

A treatment planning study of urethra-sparing intensity-modulated proton therapy for localized prostate cancer

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ABSTRACT

Background and Purpose: Urethra-sparing radiation therapy for localized prostate cancer can reduce the risk of radiation-induced genitourinary toxicity by intentionally underdosing the periurethral transitional zone. We aimed to compare the clinical impact of a urethra-sparing intensity-modulated proton therapy (US-IMPT) plan with that of conventional clinical plans without urethral dose reduction.

Materials and Methods: This study included 13 patients who had undergone proton beam therapy. The prescribed dose was 63 GyE in 21 fractions for 99% of the clinical target volume. To compare the clinical impact of the US-IMPT plan with that of the conventional clinical plan, tumor control probability (TCP) and normal tissue complication probability (NTCP) were calculated with a generalized equivalent uniform dose-based Lyman–Kutcher model using dose volume histograms. The endpoints of these model parameters for the rectum, bladder, and urethra were fistula, contraction, and urethral stricture, respectively.

Results: The mean NTCP value for the urethra in US-IMPT was significantly lower than that in the conventional clinical plan (0.6% vs. 1.2%, $p < 0.05$). There were no statistically significant differences between the conventional and US-IMPT plans regarding the mean minimum dose for the urethra with a 3-mm margin, TCP value, and NTCP value for the rectum and bladder. Additionally, the target dose coverage of all plans in the robustness analysis was within the clinically acceptable range.

Conclusions: Compared with the conventional clinically applied plans, US-IMPT plans have potential clinical advantages and may reduce the risk of genitourinary toxicities, while maintaining the same TCP and NTCP in the rectum and bladder.

1. Introduction

Proton beam therapy (PBT) is a treatment modality for localized prostate cancer that delivers a uniform dose to the target and a lower dose to the surrounding tissue. Compared with X-ray therapy, PBT can reduce the risk of adverse events, such as gastrointestinal (GI) or genitourinary (GU) toxicities [1,2]. A previous multicenter clinical study reported a lower incidence of grade 2 GI and GU toxicities using this

modality, demonstrating favorable outcomes after performing PBT [3].

Currently, the risk of GI toxicities is further reduced by transperineal insertion of a hydrogel spacer between the rectum and prostate gland [4,5]; however, it is difficult to physically distance the prostatic urinary tract and prostate gland. Thus, urethra-sparing radiation therapy (USRT) using image-guided intensity-modulated radiation therapy (IG-IMRT) may minimize GU toxicities [6–8]. Shimizu et al. demonstrated that USRT using IG-IMRT with a small safety margin through a real-time

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tumor-tracking radiation therapy system achieved a very low incidence of GU toxicities [8]. However, there have been no risk assessment reports on USRT in PBT.

Recently, intensity-modulated proton therapy (IMPT) with multi-field optimization and robust optimization has been clinically available in numerous spot-scanning PBT facilities. As this technique has a more complex dose distribution, it is expected to further reduce the risk of adverse events; however, IMPT is sensitive to uncertainties, such as the motion of the prostate during treatment because of peristaltic movement of the intestinal tract [9–11]. Moreover, we should consider uncertainties from the urethral position, as the prostatic urinary tract may shift because of the difference between urethral catheter placement during treatment planning and actual treatment without a urethral catheter [12].

To evaluate the therapeutic ratio of any particular radiotherapy modality, tumor control probability (TCP) and normal tissue complication probability (NTCP) should be assessed during treatment planning. Among plans with similar TCPs, that with the lowest NTCP should be considered superior. Several studies have compared the TCP and NTCP of various radiotherapy techniques, including external beam radiotherapy and brachytherapy. Thomsen et al. used NTCP calculations to demonstrate that USRT using IG-IMRT can spare the urethra without compromising TCP [13]. Thus, we hypothesized that urethra-sparing IMPT (US-IMPT) would lead to a significant reduction in GU toxicities through visualization of the prostatic urinary tract, without lowering the prostate cancer control. Our aim was to evaluate the risk of GU toxicities between US-IMPT and the current conventional proton therapy without urethral dose reduction.

2. Materials and Methods

2.1. Patient data

This retrospective planning study was approved by the Institutional Review Board of the Hokkaido University Hospital for Clinical Research (approval number: 018–0221). We included 13 patients with prostate cancer who had undergone real-time-image-gated-spot-scanning proton beam therapy (RGPT) (with three fiducial markers inserted into the prostate gland) at our institution between October 2019 and 2020 [14–17]. Written informed consent was obtained from all patients. Patient characteristics are presented in Supplementary Material 1. The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology for prostate cancer categorizes patients into the low risk, favorable and unfavorable intermediate risk, high risk, and very high risk groups [18]. No patients had undergone previous treatment.

2.2. Treatment planning

All patients underwent treatment planning computed tomography (CT) and magnetic resonance imaging (MRI). Three gold fiducial markers (1.5-mm diameter) were inserted into the prostate gland for the RGPT system 1 week before image acquisition for treatment planning CT and MRI. To reduce the risk of GI toxicities, all patients underwent transperineal insertion of 10 mL polyethylene glycol gel (SpaceOAR; Augmenix Inc., Waltham, MA) up to the Denonvilliers' fascia under transrectal ultrasound guidance [4,5].

In the treatment planning CT image acquisition, the patients were placed in a supine position, fixed with a vacuum cushion. We performed CT using the Optima CT580W (General Electronic Healthcare, Waukesha, WI) until September 2020, subsequently using the SOMATOM Confidence (Siemens Healthineers, Forchheim, Germany). MRI was performed using a 3.0-Tesla MRI scanner with a 32-channel sensitivity-encoding (SENSE) torso cardiac coil (Achieva TX; Philips Healthcare, Best, The Netherlands). To identify the prostatic urinary tract, we used post-urination MRI (PU-MRI) as one of our proposed, noninvasive urethral visualization techniques [19]. Briefly, PU-MRI was performed

using a noncontrast high resolution two-dimensional T2-weighted turbo spin echo imaging sequence within a few minutes after urination. The acquisition parameters of the CT and MRI have been previously reported [19]. All acquired images were co-registered with the CT image without using a urethral catheter on MIM ver.7.0.4 (MIM Software, Inc., Cleveland, OH), based on the inserted fiducial markers.

The clinical target volume (CTV) was defined based on our previous report [8] and guidelines approved by the American Society for Radiation Oncology (ASTRO), American Society of Clinical Oncology (ASCO), American Urological Association (AUA) [20], and Japanese Society for Radiation Oncology (JASTRO) [21]. The prostate was included in the CTV for all patients, and the seminal vesicle was added to the CTV for the patients with unfavorable intermediate risk or higher risk prostate cancer. The margin for the prostate to compensate for potential extracapsular extension was not added, based on the JASTRO guidelines. The planning target volume (PTV) was determined by expanding the CTV with a 3-mm margin to account for organ motion and setup uncertainties. The rectum and bladder, as solid organs, were delineated as organs at risk (OARs). The urethra was contoured within a 4-mm diameter region of interest (ROI), and the planning OAR volume of the urethra (uPRV) was uniformly expanded with an additional 3-mm margin. We modified the CTV (mCTV) by excluding the uPRV for US-IMPT. Using the implantation of the three fiducial markers and inter-portal adjustment of the patient with the RGPT system, it was possible to maintain the intrafractional displacement within the predetermined range of 2.0 mm for localized prostate cancer, which was sufficient using the RGPT system [22].

We defined US-IMPT as the urethra dose reduction plan and the clinical plan as the current conventional proton therapy without urethral dose reduction. The US-IMPT and clinical plans were calculated using the VQA treatment planning system (Hitachi Ltd., Tokyo, Japan), assuming the proton treatment with the PBT system, PROBEAT-RT (Hitachi Ltd.) [23]. The prescribed dose was 63 GyE in 21 fractions with four fields (gantry angle [deg] = 75, 100, 260, and 285) to reduce the biological effect of dose distortion by fiducial markers in the RGPT system [24]. The full width at half maximum of the spot size in the air at the isocenter varied from 6.8 mm at 220 MeV to 18.3 mm at 70.2 MeV; the elliptical of the beam was close to zero [25]. The relative biological effectiveness of the proton beam was estimated to be 1.1, compared with the photon beam.

Concerning the dose calculation in the clinical plan, all strategies were designed such that 99% of the CTV received the prescribed dose, while the distal and proximal margins were beam-specific margins for expansion from the CTV during single-field optimization [25]. Concerning the US-IMPT plan, all strategies were designed such that 99% of the mCTV received the prescribed dose, and multifield optimization with robust optimization was selected. The parameters of robust optimization were 3 mm for the setup error in the RGPT system and $\pm 3.5\%$ for the range uncertainty. The common dose constraints for the OARs were: rectum, $D_{max} < 66\text{GyE}$, $V_{50\text{GyE}} < 20\%$, and $V_{30\text{GyE}} < 50\%$; bladder, $D_{max} < 66\text{GyE}$, $V_{63\text{GyE}} < 10\text{cm}^3$, $V_{48\text{GyE}} < 25\%$, and $V_{30\text{GyE}} < 30\%$. The additional dose constraints for urethral dose reduction without compromising the target dose in the US-IMPT plan were as follows: urethra, $V_{63\text{GyE}} < 10\%$, and urethra + 3 mm, $D_{min} > 60\text{GyE}$. The dose constraint details derived from our previous treatment [8] are presented in Table 1, using the linear-quadratic model with $\alpha/\beta = 3$ and PACE-B trial [26]. They complied with the ASTRO, ASCO, and AUA guidelines [20].

2.3. Data analyses

Dose volume histograms (DVHs) were generated for all structures. The DVH parameters used for the comparison of the clinical and US-IMPT plans are presented in Table 1. The clinical impact of US-IMPT was evaluated considering the TCP and NTCP. The TCP and NTCP

Table 1
Dose constraints and summary of the DVHs analysis.

		Constraints	Acceptable	Clinical plan (n = 13)				US-IMPT plan (n = 13)				p-value
				Median	Range Min	-	Max	Median	Range Min	-	Max	
PTV	$D_{95\%}$ [GyE]	62.5 GyE $\leq D_{95\%} \leq 63.5$ GyE	N.A.	63.4	63.2	–	63.6	63.2	62.8	–	63.8	0.13
CTV	D_{max} [GyE]	69.3 GyE (110% Dose)	72.4 GyE (115% Dose)	66.1	65.0	–	67.3	66.9	65.5	–	67.4	<0.05*
mCTV	$D_{99\%}$ [GyE]	\geq Prescribed dose		64.1	63.5	–	64.6	63.6	63.3	–	63.8	<0.05*
Rectum	D_{max} [GyE]	66 GyE	68 GyE	64.3	59.4	–	65.5	64.9	60.5	–	66.4	0.09
	V_{50GyE} [%]	< 20%	N.A.	8.9%	2.2%	–	18.9%	8.1%	8.1%	–	17.2%	0.34
	V_{30GyE} [%]	< 50%	N.A.	23.9%	12.6%	–	46.8%	24.2%	8.1%	–	34.6%	0.11
Bladder	D_{max} [GyE]	< 66 GyE	< 68 GyE	65.4	64.7	–	66.2	65.8	64.9	–	66.4	0.09
	V_{63GyE} [cc]	< 10 cc	< 15 cc	3.4	1.7	–	7.7	4.8	1.9	–	9.3	<0.05*
	V_{48GyE} [%]	< 25%	< 35%	20.1%	11.5%	–	41.4%	22.2%	10.2%	–	37.5%	0.68
	V_{30GyE} [%]	< 30%	< 50%	34.4%	19.4%	–	59.3%	36.7%	17.7%	–	55.7%	0.38
Urethra	V_{63GyE} [%]	< 10%	< 20%	100.0%	98.1%	–	100.0%	6.5%	0.9%	–	15.1%	<0.05*
uPRV	D_{min} [GyE]	> 60 GyE	N.A.	61.6	59.1	–	62.7	61.2	59.2	–	62.4	0.38

US-IMPT, urethra sparing intensity modulated proton therapy; PTV, planning target volume; CTV, clinical target volume; uPRV, urethra planning organs at risk volume; mCTV, modified CTV excluding the uPRV; SD, standard deviation; N.A., not applicable.

* : statistically significant differences ($p < 0.05$)

models were used to replace the actual, inhomogeneous distribution with a homogeneous dose distribution, using the generalized equivalent uniform dose (gEUD) for the CTV or OARs. The TCP and NTCP were calculated with a gEUD-based Lyman–Kutcher-model using DVHs (Supplementary Material 2) [27–30].

Based on previous reports, the TCP and NTCP in this study were calculated using the following parameters: α/β : 1.5, 8, 3, and 7.5 GyE for the prostate, rectum, bladder, and urethra, respectively; α : –10, 5, 7, and 15 for the prostate, rectum, bladder, and urethra, respectively; γ_{50} : 2.5, 2.7, 3.6, and 3.625 for the prostate, rectum, bladder, and urethra, respectively; TCD_{50} : 65 GyE for the prostate; and TD_{50} : 80, 80, and 98 GyE for the rectum, bladder, and urethra, respectively [13,31]. The endpoints of these model parameters for the rectum, bladder, and urethra were fistula, contraction, and urethral stricture, respectively.

We examined the robustness of the clinical and US-IMPT plans to assess the effect of setup errors on the dose-volume metrics for the CTV. The CTV dose robustness was evaluated by computing the plan with 5-mm isocenter deviations in the left–right, superior–inferior, and anterior directions, and with a 4-mm isocenter deviation in the posterior direction.

2.4. Statistical analyses

The Wilcoxon signed-rank test was used for all statistical comparisons between the US-IMPT and clinical plans. Statistical significance was set at $p < 0.05$. All statistical analyses were performed using JMP Pro 14

(SAS Institute Inc., Cary, NC).

3. Results

The urethral ROI was visually detected using PU-MRI in all patients. The clinical and US-IMPT plans achieved the prescribed dose to the CTV, maintaining dose constraints (Table 1). All US-IMPT plans reduced the dose to the urethra, satisfying the dose constraints for the urethra and uPRV through the generation of doughnut-shaped dose distributions (Fig. 1 and Table 1). Fig. 2 plots the DVHs data for the PTV, CTV, mCTV, rectum, bladder, urethra, and uPRV, demonstrating that US-IMPT plans delivered lower irradiation doses to the urethra and uPRV compared with the clinical plan. The volume of the urethra receiving 63 GyE in the US-IMPT plan was significantly lower than that in the clinical plan (median [range]; clinical plan: 100.0% [98.1–100.0%], US-IMPT plan: 6.5% [0.9–15.1%]; $p < 0.05$); although there was a significant difference between the clinical and US-IMPT plans regarding the volume of the bladder receiving 63 GyE, both evaluation points in all plans were under the acceptable range. There were no significant differences in other evaluation points of the OARs between the clinical and US-IMPT plans. Moreover, although the dose for the mCTV in the US-IMPT was significantly lower than that in the clinical plan, all plans were within the clinically acceptable range; the dose in the worst case under the US-IMPT plan was 63.3 GyE (Table 1).

In the nominal plan, as shown in Table 2 and Fig. 3, the median and range of NTCP values for the urethra in the US-IMPT plan were

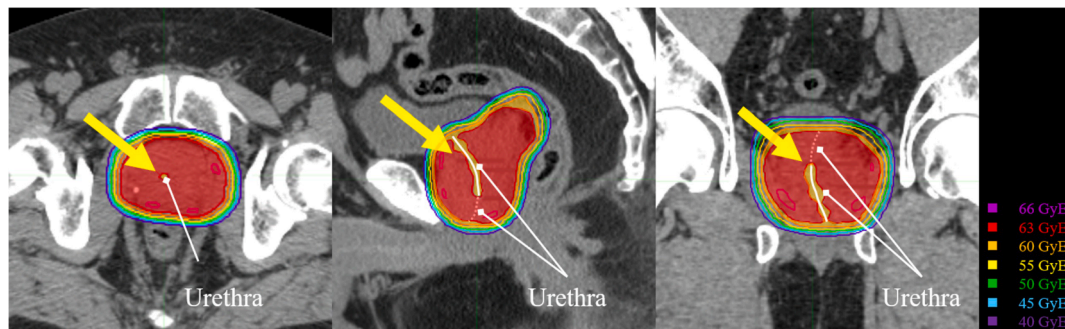


Fig. 1. The dose reduction in the CTV can be observed around the prostatic urinary tract (yellow arrow). The white line shows the urethra identified on PU-MRI on this slice, and the white dotted line shows the urethra on the other slice. US-IMPT, urethra-sparing intensity-modulated proton therapy; CTV, clinical target volume; PU-MRI, post-urination magnetic resonance imaging. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

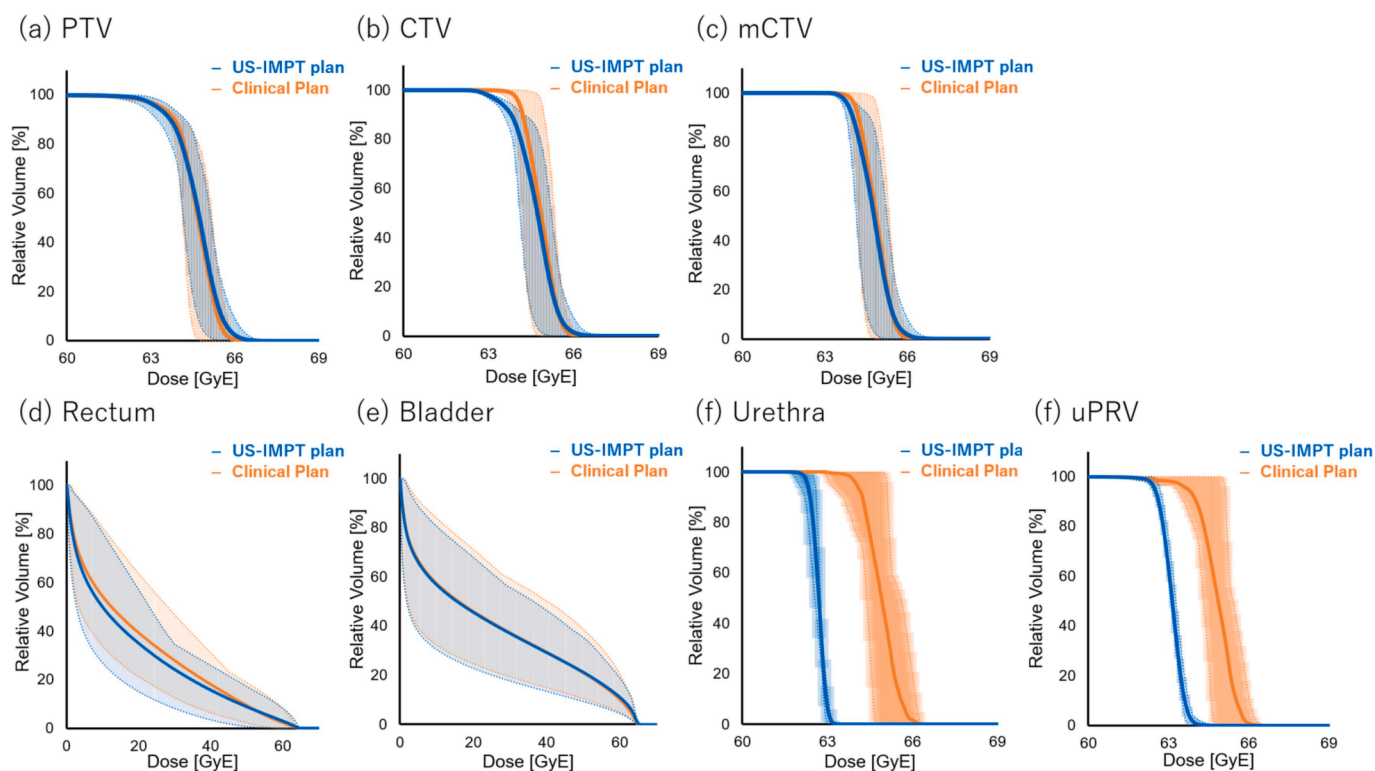


Fig. 2. Plots of dose volumes with the clinical plan (orange) and the US-IMPT plan (blue) for the DVHs of PTV, CTV, mCTV, rectum, bladder, and urethra. Solid lines represent the average DVHs of all 13 patients (both plans). The surrounding shading represents the range for the 13 patients. DVHs, dose volume histograms; ROI, region of interest; US-IMPT, urethra-sparing intensity-modulated proton therapy; CTV, clinical target volume; mCTV, modified clinical target volume; PTV, planning target volume. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 2
Summary of the TCP, NTCP, and gEUD for the CTV, Rectum, Bladder, and Urethra.

			Clinical plan (n = 13)			US-IMPT plan (n = 13)			p-value		
			Median	Range	Max	Median	Range	Max			
CTV	TCP [%]	Nominal plan	93.5%	92.4%	–	94.2%	93.3%	92.2%	–	93.8%	0.12
		Robust plan	93.5%	91.8%	–	94.4%	92.9%	90.7%	–	94.4%	<0.05*
		gEUD [GyE]	Nominal plan	84.9	83.5	–	85.9	84.6	83.2	–	85.4
		Robust plan	84.8	82.7	–	86.1	84.0	81.6	–	86.3	<0.05*
Rectum	NTCP [%]	Nominal plan	0.1%	0.0%	–	0.3%	0.0%	0.0%	–	0.3%	0.91
		Robust plan	0.1%	0.0%	–	1.1%	0.0%	0.0%	–	1.0%	0.84
		gEUD [GyE]	Nominal plan	40.1	30.4	–	46.7	39.1	25.9	–	46.4
		Robust plan	39.8	17.9	–	53.0	39.3	13.0	–	52.3	0.84
Bladder	NTCP [%]	Nominal plan	0.6%	0.2%	–	2.6%	1.2%	0.1%	–	2.4%	0.78
		Robust plan	0.6%	0.0%	–	8.2%	0.6%	0.0%	–	7.5%	0.76
		gEUD [GyE]	Nominal plan	55.9	51.2	–	62.2	56.6	50.4	–	61.9
		Robust plan	55.9	40.7	–	67.6	55.9	39.9	–	67.2	0.70
Urethra	NTCP [%]	Nominal plan	1.2%	1.0%	–	1.4%	0.6%	0.61%	–	0.65%	<0.05*
		Robust plan	1.2%	0.9%	–	1.5%	0.7%	0.5%	–	1.2%	<0.05*
		gEUD [GyE]	Nominal plan	84.9	83.5	–	85.9	84.6	83.2	–	85.4
		Robust plan	72.3	71.0	–	73.5	69.3	68.3	–	72.2	<0.05*

CTV, clinical target volume; TCP, tumor control probability; NTCP, normal tissue complication probability; gEUD, generalized equivalent uniform dose; US-IMPT, urethra sparing intensity modulated proton therapy

* : statistically significant differences (p < 0.05)

significantly lower than those in the clinical plan (clinical plan: 1.2% [1.0–1.4%]; US-IMPT plan: 0.6% [0.61–0.65%]; p < 0.05). Moreover, the median and range of gEUD for the urethra in the US-IMPT plan were significantly lower than those in the clinical plan (clinical plan: 72.2 GyE [71.5–73.0 GyE]; US-IMPT plan: 69.1 GyE [69.0–69.3 GyE]; p < 0.05). Conversely, the median and range of the TCP values in the clinical and US-IMPT plans were 93.5% (92.4–94.2%) and 93.3% (92.2–93.8%), respectively. There were no significant differences in TCP, NTCP, and gEUD for the CTV, rectum, and bladder between the clinical and US-

IMPT plans (Table 2).

As shown in Table 2, similar results were obtained in the robust evaluation. The ranges of NTCP values for the urethra in the robustness analysis were 0.9–1.5% and 0.5–1.0% for the clinical and US-IMPT plans, respectively. Conversely, the ranges of TCP values in the robustness analysis were 91.8–94.4% and 90.7–94.4% for the clinical and US-IMPT plans, respectively (Table 2). Moreover, the ranges of NTCP values for the rectum and bladder in the robustness analysis were 0.0–1.1% and 0.0–8.2%, respectively, for the clinical plan and 0.0–1.0% and

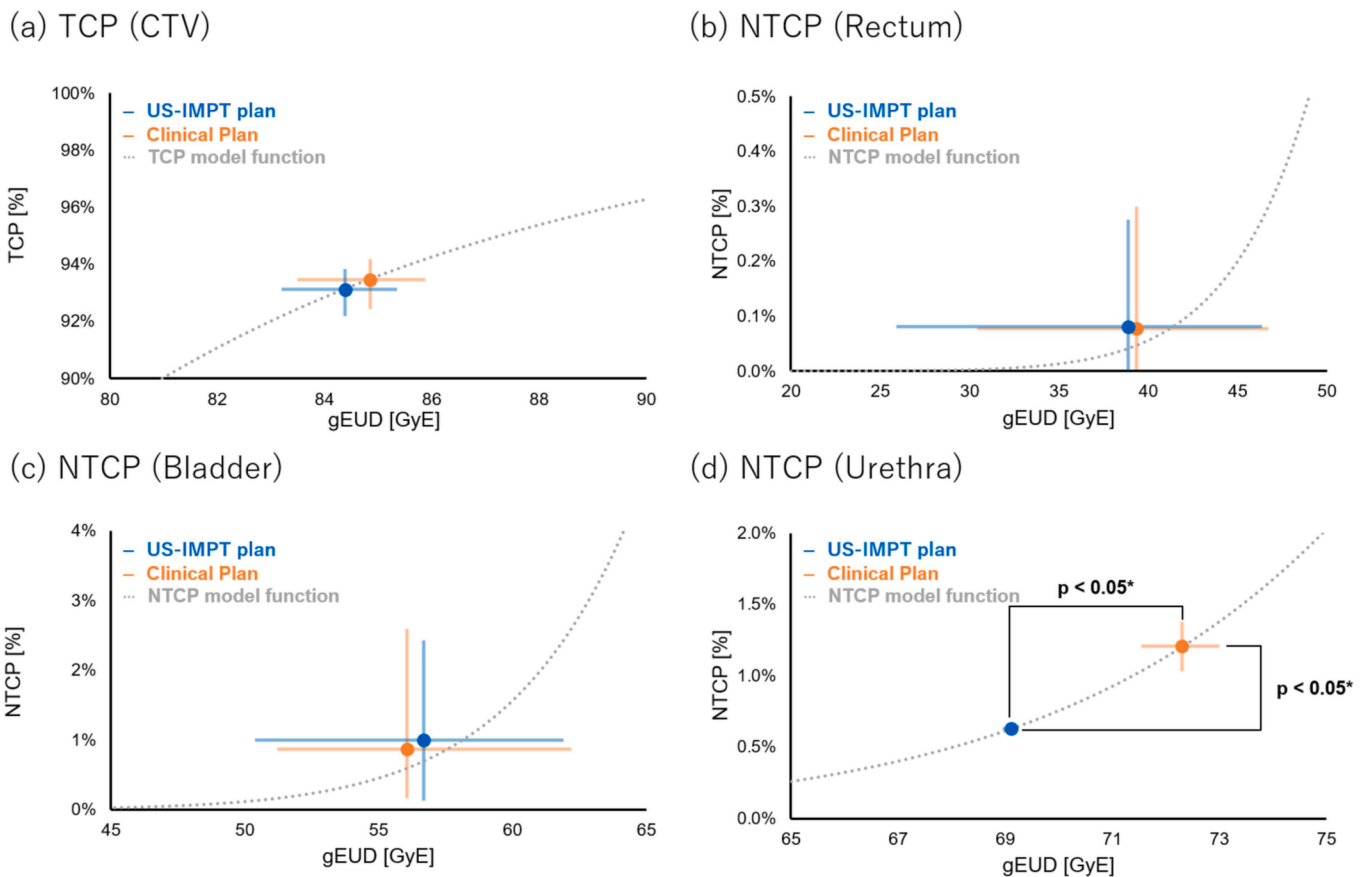


Fig. 3. Plots of the TCP and NTCP values for the clinical plan (orange) and US-IMPT plan (blue) versus gEUD. The endpoints of these NTCP model parameters for the rectum, bladder, and urethra were fistula, contraction, and urethral stricture, respectively. (a) TCP for the CTV, (b) NTCP for the rectum, (c) NTCP for the bladder, and (d) NTCP for the urethra. CTV, clinical target volume; TCP, tumor control probability; NTCP, normal tissue complication probability; gEUD, generalized equivalent uniform dose *statistically significant difference ($p < 0.05$). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

0.0–7.5%, respectively, for the US-IMPT plan (Table 2).

4. Discussion

The NTCP value for the urethra in the US-IMPT plan was found to be significantly lower than that in the clinical plan, without a significant reduction in the TCP of the CTV and NTCP of the rectum and bladder. This finding suggested that US-IMPT can reduce the risk of GU toxicities while maintaining the same clinical outcomes. We present a method for urethral dose reduction in proton therapy with a minor decrease in TCP (Fig. 3). In previous reports, the range of the estimated TCP values in proton therapy without urethral dose reduction was 88–96%, according to the model uncertainties [31]. As shown in Table 2, the TCP values in the clinical and US-IMPT plans were $> 90\%$, even in the worst case of a robust plan. These results suggested that US-IMPT can achieve a similar biochemical local control rate, compared with previous PBT.

Although urethral catheter insertion is the gold standard for identifying the prostatic urinary tract in USRT, the position may shift [12,16]. Recently, visualizing the prostatic urinary tract using MRI has become possible with developments in image acquisition equipment and technologies to reduce the impact of uncertainties due to urethral catheter placement [19,32,33]. The proposed noninvasive PU-MRI technique can overcome these issues with urethral visualization techniques [19]. The benefits of PU-MRI include its completely noninvasive nature and ability to generate a contrast between the urethra and prostate gland; this was attributed to the increase in signal intensity of the urethra caused by urine attached to the urethral wall. In this study, it was possible to identify the prostatic urinary tract using PU-MRI without using a

urethral catheter, suggesting that treatment via USRT is possible in patients who have difficulties with urethral catheter insertion.

There are several studies regarding USRT using IG-IMRT, including Phase 2 randomized trials [6–8]. USRT using IG-IMRT was reportedly able to reduce the incidence of GU toxicities by decreasing the dose to the prostatic urinary tract. The average NTCP value of the urethra in hypofractionated, four-field, three-dimensional conformal radiotherapies (20 fractions of 2.75 Gy/fraction) was $< 3.6\%$ [34]. The NTCP value of the urethra after USRT in IMRT (39 fractions of 2.0 Gy/fraction) also decreased by 2.0% when the urethra was irradiated under 76 Gy [13]. Considering the NTCP values in previous reports of USRT, the results obtained using PBT did not significantly lower the NTCP of the urethra when compared with IMRT. Therefore, our findings suggested that localized prostate cancer may be treated via PBT using the RGPT system within the same GU risk range as USRT in IMRT. Although there are many reports of PBT for localized prostate cancer without urethral dose reduction, our study is the first to evaluate the risk of GU toxicities by TCP and NTCP modeling analysis using PBT.

However, this study had some limitations. First, the US-IMPT plan is a simulation study, rather than an actual treatment plan, including the uncertainty in TCP and NTCP modeling parameters. We found that the NTCP value of the urethra in the US-IMPT plan was significantly lower than that in the clinical plan, with no significant difference in the rectum and bladder (Table 2). As the differences in NTCP values between the plans were very small, the findings require cautious interpretation while considering the model's uncertainty and the need for further data accumulation. It should be noted that the estimated TCP and NTCP values are typically subject to considerable model uncertainties. We

used an α/β of 1.5 GyE to calculate the TCP based on a previous report [31]; considering a range from 1.2 to 2.7 Gy, as published in a recent meta-analysis, would increase the robustness of the TCP estimation [35].

Since urethral stricture was the sole GU toxicity endpoint in this study, future studies should consider the uncertainty of the mathematical models for other adverse events. Moreover, Trofimov et al. calculated the EUD with $\alpha = -10^{+3}_5$ for the target volume, $\alpha = 5^{+3}_2$ for the rectum, and $\alpha = 7^{+5}_3$ for the bladder, where the subscript and superscript corresponded with the 95% confidence uncertainty margin [36]; thus, more accurate modeling parameters for TCP and NTCP calculations can be obtained by accruing further clinical data using the US-IMPT plan.

According to the findings of randomized clinical trials, USRT using IG-IMRT (including stereotactic body radiation therapy) photon radiation therapy improved urinary health-related quality of life [6,7]. Similarly, randomized studies focused on PBT are needed to confirm whether US-IMPT plans can reduce GU toxicities, and compare the findings with those obtained after performing clinical plans without urethral dose reduction. Next, the ability to spare the prostatic urinary tract during beam delivery may have been limited by uncertainties during beam delivery—despite the stringent urethral dose constraints in US-IMPT—since IMPT is sensitive to uncertainty from organ motion [10,11]. By combining our clinically implemented RGPT system and our proposed method to identify the prostatic urinary tract using PU-MRI, and creating an equal environment between the treatment planning stage and beam delivery stage, these uncertainties can be reduced [14–17]. Finally, the effect of TCP because of USRT in intraprostatic tumor localization near the urethra was not fully considered in this study, owing to missing histopathological information. Histopathological information is important in focal dose-escalated radiotherapy, and the USRT may increase the therapeutic ratio by defining the intraprostatic gross tumor volume utilizing modern imaging techniques, such as prostate-specific membrane antigen positron emission tomography [37]. The influences of TCP and NTCP in US-IMPT with focal dose-escalated radiotherapy should be investigated in future studies.

In conclusion, we demonstrated the feasibility of reducing the dose to the urethra by using IMPT dose planning based on the RGPT system and visualizing the prostatic urinary tract via PU-MRI without a urethral catheter. The results of TCP and NTCP modeling analyses suggest that US-IMPT can reduce the risk of GU toxicities without compromising tumor control by lowering the urethral dose.

5. Authors' Contributions

TY and KN contributed equally to this work SS and HA supervised the project and guarantor of the data. SS, HA, KN, and TH treated and followed up the patients. ST, TK, MT, ST, TM, KS, SK, KK, FK, TY, and KN analyzed the data. TY and KN wrote the first draft of this paper. All authors contributed to the drafting and editing of the manuscript and approved the final version.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.phro.2021.09.006>.

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