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Proton Versus CyberKnife Therapy Planning for Hypofractionated Treatment of Prostate With Focal Boost

Inhwan Yeo (PhD)*, Alexander Goughenour (BS), George Cernica (PhD), Wei Nie (PhD), Mindy Joo (PhD), Peng Wang (PhD), Jiajin Fan (PhD), Ashkan Parniani (MBA), Samir Kanani (MD)

Department of Advanced Radiation and Proton Therapy, INOVA Schar Cancer Institute, Fairfax, VA, USA

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ABSTRACT

Purpose: To compare intensity-modulated proton therapy with CyberKnife (CK) therapy for hypo-fractionated treatments of prostate with focal boost, as a first planning study for prostate with dose escalation to a dominant intraprostatic lesion (DIL).

Materials and Methods: Ten patients who possess one DIL in their prostate and their CK plans that were used to treat the planning target volume of prostate were chosen. Six of the plans were further escalated to DIL. Intensity-modulated proton therapy plans were created for the patients with robust optimization, accounting for setup and range uncertainties for the clinical target volume (CTV) of prostate. The CK plans were then compared with the proton plans.

Results: In the worst scenario of the robust evaluation, the proton plans reasonably met all objectives and constraints used in CK planning for both CTV coverage and organs-at-risk (OAR) sparing. Under the nominal scenario of the robust optimization, the proton plans produced dosimetric values comparable to those by the CK plans for both CTV and DIL coverage. The average dose to CTV, outside DIL and urethra, was found lower in the proton plans than in the CK plans due to the uncertainties. A similar trend was observed for the dose conformity to CTV. These two findings, however, were not planning objectives. Regarding organs-at-risk sparing, the proton plans in the nominal scenario were comparable to the CK plans for doses > 18.125 Gy; for doses below it, the proton performed better. This study offers a basis for a clinical trial of treatment of prostate cancer by proton that may be transferred from the CK system in our center.

Conclusion: The dosimetric objectives and constraints used in the CK plans were achieved with the proton plans.

Introduction

Radiation therapy with x-ray has been used extensively for the treatment of prostate with conventional as well as hypofractionation.[1] Proton therapy, after its introduction, has also been utilized for the treatment of prostate with mainly conventional fractionation, demonstrating a similar clinical outcome to that of photon therapy.[2,3] Over the past ten years, hypofractionation was introduced to proton therapy and has been studied in comparison with x-ray therapy, including planning studies as well as clinical outcome studies.

Proton therapy planning based on passive scattering was compared with x-ray therapy planning based on a CyberKnife (CK) system (Accuray, Madison, Wisconsin) with the Iris collimator for the dose of 36.25 Gy in 5 fractions. Both met target and normal tissue constraints, with the proton therapy providing superior sparing of the penile bulb, rectum, and urethra, as well as better dose homogeneity in prostate. In contrast, the x-ray therapy performed better in sparing the bladder and femoral heads.[4] Additionally, intensity-modulated proton therapy (IMPT) was compared with volumetric modulated arc therapy, incorporating robustness considerations such as an isocentric shift of 2 mm and an additional Hounsfield uncertainty for the proton plans.[5] Due to this uncertainty, the x-ray plan outperformed the proton plan in target conformity and organs-at-risk (OAR) sparing.[5]

The 5-year outcome of IMPT was studied for the delivery of 36.25 Gy in 5 fractions, revealing that the proton therapy was comparable with similarly fractionated x-ray therapy, with favorable late toxicity. The proton therapy also showed improved gastrointestinal toxicity, compared with conventionally and mildly

* Corresponding author.
E-mail addresses: medicphys@hotmail.com, in.yeo@inova.org (I. Yeo).

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fractionated proton therapy.[6] The long-term result of proton therapy based on passive scattering was studied, comparing the 7.5-year outcome of the dose delivery of 35 Gy in 5 fractions with that of the delivery of 60, 54, and 47 Gy in 20, 15, and 10 fractions, respectively.[7] Biochemical failure-free survival was found to be better with the latter fractionation schemes, but acute gastro-urinal toxicities were better with the former, and the late gastrointestinal and gastro-urinal toxicities were similar between the two. The different result between the two studies[6,7] due to the fractionation change may be related to the use of IMPT of the study by Kubes et al,[6] while the study by Ha et al[7] utilized passive scattering.

Proton therapy planning was investigated to deliver not only a uniform dose to prostate but also an escalated dose to dominant intraprostatic lesions (DILs) in prostate with conventional fractionation.[8,9] Proton therapy planning with passive scattering has been investigated with an escalated dose to the DILs in prostate in its comparison with intensity-modulated radiation therapy (IMRT) planning.[8] Proton therapy is provided to targets with more homogeneous but less conformal doses and to normal tissues with better intermediate-to-low doses than IMRT. A similar study was performed employing volumetric modulated arc therapy and IMPT with robust optimization, finding that IMPT resulted in a lower normal tissue complication probability.[9]

In our center, we have been treating prostate with the nominal dose of 36.25 Gy in 5 fractions and an escalated dose of 39 + Gy to DILs and the rest of prostate, whenever feasible, with a CK system. We are considering proton therapy of prostate, including DILs with the same dose fractionation using IMPT. To prepare for this, we aim to perform a planning study comparing IMPT with CK, cross-evaluating against the planning constraints used for CK. To our knowledge, this is the first study to compare IMPT with CK for the therapy of prostate involving dose escalation to the DIL.

Materials and methods

Patient selection, imaging, and contouring

Ten patients who have been treated with CK between 2021 and 2023, each with one DIL in their prostate, were selected for the study. Patients who possessed multiple DILs were excluded.

Computer-tomography (CT) simulations for the selected patients were performed on either Canon CT (Aquilion Prime 40) with the imaging parameters of 120 kV, 250 mAs, and 1-mm slice thickness or General Electric Revolution CT using the same parameters and 1.25-mm slice thickness. The patients were scanned with a comfortably filled bladder and an empty rectum and in the feet-first supine position. Three or 4 fiducials with the size of 0.5 mm × 5 mm (Visicoil, IZI Medical, Owings Mills, Maryland) were placed in the prostate. A hydrogel spacer (Boston Scientific, Quincy, Massachusetts) was placed between the prostate and the rectum prior to CT simulation. Acquired CT images were reconstructed with metal artifacts reduction before being used for planning. Magnetic resonance (MR) images with the sequences of T1 and T2 were acquired following CT simulation with a Foley catheter placed in the bladder on the same day. The MR images were registered to the planning CT on the basis of either the fiducials or soft tissues if the fiducials were not visible.

The planning target volume (PTV) of the prostate was contoured on the MR images with variable margins around the prostate gland and the proximal 1 cm of seminal vesicles, which together constituted the clinical target volume (CTV) for each patient. A setup margin in each direction was individualized for each patient, and the average values were 0.45 ± 0.15 cm superiorly, 0.49 ± 0.13 cm inferiorly, 0.46 ± 0.10 cm anteriorly, 0.28 ± 0.10 cm posteriorly, 0.45 ± 0.10 cm on the left, and 0.40 ± 0.09 cm on the right. The variable margins across the six directions were adopted to protect nearby OAR. A DIL was contoured on the T2 MR image with about a 2 mm margin around the gross lesion.

CyberKnife planning

CK plans were developed using Precision 3.3.1.2, the InCise 2 MLC, and a finite-size pencil beam algorithm as a departmental practice for the planning of prostate treatment. The algorithm is known to produce a difference of < 1% in the calculated dose from a Monte Carlo algorithm in homogeneous media.[10] Treatment plans were designed to conform to our departmental clinical standards, as shown in Table 1, based on publications and protocols,[11-17] for the dose of 36.25 Gy to the volume of 95% of PTV as a minimum and the dose of 39 Gy and more to as much of the PTV and the DIL as possible. Table 1 lists planning objectives for various parameters, such as V_{Rx} (%): the volume percentage of CTV that receives the prescribed dose of 36.25 Gy; D_m (Gy): the maximum dose at 0.03 cm^3 of the organ of interest in Gy; $V_{32.625\ Gy}$ (%): the volume percentage that receives dose < 32.625 Gy; and $V_{30\ Gy}$ (cm^3): the volume in cubic centimeters that receives dose < 30 Gy. All other terms can be similarly interpreted. The treatment beams were restricted to entering the patient from the L5 spine level through the perineum, with no beams intersecting the testicles or the penile trunk. The maximum monitor units (MUs) per beam was set to 650 MU to minimize peripheral dose. Treatment times and the numbers of beams and segments were not constrained. On average, the total planned MU was 3202, with an average of 43 beams. Clinically used plans were re-evaluated for DIL coverage and reoptimized for six patients when further dose escalation to DIL was possible. The intent was to compare not only clinical plans that have been used for treatment but also plans with full dose escalation to DIL with proton plans.

Table 1
Clinical constraints used for hypo-fractionated prostate treatment with CK.

PTV	D_{Rx} (%) > 95[11-12]				
Bladder	D_m (Gy) < 38[16]	$V_{32.625\ Gy}$ (%) < 10[11-12]		$V_{18.125\ Gy}$(%) < 40[11-12]	
Bowel	$V_{30\ Gy}$ (cm^3) < 1[14]			$V_{18.1\ Gy}$ (cm^3) < 5	
Femoral heads	D_m (Gy) < 30[17]			$V_{20\ Gy}$ (cm^3) < 10[17]	
Penile bulb	D_m (Gy) < 36.25[17]			$V_{20\ Gy}$ (cm^3) < 3[17]	
Rectum	D_m (Gy) < 38[13]	$D_{3\ cm^3}$ (Gy) < 34.4[17]	$V_{32.625\ Gy}$(%) < 10[11-12]	$V_{29\ Gy}$(%) < 20[11-12]	$V_{18.125\ Gy}$(%) < 50[11-12]
Urethra	D_m (Gy) < 38.7[17]				

Notes: Rx is the prescribed dose. V_{Rx}(%): the volume % of PTV that receives the prescribed dose of 36.25 Gy (used for clinical target volume in proton); D_m (Gy): the maximum dose at 0.03 cm^3 of the organ of interest in Gy; $V_{32.625\ Gy}$(%): the volume that receives dose smaller than 32.625 Gy in %; $V_{30\ Gy}$ (cm^3): the volume that receives dose smaller than 30 Gy in cm^3. All other terms can be similarly interpreted.
Abbreviations: CK, CyberKnife; PTV, planning target volume.

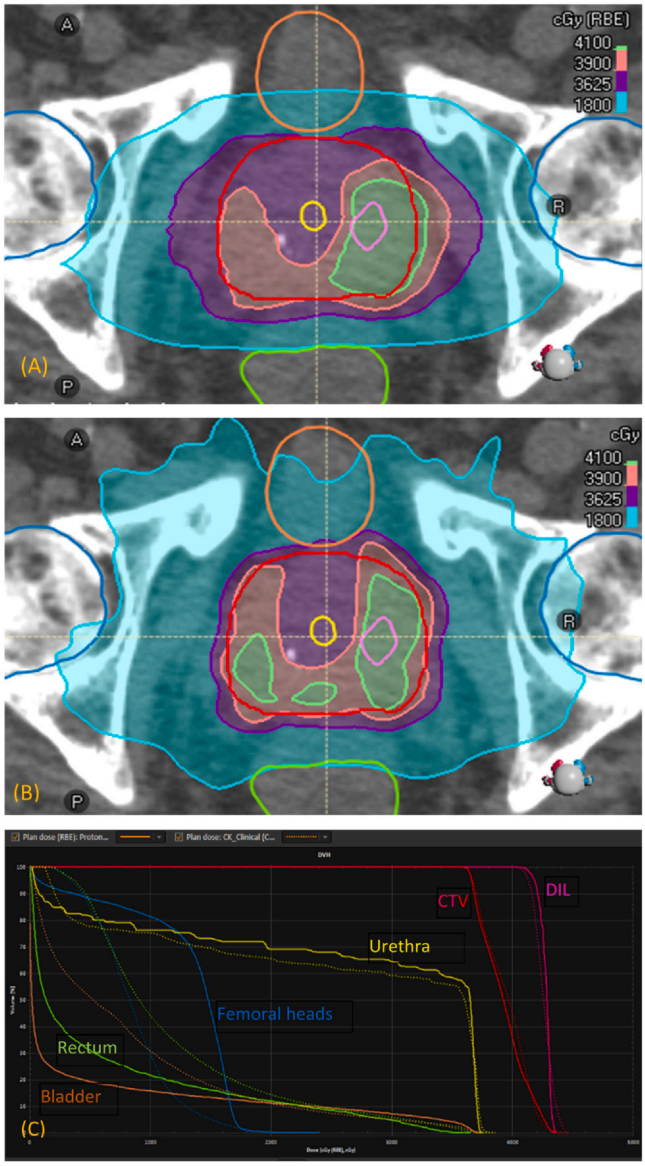

Figure. Comparison between proton and CK plans for one patient used in this study. (A): Proton plan. (B): CK plan. (C): DVH comparison where the solid lines are proton and the dotted lines are CK. The following color codes were used: pink for DIL, red for CTV, yellow for urethra, blue for femoral heads, green for rectum, and orange for bladder. **Abbreviations: CTV, clinical target volume; DIL, dominant intraprostatic lesion; RBE, relative biological effectiveness.**

Proton planning

Proton treatment plans were generated within the RayStation (RS) treatment planning system (RaySearch Laboratories, Sweden), employing a combination of pencil beam scanning, IMPT, and the Monte Carlo Version 5.2 dose calculation algorithm with the IBA Proteus Plus proton machine model. A consistent relative biological effectiveness of 1.1 was employed throughout. The prescribed dose and the dosimetric constraints used for the CK plans were similarly used, except that the plans were done on CTV and the clinical DIL, created by subtracting 2 mm isotropically from the DIL (henthforth, DIL stands for the clinical DIL). The plans were generated blindly from the CK plans. Energy layer spacing and spot spacing were set automatically with a scale of 0.6 times of sigma, and target margins were established at 1 proximal layer, 1 distal layer, and an automatic lateral margin with a scale of 0.6 times of sigma. To ensure deliverability, the plans adhered to machine limits for both minimum and maximum MUs per spot. All plans were designed with a standardized coplanar treatment field arrangement, featuring bilateral opposed beams, and eschewing the use of a range shifter. Subsequently, the optimization process focused on achieving a single-field optimization dose distribution, specifically targeting a point dose difference between fields of $< \pm 10\%$. This approach was intended to enhance robustness against proton range uncertainty. During the optimization of IMPT plans, robust optimization objectives were incorporated to achieve robust target coverage and spare OARs. A robust optimization range uncertainty, equivalent to a density uncertainty of $\pm 3.5\%$, was applied. The isocentric setup uncertainty utilized in the robust optimization process was adopted from the CTV-to-PTV margins used in each patient as the prescribed setup uncertainties of the CK treatment. It is noteworthy that left and right isocentric setup uncertainties were deliberately excluded from robust optimization, because the margin of range uncertainties in those two directions was generally much higher than the isocentric setup uncertainties. Note that the isocentric and range uncertainties may not be assumed to average out over hypo-fractions of treatment, with range uncertainty being particularly persistent. Therefore, the optimization aimed to meet full scenario of robustness whenever possible. Robust-evaluation perturbed doses were also calculated using Monte Carlo Version 5.2 dose calculation algorithm. Robust evaluation was conducted on CTV and OARs accounting for the isocentric and density uncertainties, respectively.

In the CK planning, where robust planning was not part of our clinical practice, the PTV included all setup uncertainties of the CTV, including its deformation relative to the incident beam. Therefore, it did not fully model the variety of possible positions of CTV that could assume any space within the boundary of PTV, because the boundary of PTV was always closer to the beam edge than that of CTV on average, and even when CTV is positioned at the setup limits. Consequently, the CTV placed at the center of the PTV received greater dose coverage than that of the PTV itself. On the contrary, in the proton planning, the margin around CTV was effectively managed by modeling a range uncertainty that is beam-specific, alongside a setup uncertainty for robust planning of CTV in this study. In the robust planning, CTV was adjusted by the range uncertainty that modified the stopping powers of the planning CT image voxels by $\pm 3.5\%$, and it also was moved to various positions, relative to the planned beams, that correspond to the setup uncertainty (limits in each of the six directions). Therefore, as with the CK planning, the robust planning did not model the full variety of positions but focused on CTV at the limits, the worst-case dosimetric scenarios. In this regard, the CTV coverage by the robust proton planning and the PTV coverage by the conventional CK photon planning are analogous to each other. Similarly, the CTV coverage at its nominal position by the robust planning, which places CTV at the center of all positional limits of the uncertainties, and the CTV coverage by the CK planning are also comparable. The CK plans were compared with the proton plans in the worst scenario of robustness to allow the surest and safest plans for CTV coverage and OAR sparing, respectively, by imposing on the proton plans the goals and constraints used for CK. The CK plans were also compared with the proton plans in the nominal scenario to provide the equivalent evaluation. It is important to note that the robust optimization by RS models the setup uncertainty in a rigid manner by shifting the entire patient body relative to the incident beam, while the uncertainty is modeled by the CK planning by expanding the CTV, not shifting the patient. For dose conformity comparison, we have also utilized the conformity index calculated by RS, defined as the ratio of CTV covered by the 95% isodose line to the 95% isodose volume.

Results and discussion

The Figure shows examples of dose distributions from proton planning (A) and CK planning (B) as well as a DVH comparison (C) between the two methods of planning for DIL, CTV, urethra, bladder,

Table 2
Comparison between the proton and CK plans in various dose parameters in CTV and DIL.

Prostate CTV	V_{Rx} (%)				$D_{ave\ ,CTV\text{-}GTV\text{-}Ure}$ (Gy)				Conformity index			
	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom
Ave	98.74	98.07	96.32	99.15	39.65	40.08	38.69	39.12	0.43	0.43	0.32	0.35
P-value with CK_{clin}			**< 0.01**	0.47			**0.01**	0.12			**< 0.01**	**< 0.01**
P-value with CK_{esc}			**0.02**	0.12			**< 0.01**	**0.01**			**< 0.01**	**< 0.01**
Prostate DIL	$D_{95\%}$(Gy)				D_{ave} (Gy)							
	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom				
Ave	41.58	42.89	39.84	42.07	42.61	43.86	42.39	43.76				
P-value with CK_{clin}			**0.03**	0.47			0.78	0.17				
P-value with CK_{esc}			**< 0.01**	0.30			0.09	0.91				

Notes: Ave: average value of ten patient data. $CK_{clin:}$ CK plan that is used to treat patients. CK_{esc}: CK plan with escalated dose to DIL at the limit of planning. P-wrst: robust proton plan; the data represent the worst data among several robust scenarios modeled. P-nom: nominal proton plan, resulted from the robust plan. V_{Rx} (%): the volume % of CTV that receives the prescribed dose of 36.25 Gy; $D_{ave,CTV\text{-}GTV\text{-}Ure}$: the average dose in Gy planned in the region of CTV subtracted by GTV and urethra; $D_{95\%}$ (Gy): the dose in Gy planned in the 95% of the volume of DIL; D_{ave} (Gy): the average dose in Gy in DIL.
Abbreviations: CK, CyberKnife; CTV, clinical target volume; DIL, dominant intraprostatic lesion.
P-values less than 0.05 was typed in bold.

rectum, and femoral heads, carried out in this study. Since the dose planned for the DIL varied across patients, depending on its location relative to OARs, a representative case was presented in this figure instead of a summed average across all patients. As shown in the Figure, based on our departmental practice, a dose as high as 39 Gy was provided to cover the region of CTV surrounding the urethra, which has the maximum dose constraint of 38.78 Gy to 0.03 cm^3. While a minimum dose of 36.25 Gy was provided to the volume of 95% of CTV, a dose of 41 Gy was given to most of the DIL volume. These target doses were planned as long as the OAR constraints shown in Table 1 were met. The DVH comparison in Figure C showed that, when the target coverage (CTV and DIL) is similar between the proton plan and the CK plan, the volumes of rectum and bladder that receive doses below 20 Gy were smaller with the proton plan than those with the CK plan. This is a known advantage of proton plans over x-ray plans.[8]

Table 2 compares the robust proton plan (P-wrst, the worst-case scenario, considering isocenter and density uncertainties) with the clinical CK plan (CK_{clin}) and the CK plan with further dose escalation to the DIL (CK_{esc}) for the following dose parameters: V_{Rx}, the volume percentage of CTV receiving the prescribed dose; $D_{ave,CTV\text{-}GTV\text{-}Ure}$, the average dose to CTV subtracted by DIL and urethra; conformity index for CTV; $D_{95\%}$, the dose covering 95% of the volume of DIL; and D_{ave}, the average dose in DIL. The proton plans with the nominal dose (P-nom) were also compared with the CK plans. The set of CK_{esc} included all plans with full dose escalation to the DIL: four clinical plans and six further-escalated plans. V_{Rx} was found to be slightly smaller with P-wrst compared with CK_{clin} (96.32% vs 98.74% with $P < .01$) and CK_{esc} (96.32 vs 98.07 with $P = .02$), although it satisfied the planning objectives outlined in Table 1. This can be in part attributed to the difference between proton planning and CK planning, as described in the method section. V_{Rx} with P-nom was found to be similar to (statistically indistinguishable) those with CK_{clin} (99.15 vs 98.74 with $P = .47$) and CK_{esc} (99.15 vs 98.07 with $P = .12$) when CTV was placed at the center of its planned, position limits for the robust optimization, similarly to the CK planning that is done on PTV with CTV at its center. $D_{ave,CTV\text{-}GTV\text{-}Ure}$ was smaller with P-wrst than with CK_{clin} (38.69 vs 39.65 Gy with $P = .01$) and CK_{esc} (38.69 vs 40.08 with $P < .01$). $D_{ave,CTV\text{-}GTV\text{-}Ure}$ with P-nom was found to be smaller than that with CK_{esc} (39.12 vs 40.08 with $P = .01$). These findings were explained by the following reason. Unlike V_{Rx} that is considered for the entire CTV where the prescribed dose was 36.25 Gy, $D_{ave,CTV\text{-}GTV\text{-}Ure}$ dealt with the area of CTV that surrounds the urethra and the DIL with an attempted dose > 39 Gy, while the urethra max was limited to 38.78 Gy. The robust optimization had to model the range uncertainty in addition to the isocentric setup uncertainty for the sparing of the urethra (in addition to other neighboring OARs), which limited dose to $D_{ave,CTV\text{-}GTV\text{-}Ure}$. This also explains why the dose conformity was found to be worse with P-wrst than with CK_{clin} (0.32 vs 0.43 with $P < .01$) and CK_{esc} (0.32 vs 0.43 with $P < .01$). A similar finding was observed for P-nom. In summary, in the worst-case scenario of the robust evaluation, the proton plan could meet the constraint of V_{Rx}, developed for the PTV approach by the CK planning. Moreover, V_{Rx}, based on P-nom, was found to be comparable to the CK plan (CK_{esc}). Therefore, in the coverage of V_{Rx}, the proton plans were comparable to the CK plans. Since the robust optimization, which could be a more realistic and conservative approach than the PTV approach, was available for the proton planning only, the proton may offer an advantage over the CK treatment in our center. When it comes to the trends of $D_{ave,CTV\text{-}GTV\text{-}Ure}$, and the target conformity, the proton plan was found to be less favorable than the CK plans, whether CK_{clin} or CK_{esc}, due to the uncertainties.

$D_{95\%}$ in DIL was found to be lower for plans with P-wrst than those for plans with CK_{clin} (39.84 vs 41.58 with $P = .03$) and CK_{esc} (39.84 vs 42.89 with $P < .01$). This is due to the proximity of the DIL to the bladder that constrained the planned beams, when the beams moved closer to the bladder among several scenarios of their isocentric uncertainty, to meet the dose of 38 Gy as D_m. The range uncertainty mentioned above additionally contributed to the finding. The $D_{95\%}$ was greater with P-nom than with P-wrst (42.07 vs 39.84) due to the further distance of bladder from the beam center in the nominal scenario than the worst scenario associated with P-wrst. The $D_{95\%}$ with P-nom was similar to those with CK_{clin} (42.07 vs 41.58 with $P = .47$) and CK_{esc} (42.07 vs 42.89 with $P = .30$). D_{ave} of DIL with P-wrst was similar to that with CK_{clin} (42.39 vs 42.61 with $P = .78$) and that with P-nom was comparable to that of CK_{esc} (43.76 vs 43.86 with $P = .17$), as supported by the statistical indistinguishability of the *P* values, respectively. Similarly to its finding based on V_{Rx} to CTV, the proton plan could provide a dosimetric coverage to DIL as effectively as the CK plan did based on the trend of P-nom. Moreover, the coverage can benefit from robust optimization. Note that the fraction of the CTV volume that is covered by 39 Gy and the dose to the DIL were variable across the patients, based on the anatomical characteristics of each patient (eg, distance between rectum/bladder and CTV; urethra and the rest of CTV).

Table 3 outlined the dosimetric value for each constraint that was utilized for the CK and proton planning. All constraints were met by the CK plans, but one of the rectal constraints was not met by the proton plans. For bladder, D_m with P-wrst was not statistically distinguishable from those with CK_{clin} (37.87 vs 37.91 with $P = .77$) and CK_{esc} (37.87

Table 3
Comparison between proton and CK plans in various dose parameters in bladder, rectum, urethra, femoral heads, and bowel.

Bladder	D_m (Gy) < 38				$V_{32.625\,Gy}$ (%) < 10				$V_{18.125\,Gy}$ (%) < 40			
	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom
Ave	37.91	37.86	37.87	37.50	5.42	5.47	9.74	5.81	20.80	21.03	20.38	15.19
P-value with CK_{clin}			0.77	**0.02**			**0.01**	0.72			0.92	0.16
P-value with CK_{esc}			0.93	**0.03**			**0.01**	0.76			0.88	0.18
Bladder	$V_{10\,Gy}$ (%)											
	CK_{clin}	CK_{esc}	P-wrst	P-nom								
Ave	46.16	44.38	25.84	20.34								
P-value with CK_{clin}			< **0.01**	< **0.01**								
P-value with CK_{esc}			**0.01**	< **0.01**								
Rectum	D_m (Gy) < 38				$D_{3\,cm^3}$ (Gy) < 34.4				$V_{32.625\ Gy}$ (%) < 10			
	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom
Ave	35.62	35.82	39.04[a]	35.02	27.54	27.85	32.12	24.35	2.50	2.69	7.59	1.82
P-value with CK_{clin}			**0.01**	0.67			0.08	0.30			**0.02**	0.52
P-value with CK_{esc}			< **0.01**	0.53			0.09	0.24			**0.03**	0.46
Rectum	$V_{29\,Gy}$ (%) < 20				$V_{18.125\,Gy}$ (%) < 50				$V_{10\,Gy}$ (%)			
	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom
Ave	5.19	5.39	11.60	3.92	20.95	22.54	22.69	11.35	52.83	54.92	33.21	19.78
P-value with CK_{clin}			**0.03**	0.49			0.73	**0.04**			**0.02**	< **0.01**
P-value with CK_{esc}			**0.04**	0.46			0.98	**0.02**			< **0.01**	< **0.01**
Urethra	D_m (Gy) < 38.78											
	CK_{clin}	CK_{esc}	P-wrst	P-nom								
Ave	38.23	37.74	38.42	37.74								
P-value with CK_{clin}			0.32	**0.02**								
P-value with CK_{esc}			**0.02**	1.00								
Femoral heads	D_m (Gy) < 30				$V_{20\,Gy}$ (cm^3) < 10							
	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom				
Ave	15.01	13.62	20.70	19.65	0.25	0.25	0.31	0.08				
P-value with CK_{clin}			0.07	0.11			0.83	0.28				
P-value with CK_{esc}			**0.02**	**0.03**			0.82	0.29				
Bowel	$V_{30\,Gy}$ (cm^3) < 1				$V_{18.1\,Gy}$ (cm^3) < 5							
	CK_{clin}	CK_{esc}	P-wrst	P-nom	CK_{clin}	CK_{esc}	P-wrst	P-nom				
Ave	0.07	0.16	0.42	0.09	0.37	0.49	2.94	0.50				
P-value with CK_{clin}			0.36	0.85			0.07	0.83				
P-value with CK_{esc}			0.51	0.73			0.09	0.98				

Notes: Ave: Average value of ten patient data. CK_{clin}: CK plan that is used to treat patients. CK_{esc}: CK plan with escalated dose to dominant intraprostatic lesion at the limit of planning. P-wrst: robust proton plan. P-nom: nominal proton plan, resulted from the robust plan. V_{Rx}(%): the volume % of CTV that receives the prescribed dose of 36.25 Gy; D_m (Gy): the maximum dose at 0.03 cm^3 of the organ of interest in Gy; $V_{32.625\,Gy}$(%): the volume that receives dose smaller than 32.625 Gy in %; $V_{30\,Gy}$ (cm^3): the volume that receives dose smaller than 30 Gy in cm^3. All other terms can be similarly interpreted.
Abbreviation: CK, CyberKnife.
P-values less than 0.05 was typed in bold.
[a] Violation of the given constraint.

vs 37.86 with $P = .93$). The value with P-nom was slightly smaller than those with CK_{clin} (37.50 vs 37.91 with $P = .02$) and CK_{esc} (37.50 vs 37.86 with $P = .03$). $V_{32.625\,Gy}$ with P-wrst was greater than those with CK_{clin} (9.74% vs 5.42% with $P = .01$) and CK_{esc} (9.74 vs 5.47 with $P = .01$). The value with P-nom was similar to those with CK_{clin} (5.81 vs 5.42 with $P = .72$) and CK_{esc} (5.81 vs 5.47 with $P = .76$). At $V_{18.125\,Gy}$, the proton plans were not statistically distinguishable from the CK plans. In each constraint, P-wrst met the associated constraint. Unlike the above finding, however, $V_{10\,Gy}$ was found to be substantially smaller with P-wrst than those with CK_{clin} (25.84 vs 46.16 with $P < .01$) and CK_{esc} (25.84 vs 44.38 with $P = .01$). This finding was repeated for $V_{10\,Gy}$ with P-nom. The above-mentioned greater volume values with P-wrst may not tell the inferior performance of the proton plan due to the difference between the robust planning in RS and the CK planning, explained in the method section, provided that the values of P-nom were comparable. The proton plans delivered much smaller integral dose to bladder, in particular the volume of the bladder that receives lower doses than that by the CK plans. Note that $V_{10\,Gy}$, although adopted for dose evaluation, was not used as a planning constraint for this study. At the dose range above 18.125 Gy, the proton

planning, based on the performance of P-nom, was comparable to the CK planning, while at doses below 10 Gy, the proton was superior.

For rectum, D_m was found to be greater with P-wrst than those with CK_{clin} (39.04 vs 35.62 with $P = .01$) and CK_{esc} (39.04 vs 35.82 with $P < .01$), exceeding the planning constraint of 38 Gy. In eight out of ten patients, D_m has exceeded this constraint. The reason was explained as follows. The asymmetric setup uncertainty between anterior and posterior directions (0.46 and 0.28 cm, respectively) was used in the robust optimization. It rigidly shifted the body (and CTV), relative to the beam direction, into the two directions by the specified amounts to be able to cover CTV similarly to the PTV coverage (by the two margins of the two directions, respectively) by the CK planning. The anterior shift by 0.46 cm for CTV coverage excessively modeled the posterior margin, 0.28 cm, of the CTV of the CK plan, which is applicable to the region of rectum. We could have considered the 2 margins in the opposite sense to model the associated CTV-to-PTV margins used by the CK planning in terms of the OAR point of view. In this study, we chose to adopt the former modeling (CTV coverage was preferred). Unlike the trend of D_m with P-wrst, D_m with P-nom was not statistically distinguishable from those of CK_{clin} and CK_{esc}. The trend in the findings of D_m with P-wrst and that with P-nom was repeated in the findings for $V_{32.625\,Gy}$ and $V_{29\,Gy}$. However, $V_{18.125\,Gy}$ with P-wrst was similar to those with CK_{clin} (22.69 vs 20.95 with $P = .73$) and CK_{esc} (22.69 vs 22.54 with $P = .98$), but $V_{18.125\,Gy}$ with P-nom was found to be smaller than those with CK_{clin} (11.35 vs 20.95 with $P = .04$) and CK_{esc} (11.35 vs 22.54 with $P = .02$). $D_{3\,cm^3}$ with P-wrst and with P-norm, respectively, were not distinguishable from those with CK_{clin} and CK_{esc}. Therefore, the proton planning reasonably met the constraints used by the CK planning. Similarly to the finding for bladder, $V_{10\,Gy}$ was found to be substantially smaller with P-wrst than those with CK_{clin} (33.21 vs 52.83 with $P = .02$) and CK_{esc} (33.21 vs 54.92 with $P < .01$). This finding was repeated for $V_{10\,Gy}$ with P-nom. The findings in the trend of $V_{10\,Gy}$ of bladder and rectum were not new because normal tissue saving in the low dose was documented as the characteristic of proton therapy.[8] The proton planning at the dose range ≥ 29 Gy, based on the performance of P-nom, was comparable to the CK planning; the proton at the range at or below 18.125 Gy was better.

For urethra, D_m with P-wrst was found to be greater than that with CK_{esc} and D_m with P-nom was smaller than that with CK_{clin}. For femoral heads, D_m was found to be greater with P-wrst than that with CK_{esc} (20.7 vs 13.62 with $P = .02$). A similar finding was observed for D_m with P-norm. $V_{20\,Gy}$ with P-wrst and that with P-nom, respectively, were not distinguishable from those with CK_{clin} and CK_{esc}. For bowel, $V_{30\,Gy}$ and $V_{18.1\,Gy}$ with P-wrst, respectively, were similar to those with CK_{clin} and CK_{esc}. A similar finding was observed for those with P-nom.

Hypo-fractionated stereotactic body radiation therapy by x-ray has been widely accepted based on the assumed lower α/β in tumor than in normal tissues and similar toxicities to those of conventional fractionation.[18-21] The improved quality of life through the reduction of treatment duration was an additional basis.[22] The regimen of 36.25 to 40 Gy in 5 fractions, adopted in our institution, is taken in most centers. Recently, the hypo-fractionated stereotactic body radiation therapy was pushed to fewer fractions than 5 with a greater total dose than 36.25 Gy in a few clinical trials.[23] They attempted 45 Gy in 5 fractions,[24] 40 Gy in 3 fractions,[25] and 45 Gy in 5 fractions, or 24 Gy in a single fraction.[26] Although better target delineation, planning, and delivery verification may be possible to further escalate the dose, it remains unclear whether these attempts can clearly result in improved survival or quality of life.[23] The introduction of proton therapy to the treatment of prostate was with conventional fractionation. This was recently transitioned into hypofractionation, as described in the introduction section.[6, 7] Our current study was part of this attempt.

This study was based on comparing proton planning with robust optimization with CK planning without the optimization with respect to the planning objectives and constraints of the latter. Because the intent was clinical, the CK plans that have been used for treatment without robust optimization were employed. For a pure planning comparison, the robust optimization can be done on the CK plans, which currently is not available. Note that the results of this study were based on and, therefore, were affected by the choice of two lateral beams for the proton plan and the use of the variable setup margins around CTV that were individualized for each patient.

The proton delivery time is much shorter than the CK delivery time with target tracking via fiducials (a few minutes vs 15 minutes or more in delivery time). This justified using the same CTV-to-PTV margin, used for the CK treatment, for the treatment with proton.

Conclusion

The proton planning, based on two lateral beams, in the worst-case scenario of the robust evaluation reasonably met all planning objectives and constraints used for the CK treatments of the prostate in terms of CTV coverage and OAR sparing.

The proton planning in the nominal condition of the robust optimization generated comparable dosimetric values to those by the CK plans, whether fully or nominally optimized for dose escalation to the DIL, when it comes to CTV and DIL coverage against the imposed objectives in Table 1. This implies the dosimetric equivalence of the proton planning to the CK planning for the target coverage. Regarding OAR sparing, for doses above 18.125 Gy, the proton planning, based on the performance of P-nom, was comparable to the CK planning, while for lower doses, the proton was superior. It is important to note that this conclusion was based on comparing proton planning with the robust optimization to CK planning without robust optimization, which was intended for clinical translation, instead of comparing the two planning methods equally. In this study, the proton therapy planning was compared with the CK therapy planning that has treated 350 patients with the hypofractionation at our institution. The conclusion of this study offers a foundation for a clinical study of proton therapy as an alternative option for hypo-fractionated treatment of prostate cancer at our center.

Data Sharing Statement

The data presented in this study are available on request from the corresponding author.

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Author Contributions

Inhwan Yeo: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Writing- Original draft, Writing- Review and Editing. Alex Goughenour: Conceptualization, Investigation, Methodology, Software, Writing- Original draft. George Cernica: Investigation, Software, Writing- Original draft, Writing- Review and Editing. Wei Nie: Investigation, Software. Mindy Joo and Jiajin Fan: Writing- Review and Editing. Peng Wang: Formal analysis, Writing- Review and Editing. Ashkan Parniani: Formal analysis. Samir Kanani: Data curation, Formal analysis, Methodology.

Declaration of Conflicts of Interest

The authors have no conflicts of interest to disclose.

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