Considering physical dose and a fixed proton RBE of 1.1, the 3 modalities initially investigated—(A) IMRT, (B) SB passively scattered proton beams, and (C) AO passively scattered proton beams—were all able to adequately cover the CTV79.20 while meeting the clinical constraints for the rectum and other normal tissues. As expected, IMRT delivered a more substantial low-dose bath to regions outside the tumor but nonetheless outperformed SB proton beams in terms of medium and high rectal dose levels. Surprisingly, IMRT also outperformed SB proton beams in terms of penile bulb and bladder statistics, likely because of a combination of (*1*) advanced multi-criteria optimization applied to the IMRT plans; (*2*) highly conformal IMRT margins; and (*3*) dosimetric limitations stemming from proton lateral scatter. It is anticipated that the results from the PARTIQoL randomized controlled trial (35) of IMRT versus SB proton beams—(A) versus (B)—will elucidate whether the dosimetric disparities between IMRT and SB proton beams translate into meaningful differences in health outcome, particularly in terms of patient-reported outcomes for toxicity and quality of life.

Although the dose distributions from AO passively scattered beams were substantially superior to those from SB passively scattered proton beams, they outperformed IMRT only with regard to femoral head sparing and normal tissue integral dose. The bladder statistics were worse for AO passively scattered protons than for IMRT.

Table 3 Comparison of metrics between treatment planning strategies (A) and (D) (see Table 1)

	(A) 7-field IMRT	(D) AO IMPT RBE = 1.1	(D) AO IMPT α/β = 4 Gy	(D) AO IMPT α/β = 3 Gy	(D) AO IMPT α/β = 1.5 Gy	(D) AO IMPT α/β = 0.5 Gy
CTV79.20						
Mean dose	80.3 (80.1-80.5)	80.4 (77.9-82.0)	88.1 (84.6-89.7)	91.6 (86.6-101.2)	94.8 (90.9-96.4)	99.2 (95.2-100.9)
V79.2	0.99 (0.97-1)	0.74 (0.26-0.96)	0.99 (0.97-1)	1 (0.99-1)	1 (1-1)	1 (1-1)
V77.6	1 (1-1)	0.89 (0.63-0.99)	1 (0.99-1)	1 (1-1)	1 (1-1)	1 (1-1)
D95	79.5 (79.3-79.7)	77.4 (74.4-79.5)	83.8 (80.3-85.7)	86.7 (81.9-94.9)	89.3 (85.5-91.4)	93.0 (89.2-95.1)
EUD, a = −10	80.4 (80.1-80.6)	80.2 (77.7-81.9)	87.7 (84.1-89.3)	90.9 (86.0-100.3)	94.0 (90.2-95.8)	98.2 (94.3-100.1)
	(A) 7-field IMRT	(D) AO IMPT RBE = 1.1	(D) AO IMPT α/β = 2 Gy	(D) AO IMPT α/β = 3 Gy	(D) vs (A) Sig $P = .05$?	(D) AO IMPT α/β = 6 Gy
Rectum						
Mean dose	19.7 (17.3-21.8)	4.4 (2.6-6.2)	7.6 (4.0-10.4)	6.9 (3.6-9.4)	Yes: (D)	5.7 (3.0-7.9)
EUD, a = 5	43.8 (40.8-46.6)	28.9 (25.0-31.3)	42.1 (37.0-44.6)	39.6 (34.7-42.0)	Yes: (D)	35.2 (30.7-37.5)
V30	0.20 (0.17-0.23)	0.05 (0.03-0.08)	0.10 (0.05-0.13)	0.09 (0.05-0.12)	Yes: (D)	0.07 (0.04-0.10)
V40	0.14 (0.12-0.16)	0.04 (0.02-0.05)	0.08 (0.04-0.10)	0.07 (0.04-0.09)	Yes: (D)	0.05 (0.03-0.07)
V50	0.10 (0.08-0.12)	0.02 (0.01-0.03)	0.06 (0.03-0.08)	0.05 (0.03-0.07)	Yes: (D)	0.04 (0.02-0.05)
V60	0.07 (0.05-0.09)	0.01 (0.00-0.01)	0.04 (0.02-0.06)	0.03 (0.02-0.05)	Yes: (D)	0.02 (0.01-0.03)
V70	0.04 (0.02-0.06)	0.00 (0.00-0.00)	0.03 (0.01-0.04)	0.02 (0.01-0.03)	Yes: (D)	0.01 (0.00-0.02)
V80	0.01 (0.00-0.02)	0.00 (0.00-0.00)	0.01 (0.01-0.02)	0.01 (0.00-0.01)	No	0.00 (0.00-0.00)
Maximum dose to 1 cc	79.1 (76.0-81.0)	60.7 (59.9-62.1)	86.0 (85.8-86.2)	81.5 (81.4-81.6)	Yes: (A)	73.2 (73.0-73.6)
Rectal wall						
Mean dose	19.7 (17.7-22.6)	6.6 (5.1-8.8)	10.8 (8.3-13.8)	9.9 (7.6-12.7)	Yes: (D)	8.4 (6.5-11.0)
EUD, a = 5	48.0 (45.0-50.3)	33.8 (32.1-36.2)	48.7 (46.9-51.0)	45.9 (44.1-48.2)	No	40.0 (39.3-43.2)
V30	0.21 (0.19-0.25)	0.10 (0.08-0.13)	0.14 (0.11-0.18)	0.13 (0.11-0.17)	Yes: (D)	0.12 (0.10-0.16)
V40	0.17 (0.15-0.20)	0.07 (0.06-0.10)	0.12 (0.10-0.16)	0.11 (0.09-0.15)	Yes: (D)	0.10 (0.08-0.13)
V50	0.13 (0.12-0.16)	0.05 (0.04-0.07)	0.10 (0.09-0.13)	0.09 (0.08-0.12)	Yes: (D)	0.08 (0.07-0.10)
V60	0.10 (0.08-0.13)	0.02 (0.01-0.03)	0.08 (0.07-0.11)	0.07 (0.06-0.09)	Yes: (D)	0.05 (0.02-0.07)
V70	0.07 (0.05-0.09)	0.00 (0.00-0.00)	0.06 (0.05-0.08)	0.05 (0.04-0.06)	No	0.03 (0.02-0.03)
V80	0.01 (0.00-0.04)	0.00 (0.00-0.00)	0.03 (0.03-0.04)	0.02 (0.02-0.03)	No	0.00 (0.00-0.00)
Maximum dose to 1 cc	79.0 (76.0-81.0)	60.7 (60.0-62.1)	86.0 (85.8-86.3)	81.4 (81.3-81.6)	Yes: (A)	73.2 (72.9-73.6)
Bladder						
Mean dose	17.4 (10.4-23.0)	12.8 (7.4-17.8)	14.3 (8.5-19.5)	13.7 (8.1-18.8)	Yes: (D)	12.9 (7.6-17.7)
EUD, a = 7	50.8 (47.3-54.1)	41.1 (35.2-47.3)	45.5 (39.0-51.9)	44.2 (37.8-50.5)	Yes: (D)	41.9 (35.8-48.0)
V30	0.22 (0.13-0.31)	0.15 (0.10-0.23)	0.18 (0.11-0.26)	0.17 (0.11-0.25)	Yes: (D)	0.15 (0.10-0.23)
V50	0.11 (0.07-0.18)	0.05 (0.02-0.09)	0.07 (0.04-0.11)	0.06 (0.03-0.10)	Yes: (D)	0.05 (0.02-0.09)
V60	0.07 (0.04-0.11)	0.03 (0.01-0.05)	0.04 (0.02-0.07)	0.03 (0.01-0.06)	Yes: (D)	0.03 (0.01-0.05)
V70	0.04 (0.03-0.06)	0.01 (0.00-0.02)	0.02 (0.00-0.04)	0.01 (0.00-0.03)	Yes: (D)	0.01 (0.00-0.03)
Penile bulb						
Mean dose	16.1 (7.8-25.2)	13.9 (5.5-21.1)	19.5 (8.5-28.5)	17.9 (7.6-26.5)	No	15.7 (6.4-23.5)
Femoral heads						
Mean dose	13.5 (11.6-17.3)	0.2 (0-0.7)	0.2 (0.1-0.7)	0.2 (0.1-0.7)	Yes: (D)	0.2 (0-0.6)
Normal tissue						
Mean integral energy	100.7 (77.5-135.2)	28.2 (27.0-51.8)	31.5 (21.9-37.4)	30.1 (21.9-37.4)	Yes: (D)	28.3 (19.5-33.6)

Abbreviations: CTV = clinical target volume; EUD = equivalent uniform dose, calculated according to the method described previously by Trofimov et al (8); IMPT = intensity modulated proton therapy; IMRT = intensity modulated radiation therapy; PTV = planning target volume.

In the CTV79.20 metrics, D95 refers to the dose received by 95% of the CTV79.20.

For the normal tissues, in the sixth column a sign test is applied to test for differences between modality (D) and modality (A). Where a statistically significant difference was found at the 5% level the preferable modality is stated. Constraints reported as VX refer to the fractional volume of the structure receiving X Gy(RBE). Integral energy deposition was calculated for the whole body minus the IMRT planning target volumes (assuming a body composition of water).

α/β values quoted are as applied to the Wedenberg RBE model.

Furthermore, AO passively scattered treatment plans deemed acceptable under the assumption of a fixed RBE (1.1) did not prove robust to the consideration of a variable RBE. Relative to SB proton beams, AO proton beams exhibited substantially increased mean LET values within the rectal wall. Three published RBE models consistently

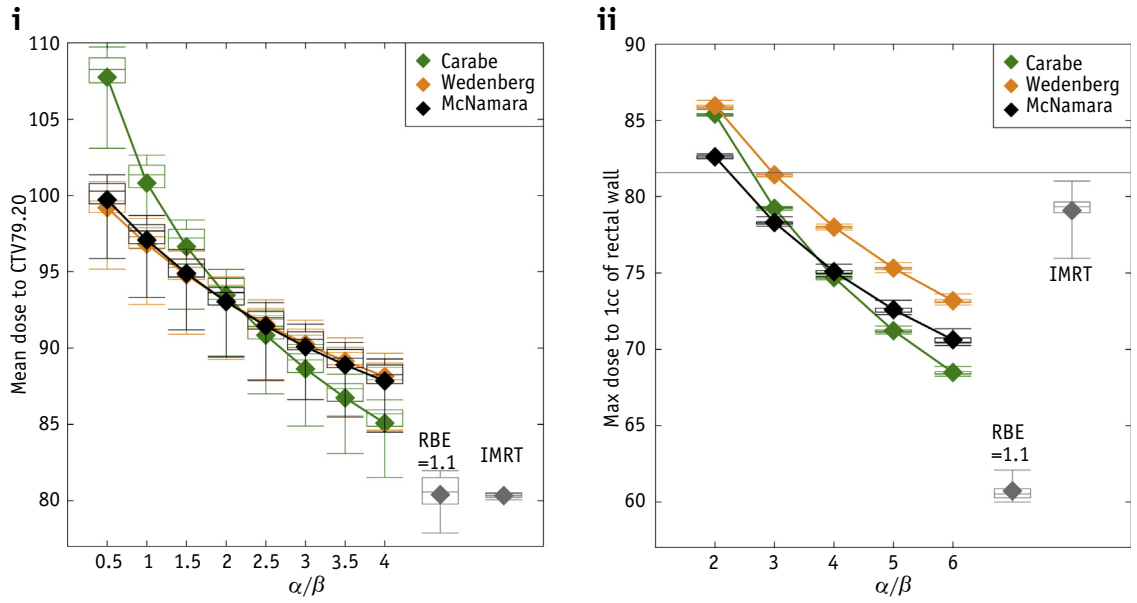

Fig. 3. Investigating sensitivity to selected relative biological effectiveness (RBE) model (20, 23, 24) and α/β value for treatment planning strategy D, anterior oblique intensity modulated proton therapy (Table 1). (i) Mean dose to the clinical target volume CTV79.20. (ii) Maximum (max) dose to 1 cc of the rectal wall. The clinical constraint that no 1 cc should receive more than 103% of the prescription dose is indicated by the solid horizontal line. *Abbreviation:* IMRT = intensity modulated radiation therapy.

indicate that the LET enhancement is likely to translate into unacceptable RBEw dose hotspots for AO proton beams. For the most extreme model, increases in rectal maximum dose of approximately 20 Gy(RBE) were calculated for an α/β of 3 Gy. Across all 3 variable RBE models and a broad range of α/β values (2-6 Gy), our clinical rectal maximum dose constraint (that no 1 cc should receive more than 103% of the prescription dose) was substantially exceeded for AO passively scattered plans. Such plans, optimized assuming a fixed RBE of 1.1, would look considerably different had they been optimized according to a variable RBE model.

A recent publication reported that across a cohort of 20 prostate patients treated using anterior oriented proton fields, 1 patient experienced late grade 2 rectal proctitis (18). However, the treatment approaches were non-standardized and heterogenous: a wide range of AO angles (10°-85°) and weights associated with the anterior portals (12.5%-100%) were considered (18).

For highly conformal (relatively small spot size) IMPT plans, we tested whether it was possible to find a ±35° AO beam angle plan that simultaneously met tumor and rectal constraints for fixed and variable RBE models, respectively. We found that typically this was not the case: whereas the AO IMPT plans achieved high physical dose conformity and minimal low dose exposure, full target coverage could not be achieved under imposition of the biological rectal dose constraint. Consequently, the question whether improvements over IMRT can be gained using AO IMPT rests on the validity of variable RBE models. If either the fixed RBE value of 1.1 or a variable RBE model could be validated in vivo, then it would be possible to use AO IMPT to dose-boost the prostate and improve normal tissue sparing relative to IMRT. However, simultaneously considering the 2 worst cases—fixed RBE for the tumor and a variable RBE for normal tissues—it was typically not possible to find an AO IMPT plan that met both rectal and target constraints, despite our consideration of a physical dose best-case scenario of zero range uncertainty.

This study did not attempt to determine the suitability of an AO IMPT approach when combined with prostate and rectum spacer gels. Such gels may mitigate both the range and RBE uncertainties associated with AO proton beams, affording us the benefit of improved AO IMPT dosimetry, with vastly reduced risk. Further research is required in this area.

In addition to the 3 proton RBE models considered in this study (20, 23, 24), several similar models have been proposed, including Wilkens and Oelfke (36), Chen and Ahmad (37), and Jones (38), among others. The local effect model (39, 40) adopts a different approach, considering track structure rather than LET. Although a detailed intercomparison of all published models is beyond the scope of this study, it is important to note that the magnitude of the effects described here must be considered to be model dependent. Strong caveats are associated with all clinical radiobiological modeling, and in vivo validation of any variable RBE model for proton therapy remains ambitious. Yet, because of its low α/β and thus potential for pronounced RBE effects, model verification may prove easier for the prostate than for other clinical sites. The models considered in this study were based on in vitro datasets for

clonogenic cell survival. If a high-quality set of original treatment planning plus outcome data could be obtained for a very large prostate patient cohort (preferably including a diverse range of dose fractionation schemes and beam angles), it would be possible to iteratively adjust a proton RBE model until a good match is obtained between the model prediction and a specific clinical outcome (41). Ultimately, it is likely that different RBE models would be required for different clinical endpoints (eg, tumor control probability vs normal tissue damage). It is also possible that posttreatment imaging studies could demonstrate LET/RBE effects, for example in terms of rectal proctitis. However, in any attempt at in vivo model verification, it would also be necessary to distinguish LET/RBE effects from possible differences between predicted and delivered proton range.

In conclusion, for a cohort without rectum spacer gels, this study (*1*) underlines the importance of resolving the question of proton RBE within the framework of an IMRT versus proton debate for the prostate and (*2*) highlights that without further LET/RBE model validation, great care must be taken if AO proton fields are to be considered. Further work could help to determine whether prostate and rectum spacers suitably mitigate both the biological and physical (range) uncertainties associated with AO proton beams.

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